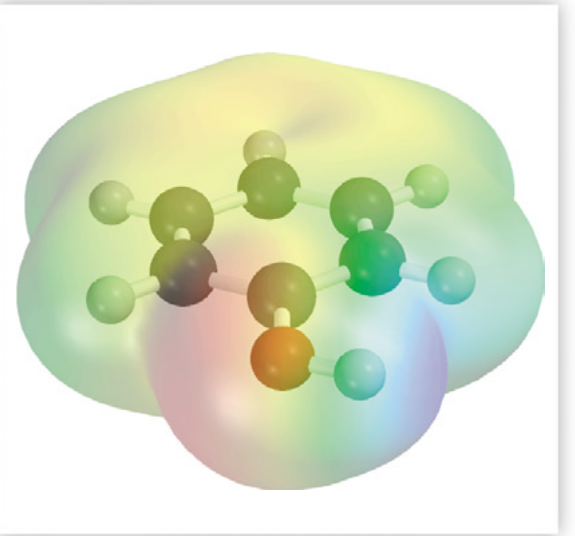


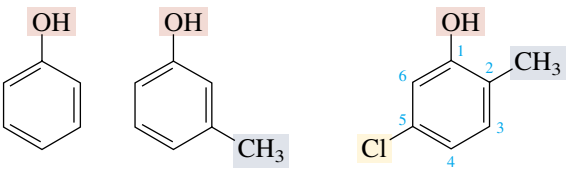
CHAPTER 24

PHENOLS

Phenols are compounds that have a hydroxyl group bonded directly to a benzene or benzenoid ring. The parent compound of this group, C_6H_5OH, called simply *phenol,* is an important industrial chemical. Many of the properties of phenols are analogous to those of alcohols, but this similarity is something of an oversimplification. Like arylamines, phenols are difunctional compounds; the hydroxyl group and the aromatic ring interact strongly, affecting each other's reactivity. This interaction leads to some novel and useful properties of phenols. A key step in the synthesis of aspirin, for example, is without parallel in the reactions of either alcohols or arenes. With periodic reminders of the ways in which phenols resemble alcohols and arenes, this chapter emphasizes the ways in which phenols are unique.

24.1 NOMENCLATURE

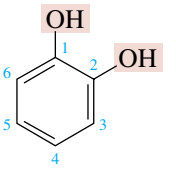
An old name for benzene was *phene,* and its hydroxyl derivative came to be called *phenol.** This, like many other entrenched common names, is an acceptable IUPAC name. Likewise, *o-, m-,* and *p*-cresol are acceptable names for the various ring-substituted hydroxyl derivatives of toluene. More highly substituted compounds are named as derivatives of phenol. Numbering of the ring begins at the hydroxyl-substituted carbon and proceeds in the direction that gives the lower number to the next substituted carbon. Substituents are cited in alphabetical order.



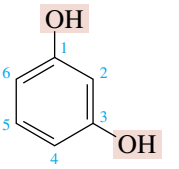
Phenol *m*-Cresol 5-Chloro-2-methylphenol

*The systematic name for phenol is *benzenol.*

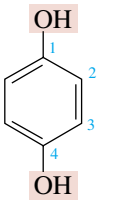
The three dihydroxy derivatives of benzene may be named as 1,2-, 1,3-, and 1,4-benzenediol, respectively, but each is more familiarly known by the common name indicated in parentheses below the structures shown here. These common names are permissible IUPAC names.



1,2-Benzenediol (pyrocatechol)



1,3-Benzenediol (resorcinol)



1,4-Benzenediol (hydroquinone)

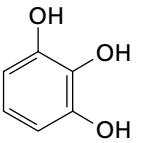
Pyrocatechol is often called *catechol.*

The common names for the two hydroxy derivatives of naphthalene are 1-naphthol and 2-naphthol. These are also acceptable IUPAC names.

PROBLEM 24.1 Write structural formulas for each of the following compounds:

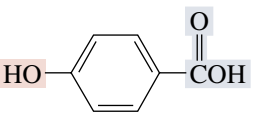
(a) Pyrogallol (1,2,3-benzenetriol)
(b) *o*-Benzylphenol
(c) 3-Nitro-1-naphthol
(d) 4-Chlororesorcinol

SAMPLE SOLUTION (a) Like the dihydroxybenzenes, the isomeric trihydroxybenzenes have unique names. Pyrogallol, used as a developer of photographic film, is 1,2,3-benzenetriol. The three hydroxyl groups occupy adjacent positions on a benzene ring.

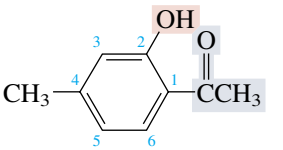


Pyrogallol (1,2,3-benzenetriol)

Carboxyl and acyl groups take precedence over the phenolic hydroxyl in determining the base name. The hydroxyl is treated as a substituent in these cases.



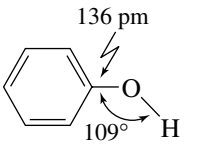
p-Hydroxybenzoic acid



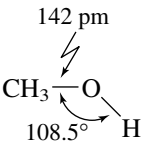
2-Hydroxy-4-methylacetophenone

24.2 STRUCTURE AND BONDING

Phenol is planar, with a C—O—H angle of 109°, almost the same as the tetrahedral angle and not much different from the 108.5° C—O—H angle of methanol:



Phenol

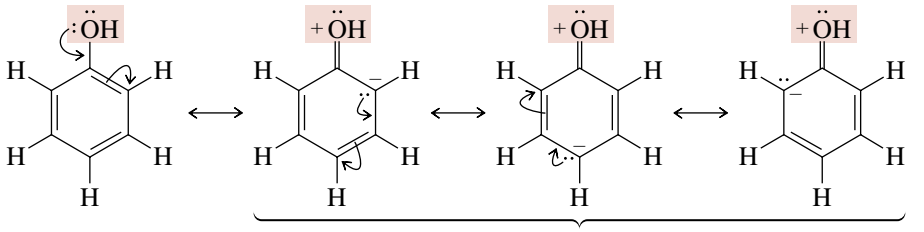


Methanol

The graphic that opened this chapter is a molecular model of phenol that shows its planar structure and electrostatic potential.

As we've seen on a number of occasions, bonds to sp^2-hybridized carbon are shorter than those to sp^3-hybridized carbon, and the case of phenols is no exception. The carbon–oxygen bond distance in phenol is slightly less than that in methanol.

In resonance terms, the shorter carbon–oxygen bond distance in phenol is attributed to the partial double-bond character that results from conjugation of the unshared electron pair of oxygen with the aromatic ring.



Most stable Lewis structure for phenol

Dipolar resonance forms of phenol

Many of the properties of phenols reflect the polarization implied by the resonance description. The hydroxyl oxygen is less basic, and the hydroxyl proton more acidic, in phenols than in alcohols. Electrophiles attack the aromatic ring of phenols much faster than they attack benzene, indicating that the ring, especially at the positions ortho and para to the hydroxyl group, is relatively "electron-rich."

24.3 PHYSICAL PROPERTIES

The physical properties of phenols are strongly influenced by the hydroxyl group, which permits phenols to form hydrogen bonds with other phenol molecules (Figure 24.1*a*) and with water (Figure 24.1*b*). Thus, phenols have higher melting points and boiling points and are more soluble in water than arenes and aryl halides of comparable molecular weight. Table 24.1 compares phenol, toluene, and fluorobenzene with regard to these physical properties.

The physical properties of some representative phenols are collected in Appendix 1.

Some ortho-substituted phenols, such as *o*-nitrophenol, have significantly lower boiling points than those of the meta and para isomers. This is because the *intramolecular* hydrogen bond that forms between the hydroxyl group and the substituent partially compensates for the energy required to go from the liquid state to the vapor.

TABLE 24.1 Comparison of Physical Properties of an Arene, a Phenol, and an Aryl Halide

	Compound		
Physical property	**Toluene, $C_6H_5CH_3$**	**Phenol, C_6H_5OH**	**Fluorobenzene, C_6H_5F**
Molecular weight	92	94	96
Melting point	−95°C	43°C	−41°C
Boiling point (1 atm)	111°C	132°C	85°C
Solubility in water (25°C)	0.05 g/100 mL	8.2 g/100 mL	0.2 g/100 mL

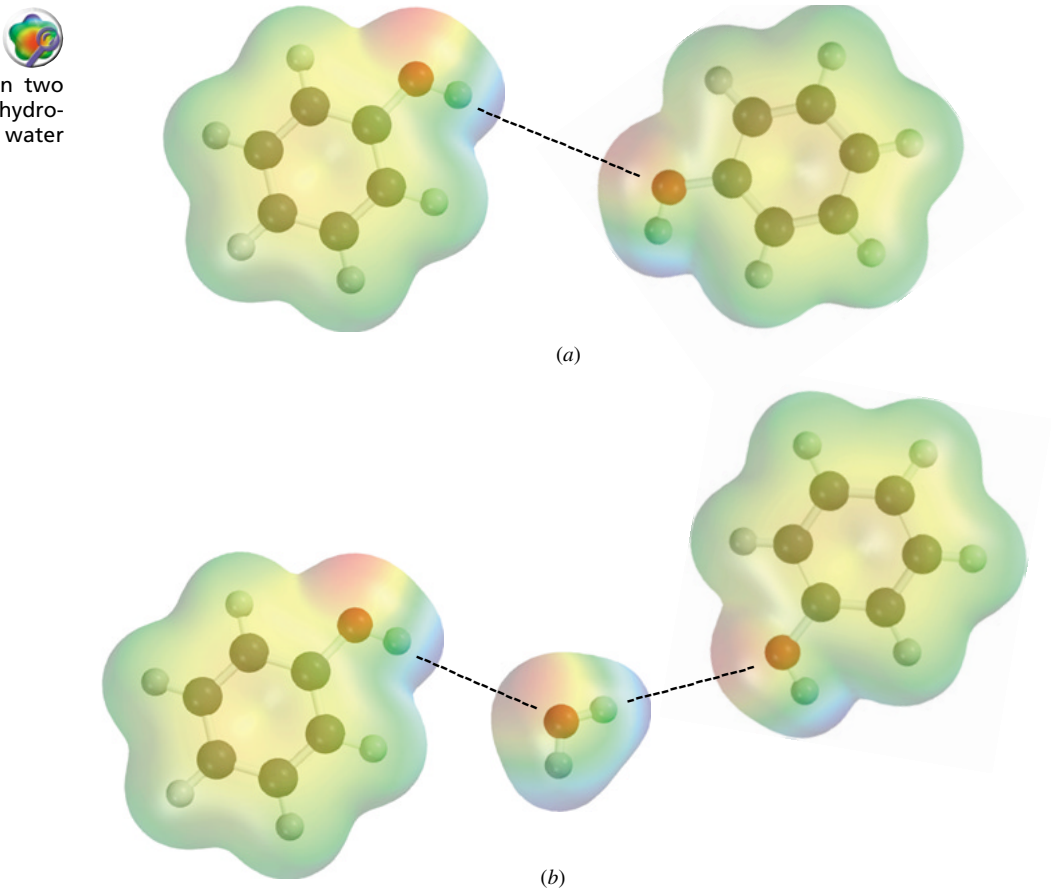
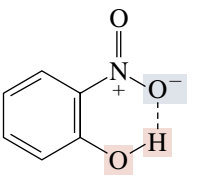


FIGURE 24.1 (*a*) A hydrogen bond between two phenol molecules; (*b*) hydrogen bonds between water and phenol molecules.



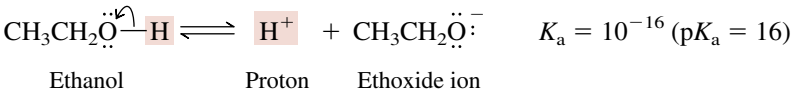
Intramolecular hydrogen bond in *o*-nitrophenol

PROBLEM 24.2 One of the hydroxybenzoic acids is known by the common name *salicylic acid.* Its methyl ester, methyl salicylate, occurs in oil of wintergreen. Methyl salicylate boils over 50°C lower than either of the other two methyl hydroxybenzoates. What is the structure of methyl salicylate? Why is its boiling point so much lower than that of either of its regioisomers?

24.4 ACIDITY OF PHENOLS

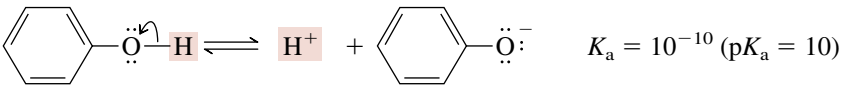
The most characteristic property of phenols is their acidity. Phenols are more acidic than alcohols but less acidic than carboxylic acids. Recall that carboxylic acids have ionization constants K_a of approximately 10^{-5} (pK_a 5), whereas the K_a's of alcohols are in the 10^{-16} to 10^{-20} range (pK_a 16–20). The K_a for most phenols is about 10^{-10} (pK_a 10).

To help us understand why phenols are more acidic than alcohols, let's compare the ionization equilibria for phenol and ethanol. In particular, consider the differences in charge delocalization in ethoxide ion and in phenoxide ion. The negative charge in ethoxide ion is localized on oxygen and is stabilized only by solvation forces.

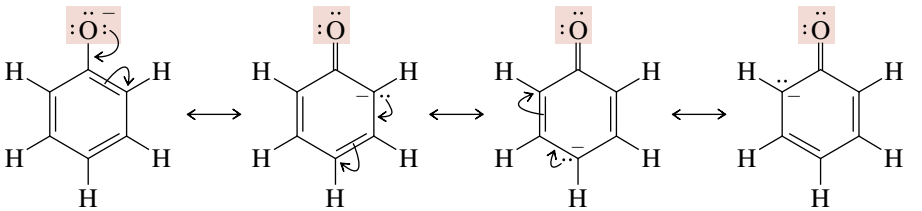


Because of its acidity, phenol was known as *carbolic acid* when Joseph Lister introduced it as an antiseptic in 1865 to prevent postoperative bacterial infections that were then a life-threatening hazard in even minor surgical procedures.

The negative charge in phenoxide ion is stabilized both by solvation and by electron delocalization into the ring.



Electron delocalization in phenoxide is represented by resonance among the structures:



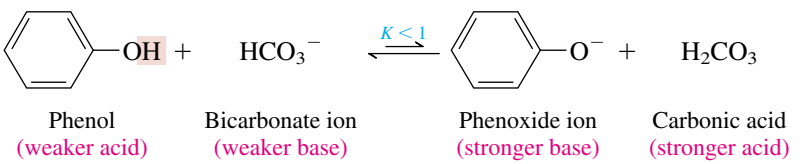
The electrostatic potential map of phenoxide ion on *Learning By Modeling* displays the delocalization of electrons into the ring.

The negative charge in phenoxide ion is shared by the oxygen and the carbons that are ortho and para to it. Delocalization of its negative charge strongly stabilizes phenoxide ion.

To place the acidity of phenol in perspective, note that although phenol is more than a million times more acidic than ethanol, it is over a hundred thousand times weaker than acetic acid. Thus, phenols can be separated from alcohols because they are more acidic, and from carboxylic acids because they are less acidic. On shaking an ether solution containing both an alcohol and a phenol with dilute sodium hydroxide, the phenol is converted quantitatively to its sodium salt, which is extracted into the aqueous phase. The alcohol remains in the ether phase.

How do we know that water is a weaker acid than phenol? What are their respective pK_a values?

On shaking an ether solution of a phenol and a carboxylic acid with dilute sodium bicarbonate, the carboxylic acid is converted quantitatively to its sodium salt and extracted into the aqueous phase. The phenol remains in the ether phase.



How do we know that carbonic acid is a stronger acid than phenol? What are their respective pK_a values?

It is necessary to keep the acidity of phenols in mind when we discuss preparation and reactions. Reactions that produce phenols, when carried out in basic solution, require an acidification step in order to convert the phenoxide ion to the neutral form of the phenol.

How do we know that hydronium ion is a stronger acid than phenol? What are their respective pK_a values?

Phenoxide ion (stronger base) | Hydronium ion (stronger acid) | Phenol (weaker acid) | Water (weaker base)

Many synthetic reactions involving phenols as nucleophiles are carried out in the presence of sodium or potassium hydroxide. Under these conditions the phenol is converted to the corresponding phenoxide ion, which is a far better nucleophile.

24.5 SUBSTITUENT EFFECTS ON THE ACIDITY OF PHENOLS

As Table 24.2 shows, most phenols have ionization constants similar to that of phenol itself. Substituent effects, in general, are small.

Alkyl substitution produces negligible changes in acidities, as do weakly electronegative groups attached to the ring.

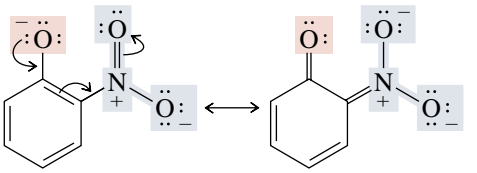
Recall from Section 24.1 that cresols are methyl-substituted derivatives of phenol.

TABLE 24.2 Acidities of Some Phenols

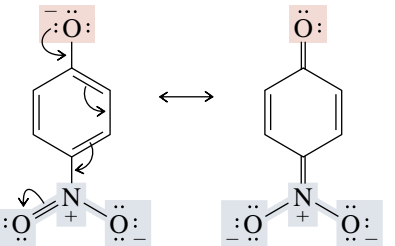
Compound name	Ionization constant K_a	pK_a
Monosubstituted phenols		
Phenol	1.0×10^{-10}	10.0
o-Cresol	4.7×10^{-11}	10.3
m-Cresol	8.0×10^{-11}	10.1
p-Cresol	5.2×10^{-11}	10.3
o-Chlorophenol	2.7×10^{-9}	8.6
m-Chlorophenol	7.6×10^{-9}	9.1
p-Chlorophenol	3.9×10^{-9}	9.4
o-Methoxyphenol	1.0×10^{-10}	10.0
m-Methoxyphenol	2.2×10^{-10}	9.6
p-Methoxyphenol	6.3×10^{-11}	10.2
o-Nitrophenol	5.9×10^{-8}	7.2
m-Nitrophenol	4.4×10^{-9}	8.4
p-Nitrophenol	6.9×10^{-8}	7.2
Di- and trinitrophenols		
2,4-Dinitrophenol	1.1×10^{-4}	4.0
3,5-Dinitrophenol	2.0×10^{-7}	6.7
2,4,6-Trinitrophenol	4.2×10^{-1}	0.4
Naphthols		
1-Naphthol	5.9×10^{-10}	9.2
2-Naphthol	3.5×10^{-10}	9.5

Only when the substituent is strongly electron-withdrawing, as is a nitro group, is a substantial change in acidity noted. The ionization constants of *o*- and *p*-nitrophenol are several hundred times greater than that of phenol. An ortho- or para-nitro group greatly stabilizes the phenoxide ion by permitting a portion of the negative charge to be carried by its own oxygens.

Electron delocalization in* o-*nitrophenoxide ion



Electron delocalization in* p-*nitrophenoxide ion



A meta-nitro group is not directly conjugated to the phenoxide oxygen and thus stabilizes a phenoxide ion to a smaller extent. *m*-Nitrophenol is more acidic than phenol but less acidic than either *o*- or *p*-nitrophenol.

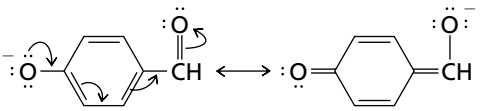
PROBLEM 24.3 Which is the stronger acid in each of the following pairs? Explain your reasoning.

(a) Phenol or *p*-hydroxybenzaldehyde

(b) *m*-Cyanophenol or *p*-cyanophenol

(c) *o*-Fluorophenol or *p*-fluorophenol

SAMPLE SOLUTION (a) The best approach when comparing the acidities of different phenols is to assess opportunities for stabilization of negative charge in their anions. Electron delocalization in the anion of *p*-hydroxybenzaldehyde is very effective because of conjugation with the formyl group.



A formyl substituent, like a nitro group, is strongly electron-withdrawing and acid-strengthening, especially when ortho or para to the hydroxyl group. *p*-Hydroxybenzaldehyde, with a K_a of 2.4×10^{-8}, is a stronger acid than phenol.

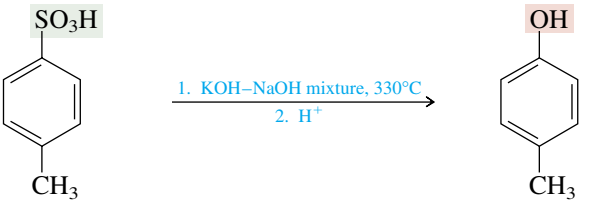
Multiple substitution by strongly electron-withdrawing groups greatly increases the acidity of phenols, as the K_a values for 2,4-dinitrophenol (K_a 1.1×10^{-4}) and 2,4,6-trinitrophenol (K_a 4.2×10^{-1}) in Table 24.2 attest.

24.6 SOURCES OF PHENOLS

Phenol was first isolated in the early nineteenth century from coal tar, and a small portion of the more than 4 billion lb of phenol produced in the United States each year comes from this source. Although significant quantities of phenol are used to prepare aspirin and dyes, most of it is converted to phenolic resins used in adhesives and plastics. Almost all the phenol produced commercially is synthetic, with several different processes in current use. These are summarized in Table 24.3.

The reaction of benzenesulfonic acid with sodium hydroxide (first entry in Table 24.3) proceeds by the addition–elimination mechanism of nucleophilic aromatic substitution (Section 23.6). Hydroxide replaces sulfite ion (SO_3^{2-}) at the carbon atom that bears the leaving group. Thus, *p*-toluenesulfonic acid is converted exclusively to *p*-cresol by an analogous reaction:

Can you recall how to prepare *p*-toluenesulfonic acid?



p-Toluenesulfonic acid — *p*-Cresol (63–72%)

PROBLEM 24.4 Write a stepwise mechanism for the conversion of *p*-toluenesulfonic acid to *p*-cresol under the conditions shown in the preceding equation.

On the other hand, ^{14}C-labeling studies have shown that the base-promoted hydrolysis of chlorobenzene (second entry in Table 24.3) proceeds by the elimination–addition mechanism and involves benzyne as an intermediate.

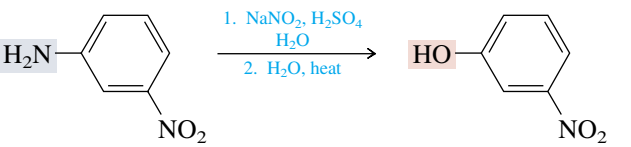
Can you recall how to prepare chlorobenzene?

PROBLEM 24.5 Write a stepwise mechanism for the hydrolysis of chlorobenzene under the conditions shown in Table 24.3.

The most widely used industrial synthesis of phenol is based on isopropylbenzene (cumene) as the starting material and is shown in the third entry of Table 24.3. The economically attractive features of this process are its use of cheap reagents (oxygen and sulfuric acid) and the fact that it yields two high-volume industrial chemicals: phenol and acetone. The mechanism of this novel synthesis forms the basis of Problem 24.29 at the end of this chapter.

Can you recall how to prepare isopropylbenzene?

The most important synthesis of phenols in the laboratory is from amines by hydrolysis of their corresponding diazonium salts, as described in Section 22.18:

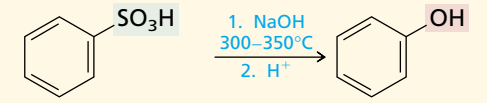
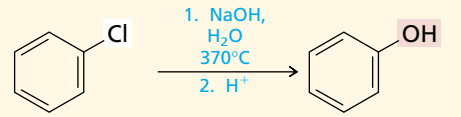
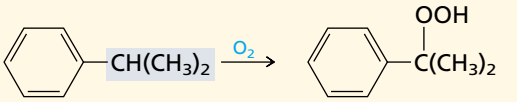
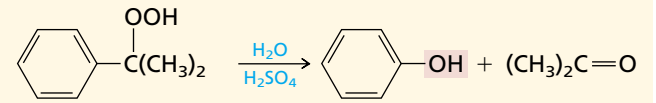


m-Nitroaniline — *m*-Nitrophenol (81–86%)

24.7 NATURALLY OCCURRING PHENOLS

Phenolic compounds are commonplace natural products. Figure 24.2 presents a sampling of some naturally occurring phenols. Phenolic natural products can arise by a number of different biosynthetic pathways. In mammals, aromatic rings are hydroxylated by way

TABLE 24.3 Industrial Syntheses of Phenol

Reaction and comments	Chemical equation
Reaction of benzenesulfonic acid with sodium hydroxide This is the oldest method for the preparation of phenol. Benzene is sulfonated and the benzenesulfonic acid heated with molten sodium hydroxide. Acidification of the reaction mixture gives phenol.	 Benzenesulfonic acid — Phenol
Hydrolysis of chlorobenzene Heating chlorobenzene with aqueous sodium hydroxide at high pressure gives phenol after acidification.	 Chlorobenzene — Phenol
From cumene Almost all the phenol produced in the United States is prepared by this method. Oxidation of cumene takes place at the benzylic position to give a hydroperoxide. On treatment with dilute sulfuric acid, this hydroperoxide is converted to phenol and acetone.	 Isopropylbenzene (cumene) — 1-Methyl-1-phenylethyl hydroperoxide
	 1-Methyl-1-phenylethyl hydroperoxide — Phenol — Acetone

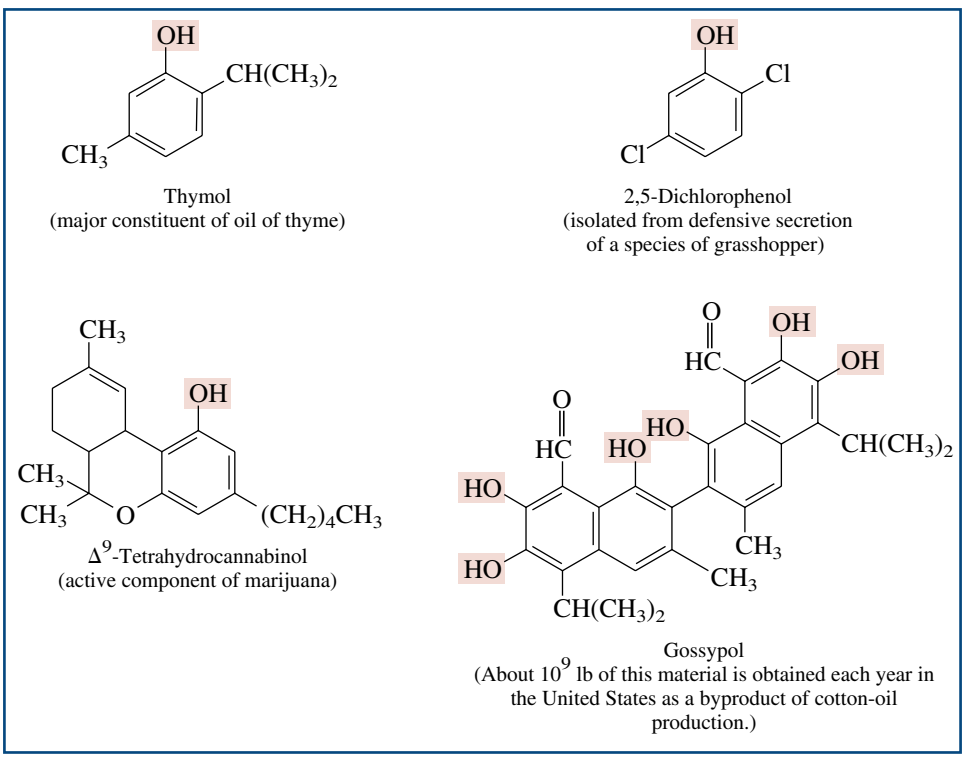
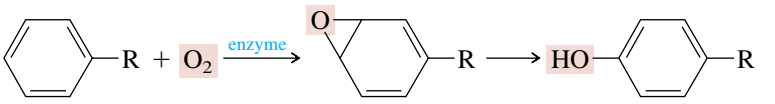


FIGURE 24.2 Some naturally occurring phenols.

of arene oxide intermediates formed by the enzyme-catalyzed reaction between an aromatic ring and molecular oxygen:



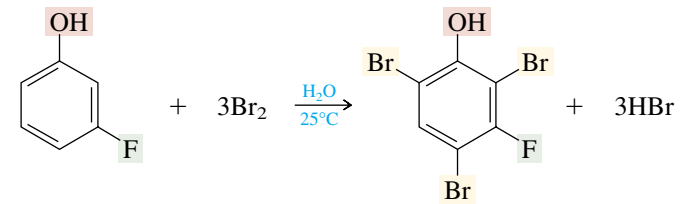
Arene Arene oxide Phenol

In plants, phenol biosynthesis proceeds by building the aromatic ring from carbohydrate precursors that already contain the required hydroxyl group.

24.8 REACTIONS OF PHENOLS: ELECTROPHILIC AROMATIC SUBSTITUTION

In most of their reactions phenols behave as nucleophiles, and the reagents that act on them are electrophiles. Either the hydroxyl oxygen or the aromatic ring may be the site of nucleophilic reactivity in a phenol. Reactions that take place on the ring lead to electrophilic aromatic substitution; Table 24.4 (p. 950) summarizes the behavior of phenols in reactions of this type.

A hydroxyl group is a very powerful activating substituent, and electrophilic aromatic substitution in phenols occurs far faster, and under milder conditions, than in benzene. The first entry in Table 24.4, for example, shows the monobromination of phenol in high yield at low temperature and in the absence of any catalyst. In this case, the reaction was carried out in the nonpolar solvent 1,2-dichloroethane. In polar solvents such as water it is difficult to limit the bromination of phenols to monosubstitution. In the following example, all three positions that are ortho or para to the hydroxyl undergo rapid substitution:



m-Fluorophenol Bromine 2,4,6-Tribromo-3-fluorophenol (95%) Hydrogen bromide

Other typical electrophilic aromatic substitution reactions—nitration (second entry), sulfonation (fourth entry), and Friedel–Crafts alkylation and acylation (fifth and sixth entries)—take place readily and are synthetically useful. Phenols also undergo electrophilic substitution reactions that are limited to only the most active aromatic compounds; these include nitrosation (third entry) and coupling with diazonium salts (seventh entry).

PROBLEM 24.6 Each of the following reactions has been reported in the chemical literature and gives a single organic product in high yield. Identify the product in each case.

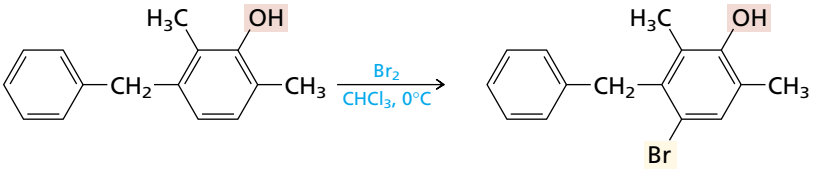
(a) 3-Benzyl-2,6-dimethylphenol treated with bromine in chloroform

(b) 4-Bromo-2-methylphenol treated with 2-methylpropene and sulfuric acid

(c) 2-Isopropyl-5-methylphenol (thymol) treated with sodium nitrite and dilute hydrochloric acid

(d) *p*-Cresol treated with propanoyl chloride and aluminum chloride

SAMPLE SOLUTION (a) The ring that bears the hydroxyl group is much more reactive than the other ring. In electrophilic aromatic substitution reactions of rings that bear several substituents, it is the most activating substituent that controls the orientation. Bromination occurs para to the hydroxyl group.



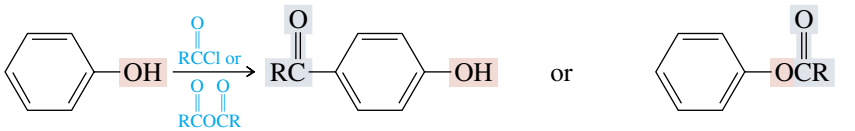
3-Benzyl-2,6-dimethylphenol

3-Benzyl-4-bromo-2,6-dimethylphenol (isolated in 100% yield)

The aromatic ring of a phenol, like that of an arylamine, is seen as an electron-rich functional unit and is capable of a variety of reactions. In some cases, however, it is the hydroxyl oxygen that reacts instead. An example of this kind of chemical reactivity is described in the following section.

24.9 ACYLATION OF PHENOLS

Acylating agents, such as acyl chlorides and carboxylic acid anhydrides, can react with phenols either at the aromatic ring (C-acylation) or at the hydroxyl oxygen (O-acylation):

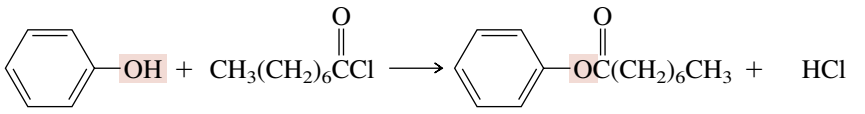


Phenol

Aryl ketone (product of C-acylation)

Aryl ester (product of O-acylation)

As shown in the sixth entry of Table 24.4, C-acylation of phenols is observed under the customary conditions of the Friedel–Crafts reaction (treatment with an acyl chloride or acid anhydride in the presence of aluminum chloride). In the absence of aluminum chloride, however, O-acylation occurs instead.



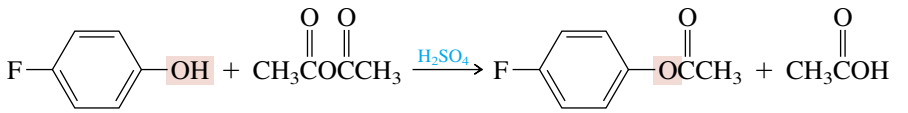
Phenol

Octanoyl chloride

Phenyl octanoate (95%)

Hydrogen chloride

The O-acylation of phenols with carboxylic acid anhydrides can be conveniently catalyzed in either of two ways. One method involves converting the acid anhydride to a more powerful acylating agent by protonation of one of its carbonyl oxygens. Addition of a few drops of sulfuric acid is usually sufficient.



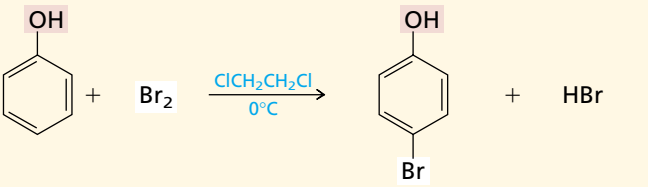
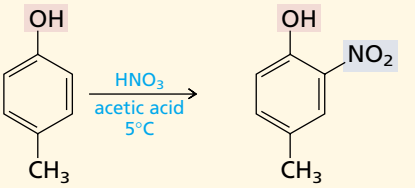
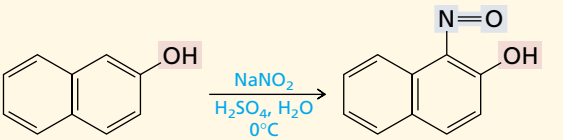
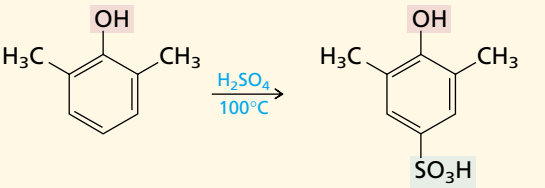
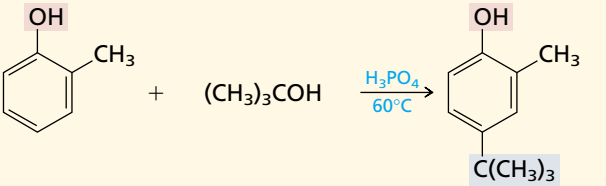
p-Fluorophenol

Acetic anhydride

p-Fluorophenyl acetate (81%)

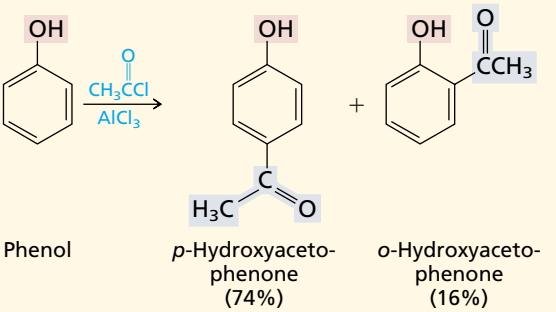
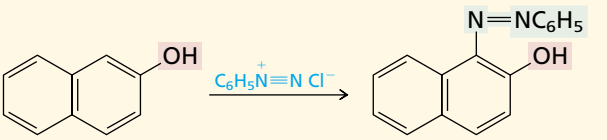
Acetic acid

TABLE 24.4 Electrophilic Aromatic Substitution Reactions of Phenols

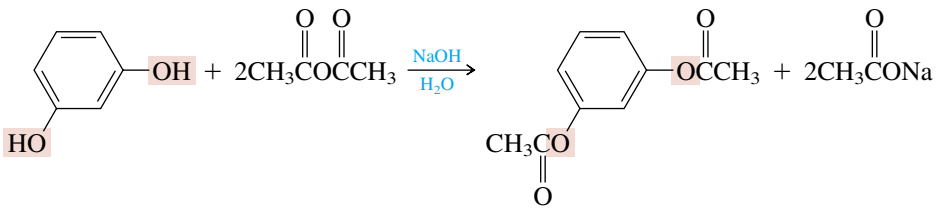
Reaction and comments	Specific example
Halogenation Bromination and chlorination of phenols occur readily even in the absence of a catalyst. Substitution occurs primarily at the position para to the hydroxyl group. When the para position is blocked, ortho substitution is observed.	 Phenol Bromine *p*-Bromophenol (93%) Hydrogen bromide
Nitration Phenols are nitrated on treatment with a dilute solution of nitric acid in either water or acetic acid. It is not necessary to use mixtures of nitric and sulfuric acids, because of the high reactivity of phenols.	 *p*-Cresol 4-Methyl-2-nitrophenol (73–77%)
Nitrosation On acidification of aqueous solutions of sodium nitrite, the nitrosonium ion (:N≡O:$^+$) is formed, which is a weak electrophile and attacks the strongly activated ring of a phenol. The product is a nitroso phenol.	 2-Naphthol 1-Nitroso-2-naphthol (99%)
Sulfonation Heating a phenol with concentrated sulfuric acid causes sulfonation of the ring.	 2,6-Dimethylphenol 4-Hydroxy-3,5-dimethylbenzenesulfonic acid (69%)
Friedel–Crafts alkylation Alcohols in combination with acids serve as sources of carbocations. Attack of a carbocation on the electron-rich ring of a phenol brings about its alkylation.	 *o*-Cresol *tert*-Butyl alcohol 4-*tert*-Butyl-2-methylphenol (63%)

(Continued)

TABLE 24.4 Electrophilic Aromatic Substitution Reactions of Phenols *(Continued)*

Reaction and comments	Specific example
Friedel–Crafts acylation In the presence of aluminum chloride, acyl chlorides and carboxylic acid anhydrides acylate the aromatic ring of phenols.	 Phenol; *p*-Hydroxyacetophenone (74%); *o*-Hydroxyacetophenone (16%)
Reaction with arenediazonium salts Adding a phenol to a solution of a diazonium salt formed from a primary aromatic amine leads to formation of an azo compound. The reaction is carried out at a pH such that a significant portion of the phenol is present as its phenoxide ion. The diazonium ion acts as an electrophile toward the strongly activated ring of the phenoxide ion.	 2-Naphthol; 1-Phenylazo-2-naphthol (48%)

An alternative approach is to increase the nucleophilicity of the phenol by converting it to its phenoxide anion in basic solution:



Resorcinol; Acetic anhydride; 1,3-Diacetoxybenzene (93%); Sodium acetate

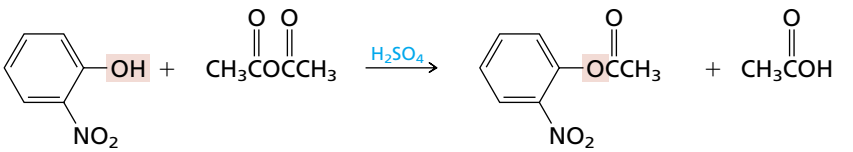
PROBLEM 24.7 Write chemical equations expressing each of the following:

(a) Preparation of *o*-nitrophenyl acetate by sulfuric acid catalysis of the reaction between a phenol and a carboxylic acid anhydride.

(b) Esterification of 2-naphthol with acetic anhydride in aqueous sodium hydroxide

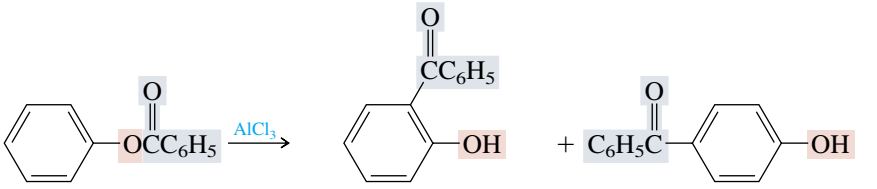
(c) Reaction of phenol with benzoyl chloride

SAMPLE SOLUTION (a) The problem specifies that an acid anhydride be used; therefore, use acetic anhydride to prepare the acetate ester of *o*-nitrophenol:



o-Nitrophenol; Acetic anhydride; *o*-Nitrophenyl acetate (isolated in 93% yield by this method); Acetic acid

The preference for O-acylation of phenols arises because these reactions are *kinetically controlled.* O-acylation is faster than C-acylation. The C-acyl isomers are more stable, however, and it is known that aluminum chloride is a very effective catalyst for the conversion of aryl esters to aryl ketones. (This isomerization is called the **Fries rearrangement.**)



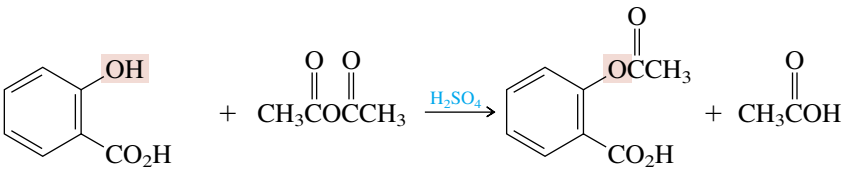
Phenyl benzoate — *o*-Hydroxybenzophenone (9%) — *p*-Hydroxybenzophenone (64%)

Thus, ring acylation of phenols is observed under Friedel–Crafts conditions because the presence of aluminum chloride causes that reaction to be subject to *thermodynamic* (*equilibrium*) *control.*

Fischer esterification, in which a phenol and a carboxylic acid condense in the presence of an acid catalyst, is not used to prepare aryl esters.

24.10 CARBOXYLATION OF PHENOLS: ASPIRIN AND THE KOLBE–SCHMITT REACTION

The best known aryl ester is *O*-acetylsalicylic acid, better known as *aspirin.* It is prepared by acetylation of the phenolic hydroxyl group of salicylic acid:

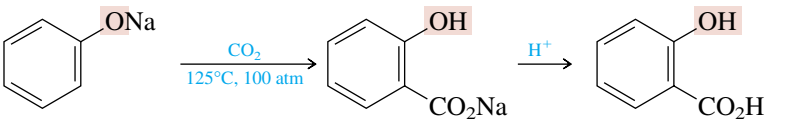


Salicylic acid (*o*-hydroxybenzoic acid) — Acetic anhydride — *O*-Acetylsalicylic acid (aspirin) — Acetic acid

An entertaining account of the history of aspirin can be found in the 1991 book *The Aspirin Wars: Money, Medicine, and 100 Years of Rampant Competition,* by Charles C. Mann.

Aspirin possesses a number of properties that make it an often-recommended drug. It is an analgesic, effective in relieving headache pain. It is also an antiinflammatory agent, providing some relief from the swelling associated with arthritis and minor injuries. Aspirin is an antipyretic compound; that is, it reduces fever. Each year, more than 40 million lb of aspirin is produced in the United States, a rate equal to 300 tablets per year for every man, woman, and child.

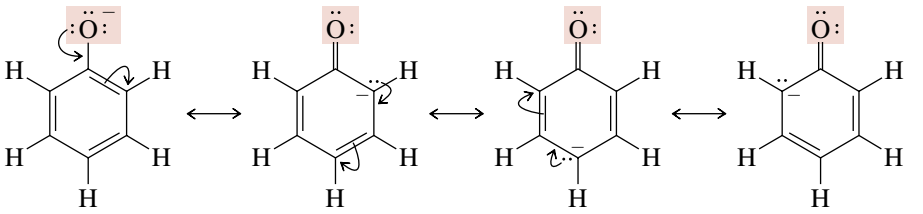
The key compound in the synthesis of aspirin, salicylic acid, is prepared from phenol by a process discovered in the nineteenth century by the German chemist Hermann Kolbe. In the Kolbe synthesis, also known as the **Kolbe–Schmitt reaction,** sodium phenoxide is heated with carbon dioxide under pressure, and the reaction mixture is subsequently acidified to yield salicylic acid:



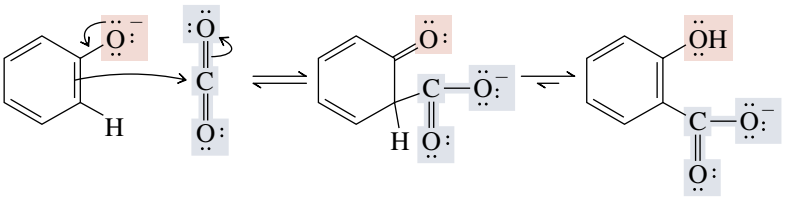
Sodium phenoxide — Sodium salicylate — Salicylic acid (79%)

Although a hydroxyl group strongly activates an aromatic ring toward electrophilic attack, an oxyanion substituent is an even more powerful activator. Electron delocalization in phenoxide anion leads to increased electron density at the positions ortho and para to oxygen.

This is the same resonance description shown in Section 24.4.

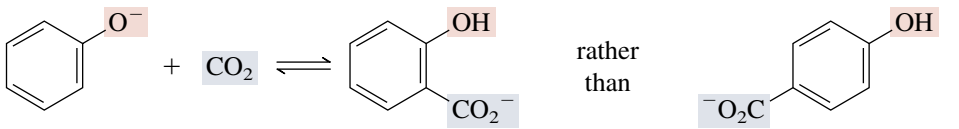


The increased nucleophilicity of the ring permits it to react with carbon dioxide. An intermediate is formed that is simply the keto form of salicylate anion:



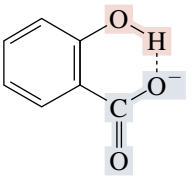
Phenoxide anion (stronger base) | Carbon dioxide | Cyclohexadienone intermediate | Salicylate anion (weaker base)

The Kolbe–Schmitt reaction is an equilibrium process governed by thermodynamic control. The position of equilibrium favors formation of the weaker base (salicylate ion) at the expense of the stronger one (phenoxide ion). Thermodynamic control is also responsible for the pronounced bias toward ortho over para substitution. Salicylate anion is a weaker base than *p*-hydroxybenzoate and so is the predominant species at equilibrium.



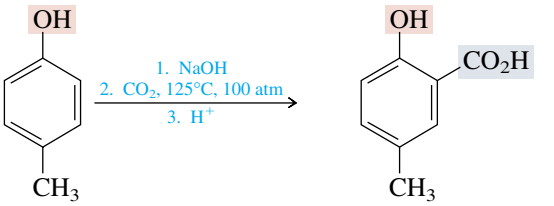
Phenoxide ion (strongest base; K_a of conjugate acid, 10^{-10}) | Carbon dioxide | Salicylate anion (weakest base; K_a of conjugate acid, 1.06×10^{-3}) | rather than | *p*-Hydroxybenzoate anion (K_a of conjugate acid, 3.3×10^{-5})

Salicylate anion is a weaker base than *p*-hydroxybenzoate because it is stabilized by intramolecular hydrogen bonding.



Intramolecular hydrogen bonding in salicylate anion

The Kolbe–Schmitt reaction has been applied to the preparation of other *o*-hydroxybenzoic acids. Alkyl derivatives of phenol behave very much like phenol itself.

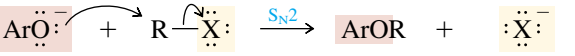


p-Cresol — 2-Hydroxy-5-methylbenzoic acid (78%)

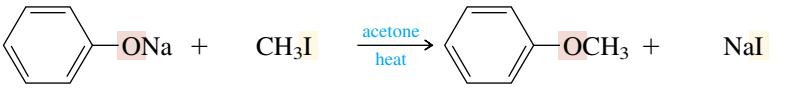
Phenols that bear strongly electron-withdrawing substituents usually give low yields of carboxylated products; their derived phenoxide anions are less basic, and the equilibrium constants for their carboxylation are smaller.

24.11 PREPARATION OF ARYL ETHERS

Aryl ethers are best prepared by the Williamson method (Section 16.6). Alkylation of the hydroxyl oxygen of a phenol takes place readily when a phenoxide anion reacts with an alkyl halide.



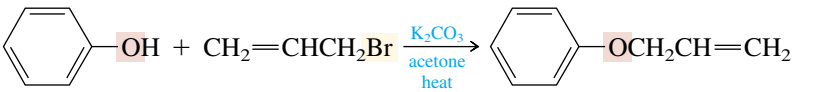
Phenoxide anion — Alkyl halide — Alkyl aryl ether — Halide anion



Sodium phenoxide — Iodomethane — Anisole (95%) — Sodium iodide

As the synthesis is normally performed, a solution of the phenol and alkyl halide is simply heated in the presence of a suitable base such as potassium carbonate:

This is an example of an S_N2 reaction in a polar aprotic solvent.



Phenol — Allyl bromide — Allyl phenyl ether (86%)

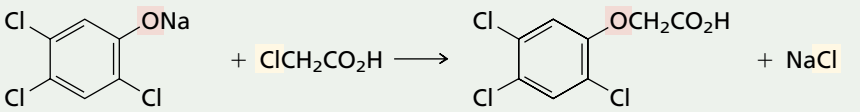
The alkyl halide must be one that reacts readily in an S_N2 process. Thus, methyl and primary alkyl halides are the most effective alkylating agents. Elimination becomes competitive with substitution when secondary alkyl halides are used and is the only reaction observed with tertiary alkyl halides.

PROBLEM 24.8 Reaction of phenol with 1,2-epoxypropane in aqueous sodium hydroxide at 150°C gives a single product, $C_9H_{12}O_2$, in 90% yield. Suggest a reasonable structure for this compound.

The reaction between an alkoxide ion and an aryl halide can be used to prepare alkyl aryl ethers only when the aryl halide is one that reacts rapidly by the addition–elimination mechanism of nucleophilic aromatic substitution (Section 23.6).

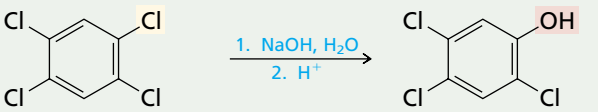
AGENT ORANGE AND DIOXIN

The once widely used herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) is prepared by reaction of the sodium salt of 2,4,5-trichlorophenol with chloroacetic acid:



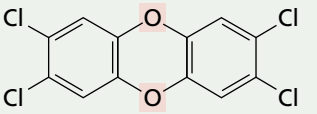
Sodium 2,4,5-trichlorophenolate | Chloroacetic acid | 2,4,5-Trichlorophenoxyacetic acid (2,4,5-T)

The starting material for this process, 2,4,5-trichlorophenol, is made by treating 1,2,4,5-tetrachlorobenzene with aqueous base. Nucleophilic aromatic substitution of one of the chlorines by an addition–elimination mechanism yields 2,4,5-trichlorophenol:



1,2,4,5-Tetrachlorobenzene | 2,4,5-Trichlorophenol

In the course of making 2,4,5-trichlorophenol, it almost always becomes contaminated with small amounts of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, better known as *dioxin.*



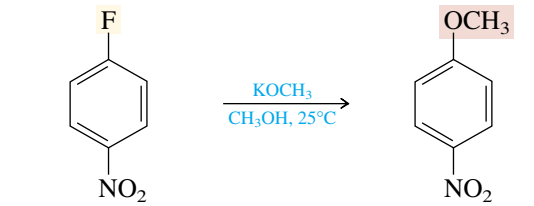
2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (dioxin)

Dioxin is carried along when 2,4,5-trichlorophenol is converted to 2,4,5-T, and enters the environment when 2,4,5-T is sprayed on vegetation. Typically, the amount of dioxin present in 2,4,5-T is very small. *Agent Orange,* a 2,4,5-T–based defoliant used on a large scale in the Vietnam War, contained about 2 ppm of dioxin.

Tests with animals have revealed that dioxin is one of the most toxic substances known. Toward mice it is about 2000 times more toxic than strychnine and about 150,000 times more toxic than sodium cyanide. Fortunately, however, available evidence indicates that humans are far more resistant to dioxin than are test animals, and so far there have been no human fatalities directly attributable to dioxin. The most prominent short-term symptom seen so far has been a severe skin disorder known as *chloracne.* Yet to be determined is the answer to the question of long-term effects. A 1991 study of the health records of over 5000 workers who were exposed to dioxin-contaminated chemicals indicated a 15% increase in incidences of cancer compared with those of a control group. Workers who were exposed to higher dioxin levels for prolonged periods exhibited a 50% increase in their risk of dying from cancer, especially soft-tissue sarcomas, compared with the control group.*

Since 1979, the use of 2,4,5-T has been regulated in the United States.

* The biological properties of dioxin include an ability to bind to a protein known as the AH (aromatic hydrocarbon) receptor. Dioxin is not a hydrocarbon, but it shares a certain structural property with aromatic hydrocarbons. Try constructing molecular models of dioxin and anthracene to see these similarities.



p-Fluoronitrobenzene *p*-Nitroanisole (93%)

PROBLEM 24.9 Which of the following two combinations of reactants is more appropriate for the preparation of *p*-nitrophenyl phenyl ether?

(a) Fluorobenzene and *p*-nitrophenol

(b) *p*-Fluoronitrobenzene and phenol

24.12 CLEAVAGE OF ARYL ETHERS BY HYDROGEN HALIDES

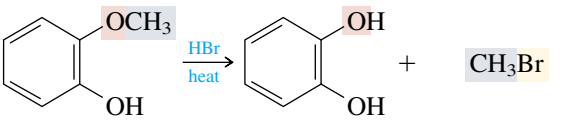
The cleavage of *dialkyl ethers* by hydrogen halides was discussed in Section 16.8, where it was noted that the same pair of alkyl halides results, irrespective of the order in which the carbon–oxygen bonds of the ether are broken.

$$\underset{\text{Dialkyl ether}}{ROR'} + \underset{\text{Hydrogen halide}}{2HX} \longrightarrow \underset{\text{Two alkyl halides}}{RX + R'X} + \underset{\text{Water}}{H_2O}$$

Cleavage of *alkyl aryl ethers* by hydrogen halides always proceeds so that the alkyl–oxygen bond is broken and yields an alkyl halide and a phenol as the *final* products.

$$\underset{\substack{\text{Alkyl aryl}\\\text{ether}}}{ArOR} + \underset{\substack{\text{Hydrogen}\\\text{halide}}}{HX} \longrightarrow \underset{\text{Phenol}}{ArOH} + \underset{\substack{\text{Alkyl}\\\text{halide}}}{RX}$$

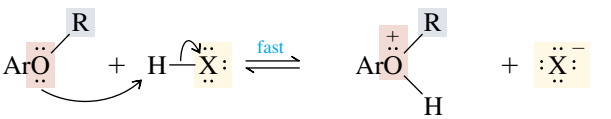
Since phenols are not converted to aryl halides by reaction with hydrogen halides, reaction proceeds no further than shown in the preceding general equation. For example,



Guaiacol Pyrocatechol (85–87%) Methyl bromide (57–72%)

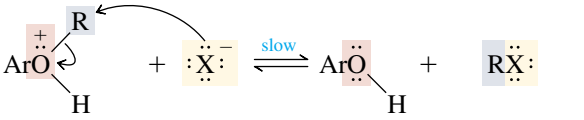
Guaiacol is obtained by chemical treatment of *lignum vitae,* the wood from a species of tree that grows in warm climates. It is sometimes used as an expectorant to help relieve bronchial congestion.

The first step in the reaction of an alkyl aryl ether with a hydrogen halide is protonation of oxygen to form an alkylaryloxonium ion:



Alkyl aryl ether Hydrogen halide Alkylaryloxonium ion Halide ion

This is followed by a nucleophilic substitution step:

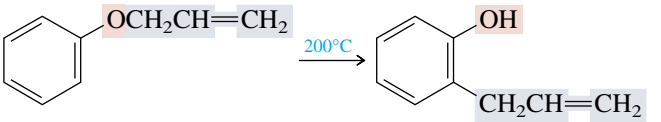


Alkylaryloxonium ion | Halide ion | Phenol | Alkyl halide

Attack by the halide nucleophile at the sp^3-hybridized carbon of the alkyl group is analogous to what takes place in the cleavage of dialkyl ethers. Attack at the sp^2-hybridized carbon of the aromatic ring is much slower. Indeed, nucleophilic aromatic substitution does not occur at all under these conditions.

24.13 CLAISEN REARRANGEMENT OF ALLYL ARYL ETHERS

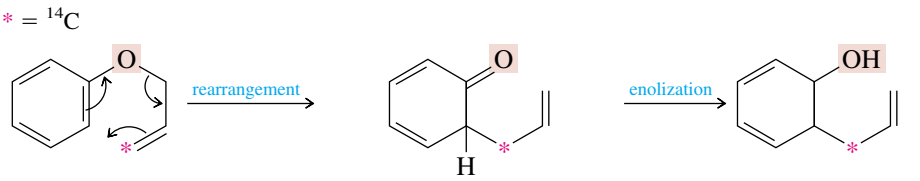
Allyl aryl ethers undergo an interesting reaction, called the **Claisen rearrangement,** on being heated. The allyl group migrates from oxygen to the ring carbon ortho to it.



Allyl phenyl ether | *o*-Allylphenol (73%)

Allyl phenyl ether is prepared by the reaction of phenol with allyl bromide, as described in Section 24.11

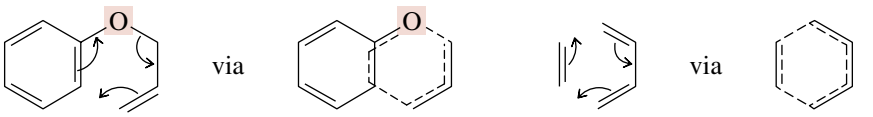
Carbon-14 labeling of the allyl group revealed that the terminal carbon of the allyl group is the one that becomes bonded to the ring and suggests a mechanism involving a concerted electron reorganization in the first step. This step is followed by enolization of the resulting cyclohexadienone to regenerate the aromatic ring.



Allyl phenyl ether | 6-Allyl-2,4-cyclohexadienone | *o*-Allylphenol

PROBLEM 24.10 The mechanism of the Claisen rearrangement of other allylic ethers of phenol is analogous to that of allyl phenyl ether. What is the product of the Claisen rearrangement of $C_6H_5OCH_2CH{=}CHCH_3$?

The transition state for the first step of the Claisen rearrangement bears much in common with the transition state for the Diels–Alder cycloaddition. Both involve a concerted six-electron reorganization.

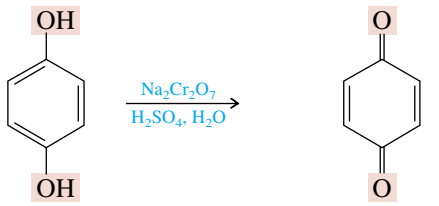


Claisen rearrangement | Diels–Alder cycloaddition

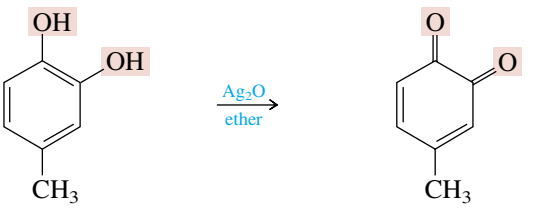
The Claisen rearrangement is an example of a **sigmatropic rearrangement.** A sigmatropic rearrangement is characterized by a transition state in which a σ bond migrates from one end of a conjugated π electron system to the other. In this case the σ bond to oxygen at one end of an allyl unit is broken and replaced by a σ bond to the ring carbon at the other end.

24.14 OXIDATION OF PHENOLS: QUINONES

Phenols are more easily oxidized than alcohols, and a large number of inorganic oxidizing agents have been used for this purpose. The phenol oxidations that are of the most use to the organic chemist are those involving derivatives of 1,2-benzenediol (pyrocatechol) and 1,4-benzenediol (hydroquinone). Oxidation of compounds of this type with silver oxide or with chromic acid yields conjugated dicarbonyl compounds called **quinones.**



Hydroquinone *p*-Benzoquinone (76–81%)

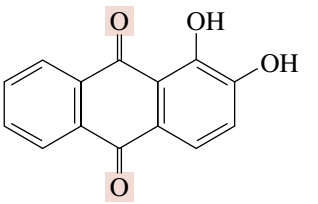


4-Methylpyrocatechol (4-methyl-1,2-benzenediol) 4-Methyl-1,2-benzoquinone (68%)

Silver oxide is a weak oxidizing agent.

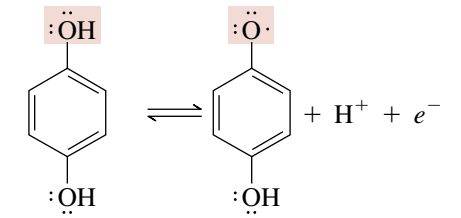
Quinones are colored; *p*-benzoquinone, for example, is yellow. Many occur naturally and have been used as dyes. *Alizarin* is a red pigment extracted from the roots of the madder plant. Its preparation from anthracene, a coal tar derivative, in 1868 was a significant step in the development of the synthetic dyestuff industry.

Quinones that are based on the anthracene ring system are called *anthraquinones.* Alizarin is one example of an *anthraquinone dye.*

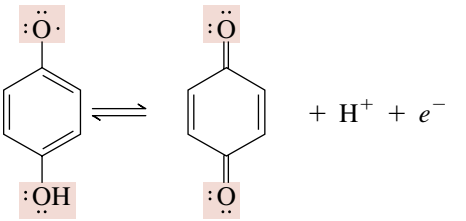


Alizarin

The oxidation–reduction process that connects hydroquinone and benzoquinone involves two 1-electron transfers:

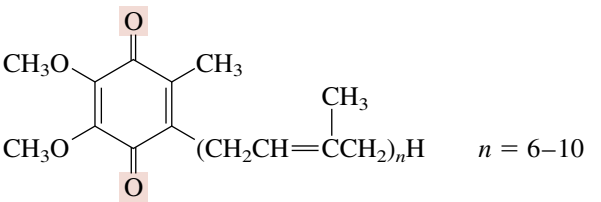


Hydroquinone



Benzoquinone

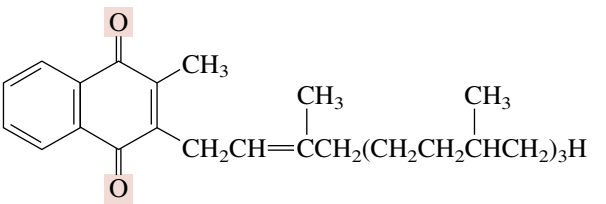
The ready reversibility of this reaction is essential to the role that quinones play in cellular respiration, the process by which an organism uses molecular oxygen to convert its food to carbon dioxide, water, and energy. Electrons are not transferred directly from the substrate molecule to oxygen but instead are transferred by way of an *electron transport chain* involving a succession of oxidation–reduction reactions. A key component of this electron transport chain is the substance known as *ubiquinone,* or coenzyme Q:



Ubiquinone (coenzyme Q)

The name *ubiquinone* is a shortened form of *ubiquitous quinone,* a term coined to describe the observation that this substance can be found in all cells. The length of its side chain varies among different organisms; the most common form in vertebrates has $n = 10$, and ubiquinones in which $n = 6$ to 9 are found in yeasts and plants.

Another physiologically important quinone is vitamin K. Here "K" stands for *koagulation* (Danish), since this substance was first identified as essential for the normal clotting of blood.



Vitamin K

Some vitamin K is provided in the normal diet, but a large proportion of that required by humans is produced by their intestinal flora.

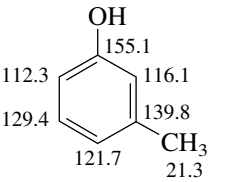
"Intestinal flora" is a general term for the bacteria, yeast, and fungi that live in the large intestine.

24.15 SPECTROSCOPIC ANALYSIS OF PHENOLS

Infrared: The infrared spectra of phenols combine features of those of alcohols and aromatic compounds. Hydroxyl absorbances resulting from O—H stretching are found in the 3600-cm^{-1} region, and the peak due to C—O stretching appears around 1200–1250 cm^{-1}. These features can be seen in the infrared spectrum of *p*-cresol, shown in Figure 24.3.

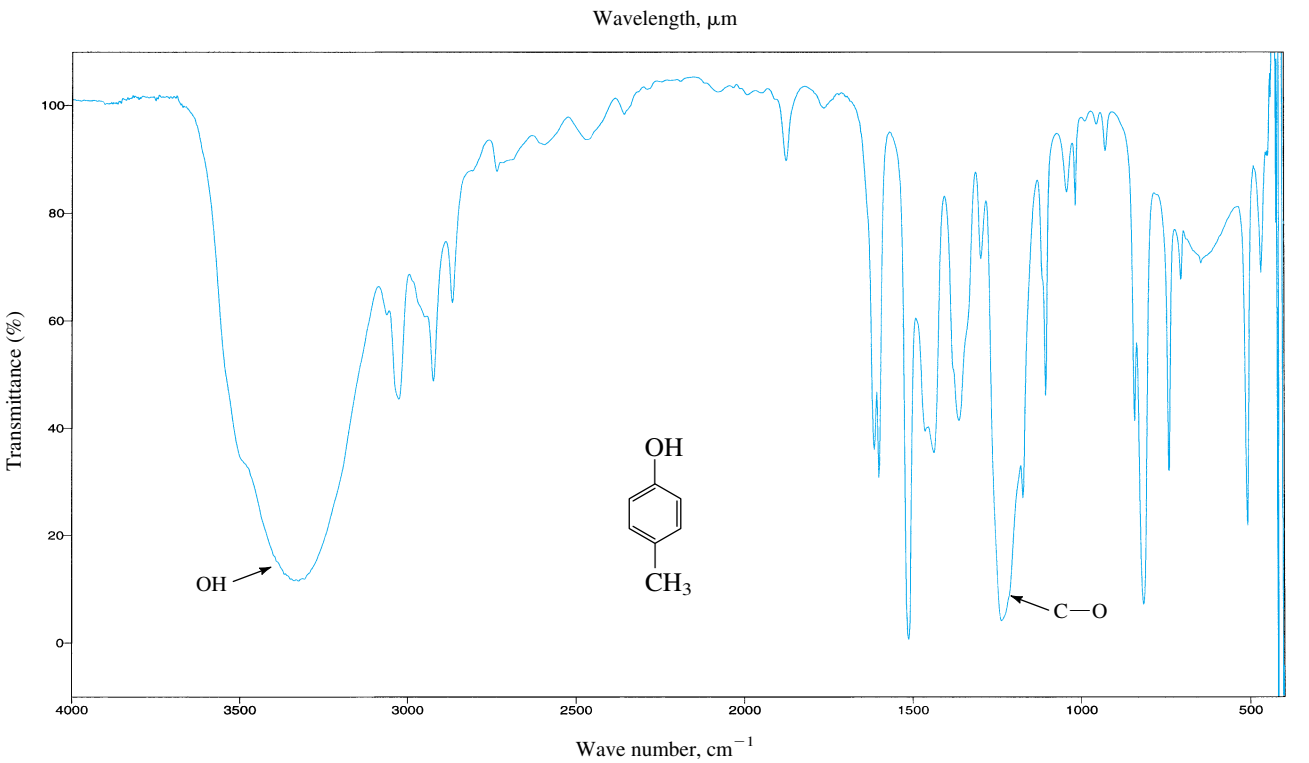
^{1}H NMR: The ^{1}H NMR signals for the hydroxyl protons of phenols are often broad, and their chemical shift, like their acidity, lies between alcohols and carboxylic acids. The range is δ 4–12 ppm, with the exact chemical shift depending on the concentration, the solvent, and the temperature. The phenolic proton in the ^{1}H NMR spectrum shown for *p*-cresol, for example, appears at δ 5.1 ppm (Figure 24.4).

^{13}C NMR: Compared with C—H, the carbon of C—O in a phenol is deshielded by about 25 ppm. In the case of *m*-cresol, for example, the C—O carbon gives the signal at lowest field.



^{13}C chemical shifts δ in *m*-cresol (ppm)

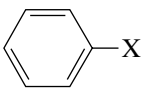
FIGURE 24.3 The infrared spectrum of *p*-cresol.



Notice, too, that the most shielded carbons of the aromatic ring are the ones that are ortho and para to the hydroxyl group in keeping with our experience that the OH group donates electrons preferentially to these positions.

The ^{13}C NMR spectrum of *m*-cresol appeared in Chapter 13 (Figure 13.21).

UV-VIS: Just as with arylamines (Section 22.20), it is informative to look at the UV-VIS behavior of phenols in terms of how the OH group affects the benzene chromophore.



	X	λ_{max}, *nm*
Benzene	H	204, 256
Aniline	NH_2	230, 280
Anilinium ion	NH_3^+	203, 254
Phenol	OH	210, 270
Phenoxide ion	O^-	235, 287

An OH group affects the UV-VIS spectrum of benzene in a way similar to that of an NH_2 group, but to a smaller extent. In basic solution, in which OH is converted to O^-, however, the shift to longer wavelengths exceeds that of an NH_2 group.

Mass Spectrometry: A peak for the molecular ion is usually quite prominent in the mass spectra of phenols. It is, for example, the most intense peak in phenol.

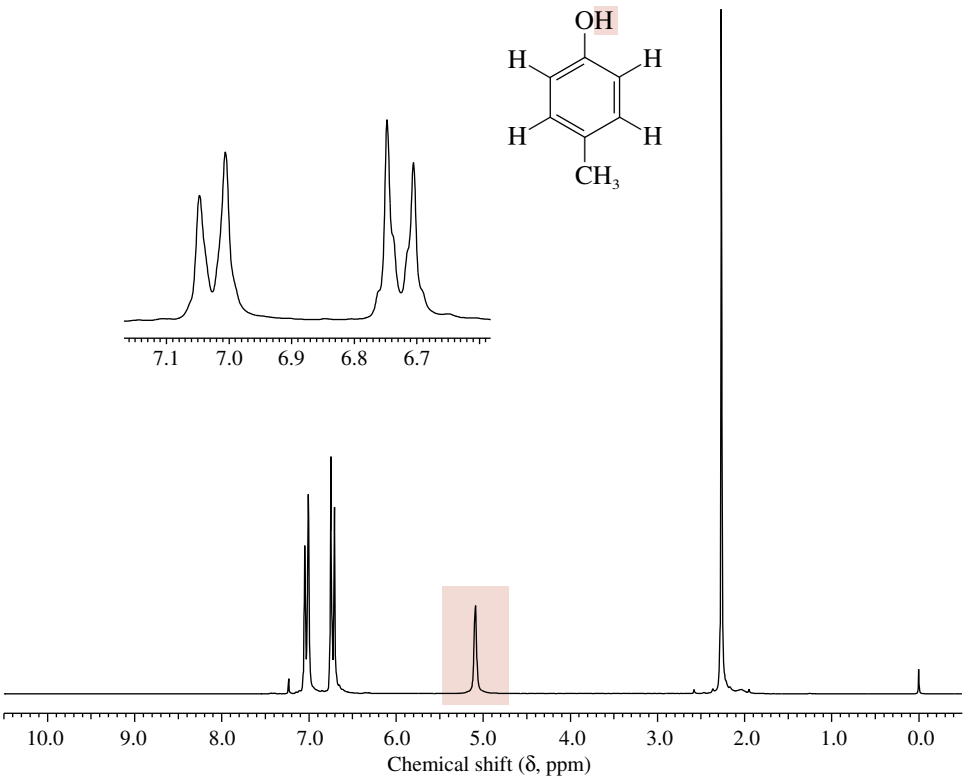


FIGURE 24.4 The 200-MHz ^1H NMR spectrum of *p*-cresol.

24.16 SUMMARY

Section 24.1 Phenol is both an important industrial chemical and the parent of a large class of compounds widely distributed as natural products. Although *benzenol* is the systematic name for C_6H_5OH, the IUPAC rules permit *phenol* to be used instead. Substituted derivatives are named on the basis of phenol as the parent compound.

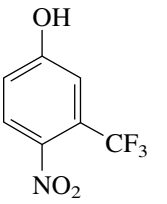
Section 24.2 Phenols are polar compounds, but less polar than alcohols. They resemble arylamines in having an electron-rich aromatic ring.

Section 24.3 The —OH group of phenols makes it possible for them to participate in hydrogen bonding. This contributes to the higher boiling points and greater water-solubility of phenolic compounds compared with arenes and aryl halides.

Section 24.4 With K_a's of approximately 10^{-10} ($pK_a = 10$), phenols are stronger acids than alcohols, but weaker than carboxylic acids. They are converted quantitatively to phenoxide anions on treatment with aqueous sodium hydroxide.

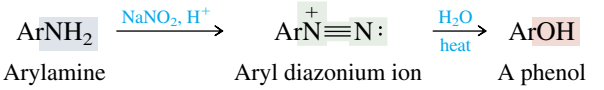
$$ArOH + NaOH \longrightarrow ArONa + H_2O$$

Section 24.5 Electron-releasing substituents attached to the ring have a negligible effect on the acidity of phenols. Strongly electron-withdrawing groups increase the acidity. The compound 4-nitro-3-(trifluoromethyl)phenol, for example, is 10,000 times more acidic than phenol.

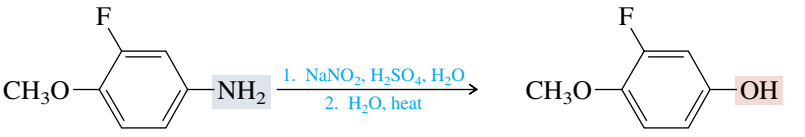


4-Nitro-3-(trifluoromethyl)phenol:
$pK_a = 6.0$

Section 24.6 Table 24.3 listed the main industrial methods for the preparation of phenol. Laboratory syntheses of phenols is usually carried out by hydrolysis of aryl diazonium salts.

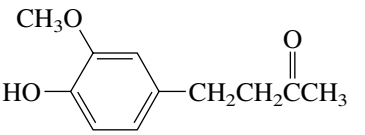


Arylamine — Aryl diazonium ion — A phenol



3-Fluoro-4-methoxyaniline — 3-Fluoro-4-methoxyphenol (70%)

Section 24.7 Many phenols occur naturally.

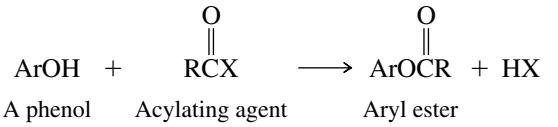


Zingerone
(responsible for spicy taste of ginger)

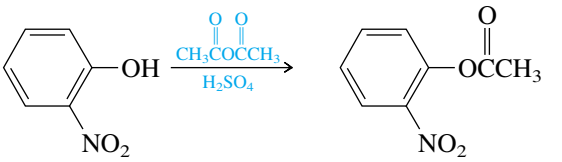
Phenol biosynthesis in plants proceeds from carbohydrate precursors, whereas the pathway in animals involves oxidation of aromatic rings.

Section 24.8 The hydroxyl group of a phenol is a strongly activating substituent, and electrophilic aromatic substitution occurs readily in phenol and its derivatives. Typical examples were presented in Table 24.4.

Section 24.9 On reaction with acyl chlorides and acid anhydrides, phenols may undergo either acylation of the hydroxyl group (O-acylation) or acylation of the ring (C-acylation). The product of C-acylation is more stable and predominates under conditions of thermodynamic control when aluminum chloride is present (see entry 6 in Table 24.4, Section 24.8). O-acylation is faster than C-acylation, and aryl esters are formed under conditions of kinetic control.

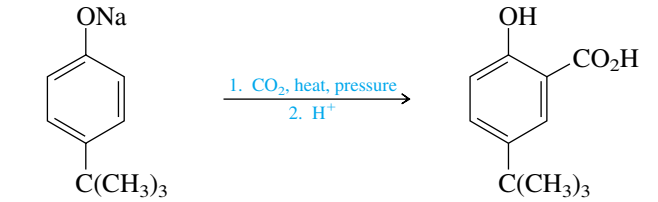


A phenol Acylating agent Aryl ester



o-Nitrophenol *o*-Nitrophenyl acetate (93%)

Section 24.10 The **Kolbe–Schmitt synthesis** of salicylic acid is a vital step in the preparation of aspirin. Phenols, as their sodium salts, undergo highly regioselective ortho carboxylation on treatment with carbon dioxide at elevated temperature and pressure.

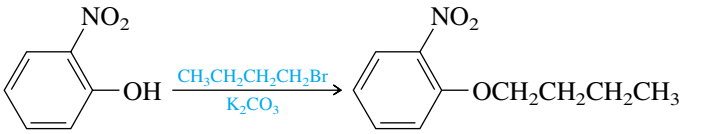


Sodium
p-tert-butylphenoxide

5-*tert*-Butyl-2-
hydroxybenzoic acid (74%)

Section 24.11 Phenoxide anions are nucleophilic toward alkyl halides, and the preparation of alkyl aryl ethers is easily achieved under S_N2 conditions.

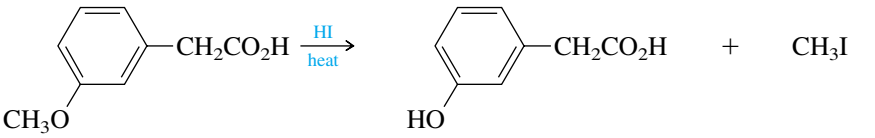
$$\underset{\text{Phenoxide anion}}{ArO^-} + \underset{\text{Alkyl halide}}{RX} \longrightarrow \underset{\text{Alkyl aryl ether}}{ArOR} + \underset{\text{Halide anion}}{X^-}$$



o-Nitrophenol — Butyl *o*-nitrophenyl ether (75/80%)

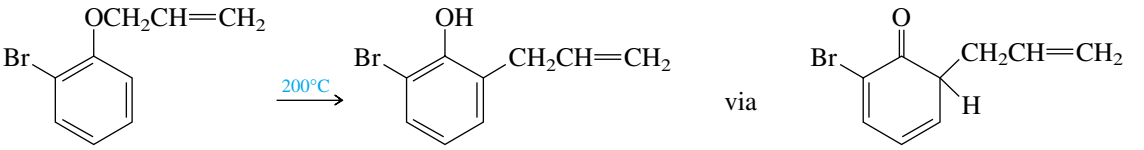
Section 24.12 The cleavage of alkyl aryl ethers by hydrogen halides yields a phenol and an alkyl halide.

$$\underset{\text{Alkyl aryl ether}}{ArOR} + \underset{\text{Hydrogen halide}}{HX} \xrightarrow{\text{heat}} \underset{\text{A phenol}}{ArOH} + \underset{\text{Alkyl halide}}{RX}$$



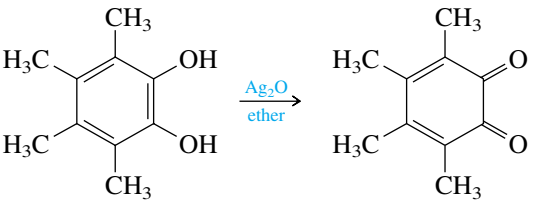
m-Methoxyphenylacetic acid — *m*-Hydroxyphenylacetic acid (72%) — Methyl iodide

Section 24.13 On being heated, allyl aryl ethers undergo a **Claisen rearrangement** to form *o*-allylphenols. A cyclohexadienone, formed by a concerted six-π-electron reorganization, is an intermediate.



Allyl *o*-bromophenyl ether — 2-Allyl-6-bromophenol (82%) — 6-Allyl-2-bromo-2,4-cyclohexadienone

Section 24.14 Oxidation of 1,2- and 1,4-benzenediols gives colored compounds known as **quinones.**



3,4,5,6-Tetramethyl-1,2-benzenediol — 3,4,5,6-Tetramethyl-1,2-benzoquinone (81%)

Section 24.15 The infrared and ^1H NMR spectra of phenols are similar to those for alcohols, except that the OH proton is somewhat less shielded in a phenol than in an alcohol. In ^{13}C NMR, an OH group deshields the carbon of

an aromatic ring to which it is attached. An OH group causes a shift in the UV-VIS spectrum of benzene to longer wavelengths. The effect is quite large in basic solution because of conversion of OH to O^-.

PROBLEMS

24.11 The IUPAC rules permit the use of common names for a number of familiar phenols and aryl ethers. These common names are listed here along with their systematic names. Write the structure of each compound.

(a) *Vanillin* (4-hydroxy-3-methoxybenzaldehyde): a component of vanilla bean oil, which contributes to its characteristic flavor

(b) *Thymol* (2-isopropyl-5-methylphenol): obtained from oil of thyme

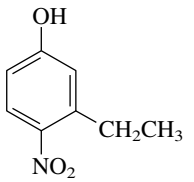
(c) *Carvacrol* (5-isopropyl-2-methylphenol): present in oil of thyme and marjoram

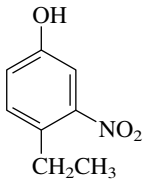
(d) *Eugenol* (4-allyl-2-methoxyphenol): obtained from oil of cloves

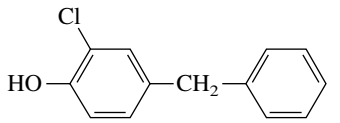
(e) *Gallic acid* (3,4,5-trihydroxybenzoic acid): prepared by hydrolysis of tannins derived from plants

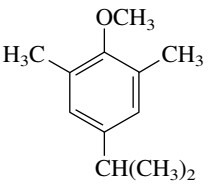
(f) *Salicyl alcohol* (o-hydroxybenzyl alcohol): obtained from bark of poplar and willow trees

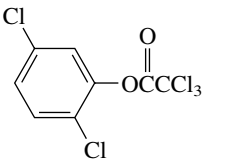
24.12 Name each of the following compounds:

(a) 

(b) 

(c) 

(d) 

(e) 

24.13 Write a balanced chemical equation for each of the following reactions:

(a) Phenol + sodium hydroxide

(b) Product of part (a) + ethyl bromide

(c) Product of part (a) + butyl *p*-toluenesulfonate

(d) Product of part (a) + acetic anhydride

(e) *o*-Cresol + benzoyl chloride

(f) *m*-Cresol + ethylene oxide

(g) 2,6-Dichlorophenol + bromine

(h) *p*-Cresol + excess aqueous bromine

(i) Isopropyl phenyl ether + excess hydrogen bromide + heat

24.14 Which phenol in each of the following pairs is more acidic? Justify your choice.

(a) 2,4,6-Trimethylphenol or 2,4,6-trinitrophenol

(b) 2,6-Dichlorophenol or 3,5-dichlorophenol

(c) 3-Nitrophenol or 4-nitrophenol

(d) Phenol or 4-cyanophenol

(e) 2,5-Dinitrophenol or 2,6-dinitrophenol

24.15 Choose the reaction in each of the following pairs that proceeds at the faster rate. Explain your reasoning.

(a) Basic hydrolysis of phenyl acetate or *m*-nitrophenyl acetate

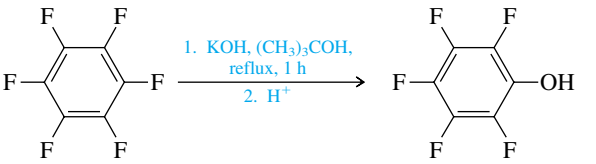
(b) Basic hydrolysis of *m*-nitrophenyl acetate or *p*-nitrophenyl acetate

(c) Reaction of ethyl bromide with phenol or with the sodium salt of phenol

(d) Reaction of ethylene oxide with the sodium salt of phenol or with the sodium salt of *p*-nitrophenol

(e) Bromination of phenol or phenyl acetate

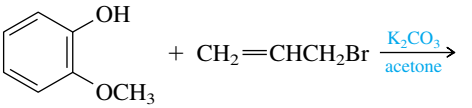
24.16 Pentafluorophenol is readily prepared by heating hexafluorobenzene with potassium hydroxide in *tert*-butyl alcohol:

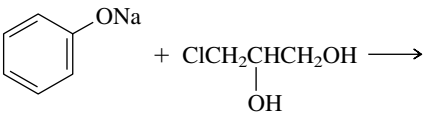


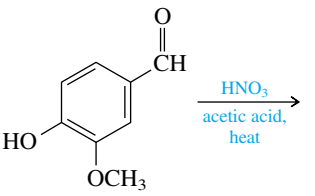
Hexafluorobenzene Pentafluorophenol (71%)

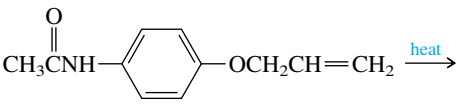
What is the most reasonable mechanism for this reaction? Comment on the comparative ease with which this conversion occurs.

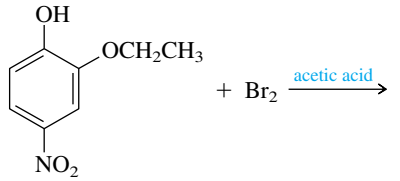
24.17 Each of the following reactions has been reported in the chemical literature and proceeds cleanly in good yield. Identify the principal organic product in each case.

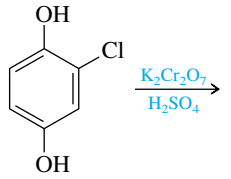
(a) 

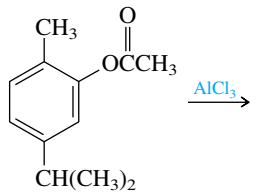
(b) 

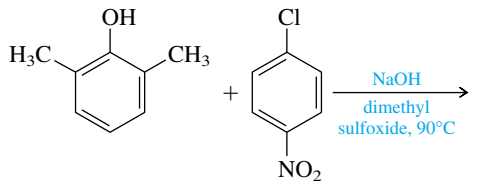
(c) 

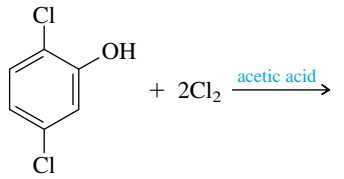
(d) 

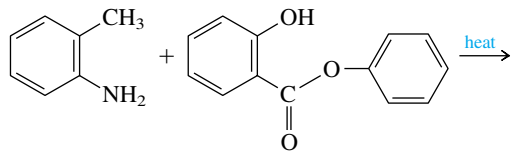
(e) 

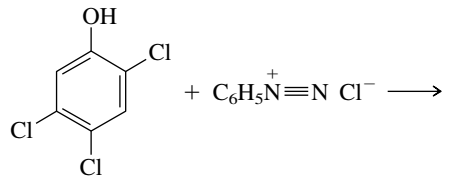
(f) 

(g) 

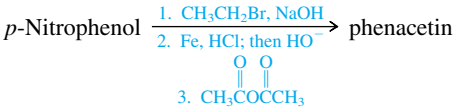
(h) 

(i) 

(j) 

(k) 

24.18 A synthesis of the analgesic substance *phenacetin* is outlined in the following equation. What is the structure of phenacetin?



24.19 Identify compounds A through C in the synthetic sequence represented by equations (a) through (c).

(a) Phenol + H_2SO_4 $\xrightarrow{\text{heat}}$ Compound A ($C_6H_6O_7S_2$)

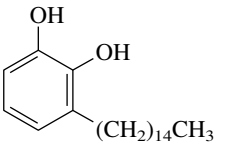
(b) Compound A + Br_2 $\xrightarrow[\text{2. } H^+]{\text{1. } HO^-}$ Compound B ($C_6H_5BrO_7S_2$)

(c) Compound B + H_2O $\xrightarrow[\text{heat}]{H^+}$ Compound C (C_6H_5BrO)

24.20 Treatment of 3,5-dimethylphenol with dilute nitric acid, followed by steam distillation of the reaction mixture, gave a compound A ($C_8H_9NO_3$, mp 66°C) in 36% yield. The nonvolatile residue from the steam distillation gave a compound B ($C_8H_9NO_3$, mp 108°C) in 25% yield on extraction with chloroform. Identify compounds A and B.

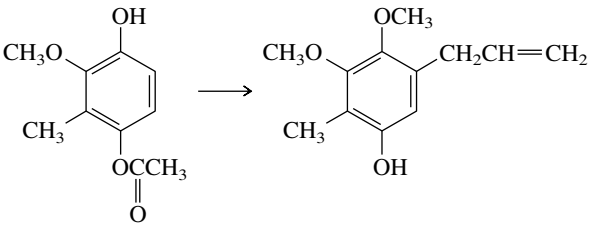
24.21 Outline a reasonable synthesis of 4-nitrophenyl phenyl ether from chlorobenzene and phenol.

24.22 As an allergen for testing purposes, synthetic 3-pentadecylcatechol is more useful than natural poison ivy extracts (of which it is one component). A stable crystalline solid, it is efficiently prepared in pure form from readily available starting materials. Outline a reasonable synthesis of this compound from 2,3-dimethoxybenzaldehyde and any necessary organic or inorganic reagents.

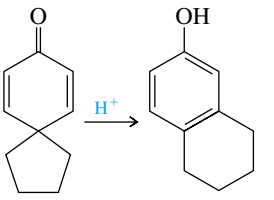


3-Pentadecylcatechol

24.23 Describe a scheme for carrying out the following synthesis. (In the synthesis reported in the literature, four separate operations were required.)



24.24 In a general reaction known as the *cyclohexadienone-phenol rearrangement,* cyclohexadienones are converted to phenols under conditions of acid catalysis. An example is



(100%)

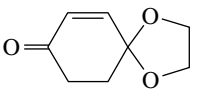
Write a reasonable mechanism for this reaction.

24.25 Treatment of *p*-hydroxybenzoic acid with aqueous bromine leads to the evolution of carbon dioxide and the formation of 2,4,6-tribromophenol. Explain.

24.26 Treatment of phenol with excess aqueous bromine is actually more complicated than expected. A white precipitate forms rapidly, which on closer examination is not 2,4,6-tribromophenol but is instead 2,4,4,6-tetrabromocyclohexadienone. Explain the formation of this product.

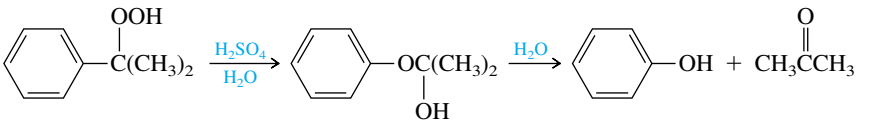
24.27 Treatment of 2,4,6-tri-*tert*-butylphenol with bromine in cold acetic acid gives the compound $C_{18}H_{29}BrO$ in quantitative yield. The infrared spectrum of this compound contains absorptions at 1630 and 1655 cm^{-1}. Its ^1H NMR spectrum shows only three peaks (all singlets), at δ 1.2, 1.3, and 6.9 ppm, in the ratio 9:18:2. What is a reasonable structure for the compound?

24.28 Compound A undergoes hydrolysis of its acetal function in dilute sulfuric acid to yield 1,2-ethanediol and compound B ($C_6H_6O_2$), mp 54°C. Compound B exhibits a carbonyl stretching band in the infrared at 1690 cm^{-1} and has two singlets in its ^1H NMR spectrum, at δ 2.9 and 6.7 ppm, in the ratio 2:1. On standing in water or ethanol, compound B is converted cleanly to an isomeric substance, compound C, mp 172–173°C. Compound C has no peaks attributable to carbonyl groups in its infrared spectrum. Identify compounds B and C.



Compound A

24.29 One of the industrial processes for the preparation of phenol, discussed in Section 24.6, includes an acid-catalyzed rearrangement of cumene hydroperoxide as a key step. This reaction proceeds by way of an intermediate hemiacetal:



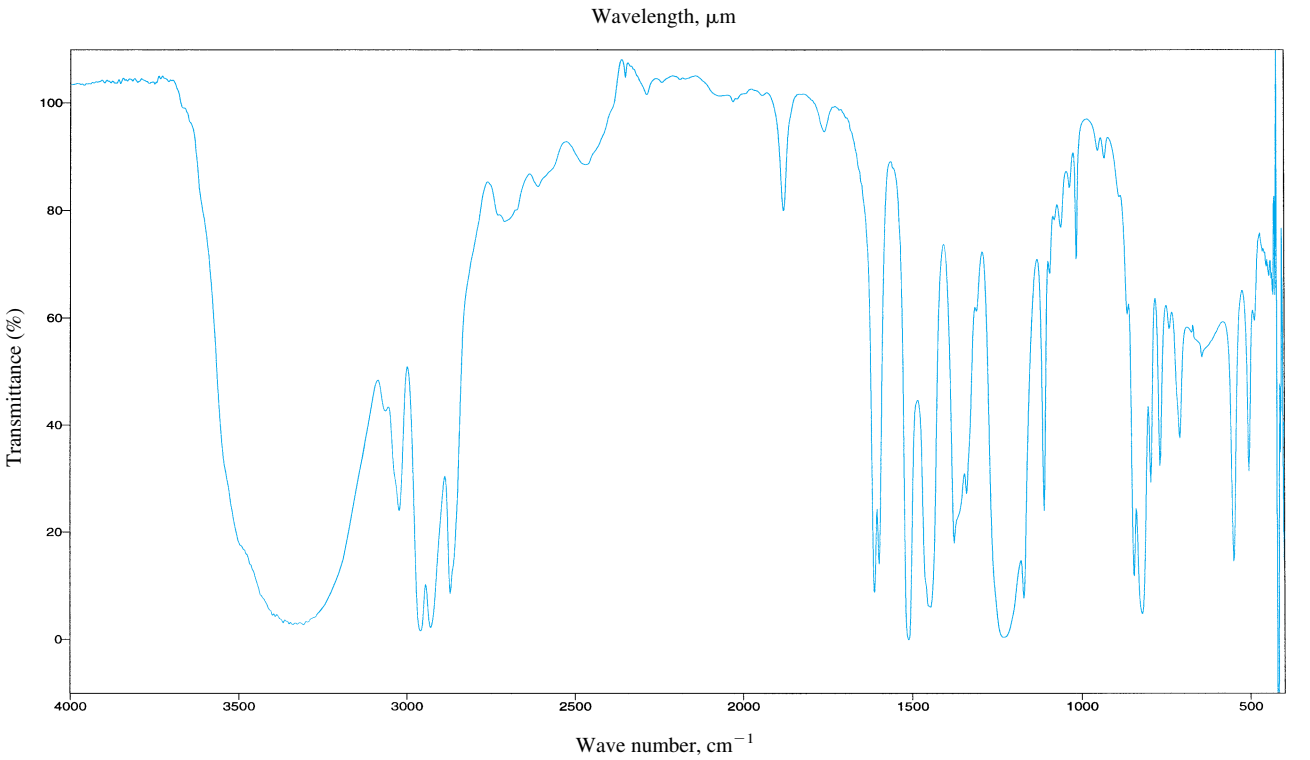
Cumene hydroperoxide — Hemiacetal — Phenol — Acetone

You learned in Section 17.8 of the relationship among hemiacetals, ketones, and alcohols; the formation of phenol and acetone is simply an example of hemiacetal hydrolysis. The formation of the hemiacetal intermediate is a key step in the synthetic procedure; it is the step in which the aryl–oxygen bond is generated. Can you suggest a reasonable mechanism for this step?

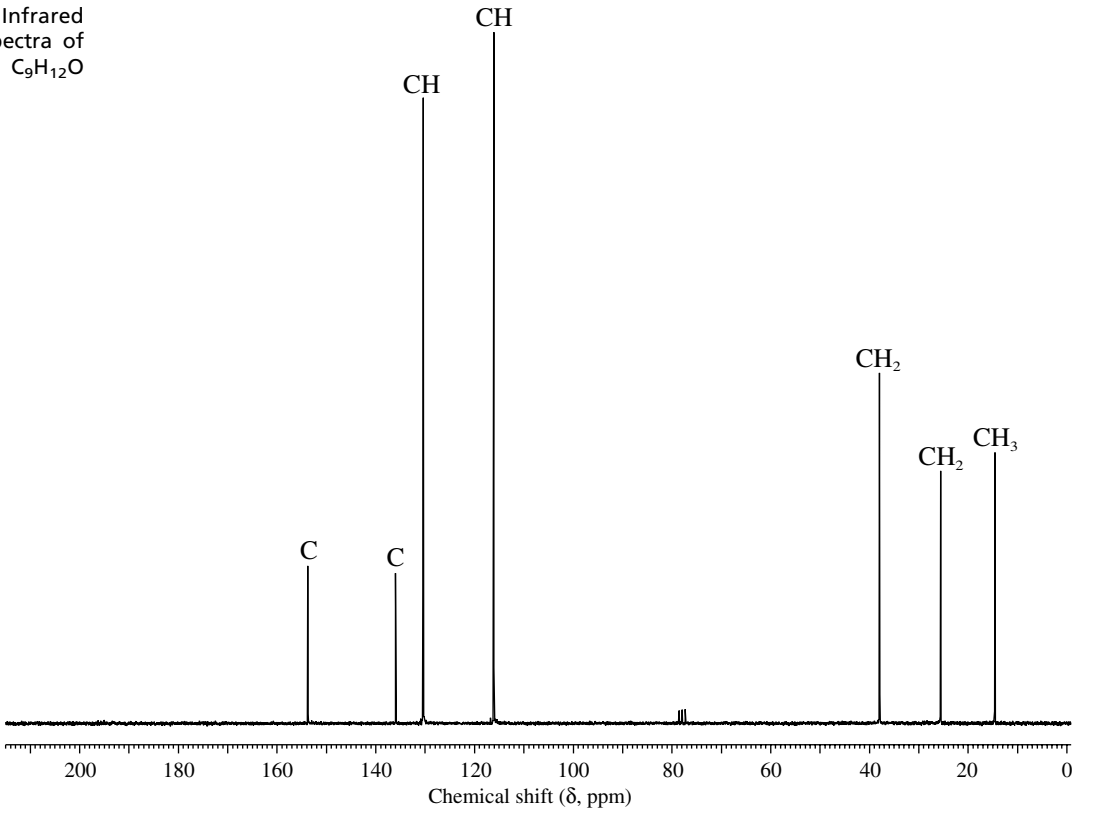
24.30 Identify the following compounds on the basis of the information provided:

(a) $C_9H_{12}O$: Its infrared and ^1H NMR spectra are shown in Figure 24.5.

(b) $C_9H_{11}BrO$: Its infrared and ^1H NMR spectra are shown in Figure 24.6.

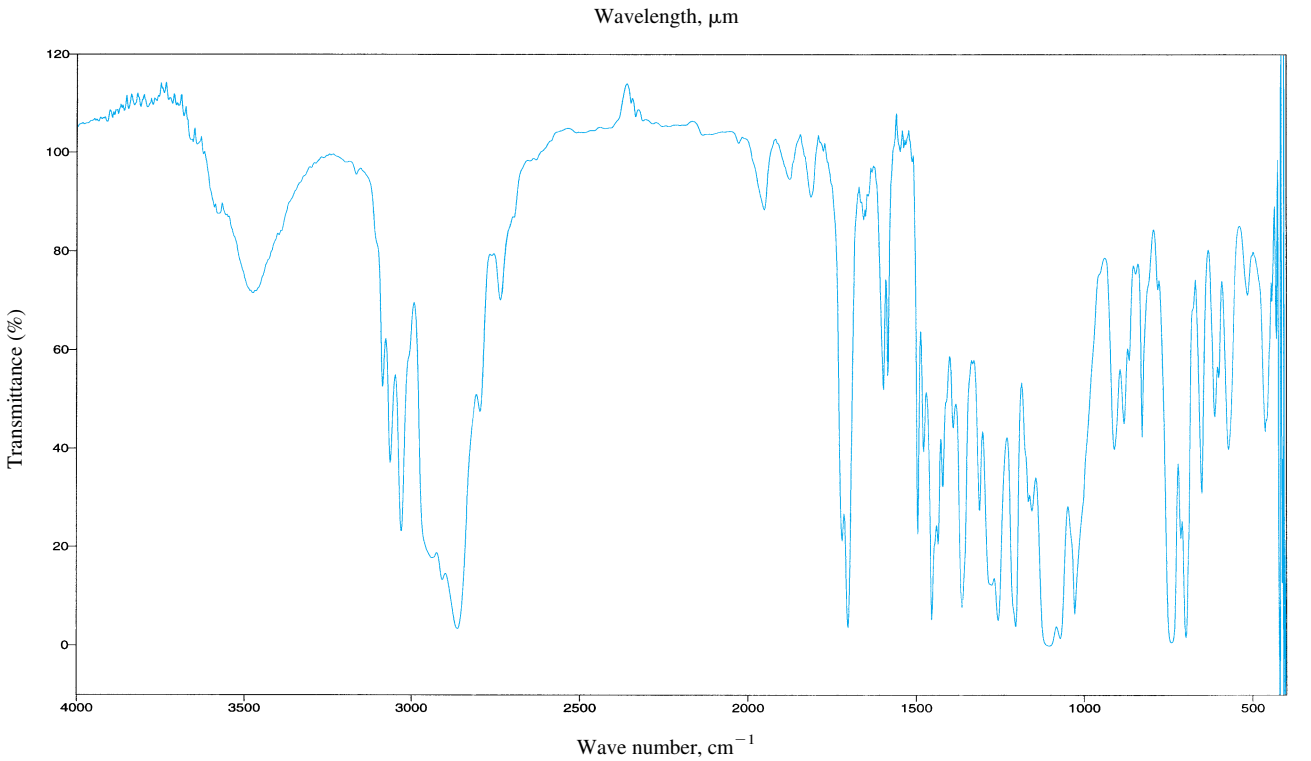


(*a*)

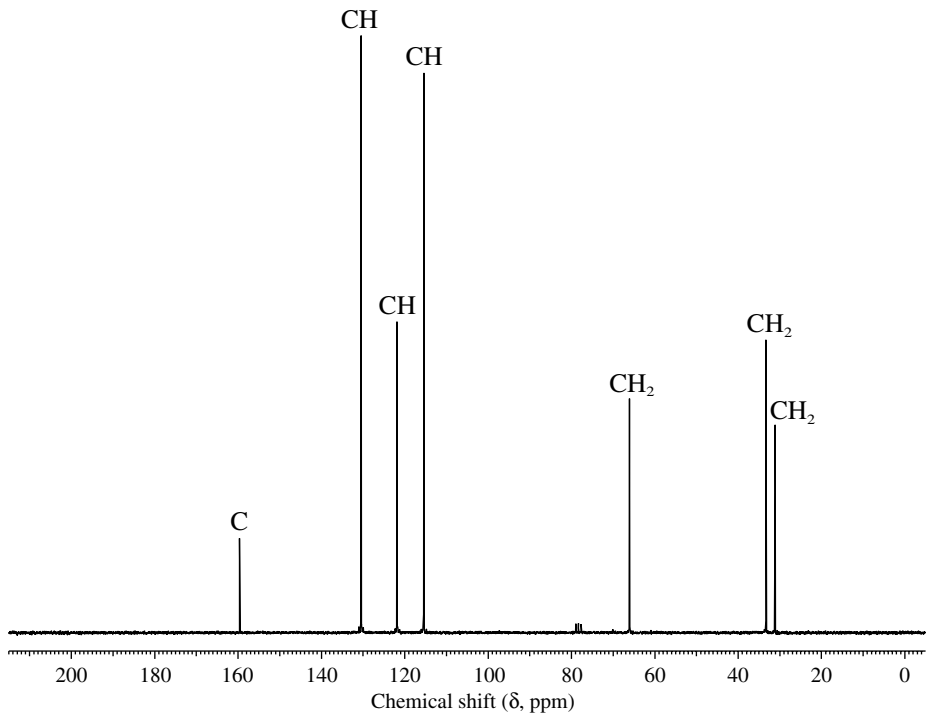


(*b*)

FIGURE 24.5 (*a*) Infrared and (*b*) ^{13}C NMR spectra of the compound $C_9H_{12}O$ (Problem 24.30a).



(*a*)



(*b*)

FIGURE 24.6 (*a*) Infrared and (*b*) ^{13}C NMR spectra of the compound $C_9H_{11}BrO$ (Problem 24.30b).