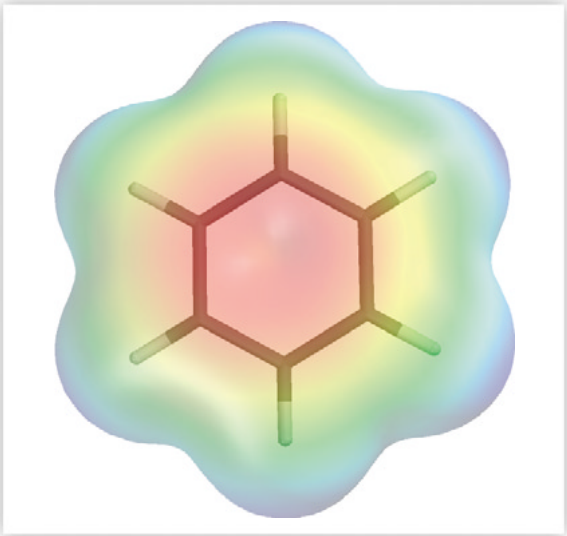
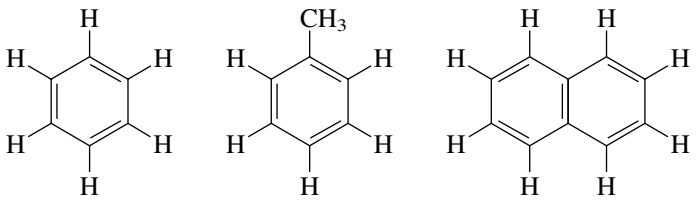


CHAPTER 11

ARENES AND AROMATICITY

In this chapter and the next we extend our coverage of conjugated systems to include **arenes.** Arenes are hydrocarbons based on the benzene ring as a structural unit. Benzene, toluene, and naphthalene, for example, are arenes.



Benzene Toluene Naphthalene

One factor that makes conjugation in arenes special is its cyclic nature. A conjugated system that closes upon itself can have properties that are much different from those of open-chain polyenes. Arenes are also referred to as **aromatic hydrocarbons.** Used in this sense, the word **"aromatic"** has nothing to do with odor but means instead that arenes are much more stable than we expect them to be based on their formulation as conjugated trienes. Our goal in this chapter is to develop an appreciation for the concept of **aromaticity**—to see what are the properties of benzene and its derivatives that reflect its special stability, and to explore the reasons for it. This chapter develops the idea of the benzene ring as a fundamental structural unit and examines the effect of a benzene ring as a substituent. The chapter following this one describes reactions that involve the ring itself.

Let's begin by tracing the history of benzene, its origin, and its structure. Many of the terms we use, including *aromaticity* itself, are of historical origin. We'll begin with the discovery of benzene.

11.1 BENZENE

In 1825, Michael Faraday isolated a new hydrocarbon from illuminating gas, which he called "bicarburet of hydrogen." Nine years later Eilhardt Mitscherlich of the University of Berlin prepared the same substance by heating benzoic acid with lime and found it to be a hydrocarbon having the empirical formula C_nH_n.

Faraday is better known in chemistry for his laws of electrolysis and in physics for proposing the relationship between electric and magnetic fields and for demonstrating the principle of electromagnetic induction.

$$\underset{\text{Benzoic acid}}{C_6H_5CO_2H} + \underset{\text{Calcium oxide}}{CaO} \xrightarrow{\text{heat}} \underset{\text{Benzene}}{C_6H_6} + \underset{\text{Calcium carbonate}}{CaCO_3}$$

Eventually, because of its relationship to benzoic acid, this hydrocarbon came to be named *benzin,* then later *benzene,* the name by which it is known today.

Benzoic acid had been known for several hundred years by the time of Mitscherlich's experiment. Many trees exude resinous materials called *balsams* when cuts are made in their bark. Some of these balsams are very fragrant, which once made them highly prized articles of commerce, especially when the trees that produced them could be found only in exotic, faraway lands. *Gum benzoin* is a balsam obtained from a tree that grows in Java and Sumatra. "Benzoin" is a word derived from the French equivalent, *benjoin,* which in turn comes from the Arabic *luban jawi,* meaning "incense from Java." Benzoic acid is itself odorless but can easily be isolated from gum benzoin.

Compounds related to benzene were obtained from similar plant extracts. For example, a pleasant-smelling resin known as *tolu balsam* was obtained from the South American tolu tree. In the 1840s it was discovered that distillation of tolu balsam gave a methyl derivative of benzene, which, not surprisingly, came to be named *toluene.*

Although benzene and toluene are not particularly fragrant compounds themselves, their origins in aromatic plant extracts led them and compounds related to them to be classified as *aromatic hydrocarbons.* Alkanes, alkenes, and alkynes belong to another class, the **aliphatic hydrocarbons.** The word "aliphatic" comes from the Greek *aleiphar* (meaning "oil" or "unguent") and was given to hydrocarbons that were obtained by the chemical degradation of fats.

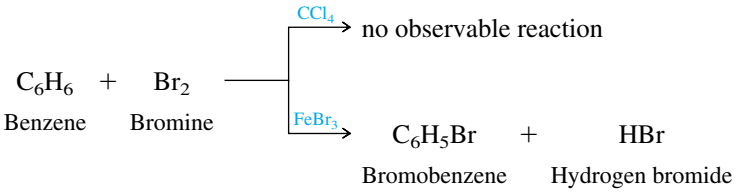
Benzene was prepared from coal tar by August W. von Hofmann in 1845. Coal tar remained the primary source for the industrial production of benzene for many years, until petroleum-based technologies became competitive about 1950. Current production is about 6 million tons per year in the United States. A substantial portion of this benzene is converted to styrene for use in the preparation of polystyrene plastics and films.

Toluene is also an important organic chemical. Like benzene, its early industrial production was from coal tar, but most of it now comes from petroleum.

11.2 KEKULÉ AND THE STRUCTURE OF BENZENE

The classification of hydrocarbons as aliphatic or aromatic took place in the 1860s when it was already apparent that there was something special about benzene, toluene, and their derivatives. Their molecular formulas (benzene is C_6H_6, toluene is C_7H_8) indicate that, like alkenes and alkynes, they are unsaturated and should undergo addition reactions. Under conditions in which bromine, for example, reacts rapidly with alkenes and

alkynes, however, benzene proved to be inert. Benzene does react with Br_2 in the presence of iron(III) bromide as a catalyst, but even then addition isn't observed. Substitution occurs instead!



Furthermore, only one monobromination product of benzene was ever obtained, which suggests that all the hydrogen atoms of benzene are equivalent. Substitution of one hydrogen by bromine gives the same product as substitution of any of the other hydrogens.

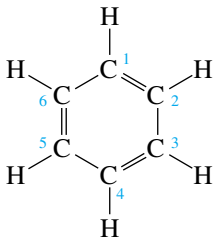
Chemists came to regard the six carbon atoms of benzene as a fundamental structural unit. Reactions could be carried out that altered its substituents, but the integrity of the benzene unit remained undisturbed. There must be something "special" about benzene that makes it inert to many of the reagents that add to alkenes and alkynes.

In 1866, only a few years after publishing his ideas concerning what we now recognize as the structural theory of organic chemistry, August Kekulé applied it to the structure of benzene. He based his reasoning on three premises:

1. Benzene is C_6H_6.
2. All the hydrogens of benzene are equivalent.
3. The structural theory requires that there be four bonds to each carbon.

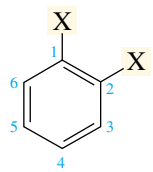
In 1861, Johann Josef Loschmidt, who was later to become a professor at the University of Vienna, privately published a book containing a structural formula for benzene similar to that which Kekulé would propose five years later. Loschmidt's book reached few readers, and his ideas were not well known.

Kekulé advanced the venturesome notion that the six carbon atoms of benzene were joined together in a ring. Four bonds to each carbon could be accommodated by a system of alternating single and double bonds with one hydrogen on each carbon.

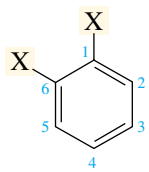


How many isomers of C_6H_6 can you write? An article in the March 1994 issue of the *Journal of Chemical Education* (pp. 222–224) claims that there are several hundred and draws structural formulas for 25 of them.

A flaw in Kekulé's structure for benzene was soon discovered. Kekulé's structure requires that 1,2- and 1,6-disubstitution patterns create different compounds (isomers).



1,2-Disubstituted derivative of benzene



1,6-Disubstituted derivative of benzene

The two substituted carbons are connected by a double bond in one but by a single bond in the other. Since no such cases of isomerism in benzene derivatives were known, and

BENZENE, DREAMS, AND CREATIVE THINKING

At ceremonies in Berlin in 1890 celebrating the twenty-fifth anniversary of his proposed structure of benzene, August Kekulé recalled the thinking that led him to it. He began by noting that the idea of the structural theory came to him during a daydream while on a bus in London. Kekulé went on to describe the origins of his view of the benzene structure.

> There I sat and wrote for my textbook; but things did not go well; my mind was occupied with other matters. I turned the chair towards the fireplace and began to doze. Once again the atoms danced before my eyes. This time smaller groups modestly remained in the background. My mental eye, sharpened by repeated apparitions of similar kind, now distinguished larger units of various shapes. Long rows, frequently joined more densely; everything in motion, twisting and turning like snakes. And behold, what was that? One of the snakes caught hold of its own tail and mockingly whirled round before my eyes. I awoke, as if by lightning; this time, too, I spent the rest of the night working out the consequences of this hypothesis.*

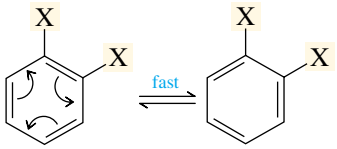
Concluding his remarks, Kekulé merged his advocacy of creative imagination with the rigorous standards of science by reminding his audience:

> Let us learn to dream, then perhaps we shall find the truth. But let us beware of publishing our dreams before they have been put to the proof by the waking understanding.

The imagery of a whirling circle of snakes evokes a vivid picture that engages one's attention when first exposed to Kekulé's model of the benzene structure. Recently, however, the opinion has been expressed that Kekulé might have engaged in some hyperbole during his speech. Professor John Wotiz of Southern Illinois University suggests that discoveries in science are the result of a disciplined analysis of a sufficient body of experimental observations to progress to a higher level of understanding. Wotiz' view that Kekulé's account is more fanciful than accurate has sparked a controversy with ramifications that go beyond the history of organic chemistry. How does creative thought originate? What can we do to become more creative? Because these are questions that have concerned psychologists for decades, the idea of a sleepy Kekulé being more creative than an alert Kekulé becomes more than simply a charming story he once told about himself.

* The Kekulé quotes are taken from the biographical article of K. Hafner published in *Angew. Chem. Internat. ed. Engl.* **18,** 641–651 (1979).

none could be found, Kekulé suggested that two isomeric structures could exist but interconverted too rapidly to be separated.



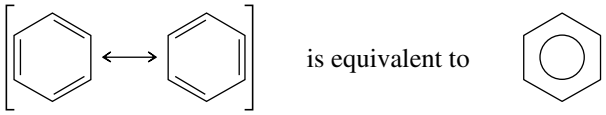
Kekulé's ideas about the structure of benzene left an important question unanswered. What is it about benzene that makes it behave so much differently from other unsaturated compounds? We'll see in this chapter that the answer is a simple one—the low reactivity of benzene and its derivatives reflects their special stability. Kekulé was wrong. *Benzene is not cyclohexatriene, nor is it a pair of rapidly equilibrating cyclohexatriene isomers.* But there was no way that Kekulé could have gotten it right given the state of chemical knowledge at the time. After all, the electron hadn't even been discovered yet. It remained for twentieth-century electronic theories of bonding to provide insight into why benzene is so stable. We'll outline these theories shortly. First, however, let's look at the structure of benzene in more detail.

Benzene is planar and its carbon skeleton has the shape of a regular hexagon. There is no evidence that it has alternating single and double bonds. As shown in Figure 11.1, all the carbon–carbon bonds are the same length (140 pm) and the 120° bond angles correspond to perfect sp^2 hybridization. Interestingly, the 140-pm bond distances in benzene are exactly midway between the typical sp^2–sp^2 single-bond distance of 146 pm and the sp^2–sp^2 double-bond distance of 134 pm. If bond distances are related to bond type, what kind of carbon–carbon bond is it that lies halfway between a single bond and a double bond in length?

11.3 A RESONANCE PICTURE OF BONDING IN BENZENE

Twentieth-century theories of bonding in benzene provide a rather clear picture of aromaticity. We'll start with a resonance description of benzene.

The two Kekulé structures for benzene have the same arrangement of atoms, but differ in the placement of electrons. Thus they are resonance forms, and neither one by itself correctly describes the bonding in the actual molecule. As a hybrid of the two Kekulé structures, benzene is often represented by a hexagon containing an inscribed circle.



The circle-in-a-hexagon symbol was first suggested by the British chemist Sir Robert Robinson to represent what he called the "aromatic sextet"—the six delocalized π electrons of the three double bonds. Robinson's symbol is a convenient time-saving shorthand device, but Kekulé-type formulas are better for counting and keeping track of electrons, especially in chemical reactions.

PROBLEM 11.1 Write structural formulas for toluene ($C_6H_5CH_3$) and for benzoic acid ($C_6H_5CO_2H$) (a) as resonance hybrids of two Kekulé forms and (b) with the Robinson symbol.

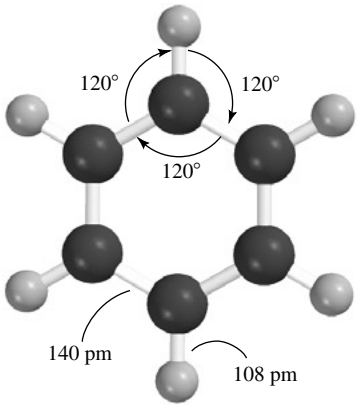


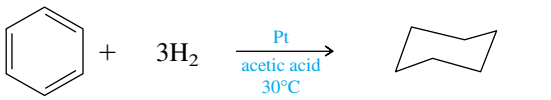
FIGURE 11.1 Bond distances and bond angles of benzene.

Since the carbons that are singly bonded in one resonance form are doubly bonded in the other, the resonance description is consistent with the observed carbon–carbon bond distances in benzene. These distances not only are all identical but also are intermediate between typical single-bond and double-bond lengths.

We have come to associate electron delocalization with increased stability. On that basis alone, benzene ought to be stabilized. It differs from other conjugated systems that we have seen, however, in that its π electrons are delocalized over a *cyclic conjugated* system. Both Kekulé structures of benzene are of equal energy, and one of the principles of resonance theory is that stabilization is greatest when the contributing structures are of similar energy. Cyclic conjugation in benzene, then, leads to a greater stabilization than is observed in noncyclic conjugated trienes. How much greater that stabilization is can be estimated from heats of hydrogenation.

11.4 THE STABILITY OF BENZENE

Hydrogenation of benzene and other arenes is more difficult than hydrogenation of alkenes and alkynes. Two of the more active catalysts are rhodium and platinum, and it is possible to hydrogenate arenes in the presence of these catalysts at room temperature and modest pressure. Benzene consumes three molar equivalents of hydrogen to give cyclohexane.



Benzene — Hydrogen (2–3 atm pressure) — Cyclohexane (100%)

Nickel catalysts, although less expensive than rhodium and platinum, are also less active. Hydrogenation of arenes in the presence of nickel requires high temperatures (100–200°C) and pressures (100 atm).

The measured heat of hydrogenation of benzene to cyclohexane is, of course, the same regardless of the catalyst and is 208 kJ/mol (49.8 kcal/mol). To put this value into perspective, compare it with the heats of hydrogenation of cyclohexene and 1,3-cyclohexadiene, as shown in Figure 11.2. The most striking feature of Figure 11.2 is that the heat of hydrogenation of benzene, with three "double bonds," is less than the heat of hydrogenation of the two double bonds of 1,3-cyclohexadiene.

Our experience has been that some 125 kJ/mol (30 kcal/mol) is given off whenever a double bond is hydrogenated. When benzene combines with three molecules of hydrogen, the reaction is far less exothermic than we would expect it to be on the basis of a 1,3,5-cyclohexatriene structure for benzene.

How much less? Since 1,3,5-cyclohexatriene does not exist (if it did, it would instantly relax to benzene), we cannot measure its heat of hydrogenation in order to compare it with benzene. We can approximate the heat of hydrogenation of 1,3,5-cyclohexatriene as being equal to three times the heat of hydrogenation of cyclohexene, or a total of 360 kJ/mol (85.8 kcal/mol). The heat of hydrogenation of benzene is 152 kJ/mol (36 kcal/mol) *less* than expected for a hypothetical 1,3,5-cyclohexatriene with noninteracting double bonds. This is the **resonance energy** of benzene. It is a measure of how much more stable benzene is than would be predicted on the basis of its formulation as a pair of rapidly interconverting 1,3,5-cyclohexatrienes.

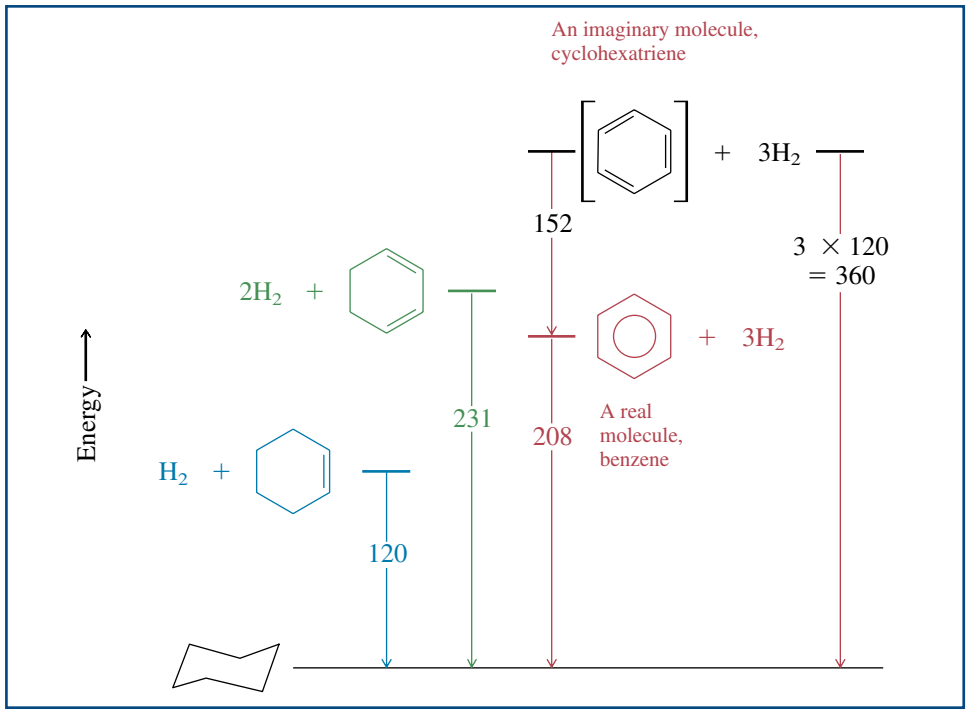
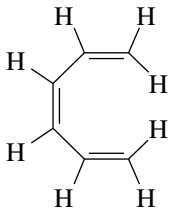


FIGURE 11.2 Heats of hydrogenation of cyclohexene, 1,3-cyclohexadiene, a hypothetical 1,3,5-cyclohexatriene, and benzene. All heats of hydrogenation are in kilojoules per mole.

We reach a similar conclusion when comparing benzene with the open-chain conjugated triene (*Z*)-1,3,5-hexatriene. Here we compare two real molecules, both conjugated trienes, but one is cyclic and the other is not. The heat of hydrogenation of (*Z*)-1,3,5-hexatriene is 337 kJ/mol (80.5 kcal/mol), a value which is 129 kJ/mol (30.7 kcal/mol) greater than that of benzene.

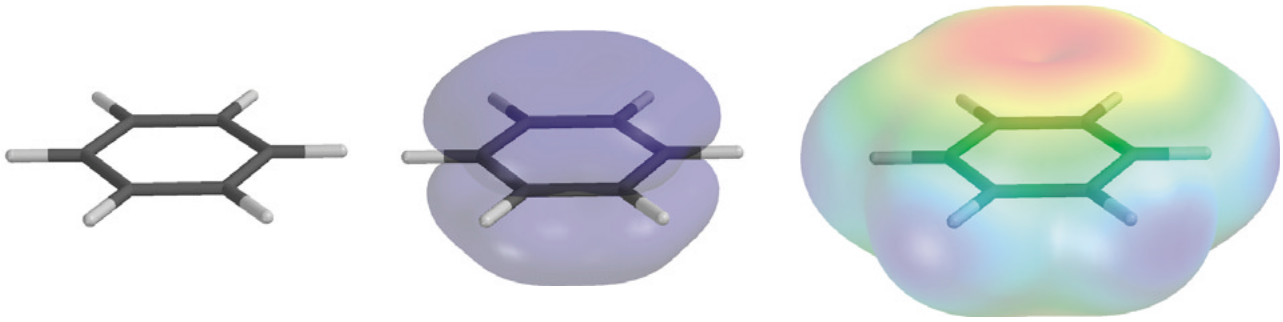


$$+ \quad 3H_2 \longrightarrow CH_3(CH_2)_4CH_3 \qquad \Delta H^\circ = -337 \text{ kJ } (-80.5 \text{ kcal})$$

(*Z*)-1,3,5-Hexatriene Hydrogen Hexane

The precise value of the resonance energy of benzene depends, as comparisons with 1,3,5-cyclohexatriene and (*Z*)-1,3,5-hexatriene illustrate, on the compound chosen as the reference. What is important is that the resonance energy of benzene is quite large, six to ten times that of a conjugated triene. It is this very large increment of resonance energy that places benzene and related compounds in a separate category that we call *aromatic*.

PROBLEM 11.2 The heats of hydrogenation of cycloheptene and 1,3,5-cycloheptatriene are 110 kJ/mol (26.3 kcal/mol) and 305 kJ/mol (73.0 kcal/mol), respectively. In both cases cycloheptane is the product. What is the resonance energy of 1,3,5-cycloheptatriene? How does it compare with the resonance energy of benzene?



(*a*) (*b*) (*c*)

FIGURE 11.3 (*a*) The framework of bonds shown in the tube model of benzene are σ bonds. (*b*) Each carbon is sp^2-hybridized and has a 2*p* orbital perpendicular to the σ framework. Overlap of the 2*p* orbitals generates a π system encompassing the entire ring. (*c*) Electrostatic potential plot of benzene. The red area in the center corresponds to the region above and below the plane of the ring where the π electrons are concentrated.

11.5 AN ORBITAL HYBRIDIZATION VIEW OF BONDING IN BENZENE

The structural facts that benzene is planar, all of the bond angles are 120°, and each carbon is bonded to three other atoms, suggest sp^2 hybridization for carbon and the framework of σ bonds shown in Figure 11.3*a*.

In addition to its three sp^2 hybrid orbitals, each carbon has a half-filled 2*p* orbital that can participate in π bonding. Figure 11.3*b* shows the continuous π system that encompasses all of the carbons that result from overlap of these 2*p* orbitals. The six π electrons of benzene are delocalized over all six carbons.

The electrostatic potential map of benzene (Figure 11.3*c*) shows regions of high electron density above and below the plane of the ring, which is where we expect the most loosely held electrons (the π electrons) to be.

11.6 THE π MOLECULAR ORBITALS OF BENZENE

The picture of benzene as a planar framework of σ bonds with six electrons in a delocalized π orbital is a useful, but superficial, one. Six electrons cannot simultaneously occupy any one orbital, be it an atomic orbital or a molecular orbital. A more rigorous molecular orbital analysis recognizes that overlap of the six 2*p* atomic orbitals of the ring carbons generates six π molecular orbitals. These six π molecular orbitals include three which are bonding and three which are antibonding. The relative energies of these orbitals and the distribution of the π electrons among them are illustrated in Figure 11.4. Benzene is said to have a **closed-shell** π electron configuration. All the bonding orbitals are filled, and there are no electrons in antibonding orbitals.

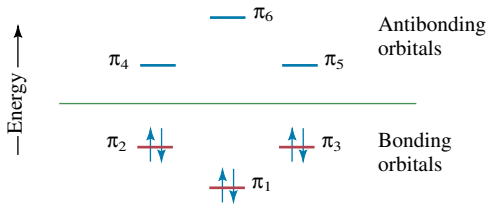


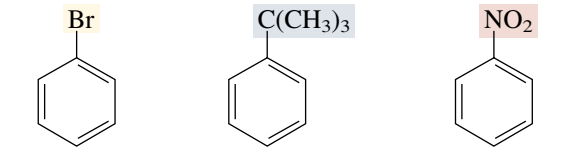
FIGURE 11.4 The π molecular orbitals of benzene arranged in order of increasing energy. The six π electrons of benzene occupy the three lowest energy orbitals, all of which are bonding. The nodal properties of these orbitals may be viewed on *Learning By Modeling.*

Higher level molecular orbital theory can provide quantitative information about orbital energies and how strongly a molecule holds its electrons. When one compares aromatic and nonaromatic species in this way, it is found that cyclic delocalization causes the π electrons of benzene to be more strongly bound (more stable) than they would be if restricted to a system with alternating single and double bonds.

We'll come back to the molecular orbital description of benzene later in this chapter (Section 11.19) to see how other conjugated polyenes compare with benzene.

11.7 SUBSTITUTED DERIVATIVES OF BENZENE AND THEIR NOMENCLATURE

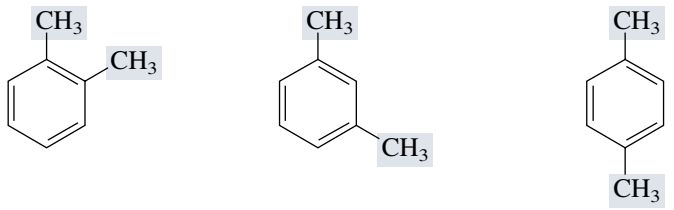
All compounds that contain a benzene ring are aromatic, and substituted derivatives of benzene make up the largest class of aromatic compounds. Many such compounds are named by attaching the name of the substituent as a prefix to *benzene.*



Bromobenzene *tert*-Butylbenzene Nitrobenzene

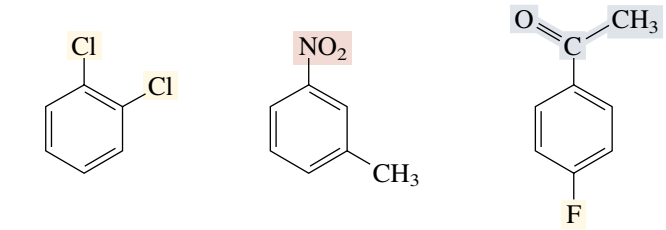
Many simple monosubstituted derivatives of benzene have common names of long standing that have been retained in the IUPAC system. Table 11.1 lists some of the most important ones.

Dimethyl derivatives of benzene are called *xylenes.* There are three xylene isomers, the *ortho* (*o*)-, *meta* (*m*)-, and *para* (*p*)- substituted derivatives.



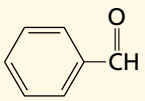
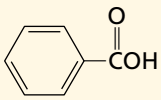
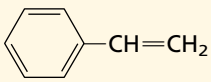
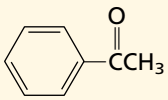
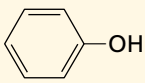
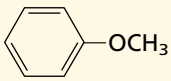
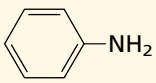
o-Xylene (1,2-dimethylbenzene) *m*-Xylene (1,3-dimethylbenzene) *p*-Xylene (1,4-dimethylbenzene)

The prefix *ortho* signifies a 1,2-disubstituted benzene ring, *meta* signifies 1,3-disubstitution, and *para* signifies 1,4-disubstitution. The prefixes *o, m,* and *p* can be used when a substance is named as a benzene derivative or when a specific base name (such as acetophenone) is used. For example,



o-Dichlorobenzene (1,2-dichlorobenzene) *m*-Nitrotoluene (3-nitrotoluene) *p*-Fluoroacetophenone (4-fluoroacetophenone)

TABLE 11.1 Names of Some Frequently Encountered Derivatives of Benzene

Structure	Systematic Name	Common Name*
	Benzenecarbaldehyde	Benzaldehyde
	Benzenecarboxylic acid	Benzoic acid
	Vinylbenzene	Styrene
	Methyl phenyl ketone	Acetophenone
	Benzenol	Phenol
	Methoxybenzene	Anisole
	Benzenamine	Aniline

*These common names are acceptable in IUPAC nomenclature and are the names that will be used in this text.

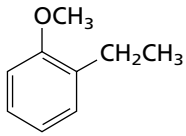
PROBLEM 11.3 Write a structural formula for each of the following compounds:

(a) *o*-Ethylanisole

(b) *m*-Chlorostyrene

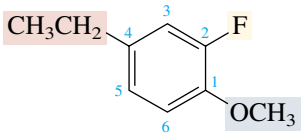
(c) *p*-Nitroaniline

SAMPLE SOLUTION (a) The parent compound in *o*-ethylanisole is anisole. Anisole, as shown in Table 11.1, has a methoxy (CH_3O—) substituent on the benzene ring. The ethyl group in *o*-ethylanisole is attached to the carbon adjacent to the one that bears the methoxy substituent.

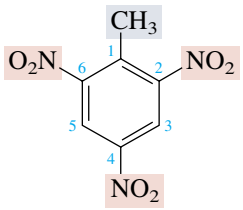


o-Ethylanisole

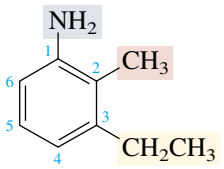
The prefixes *o, m,* and *p* are *not* used when three or more substituents are present on benzene; numerical locants must be used instead.



4-Ethyl-2-fluoroanisole



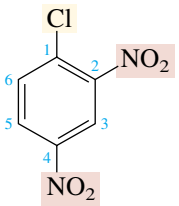
2,4,6-Trinitrotoluene



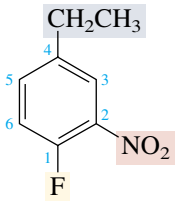
3-Ethyl-2-methylaniline

In these examples the base name of the benzene derivative determines the carbon at which numbering begins: anisole has its methoxy group at C-1, toluene its methyl group at C-1, and aniline its amino group at C-1. The direction of numbering is chosen to give the next substituted position the lowest number irrespective of what substituent it bears. *The order of appearance of substituents in the name is alphabetical.* When no simple base name other than benzene is appropriate, positions are numbered so as to give the lowest locant at the first point of difference. Thus, each of the following examples is named as a 1,2,4-trisubstituted derivative of benzene rather than as a 1,3,4-derivative:

The "first point of difference" rule was introduced in Section 2.11.

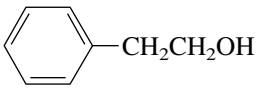


1-Chloro-2,4-dinitrobenzene

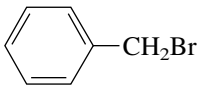


4-Ethyl-1-fluoro-2-nitrobenzene

When the benzene ring is named as a substituent, the word "phenyl" stands for C_6H_5—. Similarly, an arene named as a substituent is called an *aryl* group. A *benzyl* group is $C_6H_5CH_2$—.

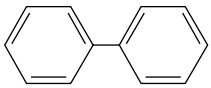


2-Phenylethanol

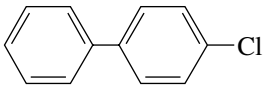


Benzyl bromide

Biphenyl is the accepted IUPAC name for the compound in which two benzene rings are connected by a single bond.



Biphenyl



p-Chlorobiphenyl

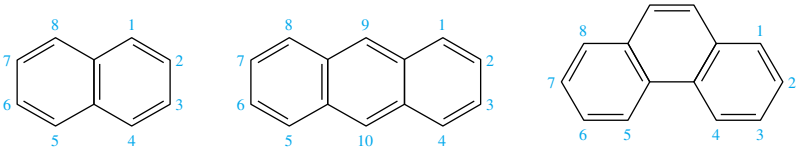
11.8 POLYCYCLIC AROMATIC HYDROCARBONS

Members of a class of arenes called **polycyclic benzenoid aromatic hydrocarbons** possess substantial resonance energies because each is a collection of benzene rings fused together.

Naphthalene is a white crystalline solid melting at 80°C that sublimes readily. It has a characteristic odor and was formerly used as a moth repellent.

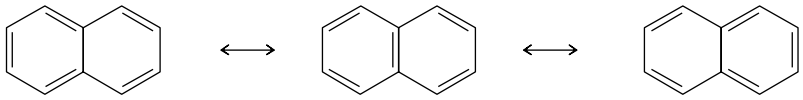
Naphthalene, anthracene, and phenanthrene are the three simplest members of this class. They are all present in **coal tar,** a mixture of organic substances formed when coal is converted to coke by heating at high temperatures (about 1000°C) in the absence of air. Naphthalene is **bicyclic** (has two rings), and its two benzene rings share a common side. Anthracene and phenanthrene are both **tricyclic** aromatic hydrocarbons. Anthracene

has three rings fused in a "linear" fashion, and "angular" fusion characterizes phenanthrene. The structural formulas of naphthalene, anthracene, and phenanthrene are shown along with the numbering system used to name their substituted derivatives:



Arene:	Naphthalene	Anthracene	Phenanthrene
Resonance energy:	255 kJ/mol (61 kcal/mol)	347 kJ/mol (83 kcal/mol)	381 kJ/mol (91 kcal/mol)

In general, the most stable resonance structure for a polycyclic aromatic hydrocarbon is the one which has the greatest number of rings that correspond to Kekulé formulations of benzene. Naphthalene provides a fairly typical example:



Most stable resonance form

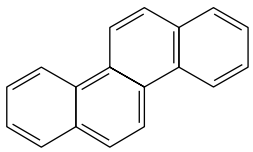
Only left ring corresponds to Kekulé benzene.

Both rings correspond to Kekulé benzene.

Only right ring corresponds to Kekulé benzene.

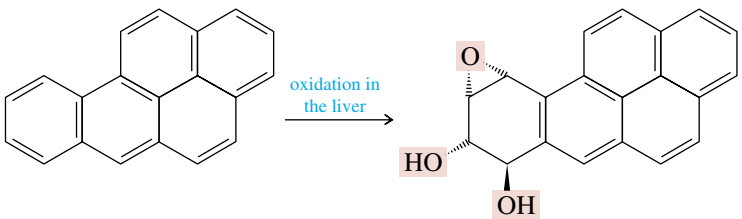
Notice that anthracene cannot be represented by any single Lewis structure in which all three rings correspond to Kekulé formulations of benzene, but phenanthrene can.

PROBLEM 11.4 Chrysene is an aromatic hydrocarbon found in coal tar. The structure shown is not the most stable resonance form. Write the most stable resonance form for chrysene.



A large number of polycyclic benzenoid aromatic hydrocarbons are known. Many have been synthesized in the laboratory, and several of the others are products of combustion. Benzo[a]pyrene, for example, is present in tobacco smoke, contaminates food cooked on barbecue grills, and collects in the soot of chimneys. Benzo[a]pyrene is a **carcinogen** (a cancer-causing substance). It is converted in the liver to an epoxy diol that can induce mutations leading to the uncontrolled growth of certain cells.

In 1775, the British surgeon Sir Percivall Pott suggested that scrotal cancer in chimney sweeps was caused by soot. This was the first proposal that cancer could be caused by chemicals present in the workplace.



Benzo[a]pyrene

7,8-Dihydroxy-9,10-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene

CARBON CLUSTERS, FULLERENES, AND NANOTUBES

The 1996 Nobel Prize in chemistry was awarded to Professors Harold W. Kroto (University of Sussex), Robert F. Curl, and Richard E. Smalley (both of Rice University) for groundbreaking work involving elemental carbon that opened up a whole new area of chemistry. The work began when Kroto wondered whether polyacetylenes of the type $HC{\equiv}C{-}(C{\equiv}C)_n{-}C{\equiv}CH$ might be present in interstellar space and discussed experiments to test this idea while visiting Curl and Smalley at Rice in the spring of 1984. Smalley had developed a method for the laser-induced evaporation of metals at very low pressure and was able to measure the molecular weights of the various clusters of atoms produced. Kroto, Curl, and Smalley felt that by applying this technique to graphite (Figure 11.5) the vaporized carbon produced might be similar to that produced by a carbon-rich star.

When the experiment was carried out in the fall of 1985, Kroto, Curl, and Smalley found that under certain conditions a species with a molecular formula of C_{60} was present in amounts much greater than any other. On speculating about what C_{60} might be, they concluded that its most likely structure is the spherical cluster of carbon atoms shown in Figure 11.6 and suggested it be called *buckminsterfullerene* because of its similarity to the geodesic domes popularized by the American architect and inventor R. Buckminster Fuller. (It is also often referred to as a "buckyball.") Other carbon clusters, some larger than C_{60} and some smaller, were also formed in the experiment, and the general term *fullerene* refers to such carbon clusters.

All of the carbon atoms in buckminsterfullerene are equivalent and are sp^2-hybridized; each one simultaneously belongs to one five-membered ring and two benzene-like six-membered rings. The strain caused by distortion of the rings from coplanarity is equally distributed among all of the carbons.

Confirmation of the structure proposed for C_{60} required isolation of enough material to allow the arsenal of modern techniques of structure determination to be applied. A quantum leap in fullerene research came in 1990 when a team led by Wolfgang Krätschmer of the Max Planck Institute for Nuclear Physics in Heidelberg and Donald Huffman of the University of Arizona successfully prepared buckminsterfullerene in amounts sufficient for its isolation, purification and detailed study. Not only was the buckminsterfullerene structure shown to be correct, but academic and industrial scientists around the world seized the opportunity afforded by the availability of C_{60} in quantity to study its properties.

Speculation about the stability of C_{60} centered on the extent to which the aromaticity associated with its 20 benzene rings is degraded by their non-

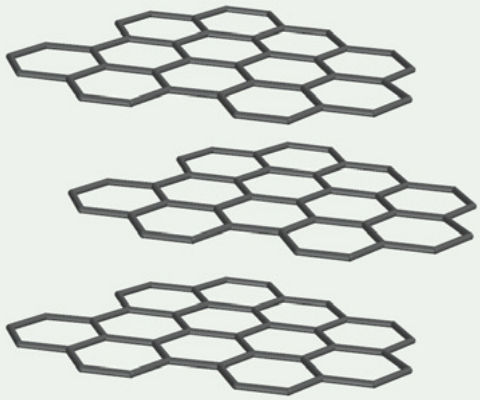


FIGURE 11.5 Graphite is a form of elemental carbon composed of parallel sheets of fused benzene-like rings.

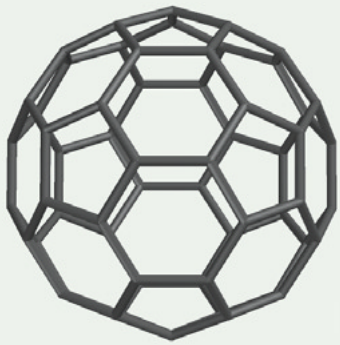


FIGURE 11.6 Buckminsterfullerene (C_{60}). Note that all carbons are equivalent and that no five-membered rings are adjacent to one another.

—Cont.

planarity and the accompanying angle strain. It is now clear that C_{60} is a relatively reactive substance, reacting with many substances toward which benzene itself is inert. Many of these reactions are characterized by the addition of nucleophilic substances to buckminsterfullerene, converting sp^2-hybridized carbons to sp^3-hybridized ones and reducing the overall strain.

The field of fullerene chemistry expanded in an unexpected direction in 1991 when Sumio Iijima of the NEC Fundamental Research Laboratories in Japan discovered fibrous carbon clusters in one of his fullerene preparations. This led, within a short time, to substances of the type portrayed in Figure 11.7 called *single-walled nanotubes.* The best way to think about this material is as a "stretched" fullerene. Take a molecule of C_{60}, cut it in half, and place a cylindrical tube of fused six-membered carbon rings between the two halves.

Thus far, the importance of carbon cluster chemistry has been in the discovery of new knowledge. Many scientists feel that the earliest industrial applications of the fullerenes will be based on their novel electrical properties. Buckminsterfullerene is an insulator, but has a high electron affinity and is a superconductor in its reduced form. Nanotubes have aroused a great deal of interest for their electrical properties and as potential sources of carbon fibers of great strength.

Although the question that began the fullerene story, the possibility that carbon clusters are formed in stars, still remains unanswered, the attempt to answer that question has opened the door to novel structures and materials.

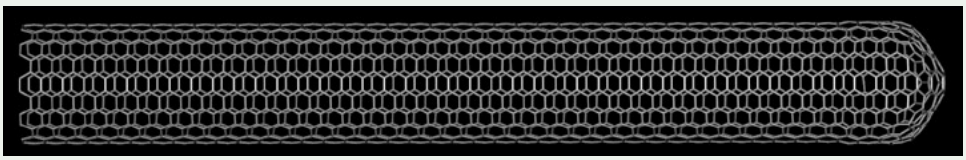


FIGURE 11.7 A portion of a nanotube. The closed end is approximately one half of a buckyball. The main length cannot close as long as all of the rings are hexagons.

11.9 PHYSICAL PROPERTIES OF ARENES

Selected physical properties for a number of arenes are listed in Appendix 1.

In general, arenes resemble other hydrocarbons in their physical properties. They are nonpolar, insoluble in water, and less dense than water. In the absence of polar substituents, intermolecular forces are weak and limited to van der Waals attractions of the induced-dipole/induced-dipole type.

At one time, benzene was widely used as a solvent. This use virtually disappeared when statistical studies revealed an increased incidence of leukemia among workers exposed to atmospheric levels of benzene as low as 1 ppm. Toluene has replaced benzene as an inexpensive organic solvent, because it has similar solvent properties but has not been determined to be carcinogenic in the cell systems and at the dose levels that benzene is.

11.10 REACTIONS OF ARENES: A PREVIEW

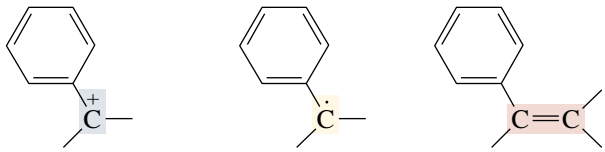
We'll examine the chemical properties of aromatic compounds from two different perspectives:

1. *One mode of chemical reactivity involves the ring itself as a functional group and includes*
   (a) Reduction
   (b) Electrophilic aromatic substitution

Reduction of arenes by catalytic hydrogenation was described in Section 11.4. A different method using Group I metals as reducing agents, which gives 1,4-cyclohexadiene derivatives, will be presented in Section 11.11. **Electrophilic aromatic substitution** is the most important reaction type exhibited by benzene and its derivatives and constitutes the entire subject matter of Chapter 12.

2. *The second family of reactions are those in which the aryl group acts as a substituent and affects the reactivity of a functional unit to which it is attached.*

A carbon atom that is directly attached to a benzene ring is called **a benzylic** carbon (analogous to the allylic carbon of C═C—**C**). A phenyl group (C_6H_5—) is an even better conjugating substituent than a vinyl group (CH_2═CH—), and benzylic carbocations and radicals are more highly stabilized than their allylic counterparts. The double bond of an alkenylbenzene is stabilized to about the same extent as that of a conjugated diene.

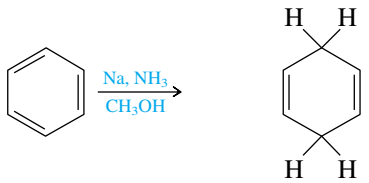


Benzylic carbocation Benzylic radical Alkenylbenzene

Reactions involving benzylic cations, benzylic radicals, and alkenylbenzenes will be discussed in Sections 11.12 through 11.17.

11.11 THE BIRCH REDUCTION

We saw in Section 9.10 that the combination of a Group I metal and liquid ammonia is a powerful reducing system capable of reducing alkynes to trans alkenes. In the presence of an alcohol, this same combination reduces arenes to *nonconjugated dienes.* Thus, treatment of benzene with sodium and methanol or ethanol in liquid ammonia converts it to 1,4-cyclohexadiene.



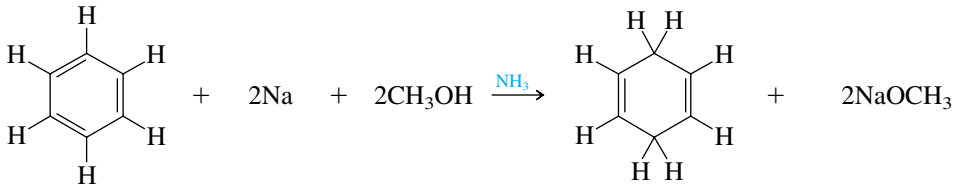
Benzene 1,4-Cyclohexadiene (80%)

Metal–ammonia–alcohol reductions of aromatic rings are known as **Birch reductions,** after the Australian chemist Arthur J. Birch, who demonstrated their usefulness beginning in the 1940s.

The mechanism by which the Birch reduction of benzene takes place is analogous to the mechanism for the metal–ammonia reduction of alkynes (Figure 11.8). It involves a sequence of four steps in which steps 1 and 3 are single-electron transfers from the metal and steps 2 and 4 are proton transfers from the alcohol.

The Birch reduction not only provides a method to prepare dienes from arenes, which cannot be accomplished by catalytic hydrogenation, but also gives a nonconjugated diene system rather than the more stable conjugated one.

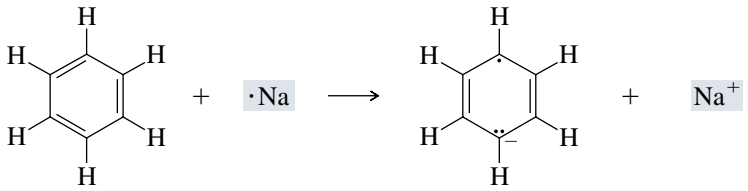
The overall reaction:



Benzene Sodium Methanol 1,4-Cyclohexadiene Sodium methoxide

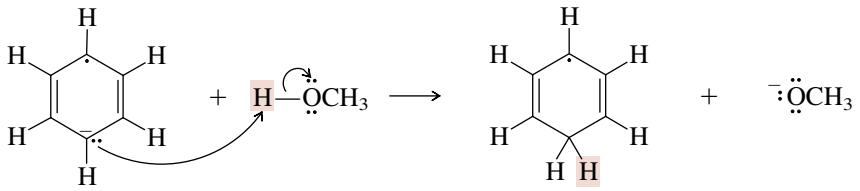
The mechanism:

Step 1: An electron is transferred from sodium (the reducing agent) to the π system of the aromatic ring. The product is an anion radical.



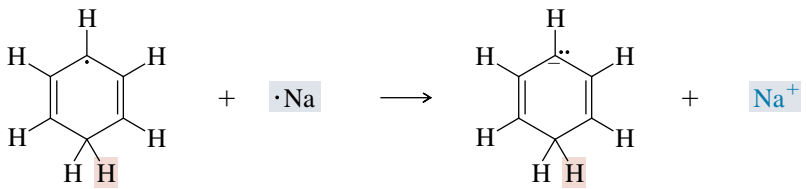
Benzene Sodium Benzene anion radical Sodium ion

Step 2: The anion radical is a strong base and abstracts a proton from methanol.



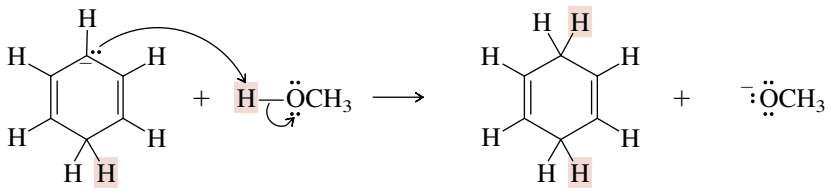
Benzene anion radical Methanol Cyclohexadienyl radical Methoxide ion

Step 3: The cyclohexadienyl radical produced in step 2 is converted to an anion by electron transfer from sodium.



Cyclohexadienyl radical Sodium Cyclohexadienyl anion Sodium ion

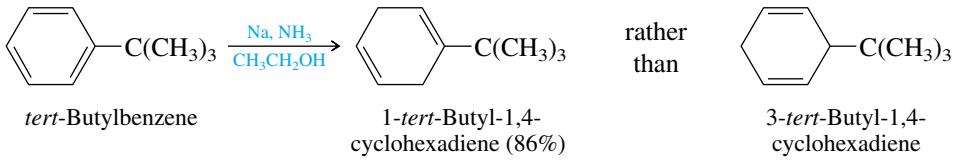
Step 4: Proton transfer from methanol to the anion gives 1,4-cyclohexadiene.



Cyclohexadienyl anion 1,4-Cyclohexadiene Methoxide ion

FIGURE 11.8 Mechanism of the Birch reduction.

Alkyl-substituted arenes give 1,4-cyclohexadienes in which the alkyl group is a substituent on the double bond.



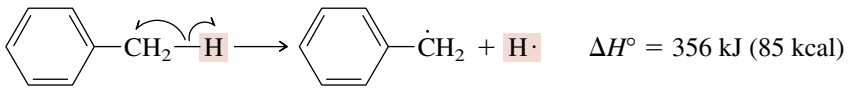
tert-Butylbenzene — 1-*tert*-Butyl-1,4-cyclohexadiene (86%) — 3-*tert*-Butyl-1,4-cyclohexadiene

PROBLEM 11.5 A single organic product was isolated after Birch reduction of *p*-xylene. Suggest a reasonable structure for this substance.

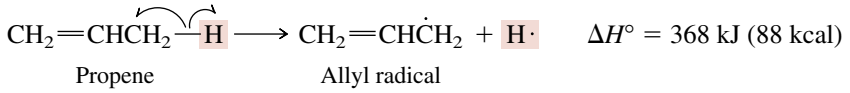
Substituents other than alkyl groups may also be present on the aromatic ring, but their reduction is beyond the scope of the present discussion.

11.12 FREE-RADICAL HALOGENATION OF ALKYLBENZENES

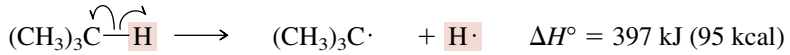
The benzylic position in alkylbenzenes is analogous to the allylic position in alkenes. Thus a benzylic C—H bond, like an allylic one, is weaker than a C—H bond of an alkane, as the bond dissociation energies of toluene, propene, and 2-methylpropane attest:



Toluene — Benzyl radical

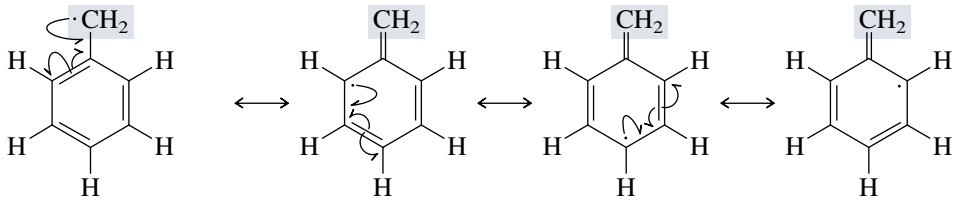


Propene — Allyl radical



2-Methylpropane — *tert*-Butyl radical

We attributed the decreased bond dissociation energy in propene to stabilization of allyl radical by electron delocalization. Similarly, electron delocalization stabilizes benzyl radical and weakens the benzylic C—H bond. The unpaired electron is shared by the benzylic carbon and by the ring carbons that are ortho and para to it.



Most stable Lewis structure of benzyl radical

In orbital terms, as represented in Figure 11.9, benzyl radical is stabilized by delocalization of electrons throughout the extended π system formed by overlap of the *p* orbital of the benzylic carbon with the π system of the ring.

The comparative ease with which a benzylic hydrogen is abstracted leads to high selectivity in free-radical halogenations of alkylbenzenes. Thus, chlorination of toluene

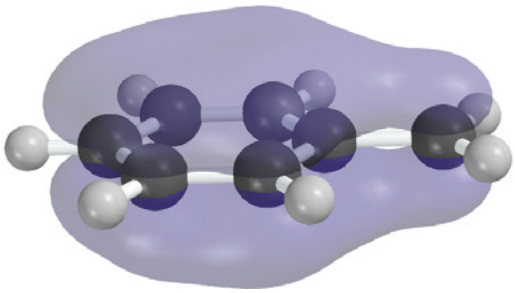
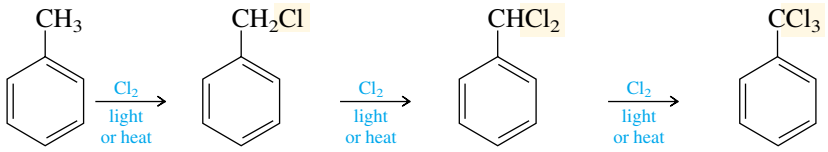


FIGURE 11.9 The benzyl radical is stabilized by overlap of its half-filled *p* orbital with the π system of the aromatic ring.

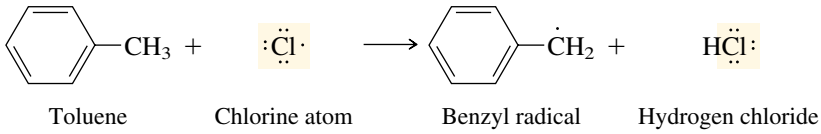
takes place exclusively at the benzylic carbon and is an industrial process for the preparation of the compounds shown.



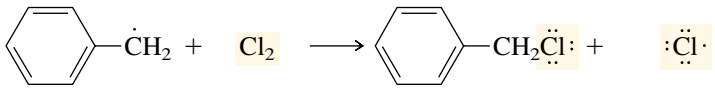
Toluene — Benzyl chloride — (Dichloromethyl)-benzene — (Trichloromethyl)-benzene

The common names of (dichloromethyl)benzene and (trichloromethyl)benzene are benzal chloride and benzotrichloride, respectively.

The propagation steps in the formation of benzyl chloride involve benzyl radical as an intermediate.



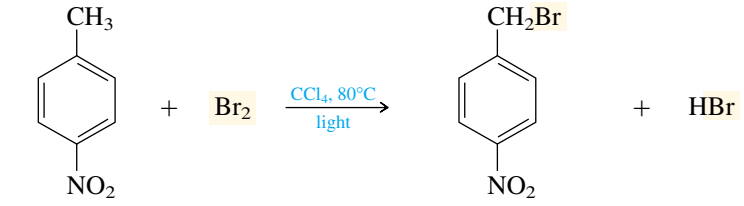
Toluene — Chlorine atom — Benzyl radical — Hydrogen chloride



Benzyl radical — Chlorine — Benzyl chloride — Chlorine atom

(Dichloromethyl)benzene and (trichloromethyl)benzene arise by further side-chain chlorination of benzyl chloride.

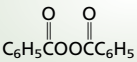
Benzylic bromination is a more commonly used laboratory procedure than chlorination and is typically carried out under conditions of photochemical initiation.

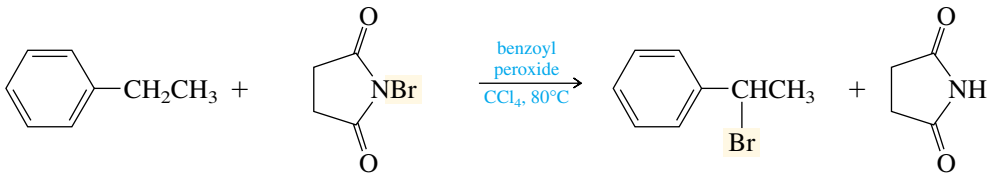


p-Nitrotoluene — Bromine — *p*-Nitrobenzyl bromide (71%) — Hydrogen bromide

As we saw when discussing allylic bromination in Section 10.4, *N*-bromosuccinimide (NBS) is a convenient free-radical brominating agent. Benzylic brominations with NBS are normally performed in carbon tetrachloride as the solvent in the presence of peroxides, which are added as initiators. As the example illustrates, free-radical bromination is selective for substitution of benzylic hydrogens.

Benzoyl peroxide is a commonly used free-radical initiator. It has the formula



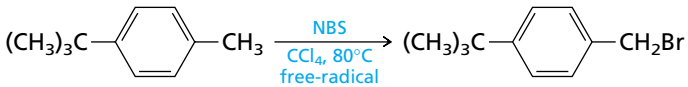


Ethylbenzene | *N*-Bromosuccinimide (NBS) | 1-Bromo-1-phenylethane (87%) | Succinimide

PROBLEM 11.6 The reaction of *N*-bromosuccinimide with the following compounds has been reported in the chemical literature. Each compound yields a single product in 95% yield. Identify the product formed from each starting material.

(a) *p-tert*-Butyltoluene (b) 4-Methyl-3-nitroanisole

SAMPLE SOLUTION (a) The only benzylic hydrogens in *p-tert*-butyltoluene are those of the methyl group that is attached directly to the ring. Substitution occurs there to give *p-tert*-butylbenzyl bromide.

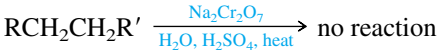


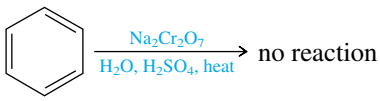
p-tert-Butyltoluene | *p-tert*-Butylbenzyl bromide

11.13 OXIDATION OF ALKYLBENZENES

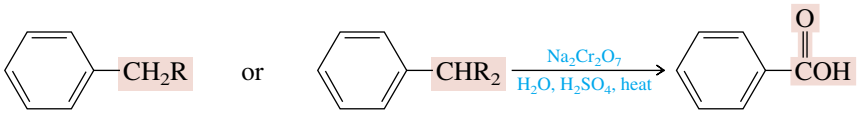
A striking example of the activating effect that a benzene ring has on reactions that take place at benzylic positions may be found in the reactions of alkylbenzenes with oxidizing agents. Chromic acid, for example, prepared by adding sulfuric acid to aqueous sodium dichromate, is a strong oxidizing agent but does not react either with benzene or with alkanes.

An alternative oxidizing agent, similar to chromic acid in its reactions with organic compounds, is potassium permanganate ($KMnO_4$).

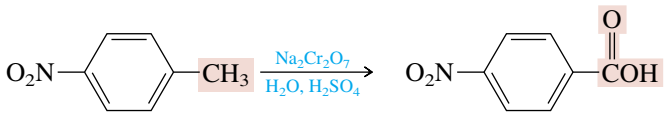




On the other hand, an alkyl side chain on a benzene ring is oxidized on being heated with chromic acid. The product is benzoic acid or a substituted derivative of benzoic acid.

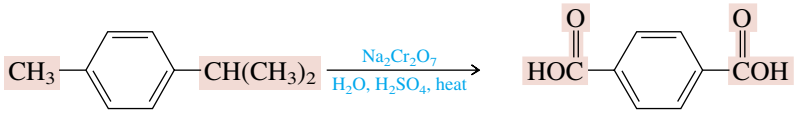


Alkylbenzene | Benzoic acid



p-Nitrotoluene | *p*-Nitrobenzoic acid (82–86%)

When two alkyl groups are present on the ring, both are oxidized.

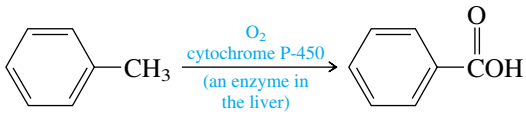


p-Isopropyltoluene *p*-Benzenedicarboxylic acid (45%)

Note that alkyl groups, regardless of their chain length, are converted to carboxyl groups (—CO_2H) attached directly to the ring. An exception is a *tert*-alkyl substituent. Because it lacks benzylic hydrogens, a *tert*-alkyl group is not susceptible to oxidation under these conditions.

PROBLEM 11.7 Chromic acid oxidation of 4-*tert*-butyl-1,2-dimethylbenzene yielded a single compound having the molecular formula $C_{12}H_{14}O_4$. What was this compound?

Side-chain oxidation of alkylbenzenes is important in certain metabolic processes. One way in which the body rids itself of foreign substances is by oxidation in the liver to compounds more easily excreted in the urine. Toluene, for example, is oxidized to benzoic acid by this process and is eliminated rather readily.

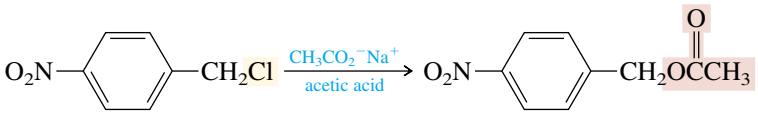


Toluene Benzoic acid

Benzene, with no alkyl side chain, undergoes a different reaction in the presence of these enzymes, which convert it to a substance capable of inducing mutations in DNA. This difference in chemical behavior seems to be responsible for the fact that benzene is carcinogenic but toluene is not.

11.14 NUCLEOPHILIC SUBSTITUTION IN BENZYLIC HALIDES

Primary benzylic halides are ideal substrates for S_N2 reactions, since they are very reactive toward good nucleophiles and cannot undergo competing elimination.



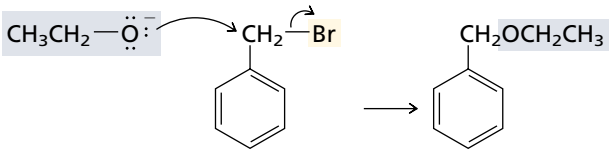
p-Nitrobenzyl chloride *p*-Nitrobenzyl acetate (78–82%)

Benzylic halides that are secondary resemble secondary alkyl halides in that they undergo substitution only when the nucleophile is weakly basic. If the nucleophile is a strong base such as sodium ethoxide, elimination by the E2 mechanism is faster than substitution.

PROBLEM 11.8 Give the structure of the principal organic product formed on reaction of benzyl bromide with each of the following reagents:

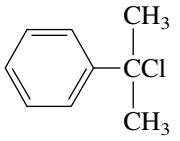
(a) Sodium ethoxide
(b) Potassium *tert*-butoxide
(c) Sodium azide
(d) Sodium hydrogen sulfide
(e) Sodium iodide (in acetone)

SAMPLE SOLUTION (a) Benzyl bromide is a primary bromide and undergoes S_N2 reactions readily. It has no hydrogens β to the leaving group and so cannot undergo elimination. Ethoxide ion acts as a nucleophile, displacing bromide and forming benzyl ethyl ether.

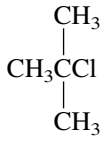


Ethoxide ion Benzyl bromide Benzyl ethyl ether

Benzylic halides resemble allylic halides in the readiness with which they form carbocations. On comparing the rate of S_N1 hydrolysis in aqueous acetone of the following two tertiary chlorides, we find that the benzylic chloride reacts over 600 times faster than does *tert*-butyl chloride.



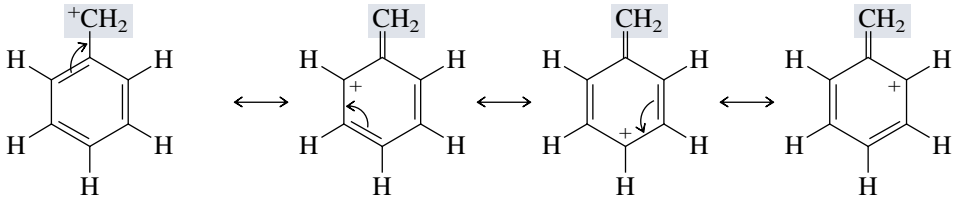
2-Chloro-2-phenylpropane



2-Chloro-2-methylpropane

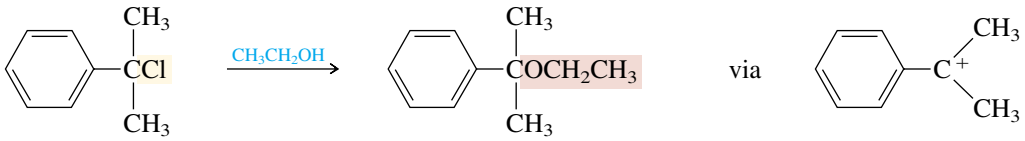
Just as the odd electron in benzyl radical is shared by the carbons ortho and para to the benzylic carbon, the positive charge in benzyl cation is shared by these same positions.

See *Learning By Modeling* for an electrostatic potential map of benzyl cation.



Most stable Lewis structure of benzyl cation

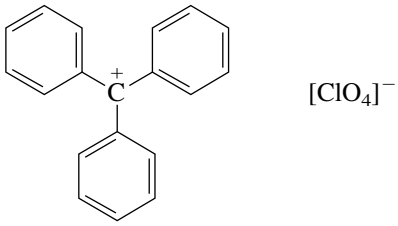
Unlike the case with allylic carbocations, however, dispersal of the positive charge does not result in nucleophilic attack at more than one carbon. There is no "benzylic rearrangement" analogous to allylic rearrangement (Section 10.2), because the aromatic stabilization would be lost if the nucleophile became bonded to one of the ring carbons. Thus, when conditions are chosen that favor S_N1 substitution over E2 elimination (solvolysis, weakly basic nucleophile), benzylic halides give a single substitution product in high yield.



2-Chloro-2-phenylpropane 2-Ethoxy-2-phenylpropane (87%)

The triphenylmethyl group is often referred to as a *trityl* group.

Additional phenyl substituents stabilize carbocations even more. Triphenylmethyl cation is particularly stable. Its perchlorate salt is ionic and stable enough to be isolated and stored indefinitely.

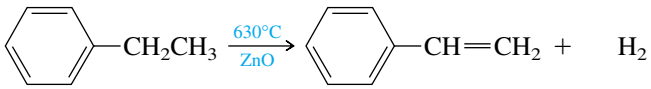


Triphenylmethyl perchlorate

11.15 PREPARATION OF ALKENYLBENZENES

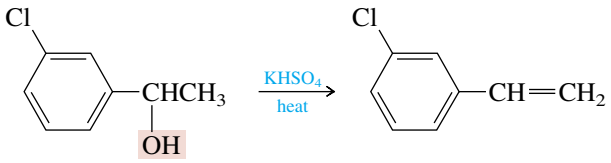
Alkenylbenzenes are prepared by the various methods described in Chapter 5 for the preparation of alkenes: *dehydrogenation, dehydration,* and *dehydrohalogenation.*

Dehydrogenation of alkylbenzenes is not a convenient laboratory method but is used industrially to convert ethylbenzene to styrene.

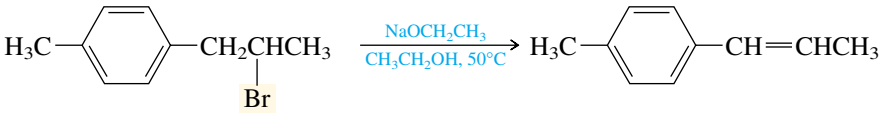


Ethylbenzene Styrene Hydrogen

Acid-catalyzed dehydration of benzylic alcohols is a useful route to alkenylbenzenes, as is dehydrohalogenation under E2 conditions.



1-(*m*-Chlorophenyl)ethanol *m*-Chlorostyrene (80–82%)

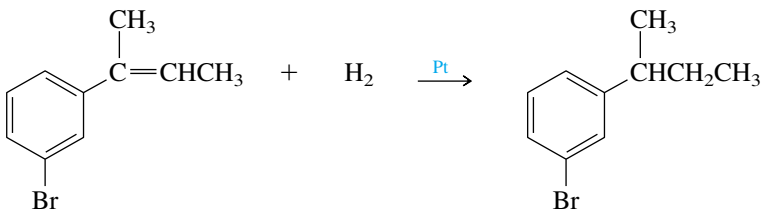


2-Bromo-1-(*p*-methylphenyl)propane 1-(*p*-Methylphenyl)propene (99%)

11.16 ADDITION REACTIONS OF ALKENYLBENZENES

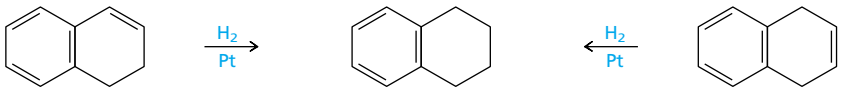
Most of the reactions of alkenes that were discussed in Chapter 6 find a parallel in the reactions of alkenylbenzenes.

Hydrogenation of the side-chain double bond of an alkenylbenzene is much easier than hydrogenation of the aromatic ring and can be achieved with high selectivity, leaving the ring unaffected.



2-(*m*-Bromophenyl)-2-butene Hydrogen 2-(*m*-Bromophenyl)butane (92%)

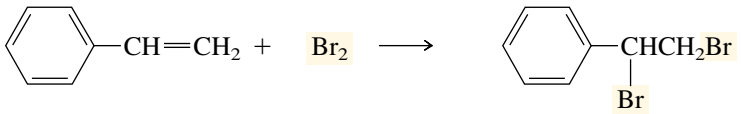
PROBLEM 11.9 Both 1,2-dihydronaphthalene and 1,4-dihydronaphthalene may be selectively hydrogenated to 1,2,3,4-tetrahydronaphthalene.



1,2-Dihydronaphthalene 1,2,3,4-Tetrahydronaphthalene 1,4-Dihydronaphthalene

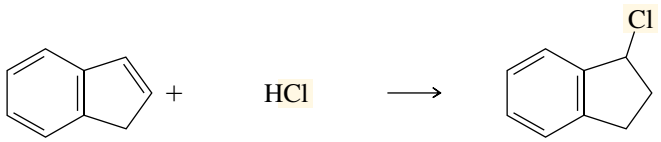
One of these isomers has a heat of hydrogenation of 101 kJ/mol (24.1 kcal/mol), and the heat of hydrogenation of the other is 113 kJ/mol (27.1 kcal/mol). Match the heat of hydrogenation with the appropriate dihydronaphthalene.

The double bond in the alkenyl side chain undergoes addition reactions that are typical of alkenes when treated with electrophilic reagents.



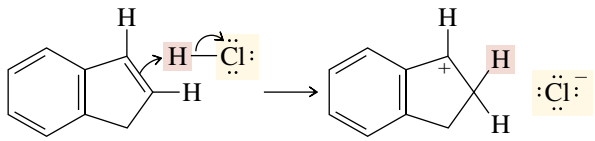
Styrene Bromine 1,2-Dibromo-1-phenylethane (82%)

The regioselectivity of electrophilic addition is governed by the ability of an aromatic ring to stabilize an adjacent carbocation. This is clearly seen in the addition of hydrogen chloride to indene. Only a single chloride is formed.



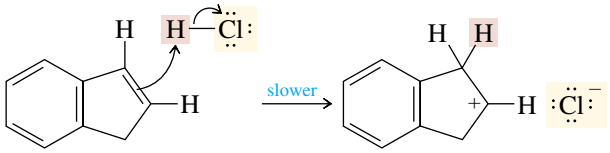
Indene Hydrogen chloride 1-Chloroindane (75–84%)

Only the benzylic chloride is formed, because protonation of the double bond occurs in the direction that gives a carbocation that is both secondary and benzylic.



Carbocation that leads to observed product

Protonation in the opposite direction also gives a secondary carbocation, but it is not benzylic.



Less stable carbocation

This carbocation does not receive the extra increment of stabilization that its benzylic isomer does and so is formed more slowly. The orientation of addition is controlled by

the rate of carbocation formation; the more stable benzylic carbocation is formed faster and is the one that determines the reaction product.

PROBLEM 11.10 Each of the following reactions has been reported in the chemical literature and gives a single organic product in high yield. Write the structure of the product for each reaction.

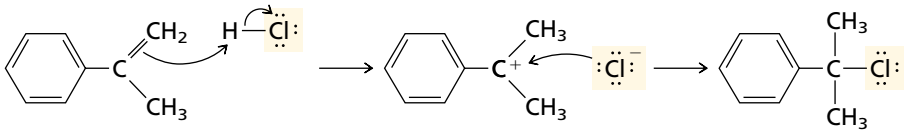
(a) 2-Phenylpropene + hydrogen chloride

(b) 2-Phenylpropene treated with diborane in tetrahydrofuran followed by oxidation with basic hydrogen peroxide

(c) Styrene + bromine in aqueous solution

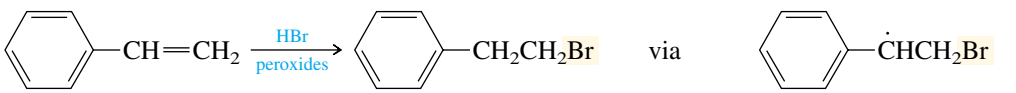
(d) Styrene + peroxybenzoic acid (two organic products in this reaction; identify both by writing a balanced equation.)

SAMPLE SOLUTION (a) Addition of hydrogen chloride to the double bond takes place by way of a tertiary benzylic carbocation.



2-Phenylpropene | Hydrogen chloride | 2-Chloro-2-phenylpropane

In the presence of peroxides, hydrogen bromide adds to the double bond of styrene with a regioselectivity opposite to Markovnikov's rule. The reaction is a free-radical addition, and the regiochemistry is governed by preferential formation of the more stable radical.



Styrene | 1-Bromo-2-phenylethane (major product) | via | 2-Bromo-1-phenylethyl radical (secondary; benzylic)

11.17 POLYMERIZATION OF STYRENE

The annual production of styrene in the United States is on the order of 8×10^9 lb, with about 65% of this output used to prepare polystyrene plastics and films. Styrofoam coffee cups are made from polystyrene. Polystyrene can also be produced in a form that is very strong and impact-resistant and is used widely in luggage, television and radio cabinets, and furniture.

As described in the box "Diene Polymers" in Chapter 10, most synthetic rubber is a copolymer of styrene and 1,3-butadiene.

Polymerization of styrene is carried out under free-radical conditions, often with benzoyl peroxide as the initiator. Figure 11.10 illustrates a step in the growth of a polystyrene chain by a mechanism analogous to that of the polymerization of ethylene (Section 6.21).

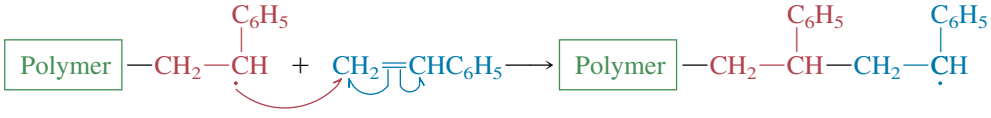


FIGURE 11.10 Chain propagation step in polymerization of styrene. The growing polymer chain has a free-radical site at the benzylic carbon. It adds to a molecule of styrene to extend the chain by one styrene unit. The new polymer chain is also a benzylic radical; it attacks another molecule of styrene, and the process repeats over and over again.

11.18 CYCLOBUTADIENE AND CYCLOOCTATETRAENE

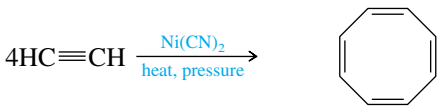
During our discussion of benzene and its derivatives, it may have occurred to you that cyclobutadiene and cyclooctatetraene might be stabilized by π electron delocalization in a manner analogous to that of benzene.

Cyclobutadiene Cyclooctatetraene

The same thought occurred to early chemists. However, the complete absence of naturally occurring compounds based on cyclobutadiene and cyclooctatetraene contrasted starkly with the abundance of compounds based on the benzene nucleus. Attempts to synthesize cyclobutadiene and cyclooctatetraene met with failure and reinforced the growing conviction that these compounds would prove to be quite unlike benzene if, in fact, they could be isolated at all.

Willstätter's most important work, for which he won the 1915 Nobel Prize in chemistry, was directed toward determining the structure of chlorophyll.

The first breakthrough came in 1911 when Richard Willstätter prepared cyclooctatetraene by a lengthy degradation of *pseudopelletierine,* a natural product obtained from the bark of the pomegranate tree. Nowadays, cyclooctatetraene is prepared from acetylene in a reaction catalyzed by nickel cyanide.



Acetylene Cyclooctatetraene (70%)

Thermochemical measurements suggest a value of only about 20 kJ/mol (about 5 kcal/mol) for the resonance energy of cyclooctatetraene, far less than the aromatic stabilization of benzene (152 kJ/mol; 36 kcal/mol).

PROBLEM 11.11 Both cyclooctatetraene and styrene have the molecular formula C_8H_8 and undergo combustion according to the equation

$$C_8H_8 + 10O_2 \longrightarrow 8CO_2 + 4H_2O$$

The measured heats of combustion are 4393 and 4543 kJ/mol (1050 and 1086 kcal/mol). Which heat of combustion belongs to which compound?

Structural studies confirm the absence of appreciable π electron delocalization in cyclooctatetraene. Its structure is as pictured in Figure 11.11—a *nonplanar* hydrocarbon with four short carbon–carbon bond distances and four long carbon–carbon bond distances. Cyclooctatetraene is satisfactorily represented by a single Lewis structure having alternating single and double bonds in a tub-shaped eight-membered ring.

All the evidence indicates that cyclooctatetraene lacks the "special stability" of benzene, and is more appropriately considered as a conjugated polyene than as an aromatic hydrocarbon.

Cyclobutadiene escaped chemical characterization for more than 100 years. Despite numerous attempts, all synthetic efforts met with failure. It became apparent not only that cyclobutadiene was not aromatic but that it was exceedingly unstable. Beginning in the 1950s, a variety of novel techniques succeeded in generating cyclobutadiene as a transient, reactive intermediate.

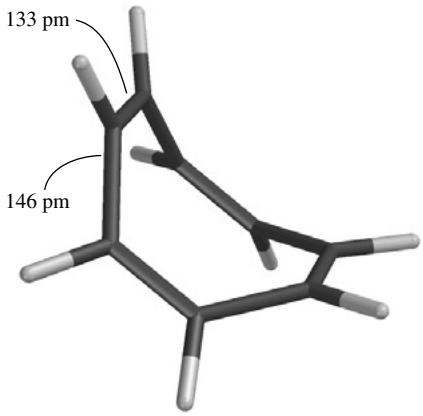
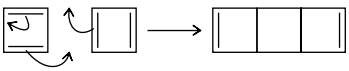


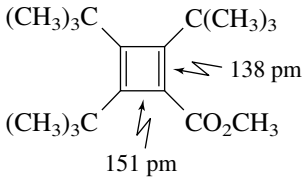
FIGURE 11.11 Molecular geometry of cyclooctatetraene. The ring is not planar, and the bond distances alternate between short double bonds and long single bonds.

PROBLEM 11.12 One of the chemical properties that make cyclobutadiene difficult to isolate is that it reacts readily with itself to give a dimer:



What reaction of dienes does this resemble?

Structural studies of cyclobutadiene and some of its derivatives reveal a pattern of alternating single and double bonds and a rectangular, rather than a square, shape. Bond distances in a stable, highly substituted derivative of cyclobutadiene illustrate this pattern of alternating short and long ring bonds.



Methyl 2,3,4-tri-*tert*-butylcyclobutadiene-1-carboxylate

Thus cyclobutadiene, like cyclooctatetraene, is not aromatic. *Cyclic conjugation, although necessary for aromaticity, is not sufficient for it.* Some other factor or factors must contribute to the special stability of benzene and its derivatives. To understand these factors, let's return to the molecular orbital description of benzene.

11.19 HÜCKEL'S RULE: ANNULENES

One of the early successes of molecular orbital theory occurred in 1931 when Erich Hückel discovered an interesting pattern in the π orbital energy levels of benzene, cyclobutadiene, and cyclooctatetraene. By limiting his analysis to monocyclic conjugated polyenes and restricting the structures to planar geometries, Hückel found that such hydrocarbons are characterized by a set of π molecular orbitals in which one orbital is lowest in energy, another is highest in energy, and the rest are distributed in pairs between them.

Hückel was a German physical chemist. Before his theoretical studies of aromaticity, Hückel collaborated with Peter Debye in developing what remains the most widely accepted theory of electrolyte solutions.

The arrangements of π orbitals for cyclobutadiene, benzene, and cyclooctatetraene as determined by Hückel are presented in Figure 11.12. Their interpretation can be summarized as follows:

Cyclobutadiene According to the molecular orbital picture, square planar cyclobutadiene should be a diradical (have two unpaired electrons). The four π electrons are distributed so that two are in the lowest energy orbital and, in accordance with Hund's rule, each of the two equal-energy nonbonding orbitals is half-filled. (Remember, Hund's rule tells us that when two orbitals have the same energy, each one is half-filled before either of them reaches its full complement of two electrons.)

Benzene As seen earlier in Figure 11.4 (Section 11.6), the six π electrons of benzene are distributed in pairs among its three bonding orbitals. All the bonding orbitals are occupied, and all the electron spins are paired.

Cyclooctatetraene Six of the eight π electrons of cyclooctatetraene occupy three bonding orbitals. The remaining two π electrons occupy, one each, the two equal-energy nonbonding orbitals. Planar cyclooctatetraene should, like square cyclobutadiene, be a diradical.

As it turns out, neither cyclobutadiene nor cyclooctatetraene is a diradical in its most stable electron configuration. The Hückel approach treats them as planar regular polygons. Because the electron configurations associated with these geometries are not particularly stable, cyclobutadiene and cyclooctatetraene adopt structures other than planar regular polygons. Cyclobutadiene, rather than possessing a square shape with two unpaired electron spins, is a spin-paired rectangular molecule. Cyclooctatetraene is nonplanar, with all its π electrons paired in alternating single and double bonds.

On the basis of his analysis Hückel proposed that only certain numbers of π electrons could lead to aromatic stabilization. Only when the number of π electrons is 2, 6, 10, 14, and so on, can a closed-shell electron configuration be realized. These results are summarized in **Hückel's rule: Among planar, monocyclic, fully conjugated polyenes, only those possessing $(4n + 2)$ π electrons, where n is an integer, will have special aromatic stability.**

Hückel's rule should not be applied to polycyclic aromatic hydrocarbons (Section 11.8). Hückel's analysis is limited to monocyclic systems.

The general term **annulene** has been coined to apply to completely conjugated monocyclic hydrocarbons. A numerical prefix specifies the number of carbon atoms. Cyclobutadiene is [4]-annulene, benzene is [6]-annulene, and cyclooctatetraene is [8]-annulene.

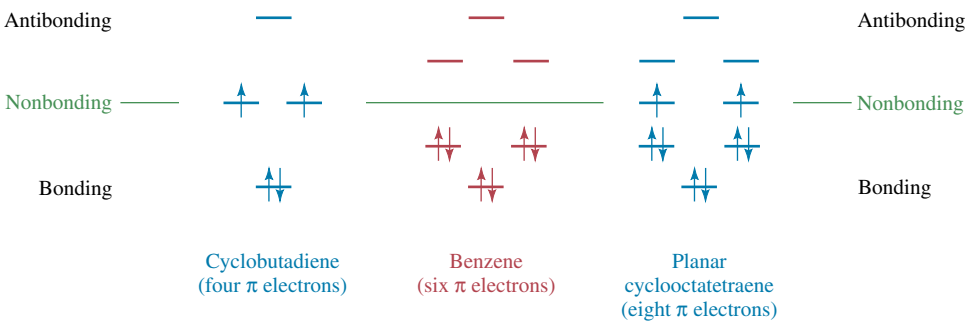
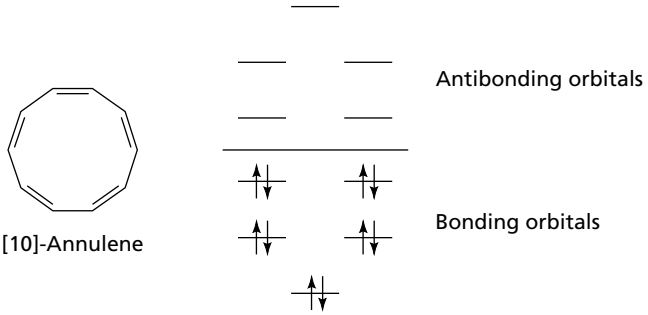


FIGURE 11.12 Distribution of π molecular orbitals and π electrons in cyclobutadiene, benzene, and planar cyclooctatetraene.

PROBLEM 11.13 Represent the π electron distribution among the π orbitals in
(a) [10]-Annulene (b) [12]-Annulene

SAMPLE SOLUTION (a) [10]-Annulene has ten carbons: ten π orbitals and ten π electrons. Like benzene, it should have a closed-shell electron configuration with all its bonding orbitals doubly occupied.



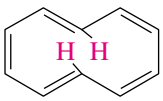
[10]-Annulene

The prospect of observing aromatic character in conjugated polyenes having 10, 14, 18, and so on π electrons spurred efforts toward the synthesis of higher annulenes. A problem immediately arises in the case of the all-cis isomer of [10]-annulene, the structure of which is shown in the preceding problem. Geometry requires a ten-sided regular polygon to have 144° bond angles; sp^2 hybridization at carbon requires 120° bond angles. Therefore, aromatic stabilization due to conjugation in all-*cis*-[10]-annulene is opposed by the destabilizing effect of 24° of angle strain at each of its carbon atoms. All-*cis*-[10]-annulene has been prepared. It is not very stable and is highly reactive.

The size of each angle of a regular polygon is given by the expression

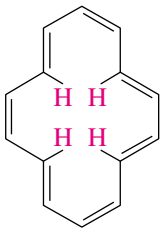
$$180° \times \frac{(\text{number of sides}) - 2}{(\text{number of sides})}$$

A second isomer of [10]-annulene (the cis, trans, cis, cis, trans stereoisomer) can have bond angles close to 120° but is destabilized by a close contact between two hydrogens directed toward the interior of the ring. In order to minimize the van der Waals strain between these hydrogens, the ring adopts a nonplanar geometry, which limits its ability to be stabilized by π electron delocalization. It, too, has been prepared and is not very stable. Similarly, the next higher $(4n + 2)$ system, [14]-annulene, is also somewhat destabilized by van der Waals strain and is nonplanar.



cis,trans,cis,cis,trans-[10]-Annulene

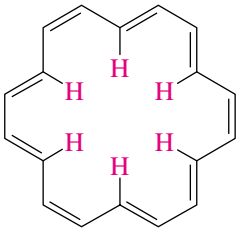
Planar geometry required for aromaticity destabilized by van der Waals repulsions between indicated hydrogens



[14]-Annulene

When the ring contains 18 carbon atoms, it is large enough to be planar while still allowing its interior hydrogens to be far enough apart that they do not interfere with one another. The [18]-annulene shown is planar or nearly so and has all its carbon–carbon bond distances in the range 137–143 pm—very much like those of benzene. Its resonance energy is estimated to be about 418 kJ/mol (100 kcal/mol). Although its structure and resonance energy attest to the validity of Hückel's rule, which predicts "special stability" for [18]-annulene, its chemical reactivity does not. [18]-Annulene

behaves more like a polyene than like benzene in that it is hydrogenated readily, undergoes addition rather than substitution with bromine, and forms a Diels–Alder adduct with maleic anhydride.

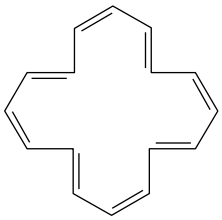


No serious repulsions among six interior hydrogens; molecule is planar and aromatic.

[18]-Annulene

Molecular models of [10]-, [14]-, [16]-, and [18]-annulene can be inspected on *Learning By Modeling*.

According to Hückel's rule, annulenes with $4n$ π electrons are not aromatic. Cyclobutadiene and cyclooctatetraene are [$4n$]-annulenes, and their properties are more in accord with their classification as cyclic polyenes than as aromatic hydrocarbons. Among higher [$4n$]-annulenes, [16]-annulene has been prepared. [16]-Annulene is not planar and shows a pattern of alternating short (average 134 pm) and long (average 146 pm) bonds typical of a nonaromatic cyclic polyene.



[16]-Annulene

PROBLEM 11.14 What does a comparison of the heats of combustion of benzene (3265 kJ/mol; 781 kcal/mol), cyclooctatetraene (4543 kJ/mol; 1086 kcal/mol), [16]-annulene (9121 kJ/mol; 2182 kcal/mol), and [18]-annulene (9806 kJ/mol; 2346 kcal/mol) reveal?

Most of the synthetic work directed toward the higher annulenes was carried out by Franz Sondheimer and his students, first at Israel's Weizmann Institute and later at the University of London. Sondheimer's research systematically explored the chemistry of these hydrocarbons and provided experimental verification of Hückel's rule.

11.20 AROMATIC IONS

Hückel realized that his molecular orbital analysis of conjugated systems could be extended beyond the realm of neutral hydrocarbons. He pointed out that cycloheptatrienyl cation contained a π system with a closed-shell electron configuration similar to that of benzene (Figure 11.13). Cycloheptatrienyl cation has a set of seven π molecular orbitals. Three of these are bonding and contain the six π electrons of the cation. These six π electrons are delocalized over seven carbon atoms, each of which contributes one $2p$ orbital to a planar, monocyclic, completely conjugated π system. Therefore, cycloheptatrienyl cation should be aromatic. It should be appreciably more stable than expected on the basis of any Lewis structure written for it.

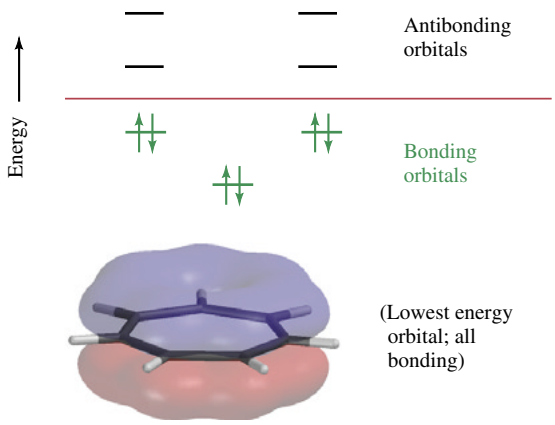
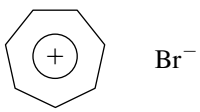


FIGURE 11.13 The π molecular orbitals of cycloheptatrienyl (tropylium) cation.

Cycloheptatriene

Cycloheptatrienyl cation
(commonly referred to as
tropylium cation)

It's important to recognize the difference between the hydrocarbon cycloheptatriene and cycloheptatrienyl (tropylium) cation. The carbocation, as we have just stated, is aromatic, whereas cycloheptatriene is not. Cycloheptatriene has six π electrons in a conjugated system, but its π system does not close upon itself. The ends of the triene system are joined by an sp^3-hybridized carbon, which prevents continuous electron delocalization. The ends of the triene system in the carbocation are joined by an sp^2-hybridized carbon, which contributes an empty *p* orbital, and allows continuous delocalization of the six π electrons. When we say cycloheptatriene is not aromatic but tropylium cation is, we are not comparing the stability of the two to each other. Cycloheptatriene is a stable hydrocarbon but does not possess the *special stability* required to be called *aromatic.* Tropylium cation, although aromatic, is still a carbocation and reasonably reactive toward nucleophiles. Its special stability does not imply a rocklike passivity but rather a much greater ease of formation than expected on the basis of the Lewis structure drawn for it. A number of observations indicate that tropylium cation is far more stable than most other carbocations. To emphasize the aromatic nature of tropylium cation, it is sometimes written in the Robinson manner, representing the aromatic sextet with a circle in the ring and including a positive charge within the circle.

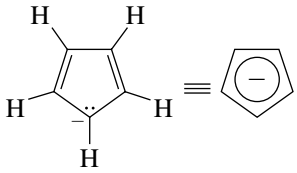


Tropylium bromide

Tropylium bromide was first prepared, but not recognized as such, in 1891. The work was repeated in 1954, and the ionic properties of tropylium bromide were demonstrated. The ionic properties of tropylium bromide are apparent in its unusually high melting point (203°C), its solubility in water, and its complete lack of solubility in diethyl ether.

PROBLEM 11.15 Write resonance structures for tropylium cation sufficient to show the delocalization of the positive charge over all seven carbons.

Cyclopentadienide anion is an *aromatic anion.* It has six π electrons delocalized over a completely conjugated planar monocyclic array of five sp^2-hybridized carbon atoms.

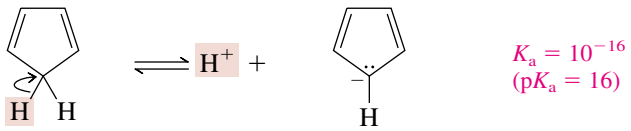


Cyclopentadienide anion

PROBLEM 11.16 Write resonance structures for cyclopentadienide anion sufficient to show the delocalization of the negative charge over all five carbons.

Figure 11.14 presents Hückel's depiction of the molecular orbitals of cyclopentadienide anion. Like benzene and tropylium cation, cyclopentadienide anion has a closed-shell configuration of six π electrons.

A convincing demonstration of the stability of cyclopentadienide anion can be found in the acidity of cyclopentadiene.



Cyclopentadiene Cyclopentadienide anion

$K_a = 10^{-16}$
($pK_a = 16$)

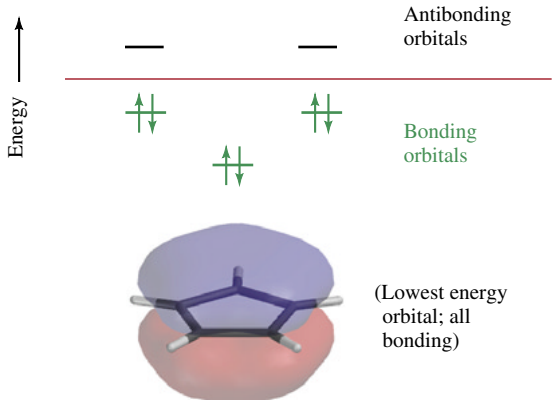
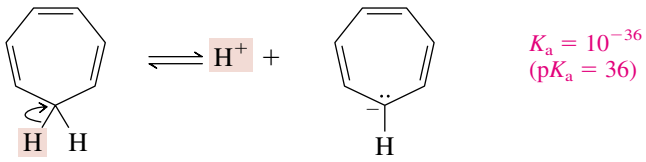


FIGURE 11.14 The π molecular orbitals of cyclopentadienide anion.

Cyclopentadiene is only a slightly weaker acid than water. The equilibrium for its deprotonation is more favorable than for other hydrocarbons because cyclopentadienide anion is aromatic. The contrast is striking when we compare this equilibrium with that for loss of a proton from cycloheptatriene.



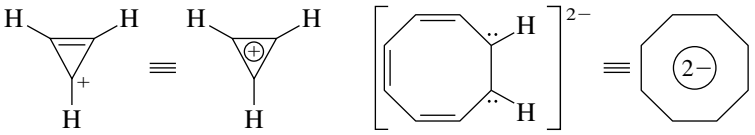
Cycloheptatriene Cycloheptatrienide anion

Resonance structures can be written that show delocalization of the negative charge over all of its seven carbons; nevertheless, because cycloheptatrienide anion contains *eight π electrons,* it is not aromatic. The equilibrium constant for formation from the parent hydrocarbon is more favorable by 10^{20} (20 pK_a units) for the aromatic cyclopentadienide anion than for the nonaromatic cycloheptatrienide anion.

PROBLEM 11.17 A standard method for the preparation of sodium cyclopentadienide (C_5H_5Na) is by reaction of cyclopentadiene with a solution of sodium amide in liquid ammonia. Write a balanced equation for this reaction.

Hückel's rule is now taken to apply to planar, monocyclic, completely conjugated systems generally, not just to neutral hydrocarbons. **A planar, monocyclic, continuous system of *p* orbitals possesses aromatic stability when it contains (4*n* + 2) π electrons.**

Other aromatic ions include cyclopropenyl cation (two π electrons) and cyclooctatetraene dianion (ten π electrons).

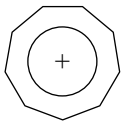


Cyclopropenyl cation Cyclooctatetraene dianion

Here, liberties have been taken with the Robinson symbol. Instead of restricting its use to a sextet of electrons, organic chemists have come to adopt it as an all-purpose symbol for cyclic electron delocalization.

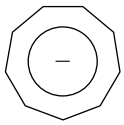
PROBLEM 11.18 Is either of the following ions aromatic?

(a)



Cyclononatetraenyl cation

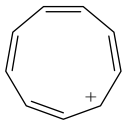
(b)



Cyclononatetraenide anion

SAMPLE SOLUTION (a) The crucial point is the number of π electrons in a cyclic conjugated system. If there are (4*n* + 2) π electrons, the ion is aromatic. Electron

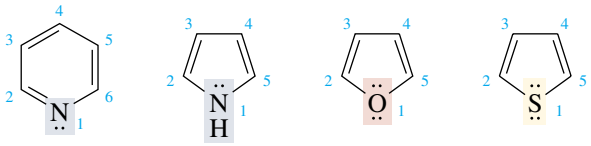
counting is easiest if we write the ion as a single Lewis structure and remember that each double bond contributes two π electrons, a negatively charged carbon contributes two, and a positively charged carbon contributes none.



Cyclononatetraenyl cation has eight π electrons; it is *not aromatic.*

11.21 HETEROCYCLIC AROMATIC COMPOUNDS

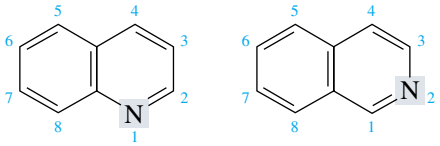
Cyclic compounds that contain at least one atom other than carbon within their ring are called **heterocyclic compounds,** and those that possess aromatic stability are called **heterocyclic aromatic compounds.** Some representative heterocyclic aromatic compounds are *pyridine, pyrrole, furan,* and *thiophene.* The structures and the IUPAC numbering system used in naming their derivatives are shown. In their stability and chemical behavior, all these compounds resemble benzene more than they resemble alkenes.



Pyridine Pyrrole Furan Thiophene

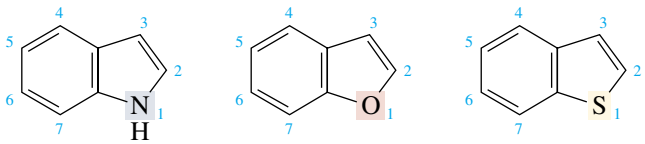
Pyridine, pyrrole, and thiophene, like benzene, are present in coal tar. Furan is prepared from a substance called *furfural* obtained from corncobs.

Heterocyclic aromatic compounds can be polycyclic as well. A benzene ring and a pyridine ring, for example, can share a common side in two different ways. One way gives a compound called *quinoline;* the other gives *isoquinoline.*



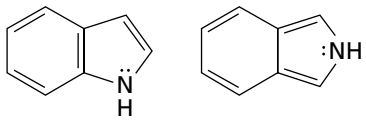
Quinoline Isoquinoline

Analogous compounds derived by fusion of a benzene ring to a pyrrole, furan, or thiophene nucleus are called *indole, benzofuran,* and *benzothiophene.*



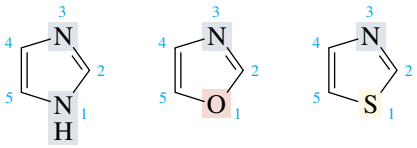
Indole Benzofuran Benzothiophene

PROBLEM 11.19 Unlike quinoline and isoquinoline, which are of comparable stability, the compounds indole and isoindole are quite different from each other. Which one is more stable? Explain the reason for your choice.



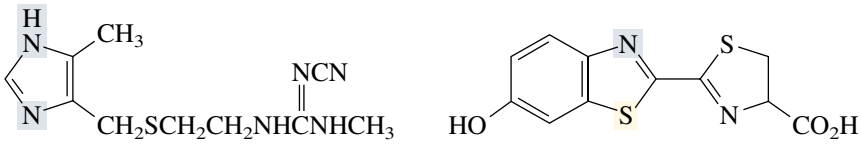
Indole Isoindole

A large group of heterocyclic aromatic compounds are related to pyrrole by replacement of one of the ring carbons β to nitrogen by a second heteroatom. Compounds of this type are called *azoles.*



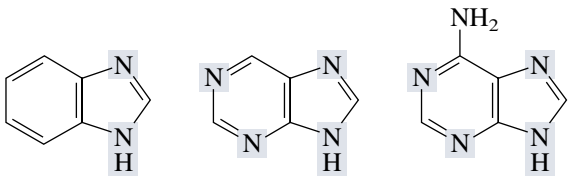
Imidazole Oxazole Thiazole

A widely prescribed drug for the treatment of gastric ulcers has the generic name *cimetidine* and is a synthetic imidazole derivative. *Firefly luciferin* is a thiazole derivative that is the naturally occurring light-emitting substance present in fireflies.



Cimetidine Firefly luciferin

Firefly luciferin is an example of an azole that contains a benzene ring fused to the five-membered ring. Such structures are fairly common. Another example is *benzimidazole,* present as a structural unit in vitamin B_{12}. Some compounds related to benzimidazole include *purine* and its amino-substituted derivative *adenine,* one of the so-called heterocyclic bases found in DNA and RNA (Chapter 27).



Benzimidazole Purine Adenine

PROBLEM 11.20 Can you deduce the structural formulas of *benzoxazole* and *benzothiazole?*

The structural types described in this section are but a tiny fraction of those possible. The chemistry of heterocyclic aromatic compounds is a rich and varied field with numerous applications.

11.22 HETEROCYCLIC AROMATIC COMPOUNDS AND HÜCKEL'S RULE

Hückel's rule can be extended to heterocyclic aromatic compounds. A single heteroatom can contribute either 0 or 2 of its lone-pair electrons as needed to the π system so as to satisfy the $(4n + 2)$ π electron requirement. The lone pair in pyridine, for example, is associated entirely with nitrogen and is not delocalized into the aromatic π system. As shown in Figure 11.15*a,* pyridine is simply a benzene ring in which a nitrogen atom has replaced a CH group. The nitrogen is sp^2-hybridized, and the three double bonds of the ring contribute the necessary six π electrons to make pyridine a heterocyclic aromatic compound. The unshared electron pair of nitrogen occupies an sp^2 orbital in the plane of the ring, not a *p* orbital aligned with the π system.

In pyrrole, on the other hand, the unshared pair belonging to nitrogen must be added to the four π electrons of the two double bonds in order to meet the six-π-electron requirement. As shown in Figure 11.15*b,* the nitrogen of pyrrole is sp^2-hybridized and the pair of electrons occupies a *p* orbital where both electrons can participate in the aromatic π system.

Pyridine and pyrrole are both weak bases, but pyridine is much more basic than pyrrole. When pyridine is protonated, its unshared pair is used to bond to a proton and, since the unshared pair is not involved in the π system, the aromatic character of the ring is little affected. When pyrrole acts as a base, the two electrons used to form a bond to hydrogen must come from the π system, and the aromaticity of the molecule is sacrificed on protonation.

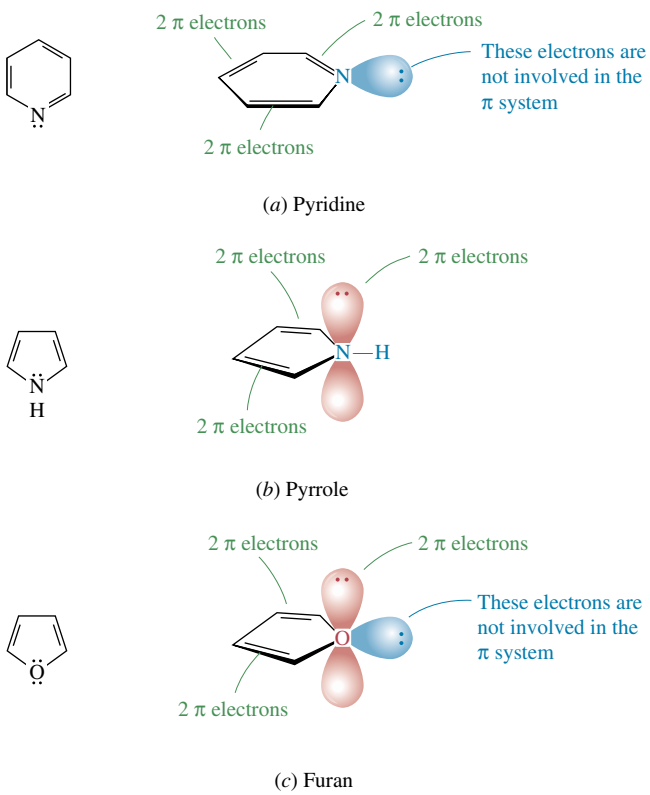
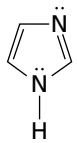


FIGURE 11.15 (*a*) Pyridine has six π electrons plus an unshared pair in a nitrogen sp^2 orbital. (*b*) Pyrrole has six π electrons. (*c*) Furan has six π electrons plus an unshared pair in an oxygen sp^2 orbital, which is perpendicular to the π system and does not interact with it.

PROBLEM 11.21 Imidazole is a much stronger base than pyrrole. Predict which nitrogen is protonated when imidazole reacts with an acid, and write a structural formula for the species formed.



Imidazole

The oxygen in furan has two unshared electron pairs (Figure 11.15*c*). One pair is like the pair in pyrrole, occupying a *p* orbital and contributing two electrons to complete the six-π-electron requirement for aromatic stabilization. The other electron pair in furan is an "extra" pair, not needed to satisfy the $4n + 2$ rule for aromaticity, and occupies an sp^2-hybridized orbital like the unshared pair in pyridine.

The bonding in thiophene is similar to that of furan.

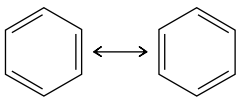
11.23 SUMMARY

Section 11.1 Benzene is the parent of a class of hydrocarbons called **arenes,** or **aromatic hydrocarbons.**

Section 11.2 An important property of aromatic hydrocarbons is that they are much more stable and less reactive than other unsaturated compounds. Benzene, for example, does not react with many of the reagents that react rapidly with alkenes. When reaction does take place, substitution rather than addition is observed. The Kekulé formulas for benzene seem inconsistent with its low reactivity and with the fact that all of the C—C bonds in benzene are the same length (140 pm).

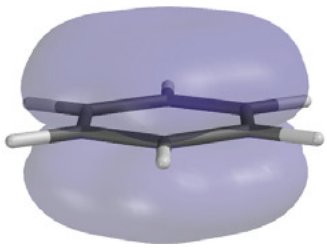
The article "A History of the Structural Theory of Benzene—The Aromatic Sextet and Hückel's Rule" in the February 1997 issue of the *Journal of Chemical Education* (pp. 194–201) is a rich source of additional information about this topic.

Section 11.3 One explanation for the structure and stability of benzene and other arenes is based on resonance, according to which benzene is regarded as a hybrid of the two Kekulé structures.



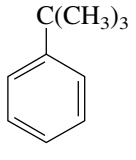
Section 11.4 The extent to which benzene is more stable than either of the Kekulé structures is its **resonance energy,** which is estimated to be 125–150 kJ/mol (30–36 kcal/mol) from heats of hydrogenation data.

Section 11.5 According to the orbital hybridization model, benzene has six π electrons, which are shared by all six sp^2-hybridized carbons. Regions of high π electron density are located above and below the plane of the ring.

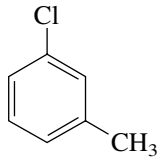


Section 11.6 A molecular orbital description of benzene has three π orbitals that are bonding and three that are antibonding. Each of the bonding orbitals is fully occupied (two electrons each), and the antibonding orbitals are vacant.

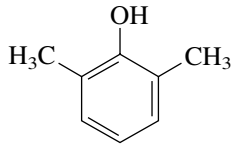
Section 11.7 Many aromatic compounds are simply substituted derivatives of benzene and are named accordingly. Many others have names based on some other parent aromatic compound.



tert-Butylbenzene

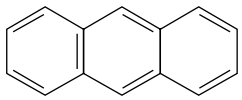


m-Chlorotoluene



2,6-Dimethylphenol

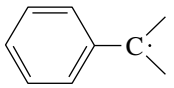
Section 11.8 **Polycyclic aromatic hydrocarbons,** of which anthracene is an example, contain two or more benzene rings fused together.



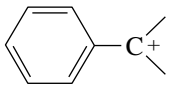
Anthracene

Section 11.9 The physical properties of arenes resemble those of other hydrocarbons.

Section 11.10 Chemical reactions of arenes can take place on the ring itself, or on a side chain. Reactions that take place on the side chain are strongly influenced by the stability of **benzylic radicals** and **benzylic carbocations.**

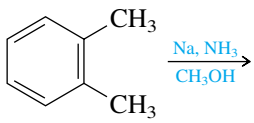


Benzylic free radical

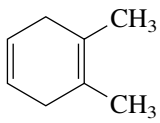


Benzylic carbocation

Section 11.11 An example of a reaction in which the ring itself reacts is the **Birch reduction.** The ring of an arene is reduced to a nonconjugated diene by treatment with a Group I metal (usually sodium) in liquid ammonia in the presence of an alcohol.



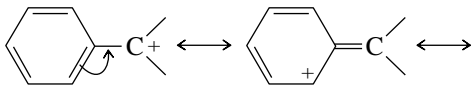
o-Xylene



1,2-Dimethyl-1,4-cyclohexadiene (92%)

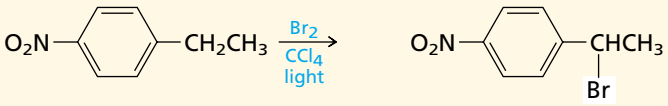
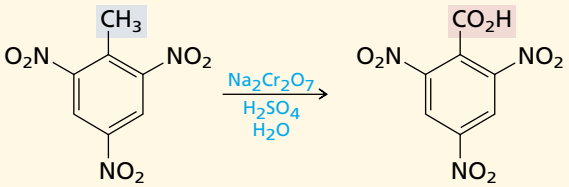
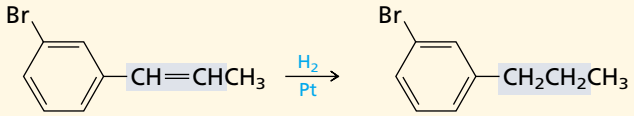
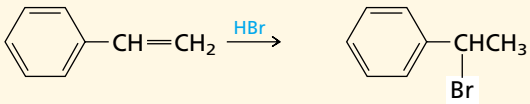
Sections 11.12–11.13 Free-radical halogenation and oxidation involve reactions at the benzylic carbon. See Table 11.2.

Section 11.14 Benzylic carbocations are intermediates in S_N1 reactions of benzylic halides and are stabilized by electron delocalization.

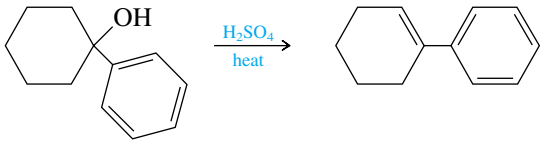


and so on

TABLE 11.2 Reactions Involving Alkyl and Alkenyl Side Chains in Arenes and Arene Derivatives

Reaction (section) and comments	General equation and specific example
Halogenation (Section 11.12) Free-radical halogenation of alkylbenzenes is highly selective for substitution at the benzylic position. In the example shown, elemental bromine was used. Alternatively, *N*-bromosuccinimide is a convenient reagent for benzylic bromination.	$ArCHR_2 \xrightarrow[\text{benzoyl peroxide}\ CCl_4,\ 80°C]{NBS} ArCR_2(Br)$ Arene → 1-Arylalkyl bromide  *p*-Ethylnitrobenzene → 1-(*p*-Nitrophenyl)ethyl bromide (77%)
Oxidation (Section 11.13) Oxidation of alkylbenzenes occurs at the benzylic position of the alkyl group and gives a benzoic acid derivative. Oxidizing agents include sodium or potassium dichromate in aqueous sulfuric acid. Potassium permanganate ($KMnO_4$) is also an effective oxidant.	$ArCHR_2 \xrightarrow{\text{oxidize}} ArCO_2H$ Arene → Arenecarboxylic acid  2,4,6-Trinitrotoluene → 2,4,6-Trinitrobenzoic acid (57–69%)
Hydrogenation (Section 11.16) Hydrogenation of aromatic rings is somewhat slower than hydrogenation of alkenes, and it is a simple matter to reduce the double bond of an unsaturated side chain in an arene while leaving the ring intact.	$ArCH{=}CR_2 + H_2 \xrightarrow{Pt} ArCH_2CHR_2$ Alkenylarene + Hydrogen → Alkylarene  1-(*m*-Bromophenyl)propene → *m*-Bromopropylbenzene (85%)
Electrophilic addition (Section 11.16) An aryl group stabilizes a benzylic carbocation and controls the regioselectivity of addition to a double bond involving the benzylic carbon. Markovnikov's rule is obeyed.	$ArCH{=}CH_2 \xrightarrow{\delta^+E{-}Y^{\delta-}} ArCH(Y){-}CH_2E$ Alkenylarene → Product of electrophilic addition  Styrene → 1-Phenylethyl bromide (85%)

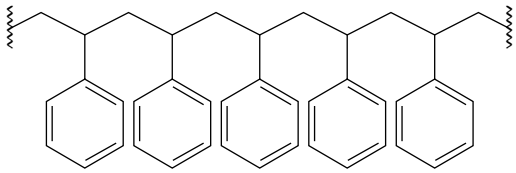
Section 11.15 The simplest alkenylbenzene is styrene ($C_6H_5CH{=}CH_2$). An aryl group stabilizes a double bond to which it is attached. Alkenylbenzenes are usually prepared by dehydration of benzylic alcohols or dehydrohalogenation of benzylic halides.



1-Phenylcyclohexanol 1-Phenylcyclohexene (83%)

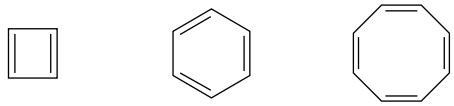
Section 11.16 Addition reactions to alkenylbenzenes occur at the double bond of the alkenyl substituent, and the regioselectivity of electrophilic addition is governed by carbocation formation at the benzylic carbon. See Table 11.2.

Section 11.17 Polystyrene is a widely used vinyl polymer prepared by the free-radical polymerization of styrene.



Polystyrene

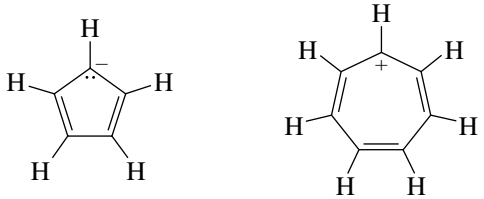
Section 11.18 Although cyclic conjugation is a necessary requirement for aromaticity, this alone is not sufficient. If it were, cyclobutadiene and cyclooctatetraene would be aromatic. They are not.



Cyclobutadiene (not aromatic) Benzene (aromatic) Cyclooctatetraene (not aromatic)

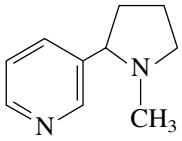
Section 11.19 An additional requirement for aromaticity is that the number of π electrons in conjugated, planar, monocyclic species must be equal to $4n + 2$, where n is an integer. This is called **Hückel's rule.** Benzene, with six π electrons, satisfies Hückel's rule for $n = 1$. Cyclobutadiene (four π electrons) and cyclooctatetraene (eight π electrons) do not. Planar, monocyclic, completely conjugated polyenes are called **annulenes.**

Section 11.20 Species with six π electrons that possess "special stability" include certain ions, such as *cyclopentadienide* anion and *cycloheptatrienyl* cation.



Cyclopentadienide anion (six π electrons) Cycloheptatrienyl cation (six π electrons)

Section 11.21 **Heterocyclic aromatic compounds** are compounds that contain at least one atom other than carbon within an aromatic ring.



Nicotine

Section 11.22 Hückel's rule can be extended to heterocyclic aromatic compounds. Unshared electron pairs of the heteroatom may be used as π electrons as necessary to satisfy the $4n + 2$ rule.

PROBLEMS

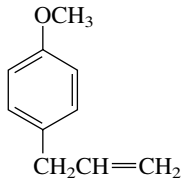
11.22 Write structural formulas and give the IUPAC names for all the isomers of $C_6H_5C_4H_9$ that contain a monosubstituted benzene ring.

11.23 Write a structural formula corresponding to each of the following:

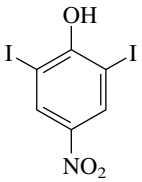
(a) Allylbenzene
(b) (*E*)-1-Phenyl-1-butene
(c) (*Z*)-2-Phenyl-2-butene
(d) (*R*)-1-Phenylethanol
(e) *o*-Chlorobenzyl alcohol
(f) *p*-Chlorophenol
(g) 2-Nitrobenzenecarboxylic acid
(h) *p*-Diisopropylbenzene
(i) 2,4,6-Tribromoaniline
(j) *m*-Nitroacetophenone
(k) 4-Bromo-3-ethylstyrene

11.24 Using numerical locants and the names in Table 11.1 as a guide, give an acceptable IUPAC name for each of the following compounds:

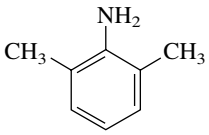
(a) Estragole (principal component of wormwood oil)



(b) Diosphenol (used in veterinary medicine to control parasites in animals)



(c) *m*-Xylidine (used in synthesis of lidocaine, a local anesthetic)



11.25 Write structural formulas and give acceptable names for all the isomeric

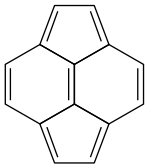
(a) Nitrotoluenes
(b) Dichlorobenzoic acids
(c) Tribromophenols
(d) Tetrafluorobenzenes
(e) Naphthalenecarboxylic acids
(f) Bromoanthracenes

11.26 Mesitylene (1,3,5-trimethylbenzene) is the most stable of the trimethylbenzene isomers. Can you think of a reason why? Which isomer do you think is the least stable? Make a molecular model of each isomer and compare their calculated strain energies with your predictions. Do space-filling models support your explanation?

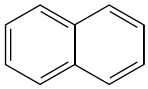
11.27 Which one of the dichlorobenzene isomers does not have a dipole moment? Which one has the largest dipole moment? Compare your answers with the dipole moments calculated using the molecular-modeling software in *Learning By Modeling*.

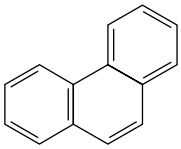
11.28 Identify the longest and the shortest carbon–carbon bonds in styrene. Make reasonable estimates of their bond distances and compare them to the distances in a molecular model.

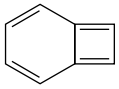
11.29 The resonance form shown is not the most stable one for the compound indicated. Write the most stable resonance form.

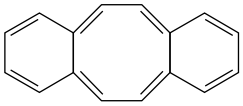


11.30 Each of the following may be represented by at least one alternative resonance structure in which all the six-membered rings correspond to Kekulé forms of benzene. Write such a resonance form for each.

(a) 

(c) 

(b) 

(d) 

The common name of isopropylbenzene is *cumene*.

11.31 Give the structure of the expected product from the reaction of isopropylbenzene with

(a) Hydrogen (3 mol), Pt

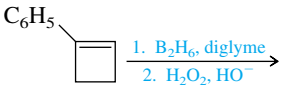
(b) Sodium and ethanol in liquid ammonia

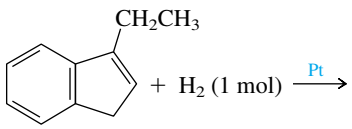
(c) Sodium dichromate, water, sulfuric acid, heat

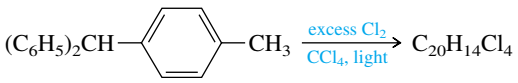
(d) *N*-Bromosuccinimide in CCl_4, heat, benzoyl peroxide

(e) The product of part (d) treated with sodium ethoxide in ethanol

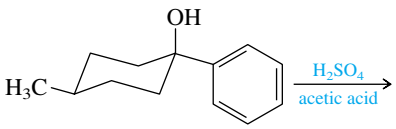
11.32 Each of the following reactions has been described in the chemical literature and gives a single organic product in good yield. Identify the product of each reaction.

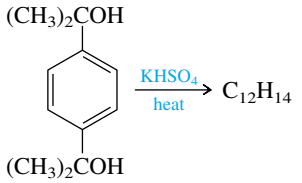
(a) 

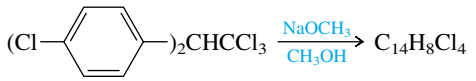
(b) 

(c) 

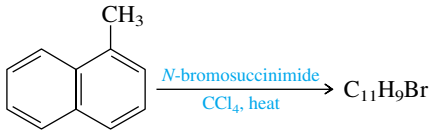
(d) 

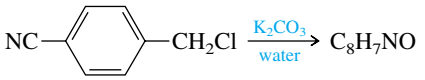
(e) 

(f) 

(g) 

(DDT)

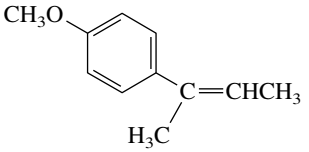
(h) 

(i) 

11.33 A certain compound A, when treated with *N*-bromosuccinimide and benzoyl peroxide under photochemical conditions in refluxing carbon tetrachloride, gave 3,4,5-tribromobenzyl bromide in excellent yield. Deduce the structure of compound A.

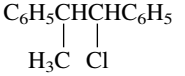
11.34 A compound was obtained from a natural product and had the molecular formula $C_{14}H_{20}O_3$. It contained three methoxy ($-OCH_3$) groups and a $-CH_2CH{=}C(CH_3)_2$ substituent. Oxidation with either chromic acid or potassium permanganate gave 2,3,5-trimethoxybenzoic acid. What is the structure of the compound?

11.35 Hydroboration–oxidation of (*E*)-2-(*p*-anisyl)-2-butene yielded an alcohol A, mp 60°C, in 72% yield. When the same reaction was performed on the *Z* alkene, an isomeric liquid alcohol B was obtained in 77% yield. Suggest reasonable structures for A and B, and describe the relationship between them.

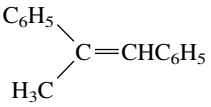


2-(*p*-Anisyl)-2-butene

11.36 Dehydrohalogenation of the diastereomeric forms of 1-chloro-1,2-diphenylpropane is stereospecific. One diastereomer yields (*E*)-1,2-diphenylpropene, and the other yields the *Z* isomer. Which diastereomer yields which alkene? Why?

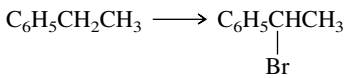


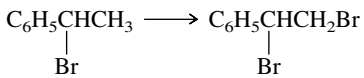
1-Chloro-1,2-diphenylpropane



1,2-Diphenylpropene

11.37 Suggest reagents suitable for carrying out each of the following conversions. In most cases more than one synthetic operation will be necessary.

(a) 

(b) 

(c) $C_6H_5CH{=}CH_2 \longrightarrow C_6H_5C{\equiv}CH$

(d) $C_6H_5C{\equiv}CH \longrightarrow C_6H_5CH_2CH_2CH_2CH_3$

(e) $C_6H_5CH_2CH_2OH \longrightarrow C_6H_5CH_2CH_2C{\equiv}CH$

(f) $C_6H_5CH_2CH_2Br \longrightarrow C_6H_5\underset{\displaystyle OH}{\underset{|}{C}}HCH_2Br$

11.38 The relative rates of reaction of ethane, toluene, and ethylbenzene with bromine atoms have been measured. The most reactive hydrocarbon undergoes hydrogen atom abstraction a million times faster than does the least reactive one. Arrange these hydrocarbons in order of decreasing reactivity.

11.39 Write the principal resonance structures of *o*-methylbenzyl cation and *m*-methylbenzyl cation. Which one has a tertiary carbocation as a contributing resonance form?

11.40 The same anion is formed by loss of the most acidic proton from 1-methyl-1,3-cyclopentadiene as from 5-methyl-1,3-cyclopentadiene. Explain.

11.41 There are two different tetramethyl derivatives of cyclooctatetraene that have methyl groups on four adjacent carbon atoms. They are both completely conjugated and are not stereoisomers. Write their structures.

11.42 Evaluate each of the following processes applied to cyclooctatetraene, and decide whether the species formed is aromatic or not.

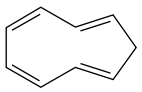
(a) Addition of one more π electron, to give $C_8H_8^-$

(b) Addition of two more π electrons, to give $C_8H_8^{2-}$

(c) Removal of one π electron, to give $C_8H_8^+$

(d) Removal of two π electrons, to give $C_8H_8^{2+}$

11.43 Evaluate each of the following processes applied to cyclononatetraene, and decide whether the species formed is aromatic or not:



Cyclononatetraene

(a) Addition of one more π electron, to give $C_9H_{10}^-$

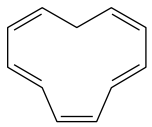
(b) Addition of two more π electrons, to give $C_9H_{10}^{2-}$

(c) Loss of H^+ from the sp^3-hybridized carbon

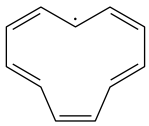
(d) Loss of H^+ from one of the sp^2-hybridized carbons

11.44 From among the molecules and ions shown, all of which are based on cycloundecapentaene, identify those which satisfy the criteria for aromaticity as prescribed by Hückel's rule.

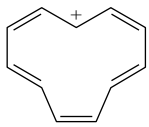
(a) Cycloundecapentaene



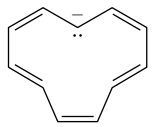
(b) Cycloundecapentaenyl radical



(c) Cycloundecapentaenyl cation



(d) Cycloundecapentaenide anion



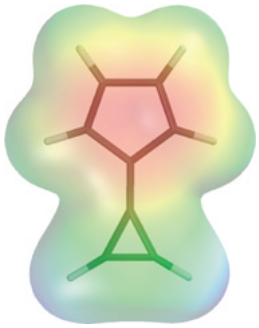
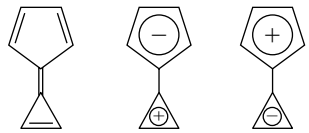


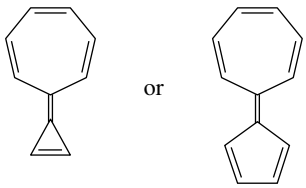
FIGURE 11.16 Electrostatic potential map of calicene (problem 11.45).

11.45 (a) Figure 11.16 is an electrostatic potential map of *calicene,* so named because its shape resembles a chalice (*calix* is the Latin word for "cup"). Both the electrostatic potential map and its calculated dipole moment (μ = 4.3 D) indicate that calicene is an unusually polar hydrocarbon. Which of the dipolar resonance forms, A or B, better corresponds to the electron distribution in the molecule? Why is this resonance form more important than the other?



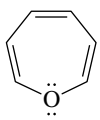
Calicene A B

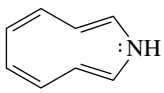
(b) Which one of the following should be stabilized by resonance to a greater extent? (*Hint:* Consider the reasonableness of dipolar resonance forms.)

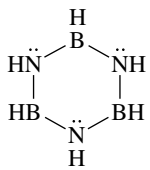


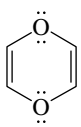
C D

11.46 Classify each of the following heterocyclic molecules as aromatic or not, according to Hückel's rule:

(a) 

(b) 

(c) 

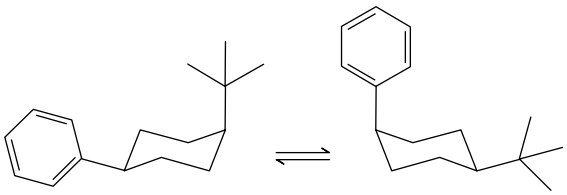
(d) 

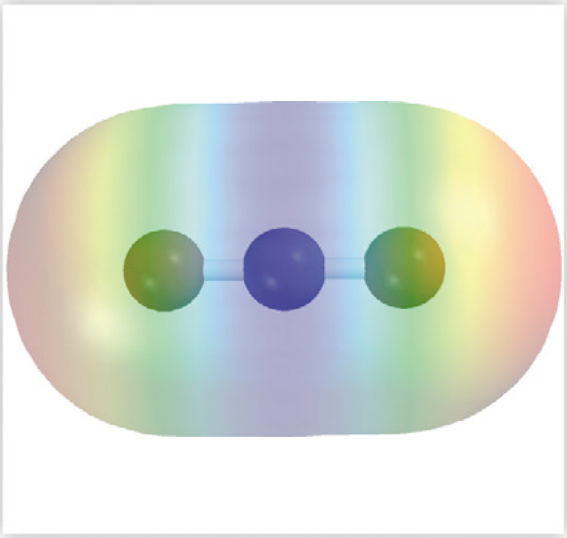
11.47 Pellagra is a disease caused by a deficiency of *niacin* ($C_6H_5NO_2$) in the diet. Niacin can be synthesized in the laboratory by the side-chain oxidation of 3-methylpyridine with chromic acid or potassium permanganate. Suggest a reasonable structure for niacin.

11.48 *Nitroxoline* is the generic name by which 5-nitro-8-hydroxyquinoline is sold as an antibacterial drug. Write its structural formula.

11.49 *Acridine* is a heterocyclic aromatic compound obtained from coal tar that is used in the synthesis of dyes. The molecular formula of acridine is $C_{13}H_9N$, and its ring system is analogous to that of anthracene except that one CH group has been replaced by N. The two most stable resonance structures of acridine are equivalent to each other, and both contain a pyridine-like structural unit. Write a structural formula for acridine.

11.50 Make molecular models of the two chair conformations of *cis*-1-*tert*-butyl-4-phenylcyclohexane. What is the strain energy calculated for each conformation by molecular mechanics? Which has a greater preference for the equatorial orientation, phenyl or *tert*-butyl?



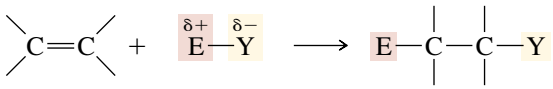


CHAPTER 12

REACTIONS OF ARENES: ELECTROPHILIC AROMATIC SUBSTITUTION

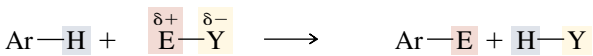
In the preceding chapter the *special stability* of benzene was described, along with reactions in which an aromatic ring was present as a substituent. In the present chapter we move from considering the aromatic ring as a substituent to studying it as a functional group. What kind of reactions are available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

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



Alkene | Electrophilic reagent | Product of electrophilic addition

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



Arene | Electrophilic reagent | Product of electrophilic aromatic substitution

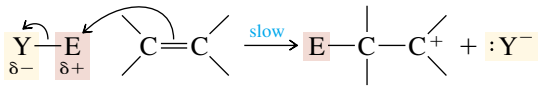
We call this reaction **electrophilic aromatic substitution;** it is one of the fundamental processes of organic chemistry.

12.1 REPRESENTATIVE ELECTROPHILIC AROMATIC SUBSTITUTION REACTIONS OF BENZENE

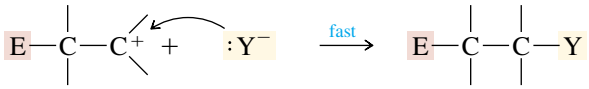
The scope of electrophilic aromatic substitution is quite large; both the arene and the electrophilic reagent are capable of wide variation. Indeed, it is this breadth of scope that makes electrophilic aromatic substitution so important. Electrophilic aromatic substitution is the method by which substituted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

12.2 MECHANISTIC PRINCIPLES OF ELECTROPHILIC AROMATIC SUBSTITUTION

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



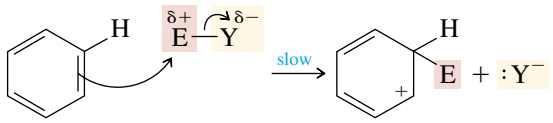
Alkene and electrophile Carbocation



Carbocation Nucleophile Product of electrophilic addition

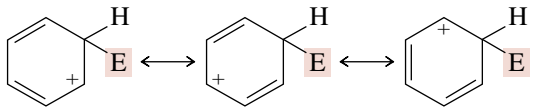
The first step is rate-determining. It is the sharing of the pair of π electrons of the alkene with the electrophile to form a carbocation. Following its formation, the carbocation undergoes rapid capture by some Lewis base present in the medium.

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



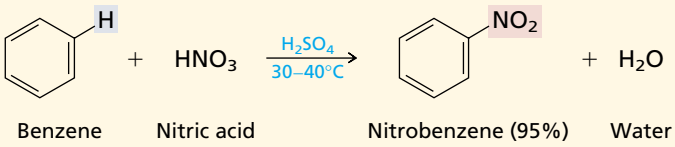
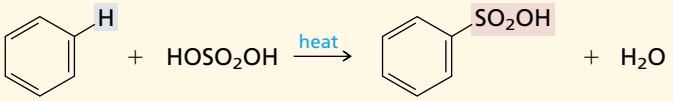
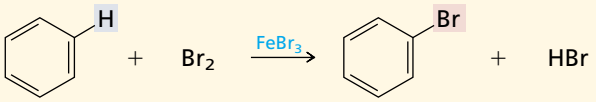
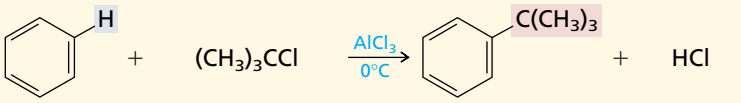
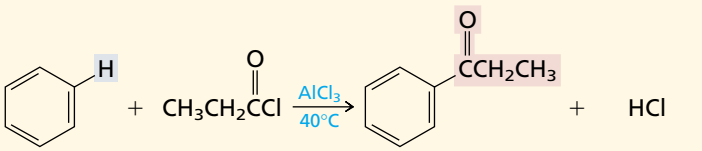
Benzene and electrophile Carbocation

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

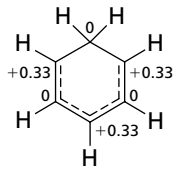


Resonance forms of a cyclohexadienyl cation

TABLE 12.1 Representative Electrophilic Aromatic Substitution Reactions of Benzene

Reaction and comments	Equation
1. Nitration Warming benzene with a mixture of nitric acid and sulfuric acid gives nitrobenzene. A nitro group (—NO_2) replaces one of the ring hydrogens.	 Benzene — Nitric acid — Nitrobenzene (95%) — Water
2. Sulfonation Treatment of benzene with hot concentrated sulfuric acid gives benzenesulfonic acid. A sulfonic acid group (—SO_2OH) replaces one of the ring hydrogens.	 Benzene — Sulfuric acid — Benzenesulfonic acid (100%) — Water
3. Halogenation Bromine reacts with benzene in the presence of iron(III) bromide as a catalyst to give bromobenzene. Chlorine reacts similarly in the presence of iron(III) chloride to give chlorobenzene.	 Benzene — Bromine — Bromobenzene (65–75%) — Hydrogen bromide
4. Friedel–Crafts alkylation Alkyl halides react with benzene in the presence of aluminum chloride to yield alkylbenzenes.	 Benzene — *tert*-Butyl chloride — *tert*-Butylbenzene (60%) — Hydrogen chloride
5. Friedel–Crafts acylation An analogous reaction occurs when acyl halides react with benzene in the presence of aluminum chloride. The products are acylbenzenes.	 Benzene — Propanoyl chloride — 1-Phenyl-1-propanone (88%) — Hydrogen chloride

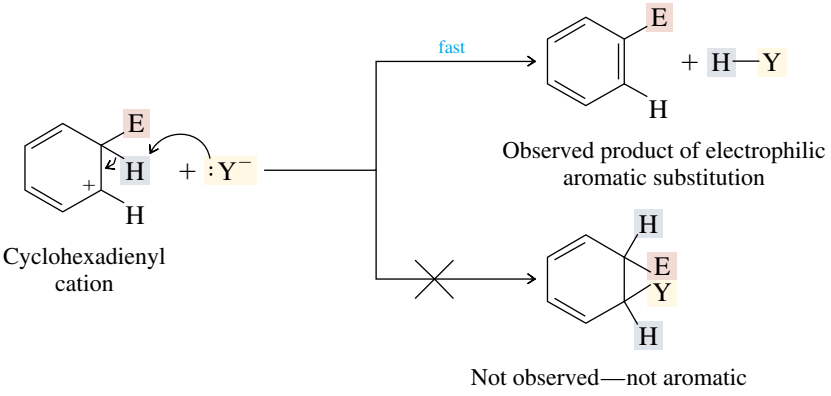
PROBLEM 12.1 In the simplest molecular orbital treatment of conjugated systems, it is assumed that the π system does not interact with the framework of σ bonds. When this MO method was used to calculate the charge distribution in cyclohexadienyl cation, it gave the results indicated. How does the charge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



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

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

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



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

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

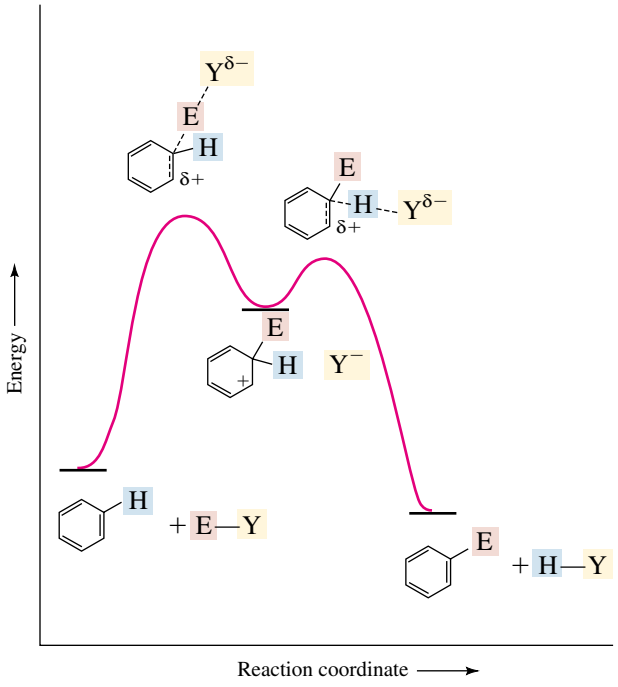


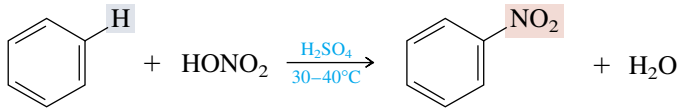
FIGURE 12.1 Energy changes associated with the two steps of electrophilic aromatic substitution.

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

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

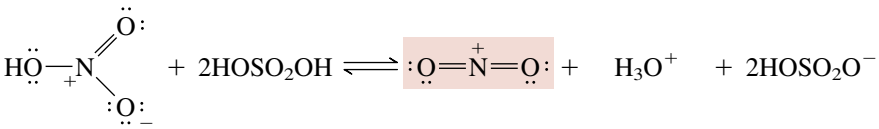
12.3 NITRATION OF BENZENE

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



Benzene Nitric acid Nitrobenzene (95%) Water

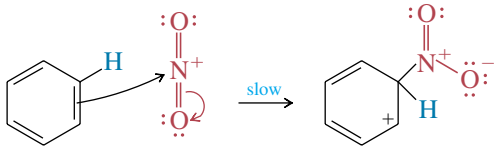
The electrophile (E^+) that reacts with benzene is *nitronium ion* ($^+NO_2$). The concentration of nitronium ion in nitric acid alone is too low to nitrate benzene at a convenient rate, but can be increased by adding sulfuric acid.



Nitric acid Sulfuric acid Nitronium ion Hydronium ion Hydrogen sulfate ion

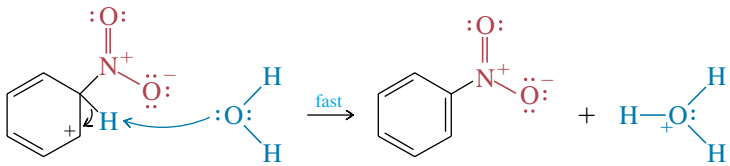
The role of nitronium ion in the nitration of benzene was demonstrated by Sir Christopher Ingold–the same person who suggested the S_N1 and S_N2 mechanisms of nucleophilic substitution and who collaborated with Cahn and Prelog on the *R* and *S* notational system.

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



Benzene and nitronium ion Cyclohexadienyl cation intermediate

Step 2: Loss of a proton from the cyclohexadienyl cation



Cyclohexadienyl cation intermediate Water Nitrobenzene Hydronium ion

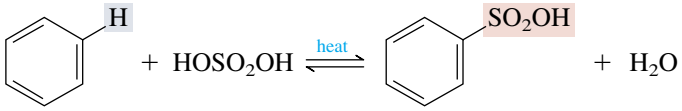
FIGURE 12.2 The mechanism of the nitration of benzene. An electrostatic potential map of nitronium ion can be viewed on *Learning By Modeling.*

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

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

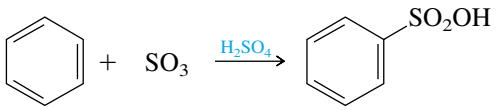
12.4 SULFONATION OF BENZENE

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



Benzene Sulfuric acid Benzenesulfonic acid Water

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



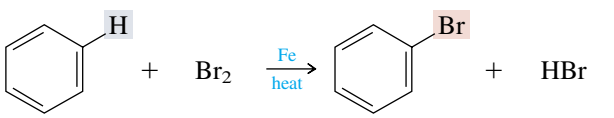
Benzene Sulfur trioxide Benzenesulfonic acid

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

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

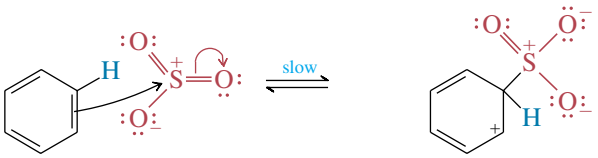
12.5 HALOGENATION OF BENZENE

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



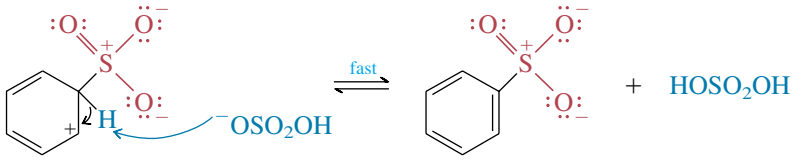
Benzene Bromine Bromobenzene (65–75%) Hydrogen bromide

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



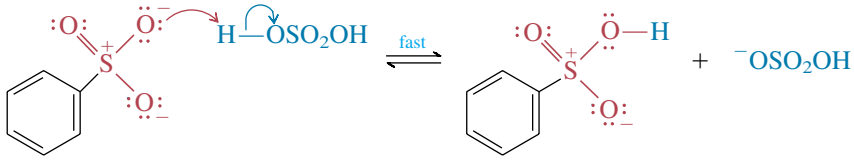
Benzene and sulfur trioxide — Cyclohexadienyl cation intermediate

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



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

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



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

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

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

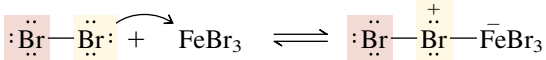
The active catalyst is not iron itself but iron(III) bromide, formed by reaction of iron and bromine.

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

Iron — Bromine — Iron(III) bromide

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

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



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

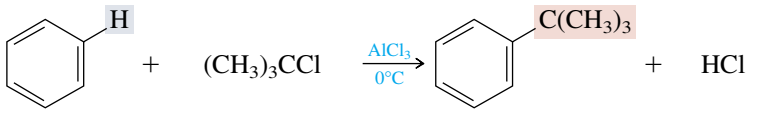
Complexation of bromine with iron(III) bromide makes bromine more electrophilic, and it attacks benzene to give a cyclohexadienyl intermediate as shown in step 1 of the mechanism depicted in Figure 12.4. In step 2, as in nitration and sulfonation, loss of a proton from the cyclohexadienyl cation is rapid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

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

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

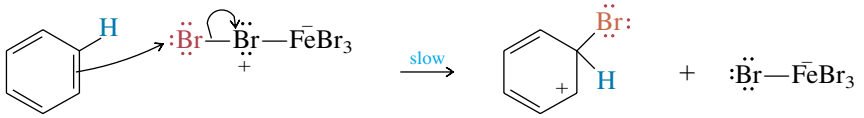
12.6 FRIEDEL–CRAFTS ALKYLATION OF BENZENE

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



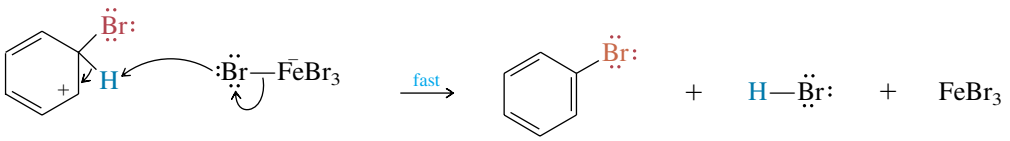
Benzene | *tert*-Butyl chloride | *tert*-Butylbenzene (60%) | Hydrogen chloride

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



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

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

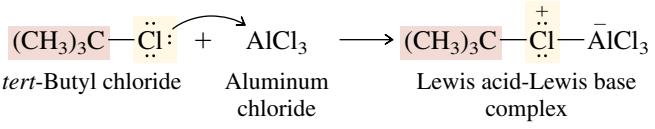


Cyclohexadienyl cation intermediate | Tetrabromoferrate ion | Bromobenzene | Hydrogen bromide | Iron(III) bromide

FIGURE 12.4 The mechanism of bromination of benzene.

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

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



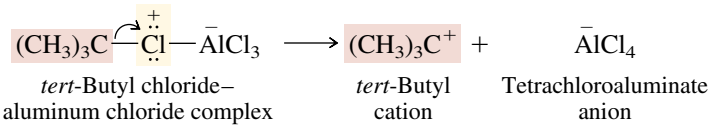
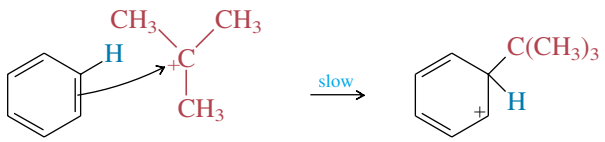


Figure 12.5 illustrates attack on the benzene ring by *tert*-butyl cation (step 1) and subsequent formation of *tert*-butylbenzene by loss of a proton from the cyclohexadienyl cation intermediate (step 2).

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

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



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

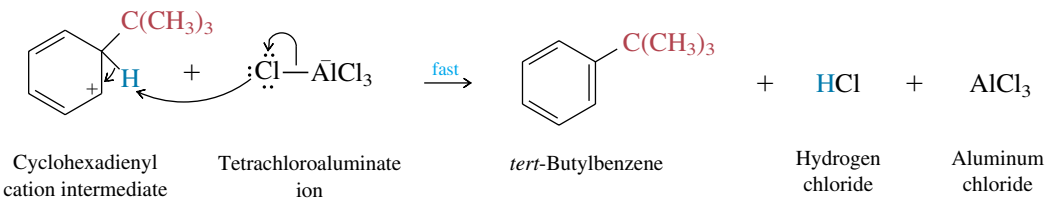
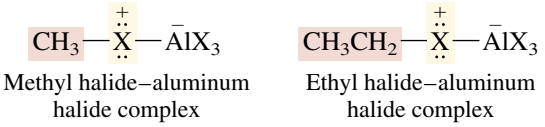


FIGURE 12.5 The mechanism of Friedel–Crafts alkylation. An electrostatic potential map of *tert*-butyl cation can be viewed on *Learning By Modeling.*

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

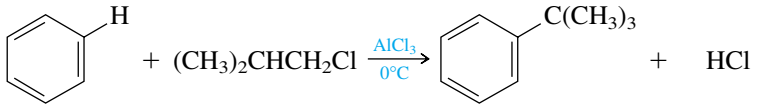


Methyl halide–aluminum halide complex

Ethyl halide–aluminum halide complex

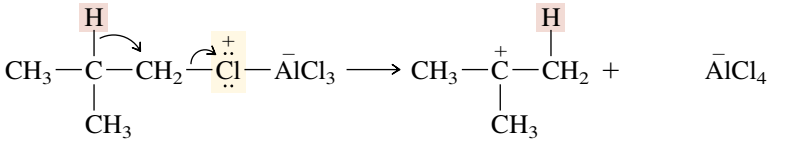
Other limitations to Friedel–Crafts reactions will be encountered in this chapter and are summarized in Table 12.4.

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



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

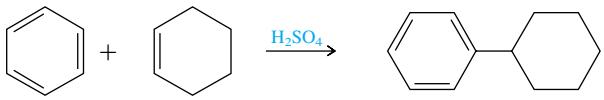
Here, the electrophile is *tert*-butyl cation formed by a hydride migration that accompanies ionization of the carbon–chlorine bond.



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

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

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

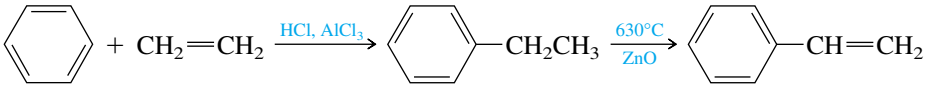


Benzene | Cyclohexene | Cyclohexylbenzene (65–68%)

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

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

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



Benzene Ethylene Ethylbenzene Styrene

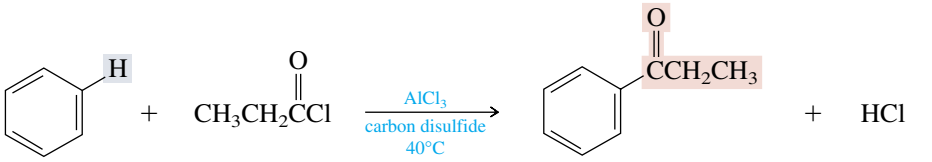
Dehydrogenation of alkylbenzenes, although useful in the industrial preparation of styrene, is not a general procedure and is not well suited to the laboratory preparation of alkenylbenzenes. In such cases an alkylbenzene is subjected to benzylic bromination (Section 11.12), and the resulting benzylic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

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

12.7 FRIEDEL–CRAFTS ACYLATION OF BENZENE

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

An acyl group has the general formula

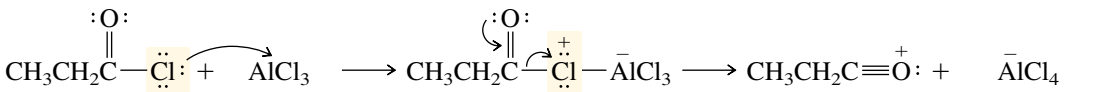


Benzene Propanoyl chloride 1-Phenyl-1-propanone (88%) Hydrogen chloride

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

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

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



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

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

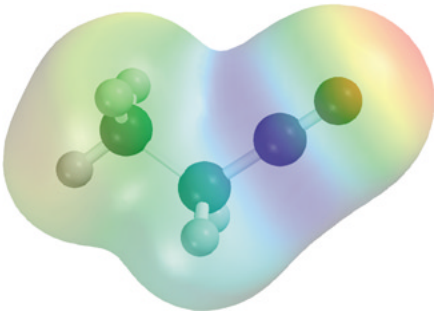
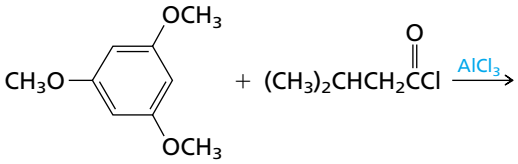


FIGURE 12.6 Electrostatic potential map of propanoyl cation [$(CH_3CH_2C{=}O)^+$]. The region of greatest positive charge (blue) is associated with the carbon of the C=O group.

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



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

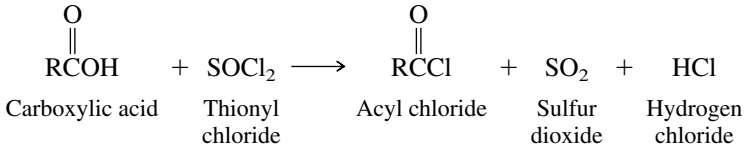
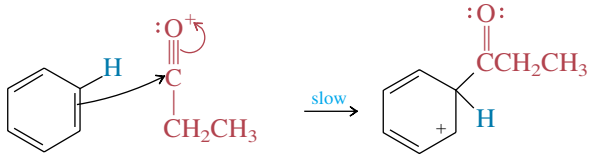
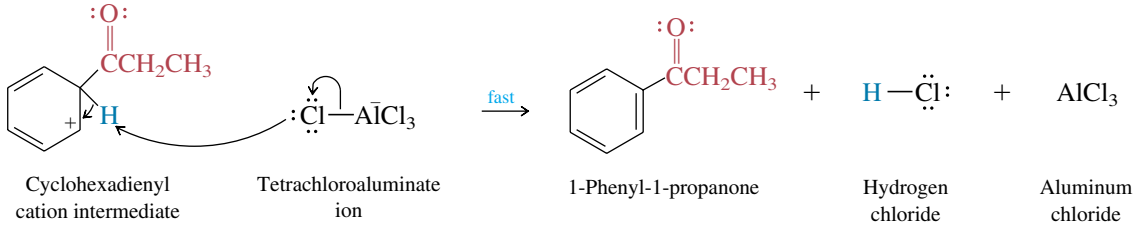


FIGURE 12.7 The mechanism of Friedel–Crafts acylation.

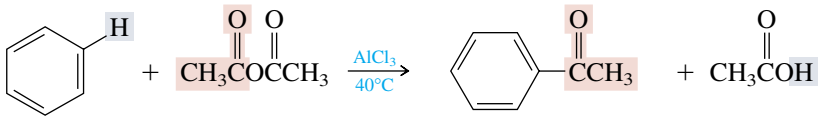
Step 1: The acyl cation attacks benzene. A pair of π electrons of benzene is used to form a covalent bond to the carbon of the acyl cation.



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



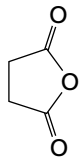
Carboxylic acid anhydrides, compounds of the type $RCOCR$ (with two carbonyl oxygens), can also serve as sources of acyl cations and, in the presence of aluminum chloride, acylate benzene. One acyl unit of an acid anhydride becomes attached to the benzene ring, while the other becomes part of a carboxylic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



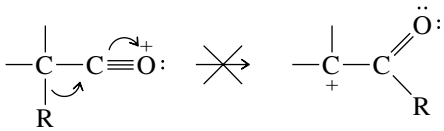
Benzene | Acetic anhydride | Acetophenone (76–83%) | Acetic acid

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

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



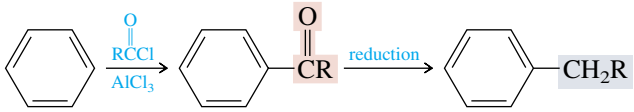
An important difference between Friedel–Crafts alkylations and acylations is that acyl cations do not rearrange. The acyl group of the acyl chloride or acid anhydride is transferred to the benzene ring unchanged. The reason for this is that an acyl cation is so strongly stabilized by resonance that it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



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

12.8 SYNTHESIS OF ALKYLBENZENES BY ACYLATION–REDUCTION

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

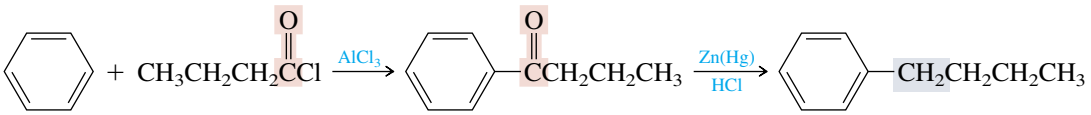


Benzene | Acylbenzene | Alkylbenzene

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

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

The synthesis of butylbenzene illustrates the acylation–reduction sequence.



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

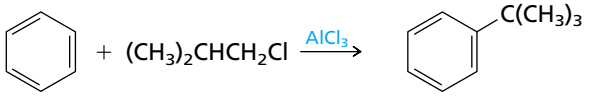
Direct alkylation of benzene using 1-chlorobutane and aluminum chloride would yield *sec*-butylbenzene by rearrangement and so could not be used.

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

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

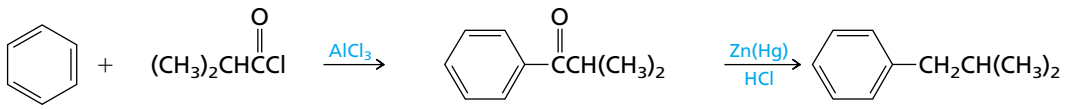
(b) Neopentylbenzene, $C_6H_5CH_2C(CH_3)_3$

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



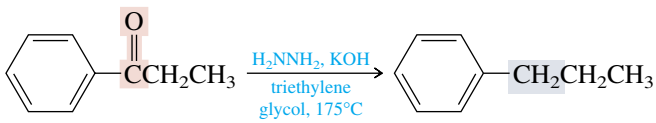
Benzene | Isobutyl chloride | *tert*-Butylbenzene (66%)

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



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

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



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

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

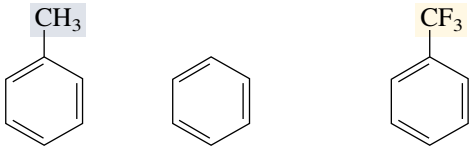
are carbon–carbon double or triple bonds affected by these methods. We will not discuss the mechanism of either the Clemmensen reduction or the Wolff–Kishner reduction, since both involve chemistry that is beyond the scope of what we have covered to this point.

12.9 RATE AND REGIOSELECTIVITY IN ELECTROPHILIC AROMATIC SUBSTITUTION

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

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

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



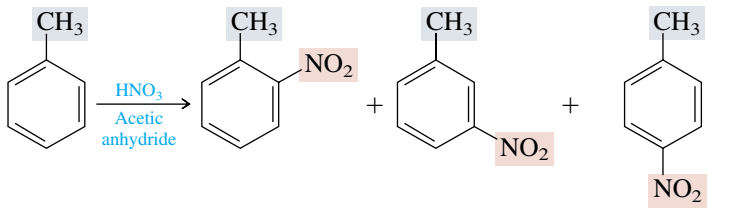
Toluene (most reactive) | Benzene | (Trifluoromethyl)benzene (least reactive)

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

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

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

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

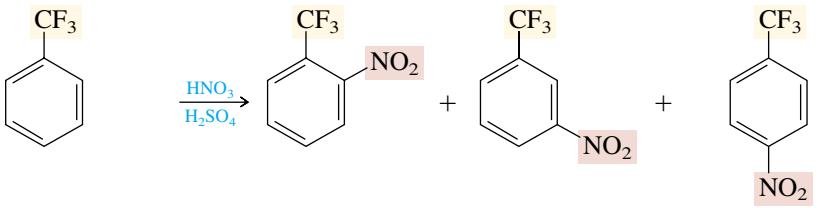


Toluene | *o*-Nitrotoluene (63%) | *m*-Nitrotoluene (3%) | *p*-Nitrotoluene (34%)

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

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

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



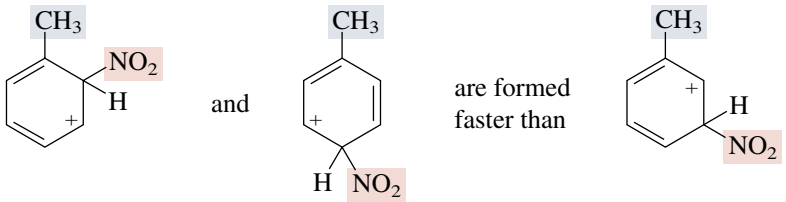
(Trifluoromethyl)benzene | *o*-Nitro(trifluoromethyl)benzene (6%) | *m*-Nitro(trifluoromethyl)benzene (91%) | *p*-Nitro(trifluoromethyl)benzene (3%)

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

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

12.10 RATE AND REGIOSELECTIVITY IN THE NITRATION OF TOLUENE

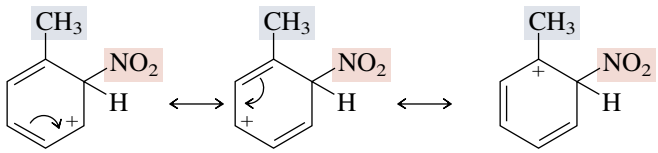
Why is there such a marked difference between methyl and trifluoromethyl substituents in their influence on electrophilic aromatic substitution? Methyl is activating and ortho, para-directing; trifluoromethyl is deactivating and meta-directing. The first point to remember is that the regioselectivity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



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

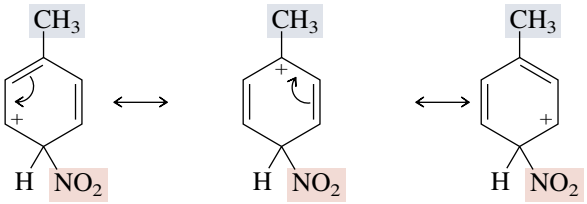
One way to assess the relative stabilities of these various intermediates is to examine electron delocalization in them using a resonance description. The cyclohexadienyl cations leading to *o*- and *p*-nitrotoluene have tertiary carbocation character. Each has a resonance form in which the positive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

Ortho attack



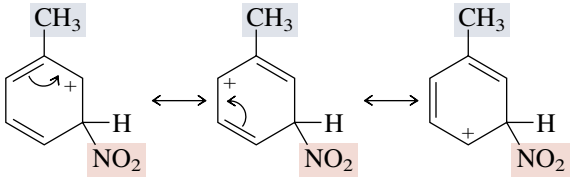
This resonance form is a tertiary carbocation

Para attack



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

Meta attack



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

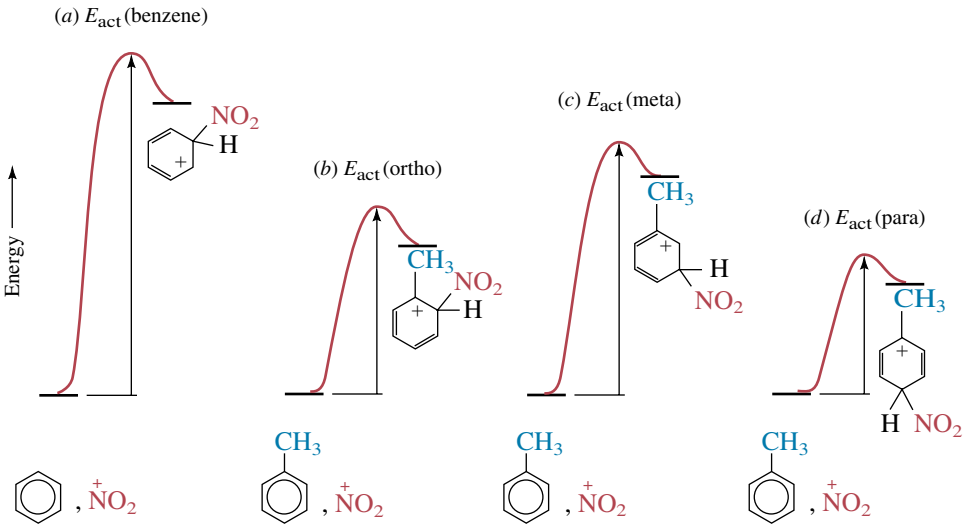
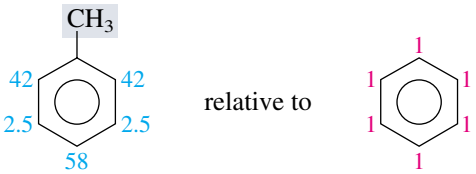


FIGURE 12.8 Comparative energy diagrams for nitronium ion attack on (*a*) benzene and at the (*b*) ortho, (*c*) meta, and (*d*) para positions of toluene. E_{act} (benzene) > E_{act} (meta) > E_{act} (ortho) > E_{act} (para).

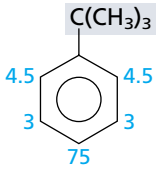
A methyl group is an *electron-releasing* substituent and activates *all* of the ring carbons of toluene toward electrophilic attack. The ortho and para positions are activated more than the meta positions. The relative rates of attack at the various positions in toluene compared with a single position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



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

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

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



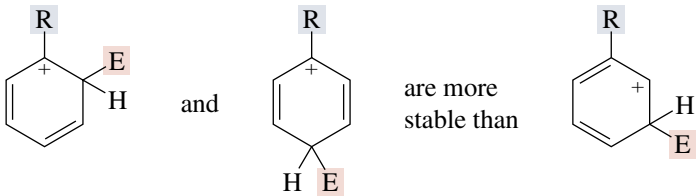
(a) How reactive is *tert*-butylbenzene toward nitration compared with benzene?
(b) How reactive is *tert*-butylbenzene toward nitration compared with toluene?
(c) Predict the distribution among the various mononitration products of *tert*-butylbenzene.

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

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

tert-Butylbenzene undergoes nitration 15 times faster than benzene.

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

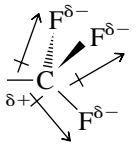


where E is any electrophile. All three structures are more stable for R = alkyl than for R = H and are formed more quickly.

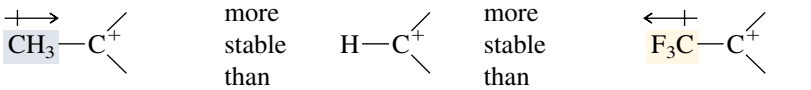
12.11 RATE AND REGIOSELECTIVITY IN THE NITRATION OF (TRIFLUOROMETHYL)BENZENE

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

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



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

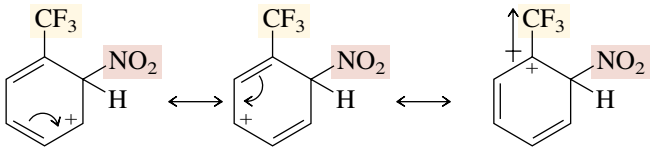


Methyl group releases electrons, stabilizes carbocation

Trifluoromethyl group withdraws electrons, destabilizes carbocation

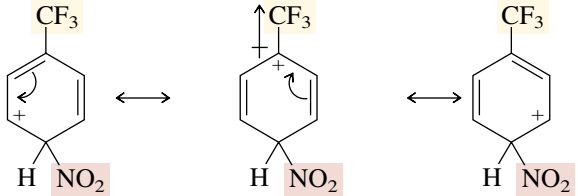
When we examine the cyclohexadienyl cation intermediates involved in the nitration of (trifluoromethyl)benzene, we find that those leading to ortho and para substitution are strongly destabilized.

Ortho attack



Positive charge on carbon bearing trifluoromethyl group; very unstable

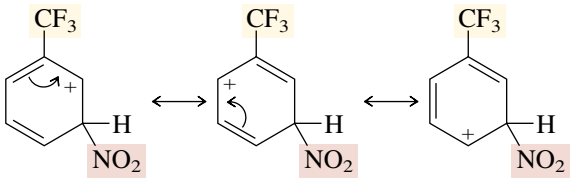
Para attack



Positive charge on carbon bearing trifluoromethyl group; very unstable

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

Meta attack



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

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

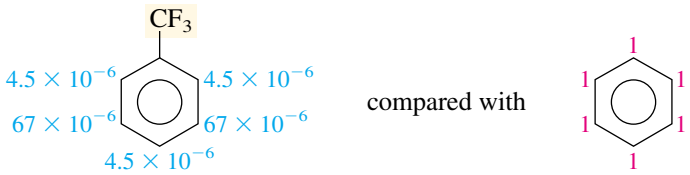


Figure 12.9 compares the energy profile for nitration of benzene with those for attack at the ortho, meta, and para positions of (trifluoromethyl)benzene. The presence of the electron-withdrawing trifluoromethyl group raises the activation energy for attack at all the ring positions, but the increase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

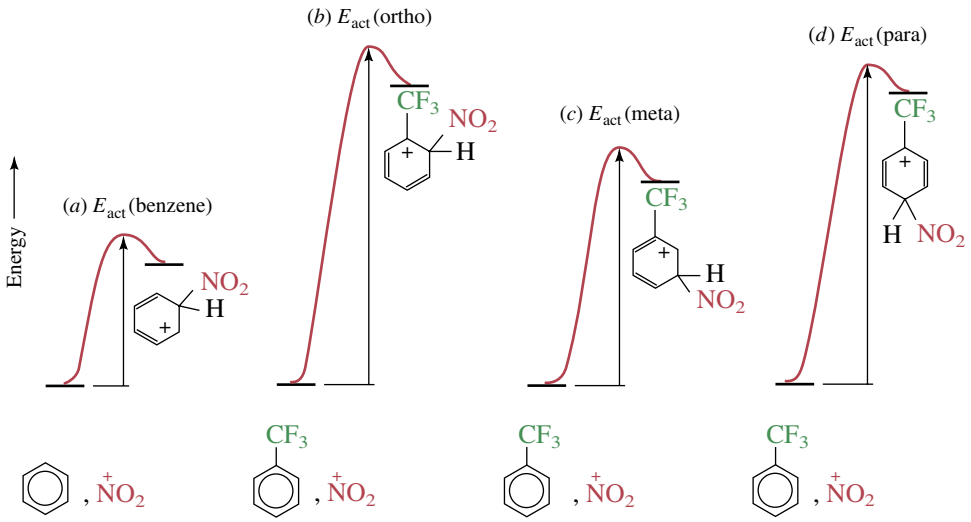


FIGURE 12.9 Comparative energy diagrams for nitronium ion attack on (*a*) benzene and at the (*b*) ortho, (*c*) meta, and (*d*) para positions of (trifluoromethyl)benzene. E_{act} (ortho) > E_{act} (para) > E_{act} (meta) > E_{act} (benzene).

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

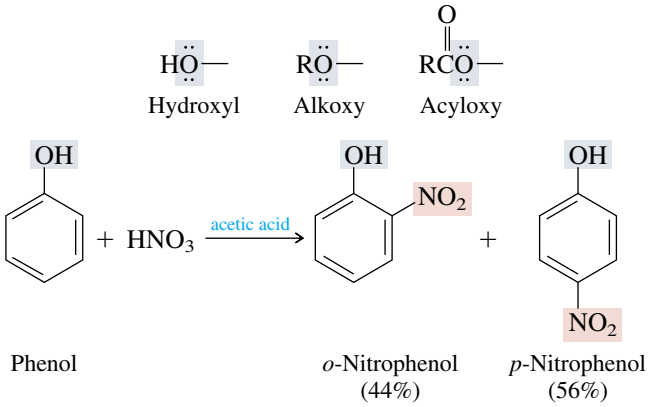
12.12 SUBSTITUENT EFFECTS IN ELECTROPHILIC AROMATIC SUBSTITUTION: ACTIVATING SUBSTITUENTS

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

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

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

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



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

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

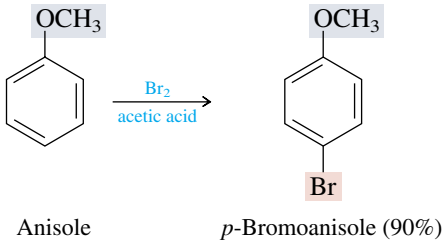
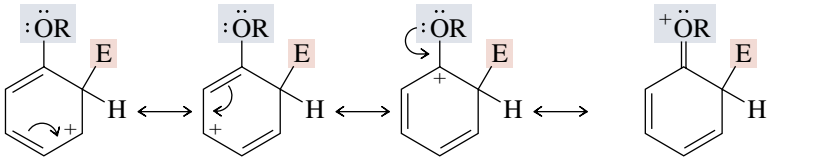


TABLE 12.2 Classification of Substituents in Electrophilic Aromatic Substitution Reactions

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

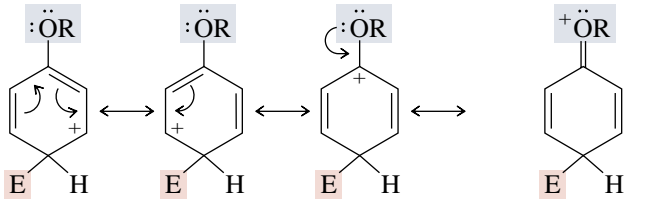
The inductive effect of hydroxyl and alkoxy groups, because of the electronegativity of oxygen, is to withdraw electrons and would seem to require that such substituents be deactivating. The electron-withdrawing inductive effect, however, is overcome by a much larger electron-releasing effect involving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

Ortho attack



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

Para attack

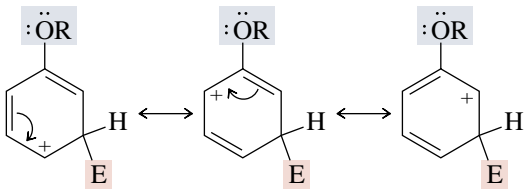


Most stable resonance form; oxygen and all carbons have octets of electrons

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

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

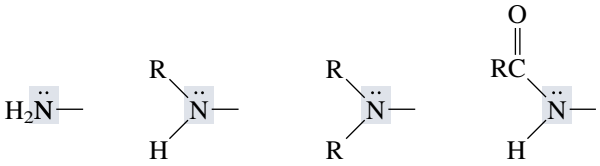
Meta attack



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

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

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



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

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

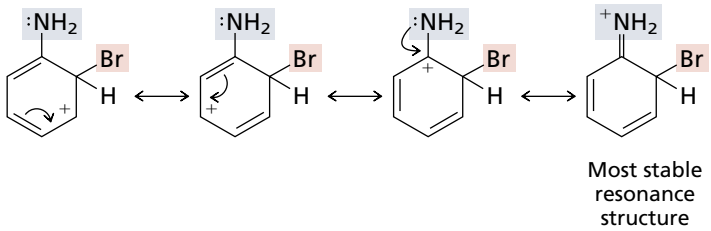
PROBLEM 12.12 Write structural formulas for the cyclohexadienyl cations formed from aniline ($C_6H_5NH_2$) during

(a) Ortho bromination (four resonance structures)

(b) Meta bromination (three resonance structures)

(c) Para bromination (four resonance structures)

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



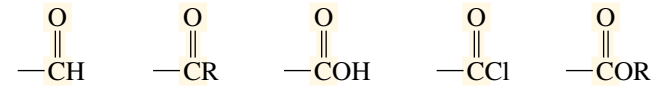
Alkyl groups are, as we saw when we discussed the nitration of toluene in Section 12.10, activating and ortho, para-directing substituents. Aryl and alkenyl substituents resemble alkyl groups in this respect; they too are activating and ortho, para-directing.

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

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

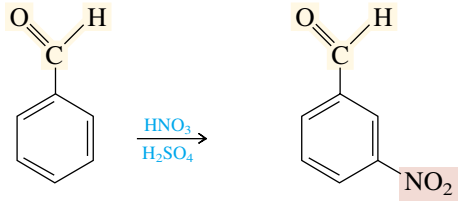
12.13 SUBSTITUENT EFFECTS IN ELECTROPHILIC AROMATIC SUBSTITUTION: STRONGLY DEACTIVATING SUBSTITUENTS

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



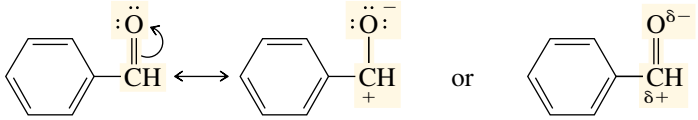
Aldehyde | Ketone | Carboxylic acid | Acyl chloride | Ester

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



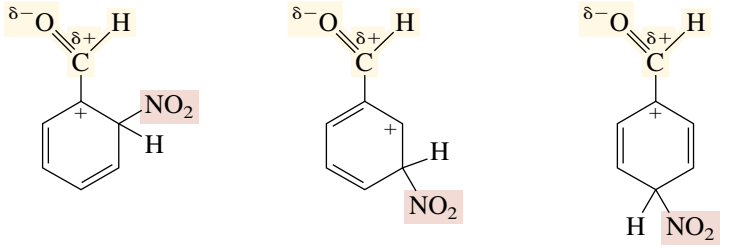
Benzaldehyde *m*-Nitrobenzaldehyde (75–84%)

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



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

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



Unstable because of adjacent positively polarized atoms

Positively polarized atoms not adjacent; most stable intermediate

Unstable because of adjacent positively polarized atoms

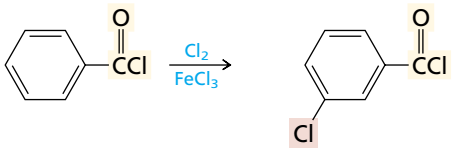
PROBLEM 12.14 Each of the following reactions has been reported in the chemical literature, and the principal organic product has been isolated in good yield. Write a structural formula for the isolated product of each reaction.

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

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

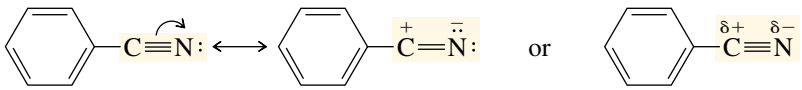
(c) Nitration of 1-phenyl-1-propanone ($C_6H_5\overset{\overset{O}{\|}}{C}CH_2CH_3$)

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



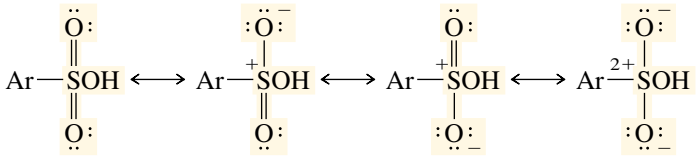
Benzoyl chloride — *m*-Chlorobenzoyl chloride (isolated in 62% yield)

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

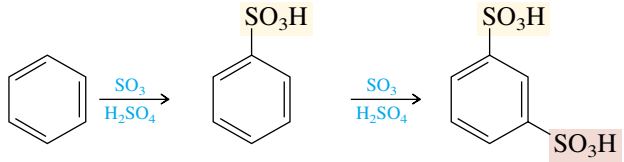


Cyano groups are electron-withdrawing, deactivating, and meta-directing.

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

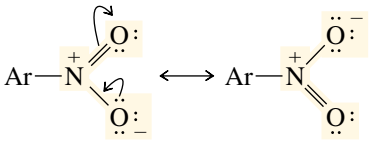


When benzene undergoes disulfonation, *m*-benzenedisulfonic acid is formed. The first sulfonic acid group to go on directs the second one meta to itself.

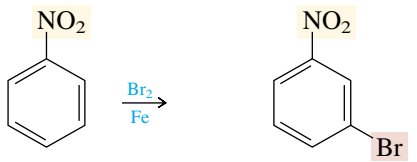


Benzene — Benzenesulfonic acid — *m*-Benzenedisulfonic acid (90%)

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



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

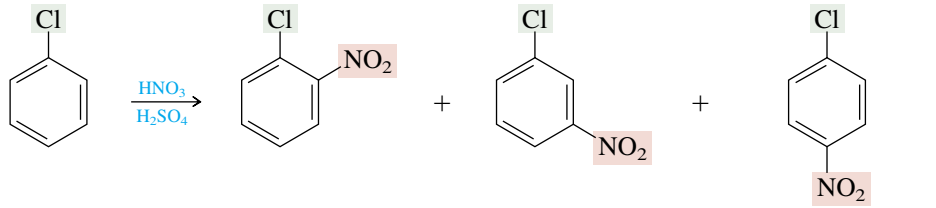


Nitrobenzene *m*-Bromonitrobenzene (60–75%)

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

12.14 SUBSTITUENT EFFECTS IN ELECTROPHILIC AROMATIC SUBSTITUTION: HALOGENS

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



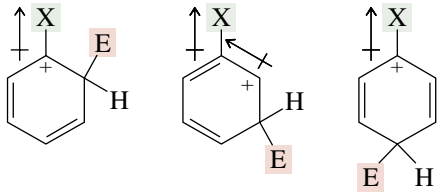
Chlorobenzene *o*-Chloronitrobenzene (30%) *m*-Chloronitrobenzene (1%) *p*-Chloronitrobenzene (69%)

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

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

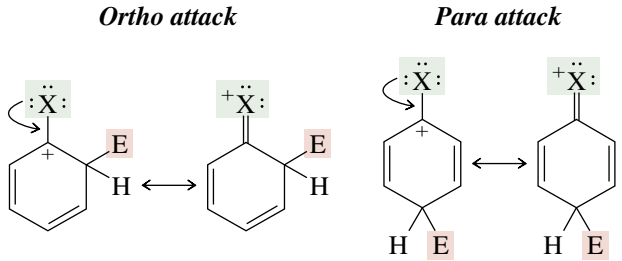
This seeming inconsistency between regioselectivity and rate can be understood by analyzing the two ways that a halogen substituent can affect the stability of a cyclohexadienyl cation. First, halogens are electronegative, and their inductive effect is to draw

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

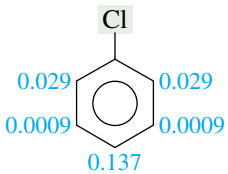


All these ions are less stable when X = F, Cl, Br, or I than when X = H

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



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



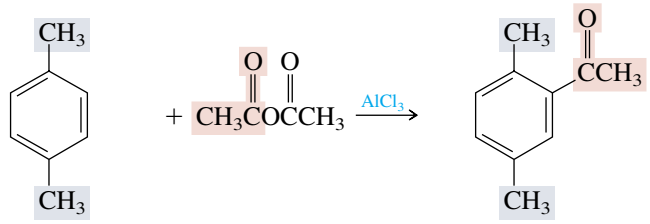
The mix of inductive and resonance effects varies from one halogen to another, but the net result is that fluorine, chlorine, bromine, and iodine are weakly deactivating, ortho, para-directing substituents.

12.15 MULTIPLE SUBSTITUENT EFFECTS

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

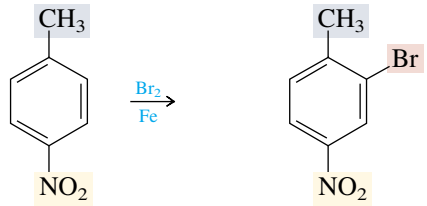
In the simplest cases all the available sites are equivalent, and substitution at any one of them gives the same product.

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



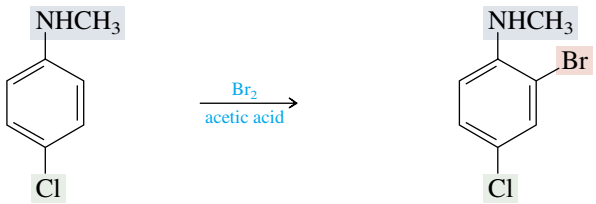
1,4-Dimethylbenzene (*p*-xylene) 2,5-Dimethylacetophenone (99%)

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



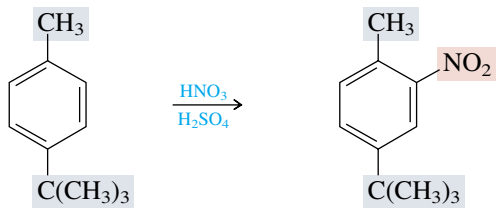
p-Nitrotoluene 2-Bromo-4-nitrotoluene (86–90%)

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



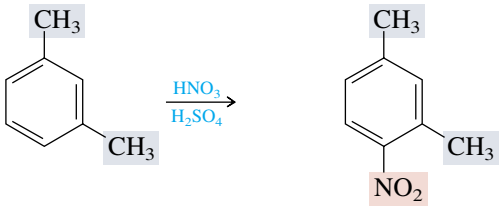
4-Chloro-*N*-methylaniline 2-Bromo-4-chloro-*N*-methylaniline (87%)

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



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

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



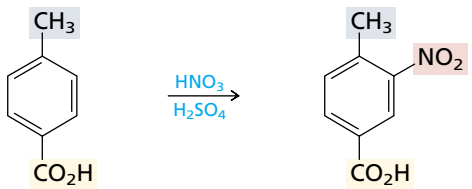
m-Xylene 2,4-Dimethyl-1-nitrobenzene (98%)

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

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

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

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



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

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

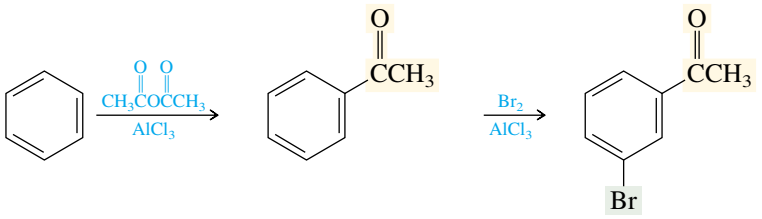
An exception to the rule that regioselectivity is controlled by the most activating substituent occurs when the directing effects of alkyl groups and halogen substituents oppose each other. Alkyl groups and halogen substituents are weakly activating and weakly deactivating, respectively, and the difference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

12.16 REGIOSELECTIVE SYNTHESIS OF DISUBSTITUTED AROMATIC COMPOUNDS

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

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

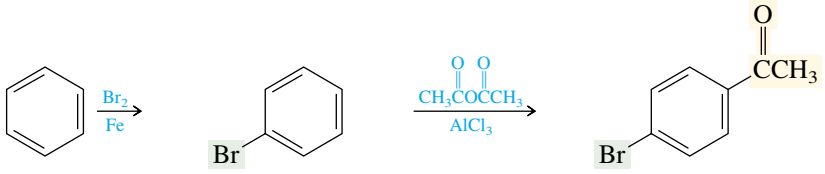
steps are carried out. When the meta-directing acetyl group is introduced first, the final product is *m*-bromoacetophenone.



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

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

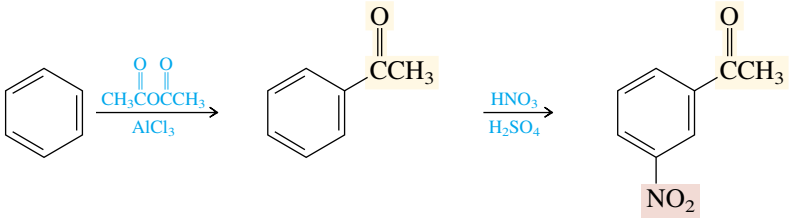
When the ortho, para-directing bromine is introduced first, the major product is *p*-bromoacetophenone (along with some of its ortho isomer, from which it is separated by distillation).



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

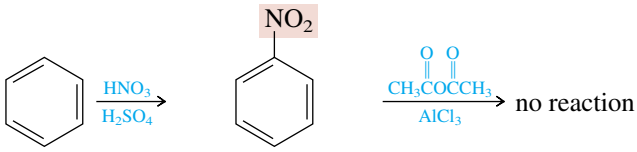
PROBLEM 12.18 Write chemical equations showing how you could prepare *m*-bromonitrobenzene as the principal organic product, starting with benzene and using any necessary organic or inorganic reagents. How could you prepare *p*-bromonitrobenzene?

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



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

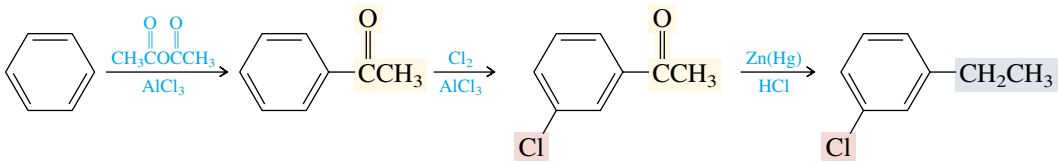
When the reverse order of steps is attempted, it is observed that the Friedel–Crafts acylation of nitrobenzene fails.



Benzene — Nitrobenzene (95%)

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

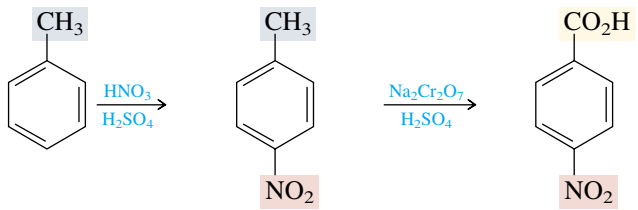
Sometimes the orientation of two substituents in an aromatic compound precludes its straightforward synthesis. *m*-Chloroethylbenzene, for example, has two ortho, para-directing groups in a meta relationship and so can't be prepared either from chlorobenzene or ethylbenzene. In cases such as this we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



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

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

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



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

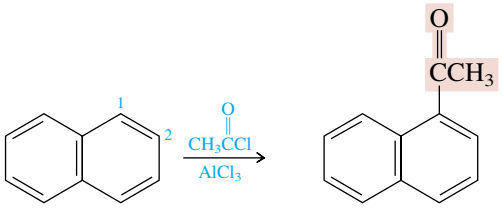
Since it may be oxidized to a carboxyl group (Section 11.13), a methyl group can be used to introduce the nitro substituent in the proper position.

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

12.17 SUBSTITUTION IN NAPHTHALENE

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

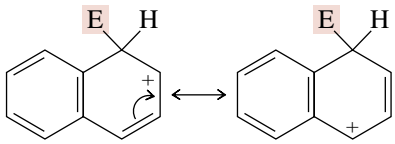
Two sites are available for substitution in naphthalene, C-1 and C-2, C-1 being normally the preferred site of electrophilic attack.



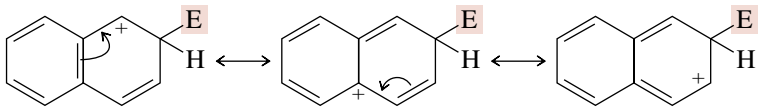
Naphthalene 1-Acetylnaphthalene (90%)

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

Attack at C-1



Attack at C-2



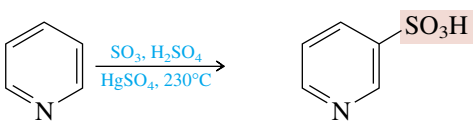
To involve allylic resonance in stabilizing the arenium ion formed during attack at C-2, the benzenoid character of the other ring is sacrificed.

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

12.18 SUBSTITUTION IN HETEROCYCLIC AROMATIC COMPOUNDS

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

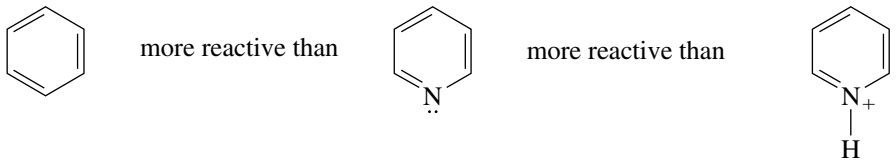
Pyridine lies near one extreme in being far less reactive than benzene toward substitution by electrophilic reagents. In this respect it resembles strongly deactivated aromatic compounds such as nitrobenzene. It is incapable of being acylated or alkylated under Friedel–Crafts conditions, but can be sulfonated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



Pyridine Pyridine-3-sulfonic acid (71%)

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

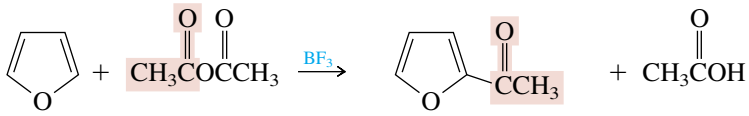
One reason for the low reactivity of pyridine is that its nitrogen atom, since it is more electronegative than a CH in benzene, causes the π electrons to be held more tightly and raises the activation energy for attack by an electrophile. Another is that the nitrogen of pyridine is protonated in sulfuric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



Benzene Pyridine Pyridinium ion

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

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

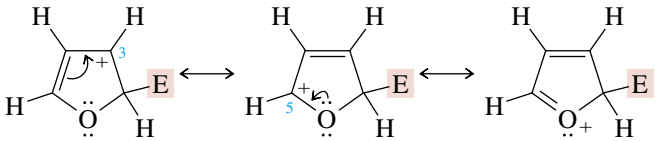


Furan Acetic anhydride 2-Acetylfuran (75–92%) Acetic acid

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

Attack at C-2

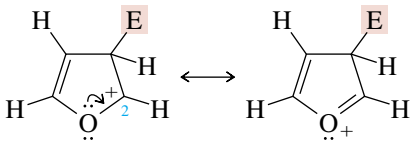
Carbocation *more stable;* positive charge shared by C-3, C-5, and O.



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

Attack at C-3

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



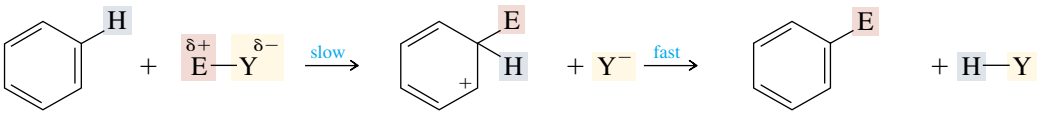
The regioselectivity of substitution in pyrrole and thiophene is like that of furan and for similar reasons.

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

12.19 SUMMARY

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

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

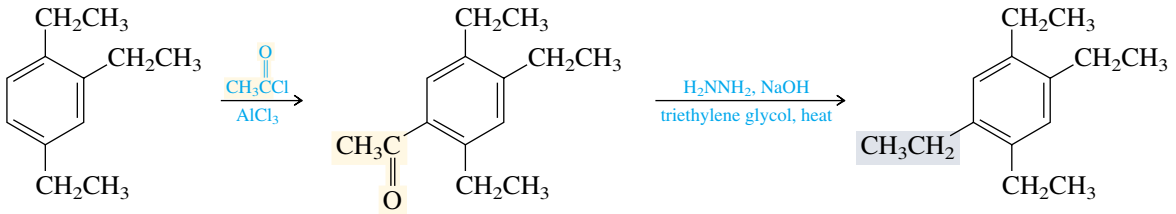


Benzene | Electrophilic reagent | Cyclohexadienyl cation intermediate | Product of electrophilic aromatic substitution

Sections 12.3–12.5 See Table 12.3

Sections 12.6–12.7 See Tables 12.3 and 12.4

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



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

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

TABLE 12.3 Representative Electrophilic Aromatic Substitution Reactions

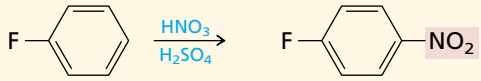
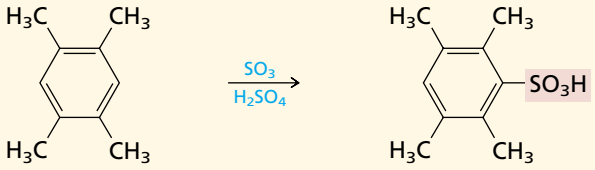
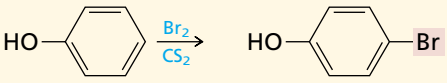
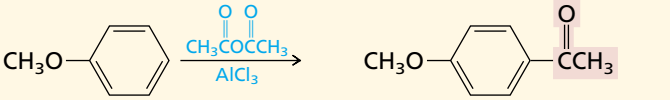
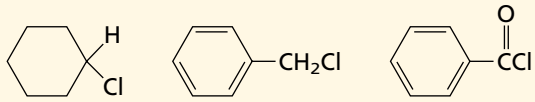
Reaction (section) and comments	General equation and specific example
Nitration (Section 12.3) The active electrophile in the nitration of benzene and its derivatives is nitronium cation ($:\ddot{O}{=}\overset{+}{N}{=}\ddot{O}:$). It is generated by reaction of nitric acid and sulfuric acid. Very reactive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

TABLE 12.4 Limitations on Friedel–Crafts Reactions

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

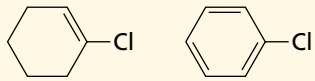
These will react with benzene under Friedel–Crafts conditions:



Alkyl halide | Benzylic halide | Acyl halide

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

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

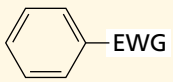


Vinylic halide | Aryl halide

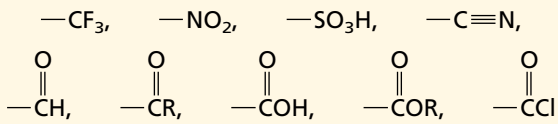
2. Rearrangement of alkyl groups can occur (Section 12.6).

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

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



EWG:

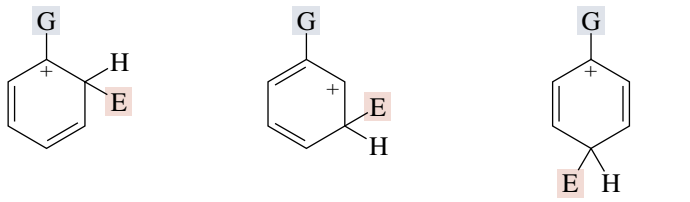


4. It is sometimes difficult to limit Friedel–Crafts alkylation to monoalkylation.

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

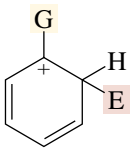
Sections 12.10–12.14

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

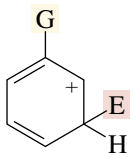


Stabilized when G is electron-releasing | Less stabilized when G is electron-releasing | Stabilized when G is electron-releasing

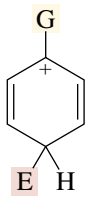
Conversely, an electron-withdrawing substituent destabilizes the cyclohexadienyl cations corresponding to ortho and para attack more than meta. Thus, meta substitution predominates.



Destabilized when G is electron-withdrawing



Less destabilized when G is electron-withdrawing



Destabilized when G is electron-withdrawing

Substituents can be arranged into three major categories:

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

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

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

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

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

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

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

PROBLEMS

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

(a) Nitration of benzene

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

(c) Bromination of toluene

(d) Bromination of (trifluoromethyl)benzene

(e) Sulfonation of anisole

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

(g) Chlorination of bromobenzene

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

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

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

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

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

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

(a) Bromination of *p*-xylene

(b) Chlorination of *m*-xylene

(c) Nitration of acetophenone

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

(e) Nitration of isopropylbenzene

(f) Bromination of nitrobenzene

(g) Sulfonation of furan

(h) Bromination of pyridine

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

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

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

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

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

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

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

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

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

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

(b) Bromination of aniline (tribromination)

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

(d) Nitration of benzoic acid (dinitration)

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

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

(g) Sulfonation of phenol (disulfonation)

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

(a) Isopropylbenzene

(b) *p*-Isopropylbenzenesulfonic acid

(c) 2-Bromo-2-phenylpropane

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

(e) *m*-Chloroacetophenone

(f) *p*-Chloroacetophenone

(g) 3-Bromo-4-methylacetophenone

(h) 2-Bromo-4-ethyltoluene

(i) 1-Bromo-3-nitrobenzene

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

(k) 3-Bromo-5-nitrobenzoic acid

(l) 2-Bromo-4-nitrobenzoic acid

(m) Diphenylmethane

(n) 1-Phenyloctane

(o) 1-Phenyl-1-octene

(p) 1-Phenyl-1-octyne

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

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

(a) *p*-Methoxybenzenesulfonic acid

(b) 2-Bromo-4-nitroanisole

(c) 4-Bromo-2-nitroanisole

(d) *p*-Methoxystyrene

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

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

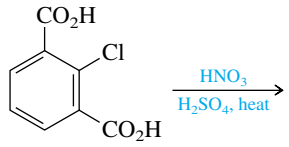
(b) Dinitration (HNO_3, H_2SO_4, 80°C).

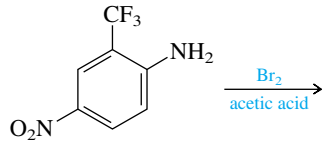
(c) Trinitration (HNO_3, H_2SO_4, 110°C). The explosive TNT (trinitrotoluene) is the major product obtained on trinitration of toluene. Which trinitrotoluene isomer is TNT?

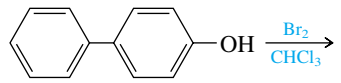
12.30 Friedel–Crafts acylation of the individual isomers of xylene with acetyl chloride and aluminum chloride yields a single product, different for each xylene isomer, in high yield in each case. Write the structures of the products of acetylation of *o-, m-,* and *p*-xylene.

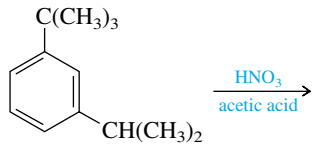
12.31 Reaction of benzanilide ($C_6H_5NHC(=O)C_6H_5$) with chlorine in acetic acid yields a mixture of two monochloro derivatives formed by electrophilic aromatic substitution. Suggest reasonable structures for these two isomers.

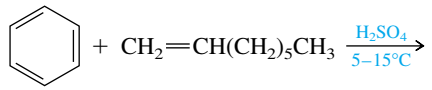
12.32 Each of the following reactions has been reported in the chemical literature and gives a predominance of a single product in synthetically acceptable yield. Write the structure of the product. Only monosubstitution is involved in each case, unless otherwise indicated.

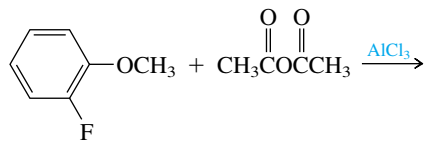
(a) 

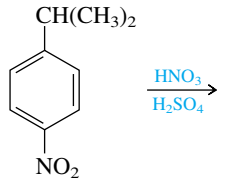
(b) 

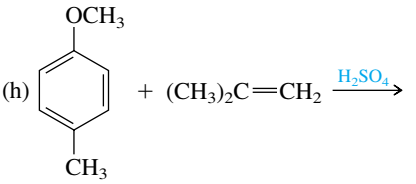
(c) 

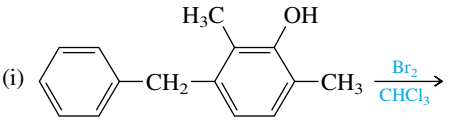
(d) 

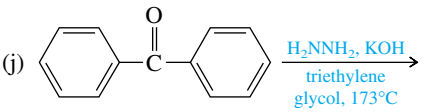
(e) 

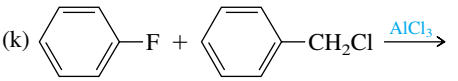
(f) 

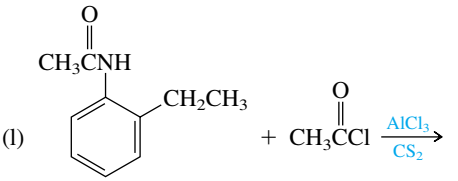
(g) 

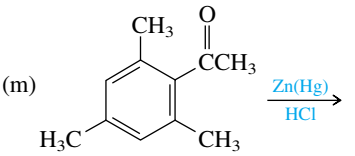
(h) 

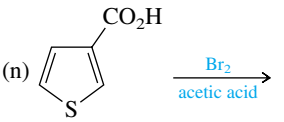
(i) 

(j) 

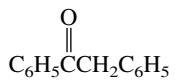
(k) 

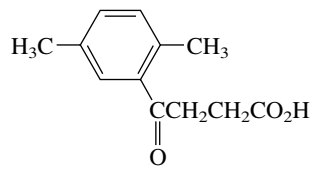
(l) 

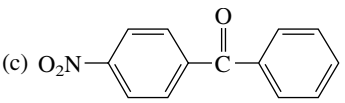
(m) 

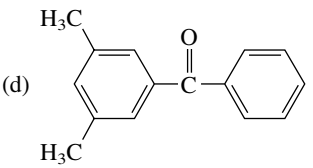
(n) 

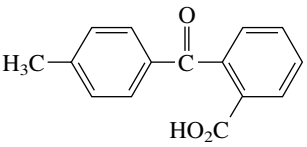
12.33 What combination of acyl chloride or acid anhydride and arene would you choose to prepare each of the following compounds by a Friedel–Crafts acylation reaction?

(a) 

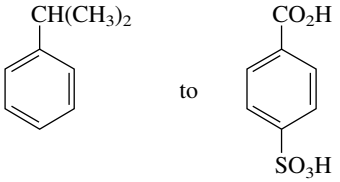
(b) 

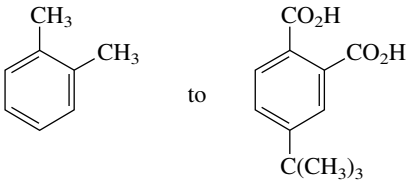
(c) 

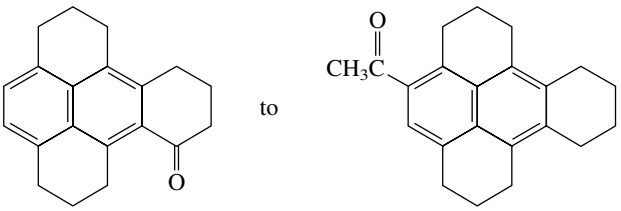
(d) 

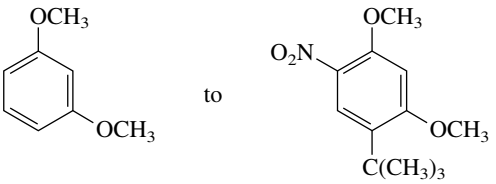
(e) 

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

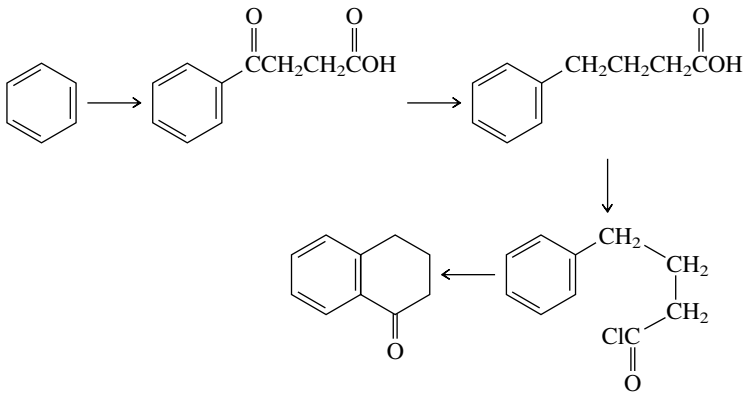
(a) 

(b) 

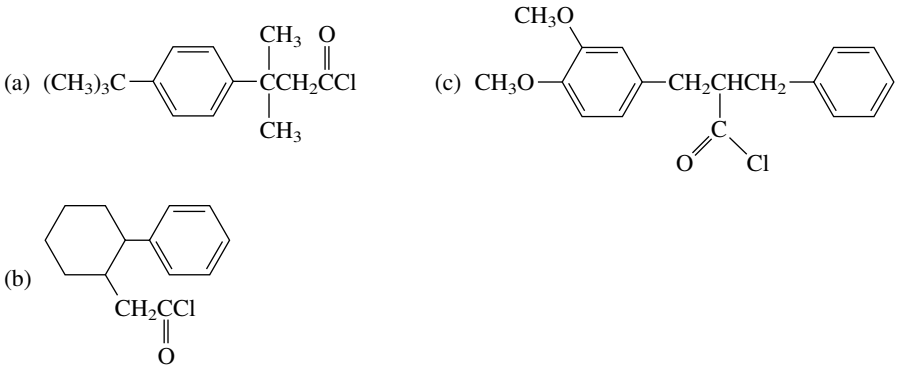
(c) 

(d) 

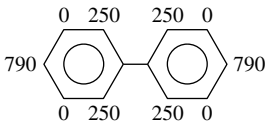
12.35 A standard synthetic sequence for building a six-membered cyclic ketone onto an existing aromatic ring is shown in outline as follows. Specify the reagents necessary for each step.



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



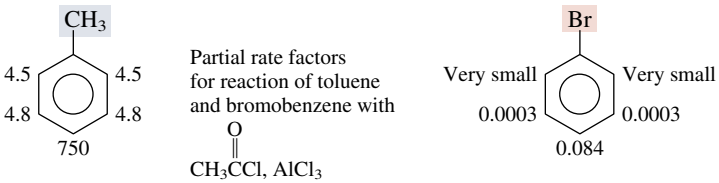
12.37 The partial rate factors for chlorination of biphenyl are as shown.



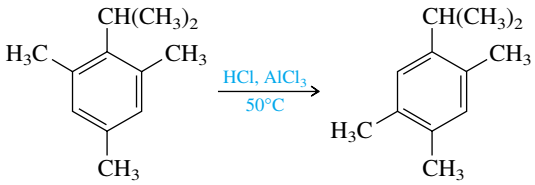
(a) What is the relative rate of chlorination of biphenyl compared with benzene?

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

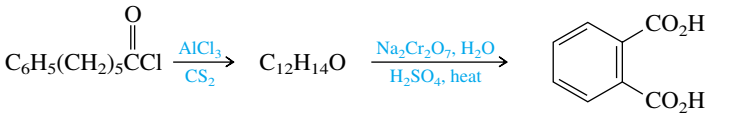
12.38 Partial rate factors may be used to estimate product distributions in disubstituted benzene derivatives. The reactivity of a particular position in *o*-bromotoluene, for example, is given by the product of the partial rate factors for the corresponding position in toluene and bromobenzene. On the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



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



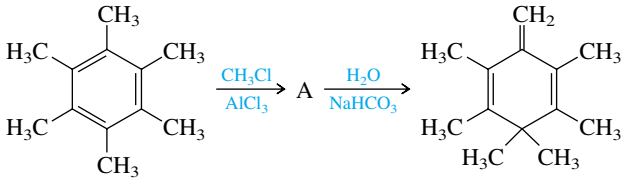
12.40 When a dilute solution of 6-phenylhexanoyl chloride in carbon disulfide was slowly added (over a period of 8 days!) to a suspension of aluminum chloride in the same solvent, it yielded a product A ($C_{12}H_{14}O$) in 67% yield. Oxidation of A gave benzene-1,2-dicarboxylic acid.



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

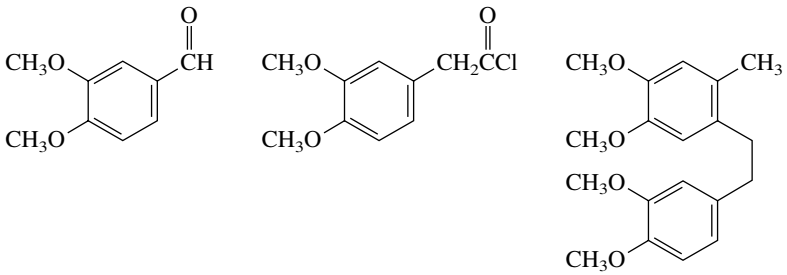
Formulate a reasonable structure for compound A.

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



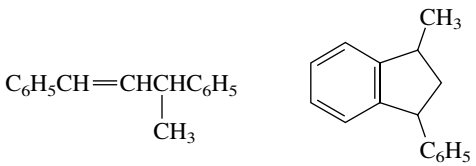
Hexamethylbenzene | Compound B

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



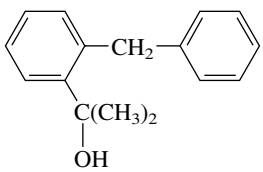
Compound A | Compound B | Compound C

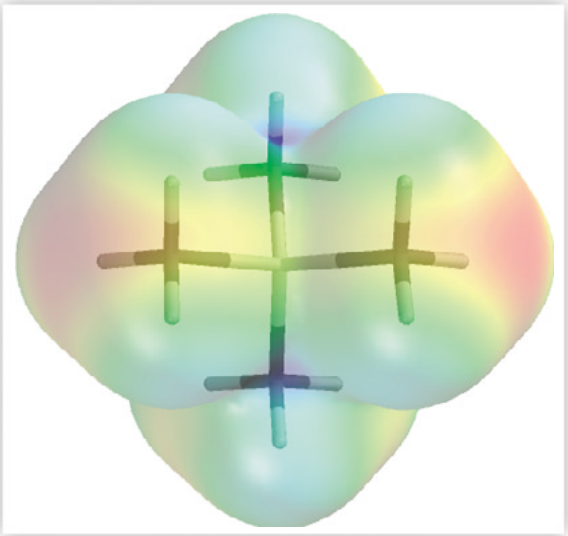
12.43 When styrene is refluxed with aqueous sulfuric acid, two "styrene dimers" are formed as the major products. One of these styrene dimers is 1,3-diphenyl-1-butene; the other is 1-methyl-3-phenylindan. Suggest a reasonable mechanism for the formation of each of these compounds.



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

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





CHAPTER 13

SPECTROSCOPY

Until the second half of the twentieth century, the structure of a substance—a newly discovered natural product, for example—was determined using information obtained from chemical reactions. This information included the identification of functional groups by chemical tests, along with the results of experiments in which the substance was broken down into smaller, more readily identifiable fragments. Typical of this approach is the demonstration of the presence of a double bond in an alkene by catalytic hydrogenation and subsequent determination of its location by ozonolysis. After considering all the available chemical evidence, the chemist proposed a candidate structure (or structures) consistent with the observations. Proof of structure was provided either by converting the substance to some already known compound or by an independent synthesis.

Qualitative tests and chemical degradation have been supplemented and to a large degree replaced by instrumental methods of structure determination. The most prominent methods and the structural clues they provide are:

- **Nuclear magnetic resonance (NMR) spectroscopy** tells us about the carbon skeleton and the environments of the hydrogens attached to it.
- **Infrared (IR) spectroscopy** reveals the presence or absence of key functional groups.
- **Ultraviolet-visible (UV-VIS) spectroscopy** probes the electron distribution, especially in molecules that have conjugated π electron systems.
- **Mass spectrometry (MS)** gives the molecular weight and formula, both of the molecule itself and various structural units within it.

As diverse as these techniques are, all of them are based on the absorption of energy by a molecule, and all measure how a molecule responds to that absorption. In describing these techniques our emphasis will be on their application to structure determination. We'll start with a brief discussion of electromagnetic radiation, which is the source of the energy that a molecule absorbs in NMR, IR, and UV-VIS spectroscopy.

13.1 PRINCIPLES OF MOLECULAR SPECTROSCOPY: ELECTROMAGNETIC RADIATION

"Modern" physics dates from Planck's proposal that energy is quantized, which set the stage for the development of quantum mechanics. Planck received the 1918 Nobel Prize in physics.

Electromagnetic radiation, of which visible light is but one example, has the properties of both particles and waves. The particles are called **photons,** and each possesses an amount of energy referred to as a **quantum.** In 1900, the German physicist Max Planck proposed that the energy of a photon (E) is directly proportional to its frequency (ν).

$$E = h\nu$$

The SI units of frequency are reciprocal seconds (s^{-1}), given the name *hertz* and the symbol Hz in honor of the nineteenth-century physicist Heinrich R. Hertz. The constant of proportionality h is called **Planck's constant** and has the value

$$h = 6.63 \times 10^{-34}\ \text{J} \cdot \text{s}$$

Electromagnetic radiation travels at the speed of light ($c = 3.0 \times 10^8$ m/s), which is equal to the product of its frequency ν and its wavelength λ:

$$c = \nu\lambda$$

The range of photon energies is called the *electromagnetic spectrum* and is shown in Figure 13.1. Visible light occupies a very small region of the electromagnetic spectrum. It is characterized by wavelengths of 4×10^{-7} m (violet) to 8×10^{-7} m (red).

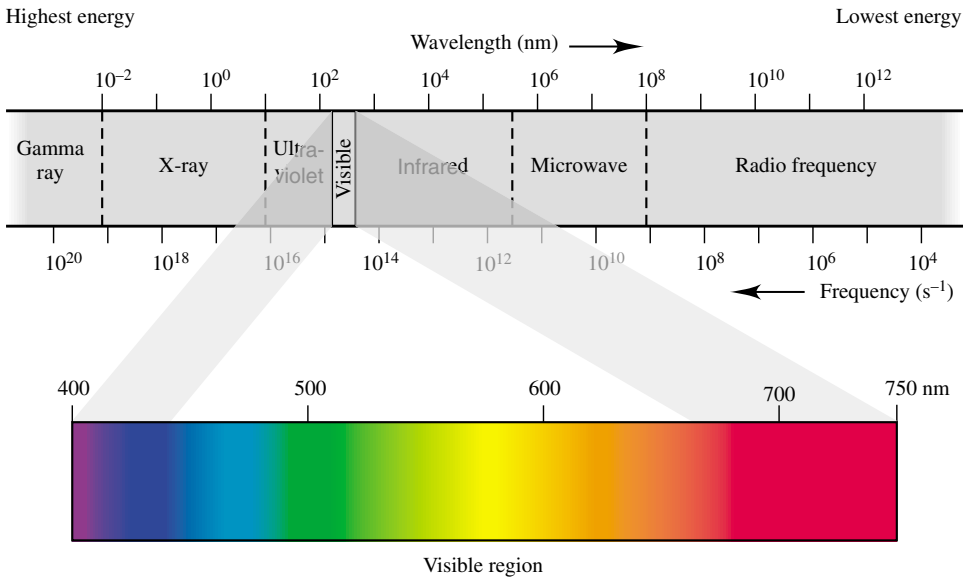


FIGURE 13.1 The electromagnetic spectrum. *(From M. Silberberg,* Chemistry, *2d edition, WCB/McGraw-Hill, 2000, p. 260.)*

When examining Figure 13.1 be sure to keep the following two relationships in mind:

1. *Frequency is inversely proportional to wavelength;* the greater the frequency, the shorter the wavelength.
2. *Energy is directly proportional to frequency;* electromagnetic radiation of higher frequency possesses more energy than radiation of lower frequency.

Depending on its source, a photon can have a vast amount of energy; gamma rays and X-rays are streams of very high energy photons. Radio waves are of relatively low energy. Ultraviolet radiation is of higher energy than the violet end of visible light. Infrared radiation is of lower energy than the red end of visible light. When a molecule is exposed to electromagnetic radiation, it may absorb a photon, increasing its energy by an amount equal to the energy of the photon. Molecules are highly selective with respect to the frequencies that they absorb. Only photons of certain specific frequencies are absorbed by a molecule. The particular photon energies absorbed by a molecule depend on molecular structure and can be measured with instruments called **spectrometers.** The data obtained are very sensitive indicators of molecular structure and have revolutionized the practice of chemical analysis.

13.2 PRINCIPLES OF MOLECULAR SPECTROSCOPY: QUANTIZED ENERGY STATES

What determines whether or not a photon is absorbed by a molecule? The most important requirement is that the energy of the photon must equal the energy difference between two states, such as two nuclear spin states, two vibrational states, or two electronic states. In physics, the term for this is *resonance*—the transfer of energy between two objects that occurs when their frequencies are matched. In molecular spectroscopy, we are concerned with the transfer of energy from a photon to a molecule, but the idea is the same. Consider, for example, two energy states of a molecule designated E_1 and E_2 in Figure 13.2. The energy difference between them is $E_2 - E_1$, or ΔE. In nuclear magnetic resonance (NMR) spectroscopy these are two different spin states of an atomic nucleus; in infrared (IR) spectroscopy, they are two different vibrational energy states; in ultraviolet-visible (UV-VIS) spectroscopy, they are two different electronic energy states. Unlike kinetic energy, which is continuous, meaning that all values of kinetic energy are available to a molecule, only certain energies are possible for electronic, vibrational, and nuclear spin states. These energy states are said to be **quantized.** More of the molecules exist in the lower energy state E_1 than in the higher energy state E_2. Excitation of a molecule from a lower state to a higher one requires the addition of an increment of energy equal to ΔE. Thus, when electromagnetic radiation is incident upon a molecule, only the frequency whose corresponding energy equals ΔE is absorbed. All other frequencies are transmitted.

Spectrometers are designed to measure the absorption of electromagnetic radiation by a sample. Basically, a spectrometer consists of a source of radiation, a compartment containing the sample through which the radiation passes, and a detector. The frequency of radiation is continuously varied, and its intensity at the detector is compared with that at the source. When the frequency is reached at which the sample absorbs radiation, the detector senses a decrease in intensity. The relation between frequency and absorption is plotted on a strip chart and is called a **spectrum.** A spectrum consists of a series of peaks at particular frequencies; its interpretation can provide structural information. Each type of spectroscopy developed independently of the others, and so the format followed in presenting the data is different for each one. An NMR spectrum looks different from an IR spectrum, and both look different from a UV-VIS spectrum.

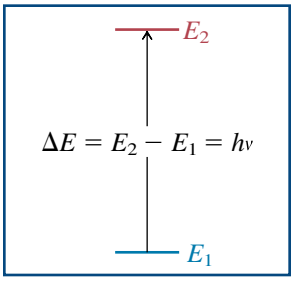


FIGURE 13.2 Two energy states of a molecule. Absorption of energy equal to $E_2 - E_1$ excites a molecule from its lower energy state to the next higher state.

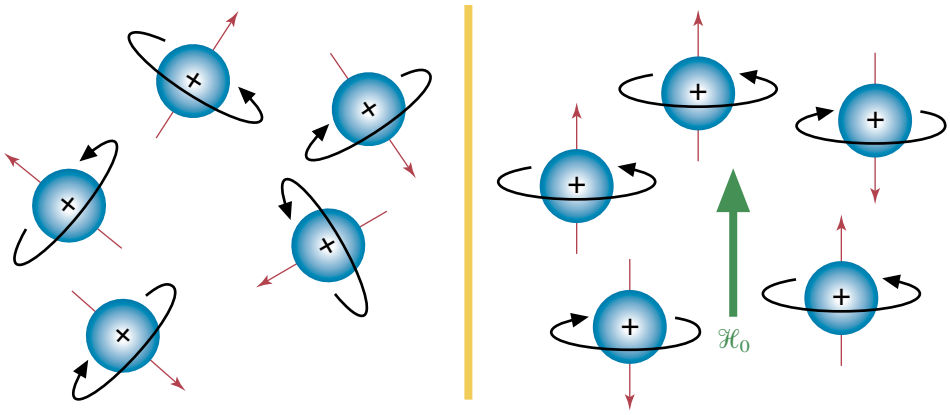
With this as background, we will now discuss spectroscopic techniques individually. NMR, IR, and UV-VIS spectroscopy provide complementary information, and all are useful. Among them, NMR provides the information that is most directly related to molecular structure and is the one we shall examine first.

13.3 INTRODUCTION TO ^{1}H NMR SPECTROSCOPY

Nuclear magnetic resonance of protons was first detected in 1946 by Edward Purcell (Harvard) and by Felix Bloch (Stanford). Purcell and Bloch shared the 1952 Nobel Prize in physics.

Nuclear magnetic resonance spectroscopy depends on the absorption of energy when the nucleus of an atom is excited from its lowest energy spin state to the next higher one. We should first point out that many elements are difficult to study by NMR, and some can't be studied at all. Fortunately though, the two elements that are the most common in organic molecules (carbon and hydrogen) have isotopes (^{1}H and ^{13}C) capable of giving NMR spectra that are rich in structural information. A proton nuclear magnetic resonance (^{1}H NMR) spectrum tells us about the environments of the various hydrogens in a molecule; a carbon-13 nuclear magnetic resonance (^{13}C NMR) spectrum does the same for the carbon atoms. Separately and together ^{1}H and ^{13}C NMR take us a long way toward determining a substance's molecular structure. We'll develop most of the general principles of NMR by discussing ^{1}H NMR, then extend them to ^{13}C NMR. The ^{13}C NMR discussion is shorter, not because it is less important than ^{1}H NMR, but because many of the same principles apply to both techniques.

Like an electron, a proton has two spin states with quantum numbers of $+\frac{1}{2}$ and $-\frac{1}{2}$. There is no difference in energy between these two nuclear spin states; a proton is just as likely to have a spin of $+\frac{1}{2}$ as $-\frac{1}{2}$. Absorption of electromagnetic radiation can only occur when the two spin states have different energies. A way to make them different is to place the sample in a magnetic field. A proton behaves like a tiny bar magnet and has a magnetic moment associated with it (Figure 13.3). In the presence of an external magnetic field $\mathcal{H}_0$, the state in which the magnetic moment of the nucleus is aligned with $\mathcal{H}_0$ is lower in energy than the one in which it opposes $\mathcal{H}_0$.



(*a*) No external magnetic field (*b*) Apply external magnetic field $\mathcal{H}_0$

FIGURE 13.3 (*a*) In the absence of an external magnetic field, the nuclear spins of the protons are randomly oriented. (*b*) In the presence of an external magnetic field $\mathcal{H}_0$, the nuclear spins are oriented so that the resulting nuclear magnetic moments are aligned either parallel or antiparallel to $\mathcal{H}_0$. The lower energy orientation is the one parallel to $\mathcal{H}_0$ and there are more nuclei that have this orientation.

As shown in Figure 13.4, the energy difference between the two states is directly proportional to the strength of the applied field. Net absorption of electromagnetic radiation requires that the lower state be more highly populated than the higher one, and quite strong magnetic fields are required to achieve the separation necessary to give a detectable signal. A magnetic field of 4.7 T, which is about 100,000 times stronger than earth's magnetic field, for example, separates the two spin states of ^{1}H by only 8×10^{-5} kJ/mol (1.9×10^{-5} kcal/mol). From Planck's equation $\Delta E = h\nu$, this energy gap corresponds to radiation having a frequency of 2×10^8 Hz (200 MHz) which lies in the radio frequency (rf) region of the electromagnetic spectrum (see Figure 13.1).

The SI unit for magnetic field strength is the tesla (T), named after Nikola Tesla, a contemporary of Thomas Edison and who, like Edison, was an inventor of electrical devices.

Frequency of electromagnetic radiation (s^{-1} or Hz) → (is proportional to) Energy difference between nuclear spin states (kJ/mol or kcal/mol) → (is proportional to) Magnetic field (T)

PROBLEM 13.1 Most of the NMR spectra in this text were recorded on a spectrometer having a field strength of 4.7 T (200 MHz for ^{1}H). The first generation of widely used NMR spectrometers were 60-MHz instruments. What was the magnetic field strength of these earlier spectrometers?

The response of an atom to the strength of the external magnetic field is different for different elements, and for different isotopes of the same element. The resonance frequencies of most nuclei are sufficiently different that an NMR experiment is sensitive only to a particular isotope of a single element. The frequency for ^{1}H is 200 MHz at 4.7 T, but that of ^{13}C is 50.4 MHz. Thus, when recording the NMR spectrum of an organic compound, we see signals only for ^{1}H or ^{13}C, but not both; ^{1}H and ^{13}C NMR spectra are recorded in separate experiments with different instrument settings.

PROBLEM 13.2 What will be the ^{13}C frequency setting of an NMR spectrometer that operates at 100 MHz for protons?

The essential features of an NMR spectrometer, shown in Figure 13.5, are not hard to understand. They consist of a magnet to align the nuclear spins, a radiofrequency (rf) transmitter as a source of energy to excite a nucleus from its lowest energy state to the next higher one, a receiver to detect the absorption of rf radiation, and a recorder to print out the spectrum.

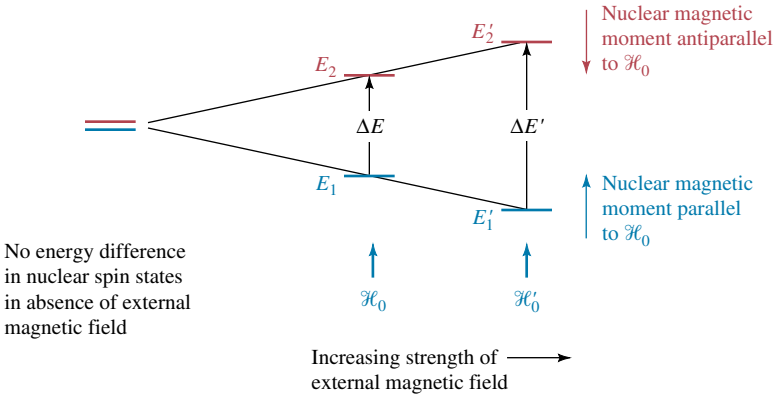


FIGURE 13.4 An external magnetic field causes the two nuclear spin states to have different energies. The difference in energy ΔE is proportional to the strength of the applied field.

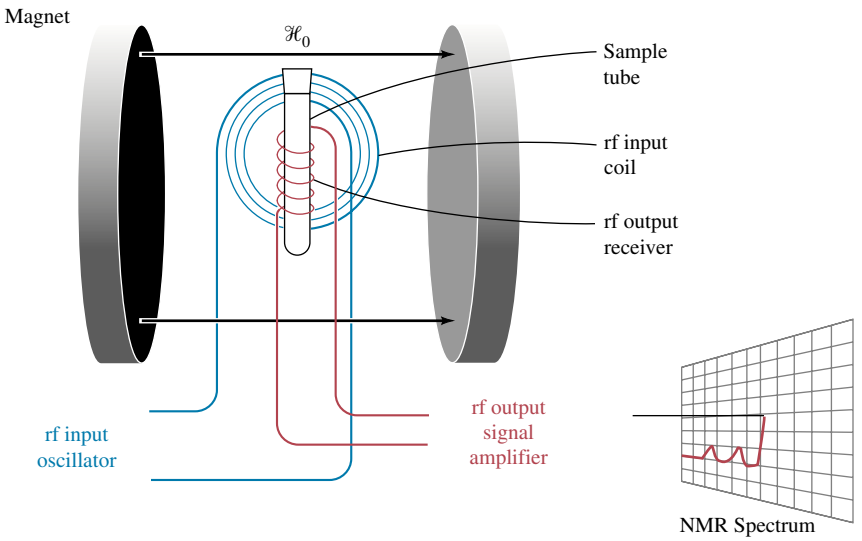


FIGURE 13.5 Diagram of a nuclear magnetic resonance spectrometer. *(From S. H. Pine, J. B. Hendrickson, D. J. Cram, and G. S. Hammond,* Organic Chemistry, *4th edition, McGraw-Hill, New York, 1980, p. 136.)*

It turns out though that there are several possible variations on this general theme. We could, for example, keep the magnetic field constant and continuously vary the radiofrequency until it matched the energy difference between the nuclear spin states. Or, we could keep the rf constant and adjust the energy levels by varying the magnetic field strength. Both methods work, and the instruments based on them are called *continuous wave* (CW) spectrometers. Many of the terms we use in NMR spectroscopy have their origin in the way CW instruments operate, but CW instruments are rarely used anymore.

CW-NMR spectrometers have been replaced by a new generation of instruments called *pulsed Fourier-transform* nuclear magnetic resonance (FT-NMR) spectrometers. FT-NMR spectrometers are far more versatile than CW instruments and are more complicated. Most of the visible differences between them lie in computerized data acquisition and analysis components that are fundamental to FT-NMR spectroscopy. But there is an important difference in how a pulsed FT-NMR experiment is carried out as well. Rather than sweeping through a range of frequencies (or magnetic field strengths), the sample is irradiated with a short, intense burst of radiofrequency radiation (the *pulse*) that excites all of the protons in the molecule. The magnetic field associated with the new orientation of nuclear spins induces an electrical signal in the receiver that decreases with time as the nuclei return to their original orientation. The resulting *free-induction decay* (FID) is a composite of the decay patterns of all of the protons in the molecule. The free-induction decay pattern is stored in a computer and converted into a spectrum by a mathematical process known as a *Fourier transform.* The pulse-relaxation sequence takes only about a second, but usually gives signals too weak to distinguish from background noise. The signal-to-noise ratio is enhanced by repeating the sequence many times, then averaging the data. Noise is random and averaging causes it to vanish; signals always appear at the same place and accumulate. All of the operations—the interval between pulses, collecting, storing, and averaging the data and converting it to a spectrum by a Fourier transform—are under computer control, which makes the actual taking of an FT-NMR spectrum a fairly routine operation.

Richard R. Ernst of the Swiss Federal Institute of Technology won the 1991 Nobel Prize in chemistry for devising pulse-relaxation NMR techniques.

Not only is pulsed FT-NMR the best method for obtaining proton spectra, it is the only practical method for many other nuclei, including ^{13}C. It also makes possible a large number of sophisticated techniques that have revolutionized NMR spectroscopy.

13.4 NUCLEAR SHIELDING AND ^{1}H CHEMICAL SHIFTS

Our discussion so far has concerned ^{1}H nuclei in general without regard for the environments of individual protons in a molecule. Protons in a molecule are connected to other atoms—carbon, oxygen, nitrogen, and so on—by covalent bonds. The electrons in these bonds, indeed all the electrons in a molecule, affect the magnetic environment of the protons. Alone, a proton would feel the full strength of the external field, but a proton in an organic molecule responds to both the external field plus any local fields within the molecule. An external magnetic field affects the motion of the electrons in a molecule, inducing local fields characterized by lines of force that circulate in the *opposite* direction from the applied field (Figure 13.6). Thus, the net field felt by a proton in a molecule will always be less than the applied field, and the proton is said to be **shielded.** All of the protons of a molecule are shielded from the applied field by the electrons, but some are less shielded than others. Sometimes the term "deshielded," is used to describe this decreased shielding of one proton relative to another.

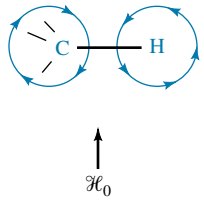


FIGURE 13.6 The induced magnetic field of the electrons in the carbon–hydrogen bond opposes the external magnetic field. The resulting magnetic field experienced by the proton and the carbon is slightly less than $\mathcal{H}_0$.

The more shielded a proton is, the greater must be the strength of the applied field in order to achieve resonance and produce a signal. A more shielded proton absorbs rf radiation at higher field strength **(upfield)** compared with one at lower field strength **(downfield).** Different protons give signals at different field strengths. *The dependence of the resonance position of a nucleus that results from its molecular environment is called its* **chemical shift.** This is where the real power of NMR lies. The chemical shifts of various protons in a molecule can be different and are characteristic of particular structural features.

Figure 13.7 shows the ^{1}H NMR spectrum of chloroform ($CHCl_3$) to illustrate how the terminology just developed applies to a real spectrum.

Instead of measuring chemical shifts in absolute terms, we measure them with respect to a standard—*tetramethylsilane* $(CH_3)_4Si$, abbreviated *TMS.* The protons of TMS are more shielded than those of most organic compounds, so all of the signals in a sample ordinarily appear at lower field than those of the TMS reference. When measured using a 100-MHz instrument, the signal for the proton in chloroform ($CHCl_3$), for example, appears 728 Hz downfield from the TMS signal. But since frequency is proportional to magnetic field strength, the same signal would appear 1456 Hz downfield from TMS on a 200-MHz instrument. We simplify the reporting of chemical shifts by converting them to parts per million (ppm) from TMS, which is assigned a value of 0. The TMS need not actually be present in the sample, nor even appear in the spectrum in order to serve as a reference.

The graphic that begins this chapter is an electrostatic potential map of tetramethylsilane. *Learning By Modeling* contains models of $(CH_3)_4Si$ and $(CH_3)_4C$ in which the greater electron density at the carbons and hydrogens of TMS is apparent both in the electrostatic potential and in the calculated atomic charges.

$$\text{Chemical shift } (\delta) = \frac{\text{position of signal} - \text{position of TMS peak}}{\text{spectrometer frequency}} \times 10^6$$

Thus, the chemical shift for the proton in chloroform is:

$$\delta = \frac{1456 \text{ Hz} - 0 \text{ Hz}}{200 \times 10^6 \text{ Hz}} \times 10^6 = 7.28 \text{ ppm}$$

When chemical shifts are reported this way, they are identified by the symbol δ and are independent of the field strength.

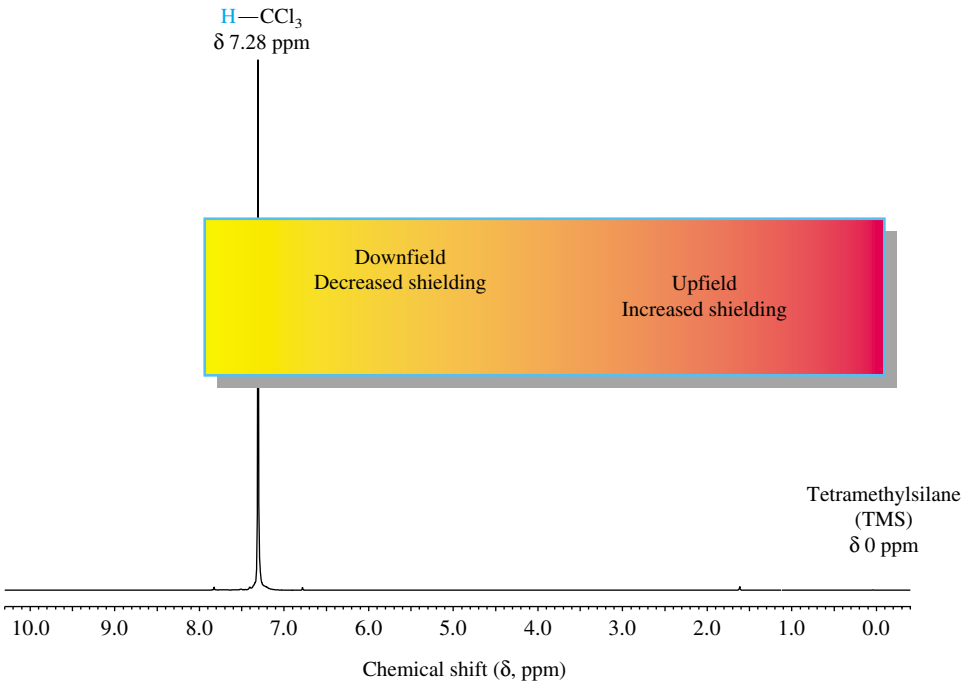


FIGURE 13.7 The 200-MHz ^{1}H NMR spectrum of chloroform ($HCCl_3$). Chemical shifts are measured along the *x*-axis in parts per million (ppm) from tetramethylsilane as the reference, which is assigned a value of zero.

PROBLEM 13.3 The ^{1}H NMR signal for bromoform ($CHBr_3$) appears at 2065 Hz when recorded on a 300-MHz NMR spectrometer. (a) What is the chemical shift of this proton? (b) Is the proton in $CHBr_3$ more shielded or less shielded than the proton in $CHCl_3$?

NMR spectra are usually run in solution and, although chloroform is a good solvent for most organic compounds, it's rarely used because its own signal at δ 7.28 ppm would be so intense that it would obscure signals in the sample. Because the magnetic properties of deuterium (D = ^{2}H) are different from those of ^{1}H, $CDCl_3$ gives no signals at all in an ^{1}H NMR spectrum and is used instead. Indeed, $CDCl_3$ is the most commonly used solvent in ^{1}H NMR spectroscopy. Likewise, D_2O is used instead of H_2O for water-soluble substances such as carbohydrates.

13.5 EFFECTS OF MOLECULAR STRUCTURE ON ^{1}H CHEMICAL SHIFTS

Nuclear magnetic resonance spectroscopy is such a powerful tool for structure determination because *protons in different environments experience different degrees of shielding and have different chemical shifts.* In compounds of the type CH_3X, for example, the shielding of the methyl protons increases as X becomes less electronegative. Inas-

Problem 13.3 in the preceding section was based on the chemical shift difference between the proton in $CHCl_3$ and the proton in $CHBr_3$ and its relation to shielding.

much as the shielding is due to the electrons, it isn't surprising to find that the chemical shift depends on the degree to which X draws electrons away from the methyl group.

Increased shielding of methyl protons
Decreasing electronegativity of attached atom

	CH_3F	CH_3OCH_3	$(CH_3)_3N$	CH_3CH_3
	Methyl fluoride	Dimethyl ether	Trimethylamine	Ethane
Chemical shift of methyl protons (δ), ppm:	4.3	3.2	2.2	0.9

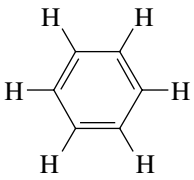
A similar trend is seen in the methyl halides, in which the protons in CH_3F are the least shielded (δ 4.3 ppm) and those of CH_3I (δ 2.2 ppm) are the most.

The deshielding effects of electronegative substituents are cumulative, as the chemical shifts for various chlorinated derivatives of methane indicate:

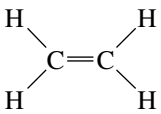
	$CHCl_3$	CH_2Cl_2	CH_3Cl
	Chloroform (trichloromethane)	Methylene chloride (dichloromethane)	Methyl chloride (chloromethane)
Chemical shift (δ), ppm:	7.3	5.3	3.1

PROBLEM 13.4 There is a difference of 4.6 ppm in the ^{1}H chemical shifts of $CHCl_3$ and CH_3CCl_3. What is the chemical shift for the protons in CH_3CCl_3? Explain your reasoning.

Vinyl protons in alkenes and aryl protons in arenes are substantially less shielded than protons in alkanes:



Benzene



Ethylene

CH_3CH_3

Ethane

	Benzene	Ethylene	Ethane
Chemical shift (δ), ppm:	7.3	5.3	0.9

One reason for the decreased shielding of vinyl and aryl protons is related to the directional properties of the induced magnetic field of the π electrons. As Figure 13.8 shows, the induced magnetic field due to the π electrons is just like that due to electrons in σ bonds; it opposes the applied magnetic field. However, all magnetic fields close upon themselves, and protons attached to a carbon–carbon double bond or an aromatic ring lie in a region where the induced field reinforces the applied field, which decreases the shielding of vinyl and aryl protons.

A similar, although much smaller, effect of π electron systems is seen in the chemical shifts of benzylic and allylic hydrogens. The methyl hydrogens in hexamethylbenzene and in 2,3-dimethyl-2-butene are less shielded than those in ethane.

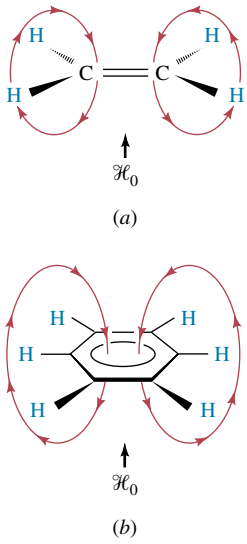
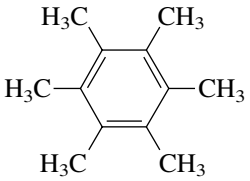
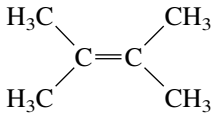


FIGURE 13.8 The induced magnetic field of the π electrons of (*a*) an alkene and (*b*) an arene reinforces the applied fields in the regions where vinyl and aryl protons are located.



Hexamethylbenzene

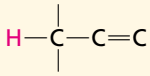
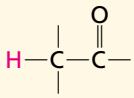
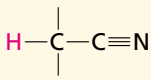
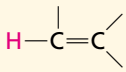
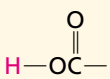


2,3-Dimethyl-2-butene

Chemical shift (δ), ppm:	2.2	1.7

Table 13.1 collects chemical-shift information for protons of various types. Within each type, methyl (CH_3) protons are more shielded than methylene (CH_2) protons, and methylene protons are more shielded than methine (CH) protons. These differences are small—only about 0.7 ppm separates a methyl proton from a methine proton of the same type. Overall, proton chemical shifts among common organic compounds encompass a range of about 12 ppm. The protons in alkanes are the most shielded, and O—H protons of carboxylic acids are the least shielded.

TABLE 13.1 Chemical Shifts of Representative Types of Protons

Type of proton	Chemical shift (δ), ppm*	Type of proton	Chemical shift (δ), ppm*
	0.9–1.8		2.2–2.9
	1.6–2.6		3.1–4.1
	2.1–2.5		2.7–4.1
	2.1–3		3.3–3.7
	2.5		
	2.3–2.8		1–3†
	4.5–6.5		0.5–5†
	6.5–8.5		6–8†
	9–10		10–13†

*Approximate values relative to tetramethylsilane; other groups within the molecule can cause a proton signal to appear outside of the range cited.
†The chemical shifts of protons bonded to nitrogen and oxygen are temperature- and concentration-dependent.

The ability of an NMR spectrometer to separate signals that have similar chemical shifts is termed its *resolving power* and is directly related to the magnetic field strength of the instrument. Two closely spaced signals at 60 MHz become well separated if a 300-MHz instrument is used. (Remember, though, that the chemical shift δ, cited in parts per million, is independent of the field strength.)

13.6 INTERPRETING PROTON NMR SPECTRA

Analyzing an NMR spectrum in terms of a unique molecular structure begins with the information contained in Table 13.1. By knowing the chemical shifts characteristic of various proton environments, the presence of a particular structural unit in an unknown compound may be inferred. An NMR spectrum also provides other useful information, including:

1. *The number of signals,* which tells us how many different kinds of protons there are.
2. *The intensity of the signals* as measured by the area under each peak, which tells us the relative ratios of the different kinds of protons.
3. *The multiplicity, or splitting, of each signal,* which tells us how many protons are vicinal to the one giving the signal.

Protons that have different chemical shifts are said to be **chemical-shift-nonequivalent** (or **chemically nonequivalent**). A separate NMR signal is given for each chemical-shift-nonequivalent proton in a substance. Figure 13.9 shows the 200-MHz ^{1}H NMR spectrum of methoxyacetonitrile (CH_3OCH_2CN), a molecule with protons in two different environments. The three protons in the CH_3O group constitute one set, the two

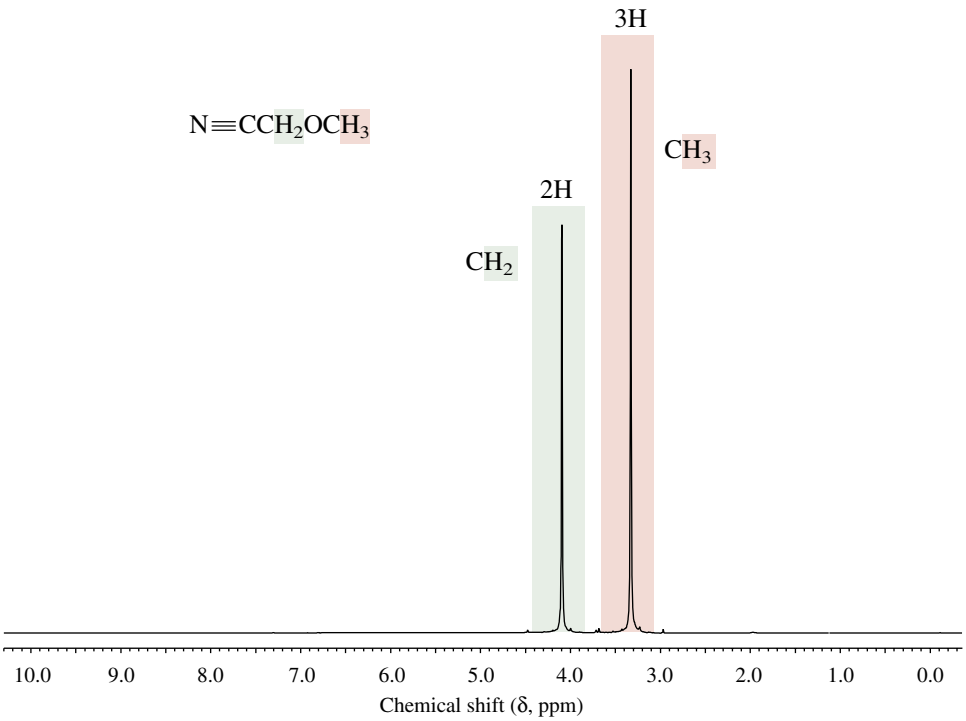


FIGURE 13.9 The 200-MHz ^{1}H NMR spectrum of methoxyacetonitrile (CH_3OCH_2CN).

protons in the OCH_2CN group the other. These two sets of protons give rise to the two peaks that we see in the NMR spectrum and can be assigned on the basis of their chemical shifts. The protons in the OCH_2CN group are connected to a carbon that bears two electronegative substituents (O and C≡N) and are less shielded than those of the CH_3O group, which are attached to a carbon that bears only one electronegative atom (O). The signal for the protons in the OCH_2CN group appears at δ 4.1 ppm; the signal corresponding to the CH_3O protons is at δ 3.3 ppm.

Another way to assign the peaks is by comparing their intensities. The three equivalent protons of the CH_3O group give rise to a more intense peak than the two equivalent protons of the OCH_2CN group. This is clear by simply comparing the heights of the peaks in the spectrum. It is better, though, to compare peak areas by a process called **integration.** This is done electronically at the time the NMR spectrum is recorded, and the integrated areas are displayed on the computer screen or printed out. Peak areas are proportional to the number of equivalent protons responsible for that signal.

It is important to remember that integration of peak areas gives relative, not absolute, proton counts. Thus, a 3:2 ratio of areas can, as in the case of CH_3OCH_2CN, correspond to a 3:2 ratio of protons. But in some other compound a 3:2 ratio of areas might correspond to a 6:4 or 9:6 ratio of protons.

PROBLEM 13.5 The 200-MHz ^1H NMR spectrum of 1,4-dimethylbenzene looks exactly like that of CH_3OCH_2CN except the chemical shifts of the two peaks are δ 2.2 ppm and δ 7.0 ppm. Assign the peaks to the appropriate protons of 1,4-dimethylbenzene.

Protons are equivalent to one another and have the same chemical shift when they are in equivalent environments. Often it is an easy matter to decide, simply by inspection, when protons are equivalent or not. In more difficult cases, mentally replacing a proton in a molecule by a "test group" can help. We'll illustrate the procedure for a simple case—the protons of propane. To see if they have the same chemical shift, replace one of the methyl protons at C-1 by chlorine, then do the same thing for a proton at C-3. Both replacements give the same molecule, 1-chloropropane. Therefore the methyl protons at C-1 are equivalent to those at C-3.

$CH_3CH_2CH_3$	$ClCH_2CH_2CH_3$	$CH_3CH_2CH_2Cl$
Propane	1-Chloropropane	1-Chloropropane

If the two structures produced by mental replacement of two different hydrogens in a molecule by a test group are the same, the hydrogens are chemically equivalent. Thus, the six methyl protons of propane are all chemically equivalent to one another and have the same chemical shift.

Replacement of either one of the methylene protons of propane generates 2-chloropropane. Both methylene protons are equivalent. Neither of them is equivalent to any of the methyl protons.

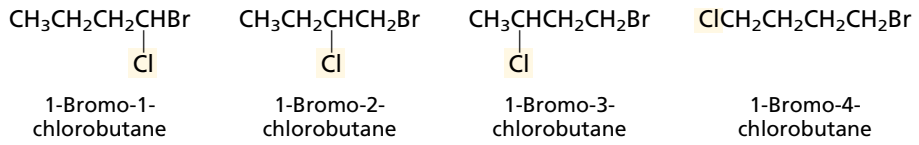
The ^1H NMR spectrum of propane contains two signals: one for the six equivalent methyl protons, the other for the pair of equivalent methylene protons.

PROBLEM 13.6 How many signals would you expect to find in the ^1H NMR spectrum of each of the following compounds?

(a) 1-Bromobutane
(b) 1-Butanol
(c) Butane
(d) 1,4-Dibromobutane

(e) 2,2-Dibromobutane
(f) 2,2,3,3-Tetrabromobutane
(g) 1,1,4-Tribromobutane
(h) 1,1,1-Tribromobutane

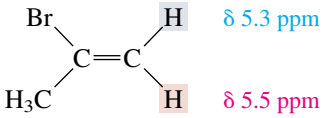
SAMPLE SOLUTION (a) To test for chemical-shift equivalence, replace the protons at C-1, C-2, C-3, and C-4 of 1-bromobutane by some test group such as chlorine. Four constitutional isomers result:



1-Bromo-1-chlorobutane | 1-Bromo-2-chlorobutane | 1-Bromo-3-chlorobutane | 1-Bromo-4-chlorobutane

Thus, separate signals will be seen for the protons at C-1, C-2, C-3, and C-4. Barring any accidental overlap, we expect to find four signals in the NMR spectrum of 1-bromobutane.

Chemical-shift nonequivalence can occur when two environments are stereochemically different. The two vinyl protons of 2-bromopropene have different chemical shifts.



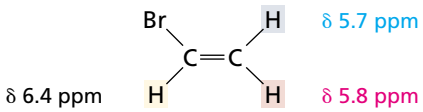
2-Bromopropene

One of the vinyl protons is cis to bromine; the other trans. Replacing one of the vinyl protons by some test group, say, chlorine, gives the *Z* isomer of 2-bromo-1-chloropropene; replacing the other gives the *E* stereoisomer. The *E* and *Z* forms of 2-bromo-1-chloropropene are stereoisomers that are not enantiomers; they are diastereomers. Protons that yield diastereomers on being replaced by some test group are described as **diastereotopic.** *The vinyl protons of 2-bromopropene are diastereotopic.* Diastereotopic protons can have different chemical shifts. Because their environments are similar, however, this difference in chemical shift is usually small, and it sometimes happens that two diastereotopic protons accidentally have the same chemical shift. Recording the spectrum on a higher field NMR spectrometer is often helpful in resolving signals with similar chemical shifts.

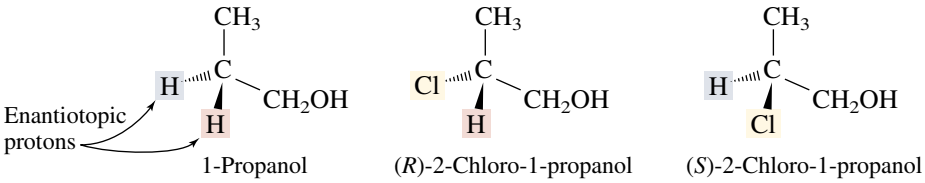
PROBLEM 13.7 How many signals would you expect to find in the ^{1}H NMR spectrum of each of the following compounds?

(a) Vinyl bromide
(b) 1,1-Dibromoethene
(c) *cis*-1,2-Dibromoethene
(d) *trans*-1,2-Dibromoethene
(e) Allyl bromide
(f) 2-Methyl-2-butene

SAMPLE SOLUTION (a) Each proton of vinyl bromide is unique and has a chemical shift different from the other two. The least shielded proton is attached to the carbon that bears the bromine. The pair of protons at C-2 are diastereotopic with respect to each other; one is cis to bromine while the other is trans to bromine. There are three proton signals in the NMR spectrum of vinyl bromide. Their observed chemical shifts are as indicated.



When enantiomers are generated by replacing first one proton and then another by a test group, the pair of protons are **enantiotopic** with respect to one another. *The methylene protons at C-2 of 1-propanol, for example, are enantiotopic.*



Enantiotopic protons can have different chemical shifts in a chiral solvent. Because the customary solvent ($CDCl_3$) used in NMR measurements is achiral, this phenomenon is not observed in routine work.

Replacing one of these protons by chlorine as a test group gives (*R*)-2-chloro-1-propanol; replacing the other gives (*S*)-2-chloro-1-propanol. Enantiotopic protons have the same chemical shift, regardless of the field strength of the NMR spectrometer.

At the beginning of this section we noted that an NMR spectrum provides structural information based on chemical shift, the number of peaks, their relative areas, and the multiplicity, or splitting, of the peaks. We have discussed the first three of these features of ^{1}H NMR spectroscopy. Let's now turn our attention to peak splitting to see what kind of information it offers.

13.7 SPIN–SPIN SPLITTING IN NMR SPECTROSCOPY

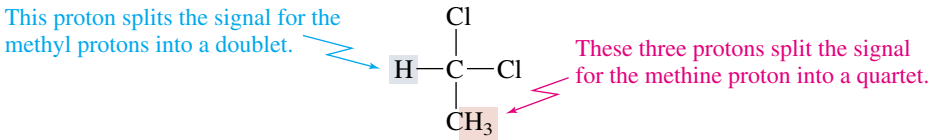
The ^{1}H NMR spectrum of CH_3OCH_2CN (see Figure 13.9) discussed in the preceding section is relatively simple because both signals are **singlets;** that is, each one consists of a single peak. It is quite common though to see a signal for a particular proton appear not as a singlet, but as a collection of peaks. The signal may be split into two peaks (a **doublet**), three peaks (a **triplet**), four peaks (a **quartet**), or even more. Figure 13.10 shows the ^{1}H NMR spectrum of 1,1-dichloroethane (CH_3CHCl_2), which is characterized by a doublet centered at δ 2.1 ppm for the methyl protons and a quartet at δ 5.9 ppm for the methine proton.

The number of peaks into which the signal for a particular proton is split is called its **multiplicity.** For simple cases the rule that allows us to predict splitting in ^{1}H NMR spectroscopy is

More complicated splitting patterns conform to an extension of the "$n + 1$" rule and will be discussed in Section 13.11.

$$\text{Multiplicity of signal for } H_a = n + 1$$

where n is equal to the number of equivalent protons that are vicinal to H_a. Two protons are vicinal to each other when they are bonded to adjacent atoms. Protons vicinal to H_a are separated from H_a by three bonds. The three methyl protons of 1,1-dichloroethane are vicinal to the methine proton and split its signal into a quartet. The single methine proton, in turn, splits the methyl protons' signal into a doublet.



The physical basis for peak splitting in 1,1-dichloroethane can be explained with the aid of Figure 13.11, which examines how the chemical shift of the methyl protons is affected by the spin of the methine proton. There are two magnetic environments for the methyl protons: one in which the magnetic moment of the methine proton is parallel to the applied field, and the other in which it is antiparallel to it. When the magnetic

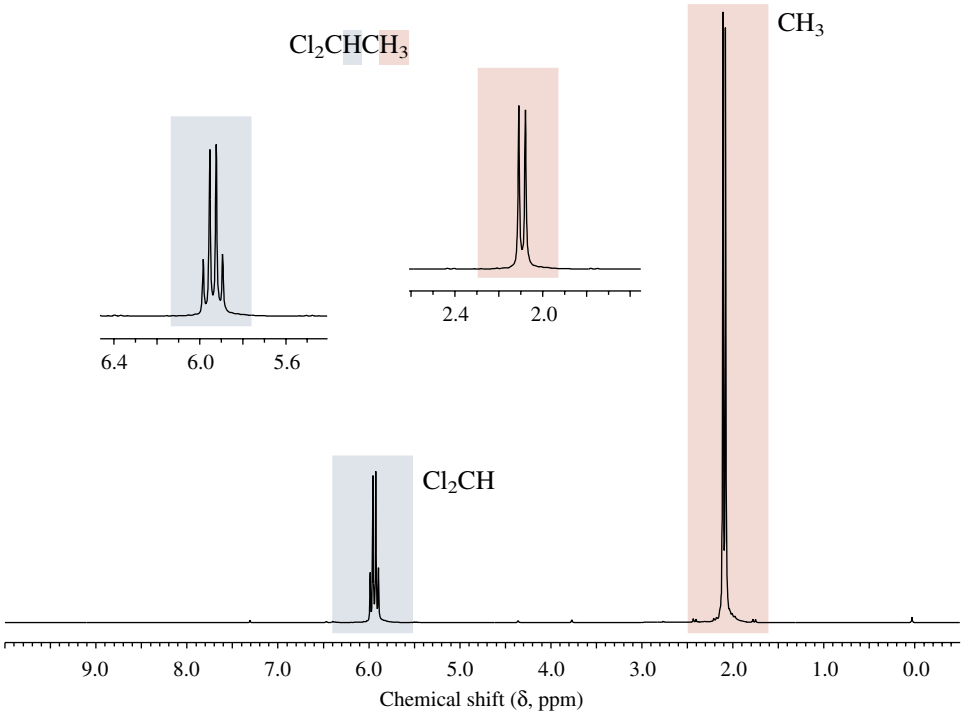
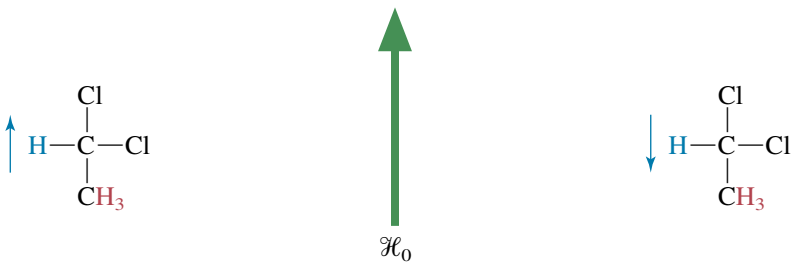


FIGURE 13.10 The 200-MHz ^{1}H NMR spectrum of 1,1-dichloroethane, showing the methine proton as a quartet and the methyl protons as a doublet. The peak multiplicities are seen more clearly in the scale-expanded insets.

moment of the methine proton is parallel to the applied field, it reinforces it. This decreases the shielding of the methyl protons and causes their signal to appear at slightly lower field strength. Conversely, when the magnetic moment of the methine proton is antiparallel to the applied field, it opposes it and increases the shielding of the methyl protons. Instead of a single peak for the methyl protons, there are two of approximately equal intensity: one at slightly higher field than the "true" chemical shift, the other at slightly lower field.

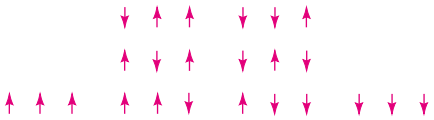
Turning now to the methine proton, its signal is split by the methyl protons into a quartet. The same kind of analysis applies here and is outlined in Figure 13.12. The methine proton "sees" eight different combinations of nuclear spins for the methyl



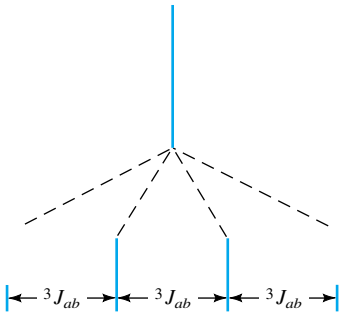
Spin of methine proton reinforces $\mathcal{H}_0$; a weaker $\mathcal{H}_0$ is needed for resonance. Methyl signal appears at lower field.

Spin of methine proton shields methyl protons from $\mathcal{H}_0$. Methyl signal appears at higher field.

FIGURE 13.11 The magnetic moments *(blue arrows)* of the two possible spin states of the methine proton affect the chemical shift of the methyl protons in 1,1-dichloroethane. When the magnetic moment is parallel to the external field $\mathcal{H}_0$ *(green arrow),* it adds to the external field and a smaller $\mathcal{H}_0$ is needed for resonance. When it is antiparallel to the external field, it subtracts from it and shields the methyl protons.



There are eight possible combinations of the nuclear spins of the three methyl protons in CH_3CHCl_2.



These eight combinations cause the signal of the $CHCl_2$ proton to be split into a quartet, in which the intensities of the peaks are in the ratio 1:3:3:1.

FIGURE 13.12 The methyl protons of 1,1-dichloroethane split the signal of the methine proton into a quartet.

protons. In one combination, the magnetic moments of all three methyl protons reinforce the applied field. At the other extreme, the magnetic moments of all three methyl protons oppose the applied field. There are three combinations in which the magnetic moments of two methyl protons reinforce the applied field, whereas one opposes it. Finally, there are three combinations in which the magnetic moments of two methyl protons oppose the applied field and one reinforces it. These eight possible combinations give rise to four distinct peaks for the methine proton, with a ratio of intensities of 1:3:3:1.

We describe the observed splitting of NMR signals as **spin–spin splitting** and the physical basis for it as **spin–spin coupling.** It has its origin in the communication of nuclear spin information between nuclei. This information is transmitted by way of the electrons in the bonds that intervene between the nuclei. Its effect is greatest when the number of bonds is small. Vicinal protons are separated by three bonds, and coupling between vicinal protons, as in 1,1-dichloroethane, is called **three-bond coupling** or **vicinal coupling.** Four-bond couplings are weaker and not normally observable.

A very important characteristic of spin–spin splitting is that protons that have the same chemical shift do not split each other's signal. Ethane, for example, shows only a single sharp peak in its NMR spectrum. Even though there is a vicinal relationship between the protons of one methyl group and those of the other, they do not split each other's signal because they are equivalent.

PROBLEM 13.8 Describe the appearance of the ^{1}H NMR spectrum of each of the following compounds. How many signals would you expect to find, and into how many peaks will each signal be split?

(a) 1,2-Dichloroethane
(b) 1,1,1-Trichloroethane
(c) 1,1,2-Trichloroethane
(d) 1,2,2-Trichloropropane
(e) 1,1,1,2-Tetrachloropropane

SAMPLE SOLUTION (a) All the protons of 1,2-dichloroethane ($ClCH_2CH_2Cl$) are chemically equivalent and have the same chemical shift. Protons that have the same chemical shift do not split each other's signal, and so the NMR spectrum of 1,2-dichloroethane consists of a single sharp peak.

Coupling of nuclear spins requires that the nuclei split each other's signal equally. The separation between the two halves of the methyl doublet in 1,1-dichloroethane is equal to the separation between any two adjacent peaks of the methine quartet. The extent to which two nuclei are coupled is known as the **coupling constant *J*** and in simple cases is equal to the separation between adjacent lines of the signal of a particular proton. The three-bond coupling constant $^3J_{ab}$ in 1,1-dichloroethane has a value of 7 Hz. *The size of the coupling constant is independent of the field strength;* the separation between adjacent peaks in 1,1-dichloroethane is 7 Hz, irrespective of whether the spectrum is recorded at 200 MHz or 500 MHz.

13.8 SPLITTING PATTERNS: THE ETHYL GROUP

At first glance, splitting may seem to complicate the interpretation of NMR spectra. In fact, it makes structure determination easier because it provides additional information. It tells us how many protons are vicinal to a proton responsible for a particular signal. With practice, we learn to pick out characteristic patterns of peaks, associating them with particular structural types. One of the most common of these patterns is that of the ethyl group, represented in the NMR spectrum of ethyl bromide in Figure 13.13.

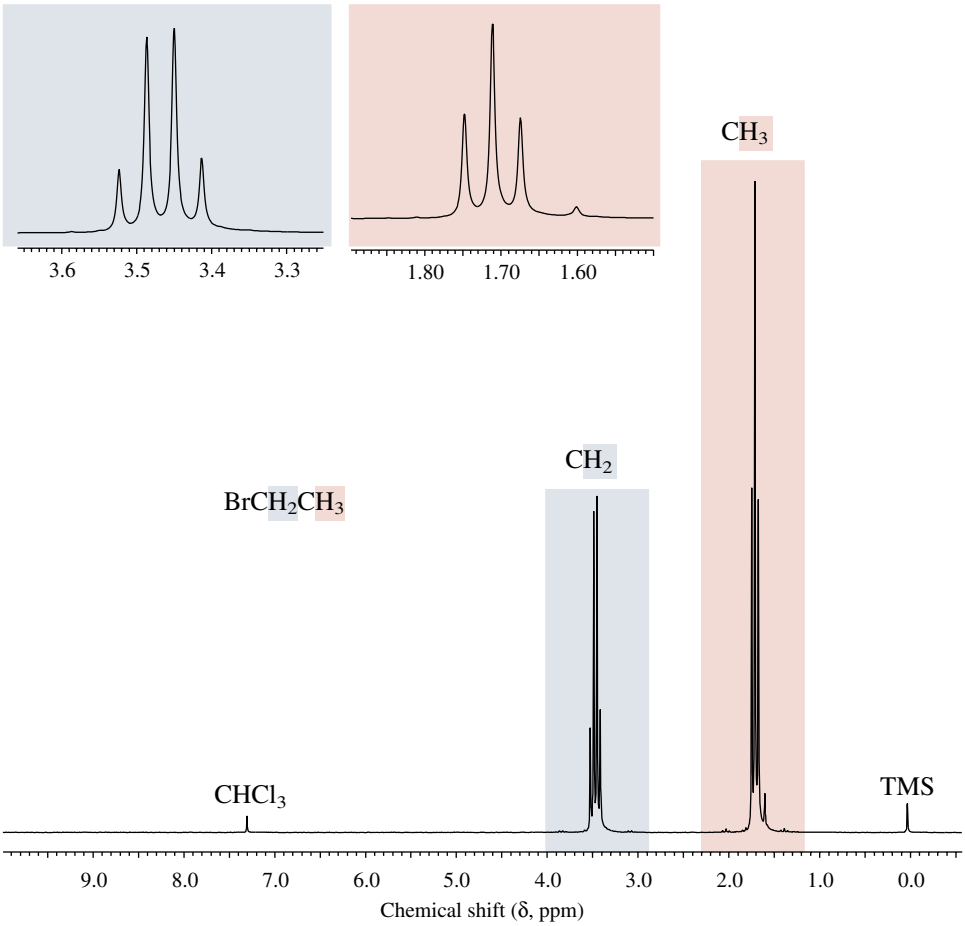
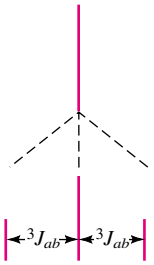


FIGURE 13.13 The 200-MHz ^{1}H NMR spectrum of ethyl bromide, showing the characteristic triplet–quartet pattern of an ethyl group.

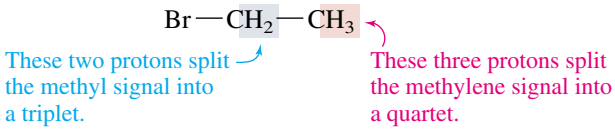
There are four possible combinations of the nuclear spins of the two methylene protons in CH_3CH_2Br.



These four combinations cause the signal of the CH_3 protons to be split into a triplet, in which the intensities of the peaks are in the ratio 1:2:1.

FIGURE 13.14 The methylene protons of ethyl bromide split the signal of the methyl protons into a triplet.

In compounds of the type CH_3CH_2X, especially where X is an electronegative atom or group, such as bromine in ethyl bromide, the ethyl group appears as a *triplet–quartet pattern.* The methylene proton signal is split into a quartet by coupling with the methyl protons. The signal for the methyl protons is a triplet because of vicinal coupling to the two protons of the adjacent methylene group.



We have discussed in the preceding section why methyl groups split the signals due to vicinal protons into a quartet. Splitting by a methylene group gives a triplet corresponding to the spin combinations shown in Figure 13.14 for ethyl bromide. The relative intensities of the peaks of this triplet are 1:2:1.

PROBLEM 13.9 Describe the appearance of the ^1H NMR spectrum of each of the following compounds. How many signals would you expect to find, and into how many peaks will each signal be split?

(a) $ClCH_2OCH_2CH_3$
(b) $CH_3CH_2OCH_3$
(c) $CH_3CH_2OCH_2CH_3$
(d) *p*-Diethylbenzene
(e) $ClCH_2CH_2OCH_2CH_3$

SAMPLE SOLUTION (a) Along with the triplet–quartet pattern of the ethyl group, the NMR spectrum of this compound will contain a singlet for the two protons of the chloromethyl group.

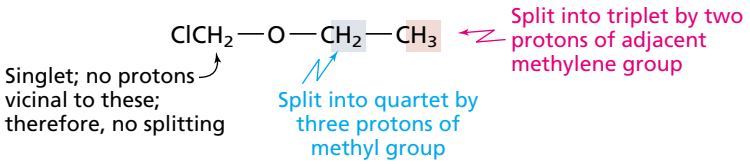


Table 13.2 summarizes the splitting patterns and peak intensities expected for coupling to various numbers of protons.

The intensities correspond to the coefficients of a binomial expansion (Pascal's triangle).

TABLE 13.2 Splitting Patterns of Common Multiplets

Number of equivalent protons to which nucleus is coupled	Appearance of multiplet	Intensities of lines in multiplet
1	Doublet	1:1
2	Triplet	1:2:1
3	Quartet	1:3:3:1
4	Pentet	1:4:6:4:1
5	Sextet	1:5:10:10:5:1
6	Septet	1:6:15:20:15:6:1

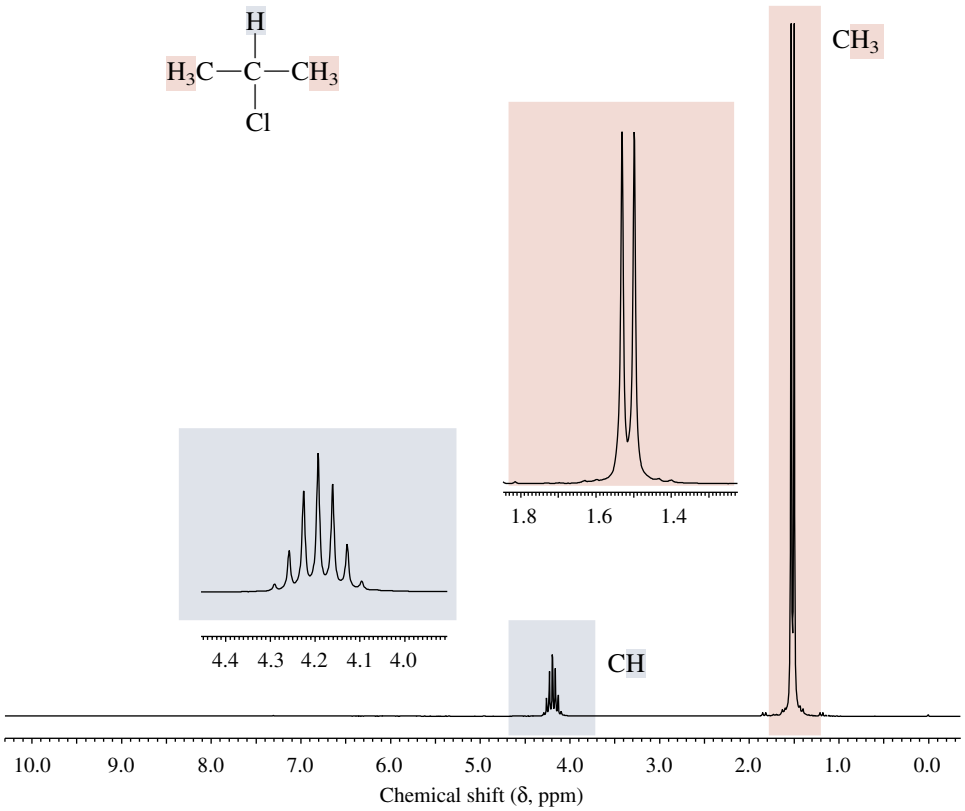
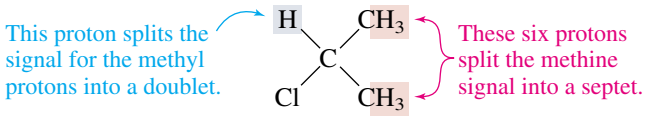


FIGURE 13.15 The 200-MHz ^{1}H NMR spectrum of isopropyl chloride, showing the doublet–septet pattern of an isopropyl group.

13.9 SPLITTING PATTERNS: THE ISOPROPYL GROUP

The NMR spectrum of isopropyl chloride (Figure 13.15) illustrates the appearance of an isopropyl group. The signal for the six equivalent methyl protons at δ 1.5 ppm is split into a doublet by the proton of the H—C—Cl unit. In turn, the H—C—Cl proton signal at δ 4.2 ppm is split into a septet by the six methyl protons. A *doublet–septet* pattern is characteristic of an isopropyl group.



13.10 SPLITTING PATTERNS: PAIRS OF DOUBLETS

We often see splitting patterns in which the intensities of the individual peaks do not match those given in Table 13.2, but are distorted in that the signals for coupled protons "lean" toward each other. This leaning is a general phenomenon, but is most easily illustrated for the case of two nonequivalent vicinal protons as shown in Figure 13.16.

$$H_1—C—C—H_2$$

The appearance of the splitting pattern of protons 1 and 2 depends on their coupling constant J and the chemical shift difference $\Delta\nu$ between them. When the ratio $\Delta\nu/J$ is large, two symmetrical 1:1 doublets are observed. We refer to this as the "AX" case, using two

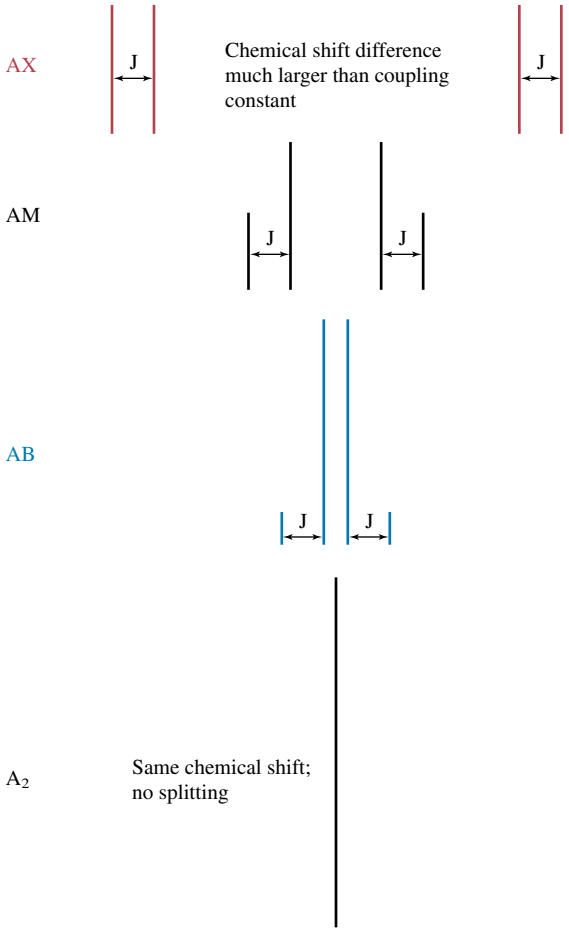
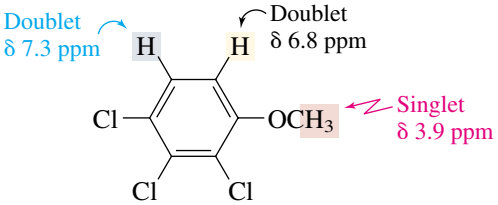


FIGURE 13.16 The appearance of the splitting pattern of two coupled protons depends on their coupling constant J and the chemical shift difference $\Delta\nu$ between them. As the ratio $\Delta\nu/J$ decreases, the doublets become increasingly distorted. When the two protons have the same chemical shift, no splitting is observed.

letters that are remote in the alphabet to stand for signals well removed from each other on the spectrum. Keeping the coupling constant the same while reducing $\Delta\nu$ leads to a steady decrease in the intensity of the outer two peaks with a simultaneous increase in the inner two as we progress from AX through AM to AB. At the extreme (A_2), the two protons have the same chemical shift, the outermost lines have disappeared, and no splitting is observed. Because of its appearance, it is easy to misinterpret an AB pattern as a quartet, rather than the pair of skewed doublets it really is.

The skewed AB pattern is clearly visible in the ^{1}H NMR spectrum of 2,3,4-trichloroanisole (Figure 13.17). In addition to the singlet at δ 3.9 ppm for the protons of the —OCH_3 group, we see doublets at δ 6.8 and δ 7.3 ppm for the two protons of the aromatic ring.



2,3,4-Trichloroanisole

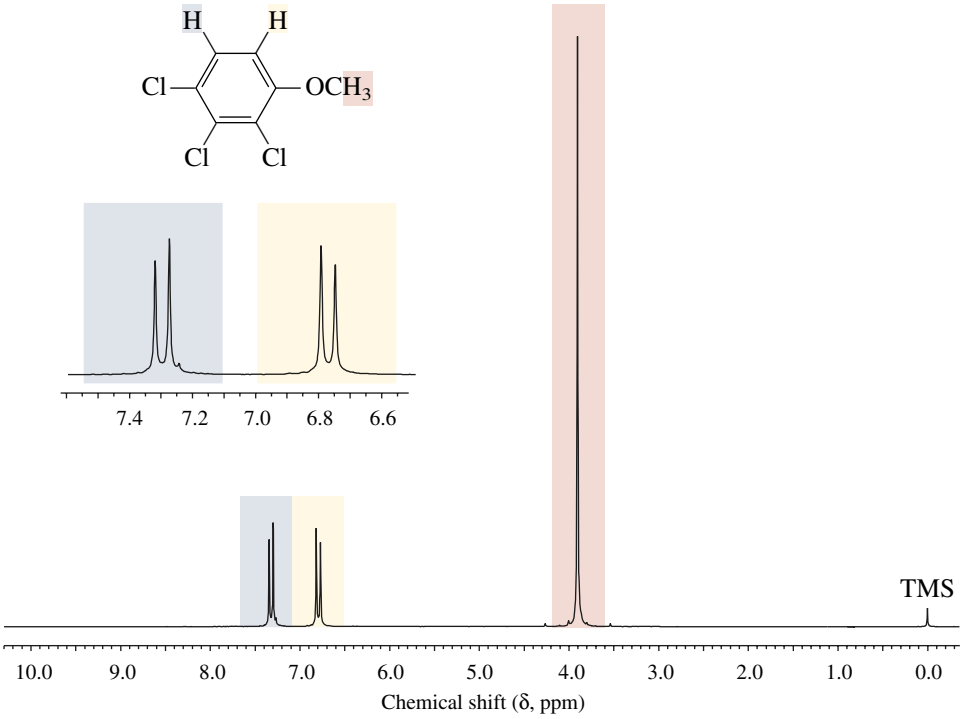
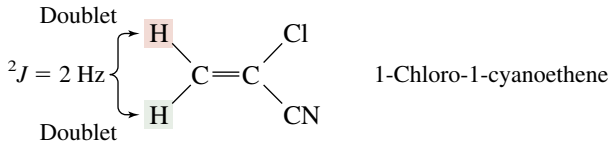


FIGURE 13.17 The 200-MHz ^{1}H NMR spectrum of 2,3,4-trichloroanisole, illustrating the splitting of the ring protons into a pair of doublets that "lean" toward each other.

A similar pattern can occur with *geminal* protons (protons bonded to the same carbon). Geminal protons are separated by two bonds, and geminal coupling is referred to as *two-bond coupling* (^2J) in the same way that vicinal coupling is referred to as *three-bond coupling* (^3J). An example of geminal coupling is provided by the compound 1-chloro-1-cyanoethene, in which the two hydrogens appear as a pair of doublets. The splitting in each doublet is 2 Hz.



1-Chloro-1-cyanoethene

The protons in 1-chloro-1-cyanoethene are *diastereotopic* (Section 13.6). They are nonequivalent and have different chemical shifts. Remember, splitting can only occur between protons that have different chemical shifts.

Splitting due to geminal coupling is seen only in CH_2 groups and only when the two protons have different chemical shifts. All three protons of a methyl (CH_3) group are equivalent and cannot split one another's signal, and, of course, there are no protons geminal to a single methine (CH) proton.

13.11 COMPLEX SPLITTING PATTERNS

All the cases we've discussed so far have involved splitting of a proton signal by coupling to other protons that were equivalent to one another. Indeed, we have stated the splitting rule in terms of the multiplicity of a signal as being equal to $n + 1$, where n is equal to the number of equivalent protons to which the proton that gives the signal is coupled. What if all the vicinal protons are not equivalent?

Figure 13.18*a* shows the signal for the proton marked Ar$\mathbf{C}\mathbf{H}_a$=CH_2 in *m*-nitrostyrene, which appears as a set of four peaks in the range δ 6.7–6.9 ppm. These four peaks are in fact a "doublet of doublets." The proton in question is *unequally*

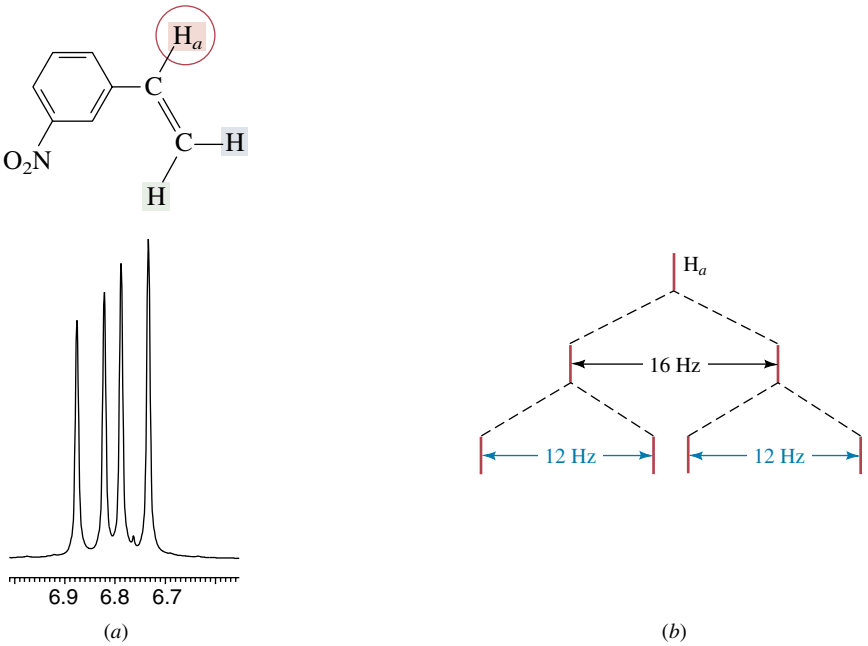


FIGURE 13.18 Splitting of a signal into a doublet of doublets by unequal coupling to two vicinal protons. (*a*) Appearance of the signal for the proton marked H_a in *m*-nitrostyrene as a set of four peaks. (*b*) Origin of these four peaks through successive splitting of the signal for H_a.

coupled to the two protons at the end of the vinyl side chain. The size of the vicinal coupling constant between protons trans to each other on a double bond is normally larger than that between cis protons. In this case the trans coupling constant is 16 Hz and the cis coupling constant is 12 Hz. Thus, as shown in Figure 13.18*b*, the signal is split into a doublet with a spacing of 16 Hz by one vicinal proton, and each line of this doublet is then split into another doublet with a spacing of 12 Hz.

You will find it revealing to construct a splitting diagram similar to that of Figure 13.18 for the case in which the cis and trans **H**—C═C—**H** coupling constants are equal. Under those circumstances the four-line pattern simplifies to a triplet, as it should for a proton equally coupled to two vicinal protons.

PROBLEM 13.10 In addition to the proton marked H_a in *m*-nitrostyrene in Figure 13.18, there are two other vinylic protons. Assuming that the coupling constant between the two geminal protons in ArCH═C**H$_2$** is 2 Hz and the vicinal coupling constants are 12 Hz (cis) and 16 Hz (trans), describe the splitting pattern for each of these other two vinylic hydrogens.

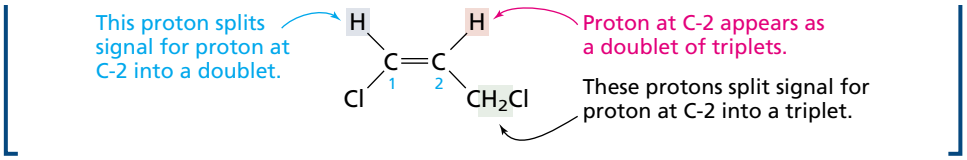
The "$n + 1$ rule" should be amended to read: *When a proton* H_a *is coupled to* H_b, H_c, H_d, *etc., and* $J_{ab} \neq J_{ac} \neq J_{ad}$, *etc., the original signal for* H_a *is split into* $n + 1$ *peaks by* n H_b *protons, each of these lines is further split into* $n + 1$ *peaks by* n H_c *protons, and each of these into* $n + 1$ *lines by* n H_d *protons, etc.* Bear in mind that because of overlapping peaks, the number of lines actually observed can be less than that expected on the basis of the splitting rule.

PROBLEM 13.11 Describe the splitting pattern expected for the proton at

(a) C-2 in (*Z*)-1,3-dichloropropene

(b) C-2 in $CH_3\overset{\displaystyle O}{\overset{\|}{C}}HCH$ (Br on the CH)

SAMPLE SOLUTION (a) The signal of the proton at C-2 is split into a doublet by coupling to the proton cis to it on the double bond, and each line of this doublet is split into a triplet by the two protons of the CH_2Cl group.



13.12 ^{1}H NMR SPECTRA OF ALCOHOLS

The hydroxyl proton of a primary alcohol RCH_2OH is vicinal to two protons, and its signal would be expected to be split into a triplet. Under certain conditions signal splitting of alcohol protons is observed, but usually it is not. Figure 13.19 presents the NMR spectrum of benzyl alcohol, showing the methylene and hydroxyl protons as singlets at δ 4.7 and 2.5 ppm, respectively. (The aromatic protons also appear as a singlet, but that is because they all accidentally have the same chemical shift and so cannot split each other.)

The reason that splitting of the hydroxyl proton of an alcohol is not observed is that it is involved in rapid exchange reactions with other alcohol molecules. Transfer of a proton from an oxygen of one alcohol molecule to the oxygen of another is quite fast and effectively *decouples* it from other protons in the molecule. Factors that slow down this exchange of OH protons, such as diluting the solution, lowering the temperature, or increasing the crowding around the OH group, can cause splitting of hydroxyl resonances.

The chemical shift of the hydroxyl proton is variable, with a range of δ 0.5–5 ppm, depending on the solvent, the temperature at which the spectrum is recorded, and the concentration of the solution. The alcohol proton shifts to lower field strength in more concentrated solutions.

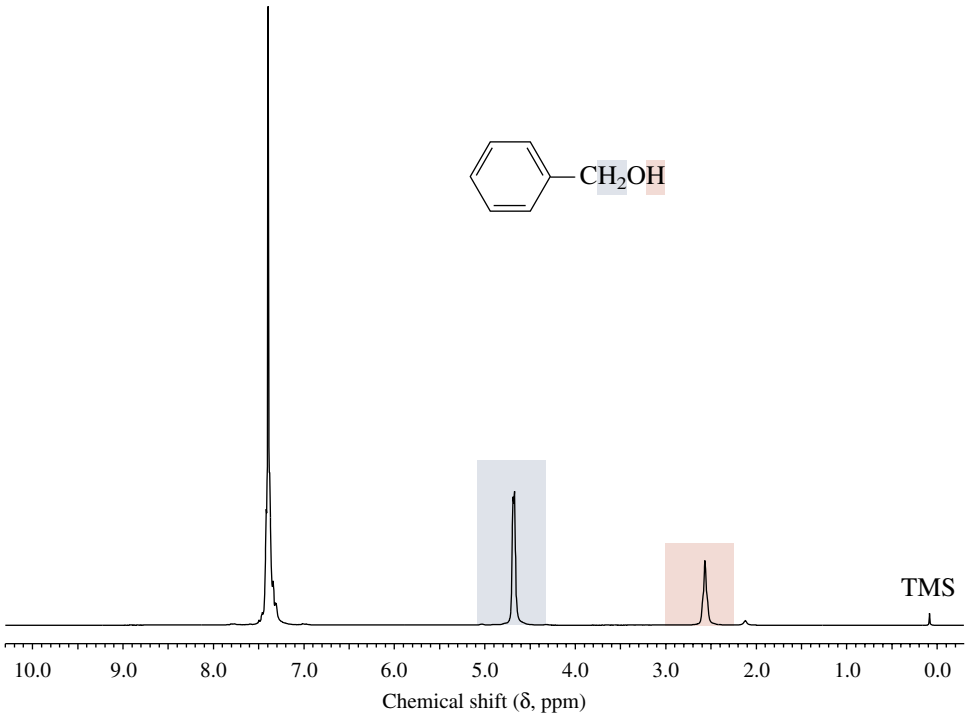


FIGURE 13.19 The 200-MHz ^{1}H NMR spectrum of benzyl alcohol. The hydroxyl proton and the methylene protons are vicinal but do not split each other because of the rapid intermolecular exchange of hydroxyl protons.

An easy way to verify that a particular signal belongs to a hydroxyl proton is to add D_2O. The hydroxyl proton is replaced by deuterium according to the equation:

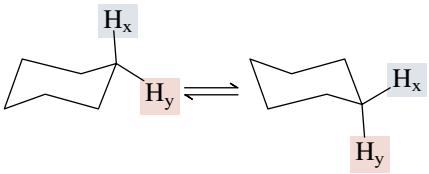
$$RCH_2OH + D_2O \rightleftharpoons RCH_2OD + DOH$$

Deuterium does not give a signal under the conditions of ^1H NMR spectroscopy. Thus, replacement of a hydroxyl proton by deuterium leads to the disappearance of the OH peak. Protons bonded to nitrogen and sulfur also undergo exchange with D_2O. Those bound to carbon normally do not, and so this technique is useful for assigning the proton resonances of OH, NH, and SH groups.

13.13 NMR AND CONFORMATIONS

We know from Chapter 3 that the protons in cyclohexane exist in two different environments: axial and equatorial. The NMR spectrum of cyclohexane, however, shows only a single sharp peak at δ 1.4 ppm. All the protons of cyclohexane appear to be equivalent in the NMR spectrum. Why?

The answer is related to the very rapid rate of ring flipping in cyclohexane.



One property of NMR spectroscopy is that it is too slow a technique to "see" the individual conformations of cyclohexane. What NMR sees is the *average* environment of the protons. Since chair–chair interconversion in cyclohexane converts each axial proton to an equatorial one and vice versa, the average environments of all the protons are the same. A single peak is observed that has a chemical shift midway between the true chemical shifts of the axial and the equatorial protons.

The rate of ring flipping can be slowed down by lowering the temperature. At temperatures on the order of −100°C, separate signals are seen for the axial and equatorial protons of cyclohexane.

13.14 ^{13}C NMR SPECTROSCOPY

We pointed out in Section 13.3 that both ^1H and ^{13}C are nuclei that can provide useful structural information when studied by NMR. Although a ^1H NMR spectrum helps us infer much about the carbon skeleton of a molecule, a ^{13}C NMR spectrum has the obvious advantage of probing the carbon skeleton directly. ^{13}C NMR spectroscopy is analogous to ^1H NMR in that the number of signals informs us about the number of different kinds of carbons, and their chemical shifts are related to particular chemical environments.

However, unlike ^1H, which is the most abundant of the hydrogen isotopes (99.985%), only 1.1% of the carbon atoms in a sample are ^{13}C. Moreover, the intensity of the signal produced by ^{13}C nuclei is far weaker than the signal produced by the same number of ^1H nuclei. In order for ^{13}C NMR to be a useful technique in structure determination, a vast increase in the signal-to-noise ratio is required. Pulsed FT-NMR provides for this, and its development was the critical breakthrough that led to ^{13}C NMR becoming the routine tool that it is today.

To orient ourselves in the information that ^{13}C NMR provides, let's compare the ^{1}H and ^{13}C NMR spectra of 1-chloropentane (Figures 13.20*a* and 13.20*b,* respectively). The ^{1}H NMR spectrum shows reasonably well defined triplets for the protons of the CH_3

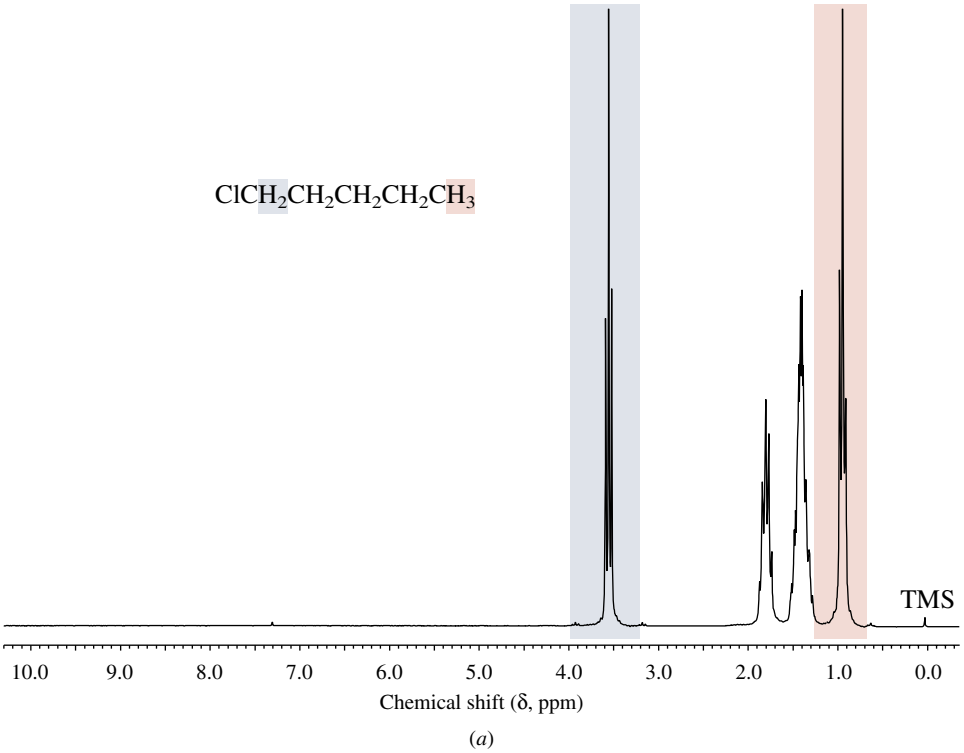


FIGURE 13.20 (*a*) The 200-MHz ^{1}H NMR spectrum and (*b*) the ^{13}C NMR spectrum of 1-chloropentane.

and CH_2Cl groups (δ 0.9 and 3.55 ppm, respectively). The signals for the six CH_2 protons at C-2, C-3, and C-4 of $CH_3CH_2CH_2CH_2CH_2Cl$, however, appear as two unresolved multiplets at δ 1.4 and 1.8 ppm.

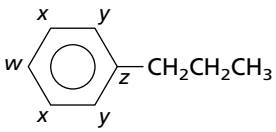
The ^{13}C NMR spectrum, on the other hand, is very simple: *a separate, distinct peak is observed for each carbon.*

Notice, too, how well-separated these ^{13}C signals are: they cover a range of over 30 ppm, compared with less than 3 ppm for the proton signals of the same compound. In general, the window for proton signals in organic molecules is about 12 ppm; ^{13}C chemical shifts span a range of over 200 ppm. The greater spread of ^{13}C chemical shifts makes it easier to interpret the spectra.

PROBLEM 13.12 How many signals would you expect to see in the ^{13}C NMR spectrum of each of the following compounds?

(a) Propylbenzene
(b) Isopropylbenzene
(c) 1,2,3-Trimethylbenzene
(d) 1,2,4-Trimethylbenzene
(e) 1,3,5-Trimethylbenzene

SAMPLE SOLUTION (a) The two ring carbons that are ortho to the propyl substituent are equivalent and so must have the same chemical shift. Similarly, the two ring carbons that are meta to the propyl group are equivalent to each other. The carbon atom para to the substituent is unique, as is the carbon that bears the substituent. Thus, there will be four signals for the ring carbons, designated *w, x, y,* and *z* in the structural formula. These four signals for the ring carbons added to those for the three nonequivalent carbons of the propyl group yield a total of *seven* signals.



Propylbenzene

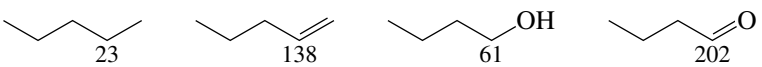
13.15 ^{13}C CHEMICAL SHIFTS

Just as chemical shifts in ^1H NMR are measured relative to the *protons* of tetramethylsilane, chemical shifts in ^{13}C NMR are measured relative to the *carbons* of tetramethylsilane as the zero point of the chemical-shift scale. Table 13.3 lists typical chemical-shift ranges for some representative types of carbon atoms.

In general, the factors that most affect ^{13}C chemical shifts are:

1. The hybridization of carbon
2. The electronegativity of the groups attached to carbon

Both can be illustrated by comparing the chemical shifts of the designated carbon in the compounds shown. (The numbers are the chemical shift of the indicated carbon in parts per million.)



Pentane 1-Pentene 1-Butanol Butanal

sp^3-Hybridized carbons are more shielded than sp^2 as the chemical shifts for C-2 in pentane versus 1-pentene and C-1 in 1-butanol versus butanal demonstrate. The effect of substituent electronegativity is evident when comparing pentane with 1-butanol and

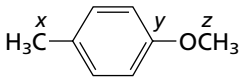
TABLE 13.3 Chemical Shifts of Representative Carbons

Type of carbon	Chemical shift (δ) ppm*	Type of carbon	Chemical shift (δ) ppm*
Hydrocarbons		**Functionally substituted carbons**	
RCH_3	0–35	RCH_2Br	20–40
R_2CH_2	15–40	RCH_2Cl	25–50
R_3CH	25–50	RCH_2NH_2	35–50
R_4C	30–40	RCH_2OH and RCH_2OR	50–65
$RC{\equiv}CR$	65–90	$RC{\equiv}N$	110–125
$R_2C{=}CR_2$	100–150	$RCOH$ and $RCOR$	160–185
	110–175	RCH and RCR	190–220

*Approximate values relative to tetramethylsilane.

1-pentene with butanal. Replacing the methyl group in pentane by the more electronegative oxygen deshields the carbon in 1-butanol. Likewise, replacing C-1 in 1-pentene by oxygen deshields the carbonyl carbon in butanal.

PROBLEM 13.13 Consider carbons *x*, *y*, and *z* in *p*-methylanisole. One has a chemical shift of δ 20 ppm, another has δ 55 ppm, and the third δ 157 ppm. Match the chemical shifts with the appropriate carbons.



sp-Hybridized carbons are a special case; they are less shielded than sp^3 but more shielded than sp^2-hybridized carbons.

13.16 ^{13}C NMR AND PEAK INTENSITIES

Two features that are fundamental to ^{1}H NMR spectroscopy—integrated areas and splitting patterns—are not very important in ^{13}C NMR.

Although it is a simple matter to integrate ^{13}C signals, it is rarely done because the observed ratios can be more misleading than helpful. The pulsed FT technique that is standard for ^{13}C NMR has the side effect of distorting the signal intensities, especially for carbons that lack attached hydrogens. Examine Figure 13.21 which shows the ^{13}C spectrum of 3-methylphenol (*m*-cresol). Notice that, contrary to what we might expect for a compound with seven peaks for seven different carbons, the intensities of these peaks are not nearly the same. The two least intense signals, those at δ 140 and δ 157 ppm, correspond to carbons that lack attached hydrogens.

PROBLEM 13.14 To which of the compounds of Problem 13.12 does the ^{13}C NMR spectrum of Figure 13.22 belong?

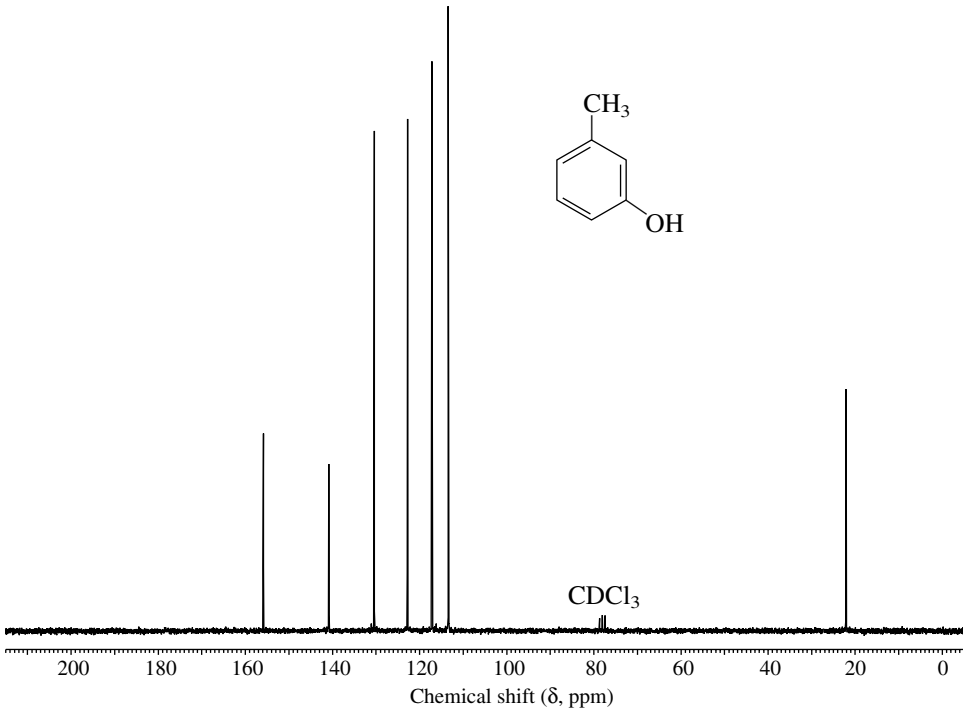


FIGURE 13.21 The ^{13}C NMR spectrum of *m*-cresol. Each of the seven carbons of *m*-cresol gives a separate peak. Integrating the spectrum would not provide useful information because the intensities of the peaks are so different, even though each one corresponds to a single carbon.

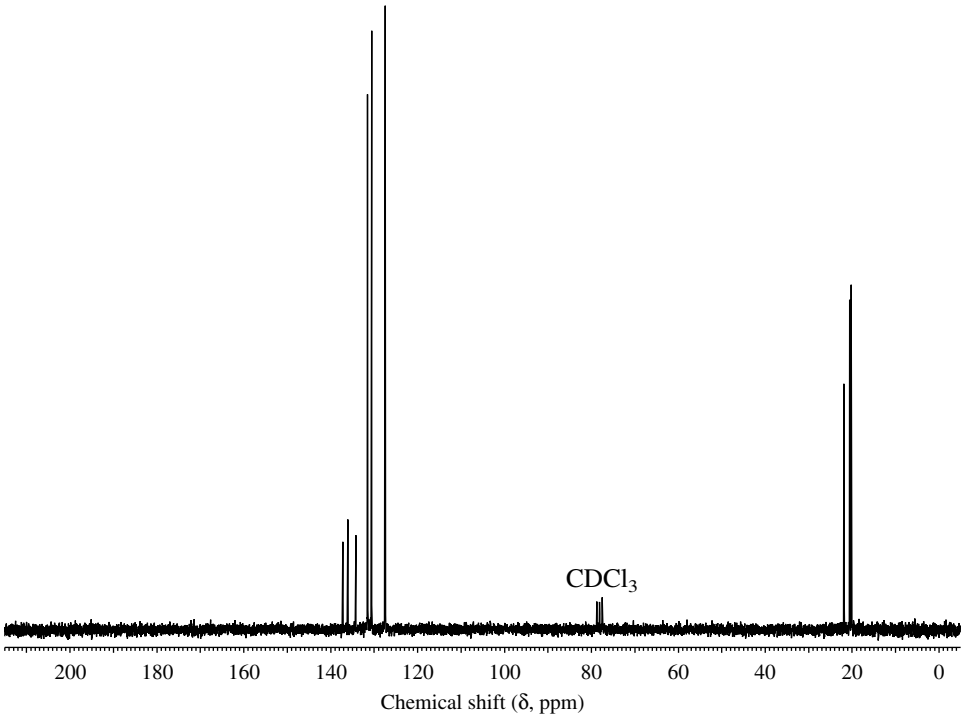


FIGURE 13.22 The ^{13}C NMR spectrum of the unknown compound of Problem 13.14.

13.17 $^{13}C—^{1}H$ COUPLING

You may have noticed another characteristic of ^{13}C NMR spectra—all of the peaks are singlets. With a spin of $\pm\frac{1}{2}$, a ^{13}C nucleus is subject to the same splitting rules that apply to ^{1}H, and we might expect to see splittings due to $^{13}C—^{13}C$ and $^{13}C—^{1}H$ couplings. We don't. Why?

The lack of splitting due to $^{13}C—^{13}C$ coupling is easy to understand. ^{13}C NMR spectra are measured on samples that contain ^{13}C at the "natural abundance" level. Only 1% of all the carbons in the sample are ^{13}C, and the probability that any molecule contains more than one ^{13}C atom is quite small.

Splitting due to $^{13}C—^{1}H$ coupling is absent for a different reason, one that has to do with the way the spectrum is run. Because a ^{13}C signal can be split not only by the protons to which it is directly attached, but also by protons separated from it by two, three, or even more bonds, the number of splittings might be so large as to make the spectrum too complicated to interpret. Thus, the spectrum is measured under conditions, called **broadband decoupling,** that suppress such splitting. In addition to pulsing the sample by a radiofrequency tuned for ^{13}C, the sample is continuously irradiated by a second rf transmitter that covers the entire frequency range for all the ^{1}H nuclei. The effect of this second rf is to decouple the ^{1}H spins from the ^{13}C spins, which causes all the ^{13}C signals to collapse to singlets.

What we gain from broadband decoupling in terms of a simple-looking spectrum comes at the expense of some useful information. For example, being able to see splitting corresponding to one-bond $^{13}C—^{1}H$ coupling would immediately tell us the number of hydrogens directly attached to each carbon. The signal for a carbon with no attached hydrogens (a *quaternary* carbon) would be a singlet, the hydrogen of a CH group would split the carbon signal into a doublet, and the signals for the carbons of a CH_2 and a CH_3 group would appear as a triplet and a quartet, respectively. Although it is possible, with a technique called *off-resonance decoupling,* to observe such one-bond couplings, identifying a signal as belonging to a quaternary carbon or to the carbon of a CH, CH_2, or CH_3 group is normally done by a method called DEPT, which is described in the next section.

13.18 USING DEPT TO COUNT THE HYDROGENS ATTACHED TO ^{13}C

In general, a simple pulse FT-NMR experiment involves the following stages:

1. Equilibration of the nuclei between the lower and higher spin states under the influence of a magnetic field
2. Application of a radiofrequency pulse to give an excess of nuclei in the higher spin state
3. Acquisition of free-induction decay data during the time interval in which the equilibrium distribution of nuclear spins is restored
4. Mathematical manipulation (Fourier transform) of the data to plot a spectrum

The pulse sequence (stages 2–3) can be repeated hundreds of times to enhance the signal-to-noise ratio. The duration of time for stage 2 is on the order of milliseconds, and that for stage 3 is about 1 second.

Major advances in NMR have been made by using a second rf transmitter to irradiate the sample at some point during the sequence. There are several such techniques, of which we'll describe just one, called *"distortionless enhancement of polarization transfer,"* abbreviated as **DEPT.**

In the DEPT routine, a second transmitter excites ^{1}H, and this affects the appearance of the ^{13}C spectrum. A typical DEPT experiment is illustrated for the case of 1-phenyl-1-pentanone in Figure 13.23. In addition to the normal spectrum shown in Fig-

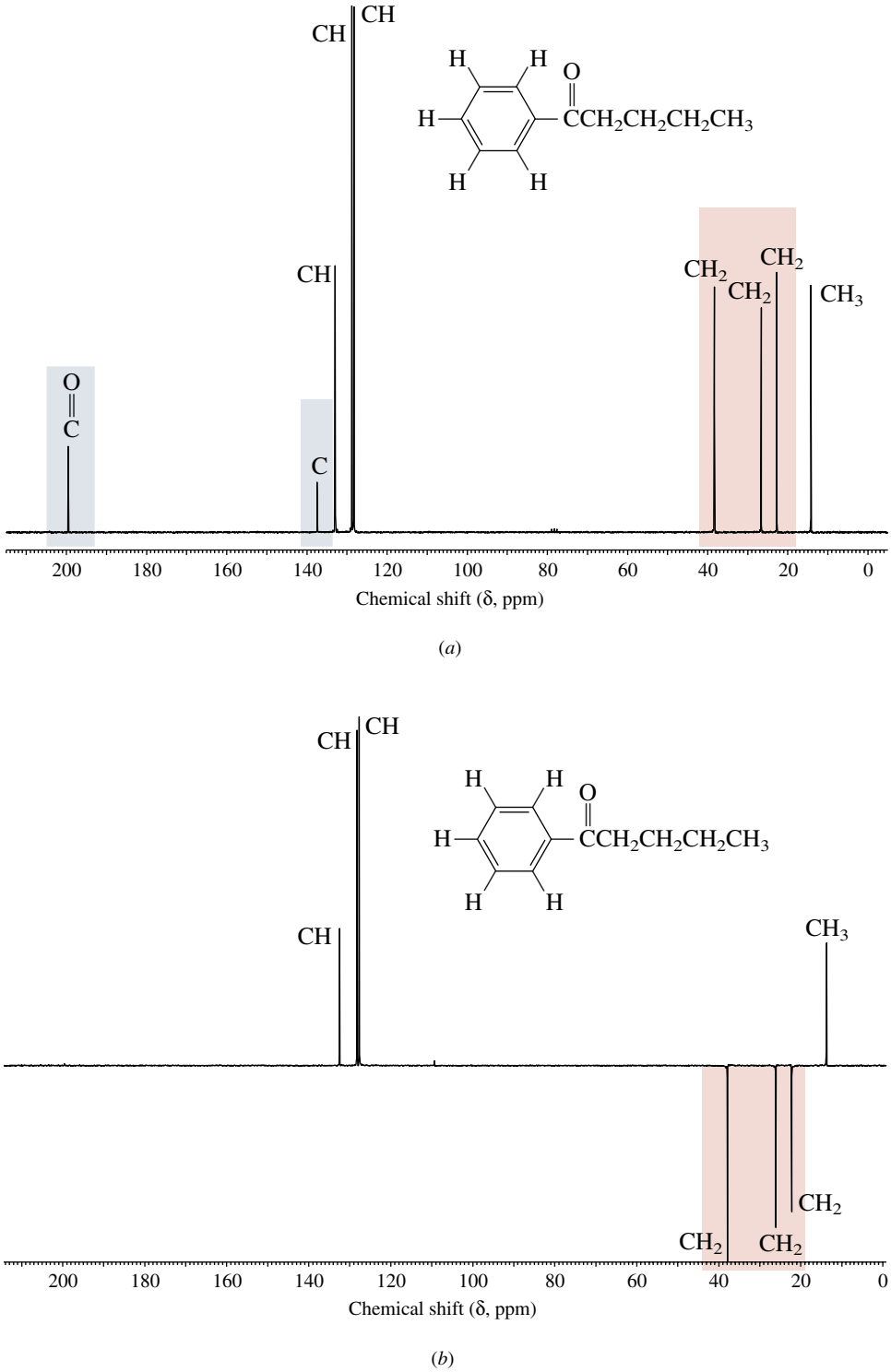


FIGURE 13.23 ^{13}C NMR spectra of 1-phenyl-1-pentanone. (*a*) Normal spectrum. (*b*) DEPT spectrum recorded using a pulse sequence in which CH_3 and CH carbons appear as positive peaks, CH_2 carbons as negative peaks, and carbons without any attached hydrogens are nulled.

ure 13.23*a,* four more spectra are run using prescribed pulse sequences. In one (Figure 13.23*b*), the signals for carbons of CH_3 and CH groups appear normally, whereas those for CH_2 groups are inverted and those for C without any attached hydrogens are nulled. In the others (not shown) different pulse sequences produce combinations of normal, nulled, and inverted peaks that allow assignments to be made to the various types of carbons with confidence.

MAGNETIC RESONANCE IMAGING

Like all photographs, a chest X-ray is a two-dimensional projection of a three-dimensional object. It is literally a collection of shadows produced by all the organs that lie between the source of the X-rays and the photographic plate. The clearest images in a chest X-ray are not the lungs (the customary reason for taking the X-ray in the first place) but rather the ribs and backbone. It would be desirable if we could limit X-ray absorption to two dimensions at a time rather than three. This is, in fact, what is accomplished by a technique known as *computerized axial tomography,* which yields its information in a form called a CT (or CAT) scan. With the aid of a computer, a CT scanner controls the movement of an X-ray source and detector with respect to the patient and to each other, stores the X-ray absorption pattern, and converts it to an image that is equivalent to an X-ray photograph of a thin section of tissue. It is a *noninvasive* diagnostic method, meaning that surgery is not involved nor are probes inserted into the patient's body.

As useful as the CT scan is, it has some drawbacks. Prolonged exposure to X-rays is harmful, and CT scans often require contrast agents to make certain organs more opaque to X-rays. Some patients are allergic to these contrast agents. An alternative technique was introduced in the 1980s that is not only safer but more versatile than X-ray tomography. This technique is *magnetic resonance imaging,* or MRI. MRI is an application of nuclear magnetic resonance spectroscopy that makes it possible to examine the inside of the human body using radiofrequency radiation, which is lower in energy (see Figure 13.1) and less damaging than X-rays and requires no imaging or contrast agents. By all rights MRI should be called NMRI, but the word "nuclear" was dropped from the name so as to avoid confusion with nuclear medicine, which involves radioactive isotopes.

Although the technology of an MRI scanner is rather sophisticated, it does what we have seen other NMR spectrometers do; it detects protons. Thus, MRI is especially sensitive to biological materials such as water and lipids that are rich in hydrogen. Figure 13.24 shows an example of the use of MRI to detect a brain tumor. Regions of the image are lighter or darker according to the relative concentration of protons and to their environments.

Using MRI as a substitute for X-ray tomography is only the first of what are many medical applications. More lie on the horizon. If, for example, the rate of data acquisition could be increased, then it would become possible to make the leap from the equivalent of still photographs to motion pictures. One could watch the inside of the body as it works—see the heart beat, see the lungs expand and contract—rather than merely examine the structure of an organ.

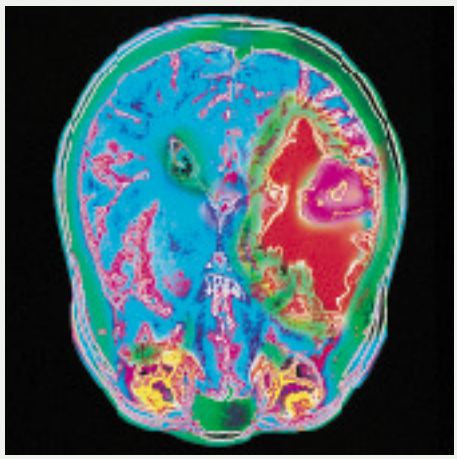


FIGURE 13.24 A magnetic resonance image of a section of a brain that has a tumor in the left hemisphere. The image has been computer-enhanced to show the tumor and the surrounding liquid in different shades of red, fatty tissues in green, the normal part of the brain in blue, and the eyeballs in yellow. *(Photograph courtesy of Simon Fraser Science Photo Library, Newcastle upon Tyne.)*

13.19 INFRARED SPECTROSCOPY

Before the advent of NMR spectroscopy, infrared (IR) spectroscopy was the instrumental method most often applied to determine the structure of organic compounds. Although NMR spectroscopy, in general, tells us more about the structure of an unknown compound, IR still retains an important place in the chemist's inventory of spectroscopic methods because of its usefulness in identifying the presence of certain *functional groups* within a molecule.

Infrared radiation is the portion of the electromagnetic spectrum (see Figure 13.1) between microwaves and visible light. The fraction of the infrared region of most use for structure determination lies between 2.5×10^{-6} m and 16×10^{-6} m in wavelength. Two units commonly employed in infrared spectroscopy are the *micrometer* and the *wave number.* One micrometer (μm) is 10^{-6} m, and infrared spectra record the region from 2.5 μm to 16 μm. Wave numbers are reciprocal centimeters (cm^{-1}), so that the region 2.5–16 μm corresponds to 4000–625 cm^{-1}. An advantage to using wave numbers is that they are directly proportional to energy. Thus, 4000 cm^{-1} is the high-energy end of the scale, and 625 cm^{-1} is the low-energy end.

Electromagnetic radiation in the 4000–625 cm^{-1} region corresponds to the separation between adjacent **vibrational energy states** in organic molecules. Absorption of a photon of infrared radiation excites a molecule from its lowest, or *ground,* vibrational state to a higher one. These vibrations include stretching and bending modes of the type illustrated for a methylene group in Figure 13.25. A single molecule can have a large number of distinct vibrations available to it, and infrared spectra of different molecules, like fingerprints, are different. Superposability of their infrared spectra is commonly offered as proof that two compounds are the same.

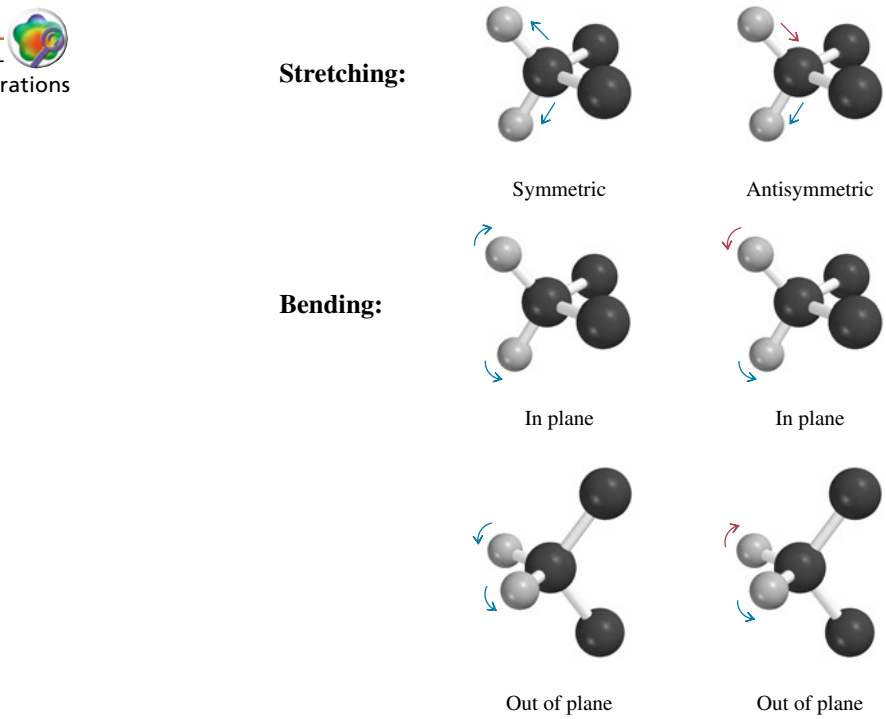


FIGURE 13.25 Stretching and bending vibrations of a methylene unit.

A typical infrared spectrum, such as that of hexane in Figure 13.26, appears as a series of absorption peaks of varying shape and intensity. Almost all organic compounds exhibit a peak or group of peaks near 3000 cm^{-1} due to carbon–hydrogen stretching. The peaks at 1460, 1380, and 725 cm^{-1} are due to various bending vibrations.

Infrared spectra can be recorded on a sample regardless of its physical state—solid, liquid, gas, or dissolved in some solvent. The spectrum in Figure 13.26 was taken on the neat sample, meaning the pure liquid. A drop or two of hexane was placed between two sodium chloride disks, through which the infrared beam is passed. Solids may be dissolved in a suitable solvent such as carbon tetrachloride or chloroform. More commonly, though, a solid sample is mixed with potassium bromide and the mixture pressed into a thin wafer, which is placed in the path of the infrared beam.

In using infrared spectroscopy for structure determination, peaks in the range 1600–4000 cm^{-1} are usually emphasized because this is the region in which the vibrations characteristic of particular functional groups are found. The region 1300–625 cm^{-1} is known as the **fingerprint region;** it is here that the pattern of peaks varies most from compound to compound. Table 13.4 lists the frequencies (in wave numbers) associated with a variety of groups commonly found in organic compounds.

Like NMR spectrometers, some IR spectrometers operate in a continuous-sweep mode, whereas others employ pulse Fourier-transform (FT-IR) technology. All the IR spectra in this text were obtained on an FT-IR instrument.

TABLE 13.4 Infrared Absorption Frequencies of Some Common Structural Units

Structural unit	Frequency, cm^{-1}	Structural unit	Frequency, cm^{-1}
Stretching vibrations			
Single bonds		**Double bonds**	
—O—H (alcohols)	3200–3600		1620–1680
—O—H (carboxylic acids)	2500–3600		
	3350–3500		
		Aldehydes and ketones	1710–1750
sp C—H	3310–3320	Carboxylic acids	1700–1725
sp^2 C—H	3000–3100	Acid anhydrides	1800–1850 and 1740–1790
sp^3 C—H	2850–2950	Acyl halides	1770–1815
sp^2 C—O	1200	Esters	1730–1750
sp^3 C—O	1025–1200	Amides	1680–1700
		Triple bonds	
		—C≡C—	2100–2200
		—C≡N	2240–2280
Bending vibrations of diagnostic value			
Alkenes:		***Substituted derivatives of benzene:***	
$RCH{=}CH_2$	910, 990	Monosubstituted	730–770 and 690–710
$R_2C{=}CH_2$	890	Ortho-disubstituted	735–770
cis-RCH=CHR′	665–730	Meta-disubstituted	750–810 and 680–730
trans-RCH=CHR′	960–980	Para-disubstituted	790–840
$R_2C{=}CHR'$	790–840		

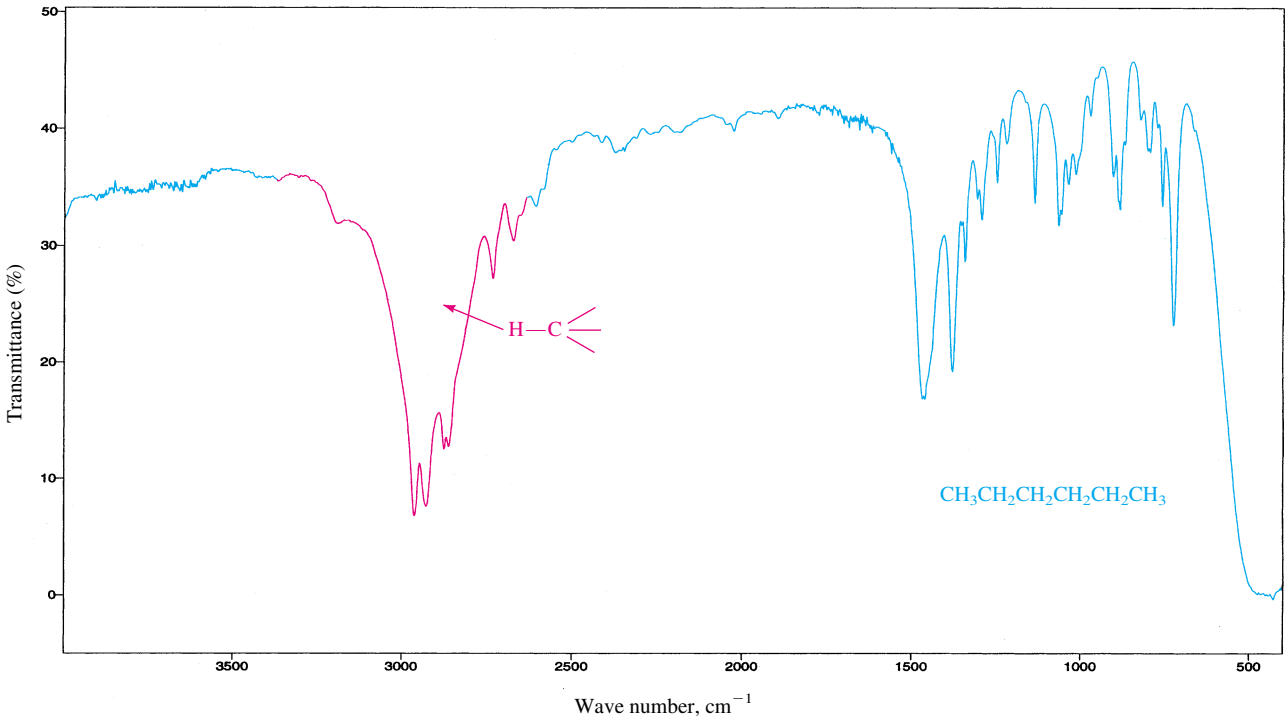


FIGURE 13.26 The infrared spectrum of hexane.

All of the calculated vibrational frequencies given on *Learning By Modeling* are too high. For example, the C=C stretching frequency of 1-hexene observed at 1640 cm^{-1} is calculated to be at 1857 cm^{-1}.

To illustrate how structural features affect infrared spectra, compare the spectrum of hexane (Figure 13.26) with that of 1-hexene (Figure 13.27). The two are quite different. In the C—H stretching region of 1-hexene, there is a peak at 3095 cm^{-1}, whereas all the C—H stretching vibrations of hexane appear below 3000 cm^{-1}. A peak or peaks above 3000 cm^{-1} is characteristic of a hydrogen bonded to sp^2-hybridized carbon. The IR spectrum of 1-hexene also displays a peak at 1640 cm^{-1} corresponding to its C=C stretching vibration. The peaks near 1000 and 900 cm^{-1} in the spectrum of 1-hexene, absent in the spectrum of hexane, are bending vibrations involving the hydrogens of the doubly bonded carbons.

Carbon–hydrogen stretching vibrations with frequencies above 3000 cm^{-1} are also found in arenes such as *tert*-butylbenzene, as shown in Figure 13.28. This spectrum also contains two intense bands at 760 and 700 cm^{-1}, which are characteristic of monosubstituted benzene rings. Other substitution patterns, some of which are listed in Table 13.4, give different combinations of peaks.

In addition to sp^2 C—H stretching modes, there are other stretching vibrations that appear at frequencies above 3000 cm^{-1}. The most important of these is the O—H stretch of alcohols. Figure 13.29 shows the IR spectrum of 2-hexanol. It contains a broad peak at 3300 cm^{-1} ascribable to O—H stretching of hydrogen-bonded alcohol groups. In dilute solution, where hydrogen bonding is less and individual alcohol molecules are present as well as hydrogen-bonded aggregates, an additional peak appears at approximately 3600 cm^{-1}.

Carbonyl groups rank among the structural units most readily revealed by IR spectroscopy. The carbon–oxygen double bond stretching mode gives rise to a very strong peak

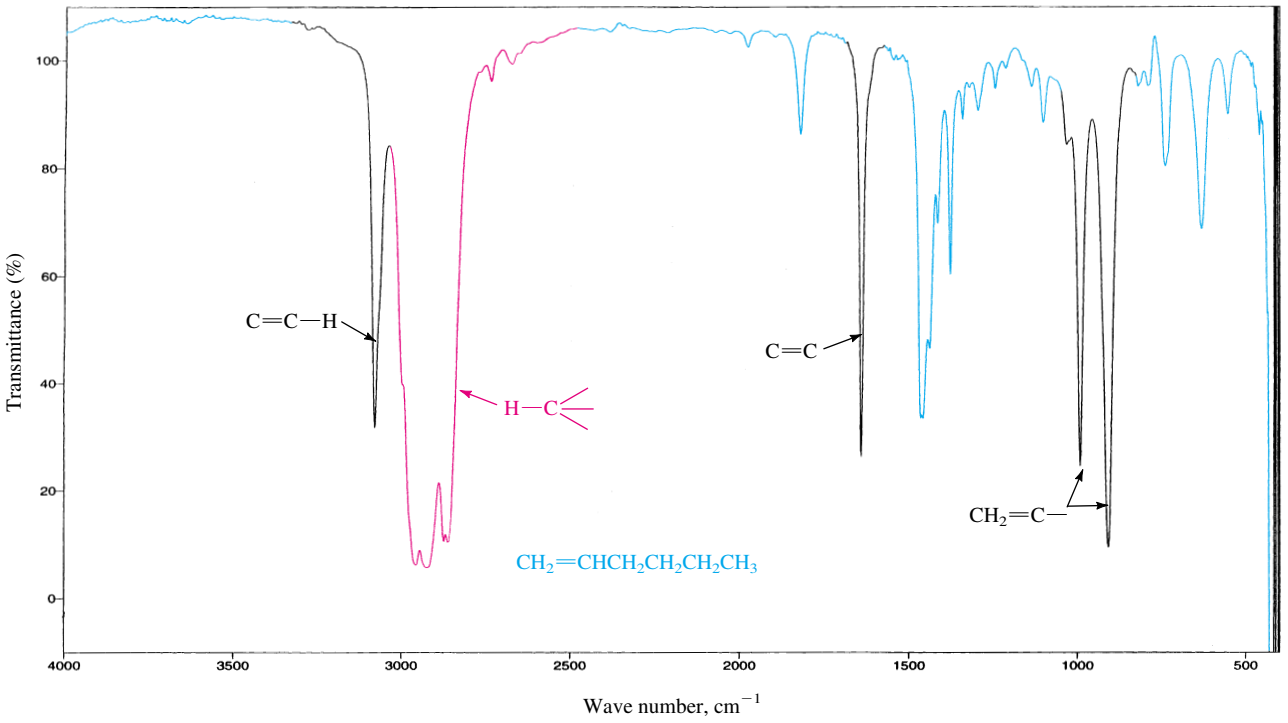


FIGURE 13.27 The infrared spectrum of 1-hexene.

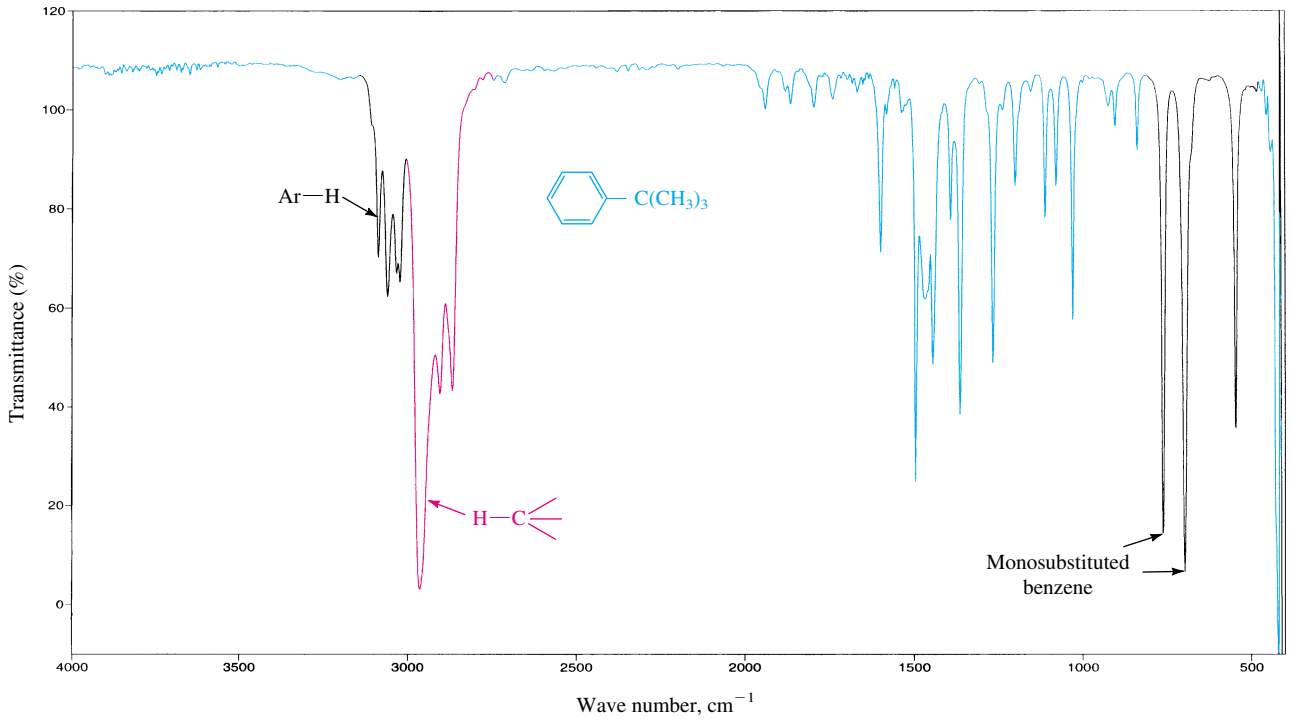


FIGURE 13.28 The infrared spectrum of *tert*-butylbenzene.

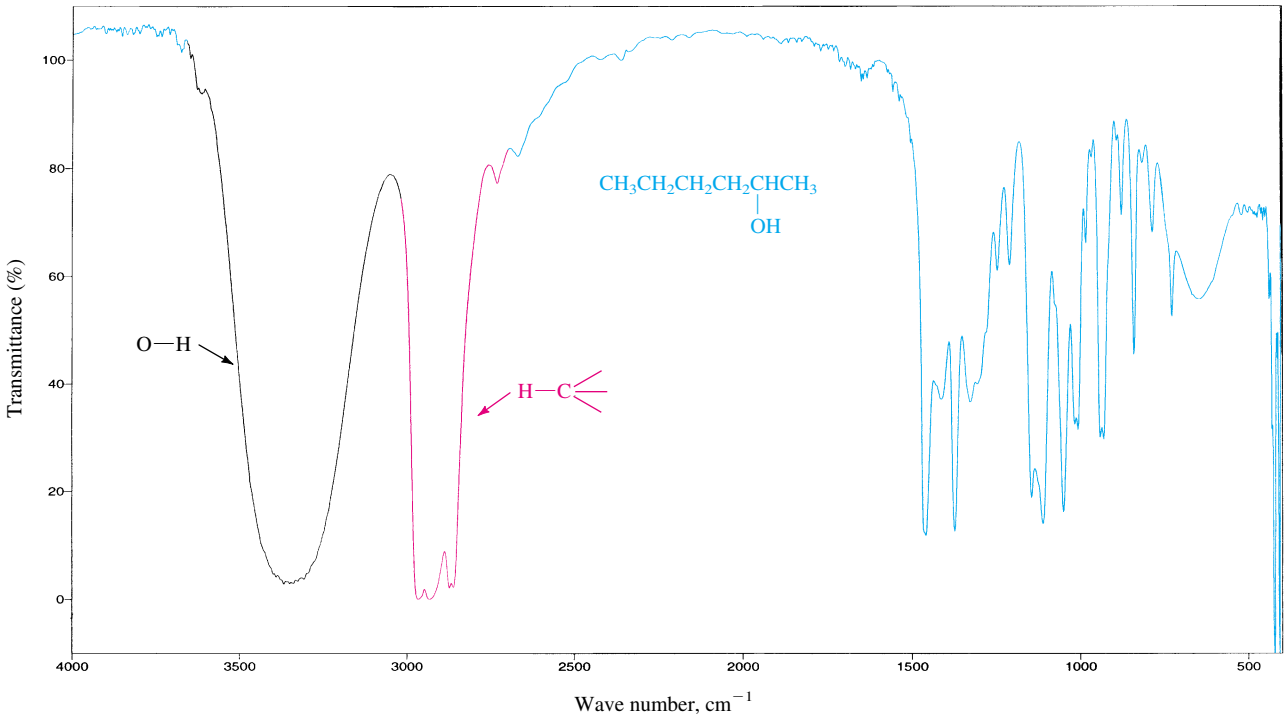
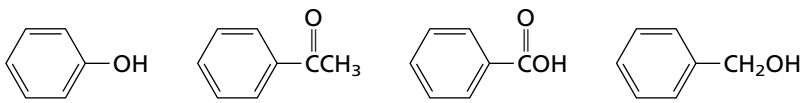


FIGURE 13.29 The infrared spectrum of 2-hexanol.

The C=O stretching frequency in 2-hexanone appears at 1720 cm^{-1}. To view this vibration on *Learning By Modeling,* select the calculated value of 1940 cm^{-1}.

in the 1650–1800 cm^{-1} region. This peak is clearly evident in the spectrum of 2-hexanone, shown in Figure 13.30. The position of the carbonyl peak varies with the nature of the substituents on the carbonyl group. Thus, characteristic frequencies are associated with aldehydes and ketones, amides, esters, and so forth, as summarized in Table 13.4.

PROBLEM 13.15 Which one of the following compounds is most consistent with the infrared spectrum given in Figure 13.31? Explain your reasoning.



Phenol Acetophenone Benzoic acid Benzyl alcohol

In later chapters, when families of compounds are discussed in detail, the infrared frequencies associated with each type of functional group will be described.

13.20 ULTRAVIOLET-VISIBLE (UV-VIS) SPECTROSCOPY

The main application of UV-VIS spectroscopy, which depends on transitions between electronic energy levels, is in identifying conjugated π electron systems.

Much greater energies separate vibrational states than nuclear spin states, and the energy differences between electronic states are greater yet. The energy required to

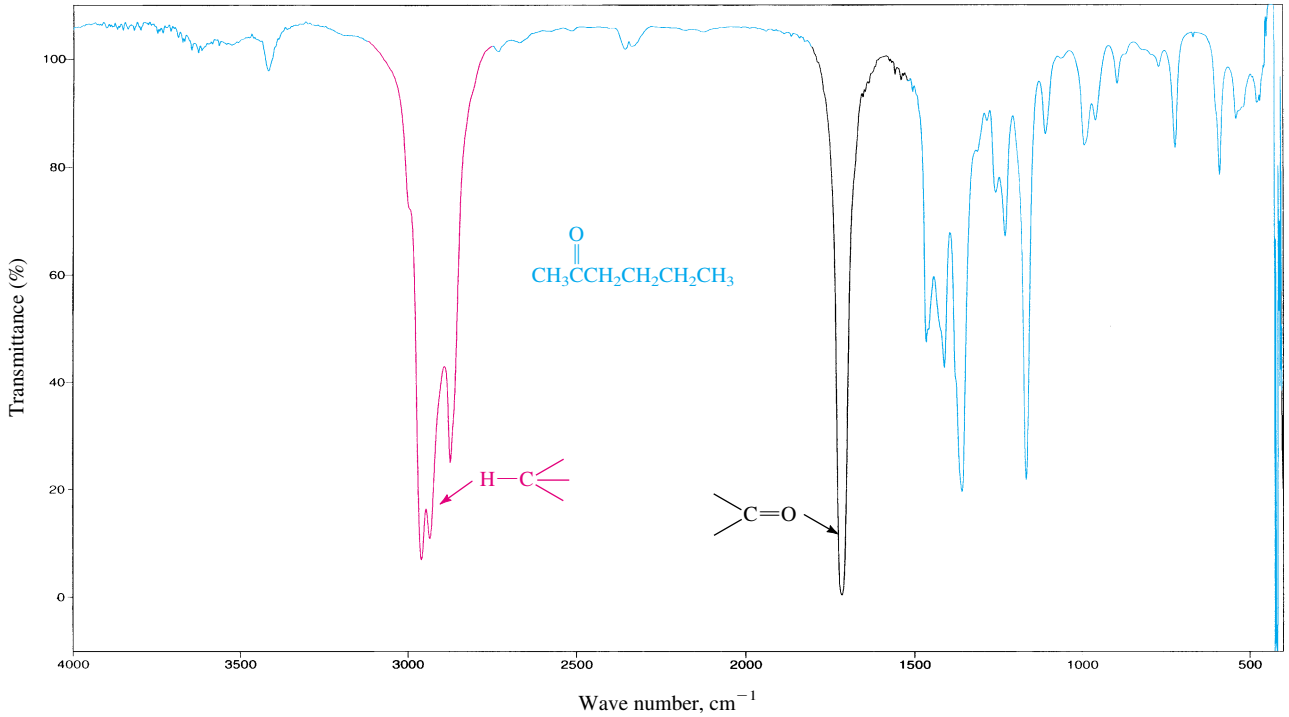


FIGURE 13.30 The infrared spectrum of 2-hexanone.

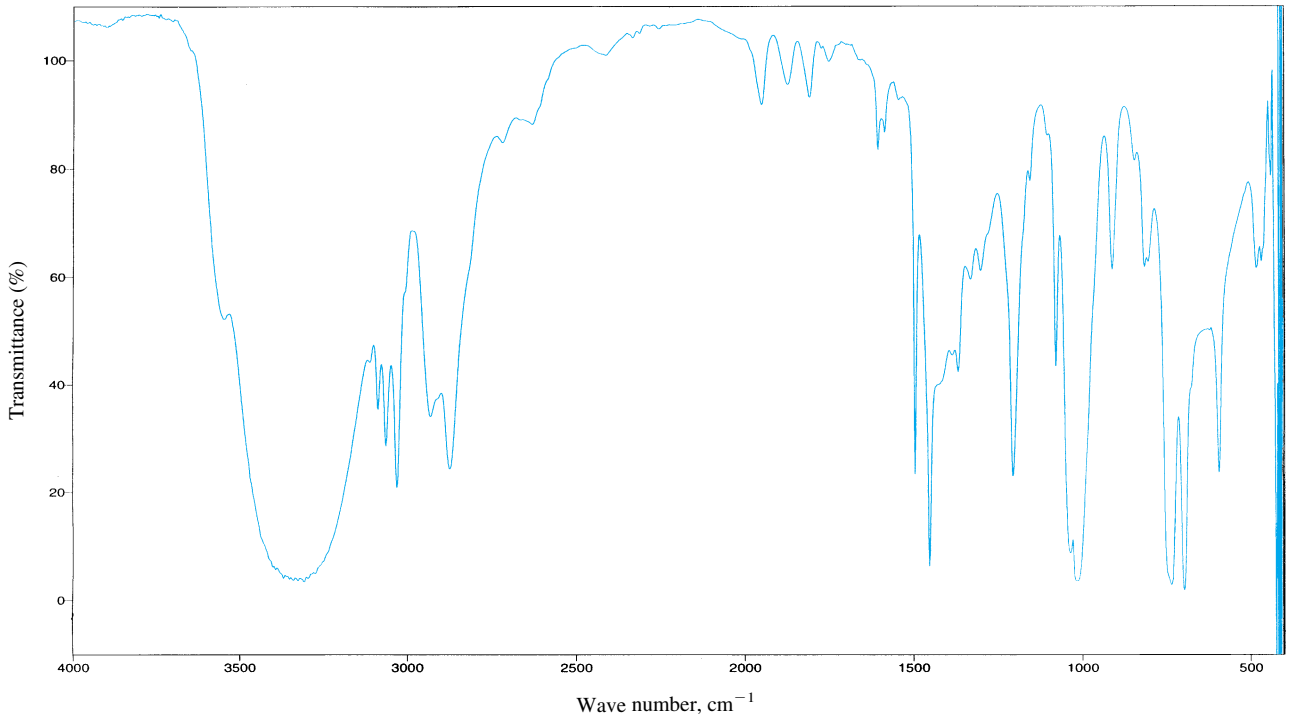


FIGURE 13.31 The infrared spectrum of the unknown compound in Problem 13.15.

promote an electron from one electronic state to the next lies in the visible and ultraviolet range of the electromagnetic spectrum (see Figure 13.1). We usually identify radiation in the UV-VIS range by its wavelength in nanometers (1 nm = 10^{-9} m). Thus, the visible region corresponds to 400–800 nm. Red light is the low-energy (long wavelength) end of the visible spectrum, violet light the high-energy (short wavelength) end. Ultraviolet light lies beyond the visible spectrum with wavelengths in the 200–400-nm range.

An important enzyme in biological electron transport called *cytochrome P450* gets its name from its UV absorption. The "P" stands for "pigment" because it is colored, and the "450" corresponds to the 450-nm absorption of one of its derivatives.

Figure 13.32 shows the UV spectrum of the conjugated diene *cis,trans*-1,3-cyclooctadiene, measured in ethanol as the solvent. As is typical of most UV spectra, the absorption is rather broad and is often spoken of as a "band" rather than a "peak." The wavelength at an absorption maximum is referred to as the λ_{max} of the band. There is only one band in the UV spectrum of 1,3-cyclooctadiene; its λ_{max} is 230 nm. In addition to λ_{max},UV-VIS bands are characterized by their **absorbance** (A), which is a measure of how much of the radiation that passes through the sample is absorbed. To correct for concentration and path length effects, absorbance is converted to **molar absorptivity** (ϵ) by dividing it by the concentration c in moles per liter and the path length l in centimeters.

Molar absorptivity used to be called the *molar extinction coefficient.*

$$\epsilon = \frac{A}{c \cdot l}$$

Molar absorptivity, when measured at λ_{max}, is cited as ϵ_{max}. It is normally expressed without units. Both λ_{max} and ϵ_{max} are affected by the solvent, which is therefore included when reporting UV-VIS spectroscopic data. Thus, you might find a literature reference expressed in the form

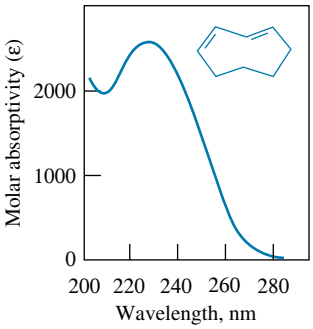
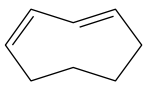


FIGURE 13.32 The ultraviolet spectrum of *cis,trans*-1,3-cyclooctadiene.



cis, trans-1,3-Cyclooctadiene
$\lambda_{max}^{ethanol}$ 230 nm
$\epsilon_{max}^{ethanol}$ 2630

Figure 13.33 illustrates the transition between electronic energy states responsible for the 230-nm UV band of *cis-trans*-1,3-cyclooctadiene. Absorption of ultraviolet radiation excites an electron from the highest occupied molecular orbital (HOMO) to the lowest unoccupied molecular orbital (LUMO). In alkenes and polyenes, both the HOMO

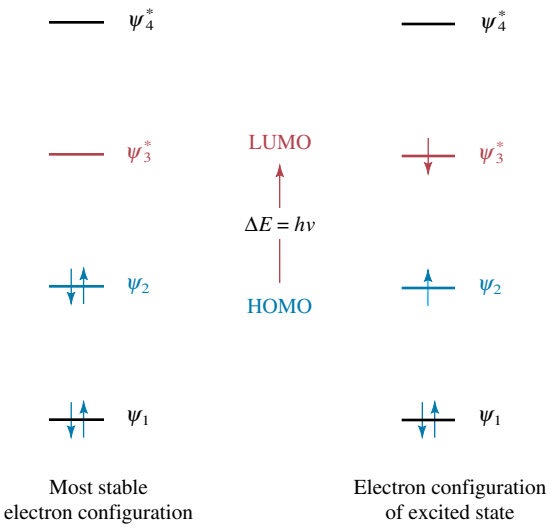


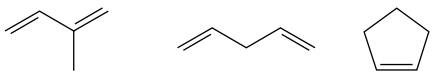
FIGURE 13.33 The π → π* transition in *cis,trans*-1,3-cyclooctadiene involves excitation of an electron from the highest occupied molecular orbital (HOMO) to the lowest unoccupied molecular orbital (LUMO).

and LUMO are π-type orbitals (rather than σ); the HOMO is the highest energy π orbital and the LUMO is the lowest energy π* orbital. Exciting one of the π electrons from a bonding π orbital to an antibonding π* orbital is referred to as a π→π* transition.

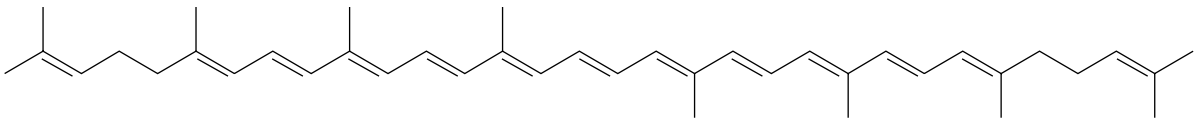
PROBLEM 13.16 λ_{max} for the π→π* transition in ethylene is 170 nm. Is the HOMO–LUMO energy difference in ethylene greater than or less than that of *cis,trans*-1,3-cyclooctadiene?

The HOMO–LUMO energy gap and, consequently, λ_{max} for the π→π* transition varies with the substituents on the double bonds. The data in Table 13.5 illustrate two substituent effects: adding methyl substituents to the double bond, and extending conjugation. Both cause λ_{max} to shift to longer wavelengths, but the effect of conjugation is the larger of the two. Based on data collected for many dienes it has been found that each methyl substituent on the double bonds causes a shift to longer wavelengths of about 5 nm, whereas extending the conjugation causes a shift of about 36 nm for each additional double bond.

PROBLEM 13.17 Which one of the C_5H_8 isomers shown has its λ_{max} at the longest wavelength?



A striking example of the effect of conjugation on light absorption occurs in *lycopene,* which is one of the pigments in ripe tomatoes. Lycopene has a conjugated system of 11 double bonds and absorbs *visible light.* It has several UV-VIS bands, each characterized by a separate λ_{max}. Its longest wavelength absorption is at 505 nm.



Lycopene

Many organic compounds such as lycopene are colored because their HOMO-LUMO energy gap is small enough that λ_{max} appears in the visible range of the spectrum.

TABLE 13.5 Absorption Maxima of Some Representative Alkenes and Polyenes*

Compound	Structure	λ_{max} (nm)
Ethylene	$H_2C{=}CH_2$	170
2-Methylpropene	$H_2C{=}C(CH_3)_2$	188
1,3-Butadiene	$H_2C{=}CHCH{=}CH_2$	217
4-Methyl-1,3-pentadiene	$H_2C{=}CHCH{=}C(CH_3)_2$	234
2,5-Dimethyl-2,4-hexadiene	$(CH_3)_2C{=}CHCH{=}C(CH_3)_2$	241
(2*E*,4*E*,6*E*)-2,4,6-Octatriene	$CH_3CH{=}CHCH{=}CHCH{=}CHCH_3$	263
(2*E*,4*E*,6*E*,8*E*)-2,4,6,8-Decatetraene	$CH_3CH{=}CH(CH{=}CH)_2CH{=}CHCH_3$	299
(2*E*,4*E*,6*E*,8*E*,10*E*)-2,4,6,8,10-Dodecapentaene	$CH_3CH{=}CH(CH{=}CH)_3CH{=}CHCH_3$	326

The value of λ_{max} refers to the longest wavelength π→π transition.

All that is required for a compound to be colored, however, is that it possess some absorption in the visible range. It often happens that a compound will have its λ_{max} in the UV region but that the peak is broad and extends into the visible. Absorption of the blue-to-violet components of visible light occurs, and the compound appears yellow.

A second type of absorption that is important in UV-VIS examination of organic compounds is the $n \rightarrow \pi^*$ transition of the carbonyl (C=O) group. One of the electrons in a lone-pair orbital of oxygen is excited to an antibonding orbital of the carbonyl group. The n in $n \rightarrow \pi^*$ identifies the electron as one of the nonbonded electrons of oxygen. This transition gives rise to relatively weak absorption peaks ($\epsilon_{max} < 100$) in the region 270–300 nm.

The structural unit associated with the electronic transition in UV-VIS spectroscopy is called a **chromophore.** Chemists often refer to *model compounds* to help interpret UV-VIS spectra. An appropriate model is a simple compound of known structure that incorporates the chromophore suspected of being present in the sample. Because remote substituents do not affect λ_{max} of the chromophore, a strong similarity between the spectrum of the model compound and that of the unknown can serve to identify the kind of π electron system present in the sample. There is a substantial body of data concerning the UV-VIS spectra of a great many chromophores, as well as empirical correlations of substituent effects on λ_{max}. Such data are helpful when using UV-VIS spectroscopy as a tool for structure determination.

13.21 MASS SPECTROMETRY

Mass spectrometry differs from the other instrumental methods discussed in this chapter in a fundamental way. It does not depend on the absorption of electromagnetic radiation but rather examines what happens when a molecule is bombarded with high-energy electrons. If an electron having an energy of about 10 electronvolts (10 eV = 230.5 kcal/mol) collides with an organic molecule, the energy transferred as a result of that collision is sufficient to dislodge one of the molecule's electrons.

$$\underset{\text{Molecule}}{A{:}B} + \underset{\text{Electron}}{e^-} \longrightarrow \underset{\text{Cation radical}}{A^{+}{\cdot}B} + \underset{\text{Two electrons}}{2e^-}$$

We say the molecule AB has been ionized by **electron impact.** The species that results, called the **molecular ion,** is positively charged and has an odd number of electrons—it is a **cation radical.** The molecular ion has the same mass (less the negligible mass of a single electron) as the molecule from which it is formed.

Although energies of about 10 eV are required, energies of about 70 eV are used. Electrons this energetic not only cause ionization of a molecule but impart a large amount of energy to the molecular ion, enough energy to break chemical bonds. The molecular ion dissipates this excess energy by dissociating into smaller fragments. Dissociation of a cation radical produces a neutral fragment and a positively charged fragment.

$$\underset{\text{Cation radical}}{A^{+}{\cdot}B} \longrightarrow \underset{\text{Cation}}{A^+} + \underset{\text{Radical}}{B{\cdot}}$$

Ionization and fragmentation produce a mixture of particles, some neutral and some positively charged. To understand what follows, we need to examine the design of an electron-impact mass spectrometer, shown in a schematic diagram in Figure 13.34. The sample is bombarded with 70-eV electrons, and the resulting positively charged ions (the

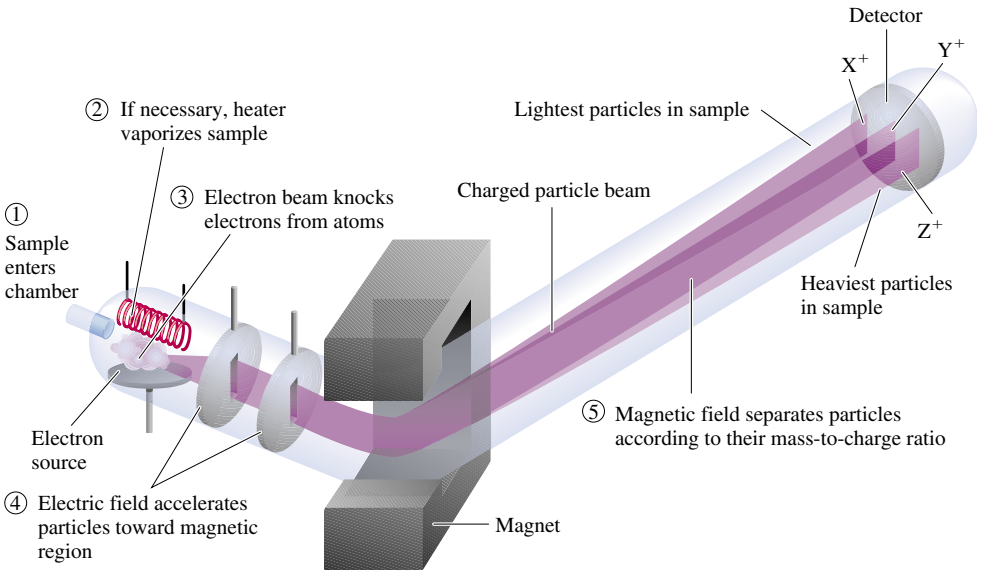


FIGURE 13.34 Diagram of a mass spectrometer. Only positive ions are detected. The cation X^+ has the lowest mass-to-charge ratio, and its path is deflected most by the magnet. The cation Z^+ has the highest mass-to-charge ratio, and its path is deflected least. *(Adapted, with permission, from M. Silberberg,* Chemistry, *2d edition, WCB/McGraw-Hill, New York, 2000, p. 56.)*

molecular ion as well as fragment ions) are directed into an analyzer tube surrounded by a magnet. This magnet deflects the ions from their original trajectory, causing them to adopt a circular path, the radius of which depends on their mass-to-charge ratio *(m/z)*. Ions of small *m/z* are deflected more than those of larger *m/z*. By varying either the magnetic field strength or the degree to which the ions are accelerated on entering the analyzer, ions of a particular *m/z* can be selectively focused through a narrow slit onto a detector, where they are counted. Scanning all *m/z* values gives the distribution of positive ions, called a **mass spectrum,** characteristic of a particular compound.

Modern mass spectrometers are interfaced with computerized data-handling systems capable of displaying the mass spectrum according to a number of different formats. Bar graphs on which relative intensity is plotted versus *m/z* are the most common. Figure 13.35 shows the mass spectrum of benzene in bar graph form.

The mass spectrum of benzene is relatively simple and illustrates some of the information that mass spectrometry provides. The most intense peak in the mass spectrum is called the **base peak** and is assigned a relative intensity of 100. Ion abundances are

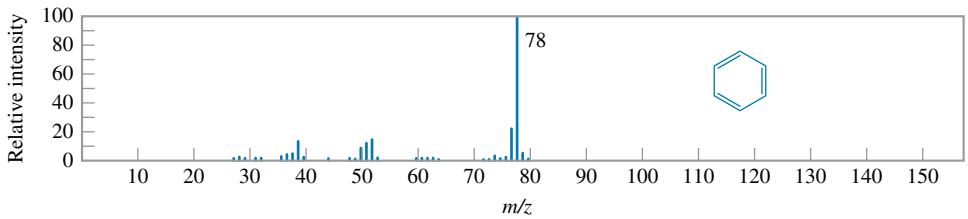
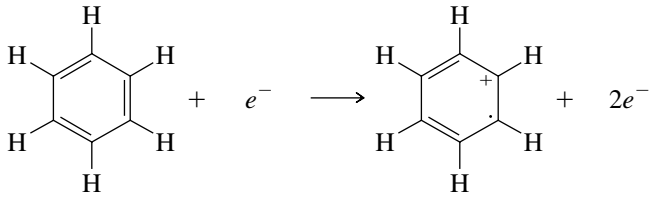


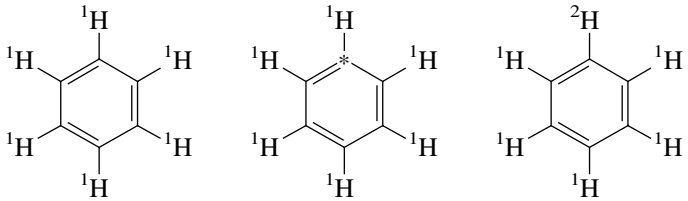
FIGURE 13.35 The mass spectrum of benzene. The peak at *m/z* = 78 corresponds to the C_6H_6 molecular ion.

proportional to peak intensities and are reported as intensities relative to the base peak. The base peak in the mass spectrum of benzene corresponds to the molecular ion (M^+) at $m/z = 78$.



Benzene does not undergo extensive fragmentation; none of the fragment ions in its mass spectrum are as abundant as the molecular ion.

There is a small peak one mass unit higher than M^+ in the mass spectrum of benzene. What is the origin of this peak? What we see in Figure 13.35 as a single mass spectrum is actually a superposition of the spectra of three isotopically distinct benzenes. Most of the benzene molecules contain only ^{12}C and ^{1}H and have a molecular mass of 78. Smaller proportions of benzene molecules contain ^{13}C in place of one of the ^{12}C atoms or ^{2}H in place of one of the protons. Both these species have a molecular mass of 79.



Not only the molecular ion peak but all the peaks in the mass spectrum of benzene are accompanied by a smaller peak one mass unit higher. Indeed, since all organic compounds contain carbon and most contain hydrogen, similar **isotopic clusters** will appear in the mass spectra of all organic compounds.

Isotopic clusters are especially apparent when atoms such as bromine and chlorine are present in an organic compound. The natural ratios of isotopes in these elements are

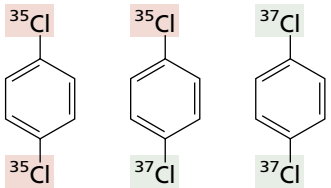
$$\frac{^{35}Cl}{^{37}Cl} = \frac{100}{32.7} \qquad \frac{^{79}Br}{^{81}Br} = \frac{100}{97.5}$$

Figure 13.36 presents the mass spectrum of chlorobenzene. There are two prominent molecular ion peaks, one at m/z 112 for $C_6H_5{}^{35}Cl$ and the other at m/z 114 for $C_6H_5{}^{37}Cl$. The peak at m/z 112 is three times as intense as the one at m/z 114.

PROBLEM 13.18 Knowing what to look for with respect to isotopic clusters can aid in interpreting mass spectra. How many peaks would you expect to see for the molecular ion in each of the following compounds? At what m/z values would these peaks appear? (Disregard the small peaks due to ^{13}C and ^{2}H.)

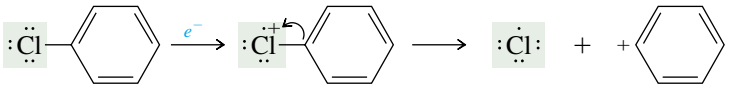
(a) *p*-Dichlorobenzene
(b) *o*-Dichlorobenzene
(c) *p*-Dibromobenzene
(d) *p*-Bromochlorobenzene

SAMPLE SOLUTION (a) The two isotopes of chlorine are ^{35}Cl and ^{37}Cl. There will be three isotopically different forms of *p*-dichlorobenzene present. They have the structures shown as follows. Each one will give an M^+ peak at a different value of *m/z*.



m/z 146 *m/z* 148 *m/z* 150

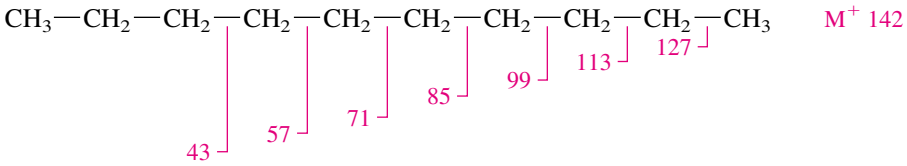
Unlike the case of benzene, in which ionization involves loss of a π electron from the ring, electron-impact-induced ionization of chlorobenzene involves loss of an electron from an unshared pair of chlorine. The molecular ion then fragments by carbon–chlorine bond cleavage.



Chlorobenzene | Molecular ion of chlorobenzene | Chlorine atom | Phenyl cation *m/z* 77

The peak at *m/z* 77 in the mass spectrum of chlorobenzene in Figure 13.36 is attributed to this fragmentation. Because there is no peak of significant intensity two atomic mass units higher, we know that the cation responsible for the peak at *m/z* 77 cannot contain chlorine.

Some classes of compounds are so prone to fragmentation that the molecular ion peak is very weak. The base peak in most unbranched alkanes, for example, is *m/z* 43, which is followed by peaks of decreasing intensity at *m/z* values of 57, 71, 85, and so on. These peaks correspond to cleavage of each possible carbon–carbon bond in the molecule. This pattern is evident in the mass spectrum of decane, depicted in Figure 13.37. The points of cleavage are indicated in the following diagram:



Many fragmentations in mass spectrometry proceed so as to form a stable carbocation, and the principles that we have developed regarding carbocation stability apply.

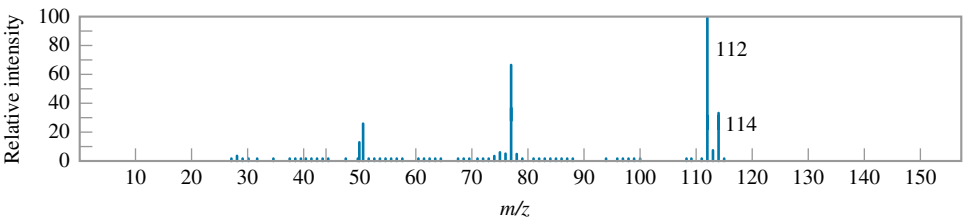


FIGURE 13.36 The mass spectrum of chlorobenzene.

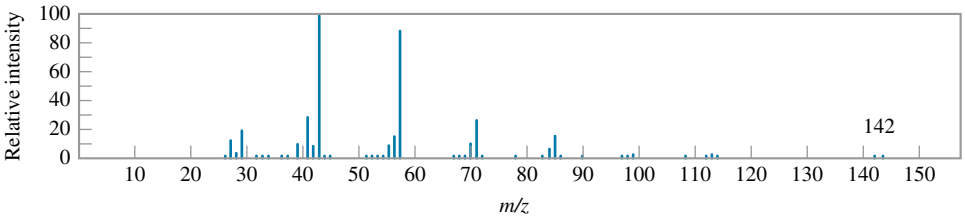


FIGURE 13.37 The mass spectrum of decane. The peak for the molecular ion is extremely small. The most prominent peaks arise by fragmentation.

GAS CHROMATOGRAPHY, GC/MS, AND MS/MS

All of the spectra in this chapter (^{1}H NMR, ^{13}C NMR, IR, UV-VIS, and MS) were obtained using pure substances. It is much more common, however, to encounter an organic substance, either formed as the product of a chemical reaction or isolated from natural sources, as but one component of a mixture. Just as the last half of the twentieth century saw a revolution in the methods available for the *identification* of organic compounds, so too has it seen remarkable advances in methods for their *separation* and *purification.*

Classical methods for separation and purification include fractional distillation of liquids and recrystallization of solids, and these two methods are routinely included in the early portions of laboratory courses in organic chemistry. Because they are capable of being adapted to work on a large scale, fractional distillation and recrystallization are the preferred methods for purifying organic substances in the pharmaceutical and chemical industries.

Some other methods are more appropriate when separating small amounts of material in laboratory-scale work and are most often encountered there. Indeed, it is their capacity to deal with exceedingly small quantities that is the strength of a number of methods that together encompass the various forms of **chromatography.** The first step in all types of chromatography involves absorbing the sample onto some material called the *stationary phase.* Next, a second phase (the *mobile phase*) is allowed to move across the stationary phase. Depending on the properties of the two phases and the components of the mixture, the mixture is separated into its components according to the rate at which each is removed from the stationary phase by the mobile phase.

In **gas chromatography** (GC), the stationary phase consists of beads of an inert solid support coated with a high-boiling liquid, and the mobile phase is a gas, usually helium. Figure 13.38 shows a typical gas chromatograph. The sample is injected by

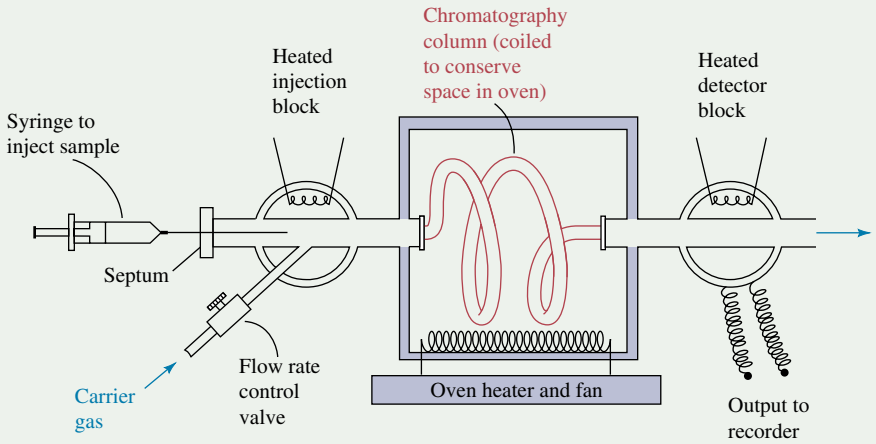


FIGURE 13.38 Diagram of a gas chromatograph. When connected to a mass spectrometer as in GC/MS, the effluent is split into two streams as it leaves the column. One stream goes to the detector, the other to the mass spectrometer. *(Adapted, with permission, from H. D. Durst and G. W. Gokel,* Experimental Organic Chemistry, *2nd ed., McGraw-Hill, New York, 1987.)*

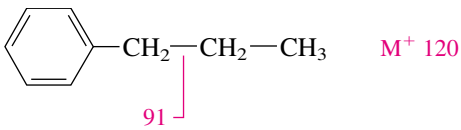
syringe onto a heated block where a stream of helium carries it onto a coiled column packed with the stationary phase. The components of the mixture move through the column at different rates. They are said to have different *retention times.* Gas chromatography is also referred to as *gas–liquid partition chromatography,* because the technique depends on how different substances partition themselves between the gas phase (dispersed in the helium carrier gas) and the liquid phase (dissolved in the coating on the beads of solid support).

Typically the effluent from a gas chromatograph is passed through a detector, which feeds a signal to a recorder whenever a substance different from pure carrier gas leaves the column. Thus, one determines the number of components in a mixture by counting the number of peaks on a strip chart. It is good practice to carry out the analysis under different conditions by varying the liquid phase, the temperature, and the flow rate of the carrier gas so as to ensure that two substances have not eluted together and given a single peak under the original conditions. Gas chromatography can also be used to identify the components of a mixture by comparing their retention times with those of authentic samples.

In **gas chromatography/mass spectrometry** (GC/MS), the effluent from a gas chromatograph is passed into a mass spectrometer and a mass spectrum is taken every few milliseconds. Thus gas chromatography is used to separate a mixture, and mass spectrometry used to analyze it. GC/MS is a very powerful analytical technique. One of its more visible applications involves the testing of athletes for steroids, stimulants, and other performance-enhancing drugs. These drugs are converted in the body to derivatives called *metabolites,* which are then excreted in the urine. When the urine is subjected to GC/MS analysis, the mass spectra of its organic components are identified by comparison with the mass spectra of known metabolites stored in the instrument's computer. Using a similar procedure, the urine of newborn infants is monitored by GC/MS for metabolite markers of genetic disorders that can be treated if detected early in life. GC/MS is also used to detect and measure the concentration of halogenated hydrocarbons in drinking water.

Although GC/MS is the most widely used analytical method that combines a chromatographic separation with the identification power of mass spectrometry, it is not the only one. Chemists have coupled mass spectrometers to most of the instruments that are used to separate mixtures. Perhaps the ultimate is **mass spectrometry/mass spectrometry** (MS/MS), in which one mass spectrometer generates and separates the molecular ions of the components of a mixture and a second mass spectrometer examines their fragmentation patterns!

Alkylbenzenes of the type $C_6H_5CH_2R$ undergo cleavage of the bond to the benzylic carbon to give *m/z* 91 as the base peak. The mass spectrum in Figure 13.39 and the following fragmentation diagram illustrate this for propylbenzene.



Although this cleavage is probably driven by the stability of benzyl cation, evidence has been obtained suggesting that tropylium cation, formed by rearrangement of benzyl cation, is actually the species responsible for the peak.

The structure of tropylium cation is given in Section 11.20.

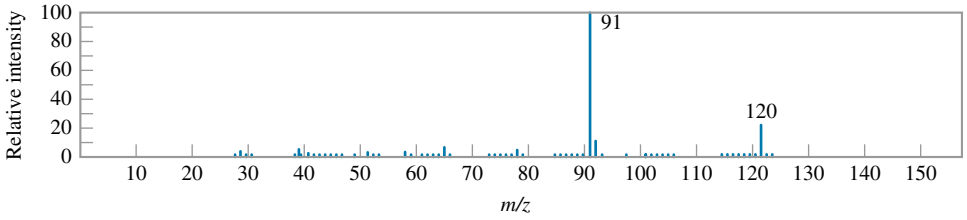
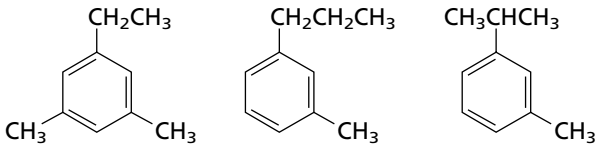


FIGURE 13.39 The mass spectrum of propylbenzene. The most intense peak is $C_7H_7^+$.

PROBLEM 13.19 The base peak appears at *m/z* 105 for one of the following compounds and at *m/z* 119 for the other two. Match the compounds with the appropriate *m/z* values for their base peaks.



Understanding how molecules fragment upon electron impact permits a mass spectrum to be analyzed in sufficient detail to deduce the structure of an unknown compound. Thousands of compounds of known structure have been examined by mass spectrometry, and the fragmentation patterns that characterize different classes are well documented. As various groups are covered in subsequent chapters, aspects of their fragmentation behavior under conditions of electron impact will be described.

13.22 MOLECULAR FORMULA AS A CLUE TO STRUCTURE

As we have just seen, interpreting the fragmentation patterns in a mass spectrum in terms of a molecule's structural units makes mass spectrometry much more than just a tool for determining molecular weights. Nevertheless, even the molecular weight can provide more information than you might think. Compare, for example, heptane and cyclopropyl acetate.

Heptane (C_7H_{16}) Cyclopropyl acetate ($C_5H_8O_2$)

Heptane and cyclopropyl acetate have different molecular formulas but have the same molecular weight—at least to a first approximation. Because we normally round off molecular weights to whole numbers, both have a molecular weight of 100 and both have a peak for their molecular ion at *m/z* 100 in a typical mass spectrum. Recall, however, that mass spectra contain isotopic clusters that differ according to the isotopes present in each ion. Using the exact values for the major isotopes of C, H, and O, we calculate *exact masses* of *m/z* of 100.1253 and 100.0524 for the molecular ions of heptane (C_7H_{16}) and cyclopropyl acetate ($C_5H_8O_2$), respectively. As similar as these values are, it is possible to distinguish between them using a *high-resolution mass spectrometer.* What this means is that the exact mass of a molecular ion can usually be translated into a unique molecular formula.

You can't duplicate these molecular weights for C_7H_{16} and $C_5H_8O_2$ by using the atomic weights given in the periodic table. Those values are for the natural-abundance mixture of isotopes. The exact values are 12.00000 for ^{12}C, 1.00783 for ^{1}H, and 15.9949 for ^{16}O.

Once we have the molecular formula, it can provide information that limits the amount of trial-and-error structure writing we have to do. Consider, for example, heptane and its molecular formula of C_7H_{16}. We know immediately that the molecular formula belongs to an alkane because it corresponds to C_nH_{2n+2}.

What about a substance with the molecular formula C_7H_{14}? This compound cannot be an alkane but may be either a cycloalkane or an alkene, because both these classes of hydrocarbons correspond to the general molecular formula C_nH_{2n}. *Any time a ring or a double bond is present in an organic molecule, its molecular formula has two fewer hydrogen atoms than that of an alkane with the same number of carbons.*

The relationship between molecular formulas, multiple bonds, and rings is referred to as the *index of hydrogen deficiency* and can be expressed by the equation:

$$\text{Index of hydrogen deficiency} = \tfrac{1}{2}(C_nH_{2n+2} - C_nH_x)$$

where C_nH_x is the molecular formula of the compound.

Other terms that mean the same thing as the index of hydrogen deficiency include *elements of unsaturation, sites of unsaturation,* and *the sum of double bonds and rings.*

A molecule that has a molecular formula of C_7H_{14} has an index of hydrogen deficiency of 1:

$$\text{Index of hydrogen deficiency} = \tfrac{1}{2}(C_7H_{16} - C_7H_{14})$$

$$\text{Index of hydrogen deficiency} = \tfrac{1}{2}(2) = 1$$

Thus, the compound has one ring or one double bond. It can't have a triple bond.

A molecule of molecular formula C_7H_{12} has four fewer hydrogens than the corresponding alkane. It has an index of hydrogen deficiency of 2 and can have two rings, two double bonds, one ring and one double bond, or one triple bond.

What about substances other than hydrocarbons, 1-heptanol [$CH_3(CH_2)_5CH_2OH$], for example? Its molecular formula ($C_7H_{16}O$) contains the same carbon-to-hydrogen ratio as heptane and, like heptane, it has no double bonds or rings. Cyclopropyl acetate ($C_5H_8O_2$), the structure of which was given at the beginning of this section, has one ring and one double bond and an index of hydrogen deficiency of 2. Oxygen atoms have no effect on the index of hydrogen deficiency.

A halogen substituent, like hydrogen is monovalent, and when present in a molecular formula is treated as if it were hydrogen for counting purposes.

A more detailed discussion can be found in the May 1995 issue of the *Journal of Chemical Education,* pp. 245–248.

How does one distinguish between rings and double bonds? This additional piece of information comes from catalytic hydrogenation experiments in which the amount of hydrogen consumed is measured exactly. Each of a molecule's double bonds consumes one molar equivalent of hydrogen, but rings are unaffected. For example, a substance with a hydrogen deficiency of 5 that takes up 3 moles of hydrogen must have two rings.

PROBLEM 13.20 How many rings are present in each of the following compounds? Each consumes 2 moles of hydrogen on catalytic hydrogenation.

(a) $C_{10}H_{18}$
(b) C_8H_8
(c) $C_8H_8Cl_2$
(d) C_8H_8O
(e) $C_8H_{10}O_2$
(f) C_8H_9ClO

SAMPLE SOLUTION (a) The molecular formula $C_{10}H_{18}$ contains four fewer hydrogens than the alkane having the same number of carbon atoms ($C_{10}H_{22}$). Therefore, the index of hydrogen deficiency of this compound is 2. Since it consumes two molar equivalents of hydrogen on catalytic hydrogenation, it must have two double bonds and no rings.

13.23 SUMMARY

Section 13.1 Structure determination in modern-day organic chemistry relies heavily on instrumental methods. Several of the most widely used ones depend on the absorption of electromagnetic radiation.

Section 13.2 Absorption of electromagnetic radiation causes a molecule to be excited from its most stable state (the *ground* state) to a higher energy state (an *excited* state).

Spectroscopic method	*Transitions between*
Nuclear magnetic resonance	Spin states of an atom's nucleus
Infrared	Vibrational states
Ultraviolet-visible	Electronic states

Mass spectrometry is not based on absorption of electromagnetic radiation, but monitors what happens when a substance is ionized by collision with a high-energy electron.

^{1}H Nuclear Magnetic Resonance Spectroscopy

Section 13.3 In the presence of an external magnetic field, the $+\frac{1}{2}$ and $-\frac{1}{2}$ nuclear spin states of a proton have slightly different energies.

Section 13.4 The energy required to "flip" the spin of a proton from the lower energy spin state to the higher state depends on the extent to which a nucleus is shielded from the external magnetic field by the molecule's electrons.

Section 13.5 Protons in different environments within a molecule have different **chemical shifts;** that is, they experience different degrees of shielding. Chemical shifts (δ) are reported in parts per million (ppm) from tetramethylsilane (TMS). Table 13.1 lists characteristic chemical shifts for various types of protons.

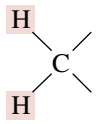
Section 13.6 In addition to *chemical shift,* a ^{1}H NMR spectrum provides structural information based on:

Number of signals, which tells how many different kinds of protons there are

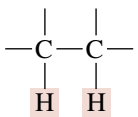
Integrated areas, which tells the ratios of the various kinds of protons

Splitting pattern, which gives information about the number of protons that are within two or three bonds of the one giving the signal

Section 13.7 **Spin-spin splitting** of NMR signals results from coupling of the nuclear spins that are separated by two bonds *(geminal coupling)* or three bonds *(vicinal coupling).*



Geminal hydrogens
are separated by two bonds



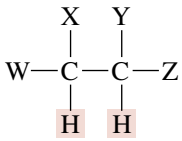
Vicinal hydrogens
are separated by three bonds

In the simplest cases, the number of peaks into which a signal is split is equal to $n + 1$, where n is the number of protons to which the proton in question is coupled. *Protons that have the same chemical shift do not split each other's signal.*

Section 13.8 The methyl protons of an ethyl group appear as a *triplet* and the methylene protons as a *quartet* in compounds of the type CH_3CH_2X.

Section 13.9 The methyl protons of an isopropyl group appear as a *doublet* and the methine proton as a *septet* in compounds of the type $(CH_3)_2CHX$.

Section 13.10 A *doublet of doublets* characterizes the signals for the protons of the type shown (where W, X, Y, and Z are not H or atoms that split H themselves).



Section 13.11 Complicated splitting patterns can result when a proton is unequally coupled to two or more protons that are different from one another.

Section 13.12 Splitting resulting from coupling to the O—H proton of alcohols is not normally observed, because the hydroxyl proton undergoes rapid intermolecular exchange with other alcohol molecules, which "decouples" it from other protons in the molecule.

Section 13.13 Many processes such as conformational changes take place faster than they can be detected by NMR. Consequently, NMR provides information about the *average* environment of a proton. For example, cyclohexane gives a single peak for its 12 protons even though, at any instant, 6 are axial and 6 are equatorial.

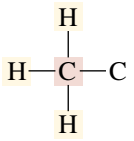
^{13}C Nuclear Magnetic Resonance Spectroscopy

Section 13.14 ^{13}C has a nuclear spin of $\pm\frac{1}{2}$ but only about 1% of all the carbons in a sample are ^{13}C. Nevertheless, high-quality ^{13}C NMR spectra can be obtained by pulse FT techniques and are a useful complement to ^{1}H NMR spectra.

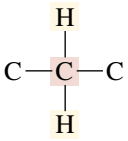
Section 13.15 ^{13}C signals are more widely separated from one another than proton signals, and ^{13}C NMR spectra are relatively easy to interpret. Table 13.3 gives chemical shift values for carbon in various environments.

Section 13.16 ^{13}C NMR spectra are rarely integrated because the pulse FT technique distorts the signal intensities.

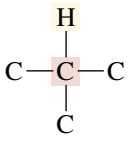
Section 13.17 Carbon signals normally appear as singlets, but several techniques are available that allow one to distinguish among the various kinds of carbons shown.



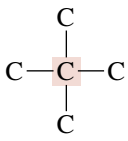
3 attached hydrogens (Primary carbon)



2 attached hydrogens (Secondary carbon)



1 attached hydrogen (Tertiary carbon)



no attached hydrogen (Quaternary carbon)

Section 13.18 One of the special techniques for distinguishing carbons according to the number of their attached hydrogens is called **DEPT.** A series of NMR measurements using different pulse sequences gives normal, nulled, and inverted peaks that allow assignment of primary, secondary, tertiary, and quaternary carbons.

Infrared Spectroscopy

Section 13.19 Infrared spectroscopy probes molecular structure by examining transitions between vibrational energy levels using electromagnetic radiation in the 625–4000-cm^{-1} range. The presence or absence of a peak at a characteristic frequency tells us whether a certain *functional group* is present. Table 13.4 lists IR absorption frequencies for common structural units.

Ultraviolet-Visible Spectroscopy

Section 13.20 Transitions between electronic energy levels involving electromagnetic radiation in the 200–800-nm range form the basis of UV-VIS spectroscopy. The absorption peaks tend to be broad but are often useful in indicating the presence of particular π *electron* systems within a molecule.

Mass Spectrometry

Section 13.21 Mass spectrometry exploits the information obtained when a molecule is ionized by electron impact and then dissociates to smaller fragments. Positive ions are separated and detected according to their mass-to-charge (*m/z*) ratio. By examining the fragments and by knowing how classes of molecules dissociate on electron impact, one can deduce the structure of a compound. Mass spectrometry is quite sensitive; as little as 10^{-9} g of compound is sufficient for analysis.

Section 13.22 A compound's molecular formula gives information about the number of double bonds and rings it contains and is a useful complement to spectroscopic methods of structure determination.

PROBLEMS

13.21 Each of the following compounds is characterized by a ^{1}H NMR spectrum that consists of only a single peak having the chemical shift indicated. Identify each compound.

(a) C_8H_{18}; δ 0.9 ppm
(b) C_5H_{10}; δ 1.5 ppm
(c) C_8H_8; δ 5.8 ppm
(d) C_4H_9Br; δ 1.8 ppm
(e) $C_2H_4Cl_2$; δ 3.7 ppm
(f) $C_2H_3Cl_3$; δ 2.7 ppm
(g) $C_5H_8Cl_4$; δ 3.7 ppm
(h) $C_{12}H_{18}$; δ 2.2 ppm
(i) $C_3H_6Br_2$; δ 2.6 ppm

13.22 Each of the following compounds is characterized by a ^{1}H NMR spectrum that consists of two peaks, both singlets, having the chemical shifts indicated. Identify each compound.

(a) C_6H_8; δ 2.7 ppm (4H) and 5.6 ppm (4H)
(b) $C_5H_{11}Br$; δ 1.1 ppm (9H) and 3.3 ppm (2H)
(c) $C_6H_{12}O$; δ 1.1 ppm (9H) and 2.1 ppm (3H)
(d) $C_6H_{10}O_2$; δ 2.2 ppm (6H) and 2.7 ppm (4H)

13.23 Deduce the structure of each of the following compounds on the basis of their ^{1}H NMR spectra and molecular formulas:

(a) C_8H_{10}; δ 1.2 ppm (triplet, 3H)
δ 2.6 ppm (quartet, 2H)
δ 7.1 ppm (broad singlet, 5H)

(b) $C_{10}H_{14}$; δ 1.3 ppm (singlet, 9H)
δ 7.0 to 7.5 ppm (multiplet, 5H)

(c) C_6H_{14}; δ 0.8 ppm (doublet, 12H)
δ 1.4 ppm (heptet, 2H)

(d) C_6H_{12}; δ 0.9 ppm (triplet, 3H)
δ 1.6 ppm (singlet, 3H)
δ 1.7 ppm (singlet, 3H)
δ 2.0 ppm (pentet, 2H)
δ 5.1 ppm (triplet, 1H)

(e) $C_4H_6Cl_4$; δ 3.9 ppm (doublet, 4H)
δ 4.6 ppm (triplet, 2H)

(f) $C_4H_6Cl_2$; δ 2.2 ppm (singlet, 3H)
δ 4.1 ppm (doublet, 2H)
δ 5.7 ppm (triplet, 1H)

(g) C_3H_7ClO; δ 2.0 ppm (pentet, 2H)
δ 2.8 ppm (singlet, 1H)
δ 3.7 ppm (triplet, 2H)
δ 3.8 ppm (triplet, 2H)

(h) $C_{14}H_{14}$; δ 2.9 ppm (singlet, 4H)
δ 7.1 ppm (broad singlet, 10H)

13.24 From among the isomeric compounds of molecular formula C_4H_9Cl, choose the one having a ^1H NMR spectrum that

(a) Contains only a single peak

(b) Has several peaks including a doublet at δ 3.4 ppm

(c) Has several peaks including a triplet at δ 3.5 ppm

(d) Has several peaks including two distinct three-proton signals, one of them a triplet at δ 1.0 ppm and the other a doublet at δ 1.5 ppm

13.25 Identify the C_3H_5Br isomers on the basis of the following information:

(a) Isomer A has the ^1H NMR spectrum shown in Figure 13.40.

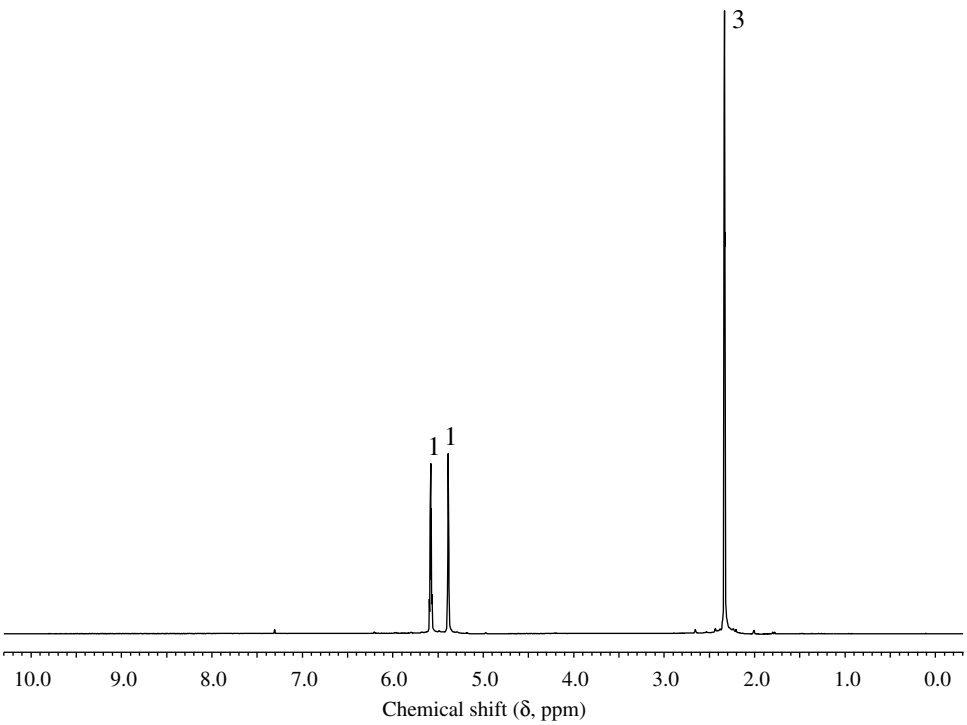


FIGURE 13.40 The 200-MHz ^1H NMR spectrum of isomer A of C_3H_5Br (Problem 13.25a).

(b) Isomer B has three peaks in its ^{13}C NMR spectrum: δ 32.6 ppm (CH_2); 118.8 ppm (CH_2); and 134.2 ppm (CH).

(c) Isomer C has two peaks in its ^{13}C NMR spectrum: δ 12.0 ppm (CH_2) and 16.8 ppm (CH). The peak at lower field is only half as intense as the one at higher field.

13.26 Identify each of the $C_4H_{10}O$ isomers on the basis of their ^{13}C NMR spectra:

(a) δ 18.9 ppm (CH_3) (two carbons)
δ 30.8 ppm (CH) (one carbon)
δ 69.4 ppm (CH_2) (one carbon)

(b) δ 10.0 ppm (CH_3)
δ 22.7 ppm (CH_3)
δ 32.0 ppm (CH_2)
δ 69.2 ppm (CH)

(c) δ 31.2 ppm (CH_3) (three carbons)
δ 68.9 ppm (C) (one carbon)

13.27 Identify the C_6H_{14} isomers on the basis of their ^{13}C NMR spectra:

(a) δ 19.1 ppm (CH_3)
δ 33.9 ppm (CH)

(b) δ 13.7 ppm (CH_3)
δ 22.8 ppm (CH_2)
δ 31.9 ppm (CH_2)

(c) δ 11.1 ppm (CH_3)
δ 18.4 ppm (CH_3)
δ 29.1 ppm (CH_2)
δ 36.4 ppm (CH)

(d) δ 8.5 ppm (CH_3)
δ 28.7 ppm (CH_3)
δ 30.2 ppm (C)
δ 36.5 ppm (CH_2)

(e) δ 14.0 ppm (CH_3)
δ 20.5 ppm (CH_2)
δ 22.4 ppm (CH_3)
δ 27.6 ppm (CH)
δ 41.6 ppm (CH_2)

13.28 A compound (C_4H_6) has two signals of approximately equal intensity in its ^{13}C NMR spectrum; one is a CH_2 carbon at δ 30.2 ppm, the other a CH at δ 136 ppm. Identify the compound.

13.29 A compound ($C_3H_7ClO_2$) exhibited three peaks in its ^{13}C NMR spectrum at δ 46.8 (CH_2), 63.5 (CH_2), and 72.0 ppm (CH). Excluding compounds that have Cl and OH on the same carbon, which are unstable, what is the most reasonable structure for this compound?

13.30 From among the compounds chlorobenzene, *o*-dichlorobenzene, and *p*-dichlorobenzene, choose the one that

(a) Gives the simplest ^1H NMR spectrum

(b) Gives the simplest ^{13}C NMR spectrum

(c) Has three peaks in its ^{13}C NMR spectrum

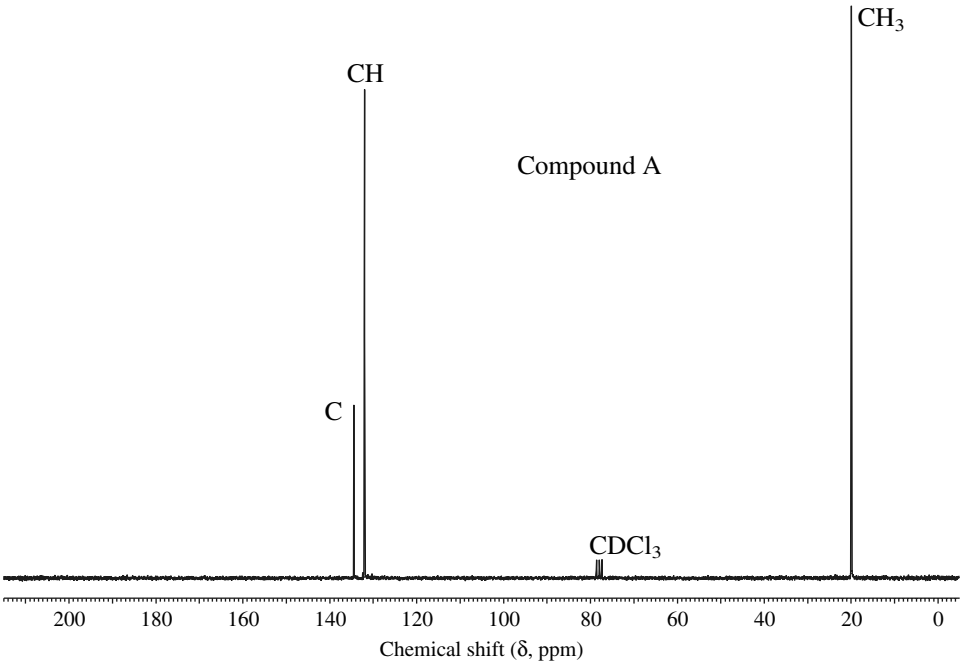
(d) Has four peaks in its ^{13}C NMR spectrum

13.31 Compounds A and B are isomers of molecular formula $C_{10}H_{14}$. Identify each one on the basis of the ^{13}C NMR spectra presented in Figure 13.41.

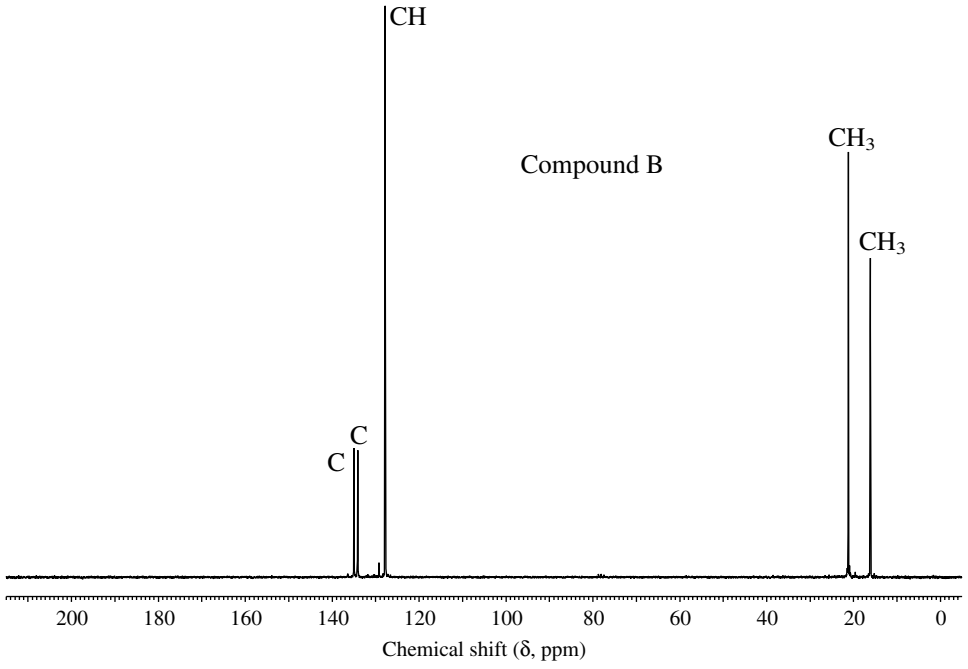
13.32 A compound ($C_8H_{10}O$) has the infrared and ^1H NMR spectra presented in Figure 13.42. What is its structure?

13.33 Deduce the structure of a compound having the mass spectrum and ^1H NMR spectrum presented in Figure 13.43.

13.34 Figure 13.44 presents several types of spectroscopic data (IR, ^1H NMR, ^{13}C NMR, and mass spectra) for a particular compound. What is it?

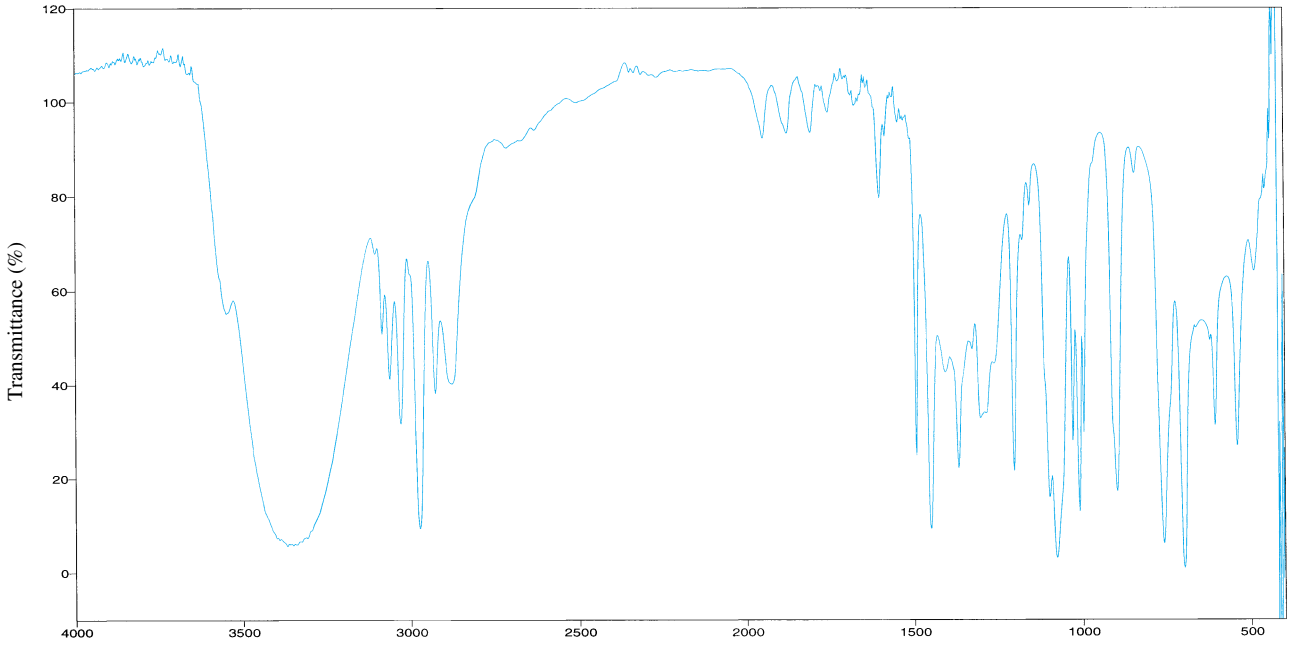


(*a*)

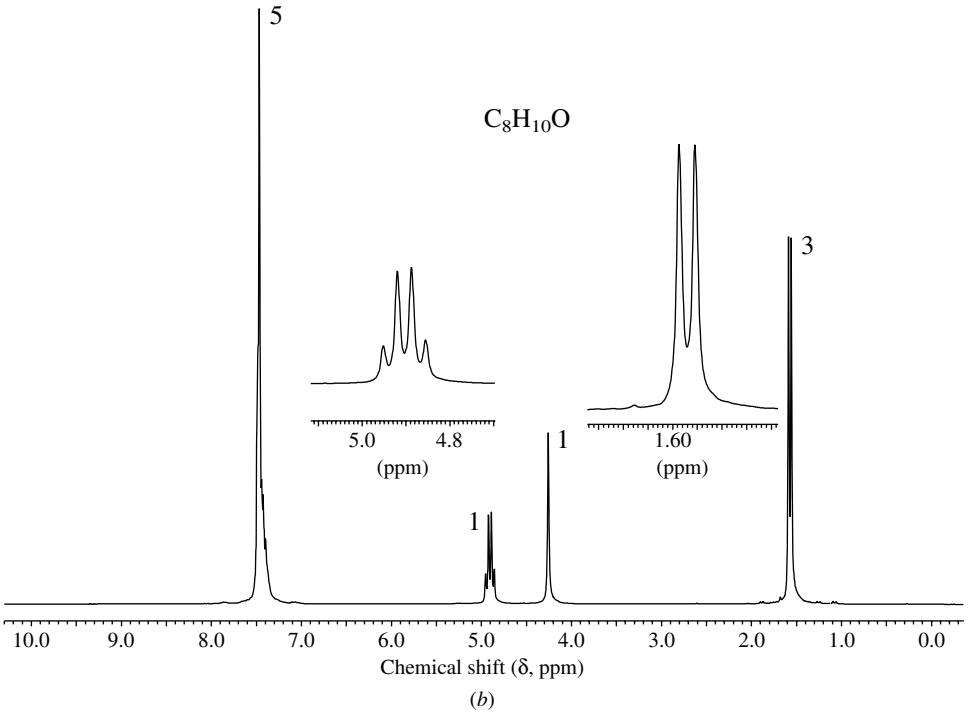


(*b*)

FIGURE 13.41 The ^{13}C NMR spectrum of (*a*) compound A and (*b*) compound B, isomers of $C_{10}H_{14}$ (Problem 13.31).

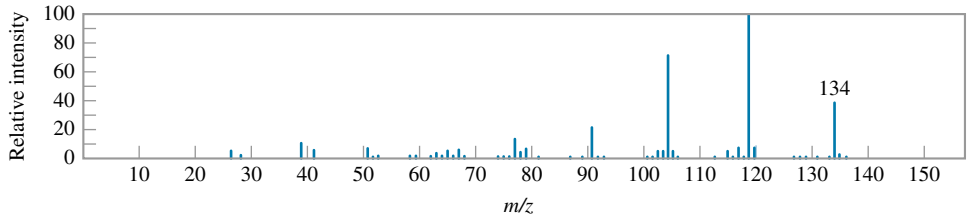


(*a*)

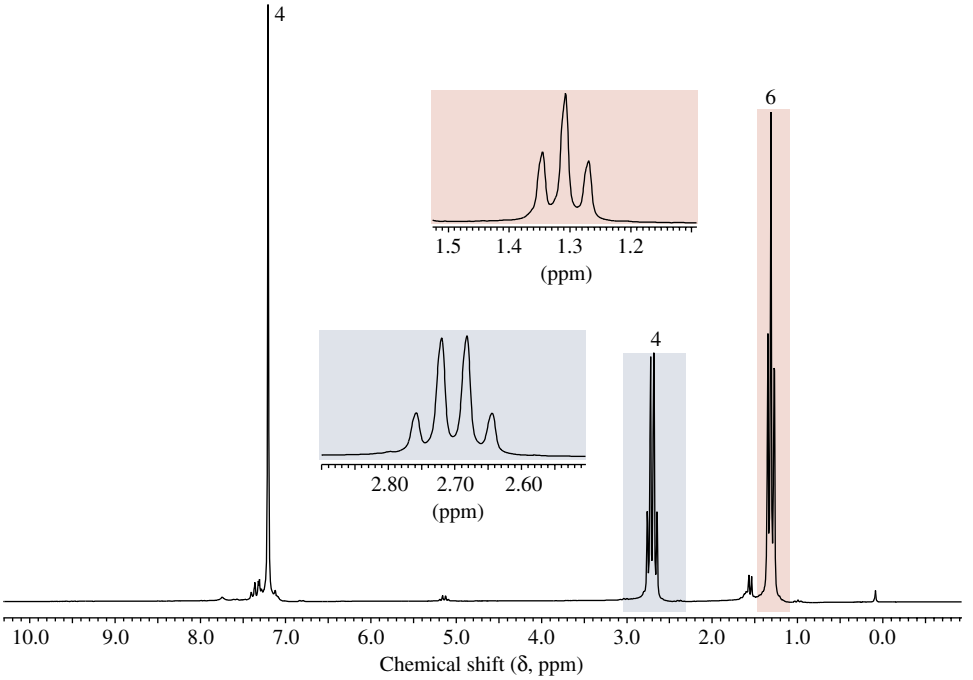


(*b*)

FIGURE 13.42 (*a*) Infrared and (*b*) 200-MHz ^{1}H NMR spectra of a compound $C_8H_{10}O$ (Problem 13.32).

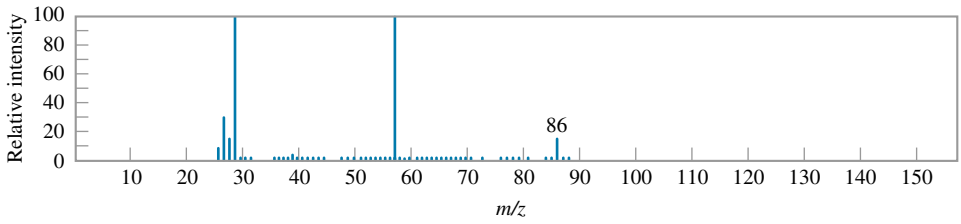


(*a*)

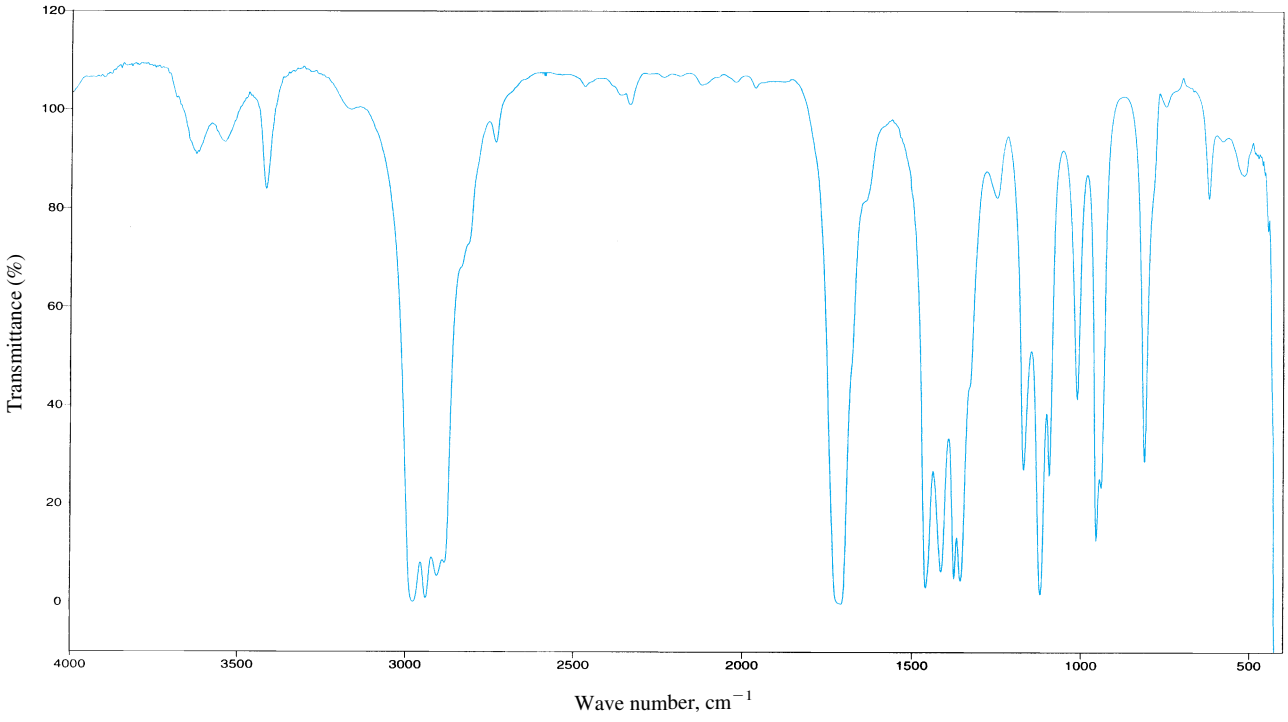


(*b*)

FIGURE 13.43 (*a*) Mass spectrum and (*b*) 200-MHz ^{1}H NMR spectrum of an unknown compound (Problem 13.33).

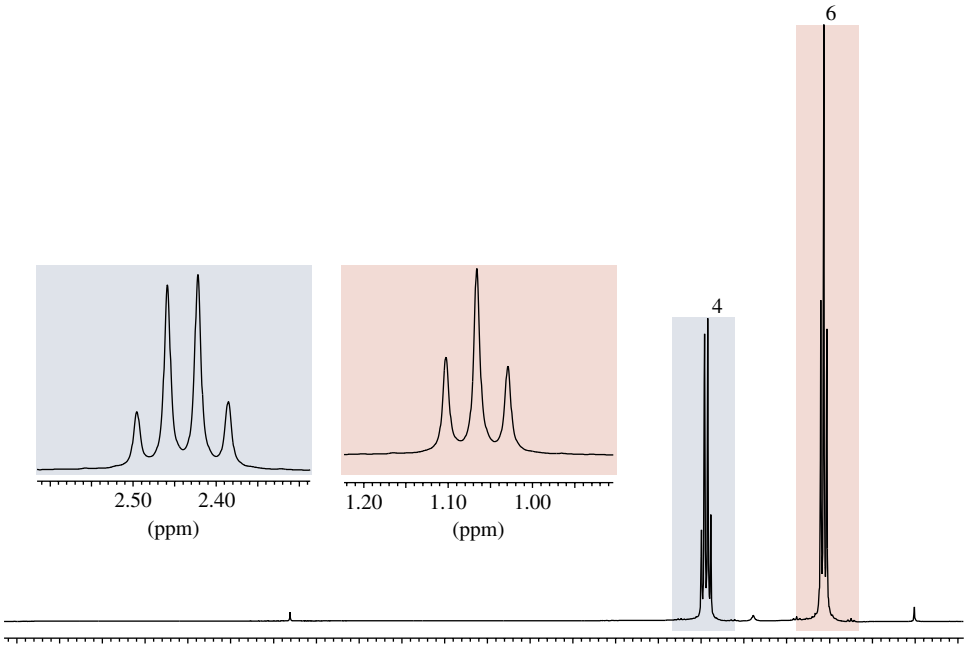


(*a*)

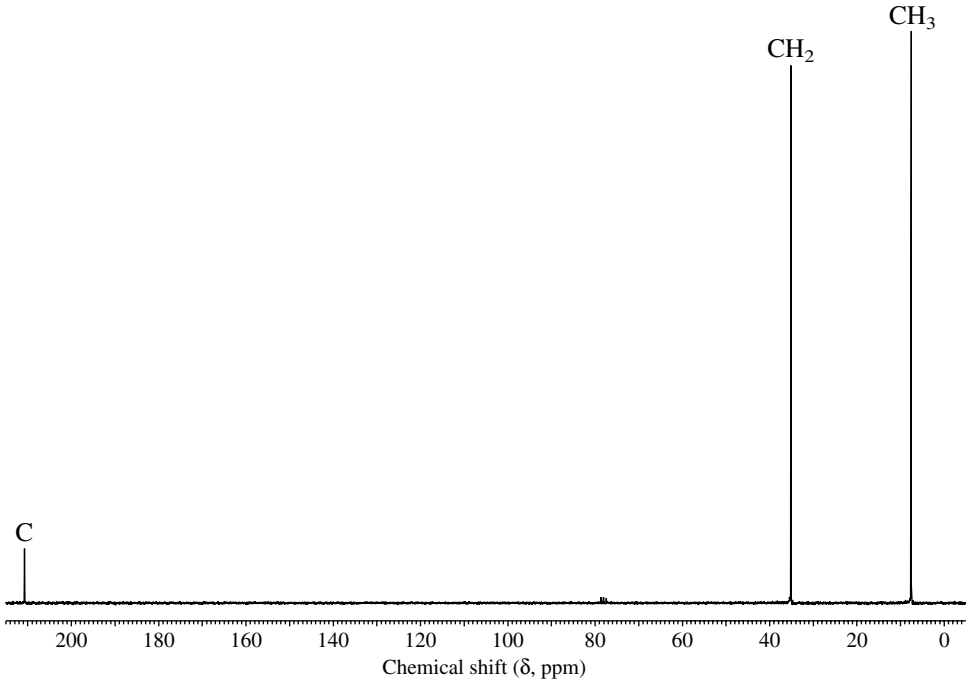


(*b*)

FIGURE 13.44 (*a*) Mass, (*b*) infrared, (*c*) 200-MHz ^{1}H NMR, and (*d*) ^{13}C NMR spectra for the compound of Problem 13.34.

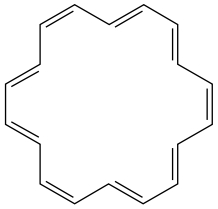

6
4
2.50
2.40
(ppm)
1.20
1.10
1.00
(ppm)
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
Chemical shift (δ, ppm)

(*c*)


CH3
CH2
C
200
180
160
140
120
100
80
60
40
20
0
Chemical shift (δ, ppm)

(*d*)

13.35 [18]-Annulene exhibits a ^{1}H NMR spectrum that is unusual in that in addition to a peak at δ 8.8 ppm, it contains a second peak having a chemical shift δ of −1.9 ppm. A negative value for the chemical shift δ indicates that the protons are *more* shielded than those of tetramethylsilane. This peak is 1.9 ppm *upfield* from the TMS peak. The high-field peak has half the area of the low-field peak. Suggest an explanation for these observations.



[18]-Annulene

13.36 ^{19}F is the only isotope of fluorine that occurs naturally, and it has a nuclear spin of $\pm\frac{1}{2}$.

(a) Into how many peaks will the proton signal in the ^{1}H NMR spectrum of methyl fluoride be split?

(b) Into how many peaks will the fluorine signal in the ^{19}F NMR spectrum of methyl fluoride be split?

(c) The chemical shift of the protons in methyl fluoride is δ 4.3 ppm. Given that the geminal ^{1}H—^{19}F coupling constant is 45 Hz, specify the δ values at which peaks are observed in the proton spectrum of this compound at 200 MHz.

13.37 In general, the vicinal coupling constant between two protons varies with the angle between the C—H bonds of the H—C—C—H unit. The coupling constant is greatest when the protons are periplanar (dihedral angle = 0° or 180°) and smallest when the angle is approximately 90°. Describe, with the aid of molecular models, how you could distinguish between *cis*-1-bromo-2-chlorocyclopropane and its trans stereoisomer on the basis of their ^{1}H NMR spectra.

The dependence of ^3J on dihedral angle is referred to as the **Karplus relationship** after Martin Karplus (Harvard University) who offered the presently accepted theoretical treatment of it.

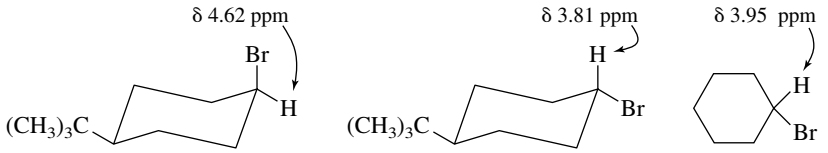
13.38 The π→π* transition in the UV spectrum of *trans*-stilbene (*trans*-$C_6H_5CH{=}CHC_6H_5$) appears at 295 nm compared with 283 nm for the cis stereoisomer. The extinction coefficient ϵ_{max} is approximately twice as great for *trans*-stilbene as for *cis*-stilbene. Both facts are normally interpreted in terms of more effective conjugation of the π electron system in *trans*-stilbene. Construct a molecular model of each stereoisomer, and identify the reason for the decreased effectiveness of conjugation in *cis*-stilbene.

13.39 ^{31}P is the only phosphorus isotope present at natural abundance and has a nuclear spin of $\pm\frac{1}{2}$. The ^{1}H NMR spectrum of trimethyl phosphite, $(CH_3O)_3P$, exhibits a doublet for the methyl protons with a splitting of 12 Hz.

(a) Into how many peaks is the ^{31}P signal split?

(b) What is the difference in chemical shift (in hertz) between the lowest and highest field peaks of the ^{31}P multiplet?

13.40 We noted in section 13.13 that an NMR spectrum is an average spectrum of the conformations populated by a molecule. From the following data, estimate the percentages of axial and equatorial bromine present in bromocyclohexane.



13.41 Infrared spectroscopy is an inherently "faster" method than NMR, and an IR spectrum is a superposition of the spectra of the various conformations, rather than an average of them. When 1,2-dichloroethane is cooled below its freezing point, the crystalline material gives an IR spectrum consistent with a single species that has a center of symmetry. At room temperature, the IR spectrum of liquid 1,2-dichloroethane retains the peaks present in the solid, but includes new peaks as well. Explain these observations.

13.42 *Microwave spectroscopy* is used to probe transitions between rotational energy levels in molecules.

(a) A typical wavelength for microwaves is 10^{-2} m, compared with 10^{-5} m for infrared radiation. Is the energy separation between rotational energy levels in a molecule greater or less than the separation between vibrational energy levels?

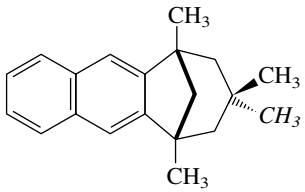
(b) Microwave ovens cook food by heating the water in the food. Absorption of microwave radiation by the water excites it to a higher rotational energy state, and it gives off this excess energy as heat when it relaxes to its ground state. Why are vibrational and electronic energy states not involved in this process?

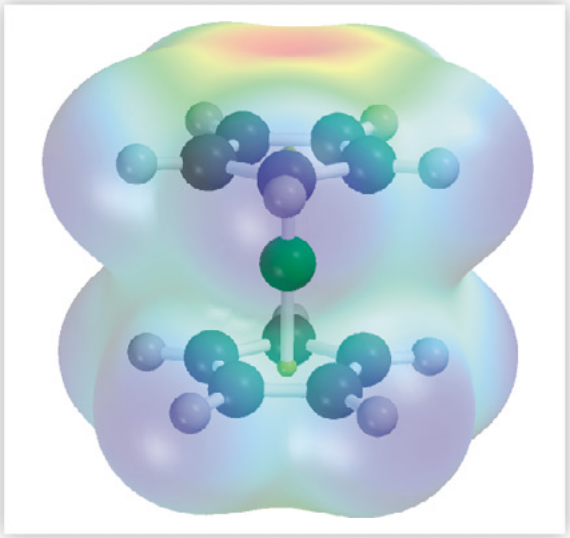
13.43 The peak in the UV-VIS spectrum of acetone [$(CH_3)_2C{=}O$] corresponding to the $n \rightarrow \pi^*$ transition appears at 279 nm when hexane is the solvent, but shifts to 262 nm in water. Which is more polar, the ground electronic state or the excited state?

13.44 A particular vibration will give an absorption peak in the infrared spectrum only if the dipole moment of the molecule changes during the vibration. Which vibration of carbon dioxide, the symmetrical stretch or the antisymmetrical stretch, is "infrared-active"?

Symmetrical stretch Antisymmetrical stretch

13.45 The protons in the methyl group shown in italics in the following structure are highly shielded and give a signal 0.38 ppm *upfield* from TMS. The other methyl group on the same carbon has a more normal chemical shift of 0.86 ppm downfield from TMS. Why is the indicated methyl group so highly shielded? (Building a molecular model can help.)





CHAPTER 14

ORGANOMETALLIC COMPOUNDS

Organometallic compounds are compounds that have a carbon–metal bond; they lie at the place where organic and inorganic chemistry meet. You are already familiar with at least one organometallic compound, sodium acetylide ($NaC{\equiv}CH$), which has an ionic bond between carbon and sodium. But just because a compound contains both a metal and carbon isn't enough to classify it as organometallic. Like sodium acetylide, sodium methoxide ($NaOCH_3$) is an ionic compound. Unlike sodium acetylide, however, the negative charge in sodium methoxide resides on oxygen, not carbon.

$Na^+ \; :\bar{C}{\equiv}CH$

Sodium acetylide
(has a carbon-to-metal bond)

$Na^+ \; \bar{:}\ddot{O}CH_3$

Sodium methoxide
(does not have a carbon-to-metal bond)

The properties of organometallic compounds are much different from those of the other classes we have studied to this point. Most important, many organometallic compounds are powerful sources of nucleophilic carbon, something that makes them especially valuable to the synthetic organic chemist. For example, the preparation of alkynes by the reaction of sodium acetylide with alkyl halides (Section 9.6) depends on the presence of a negatively charged, nucleophilic carbon in acetylide ion.

Synthetic procedures that use organometallic reagents are among the most important methods for carbon–carbon bond formation in organic chemistry. In this chapter you will learn how to prepare organic derivatives of lithium, magnesium, copper, and zinc and see how their novel properties can be used in organic synthesis. We will also finish the story of polyethylene and polypropylene begun in Chapter 6 and continued in Chapter 7 to see the unique way that organometallic compounds catalyze alkene polymerization.

14.1 ORGANOMETALLIC NOMENCLATURE

Organometallic compounds are named as substituted derivatives of metals. The metal is the base name, and the attached alkyl groups are identified by the appropriate prefix.

Cyclopropyllithium

$CH_2{=}CHNa$

Vinylsodium

$(CH_3CH_2)_2Mg$

Diethylmagnesium

When the metal bears a substituent other than carbon, the substituent is treated as if it were an anion and named separately.

CH_3MgI

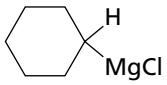
Methylmagnesium iodide

$(CH_3CH_2)_2AlCl$

Diethylaluminum chloride

PROBLEM 14.1 Both of the following organometallic reagents will be encountered later in this chapter. Suggest a suitable name for each.

(a) $(CH_3)_3CLi$

(b) 

SAMPLE SOLUTION (a) The metal lithium provides the base name for $(CH_3)_3CLi$. The alkyl group to which lithium is bonded is *tert*-butyl, and so the name of this organometallic compound is *tert*-butylithium. An alternative, equally correct name is 1,1-dimethylethyllithium.

An exception to this type of nomenclature is $NaC{\equiv}CH$, which is normally referred to as *sodium acetylide*. Both sodium acetylide and ethynylsodium are acceptable IUPAC names.

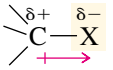
14.2 CARBON–METAL BONDS IN ORGANOMETALLIC COMPOUNDS

With an electronegativity of 2.5 (Table 14.1), carbon is neither strongly electropositive nor strongly electronegative. When carbon is bonded to an element more electronegative than itself, such as oxygen or chlorine, the electron distribution in the bond is polarized

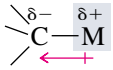
TABLE 14.1 Electronegativities of Some Representative Elements

Element	Electronegativity
F	4.0
O	3.5
Cl	3.0
N	3.0
C	2.5
H	2.1
Cu	1.9
Zn	1.6
Al	1.5
Mg	1.2
Li	1.0
Na	0.9
K	0.8

so that carbon is slightly positive and the more electronegative atom is slightly negative. Conversely, when carbon is bonded to a less electronegative element, such as a metal, the electrons in the bond are more strongly attracted toward carbon.



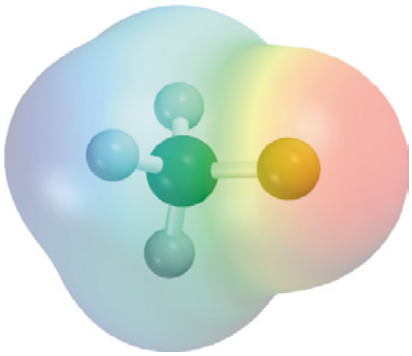
X is more electronegative than carbon



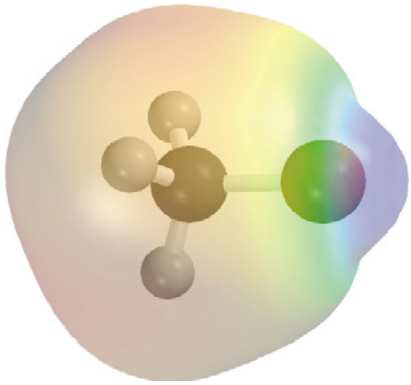
M is less electronegative than carbon

Figure 14.1 uses electrostatic potential maps to show how different the electron distribution is between methyl fluoride (CH_3F) and methyllithium (CH_3Li).

An anion that contains a negatively charged carbon is referred to as a **carbanion.** Covalently bonded organometallic compounds are said to have *carbanionic character.* As the metal becomes more electropositive, the ionic character of the carbon–metal bond becomes more pronounced. Organosodium and organopotassium compounds have ionic carbon–metal bonds; organolithium and organomagnesium compounds tend to have covalent, but rather polar, carbon–metal bonds with significant carbanionic character. *It is the carbanionic character of such compounds that is responsible for their usefulness as synthetic reagents.*



(*a*) Methyl fluoride



(*b*) Methyllithium

FIGURE 14.1 Electrostatic potential maps of (*a*) methyl fluoride and of (*b*) methyllithium. The electron distribution is reversed in the two compounds. Carbon is electron-poor (*blue*) in methyl fluoride, but electron-rich (*red*) in methyllithium.

14.3 PREPARATION OF ORGANOLITHIUM COMPOUNDS

Before we describe the applications of organometallic reagents to organic synthesis, let us examine their preparation. Organolithium compounds and other Group I organometallic compounds are prepared by the reaction of an alkyl halide with the appropriate metal.

The reaction of an alkyl halide with lithium was cited earlier (Section 2.16) as an example of an *oxidation–reduction*. Group I metals are powerful reducing agents.

$$\underset{\text{Alkyl halide}}{RX} + \underset{\text{Group I metal}}{2M} \longrightarrow \underset{\text{Group I organometallic compound}}{RM} + \underset{\text{Metal halide}}{M^+X^-}$$

$$\underset{\textit{tert}\text{-Butyl chloride}}{(CH_3)_3CCl} + \underset{\text{Lithium}}{2Li} \xrightarrow[-30^\circ C]{\text{diethyl ether}} \underset{\textit{tert}\text{-Butyllithium (75\%)}}{(CH_3)_3CLi} + \underset{\text{Lithium chloride}}{LiCl}$$

The alkyl halide can be primary, secondary, or tertiary. Alkyl iodides are the most reactive, followed by bromides, then chlorides. Fluorides are relatively unreactive.

Unlike elimination and nucleophilic substitution reactions, formation of organolithium compounds does not require that the halogen be bonded to sp^3-hybridized carbon. Compounds such as vinyl halides and aryl halides, in which the halogen is bonded to sp^2-hybridized carbon, react in the same way as alkyl halides, but at somewhat slower rates.

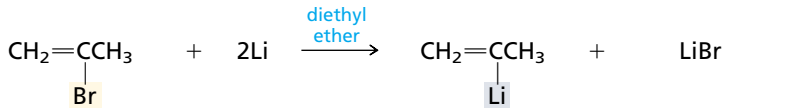
Bromobenzene — Lithium — Phenyllithium (95–99%) — Lithium bromide

Organolithium compounds are sometimes prepared in hydrocarbon solvents such as pentane and hexane, but normally diethyl ether is used. *It is especially important that the solvent be anhydrous.* Even trace amounts of water or alcohols react with lithium to form insoluble lithium hydroxide or lithium alkoxides that coat the surface of the metal and prevent it from reacting with the alkyl halide. Furthermore, organolithium reagents are strong bases and react rapidly with even weak proton sources to form hydrocarbons. We shall discuss this property of organolithium reagents in Section 14.5.

PROBLEM 14.2 Write an equation showing the formation of each of the following from the appropriate bromide:

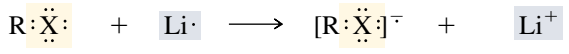
(a) Isopropenyllithium (b) *sec*-Butyllithium

SAMPLE SOLUTION (a) In the preparation of organolithium compounds from organic halides, lithium becomes bonded to the carbon that bore the halogen. Therefore, isopropenyllithium must arise from isopropenyl bromide.



Isopropenyl bromide — Lithium — Isopropenyllithium — Lithium bromide

Reaction with an alkyl halide takes place at the metal surface. In the first step, an electron is transferred from the metal to the alkyl halide.

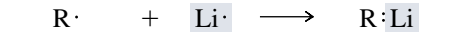


Alkyl halide — Lithium — Anion radical — Lithium cation

Having gained one electron, the alkyl halide is now negatively charged and has an odd number of electrons. It is an *anion radical.* The extra electron occupies an antibonding orbital. This anion radical fragments to an alkyl radical and a halide anion.

Anion radical — Alkyl radical — Halide anion

Following fragmentation, the alkyl radical rapidly combines with a lithium atom to form the organometallic compound.



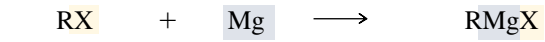
Alkyl radical — Lithium — Alkyllithium

14.4 PREPARATION OF ORGANOMAGNESIUM COMPOUNDS: GRIGNARD REAGENTS

The most important organometallic reagents in organic chemistry are organomagnesium compounds. They are called **Grignard reagents** after the French chemist Victor Grignard. Grignard developed efficient methods for the preparation of organic derivatives of magnesium and demonstrated their application in the synthesis of alcohols. For these achievements he was a corecipient of the 1912 Nobel Prize in chemistry.

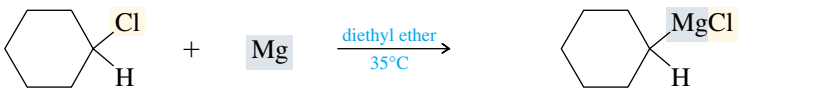
Grignard shared the prize with Paul Sabatier, who, as was mentioned in Chapter 6, showed that finely divided nickel could be used to catalyze the hydrogenation of alkenes.

Grignard reagents are prepared from organic halides by reaction with magnesium, a Group II metal.



Organic halide — Magnesium — Organomagnesium halide

(R may be methyl or primary, secondary, or tertiary alkyl; it may also be a cycloalkyl, alkenyl, or aryl group.)



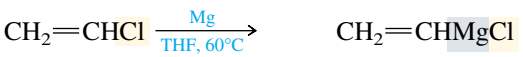
Cyclohexyl chloride — Magnesium — Cyclohexylmagnesium chloride (96%)

Bromobenzene — Magnesium — Phenylmagnesium bromide (95%)

Anhydrous diethyl ether is the customary solvent used when preparing organomagnesium compounds. Sometimes the reaction does not begin readily, but once started, it is exothermic and maintains the temperature of the reaction mixture at the boiling point of diethyl ether (35°C).

The order of halide reactivity is I > Br > Cl > F, and alkyl halides are more reactive than aryl and vinyl halides. Indeed, aryl and vinyl chlorides do not form Grignard reagents in diethyl ether. When more vigorous reaction conditions are required, tetrahydrofuran (THF) is used as the solvent.

Recall the structure of tetrahydrofuran from Section 3.15:

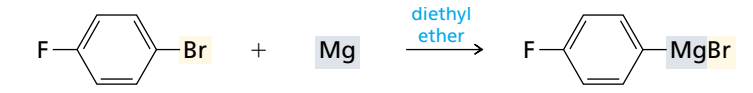


Vinyl chloride — Vinylmagnesium chloride (92%)

PROBLEM 14.3 Write the structure of the Grignard reagent formed from each of the following compounds on reaction with magnesium in diethyl ether:

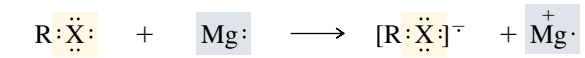
(a) *p*-Bromofluorobenzene
(b) Allyl chloride
(c) Iodocyclobutane
(d) 1-Bromocyclohexene

SAMPLE SOLUTION (a) Of the two halogen substituents on the aromatic ring, bromine reacts much faster than fluorine with magnesium. Therefore, fluorine is left intact on the ring, while the carbon–bromine bond is converted to a carbon–magnesium bond.

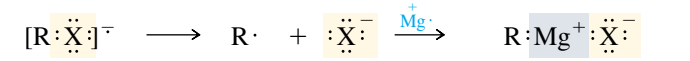


p-Bromofluorobenzene | Magnesium | *p*-Fluorophenylmagnesium bromide

The formation of a Grignard reagent is analogous to that of organolithium reagents except that each magnesium atom can participate in two separate one-electron transfer steps:



Alkyl halide | Magnesium | Anion radical

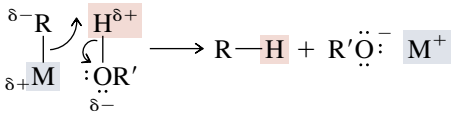


Anion radical | Alkyl radical | Halide ion | Alkylmagnesium halide

Organolithium and organomagnesium compounds find their chief use in the preparation of alcohols by reaction with aldehydes and ketones. Before discussing these reactions, let us first examine the reactions of these organometallic compounds with proton donors.

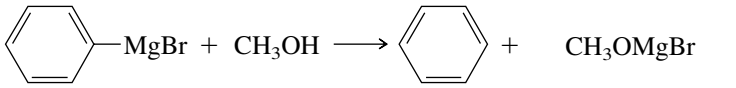
14.5 ORGANOLITHIUM AND ORGANOMAGNESIUM COMPOUNDS AS BRØNSTED BASES

Organolithium and organomagnesium compounds are stable species when prepared in suitable solvents such as diethyl ether. They are strongly basic, however, and react instantly with proton donors even as weakly acidic as water and alcohols. A proton is transferred from the hydroxyl group to the negatively polarized carbon of the organometallic compound to form a hydrocarbon.



$$CH_3CH_2CH_2CH_2Li + H_2O \longrightarrow CH_3CH_2CH_2CH_3 + LiOH$$

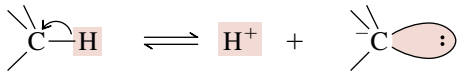
Butyllithium | Water | Butane (100%) | Lithium hydroxide



Phenylmagnesium bromide | Methanol | Benzene (100%) | Methoxymagnesium bromide

Because of their basicity organolithium compounds and Grignard reagents cannot be prepared or used in the presence of any material that bears a hydroxyl group. Nor are these reagents compatible with —NH or —SH groups, which can also convert an organolithium or organomagnesium compound to a hydrocarbon by proton transfer.

The carbon–metal bonds of organolithium and organomagnesium compounds have appreciable carbanionic character. Carbanions rank among the strongest bases that we'll see in this text. Their conjugate acids are hydrocarbons—very weak acids indeed. The equilibrium constants K_a for ionization of hydrocarbons are much smaller than the K_a's for water and alcohols.

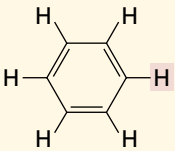
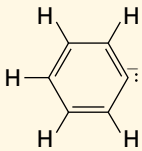


Hydrocarbon (very weak acid) Proton Carbanion (very strong base)

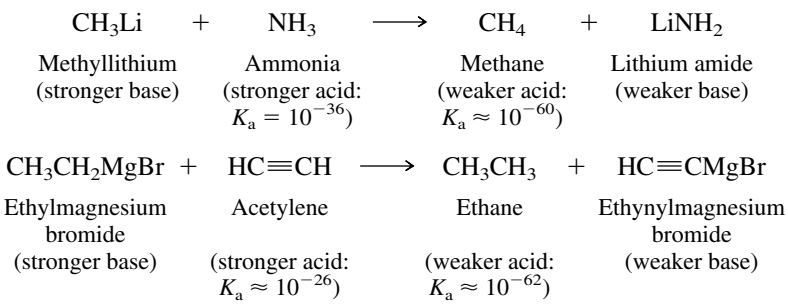
Table 14.2 presents some approximate data for the acid strengths of representative hydrocarbons.

Acidity increases in progressing from the top of Table 14.2 to the bottom. An acid will transfer a proton to the conjugate base of any acid above it in the table. Organolithium compounds and Grignard reagents act like carbanions and will abstract a proton from any substance more acidic than a hydrocarbon. Thus, N—H groups and terminal alkynes (RC≡C—H) are converted to their conjugate bases by proton transfer to organolithium and organomagnesium compounds.

TABLE 14.2 Approximate Acidities of Some Hydrocarbons and Reference Materials

Compound	Formula*	K_a	pK_a	Conjugate base
2-Methylpropane	$(CH_3)_3C—H$	10^{-71}	71	$(CH_3)_3C^-$
Ethane	$CH_3CH_2—H$	10^{-62}	62	$CH_3\bar{C}H_2$
Methane	$CH_3—H$	10^{-60}	60	H_3C^-
Ethylene	$CH_2=CH—H$	10^{-45}	45	$CH_2=\bar{C}H$
Benzene		10^{-43}	43	
Ammonia	$H_2N—H$	10^{-36}	36	$H_2\ddot{N}^-$
Acetylene	$HC\equiv C—H$	10^{-26}	26	$HC\equiv C^-$
Ethanol	$CH_3CH_2O—H$	10^{-16}	16	$CH_3CH_2\ddot{O}^-$
Water	$HO—H$	1.8×10^{-16}	15.7	$H\ddot{O}^-$

*The acidic proton in each compound is shaded in red.



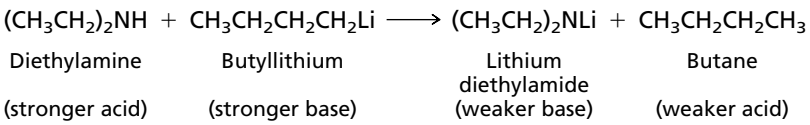
PROBLEM 14.4 Butyllithium is commercially available and is frequently used by organic chemists as a strong base. Show how you could use butyllithium to prepare solutions containing

(a) Lithium diethylamide, $(CH_3CH_2)_2NLi$

(b) Lithium 1-hexanolate, $CH_3(CH_2)_4CH_2OLi$

(c) Lithium benzenethiolate, C_6H_5SLi

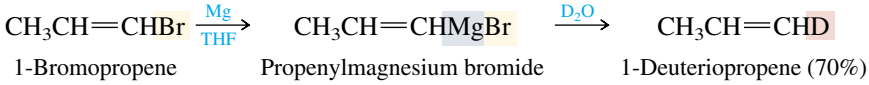
SAMPLE SOLUTION When butyllithium is used as a base, it abstracts a proton, in this case a proton attached to nitrogen. The source of lithium diethylamide must be diethylamine.



Although diethylamine is not specifically listed in Table 14.2, its strength as an acid ($K_a \approx 10^{-36}$) is, as might be expected, similar to that of ammonia.

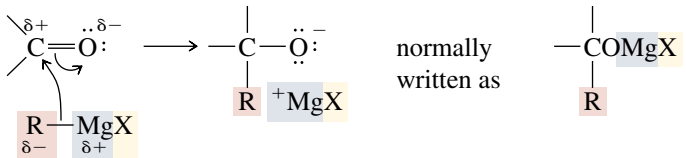
It is sometimes necessary in a synthesis to reduce an alkyl halide to a hydrocarbon. In such cases converting the halide to a Grignard reagent and then adding water or an alcohol as a proton source is a satisfactory procedure. Adding D_2O to a Grignard reagent is a commonly used method for introducing deuterium into a molecule at a specific location.

Deuterium is the mass 2 isotope of hydrogen. Deuterium oxide (D_2O) is sometimes called "heavy water."



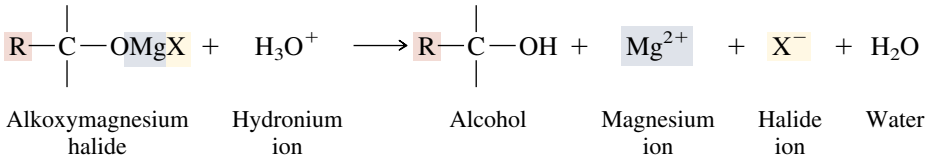
14.6 SYNTHESIS OF ALCOHOLS USING GRIGNARD REAGENTS

The main synthetic application of Grignard reagents is their reaction with certain carbonyl-containing compounds to produce alcohols. Carbon–carbon bond formation is rapid and exothermic when a Grignard reagent reacts with an aldehyde or ketone.



A carbonyl group is quite polar, and its carbon atom is electrophilic. Grignard reagents are nucleophilic and add to carbonyl groups, forming a new carbon–carbon bond. This

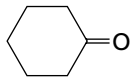
addition step leads to an alkoxymagnesium halide, which in the second stage of the synthesis is converted to an alcohol by adding aqueous acid.



The type of alcohol produced depends on the carbonyl compound. Substituents present on the carbonyl group of an aldehyde or ketone stay there—they become substituents on the carbon that bears the hydroxyl group in the product. Thus as shown in Table 14.3, formaldehyde reacts with Grignard reagents to yield primary alcohols, aldehydes yield secondary alcohols, and ketones yield tertiary alcohols.

PROBLEM 14.5 Write the structure of the product of the reaction of propylmagnesium bromide with each of the following. Assume that the reactions are worked up by the addition of dilute aqueous acid.

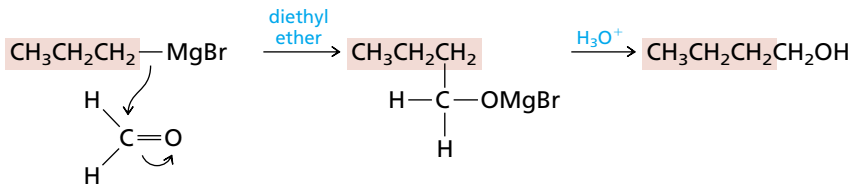
(a) Formaldehyde, HCH(=O)

(c) Cyclohexanone, 

(b) Benzaldehyde, C_6H_5CH(=O)

(d) 2-Butanone, $CH_3CCH_2CH_3$(=O)

SAMPLE SOLUTION (a) Grignard reagents react with formaldehyde to give primary alcohols having one more carbon atom than the alkyl halide from which the Grignard reagent was prepared. The product is 1-butanol.

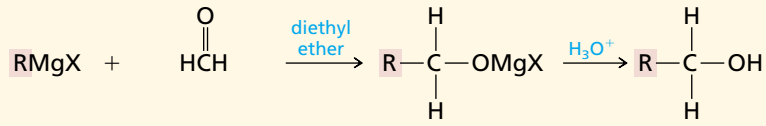
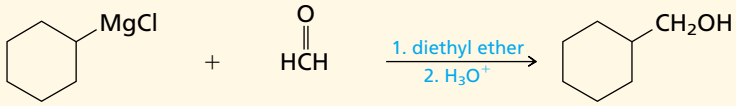
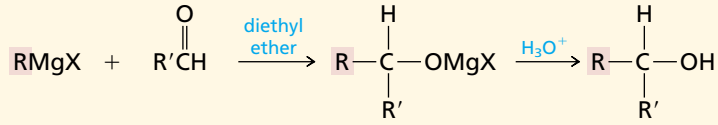
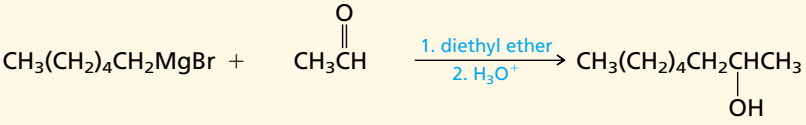
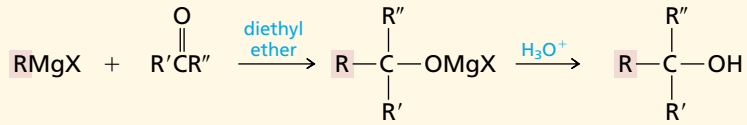
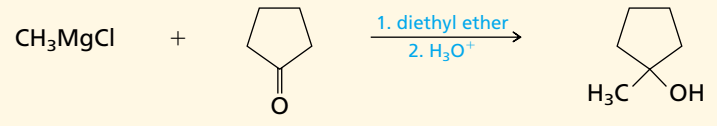


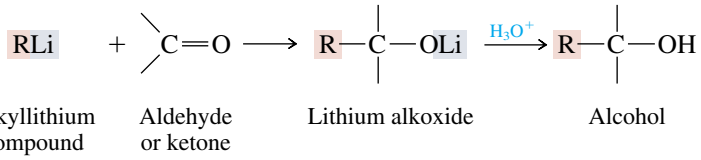
An ability to form carbon–carbon bonds is fundamental to organic synthesis. The addition of Grignard reagents to aldehydes and ketones is one of the most frequently used reactions in synthetic organic chemistry. Not only does it permit the extension of carbon chains, but since the product is an alcohol, a wide variety of subsequent functional group transformations is possible.

14.7 SYNTHESIS OF ALCOHOLS USING ORGANOLITHIUM REAGENTS

Organolithium reagents react with carbonyl groups in the same way that Grignard reagents do. In their reactions with aldehydes and ketones, organolithium reagents are somewhat more reactive than Grignard reagents.

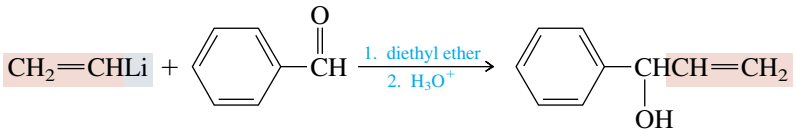
TABLE 14.3 Reactions of Grignard Reagents with Aldehydes and Ketones

Reaction	General equation and specific example
Reaction with formaldehyde Grignard reagents react with formaldehyde ($CH_2{=}O$) to give *primary alcohols* having one more carbon than the Grignard reagent.	 Grignard reagent — Formaldehyde — Primary alkoxymagnesium halide — Primary alcohol  Cyclohexylmagnesium chloride — Formaldehyde — Cyclohexylmethanol (64–69%)
Reaction with aldehydes Grignard reagents react with aldehydes (RCH=O) to give *secondary alcohols.*	 Grignard reagent — Aldehyde — Secondary alkoxymagnesium halide — Secondary alcohol  Hexylmagnesium bromide — Ethanal (acetaldehyde) — 2-Octanol (84%)
Reaction with ketones Grignard reagents react with ketones (RCR′=O) to give *tertiary alcohols.*	 Grignard reagent — Ketone — Tertiary alkoxymagnesium halide — Tertiary alcohol  Methylmagnesium chloride — Cyclopentanone — 1-Methylcyclopentanol (62%)



Alkyllithium compound | Aldehyde or ketone | Lithium alkoxide | Alcohol

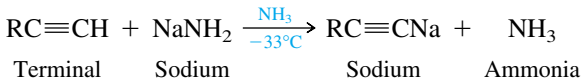
In this particular example, the product can be variously described as a *secondary* alcohol, a *benzylic* alcohol, and an *allylic* alcohol. Can you identify the structural reason for each classification?



Vinyllithium | Benzaldehyde | 1-Phenyl-2-propen-1-ol (76%)

14.8 SYNTHESIS OF ACETYLENIC ALCOHOLS

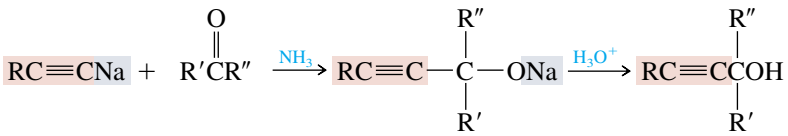
The first organometallic compounds we encountered were compounds of the type RC≡CNa obtained by treatment of terminal alkynes with sodium amide in liquid ammonia (Section 9.6):



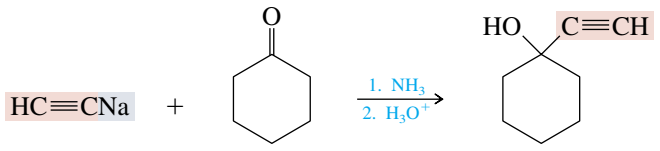
Terminal alkyne | Sodium amide | Sodium alkynide | Ammonia

These compounds are sources of the nucleophilic anion $RC{\equiv}C{:}^-$, and their reaction with primary alkyl halides provides an effective synthesis of alkynes (Section 9.6). The nucleophilicity of acetylide anions is also evident in their reactions with aldehydes and ketones, which are entirely analogous to those of Grignard and organolithium reagents.

These reactions are normally carried out in liquid ammonia because that is the solvent in which the sodium salt of the alkyne is prepared.

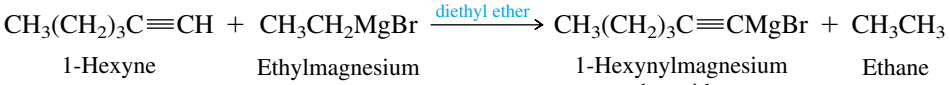


Sodium alkynide | Aldehyde or ketone | Sodium salt of an alkynyl alcohol | Alkynyl alcohol

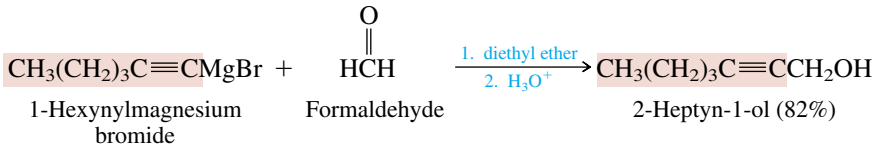


Sodium acetylide | Cyclohexanone | 1-Ethynylcyclohexanol (65–75%)

Acetylenic Grignard reagents of the type RC≡CMgBr are prepared, not from an acetylenic halide, but by an acid–base reaction in which a Grignard reagent abstracts a proton from a terminal alkyne.



1-Hexyne | Ethylmagnesium bromide | 1-Hexynylmagnesium bromide | Ethane



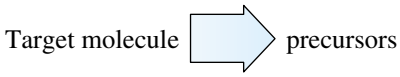
PROBLEM 14.6 Write the equation for the reaction of 1-hexyne with ethylmagnesium bromide as if it involved ethyl anion ($CH_3\ddot{C}H_2^-$) instead of CH_3CH_2MgBr and use curved arrows to represent the flow of electrons.

14.9 RETROSYNTHETIC ANALYSIS

In our earlier discussions of synthesis, we stressed the value of reasoning backward from the target molecule to suitable starting materials. A name for this process is *retrosynthetic analysis.* Organic chemists have employed this approach for many years, but the term was invented and a formal statement of its principles was set forth only relatively recently by E. J. Corey at Harvard University. Beginning in the 1960s, Corey began studies aimed at making the strategy of organic synthesis sufficiently systematic so that the power of electronic computers could be applied to assist synthetic planning.

Corey was honored with the 1990 Nobel Prize for his achievements in synthetic organic chemistry.

A symbol used to indicate a retrosynthetic step is an open arrow written from product to suitable precursors or fragments of those precursors.



Often the precursor is not defined completely, but rather its chemical nature is emphasized by writing it as a species to which it is equivalent for synthetic purposes. Thus, a Grignard reagent or an organolithium reagent might be considered synthetically equivalent to a carbanion:

Problem 14.6 at the end of the preceding section introduced this idea with the suggestion that ethylmagnesium bromide be represented as ethyl anion.

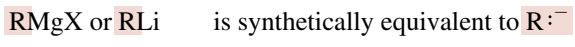
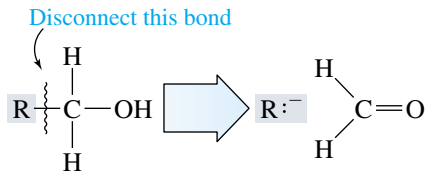
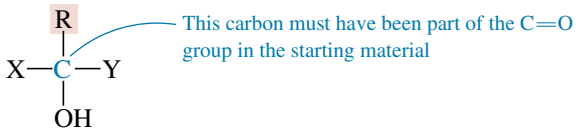


Figure 14.2 illustrates how retrosynthetic analysis can guide you in planning the synthesis of alcohols by identifying suitable Grignard reagent and carbonyl-containing precursors. In the first step, locate the carbon of the target alcohol that bears the hydroxyl group, remembering that this carbon originated in the C═O group. Next, as shown in Figure 14.2, step 2, mentally disconnect a bond between that carbon and one of its attached groups (other than hydrogen). The attached group is the group that is to be transferred from the Grignard reagent. Once you recognize these two structural fragments, the carbonyl partner and the carbanion that attacks it (Figure 14.2, step 3), you can readily determine the synthetic mode wherein a Grignard reagent is used as the synthetic equivalent of a carbanion (Figure 14.2, step 4).

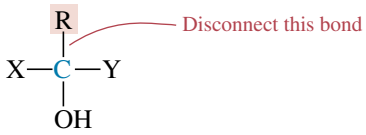
Primary alcohols, by this analysis, are seen to be the products of Grignard addition to formaldehyde:



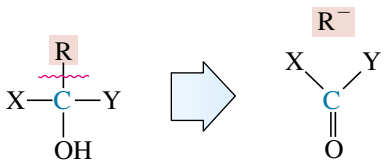
Step 1: Locate the hydroxyl-bearing carbon.



Step 2: Disconnect one of the organic substituents attached to the carbon that bears the hydroxyl group.



Step 3: Steps 1 and 2 reveal the carbonyl-containing substrate and the carbanionic fragment.



Step 4: Since a Grignard reagent may be considered as synthetically equivalent to a carbanion, this suggests the synthesis shown.

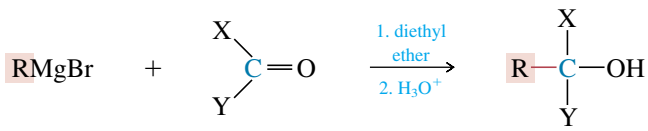
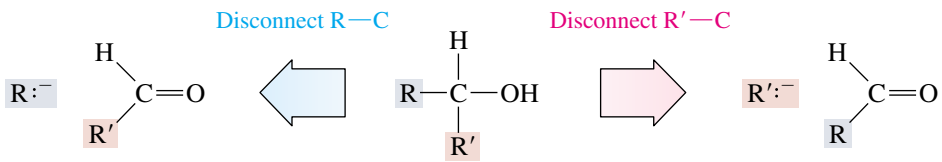
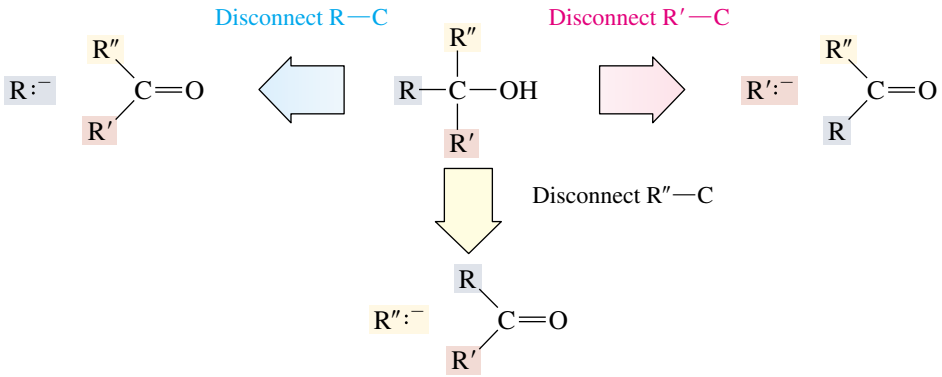


FIGURE 14.2 A retrosynthetic analysis of alcohol preparation by way of the addition of a Grignard reagent to an aldehyde or ketone.

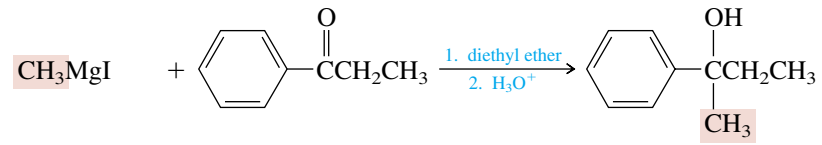
Secondary alcohols may be prepared by *two* different combinations of Grignard reagent and aldehyde:



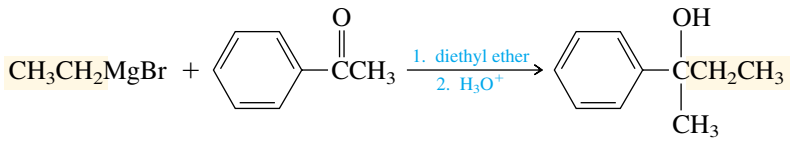
Three combinations of Grignard reagent and ketone give rise to tertiary alcohols:



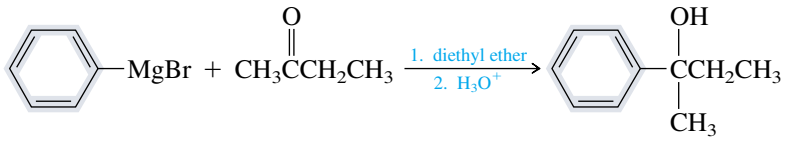
Usually, there is little to choose among the various routes leading to a particular target alcohol. For example, all three of the following combinations have been used to prepare the tertiary alcohol 2-phenyl-2-butanol:



Methylmagnesium iodide — 1-Phenyl-1-propanone — 2-Phenyl-2-butanol



Ethylmagnesium bromide — Acetophenone — 2-Phenyl-2-butanol



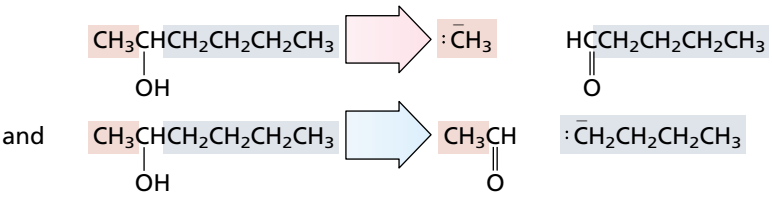
Phenylmagnesium bromide — 2-Butanone — 2-Phenyl-2-butanol

PROBLEM 14.7 Suggest two ways in which each of the following alcohols might be prepared by using a Grignard reagent:

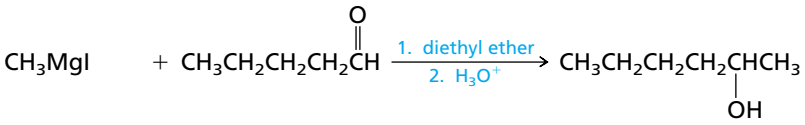
(a) 2-Hexanol, $CH_3\underset{\displaystyle OH}{\underset{|}{C}}HCH_2CH_2CH_2CH_3$

(b) 2-Phenyl-2-propanol, $C_6H_5\underset{\displaystyle OH}{\underset{|}{C}}(CH_3)_2$

SAMPLE SOLUTION (a) Since 2-hexanol is a secondary alcohol, we consider the reaction of a Grignard reagent with an aldehyde. Disconnection of bonds to the hydroxyl-bearing carbon generates two pairs of structural fragments:

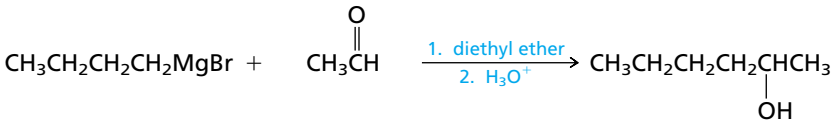


Therefore, one route involves the addition of a methyl Grignard reagent to a five-carbon aldehyde:



Methylmagnesium iodide — Pentanal — 2-Hexanol

The other requires addition of a butylmagnesium halide to a two-carbon aldehyde:

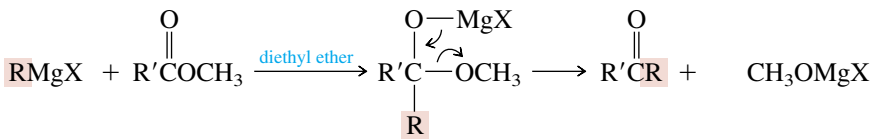


Butylmagnesium bromide — Acetaldehyde — 2-Hexanol

All that has been said in this section applies with equal force to the use of organolithium reagents in the synthesis of alcohols. Grignard reagents are one source of nucleophilic carbon; organolithium reagents are another. Both have substantial carbanionic character in their carbon–metal bonds and undergo the same kind of reaction with aldehydes and ketones.

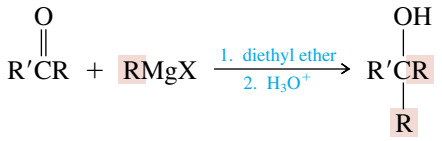
14.10 PREPARATION OF TERTIARY ALCOHOLS FROM ESTERS AND GRIGNARD REAGENTS

Tertiary alcohols can be prepared by a variation of the Grignard synthesis that employs an ester as the carbonyl component. Methyl and ethyl esters are readily available and are the types most often used. Two moles of a Grignard reagent are required per mole of ester; the first mole reacts with the ester, converting it to a ketone.

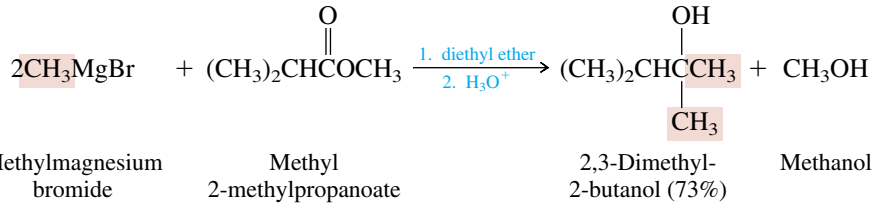


Grignard reagent — Methyl ester — Ketone — Methoxymagnesium halide

The ketone is not isolated, but reacts rapidly with the Grignard reagent to give, after adding aqueous acid, a tertiary alcohol. Ketones are more reactive than esters toward Grignard reagents, and so it is not normally possible to interrupt the reaction at the ketone stage even if only one equivalent of the Grignard reagent is used.



Two of the groups bonded to the hydroxyl-bearing carbon of the alcohol are the same because they are derived from the Grignard reagent. For example,

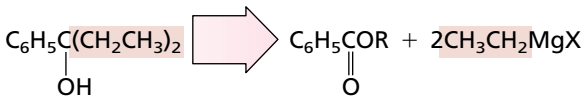


PROBLEM 14.8 What combination of ester and Grignard reagent could you use to prepare each of the following tertiary alcohols?

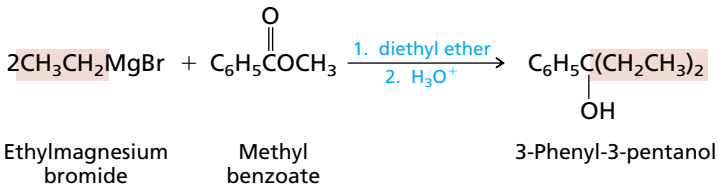
(a) $C_6H_5C(CH_2CH_3)_2$ (OH)

(b) $(C_6H_5)_2C$ (cyclopropyl) (OH)

SAMPLE SOLUTION (a) To apply the principles of retrosynthetic analysis to this case, we disconnect both ethyl groups from the tertiary carbon and identify them as arising from the Grignard reagent. The phenyl group originates in an ester of the type $C_6H_5CO_2R$ (a benzoate ester).



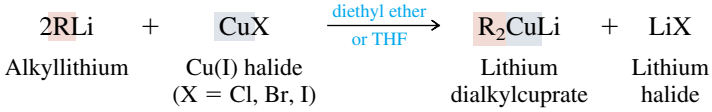
An appropriate synthesis would be



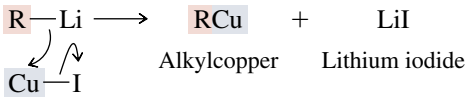
14.11 ALKANE SYNTHESIS USING ORGANOCOPPER REAGENTS

Organometallic compounds of copper have been known for a long time, but their versatility as reagents in synthetic organic chemistry has only recently been recognized. The most useful organocopper reagents are the lithium dialkylcuprates, which result when a copper(I) halide reacts with two equivalents of an alkyllithium in diethyl ether or tetrahydrofuran.

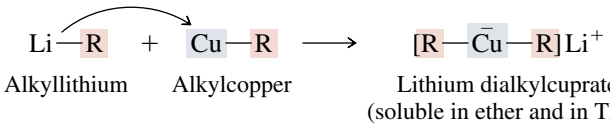
Copper(I) salts are also known as *cuprous* salts.



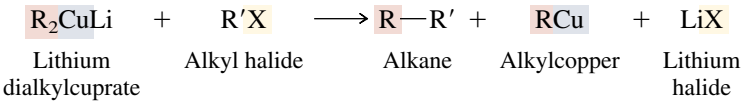
In the first stage of the preparation, one molar equivalent of alkyllithium displaces halide from copper to give an alkylcopper(I) species:



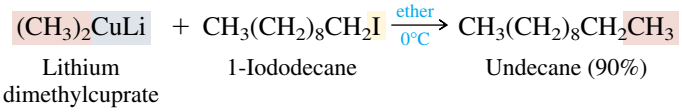
The second molar equivalent of the alkyllithium adds to the alkylcopper to give a negatively charged dialkyl-substituted derivative of copper(I) called a *dialkylcuprate* anion. It is formed as its lithium salt, a lithium dialkylcuprate.



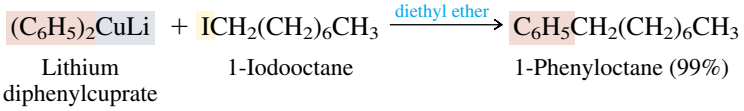
Lithium dialkylcuprates react with alkyl halides to produce alkanes by carbon–carbon bond formation between the alkyl group of the alkyl halide and the alkyl group of the dialkylcuprate:



Primary alkyl halides, especially iodides, are the best substrates. Elimination becomes a problem with secondary and tertiary alkyl halides:



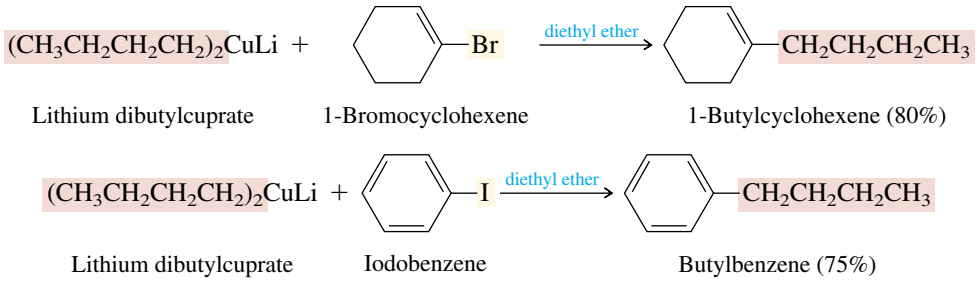
Lithium diarylcuprates are prepared in the same way as lithium dialkylcuprates and undergo comparable reactions with primary alkyl halides:



The most frequently used organocuprates are those in which the alkyl group is primary. Steric hindrance makes organocuprates that bear secondary and tertiary alkyl groups less reactive, and they tend to decompose before they react with the alkyl halide. The reaction of cuprate reagents with alkyl halides follows the usual S_N2 order: $CH_3 >$ primary $>$ secondary $>$ tertiary, and I $>$ Br $>$ Cl $>$ F. *p*-Toluenesulfonate esters are suitable substrates and are somewhat more reactive than halides. Because the alkyl halide and dialkylcuprate reagent should both be primary in order to produce satisfactory yields of coupled products, the reaction is limited to the formation of $RCH_2—CH_2R'$ and $RCH_2—CH_3$ bonds in alkanes.

A key step in the reaction mechanism appears to be nucleophilic attack on the alkyl halide by the negatively charged copper atom, but the details of the mechanism are not well understood. Indeed, there is probably more than one mechanism by which

cuprates react with organic halogen compounds. Vinyl halides and aryl halides are known to be very unreactive toward nucleophilic attack, yet react with lithium dialkylcuprates:

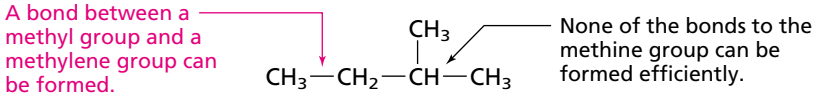


PROBLEM 14.9 Suggest a combination of organic halide and cuprate reagent appropriate for the preparation of each of the following compounds:

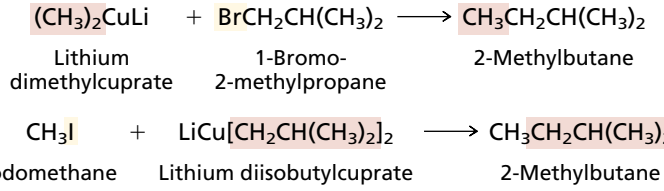
(a) 2-Methylbutane

(b) 1,3,3-Trimethylcyclopentene

SAMPLE SOLUTION (a) First inspect the target molecule to see which bonds are capable of being formed by reaction of an alkyl halide and a cuprate, bearing in mind that neither the alkyl halide nor the alkyl group of the lithium dialkylcuprate should be secondary or tertiary.

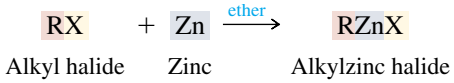


There are two combinations, both acceptable, that give the $CH_3—CH_2$ bond:



14.12 AN ORGANOZINC REAGENT FOR CYCLOPROPANE SYNTHESIS

Zinc reacts with alkyl halides in a manner similar to that of magnesium.

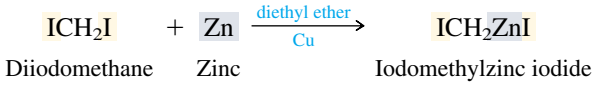


Organozinc reagents are not nearly as reactive toward aldehydes and ketones as Grignard reagents and organolithium compounds but are intermediates in certain reactions of alkyl halides.

An organozinc compound that occupies a special niche in organic synthesis is *iodomethylzinc iodide* (ICH_2ZnI), prepared by the reaction of zinc–copper couple [Zn(Cu), zinc that has had its surface activated with a little copper] with diiodomethane in ether.

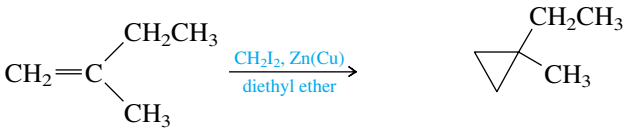
Victor Grignard was led to study organomagnesium compounds because of earlier work he performed with organic derivatives of zinc.

Iodomethylzinc iodide is known as the *Simmons–Smith reagent,* after Howard E. Simmons and Ronald D. Smith of Du Pont, who first described its use in the preparation of cyclopropanes.



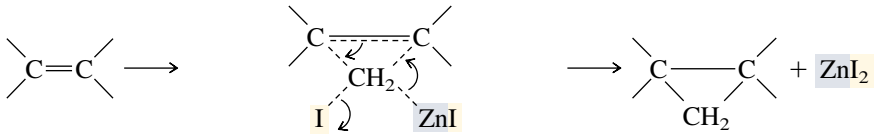
Diiodomethane Zinc Iodomethylzinc iodide

What makes iodomethylzinc iodide such a useful reagent is that it reacts with alkenes to give cyclopropanes.



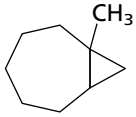
2-Methyl-1-butene 1-Ethyl-1-methylcyclopropane (79%)

This reaction is called the *Simmons–Smith reaction* and is one of the few methods available for the synthesis of cyclopropanes. Mechanistically, the Simmons–Smith reaction seems to proceed by a single-step cycloaddition of a methylene (CH_2) unit from iodomethylzinc iodide to the alkene:



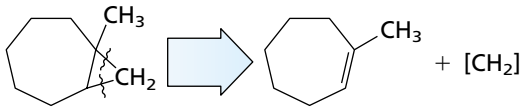
ICH_2ZnI Transition state for methylene transfer

PROBLEM 14.10 What alkenes would you choose as starting materials in order to prepare each of the following cyclopropane derivatives by reaction with iodomethylzinc iodide?

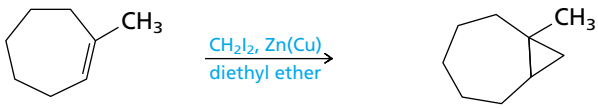
(a) 

(b) 

SAMPLE SOLUTION (a) In a cyclopropane synthesis using the Simmons–Smith reagent, you should remember that a CH_2 unit is transferred. Therefore, retrosynthetically disconnect the bonds to a CH_2 group of a three-membered ring to identify the starting alkene.

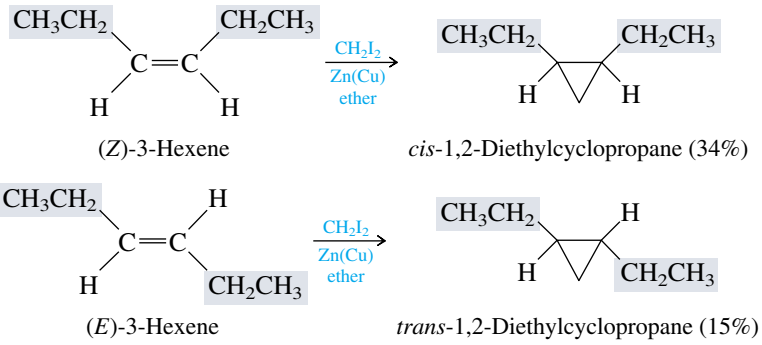


The complete synthesis is:



1-Methylcycloheptene 1-Methylbicyclo[5.1.0]octane (55%)

Methylene transfer from iodomethylzinc iodide is *stereospecific.* Substituents that were cis in the alkene remain cis in the cyclopropane.



Yields in Simmons–Smith reactions are sometimes low. Nevertheless, since it often provides the only feasible route to a particular cyclopropane derivative, it is a valuable addition to the organic chemist's store of synthetic methods.

14.13 CARBENES AND CARBENOIDS

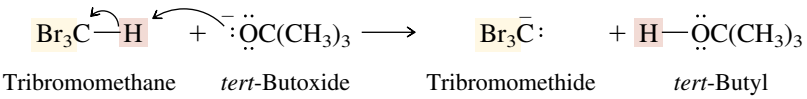
Iodomethylzinc iodide is often referred to as a **carbenoid,** meaning that it resembles a **carbene** in its chemical reactions. Carbenes are neutral molecules in which one of the carbon atoms has six valence electrons. Such carbons are *divalent;* they are directly bonded to only two other atoms and have no multiple bonds. Iodomethylzinc iodide reacts as if it were a source of the carbene H—C̈—H.

It is clear that free :CH_2 is not involved in the Simmons–Smith reaction, but there is substantial evidence to indicate that carbenes are formed as intermediates in certain other reactions that convert alkenes to cyclopropanes. The most studied examples of these reactions involve dichlorocarbene and dibromocarbene.

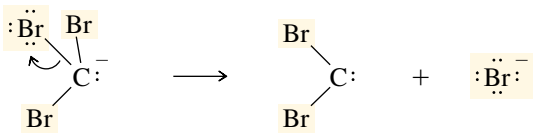
Dichlorocarbene Dibromocarbene

Carbenes are too reactive to be isolated and stored, but have been trapped in frozen argon for spectroscopic study at very low temperatures.

Dihalocarbenes are formed when trihalomethanes are treated with a strong base, such as potassium *tert*-butoxide. The trihalomethyl anion produced on proton abstraction dissociates to a dihalocarbene and a halide anion:

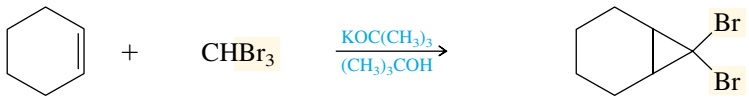


Tribromomethane *tert*-Butoxide ion Tribromomethide ion *tert*-Butyl alcohol



Tribromomethide ion Dibromocarbene Bromide ion

When generated in the presence of an alkene, dihalocarbenes undergo cycloaddition to the double bond to give dihalocyclopropanes:



Cyclohexene Tribromomethane 7,7-Dibromobicyclo[4.1.0]heptane (75%)

The reaction of dihalocarbenes with alkenes is stereospecific, and syn addition is observed.

PROBLEM 14.11 The syn stereochemistry of dibromocarbene cycloaddition was demonstrated in experiments using *cis*- and *trans*-2-butene. Give the structure of the product obtained from addition of dibromocarbene to each alkene.

The process in which a dihalocarbene is formed from a trihalomethane corresponds to an elimination in which a proton and a halide are lost from the same carbon. It is an α-*elimination* proceeding via the organometallic intermediate K^+ $[:CX_3]^-$.

14.14 TRANSITION-METAL ORGANOMETALLIC COMPOUNDS

A large number of organometallic compounds are based on transition metals. Examples include organic derivatives of iron, nickel, chromium, platinum, and rhodium. Many important industrial processes are catalyzed by transition metals or their complexes. Before we look at these processes, a few words about the structures of transition-metal complexes are in order.

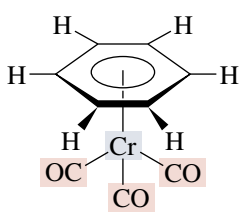
A transition-metal complex consists of a transition-metal atom or ion bearing attached groups called **ligands.** Essentially, anything attached to a metal is a ligand. A ligand can be an element (O_2, N_2), a compound (NO), or an ion (CN^-); it can be inorganic as in the examples just cited or it can be an organic ligand. Ligands differ in the number of electrons that they share with the transition metal to which they are attached. Carbon monoxide is a frequently encountered ligand in transition-metal complexes and contributes two electrons; it is best thought of in terms of the Lewis structure $:\overset{-}{C}\equiv\overset{+}{O}:$ in which carbon is the reactive site. An example of a carbonyl complex of a transition metal is nickel carbonyl, a very toxic substance, which was first prepared over a hundred years ago and is an intermediate in the purification of nickel. It forms spontaneously when carbon monoxide is passed over elemental nickel.

$$\underset{\text{Nickel}}{Ni} + \underset{\text{Carbon monoxide}}{4CO} \longrightarrow \underset{\text{Nickel carbonyl}}{Ni(CO)_4}$$

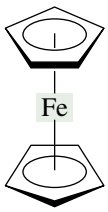
Many transition-metal complexes, including $Ni(CO)_4$, obey what is called the **18-electron rule,** which is to transition-metal complexes as the octet rule is to main-group elements. It states that for transition-metal complexes, *the number of ligands that can be attached to a metal will be such that the sum of the electrons brought by the ligands plus the valence electrons of the metal equals 18.* With an atomic number of 28, nickel has the electron configuration $[Ar]4s^23d^8$ (10 valence electrons). The 18-electron rule is satisfied by adding to these 10 the 8 electrons from four carbon monoxide ligands. A useful point to remember about the 18-electron rule when we discuss some reactions of transition-metal complexes is that if the number is less than 18, the metal is considered *coordinatively unsaturated* and can accept additional ligands.

PROBLEM 14.12 Like nickel, iron reacts with carbon monoxide to form a compound having the formula $M(CO)_n$ that obeys the 18-electron rule. What is the value of n in the formula $Fe(CO)_n$?

Not all ligands use just two electrons to bond to transition metals. Chromium has the electron configuration $[Ar]4s^2 3d^4$ (6 valence electrons) and needs 12 more to satisfy the 18-electron rule. In the compound (benzene)tricarbonylchromium, 6 of these 12 are the π electrons of the benzene ring; the remaining 6 are from the three carbonyl ligands.

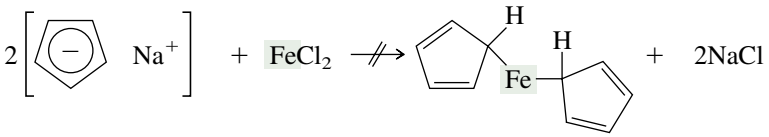


(Benzene)tricarbonylchromium



Ferrocene

Ferrocene has an even more interesting structure. A central iron is π-bonded to two cyclopentadienyl ligands in what is aptly described as a *sandwich.* It, too, obeys the 18-electron rule. Each cyclopentadienyl ligand contributes 5 electrons for a total of 10 and iron, with an electron configuration of $[Ar]4s^2 3d^6$ contributes 8. Alternatively, ferrocene can be viewed as being derived from Fe^{2+} (6 valence electrons) and two aromatic cyclopentadienide rings (6 electrons each). Indeed, ferrocene was first prepared by adding iron(II) chloride to cyclopentadienylsodium. Instead of the expected σ-bonded species shown in the equation, ferrocene was formed.



Cyclopentadienylsodium | Iron(II) chloride | (Not formed)

After ferrocene, a large number of related molecules have been prepared—even some in which uranium is the metal. There is now an entire subset of transition-metal organometallic complexes known as **metallocenes** based on cyclopentadienide ligands. These compounds are not only structurally interesting, but many of them have useful applications as catalysts for industrial processes.

Naturally occurring compounds with carbon–metal bonds are very rare. The best example of such an organometallic compound is coenzyme B_{12}, which has a carbon–cobalt σ bond (Figure 14.3). Pernicious anemia results from a coenzyme B_{12} deficiency and can be treated by adding sources of cobalt to the diet. One source of cobalt is vitamin B_{12}, a compound structurally related to, but not identical with, coenzyme B_{12}.

The first page of this chapter displayed an electrostatic potential map of ferrocene. You may wish to view a molecular model of it on *Learning By Modeling.*

Cyclopentadienylsodium is ionic. Its anion is the cyclopentadienide ion, which contains six π electrons.

14.15 ZIEGLER–NATTA CATALYSIS OF ALKENE POLYMERIZATION

In Section 6.21 we listed three main methods for polymerizing alkenes: cationic, free-radical, and coordination polymerization. In Section 7.15 we extended our knowledge of polymers to their stereochemical aspects by noting that although free-radical polymerization of propene gives atactic polypropylene, coordination polymerization produces a stereoregular polymer with superior physical properties. Because the catalysts responsible for coordination polymerization are organometallic compounds, we are now in a position to examine coordination polymerization in more detail, especially with respect to how the catalyst works.

AN ORGANOMETALLIC COMPOUND THAT OCCURS NATURALLY: COENZYME B_{12}

Pernicious anemia is a disease characterized, as are all anemias, by a deficiency of red blood cells. Unlike ordinary anemia, pernicious anemia does not respond to treatment with sources of iron, and before effective treatments were developed, was often fatal. Injection of liver extracts was one such treatment, and in 1948 chemists succeeded in isolating the "antipernicious anemia factor" from beef liver as a red crystalline compound, which they called **vitamin B_{12}.** This compound had the formula $C_{63}H_{88}CoN_{14}O_{14}P$. Its complexity precluded structure determination by classical degradation techniques, and spectroscopic methods were too primitive to be of much help. The structure was solved by Dorothy Crowfoot Hodgkin of Oxford University in 1955 using X-ray diffraction techniques and is shown in Figure 14.3*a*. Structure determination by X-ray crystallography can be superficially considered as taking a photograph of a molecule with X-rays. It is a demanding task and earned Hodgkin the 1964 Nobel Prize in chemistry. Modern structural studies by X-ray crystallography use computers to collect and analyze the diffraction data and take only a fraction of the time required years ago to solve the vitamin B_{12} structure.

The structure of vitamin B_{12} is interesting in that it contains a central cobalt atom that is surrounded by six atoms in an octahedral geometry. One substituent, the cyano (—CN) group, is what is known as an "artifact." It appears to be introduced into the molecule during the isolation process and leads to the synonym **cyanocobalamin** for vitamin B_{12}. This material is used to treat pernicious anemia, but this is not the form in which it exerts its activity. The biologically active material is called **coenzyme B_{12}** and differs from vitamin B_{12} in the substituent attached to cobalt (Figure 14.3*b*). Coenzyme B_{12} is the only known naturally occurring substance that has a carbon–metal bond. Moreover, coenzyme B_{12} was discovered before any compound containing an alkyl group σ-bonded to cobalt had ever been isolated in the laboratory!

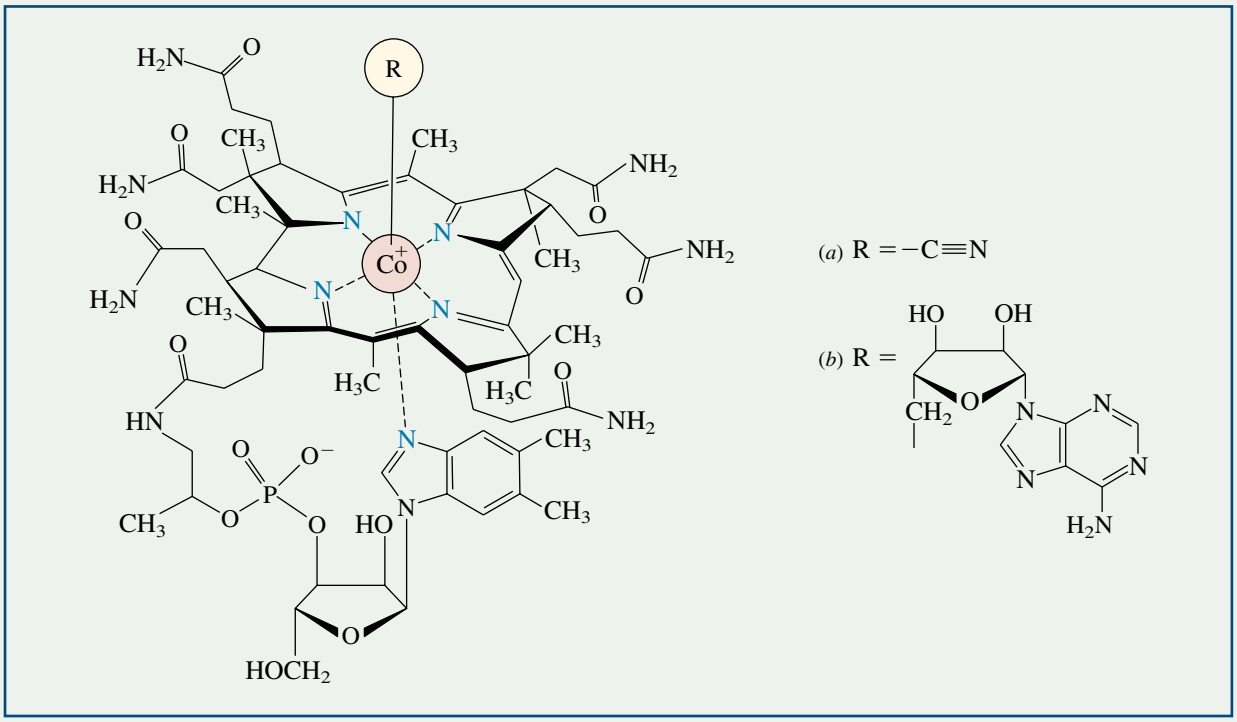


FIGURE 14.3 The structures of (*a*) vitamin B_{12} and (*b*) coenzyme B_{12}.

In the early 1950s, Karl Ziegler, then at the Max Planck Institute for Coal Research in Germany, was studying the use of aluminum compounds as catalysts for the oligomerization of ethylene.

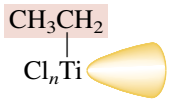
$$n\mathrm{H_2C{=}CH_2} \xrightarrow{\mathrm{Al(CH_2CH_3)_3}} \mathrm{CH_3CH_2(CH_2CH_2)_{n-2}CH{=}CH_2}$$

Ethylene — Ethylene oligomers

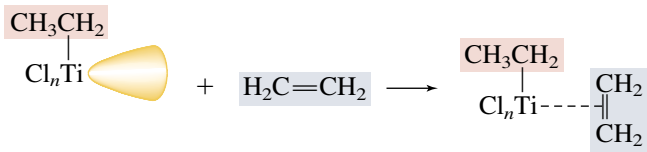
Ziegler found that adding certain metals or their compounds to the reaction mixture led to the formation of ethylene oligomers with 6–18 carbons, but others promoted the formation of very long carbon chains giving polyethylene. Both were major discoveries. The 6–18 carbon ethylene oligomers constitute a class of industrial organic chemicals known as *linear* α *olefins* that are produced at a rate of 10^9 pounds/year in the United States. The Ziegler route to polyethylene is even more important because it occurs at modest temperatures and pressures and gives *high-density polyethylene,* which has properties superior to the low-density material formed by free-radical polymerization described in Section 6.21.

A typical Ziegler catalyst is a combination of titanium tetrachloride ($TiCl_4$) and diethylaluminum chloride [$(CH_3CH_2)_2AlCl$], but other combinations such as $TiCl_3/(CH_3CH_2)_3Al$ also work as do catalysts based on metallocenes. Although still in question, a plausible mechanism for the polymerization of ethylene in the presence of such catalysts has been offered and is outlined in Figure 14.4.

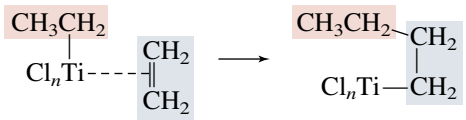
Step 1: A titanium halide and an ethylaluminum compound combine to place an ethyl group on titanium, giving the active catalyst. Titanium has one or more vacant coordination sites, shown here as an empty orbital.



Step 2: Ethylene reacts with the active form of the catalyst. The π orbital of ethylene with its two electrons overlaps with the vacant titanium orbital to bind ethylene as a ligand to titanium.



Step 3: The flow of electrons from ethylene to titanium increases the electron density at titanium and weakens the Ti–CH_2CH_3 bond. The ethyl group migrates from titanium to one of the carbons of ethylene.



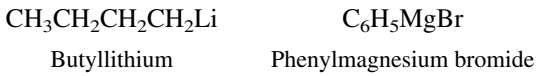
Step 4: The catalyst now has a butyl ligand on titanium instead of an ethyl group. Repeating steps 2 and 3 converts the butyl group to a hexyl group, then an octyl group, and so on. After thousands of repetitions, polyethylene is formed.

FIGURE 14.4 A proposed mechanism for the polymerization of ethylene in the presence of a Ziegler–Natta catalyst.

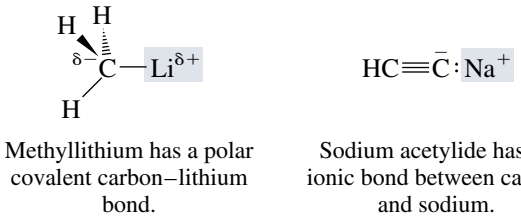
Ziegler had a working relationship with the Italian chemical company Montecatini, for which Giulio Natta of the Milan Polytechnic Institute was a consultant. When Natta used Ziegler's catalyst to polymerize propene, he discovered that the catalyst was not only effective but that it gave mainly isotactic polypropylene. (Recall from Section 7.15 that free-radical polymerization of propene gives atactic polypropylene.) Isotactic polypropylene has a higher melting point than the atactic form and can be drawn into fibers or molded into hard, durable materials. Before coordination polymerization was discovered by Ziegler and applied to propene by Natta, there was no polypropylene industry. Now, more than 10^{10} pounds of it are prepared each year in the United States. Ziegler and Natta shared the 1963 Nobel Prize in chemistry: Ziegler for discovering novel catalytic systems for alkene polymerization and Natta for stereoregular polymerization.

14.16 SUMMARY

Section 14.1 Organometallic compounds contain a carbon–metal bond. They are named as alkyl (or aryl) derivatives of metals.



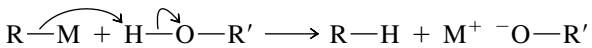
Section 14.2 Carbon is more electronegative than metals and carbon–metal bonds are polarized so that carbon bears a partial to complete negative charge and the metal bears a partial to complete positive charge.



Section 14.3 See Table 14.4

Section 14.4 See Table 14.4

Section 14.5 Organolithium compounds and Grignard reagents are strong bases and react instantly with compounds that have —OH groups.



These organometallic compounds cannot therefore be formed or used in solvents such as water and ethanol. The most commonly employed solvents are diethyl ether and tetrahydrofuran.

Section 14.6 See Tables 14.3 and 14.5

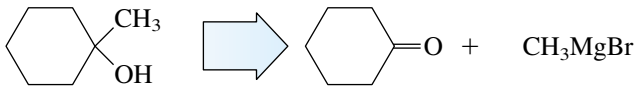
Section 14.7 See Table 14.5

Section 14.8 See Table 14.5

Section 14.9 When planning the synthesis of a compound using an organometallic reagent, or indeed any synthesis, the best approach is to reason backward from the product. This method is called **retrosynthetic analysis.** Retrosynthetic analysis of 1-methylcyclohexanol suggests it can be prepared by the reaction of methylmagnesium bromide and cyclohexanone.

TABLE 14.4 Preparation of Organometallic Reagents Used in Synthesis

Type of organometallic reagent (section) and comments	General equation for preparation and specific example
Organolithium reagents (Section 14.3) Lithium metal reacts with organic halides to produce organolithium compounds. The organic halide may be alkyl, alkenyl, or aryl. Iodides react most and fluorides least readily; bromides are used most often. Suitable solvents include hexane, diethyl ether, and tetrahydrofuran.	$RX + 2Li \longrightarrow RLi + LiX$ Alkyl halide; Lithium; Alkyllithium; Lithium halide $CH_3CH_2CH_2Br \xrightarrow[\text{diethyl ether}]{Li} CH_3CH_2CH_2Li$ Propyl bromide; Propyllithium (78%)
Grignard reagents (Section 14.4) Grignard reagents are prepared in a manner similar to that used for organolithium compounds. Diethyl ether and tetrahydrofuran are appropriate solvents.	$RX + Mg \longrightarrow RMgX$ Alkyl halide; Magnesium; Alkylmagnesium halide (Grignard reagent) $C_6H_5CH_2Cl \xrightarrow[\text{diethyl ether}]{Mg} C_6H_5CH_2MgCl$ Benzyl chloride; Benzylmagnesium chloride (93%)
Lithium dialkylcuprates (Section 14.11) These reagents contain a negatively charged copper atom and are formed by the reaction of a copper(I) salt with two equivalents of an organolithium reagent.	$2RLi + CuX \longrightarrow R_2CuLi + LiX$ Alkyllithium; Copper(I) halide; Lithium dialkylcuprate; Lithium halide $2CH_3Li + CuI \xrightarrow{\text{diethyl ether}} (CH_3)_2CuLi + LiI$ Methyllithium; Copper(I) iodide; Lithium dimethylcuprate; Lithium iodide
Iodomethylzinc iodide (Section 14.12) This is the Simmons–Smith reagent. It is prepared by the reaction of zinc (usually in the presence of copper) with diiodomethane.	$CH_2I_2 + Zn \xrightarrow[Cu]{\text{diethyl ether}} ICH_2ZnI$ Diiodomethane; Zinc; Iodomethylzinc iodide



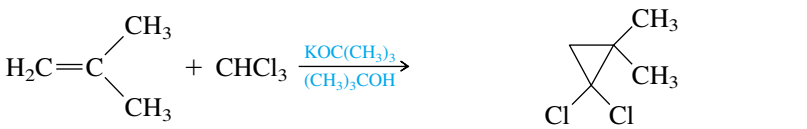
1-Methylcyclohexanol; Cyclohexanone; Methylmagnesium bromide

Section 14.10 See Table 14.5

Section 14.11 See Tables 14.4 and 14.5

Section 14.12 See Tables 14.4 and 14.5

Section 14.13 Carbenes are species that contain a *divalent carbon;* that is, a carbon with only two bonds. One of the characteristic reactions of carbenes is with alkenes to give cyclopropane derivatives.



2-Methylpropene; 1,1-Dichloro-2,2-dimethylcyclopropane (65%)

TABLE 14.5 Carbon–Carbon Bond-Forming Reactions of Organometallic Reagents

Reaction (section) and comments	General equation and specific example
Alcohol synthesis via the reaction of Grignard reagents with carbonyl compounds (Section 14.6) This is one of the most useful reactions in synthetic organic chemistry. Grignard reagents react with formaldehyde to yield primary alcohols, with aldehydes to give secondary alcohols, and with ketones to form tertiary alcohols.	$RMgX + R'CR'' \xrightarrow[2.\ H_3O^+]{1.\ \text{diethyl ether}} RCOH$ (R′, R″) Grignard reagent; Aldehyde or ketone; Alcohol $CH_3MgI + CH_3CH_2CH_2CH \xrightarrow[2.\ H_3O^+]{1.\ \text{diethyl ether}} CH_3CH_2CH_2CHCH_3$ (OH) Methylmagnesium iodide; Butanal; 2-Pentanol (82%)
Reaction of Grignard reagents with esters (Section 14.10) Tertiary alcohols in which two of the substituents on the hydroxyl carbon are the same may be prepared by the reaction of an ester with two equivalents of a Grignard reagent.	$2RMgX + R'COR'' \xrightarrow[2.\ H_3O^+]{1.\ \text{diethyl ether}} RCOH$ (R′, R) Grignard reagent; Ester; Tertiary alcohol $2C_6H_5MgBr + C_6H_5COCH_2CH_3 \xrightarrow[2.\ H_3O^+]{1.\ \text{diethyl ether}} (C_6H_5)_3COH$ Phenylmagnesium bromide; Ethyl benzoate; Triphenylmethanol (89–93%)
Synthesis of alcohols using organolithium reagents (Section 14.7) Organolithium reagents react with aldehydes and ketones in a manner similar to that of Grignard reagents to produce alcohols.	$RLi + R'CR'' \xrightarrow[2.\ H_3O^+]{1.\ \text{diethyl ether}} RCOH$ (R′, R″) Alkyllithium; Aldehyde or ketone; Alcohol Cyclopropyl–Li + $CH_3CC(CH_3)_3$ → Cyclopropyl–$CC(CH_3)_3$ (OH, CH_3) Cyclopropyllithium; 3,3-Dimethyl-2-butanone; 2-Cyclopropyl-3,3-dimethyl-2-butanol (71%)

(Continued)

Certain organometallic compounds resemble carbenes in their reactions and are referred to as **carbenoids.** Iodomethylzinc iodide (Section 14.12) is an example.

Section 14.14 Transition-metal complexes that contain one or more organic ligands offer a rich variety of structural types and reactivity. Organic ligands can be bonded to a metal by a σ bond or through its π system. **Metallocenes** are transition-metal complexes in which one or more of the ligands is a

TABLE 14.5 Carbon–Carbon Bond-Forming Reactions of Organometallic Reagents *(Continued)*

Reaction (section) and comments	General equation and specific example
Synthesis of acetylenic alcohols (Section 14.8) Sodium acetylide and acetylenic Grignard reagents react with aldehydes and ketones to give alcohols of the type C≡C—COH.	$NaC{\equiv}CH + \underset{\text{Aldehyde or ketone}}{RCR'} \xrightarrow[2.\ H_3O^+]{1.\ NH_3,\ -33^\circ C} \underset{\text{Alcohol}}{HC{\equiv}CCR'}$ (R, OH)
	$NaC{\equiv}CH + CH_3CCH_2CH_3 \xrightarrow[2.\ H_3O^+]{1.\ NH_3,\ -33^\circ C} HC{\equiv}CCCH_2CH_3$ (CH₃, OH)
	Sodium acetylide; 2-Butanone; 3-Methyl-1-pentyn-3-ol (72%)
Preparation of alkanes using lithium dialkylcuprates (Section 14.11) Two alkyl groups may be coupled together to form an alkane by the reaction of an alkyl halide with a lithium dialkylcuprate. Both alkyl groups must be primary (or methyl). Aryl and vinyl halides may be used in place of alkyl halides.	$R_2CuLi + R'CH_2X \longrightarrow RCH_2R'$
	Lithium dialkylcuprate; Primary alkyl halide; Alkane
	$(CH_3)_2CuLi + C_6H_5CH_2Cl \xrightarrow{\text{diethyl ether}} C_6H_5CH_2CH_3$
	Lithium dimethylcuprate; Benzyl chloride; Ethylbenzene (80%)
The Simmons–Smith reaction (Section 14.12) Methylene transfer from iodomethylzinc iodide converts alkenes to cyclopropanes. The reaction is a stereospecific syn addition of a CH_2 group to the double bond.	$R_2C{=}CR_2 + ICH_2ZnI \xrightarrow{\text{diethyl ether}}$ (R, R, R, R) $+ ZnI_2$
	Alkene; Iodomethylzinc iodide; Cyclopropane derivative; Zinc iodide
	Cyclopentene $\xrightarrow[\text{diethyl ether}]{CH_2I_2,\ Zn(Cu)}$ Bicyclo[3.1.0]hexane (53%)

cyclopentadienyl ring. Ferrocene was the first metallocene synthesized; its structure is shown on the opening page of this chapter.

Section 14.15 Coordination polymerization of ethylene and propene has the biggest economic impact of any organic chemical process. Ziegler–Natta polymerization is carried out in the presence of catalysts derived from transition metals such as titanium. π-Bonded and σ-bonded organometallic compounds are intermediates in coordination polymerization.

Problems

14.13 Write structural formulas for each of the following compounds. Specify which compounds qualify as organometallic compounds.

(a) Cyclopentyllithium
(b) Ethoxymagnesium chloride
(c) 2-Phenylethylmagnesium iodide
(d) Lithium divinylcuprate
(e) Sodium carbonate
(f) Benzylpotassium

14.14 *Dibal* is an informal name given to the organometallic compound $[(CH_3)_2CHCH_2]_2AlH$, used as a reducing agent in certain reactions. Can you figure out the systematic name from which "dibal" is derived?

14.15 Suggest appropriate methods for preparing each of the following compounds from the starting material of your choice.

(a) $CH_3CH_2CH_2CH_2CH_2MgI$

(b) $CH_3CH_2C{\equiv}CMgI$

(c) $CH_3CH_2CH_2CH_2CH_2Li$

(d) $(CH_3CH_2CH_2CH_2CH_2)_2CuLi$

14.16 Which compound in each of the following pairs would you expect to have the more polar carbon–metal bond? Compare the models on *Learning By Modeling* with respect to the charge on the carbon bonded to the metal.

(a) CH_3CH_2Li or $(CH_3CH_2)_3Al$

(b) $(CH_3)_2Zn$ or $(CH_3)_2Mg$

(c) CH_3CH_2MgBr or $HC{\equiv}CMgBr$

14.17 Write the structure of the principal organic product of each of the following reactions:

(a) 1-Bromopropane with lithium in diethyl ether

(b) 1-Bromopropane with magnesium in diethyl ether

(c) 2-Iodopropane with lithium in diethyl ether

(d) 2-Iodopropane with magnesium in diethyl ether

(e) Product of part (a) with copper(I) iodide

(f) Product of part (e) with 1-bromobutane

(g) Product of part (e) with iodobenzene

(h) Product of part (b) with D_2O and DCl

(i) Product of part (c) with D_2O and DCl

(j) Product of part (a) with formaldehyde in ether, followed by dilute acid

(k) Product of part (b) with benzaldehyde in ether, followed by dilute acid

(l) Product of part (c) with cycloheptanone in ether, followed by dilute acid

(m) Product of part (d) with $CH_3\overset{\overset{O}{\|}}{C}CH_2CH_3$ in ether, followed by dilute acid

(n) Product of part (b) with $C_6H_5\overset{\overset{O}{\|}}{C}OCH_3$ (2 mol) in ether, followed by dilute acid

(o) 1-Octene with diiodomethane and zinc–copper couple in ether

(p) (*E*)-2-Decene with diiodomethane and zinc–copper couple in ether

(q) (*Z*)-3-Decene with diiodomethane and zinc–copper couple in ether

(r) 1-Pentene with tribromomethane and potassium *tert*-butoxide in *tert*-butyl alcohol

14.18 Using 1-bromobutane and any necessary organic or inorganic reagents, suggest efficient syntheses of each of the following alcohols:

(a) 1-Pentanol

(b) 2-Hexanol

(c) 1-Phenyl-1-pentanol

(d) 3-Methyl-3-heptanol

(e) 1-Butylcyclobutanol

14.19 Using bromobenzene and any necessary organic or inorganic reagents, suggest efficient syntheses of each of the following:

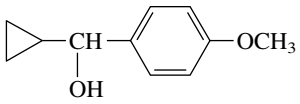
(a) Benzyl alcohol

(b) 1-Phenyl-1-hexanol

(c) Bromodiphenylmethane
(d) 4-Phenyl-4-heptanol
(e) 1-Phenylcyclooctanol
(f) *trans*-2-Phenylcyclooctanol

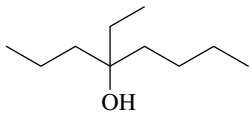
14.20 Analyze the following structures so as to determine all the practical combinations of Grignard reagent and carbonyl compound that will give rise to each:

(a) $CH_3CH_2CHCH_2CH(CH_3)_2$ (OH)

(b) 

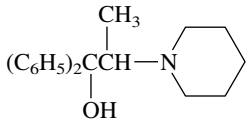
(c) $(CH_3)_3CCH_2OH$

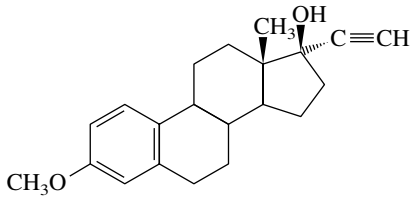
(d) 6-Methyl-5-hepten-2-ol

(e) 

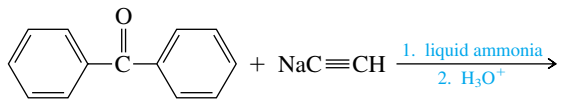
14.21 A number of drugs are prepared by reactions of the type described in this chapter. Indicate what you believe would be a reasonable last step in the synthesis of each of the following:

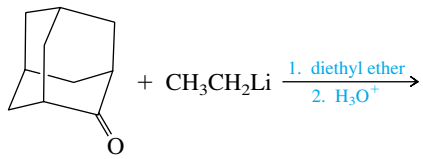
(a) $CH_3CH_2C(OH)(CH_3)C{\equiv}CH$ — *Meparfynol,* a mild hypnotic or sleep-inducing agent

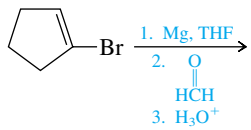
(b)  — *Diphepanol,* an antitussive (cough suppressant)

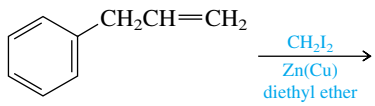
(c)  — *Mestranol,* an estrogenic component of oral contraceptive drugs

14.22 Predict the principal organic product of each of the following reactions:

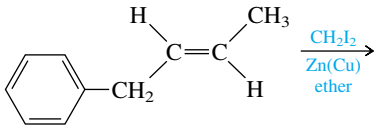
(a) 

(b) 

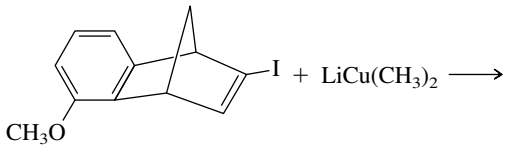
(c) 

(d) 

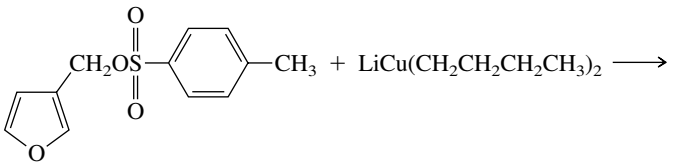
(e)



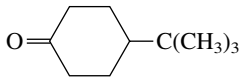
(f)



(g)



14.23 Addition of phenylmagnesium bromide to 4-*tert*-butylcyclohexanone gives two isomeric tertiary alcohols as products. Both alcohols yield the same alkene when subjected to acid-catalyzed dehydration. Suggest reasonable structures for these two alcohols.

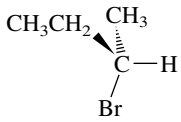


4-*tert*-Butylcyclohexanone

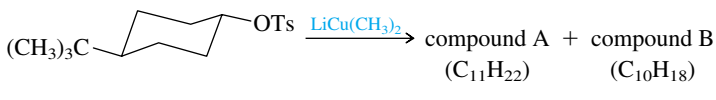
14.24 (a) Unlike other esters, which react with Grignard reagents to give tertiary alcohols, ethyl formate ($HCOCH_2CH_3$) yields a different class of alcohols on treatment with Grignard reagents. What kind of alcohol is formed in this case and why?

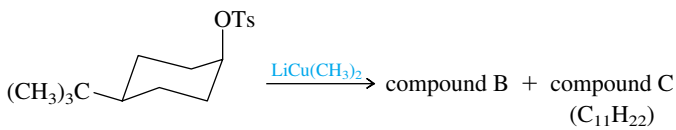
(b) Diethyl carbonate ($CH_3CH_2OCOCH_2CH_3$) reacts with excess Grignard reagent to yield alcohols of a particular type. What is the structural feature that characterizes alcohols prepared in this way?

14.25 Reaction of lithium diphenylcuprate with optically active 2-bromobutane yields 2-phenylbutane, with high net inversion of configuration. When the 2-bromobutane used has the stereostructure shown, will the 2-phenylbutane formed have the *R* or the *S* configuration?



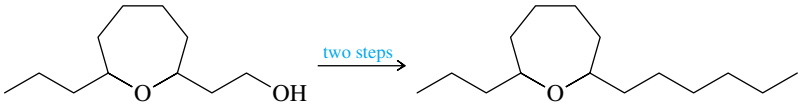
14.26 Suggest reasonable structures for compounds A, B, and C in the following reactions:





Compound C is more stable than compound A. OTs stands for toluenesulfonate.

14.27 The following conversion has been reported in the chemical literature. It was carried out in two steps, the first of which involved formation of a *p*-toluenesulfonate ester. Indicate the reagents for this step, and show how you could convert the *p*-toluenesulfonate to the desired product.



14.28 Sometimes the strongly basic properties of Grignard reagents can be turned to synthetic advantage. A chemist needed samples of butane specifically labeled with deuterium, the mass 2 isotope of hydrogen, as shown:

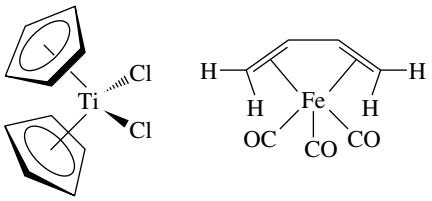
(a) $CH_3CH_2CH_2CH_2D$ (b) $CH_3CHDCH_2CH_3$

Suggest methods for the preparation of each of these using heavy water (D_2O) as the source of deuterium, butanols of your choice, and any necessary organic or inorganic reagents.

14.29 Diphenylmethane is significantly more acidic than benzene, and triphenylmethane is more acidic than either. Identify the most acidic proton in each compound, and suggest a reason for the trend in acidity.

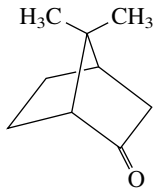
C_6H_6	$(C_6H_5)_2CH_2$	$(C_6H_5)_3CH$
Benzene $K_a \approx 10^{-45}$	Diphenylmethane $K_a \approx 10^{-34}$	Triphenylmethane $K_a \approx 10^{-32}$

14.30 The 18-electron rule is a general, but not universal, guide for assessing whether a certain transition-metal complex is stable or not. Both of the following are stable compounds, but only one obeys the 18-electron rule. Which one?



14.31 One of the main uses of the "linear α-olefins" prepared by oligomerization of ethylene is in the preparation of *linear low-density polyethylene*. Linear low-density polyethylene is a copolymer produced when ethylene is polymerized in the presence of a "linear α-olefin" such as 1-decene [$CH_2{=}CH(CH_2)_7CH_3$]. 1-Decene replaces ethylene at random points in the growing polymer chain. Can you deduce how the structure of linear low-density polyethylene differs from a linear chain of CH_2 units?

14.32 Make a molecular model of 7,7-dimethylbicyclo[2.2.1]heptan-2-one. Two diastereomeric alcohols may be formed when it reacts with methylmagnesium bromide. Which one is formed in greater amounts?



7,7-Dimethylbicyclo[2.2.1]heptan-2-one

14.33 Make molecular models of the product of addition of dichlorocarbene to:

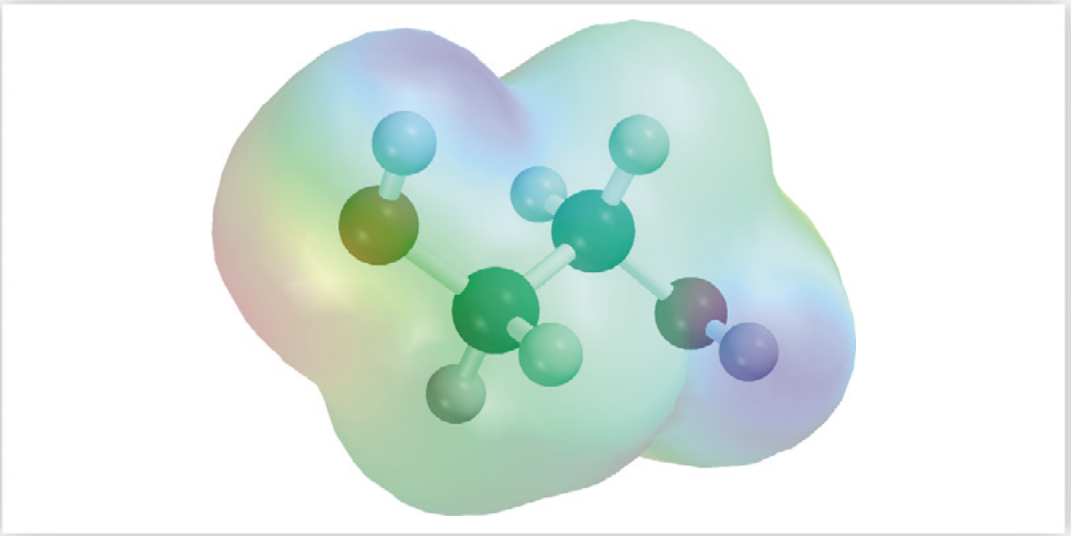
(a) *trans*-2-Butene

(b) *cis*-2-Butene

Which product is achiral? Which one is formed as a racemic mixture?

14.34 Examine the molecular model of ferrocene on *Learning By Modeling*. Does ferrocene have a dipole moment? Would you expect the cyclopentadienyl rings of ferrocene to be more reactive toward nucleophiles or electrophiles? Where is the region of highest electrostatic potential?

14.35 Inspect the electrostatic potential surface of the benzyl anion structure given on *Learning By Modeling*. What is the hybridization state of the benzylic carbon? Does the region of highest electrostatic potential lie in the plane of the molecule or perpendicular to it? Which ring carbons bear the greatest share of negative charge?



CHAPTER 15

ALCOHOLS, DIOLS, AND THIOLS

The next several chapters deal with the chemistry of various oxygen-containing functional groups. The interplay of these important classes of compounds—alcohols, ethers, aldehydes, ketones, carboxylic acids, and derivatives of carboxylic acids—is fundamental to organic chemistry and biochemistry.

ROH	ROR′	RCH (O)	RCR′ (O)	RCOH (O)
Alcohol	Ether	Aldehyde	Ketone	Carboxylic acid

We'll start by discussing in more detail a class of compounds already familiar to us, *alcohols.* Alcohols were introduced in Chapter 4 and have appeared regularly since then. With this chapter we extend our knowledge of alcohols, particularly with respect to their relationship to carbonyl-containing compounds. In the course of studying alcohols, we shall also look at some relatives. **Diols** are alcohols in which two hydroxyl groups (—OH) are present; **thiols** are compounds that contain an —SH group. **Phenols,** compounds of the type ArOH, share many properties in common with alcohols but are sufficiently different from them to warrant separate discussion in Chapter 24.

This chapter is a transitional one. It ties together much of the material encountered earlier and sets the stage for our study of other oxygen-containing functional groups in the chapters that follow.

15.1 SOURCES OF ALCOHOLS

Until the 1920s, the major source of *methanol* was as a byproduct in the production of charcoal from wood—hence, the name *wood alcohol.* Now, most of the more than 10

Carbon monoxide is obtained from coal, and hydrogen is one of the products formed when natural gas is converted to ethylene and propene (Section 5.1).

billion lb of methanol used annually in the United States is synthetic, prepared by reduction of carbon monoxide with hydrogen.

$$\underset{\text{Carbon monoxide}}{CO} + \underset{\text{Hydrogen}}{2H_2} \xrightarrow[400^\circ C]{ZnO/Cr_2O_3} \underset{\text{Methanol}}{CH_3OH}$$

Almost half of this methanol is converted to formaldehyde as a starting material for various resins and plastics. Methanol is also used as a solvent, as an antifreeze, and as a convenient clean-burning liquid fuel. This last property makes it a candidate as a fuel for automobiles—methanol is already used to power Indianapolis-class race cars—but extensive emissions tests remain to be done before it can be approved as a gasoline substitute. Methanol is a colorless liquid, boiling at 65°C, and is miscible with water in all proportions. It is poisonous; drinking as little as 30 mL has been fatal. Ingestion of sublethal amounts can lead to blindness.

When vegetable matter ferments, its carbohydrates are converted to *ethanol* and carbon dioxide by enzymes present in yeast. Fermentation of barley produces beer; grapes give wine. The maximum ethanol content is on the order of 15%, because higher concentrations inactivate the enzymes, halting fermentation. Since ethanol boils at 78°C

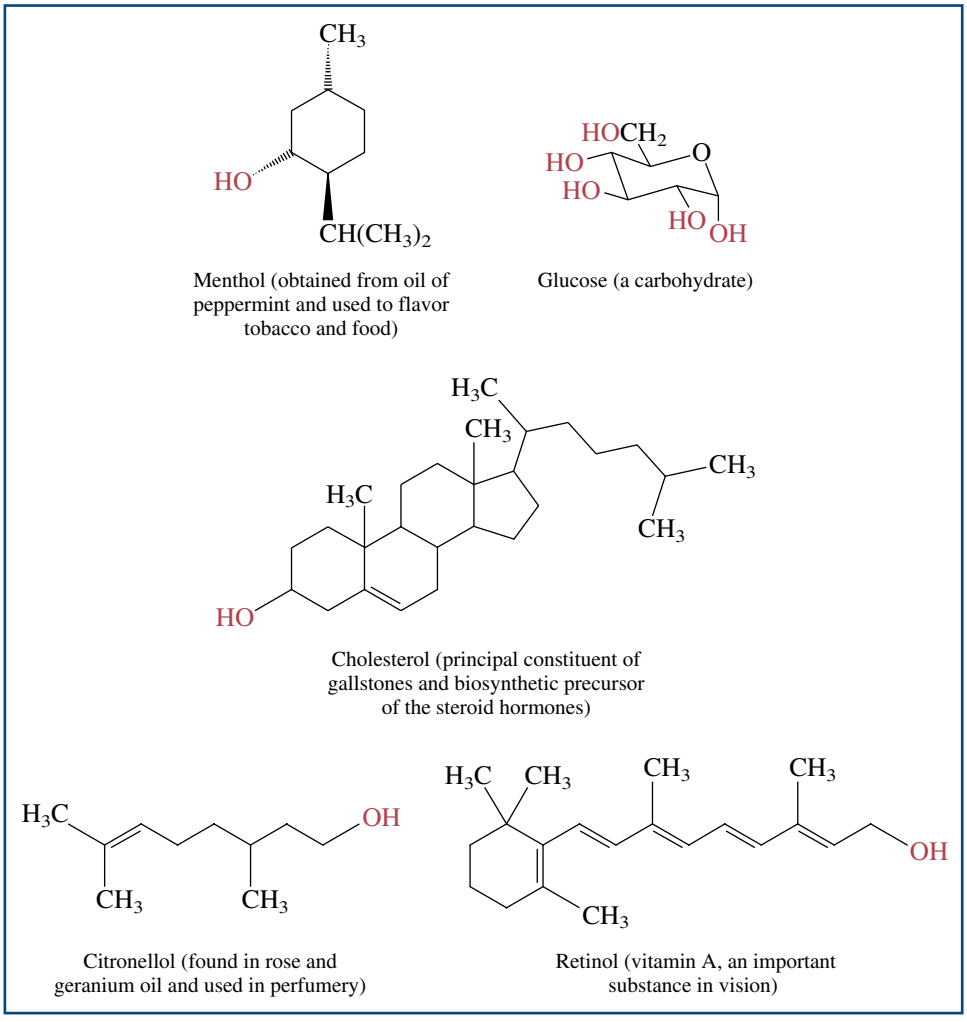


FIGURE 15.1 Some naturally occurring alcohols.

and water at 100°C, distillation of the fermentation broth can be used to give "distilled spirits" of increased ethanol content. Whiskey is the aged distillate of fermented grain and contains slightly less than 50% ethanol. Brandy and cognac are made by aging the distilled spirits from fermented grapes and other fruits. The characteristic flavors, odors, and colors of the various alcoholic beverages depend on both their origin and the way they are aged.

Synthetic ethanol is derived from petroleum by hydration of ethylene. In the United States, some 700 million lb of synthetic ethanol is produced annually. It is relatively inexpensive and useful for industrial applications. To make it unfit for drinking, it is *denatured* by adding any of a number of noxious materials, a process that exempts it from the high taxes most governments impose on ethanol used in beverages.

Some of the substances used to denature ethanol include methanol, benzene, pyridine, castor oil, and gasoline.

Our bodies are reasonably well equipped to metabolize ethanol, making it less dangerous than methanol. Alcohol abuse and alcoholism, however, have been and remain persistent problems.

Isopropyl alcohol is prepared from petroleum by hydration of propene. With a boiling point of 82°C, isopropyl alcohol evaporates quickly from the skin, producing a cooling effect. Often containing dissolved oils and fragrances, it is the major component of rubbing alcohol. Isopropyl alcohol possesses weak antibacterial properties and is used to maintain medical instruments in a sterile condition and to clean the skin before minor surgery.

Methanol, ethanol, and isopropyl alcohol are included among the readily available starting materials commonly found in laboratories where organic synthesis is carried out. So, too, are many other alcohols. All alcohols of four carbons or fewer, as well as most of the five- and six-carbon alcohols and many higher alcohols, are commercially available at low cost. Some occur naturally; others are the products of efficient syntheses. Figure 15.1 presents the structures of a few naturally occurring alcohols. Table 15.1 summarizes the reactions encountered in earlier chapters that give alcohols and illustrates a thread that runs through the fabric of organic chemistry: *a reaction that is characteristic of one functional group often serves as a synthetic method for preparing another.*

As Table 15.1 indicates, reactions leading to alcohols are not in short supply. Nevertheless, several more will be added to the list in the present chapter—testimony to the

TABLE 15.1 Summary of Reactions Discussed in Earlier Chapters That Yield Alcohols

Reaction (section) and comments	General equation and specific example
Acid-catalyzed hydration of alkenes (Section 6.10) The elements of water add to the double bond in accordance with Markovnikov's rule.	$R_2C{=}CR_2 + H_2O \xrightarrow{H^+} R_2CHCR_2$ (OH) Alkene Water Alcohol $(CH_3)_2C{=}CHCH_3 \xrightarrow[H_2SO_4]{H_2O} CH_3CCH_2CH_3$ (CH₃ and OH) 2-Methyl-2-butene 2-Methyl-2-butanol (90%)

(Continued)

TABLE 15.1 Summary of Reactions Discussed in Earlier Chapters That Yield Alcohols *(Continued)*

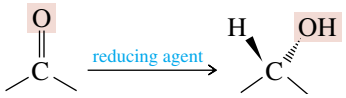
Reaction (section) and comments	General equation and specific example
Hydroboration–oxidation of alkenes (Section 6.11) The elements of water add to the double bond with regioselectivity opposite to that of Markovnikov's rule. This is a very good synthetic method; addition is syn, and no rearrangements are observed.	$R_2C{=}CR_2 \xrightarrow[2.\ H_2O_2,\ HO^-]{1.\ B_2H_6} R_2CHCR_2$ (OH) Alkene — Alcohol $CH_3(CH_2)_7CH{=}CH_2 \xrightarrow[2.\ H_2O_2,\ HO^-]{1.\ B_2H_6,\ \text{diglyme}} CH_3(CH_2)_7CH_2CH_2OH$ 1-Decene — 1-Decanol (93%)
Hydrolysis of alkyl halides (Section 8.1) A reaction useful only with substrates that do not undergo E2 elimination readily. It is rarely used for the synthesis of alcohols, since alkyl halides are normally prepared from alcohols.	$RX + HO^- \longrightarrow ROH + X^-$ Alkyl halide — Hydroxide ion — Alcohol — Halide ion 2,4,6-Trimethylbenzyl chloride $\xrightarrow[\text{heat}]{H_2O,\ Ca(OH)_2}$ 2,4,6-Trimethylbenzyl alcohol (78%)
Reaction of Grignard reagents with aldehydes and ketones (Section 14.6) A method that allows for alcohol preparation with formation of new carbon–carbon bonds. Primary, secondary, and tertiary alcohols can all be prepared.	$RMgX + R'CR'' \xrightarrow[2.\ H_3O^+]{1.\ \text{diethyl ether}} RCOH$ (R′, R″) Grignard reagent — Aldehyde or ketone — Alcohol Cyclopentylmagnesium bromide + Formaldehyde $\xrightarrow[2.\ H_3O^+]{1.\ \text{diethyl ether}}$ Cyclopentylmethanol (62–64%)
Reaction of organolithium reagents with aldehydes and ketones (Section 14.7) Organolithium reagents react with aldehydes and ketones in a manner similar to that of Grignard reagents to form alcohols.	$RLi + R'CR'' \xrightarrow[2.\ H_3O^+]{1.\ \text{diethyl ether}} RCOH$ (R′, R″) Organolithium reagent — Aldehyde or ketone — Alcohol $CH_3CH_2CH_2CH_2Li$ + Acetophenone $\xrightarrow[2.\ H_3O^+]{1.\ \text{diethyl ether}}$ 2-Phenyl-2-hexanol (67%)

(Continued)

TABLE 15.1 Summary of Reactions Discussed in Earlier Chapters That Yield Alcohols ***(Continued)***

Reaction (section) and comments	General equation and specific example
Reaction of Grignard reagents with esters (Section 14.10) Produces tertiary alcohols in which two of the substituents on the hydroxyl-bearing carbon are derived from the Grignard reagent.	$2RMgX + R'COR'' \xrightarrow[2.\ H_3O^+]{1.\ \text{diethyl ether}} RCOH + R''OH$ (R′ and R on the alcohol)
	$2CH_3CH_2CH_2CH_2CH_2MgBr + CH_3COCH_2CH_3 \xrightarrow[2.\ H_3O^+]{1.\ \text{diethyl ether}}$ 6-Methyl-6-undecanol (75%)
	Pentylmagnesium bromide; Ethyl acetate

importance of alcohols in synthetic organic chemistry. Some of these methods involve reduction of carbonyl groups:

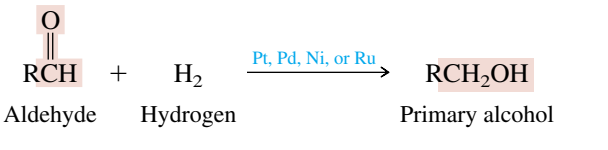


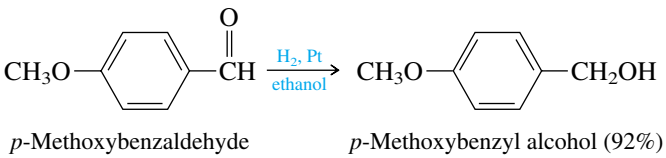
We will begin with the reduction of aldehydes and ketones.

Recall from Section 2.16 that reduction corresponds to a decrease in the number of bonds between carbon and oxygen or an increase in the number of bonds between carbon and hydrogen (or both).

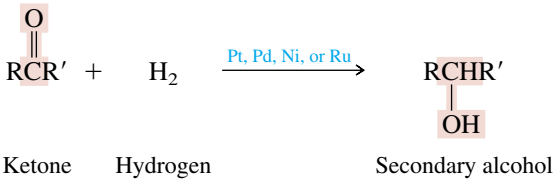
15.2 PREPARATION OF ALCOHOLS BY REDUCTION OF ALDEHYDES AND KETONES

The most obvious way to reduce an aldehyde or a ketone to an alcohol is by hydrogenation of the carbon–oxygen double bond. Like the hydrogenation of alkenes, the reaction is exothermic but exceedingly slow in the absence of a catalyst. Finely divided metals such as platinum, palladium, nickel, and ruthenium are effective catalysts for the hydrogenation of aldehydes and ketones. Aldehydes yield primary alcohols:

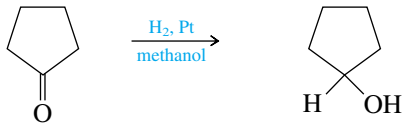




Ketones yield secondary alcohols:



Ketone Hydrogen Secondary alcohol

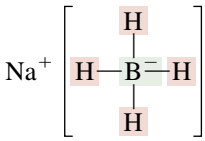


Cyclopentanone Cyclopentanol (93–95%)

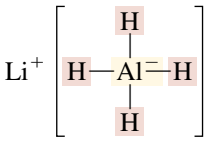
PROBLEM 15.1 Which of the isomeric $C_4H_{10}O$ alcohols can be prepared by hydrogenation of aldehydes? Which can be prepared by hydrogenation of ketones? Which cannot be prepared by hydrogenation of a carbonyl compound?

For most laboratory-scale reductions of aldehydes and ketones, catalytic hydrogenation has been replaced by methods based on metal hydride reducing agents. The two most common reagents are sodium borohydride and lithium aluminum hydride.

Compare the electrostatic potential maps of CH_4, BH_4^-, and AlH_4^- on *Learning By Modeling*. Notice how different the electrostatic potentials associated with hydrogen are.

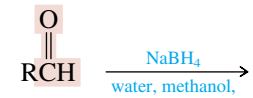


Sodium borohydride ($NaBH_4$)

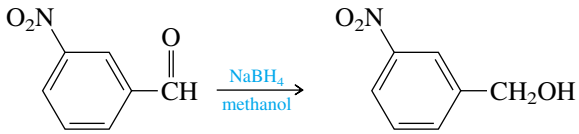


Lithium aluminum hydride ($LiAlH_4$)

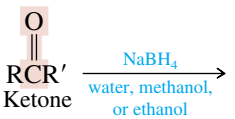
Sodium borohydride is especially easy to use, needing only to be added to an aqueous or alcoholic solution of an aldehyde or a ketone:

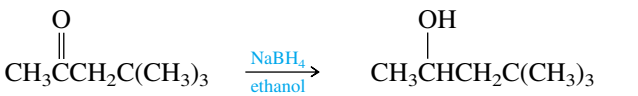


Aldehyde Primary alcohol



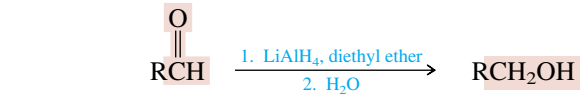
m-Nitrobenzaldehyde *m*-Nitrobenzyl alcohol (82%)



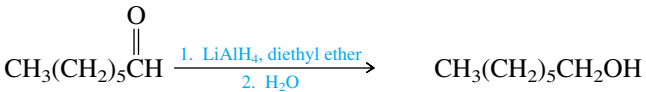


4,4-Dimethyl-2-pentanone 4,4-Dimethyl-2-pentanol (85%)

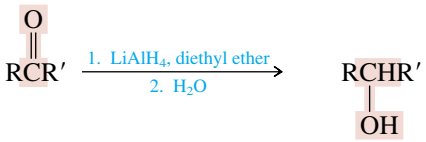
Lithium aluminum hydride reacts violently with water and alcohols, so it must be used in solvents such as anhydrous diethyl ether or tetrahydrofuran. Following reduction, a separate hydrolysis step is required to liberate the alcohol product:



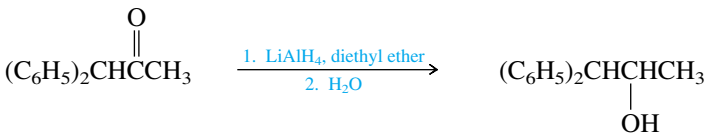
Aldehyde — Primary alcohol



Heptanal — 1-Heptanol (86%)

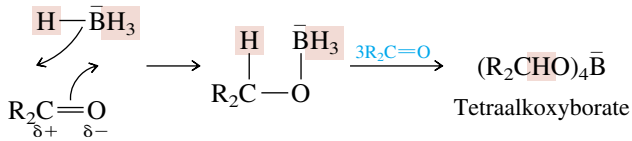


Ketone — Secondary alcohol



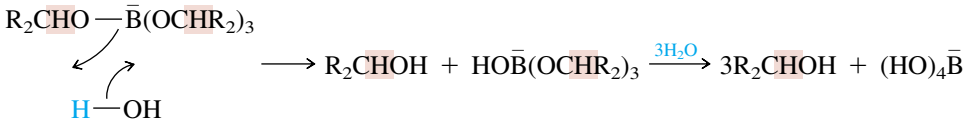
1,1-Diphenyl-2-propanone — 1,1-Diphenyl-2-propanol (84%)

Sodium borohydride and lithium aluminum hydride react with carbonyl compounds in much the same way that Grignard reagents do, except that they function as *hydride donors* rather than as carbanion sources. Borohydride transfers a hydrogen with its pair of bonding electrons to the positively polarized carbon of a carbonyl group. The negatively polarized oxygen attacks boron. Ultimately, all four of the hydrogens of borohydride are transferred and a tetraalkoxyborate is formed.

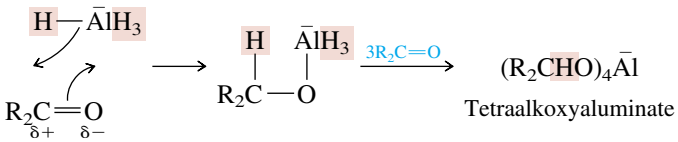


Tetraalkoxyborate

Hydrolysis or alcoholysis converts the tetraalkoxyborate intermediate to the corresponding alcohol. The following equation illustrates the process for reactions carried out in water. An analogous process occurs in methanol or ethanol and yields the alcohol and $(CH_3O)_4B^-$ or $(CH_3CH_2O)_4B^-$.



A similar series of hydride transfers occurs when aldehydes and ketones are treated with lithium aluminum hydride.



Addition of water converts the tetraalkoxyaluminate to the desired alcohol.

$$\underset{\text{Tetraalkoxyaluminate}}{(R_2CHO)_4\bar{A}l} + 4H_2O \longrightarrow \underset{\text{Alcohol}}{4R_2CHOH} + \bar{A}l(OH)_4$$

An undergraduate laboratory experiment related to Problem 15.2 appears in the March 1996 issue of the *Journal of Chemical Education*, pp. 264–266.

PROBLEM 15.2 Sodium borodeuteride ($NaBD_4$) and lithium aluminum deuteride ($LiAlD_4$) are convenient reagents for introducing deuterium, the mass 2 isotope of hydrogen, into organic compounds. Write the structure of the organic product of the following reactions, clearly showing the position of all the deuterium atoms in each:

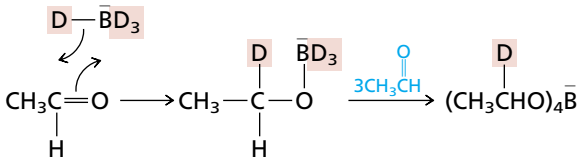
(a) Reduction of CH_3CH (acetaldehyde) with $NaBD_4$ in H_2O

(b) Reduction of CH_3CCH_3 (acetone) with $NaBD_4$ in CH_3OD

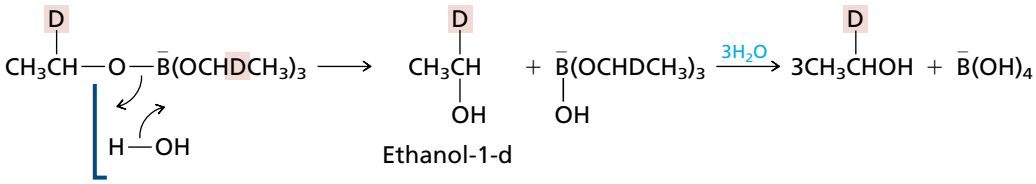
(c) Reduction of C_6H_5CH (benzaldehyde) with $NaBD_4$ in CD_3OH

(d) Reduction of HCH (formaldehyde) with $LiAlD_4$ in diethyl ether, followed by addition of D_2O

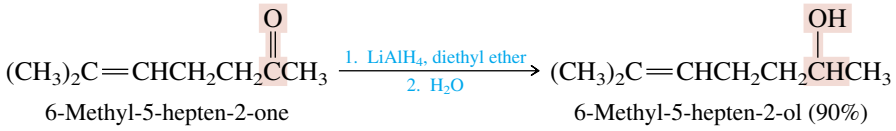
SAMPLE SOLUTION (a) Sodium borodeuteride transfers deuterium to the carbonyl group of acetaldehyde, forming a C—D bond.



Hydrolysis of $(CH_3CHDO)_4\bar{B}$ in H_2O leads to the formation of ethanol, retaining the C—D bond formed in the preceding step while forming an O—H bond.



Neither sodium borohydride nor lithium aluminum hydride reduces isolated carbon–carbon double bonds. This makes possible the selective reduction of a carbonyl group in a molecule that contains both carbon–carbon and carbon–oxygen double bonds.



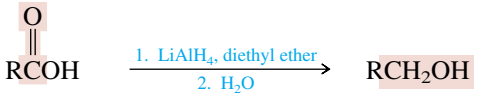
6-Methyl-5-hepten-2-one

6-Methyl-5-hepten-2-ol (90%)

Catalytic hydrogenation would not be suitable for this transformation, because H_2 adds to carbon–carbon double bonds faster than it reduces carbonyl groups.

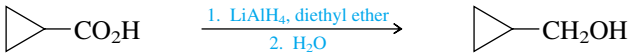
15.3 PREPARATION OF ALCOHOLS BY REDUCTION OF CARBOXYLIC ACIDS AND ESTERS

Carboxylic acids are exceedingly difficult to reduce. Acetic acid, for example, is often used as a solvent in catalytic hydrogenations because it is inert under the reaction conditions. A very powerful reducing agent is required to convert a carboxylic acid to a primary alcohol. Lithium aluminum hydride is that reducing agent.



Carboxylic acid

Primary alcohol

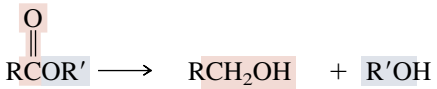


Cyclopropanecarboxylic acid

Cyclopropylmethanol (78%)

Sodium borohydride is not nearly as potent a hydride donor as lithium aluminum hydride and does not reduce carboxylic acids.

Esters are more easily reduced than carboxylic acids. Two alcohols are formed from each ester molecule. The acyl group of the ester is cleaved, giving a primary alcohol.

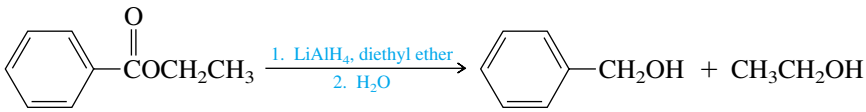


Ester

Primary alcohol

Alcohol

Lithium aluminum hydride is the reagent of choice for reducing esters to alcohols.



Ethyl benzoate

Benzyl alcohol (90%)

Ethanol

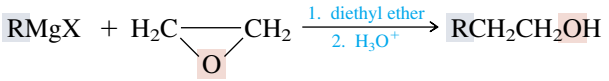
PROBLEM 15.3 Give the structure of an ester that will yield a mixture containing equimolar amounts of 1-propanol and 2-propanol on reduction with lithium aluminum hydride.

Sodium borohydride reduces esters, but the reaction is too slow to be useful. Hydrogenation of esters requires a special catalyst and extremely high pressures and temperatures; it is used in industrial settings but rarely in the laboratory.

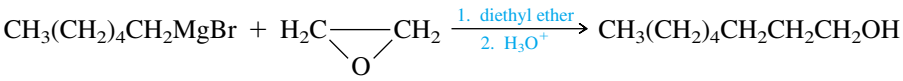
15.4 PREPARATION OF ALCOHOLS FROM EPOXIDES

Although the chemical reactions of epoxides will not be covered in detail until the following chapter, we shall introduce their use in the synthesis of alcohols here.

Grignard reagents react with ethylene oxide to yield primary alcohols containing two more carbon atoms than the alkyl halide from which the organometallic compound was prepared.



Grignard reagent | Ethylene oxide | Primary alcohol

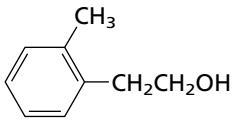


Hexylmagnesium bromide | Ethylene oxide | 1-Octanol (71%)

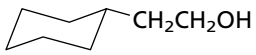
Organolithium reagents react with epoxides in a similar manner.

PROBLEM 15.4 Each of the following alcohols has been prepared by reaction of a Grignard reagent with ethylene oxide. Select the appropriate Grignard reagent in each case.

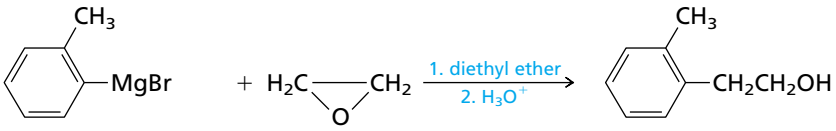
(a)



(b)

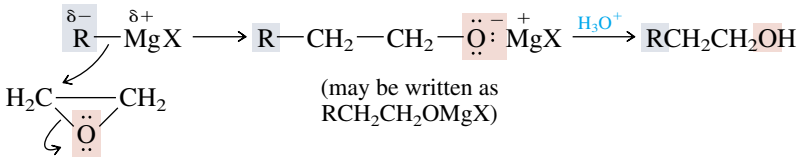


SAMPLE SOLUTION (a) Reaction with ethylene oxide results in the addition of a $-CH_2CH_2OH$ unit to the Grignard reagent. The Grignard reagent derived from *o*-bromotoluene (or *o*-chlorotoluene or *o*-iodotoluene) is appropriate here.



o-Methylphenylmagnesium bromide | Ethylene oxide | 2-(*o*-Methylphenyl)ethanol (66%)

Epoxide rings are readily opened with cleavage of the carbon–oxygen bond when attacked by nucleophiles. Grignard reagents and organolithium reagents react with ethylene oxide by serving as sources of nucleophilic carbon.

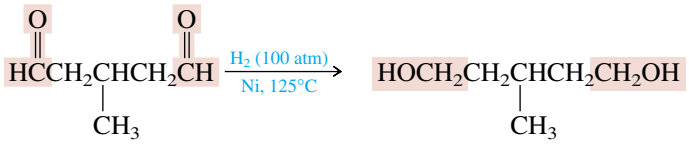


(may be written as RCH_2CH_2OMgX)

This kind of chemical reactivity of epoxides is rather general. Nucleophiles other than Grignard reagents react with epoxides, and epoxides more elaborate than ethylene oxide may be used. All these features of epoxide chemistry will be discussed in Sections 16.11 and 16.12.

15.5 PREPARATION OF DIOLS

Much of the chemistry of diols—compounds that bear two hydroxyl groups—is analogous to that of alcohols. Diols may be prepared, for example, from compounds that contain two carbonyl groups, using the same reducing agents employed in the preparation of alcohols. The following example shows the conversion of a dialdehyde to a diol by catalytic hydrogenation. Alternatively, the same transformation can be achieved by reduction with sodium borohydride or lithium aluminum hydride.

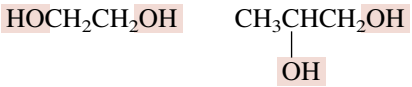


3-Methylpentanedial — 3-Methyl-1,5-pentanediol (81–83%)

Diols are almost always given substitutive IUPAC names. As the name of the product in the example indicates, the substitutive nomenclature of diols is similar to that of alcohols. The suffix *-diol* replaces *-ol,* and two locants, one for each hydroxyl group, are required. Note that the final *-e* of the alkane basis name is retained when the suffix begins with a consonant *(-diol),* but dropped when the suffix begins with a vowel *(-ol).*

PROBLEM 15.5 Write equations showing how 3-methyl-1,5-pentanediol could be prepared from a dicarboxylic acid or a diester.

Vicinal diols are diols that have their hydroxyl groups on adjacent carbons. Two commonly encountered vicinal diols are 1,2-ethanediol and 1,2-propanediol.

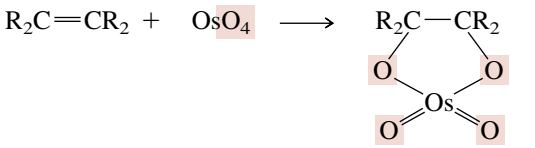


1,2-Ethanediol (ethylene glycol) — 1,2-Propanediol (propylene glycol)

Ethylene glycol and propylene glycol are prepared industrially from the corresponding alkenes by way of their epoxides. Some applications were given in the box in Section 6.21.

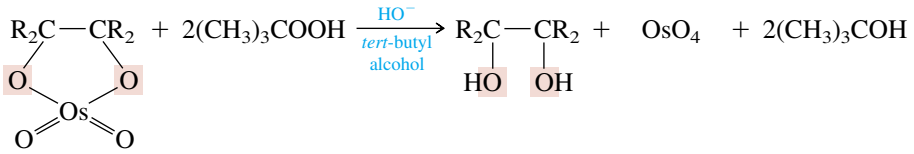
Ethylene glycol and *propylene glycol* are common names for these two diols and are acceptable IUPAC names. Aside from these two compounds, the IUPAC system does not use the word "glycol" for naming diols.

In the laboratory, vicinal diols are normally prepared from alkenes using the reagent *osmium tetraoxide* (OsO_4). Osmium tetraoxide reacts rapidly with alkenes to give cyclic osmate esters.



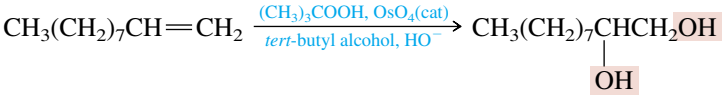
Alkene — Osmium tetraoxide — Cyclic osmate ester

Osmate esters are fairly stable but are readily cleaved in the presence of an oxidizing agent such as *tert*-butyl hydroperoxide.



tert-Butyl hydroperoxide | Vicinal diol | Osmium tetraoxide | *tert*-Butyl alcohol

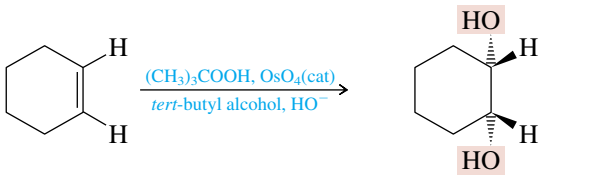
Since osmium tetraoxide is regenerated in this step, alkenes can be converted to vicinal diols using only catalytic amounts of osmium tetraoxide, which is both toxic and expensive. The entire process is performed in a single operation by simply allowing a solution of the alkene and *tert*-butyl hydroperoxide in *tert*-butyl alcohol containing a small amount of osmium tetraoxide and base to stand for several hours.



1-Decene | 1,2-Decanediol (73%)

Overall, the reaction leads to addition of two hydroxyl groups to the double bond and is referred to as **hydroxylation.** Both oxygens of the diol come from osmium tetraoxide via the cyclic osmate ester. The reaction of OsO_4 with the alkene is a syn addition, and the conversion of the cyclic osmate to the diol involves cleavage of the bonds between oxygen and osmium. Thus, both hydroxyl groups of the diol become attached to the same face of the double bond; *syn hydroxylation of the alkene is observed.*

Construct a molecular model of *cis*-1,2-cyclohexanediol. What is the orientation of the OH groups, axial or equatorial?



Cyclohexene | *cis*-1,2-Cyclohexanediol (62%)

PROBLEM 15.6 Give the structures, including stereochemistry, for the diols obtained by hydroxylation of *cis*-2-butene and *trans*-2-butene.

A complementary method, one that gives anti hydroxylation of alkenes by way of the hydrolysis of epoxides, will be described in Section 16.13.

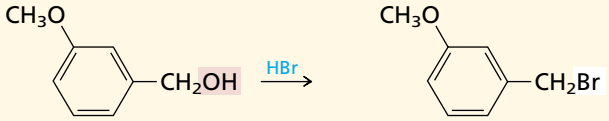
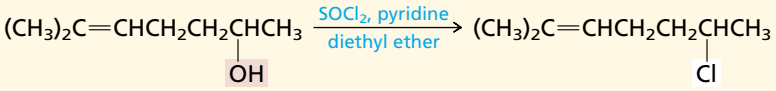
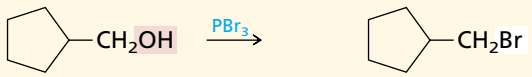
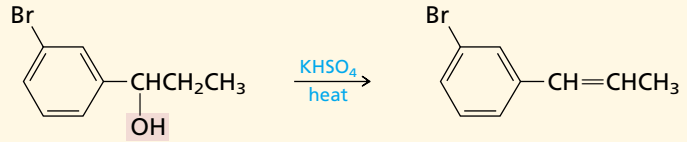
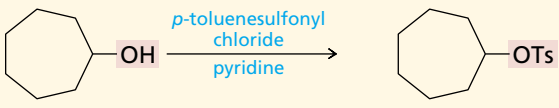
15.6 REACTIONS OF ALCOHOLS: A REVIEW AND A PREVIEW

Alcohols are versatile starting materials for the preparation of a variety of organic functional groups. Several reactions of alcohols have already been seen in earlier chapters and are summarized in Table 15.2. The remaining sections of this chapter add to the list.

15.7 CONVERSION OF ALCOHOLS TO ETHERS

Primary alcohols are converted to ethers on heating in the presence of an acid catalyst, usually sulfuric acid.

TABLE 15.2 Summary of Reactions of Alcohols Discussed in Earlier Chapters

Reaction (section) and comments	General equation and specific example
Reaction with hydrogen halides (Section 4.8) The order of alcohol reactivity parallels the order of carbocation stability: $R_3C^+ > R_2CH^+ > RCH_2^+ > CH_3^+$. Benzylic alcohols react readily.	$ROH + HX \longrightarrow RX + H_2O$ Alcohol — Hydrogen halide — Alkyl halide — Water  *m*-Methoxybenzyl alcohol — *m*-Methoxybenzyl bromide (98%)
Reaction with thionyl chloride (Section 4.14) Thionyl chloride converts alcohols to alkyl chlorides.	$ROH + SOCl_2 \longrightarrow RCl + SO_2 + HCl$ Alcohol — Thionyl chloride — Alkyl chloride — Sulfur dioxide — Hydrogen chloride  6-Methyl-5-hepten-2-ol — 6-Chloro-2-methyl-2-heptene (67%)
Reaction with phosphorus trihalides (Section 4.14) Phosphorus trichloride and phosphorus tribromide convert alcohols to alkyl halides.	$3ROH + PX_3 \longrightarrow 3RX + H_3PO_3$ Alcohol — Phosphorus trihalide — Alkyl halide — Phosphorous acid  Cyclopentylmethanol — (Bromomethyl)cyclopentane (50%)
Acid-catalyzed dehydration (Section 5.9) This is a frequently used procedure for the preparation of alkenes. The order of alcohol reactivity parallels the order of carbocation stability: $R_3C^+ > R_2CH^+ > RCH_2^+$. Benzylic alcohols react readily. Rearrangements are sometimes observed.	$R_2CCHR_2 \xrightarrow[\text{heat}]{H^+} R_2C{=}CR_2 + H_2O$ OH Alcohol — Alkene — Water  1-(*m*-Bromophenyl)-1-propanol — 1-(*m*-Bromophenyl)propene (71%)
Conversion to *p*-toluenesulfonate esters (Section 8.14) Alcohols react with *p*-toluenesulfonyl chloride to give *p*-toluenesulfonate esters. Sulfonate esters are reactive substrates for nucleophilic substitution and elimination reactions. The *p*-toluenesulfonate group is often abbreviated —OTs.	$ROH + H_3C\text{—}C_6H_4\text{—}SO_2Cl \longrightarrow ROS(=O)_2\text{—}C_6H_4\text{—}CH_3 + HCl$ Alcohol — *p*-Toluenesulfonyl chloride — Alkyl *p*-toluenesulfonate — Hydrogen chloride  Cycloheptanol — Cycloheptyl *p*-toluenesulfonate (83%)

$$2RCH_2OH \xrightarrow{H^+,\ heat} RCH_2OCH_2R + H_2O$$

Primary alcohol — Dialkyl ether — Water

This kind of reaction is called a **condensation.** A condensation is a reaction in which two molecules combine to form a larger one while liberating a small molecule. In this case two alcohol molecules combine to give an ether and water.

$$2CH_3CH_2CH_2CH_2OH \xrightarrow[130°C]{H_2SO_4} CH_3CH_2CH_2CH_2OCH_2CH_2CH_2CH_3 + H_2O$$

1-Butanol — Dibutyl ether (60%) — Water

When applied to the synthesis of ethers, the reaction is effective only with primary alcohols. Elimination to form alkenes predominates with secondary and tertiary alcohols.

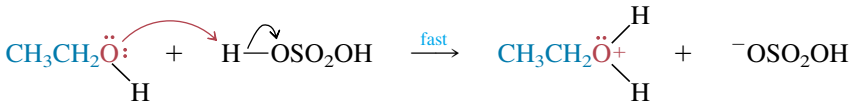
Diethyl ether is prepared on an industrial scale by heating ethanol with sulfuric acid at 140°C. At higher temperatures elimination predominates, and ethylene is the major product. A mechanism for the formation of diethyl ether is outlined in Figure 15.2.

Overall Reaction:

$$2CH_3CH_2OH \xrightarrow[140°C]{H_2SO_4} CH_3CH_2OCH_2CH_3 + H_2O$$

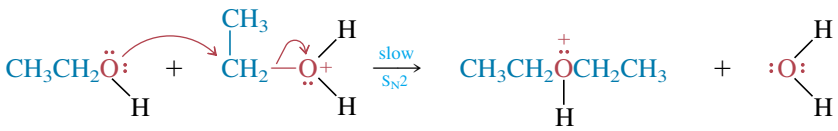
Ethanol — Diethyl ether — Water

Step 1: Proton transfer from the acid catalyst to the oxygen of the alcohol to produce an alkyloxonium ion



Ethyl alcohol — Sulfuric acid — Ethyloxonium ion — Hydrogen sulfate ion

Step 2: Nucleophilic attack by a molecule of alcohol on the alkyloxonium ion formed in step 1



Ethyl alcohol — Ethyloxonium ion — Diethyloxonium ion — Water

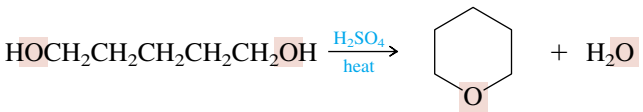
Step 3: The product of step 2 is the conjugate acid of the dialkyl ether. It is deprotonated in the final step of the process to give the ether.

Diethyloxonium ion — Hydrogen sulfate ion — Diethyl ether — Sulfuric acid

FIGURE 15.2 The mechanism of acid-catalyzed formation of diethyl ether from ethyl alcohol. As an alternative in the third step, the Brønsted base that abstracts the proton could be a molecule of the starting alcohol.

The individual steps of this mechanism are analogous to those seen earlier. Nucleophilic attack on a protonated alcohol was encountered in the reaction of primary alcohols with hydrogen halides (Section 4.13), and the nucleophilic properties of alcohols were discussed in the context of solvolysis reactions (Section 8.7). Both the first and the last steps are proton-transfer reactions between oxygens.

Diols react intramolecularly to form cyclic ethers when a five-membered or six-membered ring can result.



1,5-Pentanediol — Oxane (76%) — Water

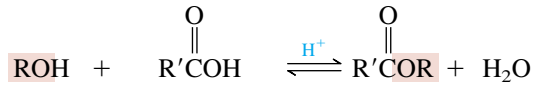
Oxane is also called tetrahydropyran.

In these intramolecular ether-forming reactions, the alcohol may be primary, secondary, or tertiary.

PROBLEM 15.7 On the basis of the mechanism for the acid-catalyzed formation of diethyl ether from ethanol in Figure 15.2, write a stepwise mechanism for the formation of oxane from 1,5-pentanediol (see the equation in the preceding paragraph).

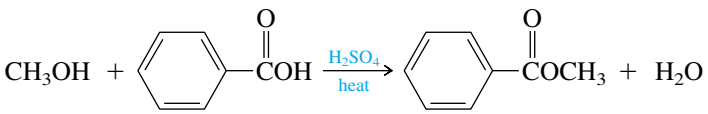
15.8 ESTERIFICATION

Acid-catalyzed condensation of an alcohol and a carboxylic acid yields an ester and water and is known as the **Fischer esterification.**



Alcohol — Carboxylic acid — Ester — Water

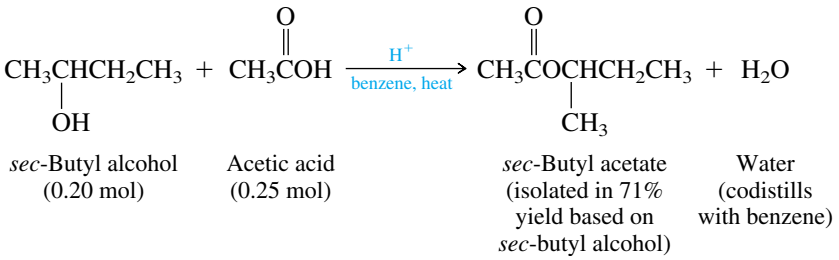
Fischer esterification is reversible, and the position of equilibrium lies slightly to the side of products when the reactants are simple alcohols and carboxylic acids. When the Fischer esterification is used for preparative purposes, the position of equilibrium can be made more favorable by using either the alcohol or the carboxylic acid in excess. In the following example, in which an excess of the alcohol was employed, the yield indicated is based on the carboxylic acid as the limiting reactant.



Methanol (0.6 mol) — Benzoic acid (0.1 mol) — Methyl benzoate (isolated in 70% yield based on benzoic acid) — Water

An *azeotropic mixture* contains two or more substances that distill together at a constant boiling point. The benzene–water azeotrope contains 9% water and boils at 69°C.

Another way to shift the position of equilibrium to favor the formation of ester is by removing water from the reaction mixture. This can be accomplished by adding benzene as a cosolvent and distilling the azeotropic mixture of benzene and water.



sec-Butyl alcohol (0.20 mol) | Acetic acid (0.25 mol) | *sec*-Butyl acetate (isolated in 71% yield based on *sec*-butyl alcohol) | Water (codistills with benzene)

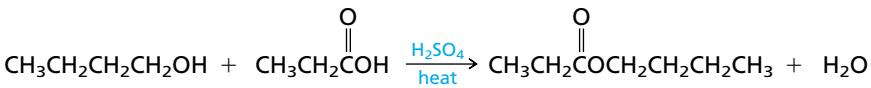
For steric reasons, the order of alcohol reactivity in the Fischer esterification is CH_3OH > primary > secondary > tertiary.

PROBLEM 15.8 Write the structure of the ester formed in each of the following reactions:

(a) $CH_3CH_2CH_2CH_2OH + CH_3CH_2COH \xrightarrow[\text{heat}]{H_2SO_4}$

(b) $2CH_3OH + HOC(C_6H_4)COH \xrightarrow[\text{heat}]{H_2SO_4} (C_{10}H_{10}O_4)$

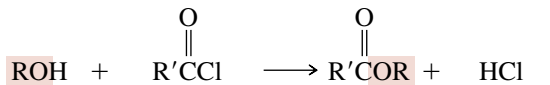
SAMPLE SOLUTION (a) By analogy to the general equation and to the examples cited in this section, we can write the equation



1-Butanol | Propanoic acid | Butyl propanoate | Water

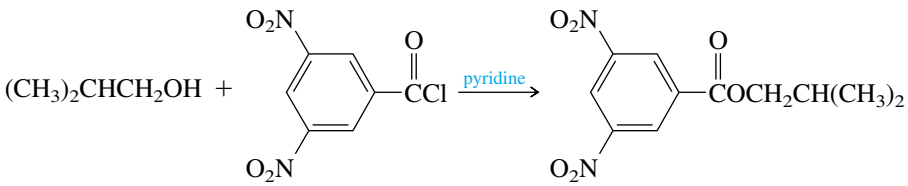
As actually carried out in the laboratory, 3 mol of propanoic acid was used per mole of 1-butanol, and the desired ester was obtained in 78% yield.

Esters are also formed by the reaction of alcohols with acyl chlorides:



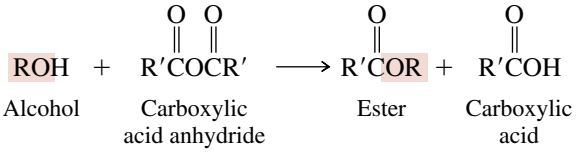
Alcohol | Acyl chloride | Ester | Hydrogen chloride

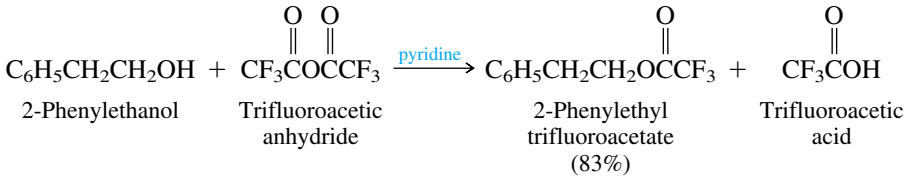
This reaction is normally carried out in the presence of a weak base such as pyridine, which reacts with the hydrogen chloride that is formed.



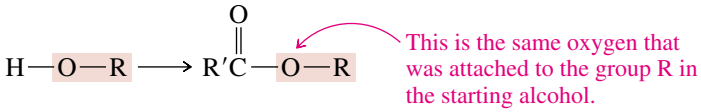
Isobutyl alcohol | 3,5-Dinitrobenzoyl chloride | Isobutyl 3,5-dinitrobenzoate (86%)

Carboxylic acid anhydrides react similarly to acyl chlorides.

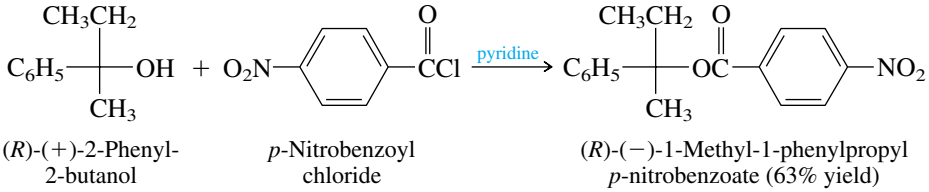




The mechanisms of the Fischer esterification and the reactions of alcohols with acyl chlorides and acid anhydrides will be discussed in detail in Chapters 19 and 20 after some fundamental principles of carbonyl group reactivity have been developed. For the present, it is sufficient to point out that most of the reactions that convert alcohols to esters leave the C—O bond of the alcohol intact.



The acyl group of the carboxylic acid, acyl chloride, or acid anhydride is transferred to the oxygen of the alcohol. This fact is most clearly evident in the esterification of chiral alcohols, where, since none of the bonds to the stereogenic center is broken in the process, *retention of configuration is observed.*



Make a molecular model corresponding to the stereochemistry of the Fischer projection of 2-phenyl-2-butanol shown in the equation and verify that it has the *R* configuration.

PROBLEM 15.9 A similar conclusion may be drawn by considering the reactions of the cis and trans isomers of 4-*tert*-butylcyclohexanol with acetic anhydride. On the basis of the information just presented, predict the product formed from each stereoisomer.

The reaction of alcohols with acyl chlorides is analogous to their reaction with *p*-toluenesulfonyl chloride described earlier (Section 8.14 and Table 15.2). In those reactions, a *p*-toluenesulfonate ester was formed by displacement of chloride from the sulfonyl group by the oxygen of the alcohol. Carboxylic esters arise by displacement of chloride from a carbonyl group by the alcohol oxygen.

15.9 ESTERS OF INORGANIC ACIDS

Although the term "ester," used without a modifier, is normally taken to mean an ester of a carboxylic acid, alcohols can react with inorganic acids in a process similar to the

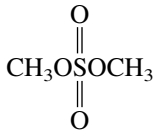
Fischer esterification. The products are esters of inorganic acids. For example, *alkyl nitrates* are esters formed by the reaction of alcohols with *nitric acid.*

$$\underset{\text{Alcohol}}{ROH} + \underset{\text{Nitric acid}}{HONO_2} \xrightarrow{H^+} \underset{\text{Alkyl nitrate}}{RONO_2} + \underset{\text{Water}}{H_2O}$$

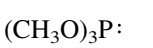
$$\underset{\text{Methanol}}{CH_3OH} + \underset{\text{Nitric acid}}{HONO_2} \xrightarrow{H_2SO_4} \underset{\text{Methyl nitrate (66–80\%)}}{CH_3ONO_2} + \underset{\text{Water}}{H_2O}$$

PROBLEM 15.10 Alfred Nobel's fortune was based on his 1866 discovery that nitroglycerin, which is far too shock-sensitive to be transported or used safely, can be stabilized by adsorption onto a substance called *kieselguhr* to give what is familiar to us as *dynamite.* Nitroglycerin is the trinitrate of glycerol (1,2,3-propanetriol). Write a structural formula or construct a molecular model of nitroglycerin.

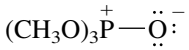
Dialkyl sulfates are esters of *sulfuric acid,* **trialkyl phosphites** are esters of *phosphorous acid* (H_3PO_3), and **trialkyl phosphates** are esters of *phosphoric acid* (H_3PO_4).



Dimethyl sulfate



Trimethyl phosphite



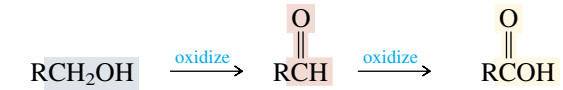
Trimethyl phosphate

Some esters of inorganic acids, such as dimethyl sulfate, are used as reagents in synthetic organic chemistry. Certain naturally occurring alkyl phosphates play an important role in biological processes.

15.10 OXIDATION OF ALCOHOLS

Oxidation of an alcohol yields a carbonyl compound. Whether the resulting carbonyl compound is an aldehyde, a ketone, or a carboxylic acid depends on the alcohol and on the oxidizing agent.

Primary alcohols may be oxidized either to an aldehyde or to a carboxylic acid:

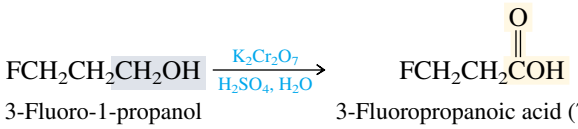


Primary alcohol — Aldehyde — Carboxylic acid

Vigorous oxidation leads to the formation of a carboxylic acid, but there are a number of methods that permit us to stop the oxidation at the intermediate aldehyde stage. The reagents that are most commonly used for oxidizing alcohols are based on high-oxidation-state transition metals, particularly chromium(VI).

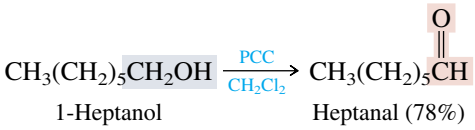
Chromic acid (H_2CrO_4) is a good oxidizing agent and is formed when solutions containing chromate (CrO_4^{2-}) or dichromate ($Cr_2O_7^{2-}$) are acidified. Sometimes it is possible to obtain aldehydes in satisfactory yield before they are further oxidized, but in most cases carboxylic acids are the major products isolated on treatment of primary alcohols with chromic acid.

Potassium permanganate ($KMnO_4$) will also oxidize primary alcohols to carboxylic acids. What is the oxidation state of manganese in $KMnO_4$?

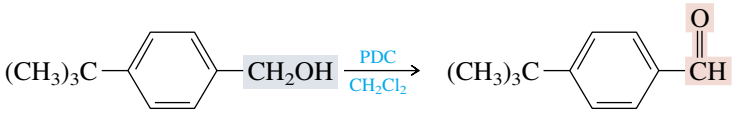


3-Fluoro-1-propanol 3-Fluoropropanoic acid (74%)

Conditions that do permit the easy isolation of aldehydes in good yield by oxidation of primary alcohols employ various Cr(VI) species as the oxidant in *anhydrous* media. Two such reagents are **pyridinium chlorochromate (PCC),** $C_5H_5NH^+\ ClCrO_3^-$, and **pyridinium dichromate (PDC),** $(C_5H_5NH)_2^{2+}\ Cr_2O_7^{2-}$; both are used in dichloromethane.



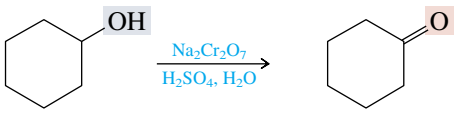
1-Heptanol Heptanal (78%)



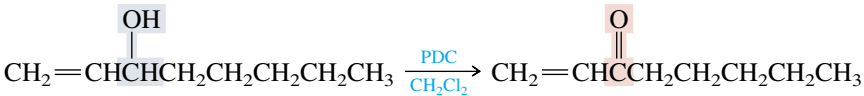
p-tert-Butylbenzyl alcohol *p-tert*-Butylbenzaldehyde (94%)

Secondary alcohols are oxidized to ketones by the same reagents that oxidize primary alcohols:

Secondary alcohol Ketone

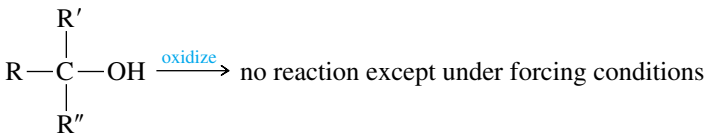


Cyclohexanol Cyclohexanone (85%)



1-Octen-3-ol 1-Octen-3-one (80%)

Tertiary alcohols have no hydrogen on their hydroxyl-bearing carbon and do not undergo oxidation readily:

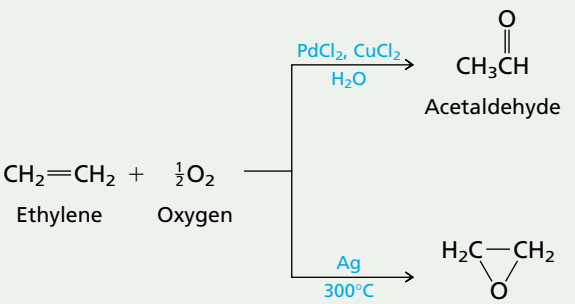


In the presence of strong oxidizing agents at elevated temperatures, oxidation of tertiary alcohols leads to cleavage of the various carbon–carbon bonds at the hydroxyl-bearing carbon atom, and a complex mixture of products results.

ECONOMIC AND ENVIRONMENTAL FACTORS IN ORGANIC SYNTHESIS

Beyond the obvious difference in scale that is evident when one compares preparing tons of a compound versus preparing just a few grams of it, there are sharp distinctions between "industrial" and "laboratory" syntheses. On a laboratory scale, a chemist is normally concerned only with obtaining a modest amount of a substance. Sometimes making the compound is an end in itself, but on other occasions the compound is needed for some further study of its physical, chemical, or biological properties. Considerations such as the cost of reagents and solvents tend to play only a minor role when planning most laboratory syntheses. Faced with a choice between two synthetic routes to a particular compound, one based on the cost of chemicals and the other on the efficient use of a chemist's time, the decision is almost always made in favor of the latter.

Not so for synthesis in the chemical industry, where not only must a compound be prepared on a large scale, but it must be prepared at low cost. There is a pronounced bias toward reactants and reagents that are both abundant and inexpensive. The oxidizing agent of choice, for example, in the chemical industry is O_2, and extensive research has been devoted to developing catalysts for preparing various compounds by air oxidation of readily available starting materials. To illustrate, air and ethylene are the reactants for the industrial preparation of both acetaldehyde and ethylene oxide. Which of the two products is obtained depends on the catalyst employed.



Dating approximately from the creation of the U.S. Environmental Protection Agency (EPA) in 1970, dealing with the byproducts of synthetic procedures has become an increasingly important consideration in designing a chemical synthesis. In terms of changing the strategy of synthetic planning, the chemical industry actually had a shorter road to travel than the pharmaceutical industry, academic laboratories, and research institutes. Simple business principles had long dictated that waste chemicals represented wasted opportunities. It made better sense for a chemical company to recover the solvent from a reaction and use it again than to throw it away and buy more. Similarly, it was far better to find a "value-added" use for a byproduct from a reaction than to throw it away. By raising the cost of generating chemical waste, environmental regulations increased the economic incentive to design processes that produced less of it.

The term "environmentally benign" synthesis has been coined to refer to procedures explicitly designed to minimize the formation of byproducts that present disposal problems. Both the National Science Foundation and the Environmental Protection Agency have allocated a portion of their grant budgets to encourage efforts in this vein.

The application of environmentally benign principles to laboratory-scale synthesis can be illustrated by revisiting the oxidation of alcohols. As noted in Section 15.10, the most widely used methods involve Cr(VI)-based oxidizing agents. Cr(VI) compounds are carcinogenic, however, and appear on the EPA list of compounds requiring special disposal methods. The best way to replace Cr(VI)-based oxidants would be to develop catalytic methods analogous to those used in industry. Another approach would be to use oxidizing agents that are less hazardous, such as sodium hypochlorite. Aqueous solutions of sodium hypochlorite are available as "swimming-pool chlorine," and procedures for their use in oxidizing secondary alcohols to ketones have been developed. One is described on page 71 of the January 1991 edition of the *Journal of Chemical Education.*

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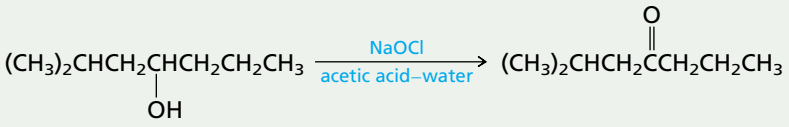


2-Methyl-4-heptanol 2-Methyl-4-heptanone (77%)

There is a curious irony in the nomination of hypochlorite as an environmentally benign oxidizing agent. It comes at a time of increasing pressure to eliminate chlorine and chlorine-containing compounds from the environment to as great a degree as possible. Any all-inclusive assault on chlorine needs to be carefully scrutinized, especially when one remembers that chlorination of the water supply has probably done more to extend human life than any other public health measure ever undertaken. (The role of chlorine in the formation of chlorinated hydrocarbons in water is discussed in Section 18.7.)

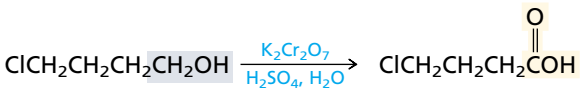
PROBLEM 15.11 Predict the principal organic product of each of the following reactions:

(a) $ClCH_2CH_2CH_2CH_2OH \xrightarrow[H_2SO_4,\ H_2O]{K_2Cr_2O_7}$

(b) $CH_3CHCH_2CH_2CH_2CH_2CH_2CH_3$ (OH) $\xrightarrow[H_2SO_4,\ H_2O]{Na_2Cr_2O_7}$

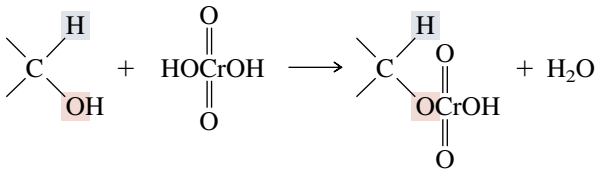
(c) $CH_3CH_2CH_2CH_2CH_2CH_2CH_2OH \xrightarrow[CH_2Cl_2]{PCC}$

SAMPLE SOLUTION (a) The reactant is a primary alcohol and so can be oxidized either to an aldehyde or to a carboxylic acid. Aldehydes are the major products only when the oxidation is carried out in anhydrous media. Carboxylic acids are formed when water is present. The reaction shown produced 4-chlorobutanoic acid in 56% yield.



4-Chloro-1-butanol 4-Chlorobutanoic acid

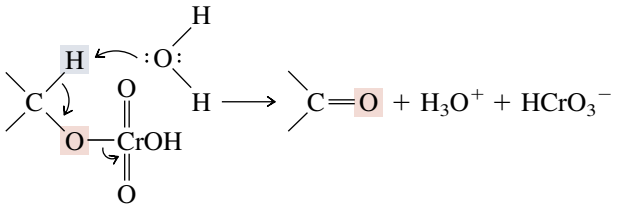
The mechanisms by which transition-metal oxidizing agents convert alcohols to aldehydes and ketones are rather complicated and will not be dealt with in detail here. In broad outline, chromic acid oxidation involves initial formation of an alkyl chromate:



Alcohol Chromic acid Alkyl chromate

An alkyl chromate is an example of an ester of an inorganic acid (Section 15.9).

This alkyl chromate then undergoes an elimination reaction to form the carbon–oxygen double bond.

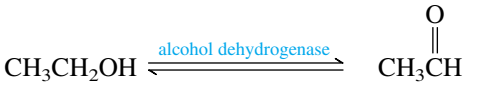


Alkyl chromate — Aldehyde or ketone

In the elimination step, chromium is reduced from Cr(VI) to Cr(IV). Since the eventual product is Cr(III), further electron-transfer steps are also involved.

15.11 BIOLOGICAL OXIDATION OF ALCOHOLS

Many biological processes involve oxidation of alcohols to carbonyl compounds or the reverse process, reduction of carbonyl compounds to alcohols. Ethanol, for example, is metabolized in the liver to acetaldehyde. Such processes are catalyzed by enzymes; the enzyme that catalyzes the oxidation of ethanol is called *alcohol dehydrogenase.*



Ethanol — Acetaldehyde

In addition to enzymes, biological oxidations require substances known as *coenzymes.* Coenzymes are organic molecules that, in concert with an enzyme, act on a substrate to bring about chemical change. Most of the substances that we call vitamins are coenzymes. The coenzyme contains a functional group that is complementary to a functional group of the substrate; the enzyme catalyzes the interaction of these mutually complementary functional groups. If ethanol is oxidized, some other substance must be reduced. This other substance is the oxidized form of the coenzyme *nicotinamide adenine dinucleotide* (NAD). Chemists and biochemists abbreviate the oxidized form of this

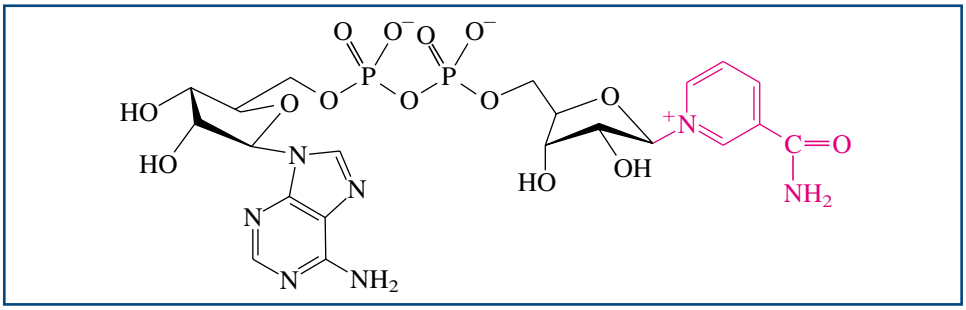
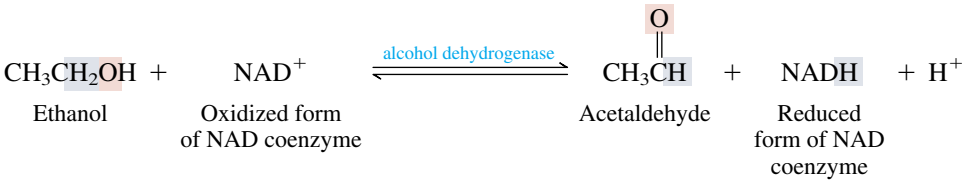
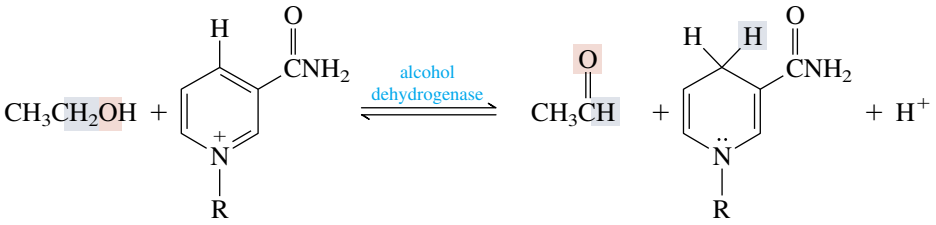


FIGURE 15.3 Structure of NAD^+, the oxidized form of the coenzyme nicotinamide adenine dinucleotide.

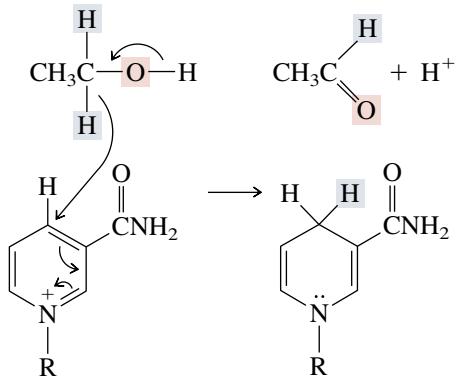
coenzyme as NAD^+ and its reduced form as NADH. More completely, the chemical equation for the biological oxidation of ethanol may be written:



The structure of the oxidized form of nicotinamide adenine dinucleotide is shown in Figure 15.3. The only portion of the coenzyme that undergoes chemical change in the reaction is the substituted pyridine ring of the nicotinamide unit (shown in red in Figure 15.3). If the remainder of the coenzyme molecule is represented by R, its role as an oxidizing agent is shown in the equation



According to one mechanistic interpretation, a hydrogen with a pair of electrons is transferred from ethanol to NAD^+, forming acetaldehyde and converting the positively charged pyridinium ring to a dihydropyridine:

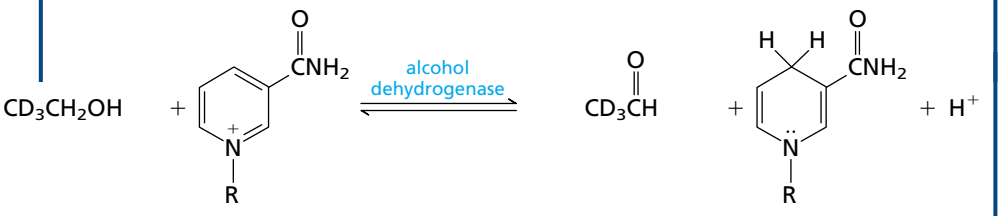


The pyridinium ring of NAD^+ serves as an acceptor of hydride (a proton plus two electrons) in this picture of its role in biological oxidation.

PROBLEM 15.12 The mechanism of enzymatic oxidation has been studied by isotopic labeling with the aid of deuterated derivatives of ethanol. Specify the number of deuterium atoms that you would expect to find attached to the dihydropyridine ring of the reduced form of the nicotinamide adenine dinucleotide coenzyme following enzymatic oxidation of each of the alcohols given:

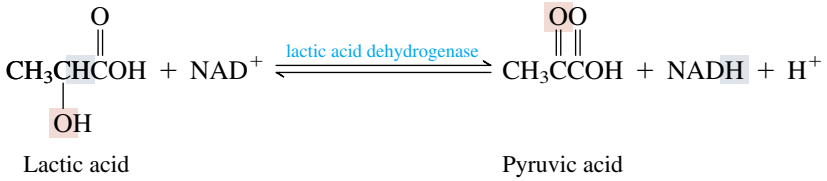
(a) CD_3CH_2OH (b) CH_3CD_2OH (c) CH_3CH_2OD

SAMPLE SOLUTION According to the proposed mechanism for biological oxidation of ethanol, the hydrogen that is transferred to the coenzyme comes from C-1 of ethanol. Therefore, the dihydropyridine ring will bear no deuterium atoms when CD_3CH_2OH is oxidized, because all the deuterium atoms of the alcohol are attached to C-2.



The reverse reaction also occurs in living systems; NADH reduces acetaldehyde to ethanol in the presence of alcohol dehydrogenase. In this process, NADH serves as a hydride donor and is oxidized to NAD^+ while acetaldehyde is reduced.

The NAD^+–NADH coenzyme system is involved in a large number of biological oxidation–reductions. Another reaction similar to the ethanol–acetaldehyde conversion is the oxidation of lactic acid to pyruvic acid by NAD^+ and the enzyme *lactic acid dehydrogenase:*

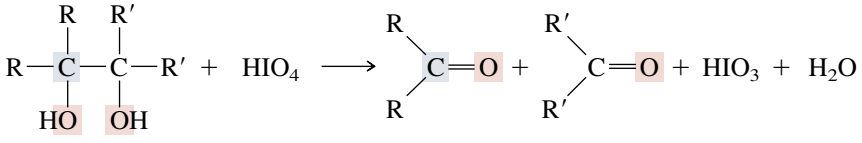


We shall encounter other biological processes in which the $NAD^+ \rightleftharpoons$ NADH interconversion plays a prominent role in biological oxidation–reduction.

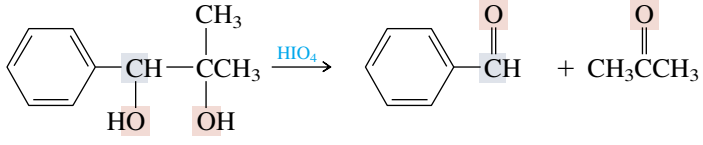
15.12 OXIDATIVE CLEAVAGE OF VICINAL DIOLS

A reaction characteristic of vicinal diols is their oxidative cleavage on treatment with periodic acid (HIO_4). The carbon–carbon bond of the vicinal diol unit is broken and two carbonyl groups result. Periodic acid is reduced to iodic acid (HIO_3).

What is the oxidation state of iodine in HIO_4? In HIO_3?



Can you remember what reaction of an alkene would give the same products as the periodic acid cleavage shown here?

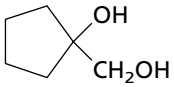


This reaction occurs only when the hydroxyl groups are on adjacent carbons.

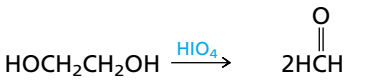
PROBLEM 15.13 Predict the products formed on oxidation of each of the following with periodic acid:

(a) $HOCH_2CH_2OH$

(b) $(CH_3)_2CHCH_2\underset{\displaystyle HO}{\underset{|}{C}}H\underset{\displaystyle OH}{\underset{|}{C}}HCH_2C_6H_5$

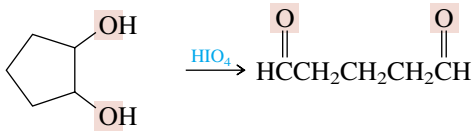
(c) 

SAMPLE SOLUTION (a) The carbon–carbon bond of 1,2-ethanediol is cleaved by periodic acid to give two molecules of formaldehyde:



1,2-Ethanediol Formaldehyde

Cyclic diols give dicarbonyl compounds. The reactions are faster when the hydroxyl groups are cis than when they are trans, but both stereoisomers are oxidized by periodic acid.



1,2-Cyclopentanediol (either stereoisomer) Pentanedial

Periodic acid cleavage of vicinal diols is often used for analytical purposes as an aid in structure determination. By identifying the carbonyl compounds produced, the constitution of the starting diol may be deduced. This technique finds its widest application with carbohydrates and will be discussed more fully in Chapter 25.

15.13 PREPARATION OF THIOLS

Sulfur lies just below oxygen in the periodic table, and many oxygen-containing organic compounds have sulfur analogs. The sulfur analogs of alcohols (ROH) are **thiols (RSH).** Thiols are given substitutive IUPAC names by appending the suffix *-thiol* to the name of the corresponding alkane, numbering the chain in the direction that gives the lower locant to the carbon that bears the —SH group. As with diols (Section 15.5), the final *-e* of the alkane name is retained. When the —SH group is named as a substituent, it is called a *mercapto* group. It is also often referred to as a *sulfhydryl* group, but this is a generic term, not used in systematic nomenclature.

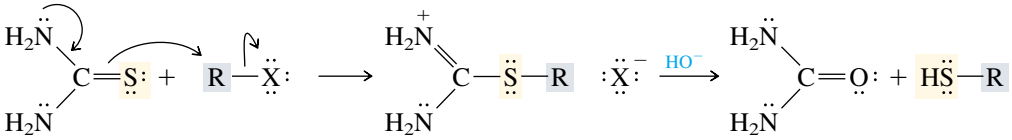
Thiols have a marked tendency to bond to mercury, and the word *mercaptan* comes from the Latin *mercurium captans,* which means "seizing mercury." The drug *dimercaprol* is used to treat mercury and lead poisoning; it is 2,3-dimercapto-1-propanol.

$(CH_3)_2CHCH_2CH_2SH$	$HSCH_2CH_2OH$	$HSCH_2CH_2CH_2SH$
3-Methyl-1-butanethiol	2-Mercaptoethanol	1,3-Propanedithiol

At one time thiols were named *mercaptans.* Thus, CH_3CH_2SH was called "ethyl mercaptan" according to this system. This nomenclature was abandoned beginning with

the 1965 revision of the IUPAC rules but is still sometimes encountered, especially in the older literature.

The preparation of thiols involves nucleophilic substitution of the S_N2 type on alkyl halides and uses the reagent *thiourea* as the source of sulfur. Reaction of the alkyl halide with thiourea gives a compound known as an *isothiouronium salt* in the first step. Hydrolysis of the isothiouronium salt in base gives the desired thiol (along with urea):



Both steps can be carried out sequentially without isolating the isothiouronium salt.

$$CH_3(CH_2)_4CH_2Br \xrightarrow[2.\ NaOH]{1.\ (H_2N)_2C{=}S} CH_3(CH_2)_4CH_2SH$$

1-Bromohexane — 1-Hexanethiol (84%)

PROBLEM 15.14 Outline a synthesis of 1-hexanethiol from 1-hexanol.

15.14 PROPERTIES OF THIOLS

A historical account of the analysis of skunk scent and a modern determination of its composition appear in the March 1978 issue of the *Journal of Chemical Education.*

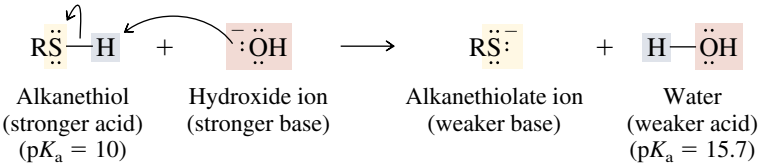
When one encounters a thiol for the first time, especially a low-molecular-weight thiol, its most obvious property is its foul odor. Ethanethiol is added to natural gas so that leaks can be detected without special equipment—your nose is so sensitive that it can detect less than one part of ethanethiol in 10,000,000,000 parts of air! The odor of thiols weakens with the number of carbons, because both the volatility and the sulfur content decrease. 1-Dodecanethiol, for example, has only a faint odor.

PROBLEM 15.15 The main components of a skunk's scent fluid are 3-methyl-1-butanethiol and *cis*- and *trans*-2-butene-1-thiol. Write structural formulas for each of these compounds.

Compare the boiling points of H_2S (−60°C) and H_2O (100°C).

The S—H bond is less polar than the O—H bond, and hydrogen bonding in thiols is much weaker than that of alcohols. Thus, methanethiol (CH_3SH) is a gas at room temperature (bp 6°C), and methanol (CH_3OH) is a liquid (bp 65°C).

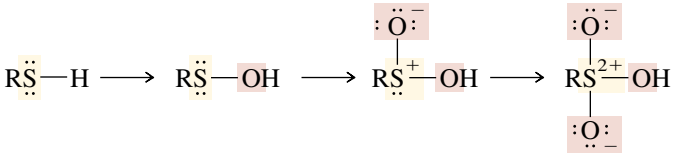
Thiols are weak acids, but are far more acidic than alcohols. We have seen that most alcohols have K_a values in the range 10^{-16} to 10^{-19} (pK_a = 16 to 19). The corresponding values for thiols are about $K_a = 10^{-10}$ (pK_a = 10). The significance of this difference is that a thiol can be quantitatively converted to its conjugate base (RS^-), called an **alkanethiolate** anion, by hydroxide:



Thiols, therefore, dissolve in aqueous media when the pH is greater than 10.

Another difference between thiols and alcohols concerns their oxidation. We have seen earlier in this chapter that oxidation of alcohols gives compounds having carbonyl

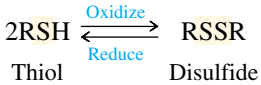
groups. Analogous oxidation of thiols to compounds with C═S functions does *not* occur. Only sulfur is oxidized, not carbon, and compounds containing sulfur in various oxidation states are possible. These include a series of acids classified as *sulfenic, sulfinic,* and *sulfonic* according to the number of oxygens attached to sulfur.



Thiol Sulfenic acid Sulfinic acid Sulfonic acid

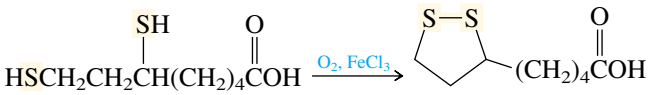
Of these the most important are the sulfonic acids. In general, however, sulfonic acids are not prepared by oxidation of thiols. Arenesulfonic acids ($ArSO_3H$), for example, are prepared by sulfonation of arenes (Section 12.4).

One of the most important oxidative processes, especially from a biochemical perspective, is the oxidation of thiols to **disulfides.**



Thiol Disulfide

Although a variety of oxidizing agents are available for this transformation, it occurs so readily that thiols are slowly converted to disulfides by the oxygen in the air. Dithiols give cyclic disulfides by intramolecular sulfur–sulfur bond formation. An example of a cyclic disulfide is the coenzyme α-*lipoic acid.* The last step in the laboratory synthesis of α-lipoic acid is an iron(III)-catalyzed oxidation of the dithiol shown:



6,8-Dimercaptooctanoic acid α-Lipoic acid (78%)

Rapid and reversible making and breaking of the sulfur–sulfur bond is essential to the biological function of α-lipoic acid.

15.15 SPECTROSCOPIC ANALYSIS OF ALCOHOLS

Infrared: We discussed the most characteristic features of the infrared spectra of alcohols earlier (Section 13.19). The O—H stretching vibration is especially easy to identify, appearing in the 3200–3650 cm^{-1} region. As the infrared spectrum of cyclohexanol, presented in Figure 15.4, demonstrates, this peak is seen as a broad absorption of moderate intensity. The C—O bond stretching of alcohols gives rise to a moderate to strong absorbance between 1025 and 1200 cm^{-1}. It appears at 1070 cm^{-1} in cyclohexanol, a typical secondary alcohol, but is shifted to slightly higher energy in tertiary alcohols and slightly lower energy in primary alcohols.

^{1}H NMR: The most helpful signals in the NMR spectrum of alcohols result from the hydroxyl proton and the proton in the H—C—O unit of primary and secondary alcohols.

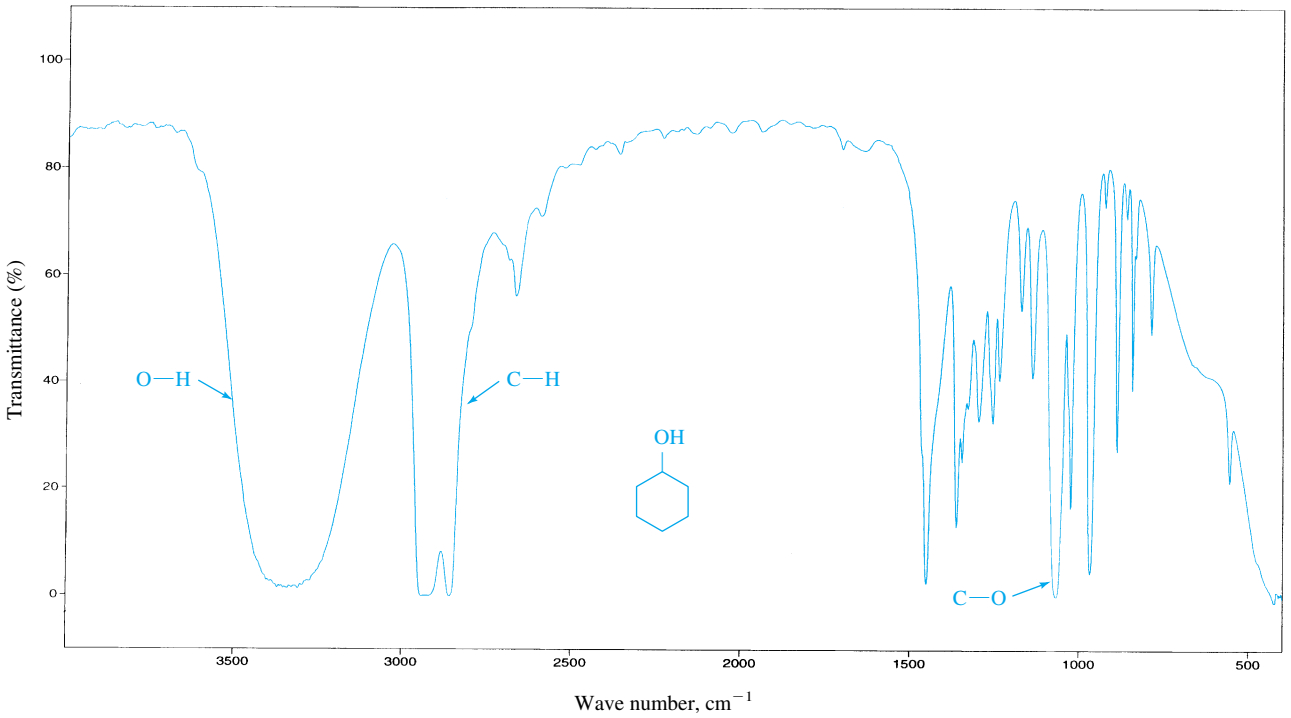
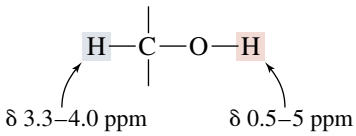


FIGURE 15.4 The infrared spectrum of cyclohexanol.



The chemical shift of the hydroxyl proton signal is variable, depending on solvent, temperature, and concentration. Its precise position is not particularly significant in structure determination. Because the signals due to hydroxyl protons are not usually split by other protons in the molecule and are often rather broad, they are often fairly easy to identify. To illustrate, Figure 15.5 shows the ^{1}H NMR spectrum of 2-phenylethanol, in which the hydroxyl proton signal appears as a singlet at δ 4.5 ppm. Of the two triplets in this spectrum, the one at lower field strength (δ 4.0 ppm) corresponds to the protons of the CH_2O unit. The higher-field strength triplet at δ 3.1 ppm arises from the benzylic CH_2 group. The assignment of a particular signal to the hydroxyl proton can be confirmed by adding D_2O. The hydroxyl proton is replaced by deuterium, and its ^{1}H NMR signal disappears.

^{13}C NMR: The electronegative oxygen of an alcohol decreases the shielding of the carbon to which it is attached. The chemical shift for the carbon of the C—OH unit is 60–75 ppm for most alcohols. Compared with an attached H, an attached OH causes a downfield shift of 35–50 ppm in the carbon signal.

$CH_3CH_2CH_2CH_3$	$CH_3CH_2CH_2CH_2OH$
δ 13.0 ppm	δ 61.4 ppm
Butane	1-Butanol

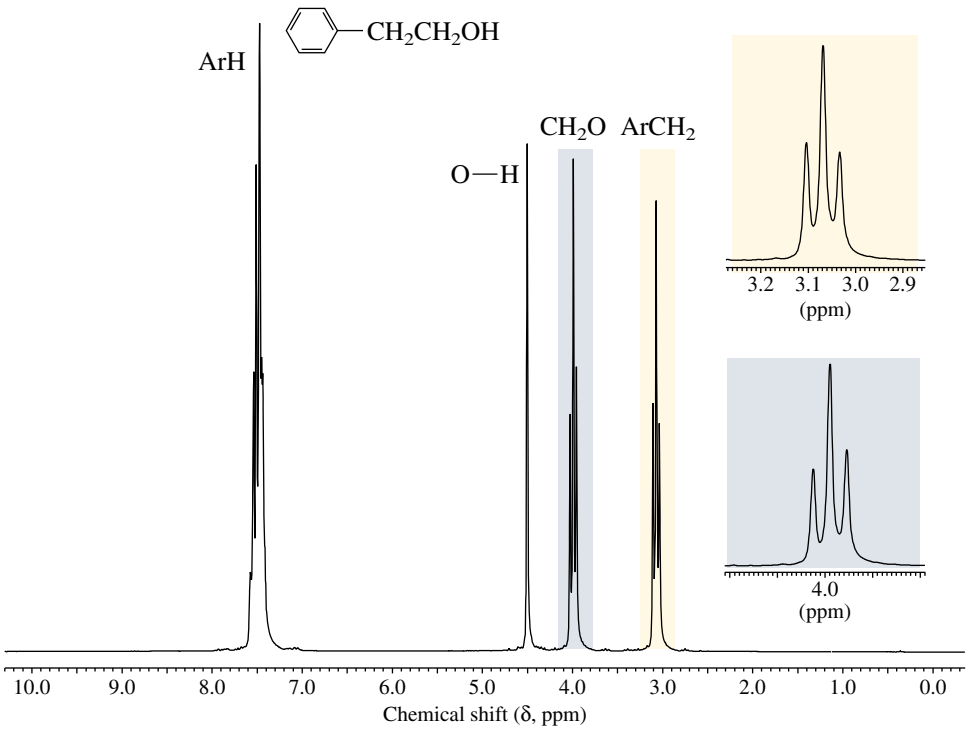
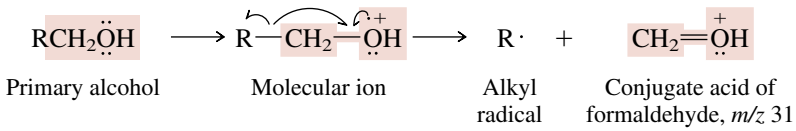


FIGURE 15.5 The 200-MHz ^{1}H NMR spectrum of 2-phenylethanol ($C_6H_5CH_2CH_2OH$).

UV-VIS: Unless there are other chromophores in the molecule, alcohols are transparent above about 200 nm; λ_{max} for methanol, for example, is 177 nm.

Mass Spectrometry: The molecular ion peak is usually quite small in the mass spectrum of an alcohol. A peak corresponding to loss of water is often evident. Alcohols also fragment readily by a pathway in which the molecular ion loses an alkyl group from the hydroxyl-bearing carbon to form a stable cation. Thus, the mass spectra of most primary alcohols exhibit a prominent peak at *m/z* 31.



PROBLEM 15.16 Three of the most intense peaks in the mass spectrum of 2-methyl-2-butanol appear at *m/z* 59, 70, and 73. Explain the origin of these peaks.

15.17 SUMMARY

Section 15.1 Functional group interconversions involving alcohols either as reactants or as products are the focus of this chapter. Alcohols are commonplace natural products. Table 15.1 summarizes reactions discussed in earlier sections that can be used to prepare alcohols.

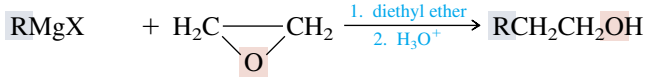
Section 15.2 Alcohols can be prepared from carbonyl compounds by reduction of aldehydes and ketones. See Table 15.3.

TABLE 15.3 Preparation of Alcohols by Reduction of Carbonyl Functional Groups

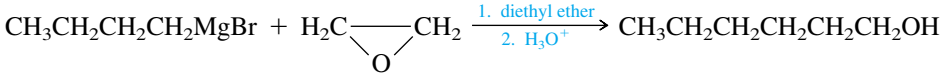
Carbonyl compound	Product of reduction of carbonyl compound by specified reducing agent: Lithium aluminum hydride ($LiAlH_4$)	Sodium borohydride ($NaBH_4$)	Hydrogen (in the presence of a catalyst)
Aldehyde RCH(=O) (Section 15.2)	Primary alcohol RCH_2OH	Primary alcohol RCH_2OH	Primary alcohol RCH_2OH
Ketone RC(=O)R′ (Section 15.2)	Secondary alcohol RCHR′(OH)	Secondary alcohol RCHR′(OH)	Secondary alcohol RCHR′(OH)
Carboxylic acid RC(=O)OH (Section 15.3)	Primary alcohol RCH_2OH	Not reduced	Not reduced
Carboxylic ester RC(=O)OR′ (Section 15.3)	Primary alcohol RCH_2OH plus R′OH	Reduced too slowly to be of practical value	Requires special catalyst, high pressures and temperatures

Section 15.3 Alcohols can be prepared from carbonyl compounds by reduction of carboxylic acids and esters. See Table 15.3.

Section 15.4 Grignard and organolithium reagents react with ethylene oxide to give primary alcohols.

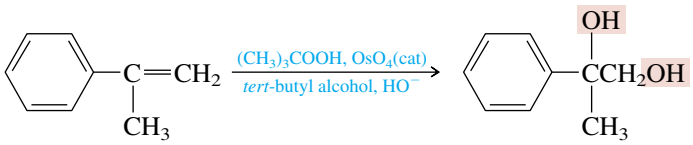


Grignard reagent — Ethylene oxide — Primary alcohol



Butylmagnesium bromide — Ethylene oxide — 1-Hexanol (60–62%)

Section 15.5 Osmium tetraoxide is a key reactant in the conversion of alkenes to vicinal diols.



2-Phenylpropene — 2-Phenyl-1,2-propanediol (71%)

The reaction is called **hydroxylation** and proceeds by syn addition to the double bond.

Section 15.6 Table 15.2 summarizes reactions of alcohols that were introduced in earlier chapters.

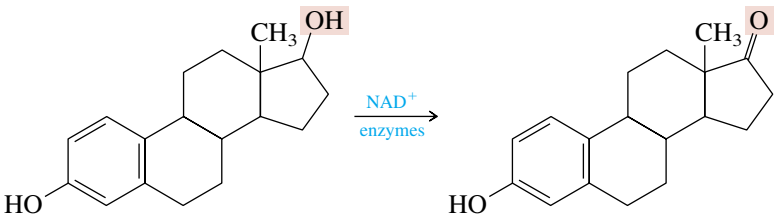
Section 15.7 See Table 15.4

Section 15.8 See Table 15.4

Section 15.9 See Table 15.4

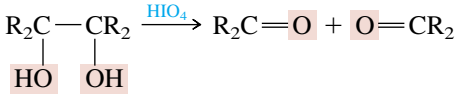
Section 15.10 See Table 15.5

Section 15.11 Oxidation of alcohols to aldehydes and ketones is a common biological reaction. Most require a coenzyme such as the oxidized form of nicotinamide adenine dinucleotide (NAD^+).

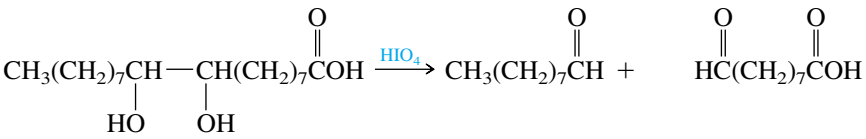


Estradiol Estrone

Section 15.12 Periodic acid cleaves vicinal diols; two aldehydes, two ketones, or an aldehyde and a ketone are formed.

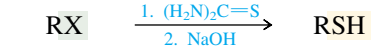


Diol Two carbonyl-containing compounds

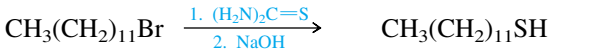


9,10-Dihydroxyoctadecanoic acid Nonanal (89%) 9-Oxononanoic acid (76%)

Section 15.13 **Thiols,** compounds of the type RSH, are prepared by the reaction of alkyl halides with thiourea. An intermediate isothiouronium salt is formed, which is then subjected to basic hydrolysis.



Alkyl halide Alkanethiol



1-Bromododecane 1-Dodecanethiol (79–83%)

Section 15.14 Thiols are more acidic than alcohols and are readily deprotonated by reaction with aqueous base. Thiols can be oxidized to disulfides (RSSR), sulfenic acids (RSOH), sulfinic acids (RSO_2H), and sulfonic acids (RSO_3H).

TABLE 15.4 Summary of Reactions of Alcohols Presented in This Chapter

Reaction (section) and comments	General equation and specific example
Conversion to dialkyl ethers (Section 15.7) On being heated in the presence of an acid catalyst, two molecules of a primary alcohol combine to form an ether and water. Diols can undergo an intramolecular condensation if a five-membered or six-membered cyclic ether results.	$2RCH_2OH \xrightarrow[\text{heat}]{H^+} RCH_2OCH_2R + H_2O$ Alcohol → Dialkyl ether + Water $2(CH_3)_2CHCH_2CH_2OH \xrightarrow[150^\circ C]{H_2SO_4} (CH_3)_2CHCH_2CH_2OCH_2CH_2CH(CH_3)_2$ 3-Methyl-1-butanol → Di-(3-methylbutyl) ether (27%)
Fischer esterification (Section 15.8) Alcohols and carboxylic acids yield an ester and water in the presence of an acid catalyst. The reaction is an equilibrium process that can be driven to completion by using either the alcohol or the acid in excess or by removing the water as it is formed.	$ROH + R'COH \xrightarrow{H^+} R'COR + H_2O$ Alcohol + Carboxylic acid → Ester + Water $CH_3CH_2CH_2CH_2CH_2OH + CH_3COH \xrightarrow{H^+} CH_3COCH_2CH_2CH_2CH_2CH_3$ 1-Pentanol + Acetic acid → Pentyl acetate (71%)
Esterification with acyl chlorides (Section 15.8) Acyl chlorides react with alcohols to give esters. The reaction is usually carried out in the presence of pyridine.	$ROH + R'CCl \longrightarrow R'COR + HCl$ Alcohol + Acyl chloride → Ester + Hydrogen chloride $(CH_3)_3COH + CH_3CCl \xrightarrow{\text{pyridine}} CH_3COC(CH_3)_3$ *tert*-Butyl alcohol + Acetyl chloride → *tert*-Butyl acetate (62%)
Esterification with carboxylic acid anhydrides (Section 15.8) Carboxylic acid anhydrides react with alcohols to form esters in the same way that acyl chlorides do.	$ROH + R'COCR' \longrightarrow R'COR + R'COH$ Alcohol + Carboxylic acid anhydride → Ester + Carboxylic acid *m*-Methoxybenzyl alcohol + Acetic anhydride → *m*-Methoxybenzyl acetate (99%)
Formation of esters of inorganic acids (Section 15.9) Alkyl nitrates, dialkyl sulfates, trialkyl phosphites, and trialkyl phosphates are examples of alkyl esters of inorganic acids. In some cases, these compounds are prepared by the direct reaction of an alcohol and the inorganic acid.	$ROH + HONO_2 \xrightarrow{H^+} RONO_2 + H_2O$ Alcohol + Nitric acid → Alkyl nitrate + Water Cyclopentanol → Cyclopentyl nitrate (69%)

TABLE 15.5 Oxidation of Alcohols

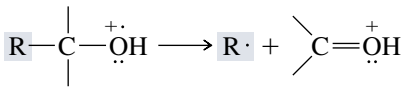
Class of alcohol	Desired product	Suitable oxidizing agent(s)
Primary, RCH_2OH	Aldehyde RCH (O double-bonded)	PCC* PDC
Primary, RCH_2OH	Carboxylic acid $RCOH$ (O double-bonded)	$Na_2Cr_2O_7$, H_2SO_4, H_2O H_2CrO_4
Secondary, $RCHR'$ (OH)	Ketone RCR' (O double-bonded)	PCC PDC $Na_2Cr_2O_7$, H_2SO_4, H_2O H_2CrO_4

*PCC is pyridinium chlorochromate; PDC is pyridinium dichromate. Both are used in dichloromethane.

Section 15.15 The hydroxyl group of an alcohol has its O—H and C—O stretching vibrations at 3200–3650 and 1025–1200 cm^{-1}, respectively.

The chemical shift of the proton of an O—H group is variable (δ 1–5 ppm) and depends on concentration, temperature, and solvent. Oxygen deshields both the proton and the carbon of an H—C—O unit. Typical NMR chemical shifts are δ 3.3–4.0 ppm for ^1H and 60–75 ppm for ^{13}C of H—C—O.

The most intense peaks in the mass spectrum of an alcohol correspond to the ion formed according to carbon–carbon cleavage of the type shown:



PROBLEMS

15.17 Write chemical equations, showing all necessary reagents, for the preparation of 1-butanol by each of the following methods:

(a) Hydroboration–oxidation of an alkene

(b) Use of a Grignard reagent

(c) Use of a Grignard reagent in a way different from part (b)

(d) Reduction of a carboxylic acid

(e) Reduction of a methyl ester

(f) Reduction of a butyl ester

(g) Hydrogenation of an aldehyde

(h) Reduction with sodium borohydride

15.18 Write chemical equations, showing all necessary reagents, for the preparation of 2-butanol by each of the following methods:

(a) Hydroboration–oxidation of an alkene

(b) Use of a Grignard reagent

(c) Use of a Grignard reagent different from that used in part (b)

(d–f) Three different methods for reducing a ketone

15.19 Write chemical equations, showing all necessary reagents, for the preparation of *tert*-butyl alcohol by:

(a) Reaction of a Grignard reagent with a ketone

(b) Reaction of a Grignard reagent with an ester of the type $RCOCH_3$

15.20 Which of the isomeric $C_5H_{12}O$ alcohols can be prepared by lithium aluminum hydride reduction of:

(a) An aldehyde

(b) A ketone

(c) A carboxylic acid

(d) An ester of the type $RCOCH_3$

15.21 Evaluate the feasibility of the route

$$RH \xrightarrow[\text{light or heat}]{Br_2} RBr \xrightarrow{KOH} ROH$$

as a method for preparing

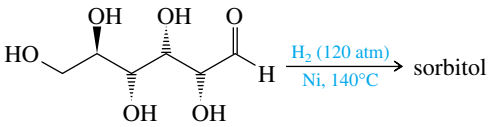
(a) 1-Butanol from butane

(b) 2-Methyl-2-propanol from 2-methylpropane

(c) Benzyl alcohol from toluene

(d) (*R*)-1-Phenylethanol from ethylbenzene

15.22 Sorbitol is a sweetener often substituted for cane sugar, since it is better tolerated by diabetics. It is also an intermediate in the commercial synthesis of vitamin C. Sorbitol is prepared by high-pressure hydrogenation of glucose over a nickel catalyst. What is the structure (including stereochemistry) of sorbitol?



Glucose

15.23 Write equations showing how 1-phenylethanol ($C_6H_5CHCH_3$, OH) could be prepared from each of the following starting materials:

(a) Bromobenzene

(b) Benzaldehyde

(c) Benzyl alcohol

(d) Acetophenone

(e) Benzene

15.24 Write equations showing how 2-phenylethanol ($C_6H_5CH_2CH_2OH$) could be prepared from each of the following starting materials:

(a) Bromobenzene

(b) Styrene

(c) 2-Phenylethanal ($C_6H_5CH_2CHO$)

(d) Ethyl 2-phenylethanoate ($C_6H_5CH_2CO_2CH_2CH_3$)

(e) 2-Phenylethanoic acid ($C_6H_5CH_2CO_2H$)

15.25 Outline practical syntheses of each of the following compounds from alcohols containing no more than four carbon atoms and any necessary organic or inorganic reagents. In many cases the desired compound can be made from one prepared in an earlier part of the problem.

(a) 1-Butanethiol

(b) 1-Hexanol

(c) 2-Hexanol

(d) Hexanal, $CH_3CH_2CH_2CH_2CH_2CH{=}O$

(e) 2-Hexanone, $CH_3\overset{\overset{O}{\|}}{C}CH_2CH_2CH_2CH_3$

(f) Hexanoic acid, $CH_3(CH_2)_4CO_2H$

(g) Ethyl hexanoate, $CH_3(CH_2)_4\overset{\overset{O}{\|}}{C}OCH_2CH_3$

(h) 2-Methyl-1,2-propanediol

(i) 2,2-Dimethylpropanal, $(CH_3)_3\overset{\overset{O}{\|}}{C}CH$

15.26 Outline practical syntheses of each of the following compounds from benzene, alcohols, and any necessary organic or inorganic reagents:

(a) 1-Chloro-2-phenylethane

(b) 2-Methyl-1-phenyl-1-propanone, $C_6H_5\overset{\overset{O}{\|}}{C}CH(CH_3)_2$

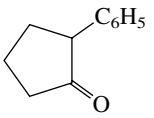
(c) Isobutylbenzene, $C_6H_5CH_2CH(CH_3)_2$

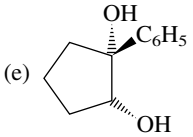
15.27 Show how each of the following compounds can be synthesized from cyclopentanol and any necessary organic or inorganic reagents. In many cases the desired compound can be made from one prepared in an earlier part of the problem.

(a) 1-Phenylcyclopentanol

(b) 1-Phenylcyclopentene

(c) *trans*-2-Phenylcyclopentanol

(d) 

(e) 

(f) $C_6H_5\overset{\overset{O}{\|}}{C}CH_2CH_2CH_2\overset{\overset{O}{\|}}{C}H$

(g) 1-Phenyl-1,5-pentanediol

15.28 Write the structure of the principal organic product formed in the reaction of 1-propanol with each of the following reagents:

(a) Sulfuric acid (catalytic amount), heat at 140°C

(b) Sulfuric acid (catalytic amount), heat at 200°C

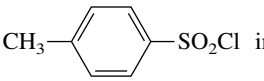
(c) Nitric acid (H_2SO_4 catalyst)

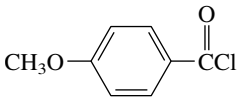
(d) Pyridinium chlorochromate (PCC) in dichloromethane

(e) Potassium dichromate ($K_2Cr_2O_7$) in aqueous sulfuric acid, heat

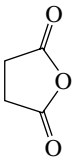
(f) Sodium amide ($NaNH_2$)

(g) Acetic acid ($CH_3\overset{\overset{O}{\|}}{C}OH$) in the presence of dissolved hydrogen chloride

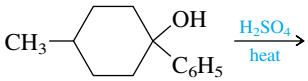
(h)  in the presence of pyridine

(i)  in the presence of pyridine

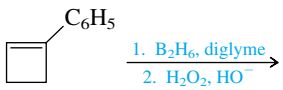
(j) $C_6H_5\overset{\overset{O}{\|}}{C}O\overset{\overset{O}{\|}}{C}C_6H_5$ in the presence of pyridine

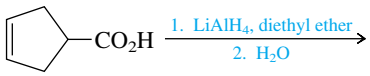
(k)  in the presence of pyridine

15.29 Each of the following reactions has been reported in the chemical literature. Predict the product in each case, showing stereochemistry where appropriate.

(a) 

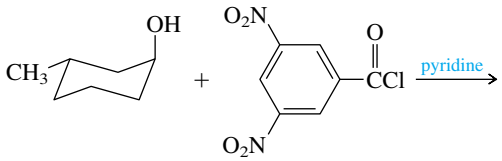
(b) $(CH_3)_2C{=}C(CH_3)_2 \xrightarrow[(CH_3)_3COH,\ HO^-]{(CH_3)_3COOH,\ OsO_4(cat)}$

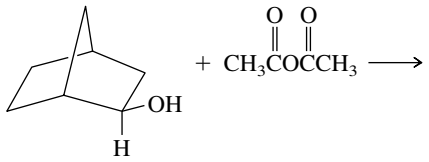
(c) 

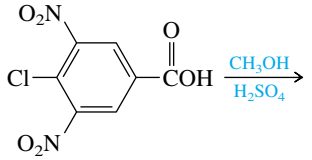
(d) 

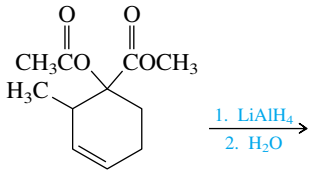
(e) $CH_3\underset{\underset{OH}{|}}{C}HC{\equiv}C(CH_2)_3CH_3 \xrightarrow[H_2SO_4,\ H_2O,\ acetone]{H_2CrO_4}$

(f) $CH_3\overset{\overset{O}{\|}}{C}CH_2CH{=}CHCH_2\overset{\overset{O}{\|}}{C}CH_3 \xrightarrow[2.\ H_2O]{1.\ LiAlH_4,\ diethyl\ ether}$

(g) 

(h) 

(i) 

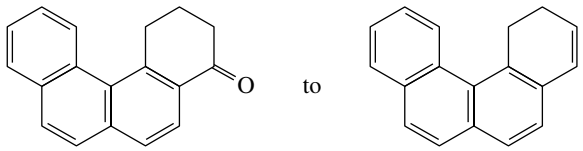
(j) 

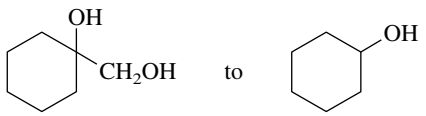
(k) Product of part (j) $\xrightarrow[CH_3OH,\ H_2O]{HIO_4}$

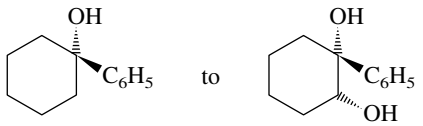
15.30 On heating 1,2,4-butanetriol in the presence of an acid catalyst, a cyclic ether of molecular formula $C_4H_8O_2$ was obtained in 81–88% yield. Suggest a reasonable structure for this product.

15.31 Give the Cahn–Ingold–Prelog *R* and *S* descriptors for the diol(s) formed from *cis*-2-pentene and *trans*-2-pentene on treatment with the osmium tetraoxide/*tert*-butyl hydroperoxide reagent.

15.32 Suggest reaction sequences and reagents suitable for carrying out each of the following conversions. Two synthetic operations are required in each case.

(a) 

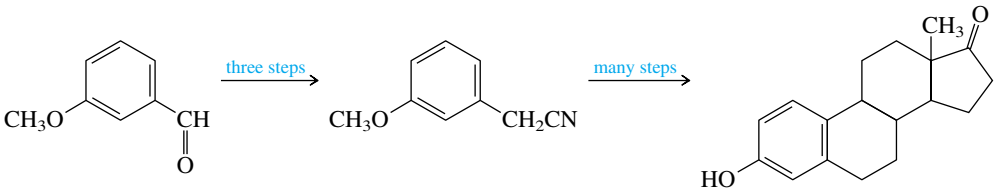
(b) 

(c) 

15.35 (a) The cis isomer of 3-hexen-1-ol ($CH_3CH_2CH{=}CHCH_2CH_2OH$) has the characteristic odor of green leaves and grass. Suggest a synthesis for this compound from acetylene and any necessary organic or inorganic reagents.

(b) One of the compounds responsible for the characteristic odor of ripe tomatoes is the cis isomer of $CH_3CH_2CH{=}CHCH_2CH{=}O$. How could you prepare this compound?

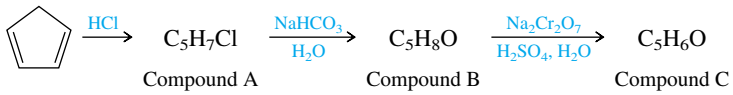
15.36 R. B. Woodward was one of the leading organic chemists of the middle part of the twentieth century. Known primarily for his achievements in the synthesis of complex natural products, he was awarded the Nobel Prize in chemistry in 1965. He entered Massachusetts Institute of Technology as a 16-year-old freshman in 1933 and four years later was awarded the Ph.D. While a student there he carried out a synthesis of *estrone,* a female sex hormone. The early stages of Woodward's estrone synthesis required the conversion of *m*-methoxybenzaldehyde to *m*-methoxybenzyl cyanide, which was accomplished in three steps:



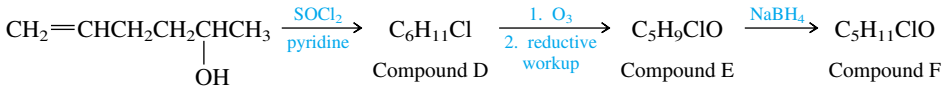
Estrone

Suggest a reasonable three-step sequence, showing all necessary reagents, for the preparation of *m*-methoxybenzyl cyanide from m-methoxybenzaldehyde.

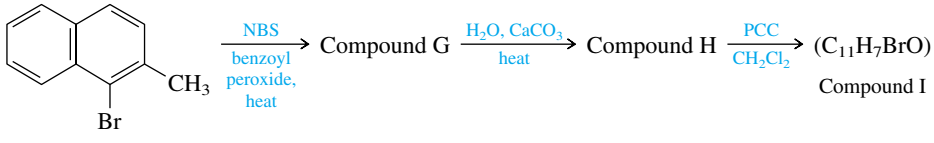
15.37 Complete the following series of equations by writing structural formulas for compounds A through I:

(a) 

Compound A Compound B Compound C

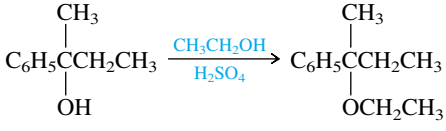
(b) 

Compound D Compound E Compound F

(c) 

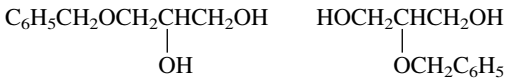
Compound I

15.38 When 2-phenyl-2-butanol is allowed to stand in ethanol containing a few drops of sulfuric acid, the following ether is formed:



Suggest a reasonable mechanism for this reaction based on the observation that the ether produced from optically active alcohol is racemic, and that alkenes can be shown not to be intermediates in the reaction.

15.39 Suggest a chemical test that would permit you to distinguish between the two glycerol monobenzyl ethers shown.

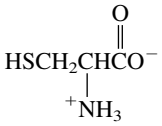


1-*O*-Benzylglycerol

2-*O*-Benzylglycerol

15.40 Choose the correct enantiomer of 2-butanol that would permit you to prepare (*R*)-2-butanethiol by way of a *p*-toluenesulfonate ester.

15.41 The amino acid *cysteine* has the structure shown:



Cysteine

(a) A second sulfur-containing amino acid called *cystine* ($C_6H_{12}N_2O_4S_2$) is formed when cysteine undergoes biological oxidation. Suggest a reasonable structure for cystine.

(b) Another metabolic pathway converts cysteine to *cysteine sulfinic acid* ($C_3H_7NO_4S$), then to *cysteic acid* ($C_3H_7NO_5S$). What are the structures of these two compounds?

15.42 A diol ($C_8H_{18}O_2$) does not react with periodic acid. Its ^{1}H NMR spectrum contains three singlets at δ 1.2 (12 protons), 1.6 (4 protons), and 2.0 ppm (2 protons). What is the structure of this diol?

15.43 Identify compound A ($C_8H_{10}O$) on the basis of its ^{1}H NMR spectrum (Figure 15.6). The broad peak at δ 2.1 ppm disappears when D_2O is added.

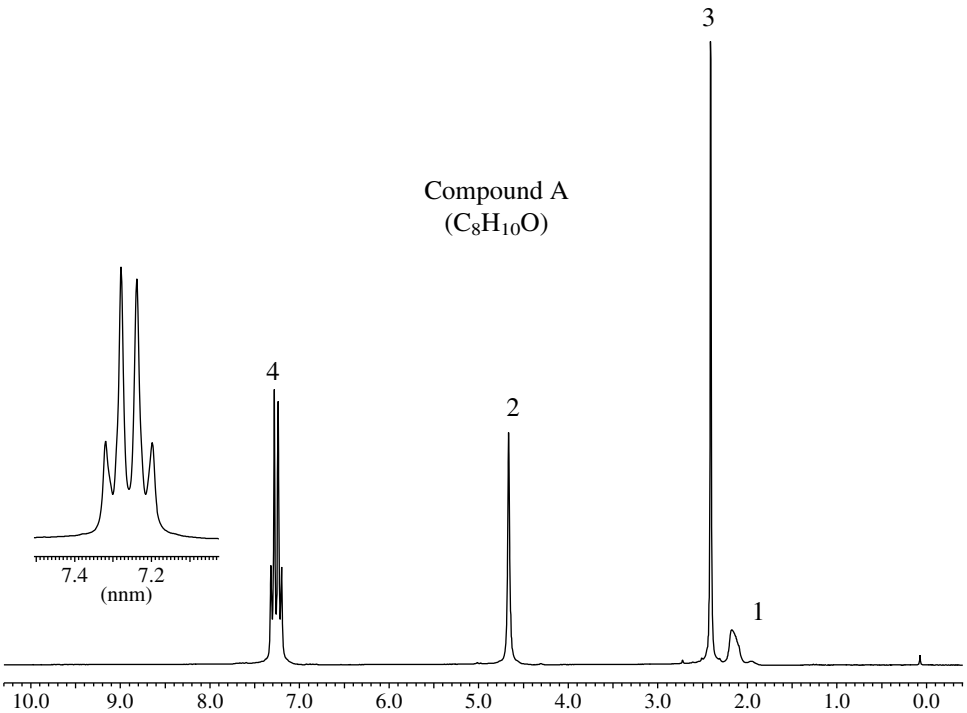


FIGURE 15.6 The 200-MHz ^{1}H NMR spectrum of compound A ($C_8H_{10}O$) (Problem 15.43).

15.44 Identify each of the following ($C_4H_{10}O$) isomers on the basis of their ^{13}C NMR spectra:

(a) δ 31.2 ppm: CH_3
δ 68.9 ppm: C

(b) δ 10.0 ppm: CH_3
δ 22.7 ppm: CH_3
δ 32.0 ppm: CH_2
δ 69.2 ppm: CH

(c) δ 18.9 ppm: CH_3, area 2
δ 30.8 ppm: CH, area 1
δ 69.4 ppm: CH_2, area 1

15.45 A compound $C_3H_7ClO_2$ exhibited three peaks in its ^{13}C NMR spectrum at δ 46.8 (CH_2), δ 63.5 (CH_2), and δ 72.0 ppm (CH). What is the structure of this compound?

15.46 A compound $C_6H_{14}O$ has the ^{13}C NMR spectrum shown in Figure 15.7. Its mass spectrum has a prominent peak at *m/z* 31. Suggest a reasonable structure for this compound.

15.47 Refer to *Learning By Modeling* and compare the properties calculated for CH_3CH_2OH and CH_3CH_2SH. Which has the greater dipole moment? Compare the charges at carbon and hydrogen in C—O—H versus C—S—H. Why does ethanol have a higher boiling point than ethanethiol?

15.48 Construct molecular models of the gauche and anti conformations of 1,2-ethanediol and explore the possibility of intramolecular hydrogen bond formation in each one.

15.49 Intramolecular hydrogen bonding is present in the chiral diastereomer of 2,2,5,5-tetramethylhexane-3,4-diol, but absent in the meso diastereomer. Construct molecular models of each, and suggest a reason for the difference between the two.

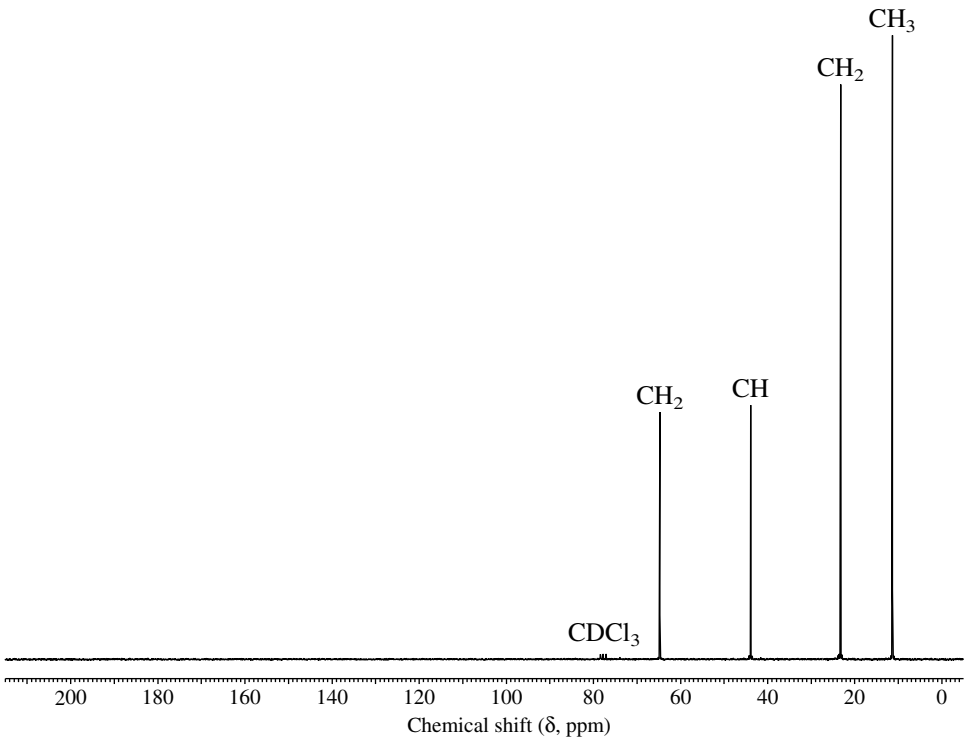


FIGURE 15.7 The ^{13}C NMR spectrum of the compound $C_6H_{14}O$ (Problem 15.46).