# 11

Competition occurs throughout nature. In chemistry, competition often occurs between alternative reaction pathways, such as in the substitution and elimination reactions of alkyl halides. *Cheryl Ann Quigley/Shutterstock*

Reactions of Alkyl Halides: Nucleophilic Substitutions and Eliminations

We saw in the preceding chapter that the carbon–halogen bond in an alkyl halide is polar and that the carbon atom is electron-poor. Thus, alkyl halides are electrophiles, and much of their chemistry involves polar reactions with nucleophiles and bases. Alkyl halides do one of two things when they react with a nucleophile/base, such as hydroxide ion: either they undergo *substitution* of the X group by the nucleophile, or they undergo *elimination* of HX to yield an alkene.
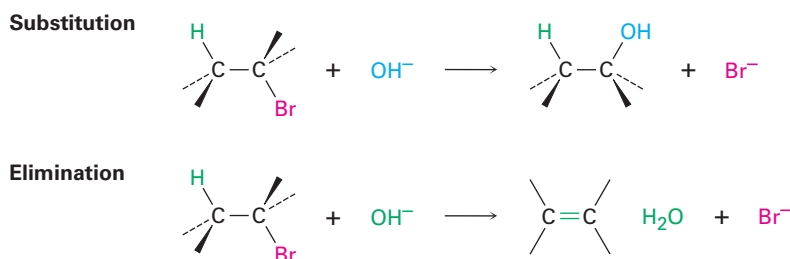

Why This Chapter?

Nucleophilic substitution and base-induced elimination are two of the most widely occurring and versatile reaction types in organic chemistry, both in the laboratory and in biological pathways. We'll look at them closely in this chapter to see how they occur, what their characteristics are, and how they can be used. We'll begin with substitution reactions.

11.1 The Discovery of Nucleophilic Substitution Reactions

The discovery of the nucleophilic substitution reaction of alkyl halides dates back to work carried out in 1896 by the German chemist Paul Walden. Walden

372

found that the pure enantiomeric (+)- and (−)-malic acids could be inter-converted through a series of simple substitution reactions. When Walden treated (−)-malic acid with PCl_5, he isolated (+)-chlorosuccinic acid. This, on treatment with wet Ag_2O, gave (+)-malic acid. Similarly, reaction of (+)-malic acid with PCl_5 gave (−)-chlorosuccinic acid, which was converted into (−)-malic acid when treated with wet Ag_2O. The full cycle of reactions is shown in **Figure 11.1**.
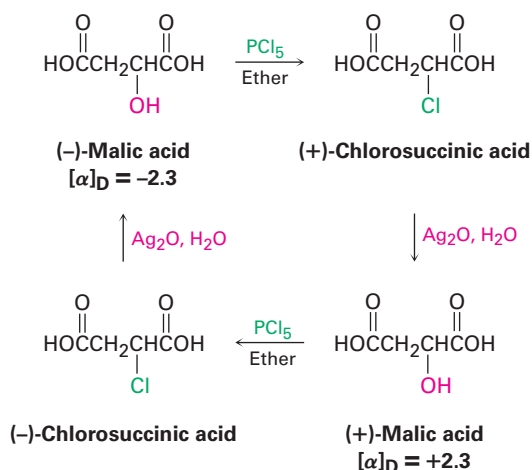
Figure 11.1 Walden's cycle of reactions interconverting (+)- and (−)-malic acids.

At the time, the results were astonishing. The eminent chemist Emil Fischer called Walden's discovery "the most remarkable observation made in the field of optical activity since the fundamental observations of Pasteur." Because (−)-malic acid was converted into (+)-malic acid, *some reactions in the cycle must have occurred with a change, or inversion, in configuration at the chirality center*. But which ones, and how? (Remember from **Section 5.5** that the direction of light rotation and the configuration of a chirality center aren't directly related. You can't tell by looking at the sign of rotation whether a change in configuration has occurred during a reaction.)

Today, we refer to the transformations taking place in Walden's cycle as **nucleophilic substitution reactions** because each step involves the substitution of one nucleophile (chloride ion, Cl^-, or hydroxide ion, HO^-) by another. Nucleophilic substitution reactions are one of the most common and versatile reaction types in organic chemistry.

$$R-X \ + \ Nu:^- \ \longrightarrow \ R-Nu \ + \ X:^-$$

Following the work of Walden, further investigations were undertaken during the 1920s and 1930s to clarify the mechanism of nucleophilic substitution reactions and to find out how inversions of configuration occur. Among the first series studied was one that interconverted the two enantiomers of 1-phenyl-2-propanol **(Figure 11.2).** Although this particular series of reactions involves nucleophilic substitution of an alkyl *p*-toluenesulfonate (called a *tosylate*) rather than an alkyl halide, exactly the same type of reaction is involved as that studied by Walden. For all practical purposes, the entire tosylate group acts as if it were simply a halogen substituent. (In fact, when you see a tosylate

substituent in a molecule, do a mental substitution and tell yourself that you're dealing with an alkyl halide.)

Figure 11.2 A Walden cycle interconverting (+) and (−) enantiomers of 1-phenyl-2-propanol. Chirality centers are marked by asterisks, and the bonds broken in each reaction are indicated by red wavy lines. The inversion of chirality occurs in step **2**, where acetate ion substitutes for tosylate ion.
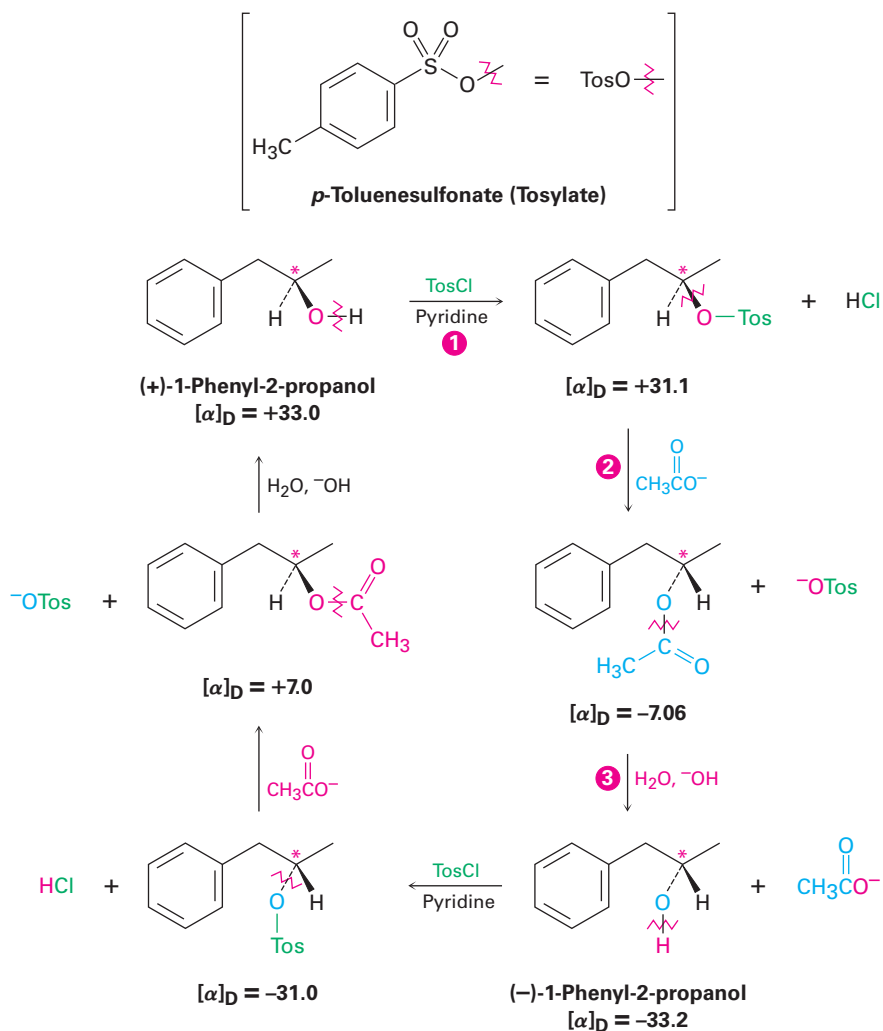
In the three-step reaction sequence shown in Figure 11.2, (+)-1-phenyl-2-propanol is interconverted with its (−) enantiomer, so at least one of the three steps must involve an inversion of configuration at the chirality center. Step 1, formation of a tosylate, occurs by breaking the O–H bond of the alcohol rather than the C–O bond to the chiral carbon, so the configuration around carbon is unchanged. Similarly, step 3, hydroxide-ion cleavage of the acetate, takes place without breaking the C–O bond at the chirality center. *The inversion of stereochemical configuration must therefore take place in step 2, the nucleophilic substitution of tosylate ion by acetate ion.*
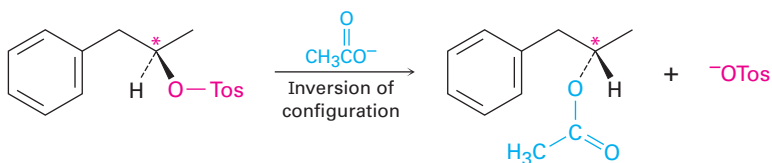
From this and nearly a dozen other series of similar reactions, workers concluded that the nucleophilic substitution reaction of a primary or secondary alkyl halide or tosylate always proceeds with inversion of configuration. (Tertiary alkyl halides and tosylates, as we'll see shortly, give different stereochemical results and react by a different mechanism.)

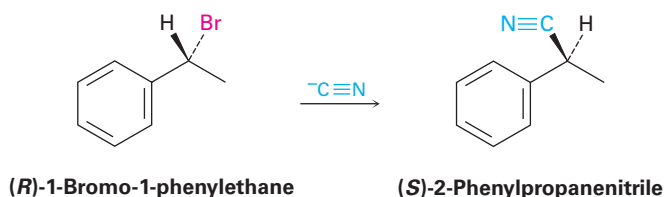| Predicting the Stereochemistry of a Nucleophilic Substitution Reaction	Worked Example 11.1

What product would you expect from a nucleophilic substitution reaction of (R)-1-bromo-1-phenylethane with cyanide ion, $^-C\equiv N$, as nucleophile? Show the stereochemistry of both reactant and product, assuming that inversion of configuration occurs.
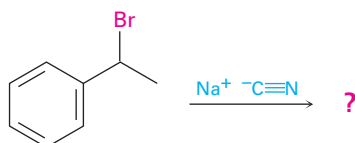
Strategy

Draw the R enantiomer of the reactant, and then change the configuration of the chirality center while replacing the $^-$Br with a $^-$CN.

Solution


(R)-1-Bromo-1-phenylethane   (S)-2-Phenylpropanenitrile

Problem 11.1

What product would you expect to obtain from a nucleophilic substitution reaction of (S)-2-bromohexane with acetate ion, $CH_3CO_2^-$? Assume that inversion of configuration occurs, and show the stereochemistry of both reactant and product.

11.2 The S$_N$2 Reaction

In every chemical reaction, there is a direct relationship between the rate at which the reaction occurs and the concentrations of the reactants. When we measure this relationship, we measure the **kinetics** of the reaction. For example, let's look at the kinetics of a simple nucleophilic substitution—the reaction of CH_3Br with OH^- to yield CH_3OH plus Br^-.
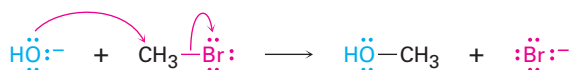
At a given temperature, solvent, and concentration of reactants, the substitution occurs at a certain rate. If we double the concentration of OH^-, the frequency of encounter between the reaction partners doubles and we find that the reaction rate also doubles. Similarly, if we double the concentration of

CH_3Br, the reaction rate again doubles. We call such a reaction, in which the rate is linearly dependent on the concentrations of two species, a **second-order reaction**. Mathematically, we can express this second-order dependence of the nucleophilic substitution reaction by setting up a *rate equation*. As either [RX] or [⁻OH] changes, the rate of the reaction changes proportionately.

$$\text{Reaction rate} = \text{Rate of disappearance of reactant}$$

$$= k \times [RX] \times [^-OH]$$

where

$[RX] = CH_3Br$ concentration in molarity

$[^-OH] = {}^-OH$ concentration in molarity

$k = $ A constant value (the rate constant)

A mechanism that accounts for both the inversion of configuration and the second-order kinetics that are observed with nucleophilic substitution reactions was suggested in 1937 by the British chemists E. D. Hughes and Christopher Ingold, who formulated what they called the **S_N2 reaction**—short for *substitution, nucleophilic, bimolecular*. (*Bimolecular* means that two molecules, nucleophile and alkyl halide, take part in the step whose kinetics are measured.)

The essential feature of the S_N2 mechanism is that it takes place in a single step without intermediates when the incoming nucleophile reacts with the alkyl halide or tosylate (the *substrate*) from a direction opposite the group that is displaced (the *leaving group*). As the nucleophile comes in on one side of the substrate and bonds to the carbon, the halide or tosylate departs from the other side, thereby inverting the stereochemical configuration. The process is shown in **Figure 11.3** for the reaction of (S)-2-bromobutane with HO⁻ to give (R)-2-butanol.
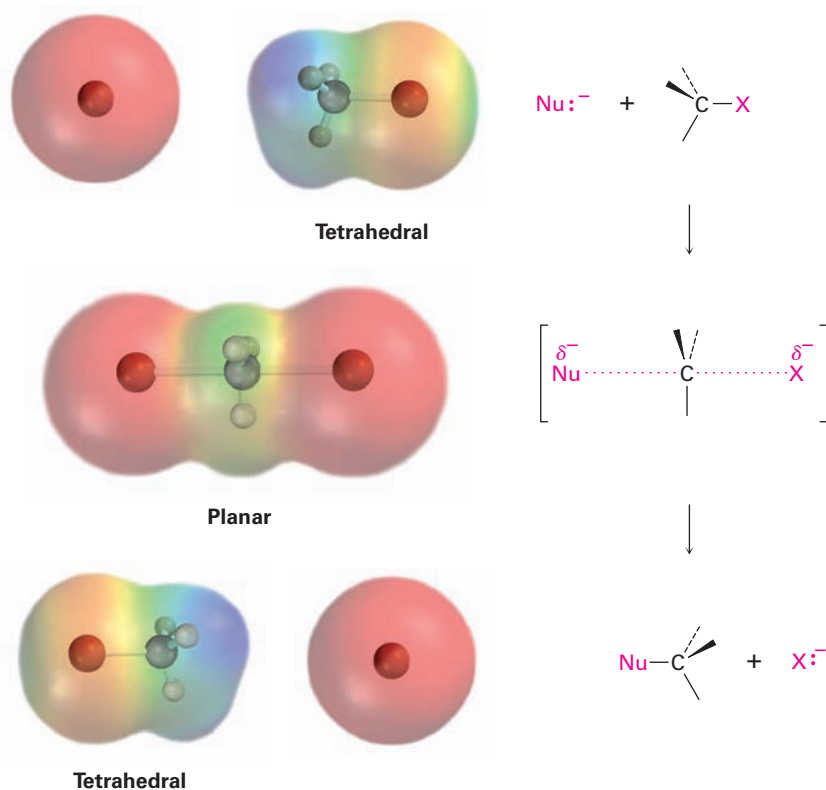
Figure 11.3 | MECHANISM

The mechanism of the S_N2 reaction. The reaction takes place in a single step when the incoming nucleophile approaches from a direction 180° away from the leaving halide ion, thereby inverting the stereochemistry at carbon.

1 The nucleophile –OH uses its lone-pair electrons to attack the alkyl halide carbon 180° away from the departing halogen. This leads to a transition state with a partially formed C–OH bond and a partially broken C–Br bond.

(S)-2-Bromobutane

Transition state

2 The stereochemistry at carbon is inverted as the C–OH bond forms fully and the bromide ion departs with the electron pair from the former C–Br bond.

(R)-2-Butanol

© John McMurry
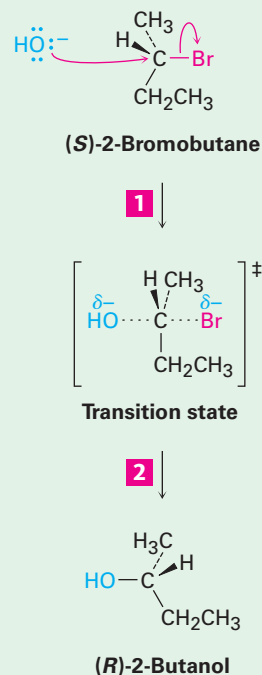
As shown in Figure 11.3, the S$_N$2 reaction occurs when an electron pair on the nucleophile Nu:$^-$ forces out the group X:$^-$, which takes with it the electron pair from the former C—X bond. This occurs through a transition state in which the new Nu—C bond is partially forming at the same time that the old C—X bond is partially breaking and in which the negative charge is shared by both the incoming nucleophile and the outgoing halide ion. The transition state for this inversion has the remaining three bonds to carbon in a planar arrangement **(Figure 11.4)**.

Figure 11.4 The transition state of an S$_N$2 reaction has a planar arrangement of the carbon atom and the remaining three groups. Electrostatic potential maps show that **negative charge** is delocalized in the transition state.

Tetrahedral

Planar

Tetrahedral

The mechanism proposed by Hughes and Ingold is fully consistent with experimental results, explaining both stereochemical and kinetic data. Thus, the requirement for backside approach of the entering nucleophile from a direction 180° away from the departing X group causes the stereochemistry of the substrate to invert, much like an umbrella turning inside out in the wind. The Hughes–Ingold mechanism also explains why second-order kinetics are found: the S$_N$2 reaction occurs in a single step that involves both alkyl halide and nucleophile. Two molecules are involved in the step whose rate is measured.

Problem 11.2

What product would you expect to obtain from S$_N$2 reaction of OH$^-$ with (*R*)-2-bromo-butane? Show the stereochemistry of both reactant and product.

Problem 11.3

Assign configuration to the following substance, and draw the structure of the product that would result on nucleophilic substitution reaction with HS^- (reddish brown = Br):
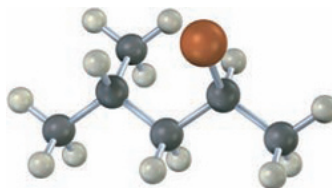
# 11.3 Characteristics of the S_N2 Reaction

Now that we know how S_N2 reactions occur, we need to see how they can be used and what variables affect them. Some S_N2 reactions are fast, and some are slow; some take place in high yield and others in low yield. Understanding the factors involved can be of tremendous value. Let's begin by recalling a few things about reaction rates in general.

The rate of a chemical reaction is determined by the activation energy $\Delta G^{\ddagger}$, the energy difference between reactant ground state and transition state. A change in reaction conditions can affect $\Delta G^{\ddagger}$ either by changing the reactant energy level or by changing the transition-state energy level. Lowering the reactant energy or raising the transition-state energy increases $\Delta G^{\ddagger}$ and decreases the reaction rate; raising the reactant energy or decreasing the transition-state energy decreases $\Delta G^{\ddagger}$ and increases the reaction rate **(Figure 11.5)**. We'll see examples of all these effects as we look at S_N2 reaction variables.
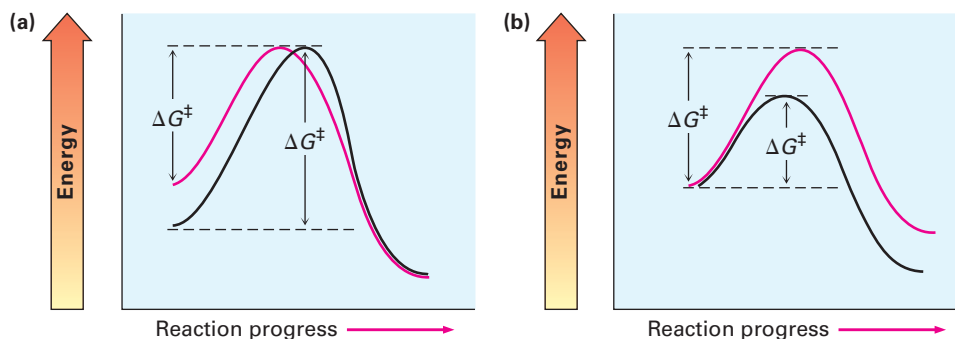

Figure 11.5 The effects of changes in reactant and transition-state energy levels on reaction rate. **(a)** A higher reactant energy level (red curve) corresponds to a faster reaction (smaller $\Delta G^{\ddagger}$). **(b)** A higher transition-state energy level (red curve) corresponds to a slower reaction (larger $\Delta G^{\ddagger}$).

The Substrate: Steric Effects in the S_N2 Reaction

The first S_N2 reaction variable to look at is the structure of the substrate. Because the S_N2 transition state involves partial bond formation between the incoming nucleophile and the alkyl halide carbon atom, it seems reasonable that a hindered, bulky substrate should prevent easy approach of the nucleophile, making bond formation difficult. In other words, the transition state for reaction of

a sterically hindered substrate, whose carbon atom is "shielded" from approach of the incoming nucleophile, is higher in energy and forms more slowly than the corresponding transition state for a less hindered substrate **(Figure 11.6)**.
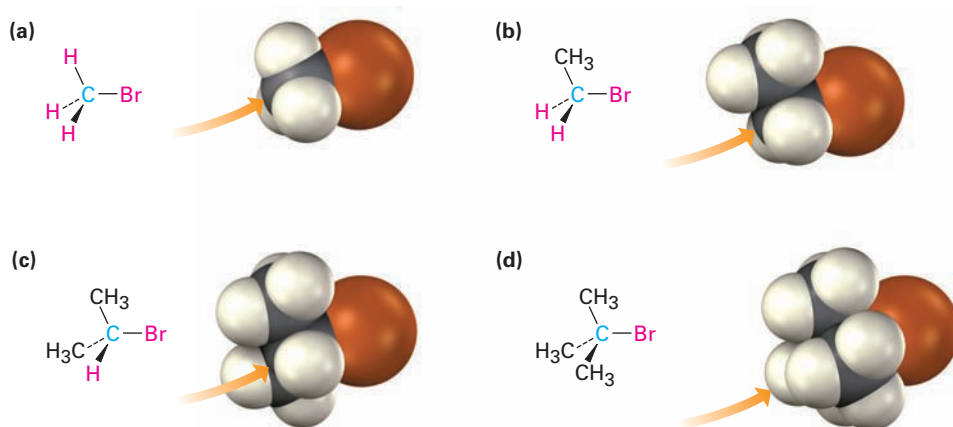
Figure 11.6 Steric hindrance to the S$_N$2 reaction. As the models indicate, the carbon atom in **(a)** bromomethane is readily accessible, resulting in a fast S$_N$2 reaction. The carbon atoms in **(b)** bromoethane (primary), **(c)** 2-bromopropane (secondary), and **(d)** 2-bromo-2-methylpropane (tertiary) are successively more hindered, resulting in successively slower S$_N$2 reactions.

As Figure 11.6 shows, the difficulty of nucleophile approach increases as the three substituents bonded to the halo-substituted carbon atom increase in size. Methyl halides are by far the most reactive substrates in S$_N$2 reactions, followed by primary alkyl halides such as ethyl and propyl. Alkyl branching at the reacting center, as in isopropyl halides (2°), slows the reaction greatly, and further branching, as in *tert*-butyl halides (3°), effectively halts the reaction. Even branching one carbon removed from the reacting center, as in 2,2-dimethylpropyl *(neopentyl)* halides, greatly slows nucleophilic displacement. As a result, S$_N$2 reactions occur only at relatively unhindered sites and are normally useful only with methyl halides, primary halides, and a few simple secondary halides. Relative reactivities for some different substrates are as follows:

	Tertiary	Neopentyl	Secondary	Primary	Methyl
Relative reactivity	< 1	1	500	40,000	2,000,000
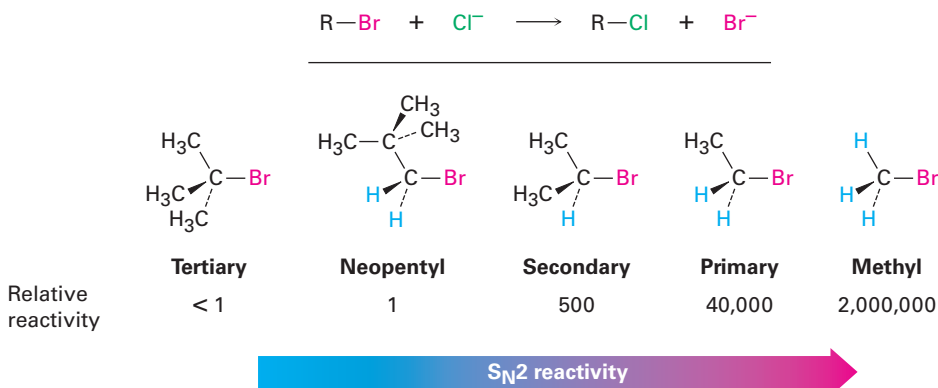
Vinylic halides (R$_2$C=CRX) and aryl halides are not shown on this reactivity list because they are unreactive toward S$_N$2 displacement. This lack of reactivity is due to steric factors: the incoming nucleophile would have to approach in

the plane of the carbon–carbon double bond and burrow through part of the molecule to carry out a backside displacement.


Vinylic halide   **Aryl halide**
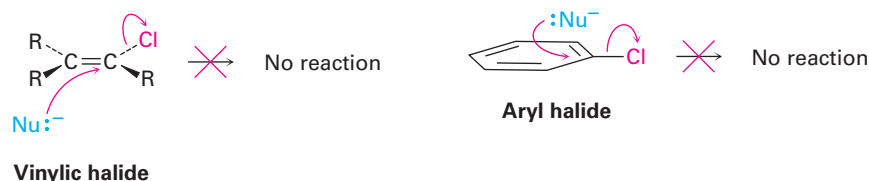
The Nucleophile

Another variable that has a major effect on the S_N2 reaction is the nature of the nucleophile. Any species, either neutral or negatively charged, can act as a nucleophile as long as it has an unshared pair of electrons; that is, as long as it is a Lewis base. If the nucleophile is negatively charged, the product is neutral; if the nucleophile is neutral, the product is positively charged.
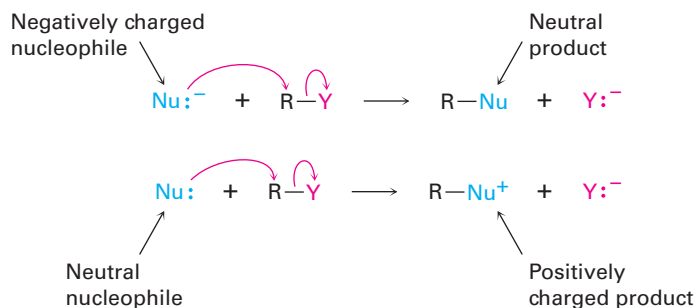
A wide array of substances can be prepared using nucleophilic substitution reactions. In fact, we've already seen examples in previous chapters. The reaction of an acetylide anion with an alkyl halide discussed in **Section 9.8**, for instance, is an S_N2 reaction in which the acetylide nucleophile displaces a halide leaving group.

$$R-C\equiv C:^- \quad + \quad CH_3Br \quad \xrightarrow[\text{reaction}]{S_N2} \quad R-C\equiv C-CH_3 \quad + \quad Br^-$$
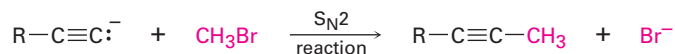
An acetylide anion

Table 11.1 lists some nucleophiles in the order of their reactivity, shows the products of their reactions with bromomethane, and gives the relative rates of their reactions. Clearly, there are large differences in the rates at which various nucleophiles react.

What are the reasons for the reactivity differences observed in Table 11.1? Why do some reactants appear to be much more "nucleophilic" than others? The answers to these questions aren't straightforward. Part of the problem is that the term *nucleophilicity* is imprecise. The term is usually taken to be a measure of the affinity of a nucleophile for a carbon atom in the S_N2 reaction, but the reactivity of a given nucleophile can change from one reaction to the next. The exact nucleophilicity of a species in a given reaction depends on the substrate, the solvent, and even the reactant concentrations. Detailed explanations

Table 11.1 Some S$_N$2 Reactions with Bromomethane

Nu:$^-$ + CH$_3$Br $\rightarrow$ CH$_3$Nu + Br$^-$				
Nucleophile		**Product**		**Relative rate of reaction**
Formula	**Name**	**Formula**	**Name**	
H$_2$O	Water	CH$_3$OH$_2^+$	Methylhydronium ion	1
CH$_3$CO$_2^-$	Acetate	CH$_3$CO$_2$CH$_3$	Methyl acetate	500
NH$_3$	Ammonia	CH$_3$NH$_3^+$	Methylammonium ion	700
Cl$^-$	Chloride	CH$_3$Cl	Chloromethane	1,000
HO$^-$	Hydroxide	CH$_3$OH	Methanol	10,000
CH$_3$O$^-$	Methoxide	CH$_3$OCH$_3$	Dimethyl ether	25,000
I$^-$	Iodide	CH$_3$I	Iodomethane	100,000
$^-$CN	Cyanide	CH$_3$CN	Acetonitrile	125,000
HS$^-$	Hydrosulfide	CH$_3$SH	Methanethiol	125,000

for the observed nucleophilicities aren't always simple, but some trends can be detected in the data of Table 11.1.

- **Nucleophilicity roughly parallels basicity** when comparing nucleophiles that have the same reacting atom. Thus, OH$^-$ is both more basic and more nucleophilic than acetate ion, CH$_3$CO$_2^-$, which in turn is more basic and more nucleophilic than H$_2$O. Since "nucleophilicity" is usually taken as the affinity of a Lewis base for a carbon atom in the S$_N$2 reaction and "basicity" is the affinity of a base for a proton, it's easy to see why there might be a correlation between the two kinds of behavior.

- **Nucleophilicity usually increases going down a column of the periodic table.** Thus, HS$^-$ is more nucleophilic than HO$^-$, and the halide reactivity order is I$^-$ > Br$^-$ > Cl$^-$. Going down the periodic table, elements have their valence electrons in successively larger shells where they are successively farther from the nucleus, less tightly held, and consequently more reactive. The matter is complex, though, and the nucleophilicity order can change depending on the solvent.

- **Negatively charged nucleophiles are usually more reactive than neutral ones.** As a result, S$_N$2 reactions are often carried out under basic conditions rather than neutral or acidic conditions.

Problem 11.4
What product would you expect from S$_N$2 reaction of 1-bromobutane with each of the following?
(a) NaI   **(b)** KOH   **(c)** H—C≡C—Li   **(d)** NH$_3$

Problem 11.5
Which substance in each of the following pairs is more reactive as a nucleophile? Explain.
(a) (CH$_3$)$_2$N$^-$ or (CH$_3$)$_2$NH   **(b)** (CH$_3$)$_3$B or (CH$_3$)$_3$N   **(c)** H$_2$O or H$_2$S

The Leaving Group

Still another variable that can affect the S_N2 reaction is the nature of the group displaced by the incoming nucleophile. Because the leaving group is expelled with a negative charge in most S_N2 reactions, the best leaving groups are those that best stabilize the negative charge in the transition state. The greater the extent of charge stabilization by the leaving group, the lower the energy of the transition state and the more rapid the reaction. But as we saw in **Section 2.8**, those groups that best stabilize a negative charge are also the weakest bases. Thus, weak bases such as Cl^-, Br^-, and tosylate ion make good leaving groups, while strong bases such as OH^- and NH_2^- make poor leaving groups.

|	OH^-, NH_2^-, OR^-	F^-	Cl^-	Br^-	I^-	$TosO^-$
Relative reactivity	<<1	1	200	10,000	30,000	60,000

Leaving group reactivity

It's just as important to know which are poor leaving groups as to know which are good, and the preceding data clearly indicate that F^-, HO^-, RO^-, and H_2N^- are not displaced by nucleophiles. In other words, alkyl fluorides, alcohols, ethers, and amines do not typically undergo S_N2 reactions. To carry out an S_N2 reaction with an alcohol, it's necessary to convert the ^-OH into a better leaving group. This, in fact, is just what happens when a primary or secondary alcohol is converted into either an alkyl chloride by reaction with $SOCl_2$ or an alkyl bromide by reaction with PBr_3 **(Section 10.5)**.
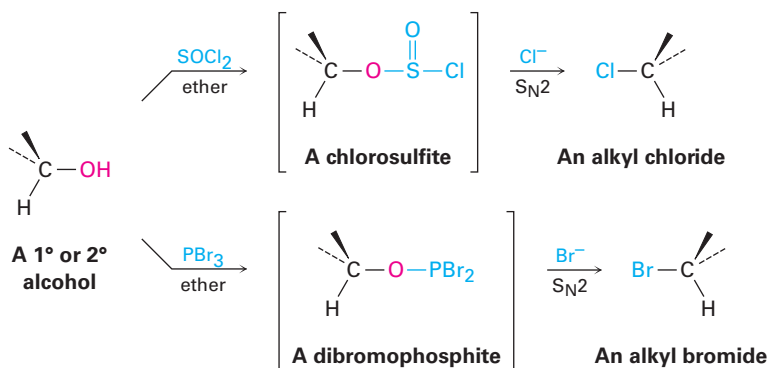
Alternatively, an alcohol can be made more reactive toward nucleophilic substitution by treating it with *para*-toluenesulfonyl chloride to form a tosylate. As noted previously, tosylates are even more reactive than halides in nucleophilic substitutions. Note that tosylate formation does not change the configuration of the oxygen-bearing carbon because the C–O bond is not broken.
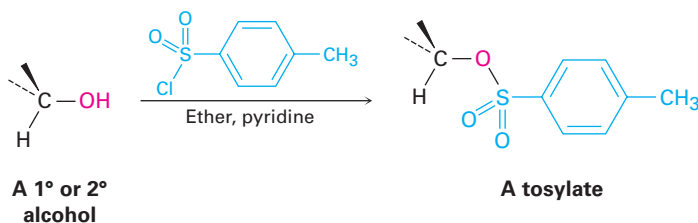
The one general exception to the rule that ethers don't typically undergo S$_N$2 reactions occurs with epoxides, the three-membered cyclic ethers that we saw in **Section 8.7**. Epoxides, because of the angle strain in the three-membered ring, are much more reactive than other ethers. They react with aqueous acid to give 1,2-diols, as we saw in **Section 8.7**, and they react readily with many other nucleophiles as well. Propene oxide, for instance, reacts with HCl to give 1-chloro-2-propanol by S$_N$2 backside attack on the less hindered primary carbon atom. We'll look at the process in more detail in **Section 18.6**.


Propene oxide   **1-Chloro-2-propanol**
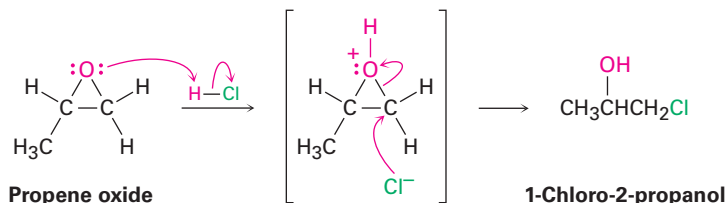
Problem 11.6

Rank the following compounds in order of their expected reactivity toward S$_N$2 reaction:

CH_3Br, CH_3OTos, $(CH_3)_3CCl$, $(CH_3)_2CHCl$

The Solvent

The rates of S$_N$2 reactions are strongly affected by the solvent. Protic solvents—those that contain an −OH or −NH group—are generally the worst for S$_N$2 reactions, while polar aprotic solvents, which are polar but don't have an −OH or −NH group, are the best.

Protic solvents, such as methanol and ethanol, slow down S$_N$2 reactions by **solvation** of the reactant nucleophile. The solvent molecules hydrogen bond to the nucleophile and form a cage around it, thereby lowering its energy and reactivity.

A solvated anion
(reduced nucleophilicity due to
enhanced ground-state stability)
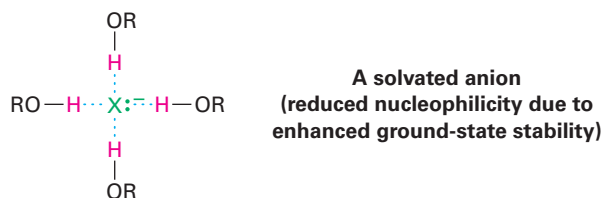
In contrast with protic solvents, which decrease the rates of S$_N$2 reactions by lowering the ground-state energy of the nucleophile, polar aprotic solvents increase the rates of S$_N$2 reactions by raising the ground-state energy of the nucleophile. Acetonitrile (CH_3CN), dimethylformamide [$(CH_3)_2NCHO$, abbreviated DMF], dimethyl sulfoxide [$(CH_3)_2SO$, abbreviated DMSO], and

hexamethylphosphoramide {[(CH$_3$)$_2$N]$_3$PO, abbreviated HMPA} are particu-
larly useful. These solvents can dissolve many salts because of their high
polarity, but they tend to solvate metal cations rather than nucleophilic
anions. As a result, the bare unsolvated anions have a greater nucleophilicity
and S$_N$2 reactions take place at correspondingly faster rates. For instance, a
rate increase of 200,000 has been observed on changing from methanol to
HMPA for the reaction of azide ion with 1-bromobutane.

$$CH_3CH_2CH_2CH_2-Br \ + \ N_3^- \ \longrightarrow \ CH_3CH_2CH_2CH_2-N_3 \ + \ Br^-$$

| Solvent	CH$_3$OH	H$_2$O	DMSO	DMF	CH$_3$CN	HMPA
Relative reactivity	1	7	1300	2800	5000	200,000

Solvent reactivity ⟶

Problem 11.7
Organic solvents like benzene, ether, and chloroform are neither protic nor strongly polar.
What effect would you expect these solvents to have on the reactivity of a nucleophile in
S$_N$2 reactions?

A Summary of S$_N$2 Reaction Characteristics

The effects on S$_N$2 reactions of the four variables—substrate structure, nucleo-
phile, leaving group, and solvent—are summarized in the following statements
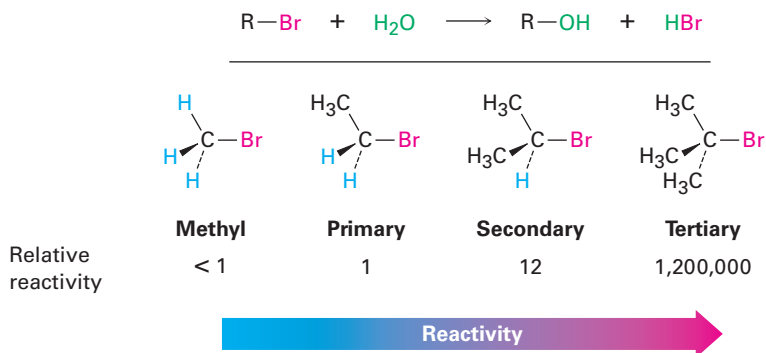and in the energy diagrams of **Figure 11.7**:

Substrate	Steric hindrance raises the energy of the S$_N$2 transition state, increasing $\Delta G^{\ddagger}$ and decreasing the reaction rate **(Figure 11.7a)**. As a result, S$_N$2 reactions are best for methyl and primary substrates. Secondary substrates react slowly, and tertiary substrates do not react by an S$_N$2 mechanism.
Nucleophile	Basic, negatively charged nucleophiles are less stable and have a higher ground-state energy than neutral ones, decreasing $\Delta G^{\ddagger}$ and increasing the S$_N$2 reaction rate **(Figure 11.7b)**.
Leaving group	Good leaving groups (more stable anions) lower the energy of the transition state, decreasing $\Delta G^{\ddagger}$ and increasing the S$_N$2 reaction rate **(Figure 11.7c)**.
Solvent	Protic solvents solvate the nucleophile, thereby lowering its ground-state energy, increasing $\Delta G^{\ddagger}$, and decreasing the S$_N$2 reaction rate. Polar aprotic solvents surround the accompanying cation but not the nucleophilic anion, thereby raising the groundstate energy of the nucleo-phile, decreasing $\Delta G^{\ddagger}$, and increasing the reaction rate **(Figure 11.7d)**.
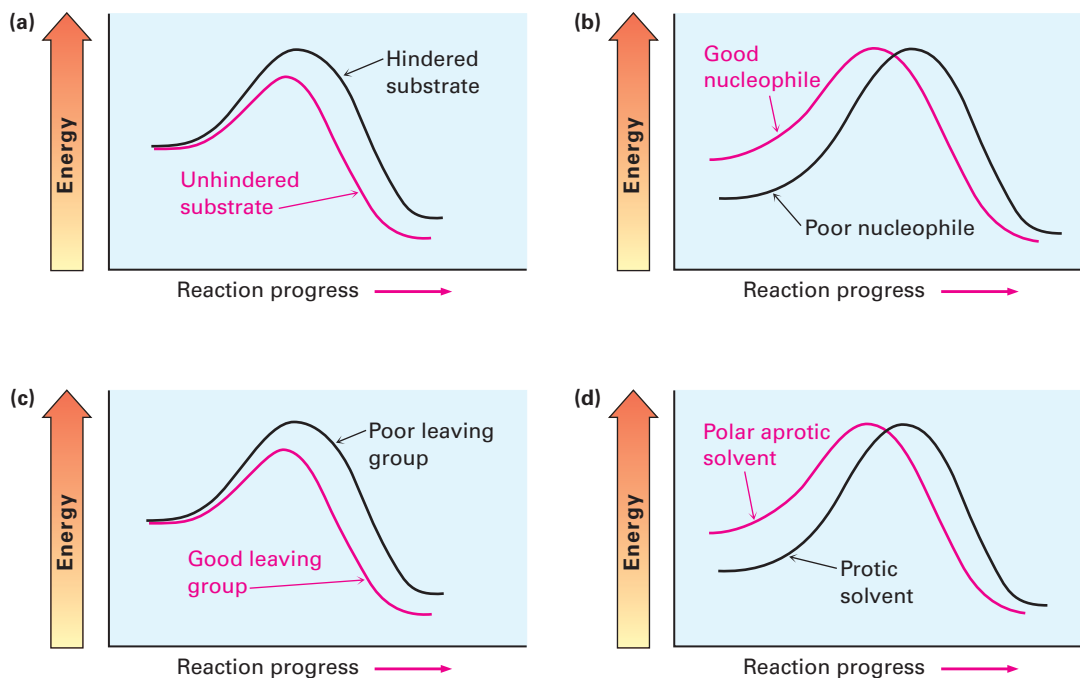
Figure 11.7 Energy diagrams showing the effects of **(a)** substrate, **(b)** nucleophile, **(c)** leaving group, and **(d)** solvent on S$_N$2 reaction rates. Substrate and leaving group effects are felt primarily in the transition state. Nucleophile and solvent effects are felt primarily in the reactant ground state.

11.4 The S$_N$1 Reaction

Most nucleophilic substitutions take place by the S$_N$2 pathway just discussed. The reaction is favored when carried out with an unhindered substrate and a negatively charged nucleophile in a polar aprotic solvent, but is disfavored when carried out with a hindered substrate and a neutral nucleophile in a protic solvent. You might therefore expect the reaction of a tertiary substrate (hindered) with water (neutral, protic) to be among the slowest of substitution reactions. Remarkably, however, the opposite is true. The reaction of the tertiary halide $(CH_3)_3CBr$ with H_2O to give the alcohol 2-methyl-2-propanol is more than *1 million times* as fast as the corresponding reaction of CH_3Br to give methanol.

$$R-Br \;+\; H_2O \;\longrightarrow\; R-OH \;+\; HBr$$

	Methyl	Primary	Secondary	Tertiary
Relative reactivity	< 1	1	12	1,200,000

What's going on here? Clearly, a nucleophilic substitution reaction is occurring—a halogen is replacing a hydroxyl group—yet the reactivity order seems backward. These reactions can't be taking place by the S$_N$2 mechanism we've

been discussing, and we must therefore conclude that they are occurring by an alternative substitution mechanism. This alternative mechanism is called the **S_N1 reaction**, for *substitution, nucleophilic, unimolecular.*

In contrast to the S_N2 reaction of CH_3Br with OH^-, the S_N1 reaction of $(CH_3)_3CBr$ with H_2O has a rate that depends only on the alkyl halide concentration and is independent of the H_2O concentration. In other words, the reaction is a **first-order process**; the concentration of the nucleophile does not appear in the rate equation.

$$\text{Reaction rate} = \text{Rate of disappearance of alkyl halide}$$

$$= k \times [RX]$$

To explain this result, we need to know more about kinetics measurements. Many organic reactions occur in several steps, one of which usually has a higher-energy transition state than the others and is therefore slower. We call this step with the highest transition-state energy the *rate-limiting step,* or *rate-determining step.* No reaction can proceed faster than its rate-limiting step, which acts as a kind of traffic jam, or bottleneck. In the S_N1 reaction of $(CH_3)_3CBr$ with H_2O, the fact that the nucleophile concentration does not appear in the first-order rate equation means that it is not involved in the rate-limiting step and must therefore be involved in some other, non–rate-limiting step. The mechanism shown in **Figure 11.8** accounts for these observations.

Figure 11.8 | MECHANISM

The mechanism of the S_N1 reaction of 2-bromo-2-methylpropane with H_2O involves three steps. Step **1**—the spontaneous, unimolecular dissociation of the alkyl bromide to yield a carbocation—is rate-limiting.
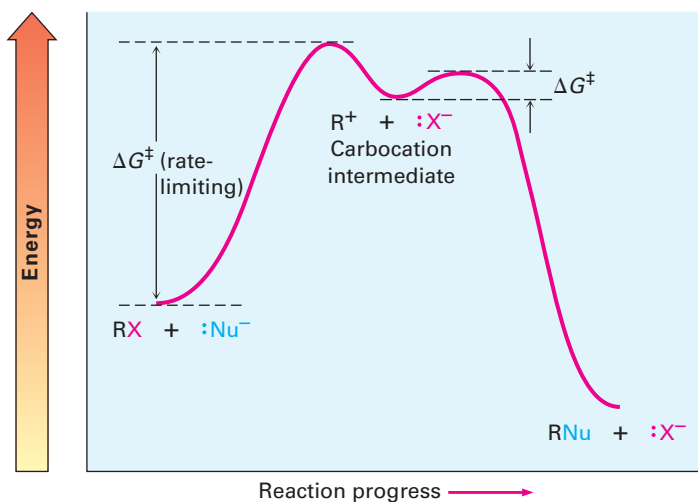
1 Spontaneous dissociation of the alkyl bromide occurs in a slow, rate-limiting step to generate a carbocation intermediate plus bromide ion.

2 The carbocation intermediate reacts with water as nucleophile in a fast step to yield protonated alcohol as product.

3 Loss of a proton from the protonated alcohol intermediate then gives the neutral alcohol product.


© John McMurry
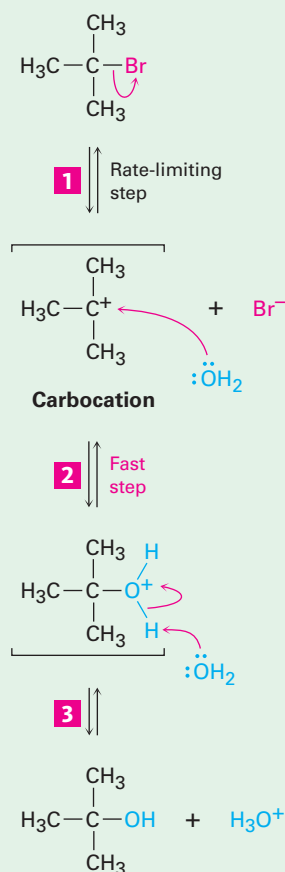
Unlike what happens in an S$_N$2 reaction, where the leaving group is displaced at the same time the incoming nucleophile approaches, an S$_N$1 reaction takes place by loss of the leaving group *before* the nucleophile approaches. 2-Bromo-2-methylpropane spontaneously dissociates to the *tert*-butyl carbocation plus Br$^-$ in a slow rate-limiting step, and the intermediate carbocation is then immediately trapped by the nucleophile water in a faster second step. Water is not a reactant in the step whose rate is measured. The energy diagram is shown in **Figure 11.9**.

Figure 11.9 An energy diagram for an S$_N$1 reaction. The rate-limiting step is the spontaneous dissociation of the alkyl halide to give a carbocation intermediate. Reaction of the carbocation with a nucleophile then occurs in a second, faster step.

Because an S$_N$1 reaction occurs through a carbocation intermediate, its stereochemical outcome is different from that of an S$_N$2 reaction. Carbocations, as we've seen, are planar, sp^2-hybridized, and achiral. Thus, if we carry out an S$_N$1 reaction on one enantiomer of a chiral reactant and go through an achiral carbocation intermediate, the product must lose its optically activity **(Section 8.12)**. That is, the symmetrical intermediate carbocation can react with a nucleophile equally well from either side, leading to a racemic, 50:50 mixture of enantiomers **(Figure 11.10)**.
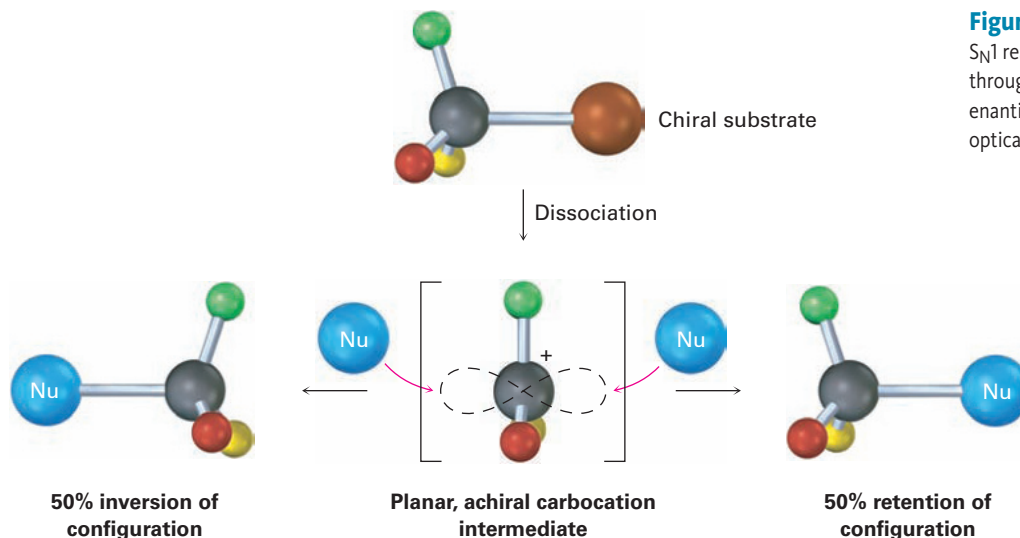

Figure 11.10 Stereochemistry of the S$_N$1 reaction. Because the reaction goes through an achiral intermediate, an enantiomerically pure reactant gives an optically inactive. racemic product.

Chiral substrate

Dissociation

50% inversion of configuration

Planar, achiral carbocation intermediate

50% retention of configuration

The conclusion that S_N1 reactions on enantiomerically pure substrates should give racemic products is nearly, but not exactly, what is found. In fact, few S_N1 displacements occur with complete racemization. Most give a minor (0–20%) excess of inversion. The reaction of (R)-6-chloro-2,6-dimethyloctane with H_2O, for example, leads to an alcohol product that is approximately 80% racemized and 20% inverted (80% R,S + 20% S is equivalent to 40% R + 60% S).

(R)-6-Chloro-2,6-dimethyloctane   60% S   40% R
                                              (inversion)   (retention)
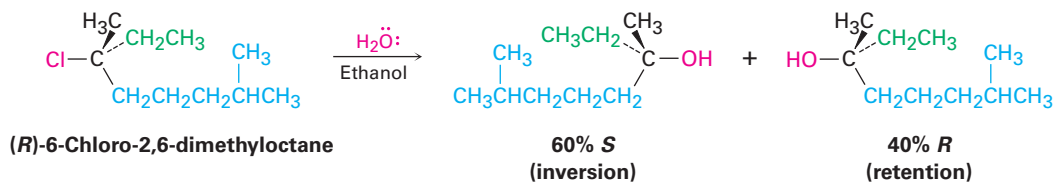
This lack of complete racemization in S_N1 reactions is due to the fact that *ion pairs* are involved. According to this explanation, first proposed by Saul Winstein at UCLA, dissociation of the substrate occurs to give a structure in which the two ions are still loosely associated and in which the carbocation is effectively shielded from reaction on one side by the departing anion. If a certain amount of substitution occurs before the two ions fully diffuse apart, then a net inversion of configuration will be observed **(Figure 11.11)**.
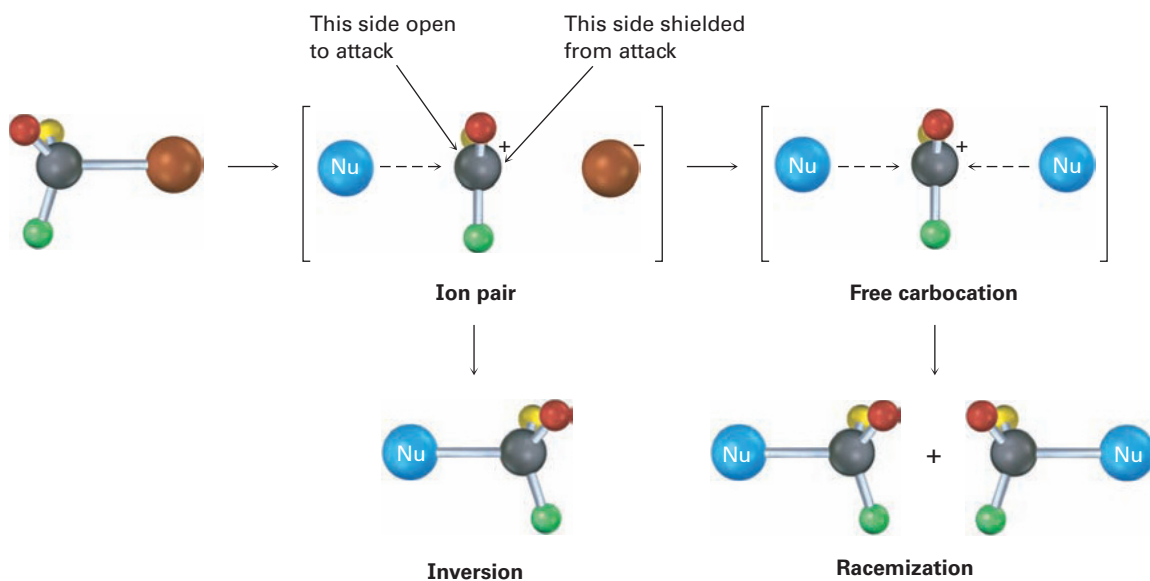
Figure 11.11 Ion-pairs in an S_N1 reaction. The leaving group shields one side of the carbocation intermediate from reaction with the nucleophile, thereby leading to some inversion of configuration rather than complete racemization.
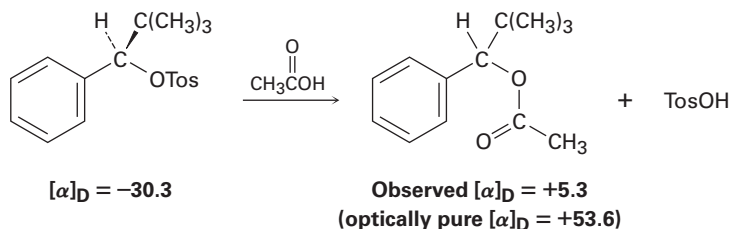
Problem 11.8
What product(s) would you expect from reaction of (S)-3-chloro-3-methyloctane with acetic acid? Show the stereochemistry of both reactant and product.

Problem 11.9
Among the many examples of S_N1 reactions that occur with incomplete racemization, the optically pure tosylate of 2,2-dimethyl-1-phenyl-1-propanol ($[\alpha]_D = -30.3$) gives the

corresponding acetate ([α]$_D$ = +5.3) when heated in acetic acid. If complete inversion had occurred, the optically pure acetate would have had [α]$_D$ = +53.6. What percentage racemization and what percentage inversion occurred in this reaction?

[α]$_D$ = −30.3

Observed [α]$_D$ = +5.3
(optically pure [α]$_D$ = +53.6)

Problem 11.10
Assign configuration to the following substrate, and show the stereochemistry and identity of the product you would obtain by S$_N$1 reaction with water (reddish brown = Br):
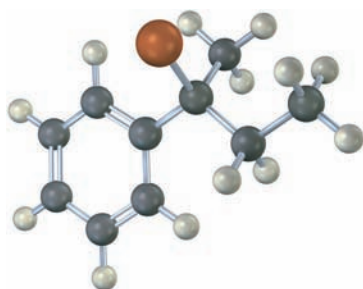
11.5 Characteristics of the S$_N$1 Reaction

Just as the S$_N$2 reaction is strongly influenced by the structure of the substrate, the leaving group, the nucleophile, and the solvent, the S$_N$1 reaction is similarly influenced. Factors that lower $\Delta G^{\ddagger}$, either by lowering the energy level of the transition state or by raising the energy level of the ground state, favor faster S$_N$1 reactions. Conversely, factors that raise $\Delta G^{\ddagger}$, either by raising the energy level of the transition state or by lowering the energy level of the reactant, slow down the S$_N$1 reaction.

Key **IDEAS**

Test your knowledge of Key Ideas by answering end-of-chapter exercises marked with ▲.

The Substrate

According to the Hammond postulate **(Section 7.10)**, any factor that stabilizes a high-energy intermediate also stabilizes the transition state leading to that intermediate. Since the rate-limiting step in an S$_N$1 reaction is the spontaneous, unimolecular dissociation of the substrate to yield a carbocation, the reaction is favored whenever a stabilized carbocation intermediate is formed. The more stable the carbocation intermediate, the faster the S$_N$1 reaction.

We saw in **Section 7.9** that the stability order of alkyl carbocations is $3° > 2° > 1° > -CH_3$. To this list we must also add the resonance-stabilized allyl and benzyl cations. Just as allylic radicals are unusually stable because

the unpaired electron can be delocalized over an extended π orbital system **(Section 10.4)**, so allylic and benzylic carbocations are unusually stable. (The word **benzylic** means "next to an aromatic ring.") As **Figure 11.12** indicates, an allylic cation has two resonance forms. In one form the double bond is on the "left"; in the other form it's on the "right." A benzylic cation has five resonance forms, all of which contribute to the overall resonance hybrid.
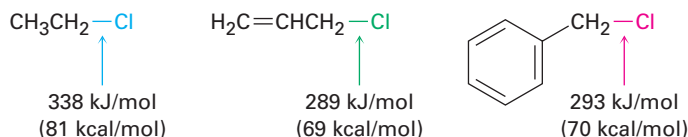

Allyl carbocation

Benzyl carbocation
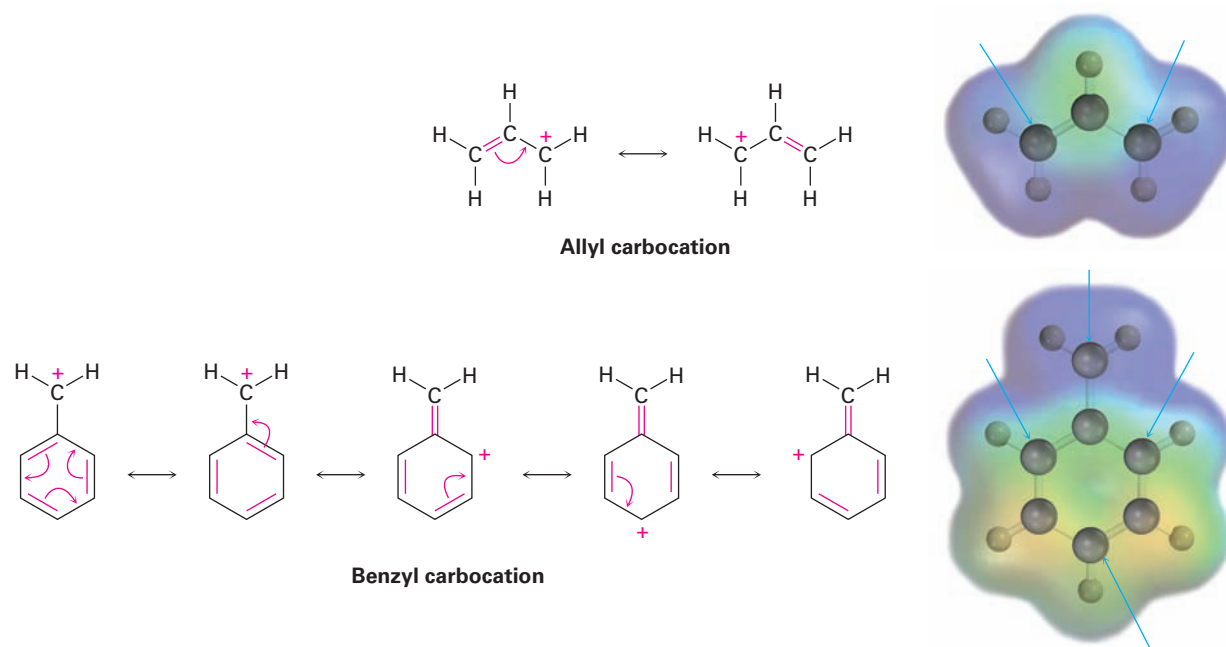
Figure 11.12 Resonance forms of allylic and benzylic carbocations. The positive charge is delocalized over the π system in both. **Electron-poor atoms** are indicated by blue arrows.

Because of resonance stabilization, a primary allylic or benzylic carbocation is about as stable as a secondary alkyl carbocation and a secondary allylic or benzylic carbocation is about as stable as a tertiary alkyl carbocation. This stability order of carbocations is the same as the order of S_N1 reactivity for alkyl halides and tosylates.


Methyl < **Primary** < **Allylic** ≈ **Benzylic** ≈ **Secondary** < **Tertiary**

Carbocation stability
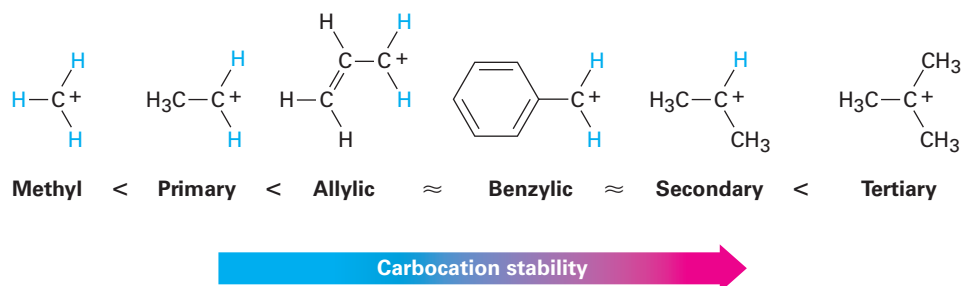
We should also note parenthetically that primary allylic and benzylic substrates are particularly reactive in S$_N$2 reactions as well as in S$_N$1 reactions. Allylic and benzylic C—X bonds are about 50 kJ/mol (12 kcal/mol) weaker than the corresponding saturated bonds and are therefore more easily broken.

CH_3CH_2—Cl H_2C=$CHCH_2$—Cl CH_2—Cl

338 kJ/mol   289 kJ/mol   293 kJ/mol
(81 kcal/mol)   (69 kcal/mol)   (70 kcal/mol)

Problem 11.11
Rank the following substances in order of their expected S$_N$1 reactivity:

CH_3CH_2Br H_2C=$CHCHCH_3$ H_2C=$CHBr$ CH_3CHCH_3
                        | |
                        Br   Br
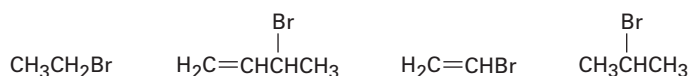
Problem 11.12
3-Bromo-1-butene and 1-bromo-2-butene undergo S$_N$1 reaction at nearly the same rate even though one is a secondary halide and the other is primary. Explain.

The Leaving Group

We said during the discussion of S$_N$2 reactivity that the best leaving groups are those that are most stable; that is, those that are the conjugate bases of strong acids. An identical reactivity order is found for the S$_N$1 reaction because the leaving group is directly involved in the rate-limiting step. Thus, the S$_N$1 reactivity order is

HO^- < Cl^- < Br^- < I^- ≈ $TosO^-$ H_2O

Leaving group reactivity

Note that in the S$_N$1 reaction, which is often carried out under acidic conditions, neutral water is sometimes the leaving group. This occurs, for example, when an alkyl halide is prepared from a tertiary alcohol by reaction with HBr or HCl **(Section 10.5)**. As shown in **Figure 11.13**, the alcohol is first protonated and then spontaneously loses H_2O to generate a carbocation, which reacts with halide ion to give the alkyl halide. Knowing that an S$_N$1 reaction is involved in the conversion of alcohols to alkyl halides explains why the reaction works well only for tertiary alcohols. Tertiary alcohols react fastest because they give the most stable carbocation intermediates.
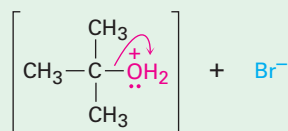
Figure 11.13 | **MECHANISM**

The mechanism of the S_N1 reaction of a tertiary alcohol with HBr to yield an alkyl halide. Neutral water is the leaving group (step **2**).
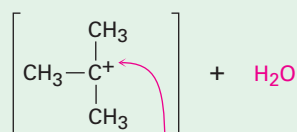
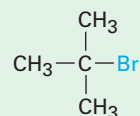**1** The –OH group is first protonated by HBr.
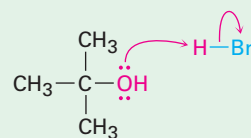
2 Spontaneous dissociation of the protonated alcohol occurs in a slow, rate-limiting step to yield a carbocation intermediate plus water.

Carbocation

3 The carbocation intermediate reacts with bromide ion in a fast step to yield the neutral substitution product.

© John McMurry

The Nucleophile

The nature of the nucleophile plays a major role in the S_N2 reaction but does not affect an S_N1 reaction. Because the S_N1 reaction occurs through a rate-limiting step in which the added nucleophile has no part, the nucleophile can't affect the reaction rate. The reaction of 2-methyl-2-propanol with HX, for instance, occurs at the same rate regardless of whether X is Cl, Br, or I. Furthermore, neutral nucleophiles are just as effective as negatively charged ones, so S_N1 reactions frequently occur under neutral or acidic conditions.

2-Methyl-2-propanol   (Same rate for X = Cl, Br, I)

The Solvent

What about the solvent? Do solvents have the same effect in S_N1 reactions that they have in S_N2 reactions? The answer is both yes and no. Yes, solvents have a
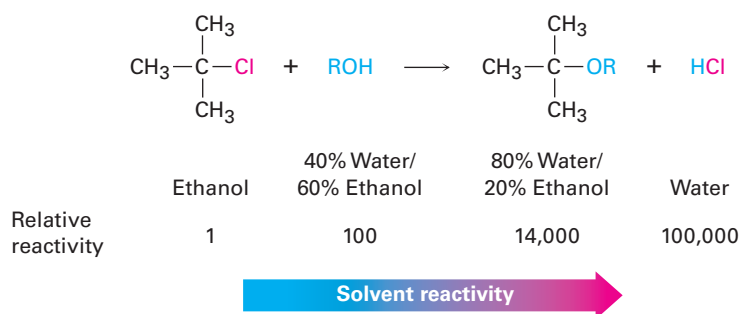
large effect on S$_N$1 reactions, but no, the reasons for the effects on S$_N$1 and S$_N$2 reactions are not the same. Solvent effects in the S$_N$2 reaction are due largely to stabilization or destabilization of the nucleophile *reactant,* while solvent effects in the S$_N$1 reaction are due largely to stabilization or destabilization of the *transition state.*

The Hammond postulate says that any factor stabilizing the intermediate carbocation should increase the rate of an S$_N$1 reaction. Solvation of the carbocation—the interaction of the ion with solvent molecules—has just such an effect. Solvent molecules orient around the carbocation so that the electron-rich ends of the solvent dipoles face the positive charge **(Figure 11.14)**, thereby lowering the energy of the ion and favoring its formation.
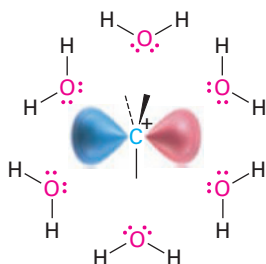
Figure 11.14 Solvation of a carbocation by water. The electron-rich oxygen atoms of solvent molecules orient around the positively charged carbocation and thereby stabilize it.

The properties of a solvent that contribute to its ability to stabilize ions by solvation are related to the solvent's polarity. S$_N$1 reactions take place much more rapidly in strongly polar solvents, such as water and methanol, than in less polar solvents, such as ether and chloroform. In the reaction of 2-chloro-2-methylpropane, for example, a rate increase of 100,000 is observed on going from ethanol (less polar) to water (more polar). The rate increases on going from a hydrocarbon solvent to water are so large they can't be measured accurately.

	Ethanol	40% Water/ 60% Ethanol	80% Water/ 20% Ethanol	Water
Relative reactivity	1	100	14,000	100,000

Solvent reactivity

It should be emphasized again that both the S$_N$1 and the S$_N$2 reaction show solvent effects, but that they do so for different reasons. S$_N$2 reactions are *disfavored* in protic solvents because the *ground-state energy* of the nucleophile is lowered by solvation. S$_N$1 reactions are *favored* in protic solvents because the *transition-state energy* leading to carbocation intermediate is lowered by solvation.

## A Summary of S$_N$1 Reaction Characteristics

The effects on S$_N$1 reactions of the four variables—substrate, leaving group, nucleophile, and solvent—are summarized in the following statements:

Substrate	The best substrates yield the most stable carbocations. As a result, S$_N$1 reactions are best for tertiary, allylic, and benzylic halides.
Leaving group	Good leaving groups increase the reaction rate by lowering the energy level of the transition state for carbocation formation.
Nucleophile	The nucleophile must be nonbasic to prevent a competitive elimination of HX **(Section 11.7)**, but otherwise does not affect the reaction rate. Neutral nucleophiles work well.
Solvent	Polar solvents stabilize the carbocation intermediate by solvation, thereby increasing the reaction rate.

Worked Example
11.2

Predicting the Mechanism of a Nucleophilic Substitution Reaction

Predict whether each of the following substitution reactions is likely to be S$_N$1 or S$_N$2:

(a)

(b)
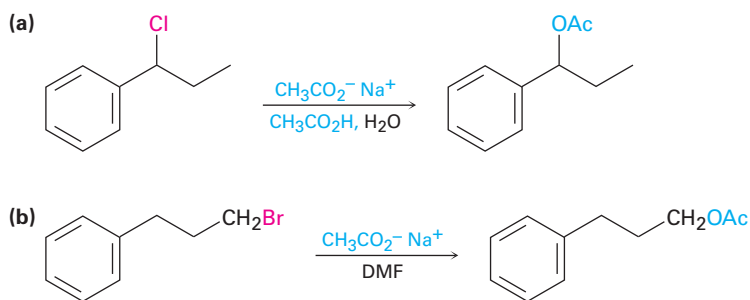
Strategy

Look at the substrate, leaving group, nucleophile, and solvent. Then decide from the summaries at the ends of **Sections 11.3 and 11.5** whether an S$_N$1 or an S$_N$2 reaction is favored. S$_N$1 reactions are favored by tertiary, allylic, or benzylic substrates, by good leaving groups, by nonbasic nucleophiles, and by protic solvents. S$_N$2 reactions are favored by primary substrates, by good leaving groups, by good nucleophiles, and by polar aprotic solvents.

Solution

(a) This is likely to be an S$_N$1 reaction because the substrate is secondary and benzylic, the nucleophile is weakly basic, and the solvent is protic.

(b) This is likely to be an S$_N$2 reaction because the substrate is primary, the nucleophile is a reasonably good one, and the solvent is polar aprotic.

Problem 11.13

Predict whether each of the following substitution reactions is likely to be S_N1 or S_N2:

(a)

(b)

$$H_2C{=}CCH_2Br \xrightarrow[CH_3CN]{Na^+ \ {}^-SCH_3} H_2C{=}CCH_2SCH_3$$

with CH_3 groups
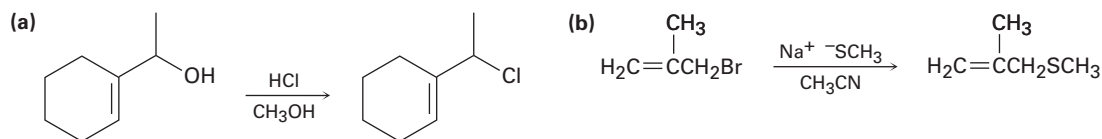
11.6 Biological Substitution Reactions

Both S_N1 and S_N2 reactions are well-known in biological chemistry, particularly in the pathways for biosynthesis of the many thousands of plant-derived substances called *terpenoids*, which we'll discuss in **Section 27.5**. Unlike what typically happens in the laboratory, however, the substrate in a biological substitution reaction is usually an organodiphosphate rather than an alkyl halide. Thus, the leaving group is the diphosphate ion, abbreviated PP_i, rather than a halide ion. In fact, it's useful to think of the diphosphate group as the "biological equivalent" of a halogen. The dissociation of an organodiphosphate in a biological reaction is typically assisted by complexation to a divalent metal cation such as Mg^{2+} to help neutralize charge and make the diphosphate a better leaving group.

An organodiphosphate   Diphosphate ion
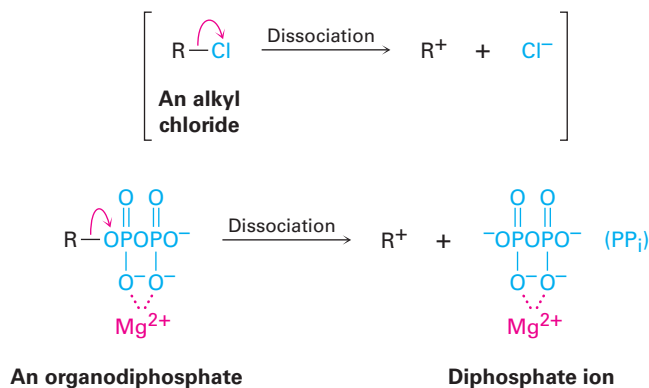
Two S_N1 reactions occur during the biosynthesis of geraniol, a fragrant alcohol found in roses and used in perfumery. Geraniol biosynthesis begins with dissociation of dimethylallyl diphosphate to give an allylic carbocation, which reacts with isopentenyl diphosphate **(Figure 11.15)**. From the viewpoint of isopentenyl diphosphate, the reaction is an electrophilic alkene addition, but from the viewpoint of dimethylallyl diphosphate, the process is an S_N1 reaction in which the carbocation intermediate reacts with a double bond as the nucleophile.

Following this initial S_N1 reaction, loss of the *pro-R* hydrogen gives geranyl diphosphate, itself an allylic diphosphate that dissociates a second time. Reaction of the geranyl carbocation with water in a second S_N1 reaction, followed by loss of a proton, then yields geraniol.
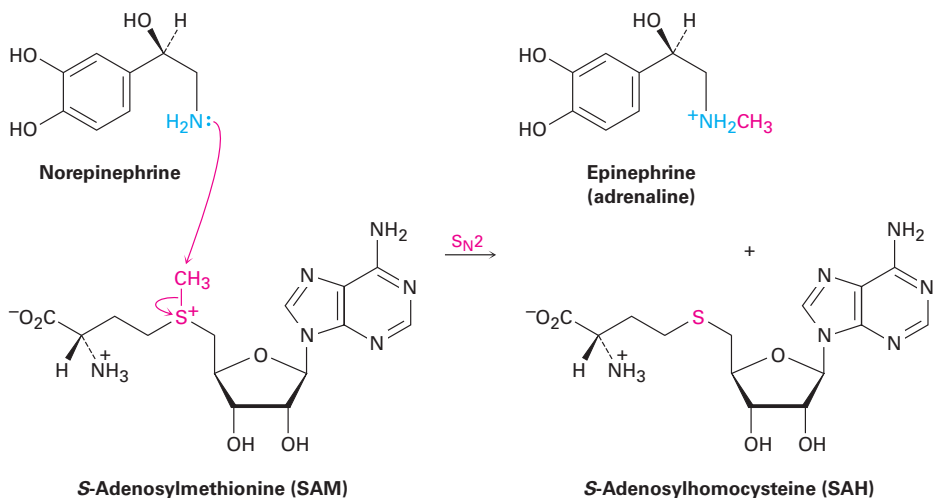
Figure 11.15 Biosynthesis of geraniol from dimethylallyl diphosphate. Two S_N1 reactions occur, both with diphosphate ion as the leaving group.
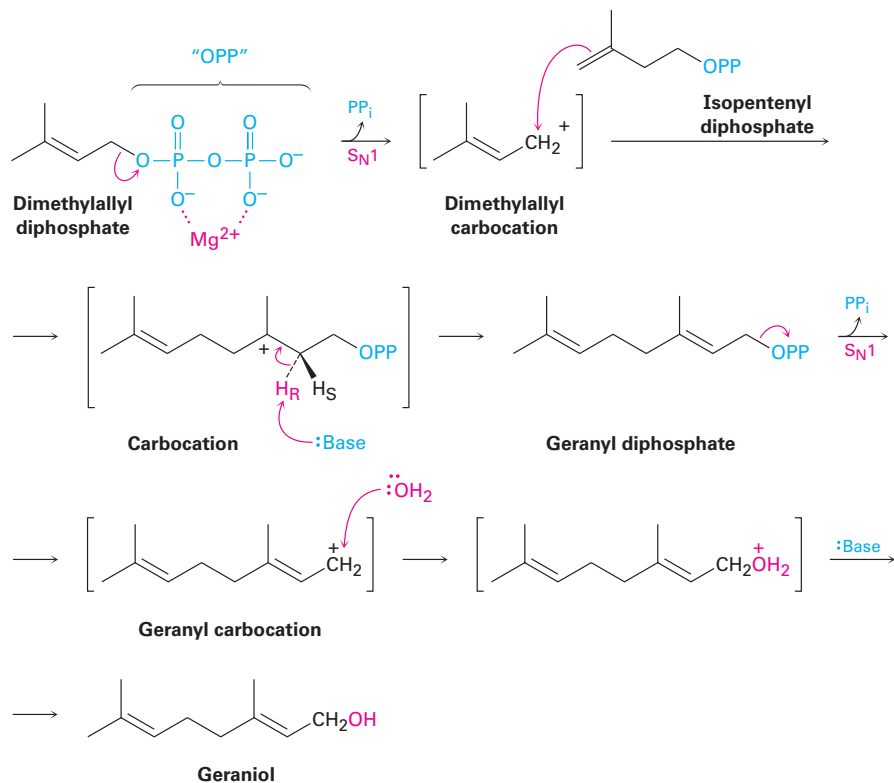

S_N2 reactions are involved in almost all biological methylations, which transfer a $-CH_3$ group from an electrophilic donor to a nucleophile. The donor is *S*-adenosylmethionine (abbreviated SAM), which contains a positively charged sulfur (a sulfonium ion, **Section 5.12**), and the leaving group is the neutral *S*-adenosylhomocysteine molecule. In the biosynthesis of epinephrine (adrenaline) from norepinephrine, for instance, the nucleophilic nitrogen atom of norepinephrine attacks the electrophilic methyl carbon atom of S-adenosylmethionine in an S_N2 reaction, displacing *S*-adenosylhomocysteine **(Figure 11.16)**. In effect, *S*-adenosylmethionine is simply a biological equivalent of CH_3Cl.

Figure 11.16 The biosynthesis of epinephrine from norepinephrine occurs by an S_N2 reaction with *S*-adenosylmethionine.

Problem 11.14

Review the mechanism of geraniol biosynthesis shown in Figure 11.15, and propose a mechanism for the biosynthesis of limonene from linalyl diphosphate.

Linalyl diphosphate   **Limonene**
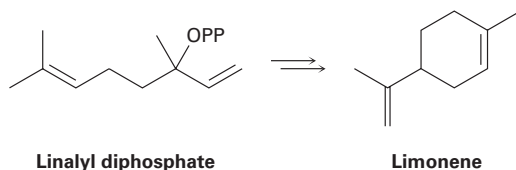
11.7 Elimination Reactions: Zaitsev's Rule

We said at the beginning of this chapter that two kinds of reactions can take place when a nucleophile/Lewis base reacts with an alkyl halide. The nucleophile can either substitute for the halide by reaction at carbon or can cause elimination of HX by reaction at a neighboring hydrogen:

Substitution
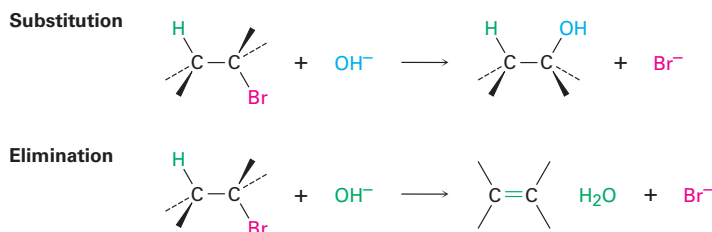
Elimination

Elimination reactions are more complex than substitution reactions for several reasons. One is the problem of regiochemistry. What products result by loss of HX from an unsymmetrical halide? In fact, elimination reactions almost always give mixtures of alkene products, and the best we can usually do is to predict which will be the major product.

According to **Zaitsev's rule**, formulated in 1875 by the Russian chemist Alexander Zaitsev, base-induced elimination reactions generally (although not always) give the more stable alkene product—that is, the alkene with more alkyl substituents on the double-bond carbons. In the following two cases, for example, the more highly substituted alkene product predominates.

***Key* IDEAS**

Test your knowledge of Key Ideas by answering end-of-chapter exercises marked with ▲.

ZAITSEV'S RULE
In the elimination of HX from an alkyl halide, the more highly substituted alkene product predominates.
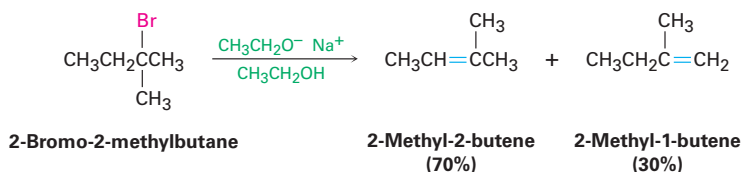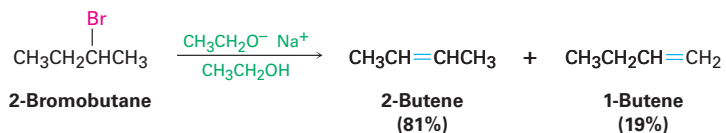
$CH_3CH_2CHCH_3$ $\xrightarrow[CH_3CH_2OH]{CH_3CH_2O^- \ Na^+}$ $CH_3CH=CHCH_3$ + $CH_3CH_2CH=CH_2$

2-Bromobutane   **2-Butene**   **1-Butene**
                                        (81%)   **(19%)**

$CH_3CH_2CCH_3$ $\xrightarrow[CH_3CH_2OH]{CH_3CH_2O^- \ Na^+}$ $CH_3CH=CCH_3$ + $CH_3CH_2C=CH_2$

2-Bromo-2-methylbutane   **2-Methyl-2-butene**   **2-Methyl-1-butene**
                                        (70%)   **(30%)**

Another factor that complicates a study of elimination reactions is that they can take place by different mechanisms, just as substitutions can. We'll consider three of the most common mechanisms—the E1, E2, and E1cB reactions—which differ in the timing of C−H and C−X bond-breaking.

In the E1 reaction, the C−X bond breaks first to give a carbocation intermediate that undergoes subsequent base abstraction of H⁺ to yield the alkene. In the E2 reaction, base-induced C−H bond cleavage is simultaneous with C−X bond cleavage, giving the alkene in a single step. In the E1cB reaction (cB for "conjugate base"), base abstraction of the proton occurs first, giving a carbanion (R:⁻) intermediate. This anion, the conjugate base of the reactant "acid," then undergoes loss of X⁻ in a subsequent step to give the alkene. All three mechanisms occur frequently in the laboratory, but the E1cB mechanism predominates in biological pathways.

E1 Reaction: C−X bond breaks first to give a carbocation intermediate, followed by base removal of a proton to yield the alkene.

Carbocation
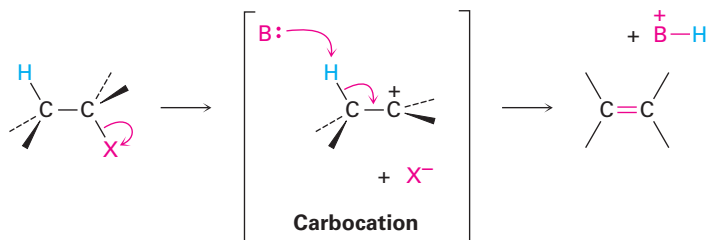
E2 Reaction: C−H and C−X bonds break simultaneously, giving the alkene in a single step without intermediates.
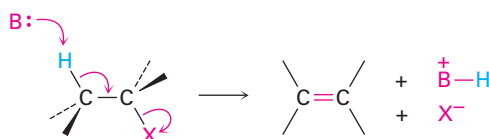
E1cB Reaction: C−H bond breaks first, giving a carbanion intermediate that loses X⁻ to form the alkene.

Carbanion
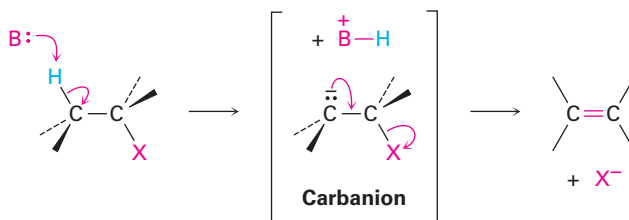
<table>
<tr><td>**Predicting the Product of an Elimination Reaction**</td><td>**Worked Example 11.3**</td></tr>
</table>

What product would you expect from reaction of 1-chloro-1-methylcyclohexane with KOH in ethanol?
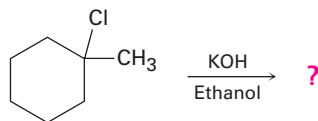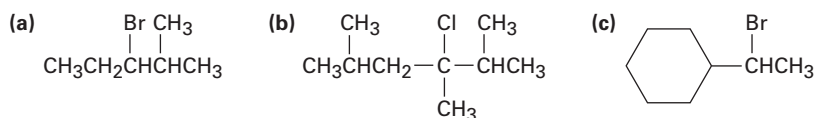

Strategy

Treatment of an alkyl halide with a strong base such as KOH yields an alkene. To find the products in a specific case, locate the hydrogen atoms on each carbon next to the leaving group, and then generate the potential alkene products by removing HX in as many ways as possible. The major product will be the one that has the most highly substituted double bond—in this case, 1-methylcyclohexene.

Solution

1-Chloro-1-methyl-cyclohexane   **1-Methylcyclohexene (major)**   **Methylenecyclohexane (minor)**
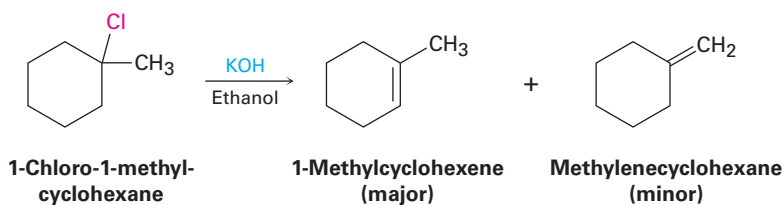
Problem 11.15

Ignoring double-bond stereochemistry, what products would you expect from elimination reactions of the following alkyl halides? Which product will be the major product in each case?

(a)

$$\underset{CH_3CH_2CHCHCH_3}{\overset{Br\ CH_3}{|\ \ \ |}}$$

(b)

$$\underset{CH_3CHCH_2-C-CHCH_3}{\overset{CH_3\qquad Cl\ CH_3}{|\qquad\ \ |\ \ |}}$$
$$\underset{\qquad\qquad\quad CH_3}{\qquad\qquad\quad |}$$

(c)

Problem 11.16

What alkyl halides might the following alkenes have been made from?

(a)

$$\underset{CH_3CHCH_2CH_2CHCH=CH_2}{\overset{CH_3\qquad\quad CH_3}{|\qquad\qquad |}}$$

(b)
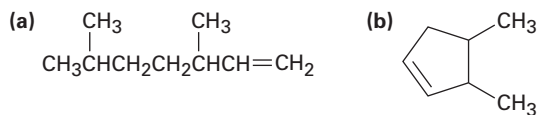
11.8 The E2 Reaction and the Deuterium Isotope Effect

The **E2 reaction** (for *elimination, bimolecular*) occurs when an alkyl halide is treated with a strong base, such as hydroxide ion or alkoxide ion (RO^-). It is the most commonly occurring pathway for elimination and can be formulated as shown in **Figure 11.17**.

Figure 11.17 | MECHANISM

Mechanism of the E2 reaction of an alkyl halide. The reaction takes place in a single step through a transition state in which the double bond begins to form at the same time the H and X groups are leaving.

1 Base (B:) attacks a neighboring hydrogen and begins to remove the H at the same time as the alkene double bond starts to form and the X group starts to leave.

2 Neutral alkene is produced when the C–H bond is fully broken and the X group has departed with the C–X bond electron pair.

Transition state
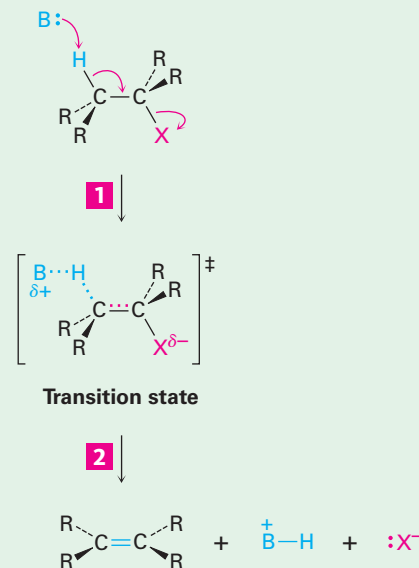
© John McMurry

Like the S_N2 reaction, the E2 reaction takes place in one step without intermediates. As the base begins to abstract H⁺ from a carbon next to the leaving group, the C–H bond begins to break, a C=C bond begins to form, and the leaving group begins to depart, taking with it the electron pair from the C–X bond. Among the pieces of evidence supporting this mechanism is that E2 reactions show second-order kinetics and follow the rate law: rate = k × [RX] × [Base]. That is, both base and alkyl halide take part in the rate-limiting step.

A second piece of evidence in support of the E2 mechanism is provided by a phenomenon known as the **deuterium isotope effect**. For reasons that we won't go into, a carbon–hydrogen bond is weaker by about 5 kJ/mol (1.2 kcal/mol) than the corresponding carbon–deuterium bond. Thus, a C–H bond is more easily broken than an equivalent C–D bond, and the rate of C–H bond cleavage is faster. For instance, the base-induced elimination of HBr from 1-bromo-2-phenylethane proceeds 7.11 times as fast as the corresponding elimination of DBr from 1-bromo-2,2-dideuterio-2-phenylethane. This result tells us that the C–H (or C–D) bond is broken in the rate-limiting step, consistent with our picture of the E2 reaction as a one-step process. If it were otherwise, we couldn't measure a rate difference.

(H)—Faster reaction
(D)—Slower reaction
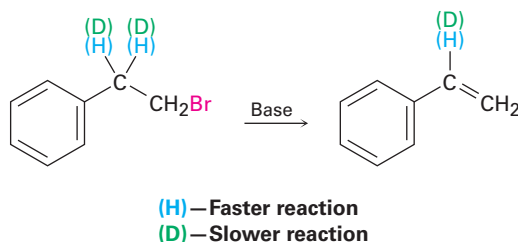
Yet a third piece of mechanistic evidence involves the stereochemistry of E2 eliminations. As shown by a large number of experiments, E2 reactions occur

with *periplanar* geometry, meaning that all four reacting atoms—the hydrogen, the two carbons, and the leaving group—lie in the same plane. Two such geometries are possible: **syn periplanar** geometry, in which the H and the X are on the same side of the molecule, and **anti periplanar** geometry, in which the H and the X are on opposite sides of the molecule. Of the two, anti periplanar geometry is energetically preferred because it allows the substituents on the two carbons to adopt a staggered relationship, whereas syn geometry requires that the substituents be eclipsed.
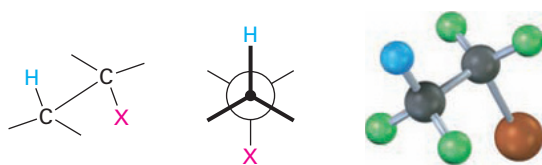
Anti periplanar geometry
(staggered, lower energy)
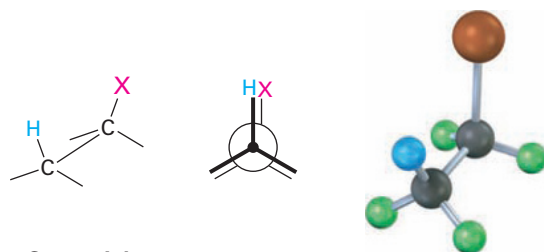
Syn periplanar geometry
(eclipsed, higher energy)

What's so special about periplanar geometry? Because the sp^3 σ orbitals in the reactant C−H and C−X bonds must overlap and become p π orbitals in the alkene product, there must also be some overlap in the transition state. This can occur most easily if all the orbitals are in the same plane to begin with—that is, if they're periplanar **(Figure 11.18)**.
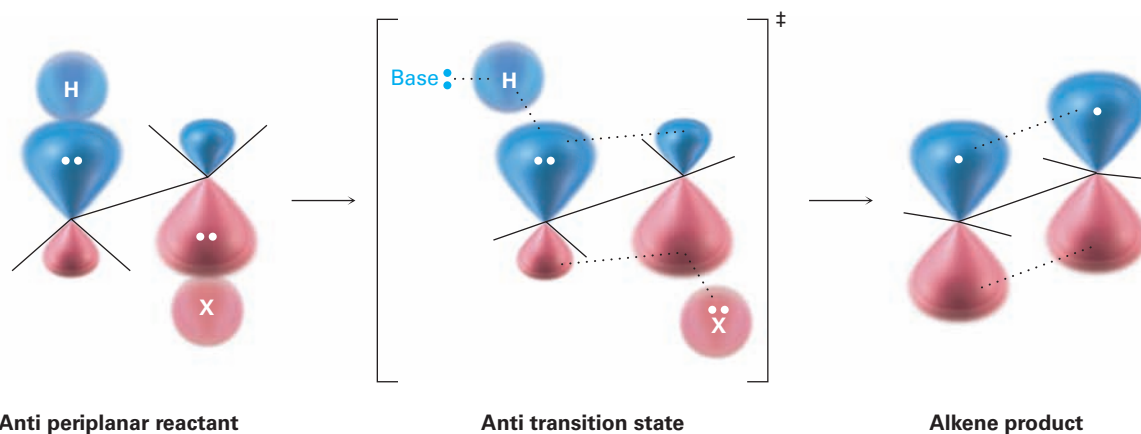
Anti periplanar reactant   **Anti transition state**   **Alkene product**

Figure 11.18 The transition state for the E2 reaction of an alkyl halide with base. Overlap of the developing p orbitals in the transition state requires periplanar geometry of the reactant.

You can think of E2 elimination reactions with periplanar geometry as being similar to S_N2 reactions with 180° geometry. In an S_N2 reaction, an electron pair from the incoming nucleophile pushes out the leaving group on the opposite side of the molecule. In an E2 reaction, an electron pair from a neighboring C–H bond pushes out the leaving group on the opposite side of the molecule.

S_N2 reaction
(backside attack)

E2 reaction
(anti periplanar)
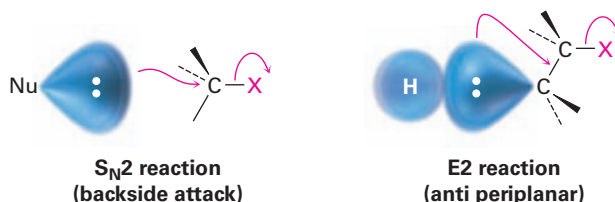
Anti periplanar geometry for E2 eliminations has specific stereochemical consequences that provide strong evidence for the proposed mechanism. To take just one example, *meso*-1,2-dibromo-1,2-diphenylethane undergoes E2 elimination on treatment with base to give only the *E* alkene. None of the isomeric *Z* alkene is formed because the transition state leading to the *Z* alkene would have to have syn periplanar geometry and would thus be higher in energy.

KOH
Ethanol

Ph =

meso-**1,2-Dibromo-**
1,2-diphenylethane
(anti periplanar geometry)

(*E*)-1-Bromo-
1,2-diphenylethylene
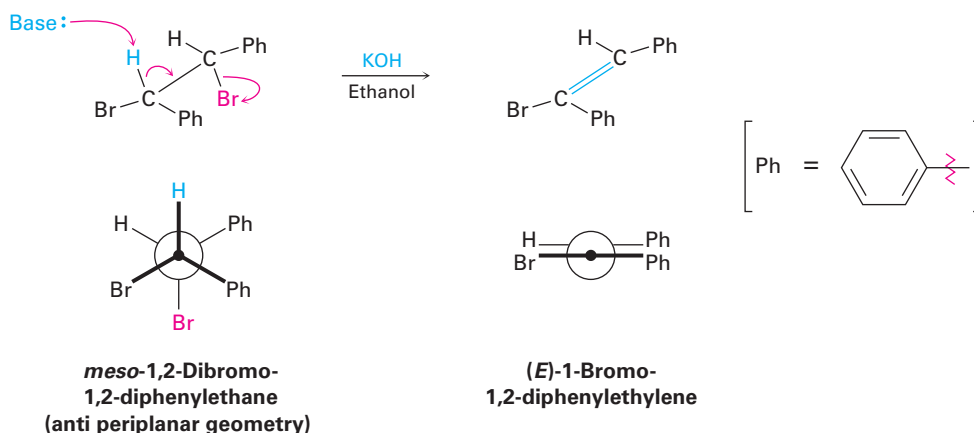
Worked Example
11.4

Predicting the Double-Bond Stereochemistry of the Product in an E2 Reaction

What stereochemistry do you expect for the alkene obtained by E2 elimination of (1*S*,2*S*)-1,2-dibromo-1,2-diphenylethane?

Strategy

Draw (1*S*,2*S*)-1,2-dibromo-1,2-diphenylethane so that you can see its stereochemistry and so that the −H and −Br groups to be eliminated are anti periplanar. Then carry out the elimination while keeping all substituents in approximately their same positions, and see what alkene results.

Solution

Anti periplanar elimination of HBr gives (*Z*)-1-bromo-1,2-diphenylethylene.
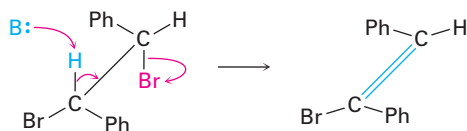
Problem 11.17

What stereochemistry do you expect for the alkene obtained by E2 elimination of (1*R*,2*R*)-1,2-dibromo-1,2-diphenylethane? Draw a Newman projection of the reacting conformation.

Problem 11.18

What stereochemistry do you expect for the trisubstituted alkene obtained by E2 elimination of the following alkyl halide on treatment with KOH? (Reddish brown = Br.)
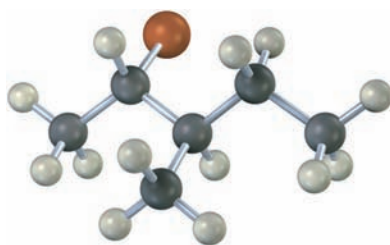
11.9 The E2 Reaction and Cyclohexane Conformation

Anti periplanar geometry for E2 reactions is particularly important in cyclohexane rings, where chair geometry forces a rigid relationship between the substituents on neighboring carbon atoms **(Section 4.8)**. The anti periplanar requirement for E2 reactions overrides Zaitsev's rule and can be met in cyclohexanes only if the hydrogen and the leaving group are trans diaxial **(Figure 11.19)**. If either the leaving group or the hydrogen is equatorial, E2 elimination can't occur.

Axial chlorine: H and Cl are anti periplanar
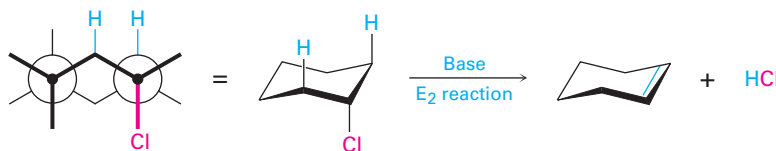
Equatorial chlorine: H and Cl are not anti periplanar
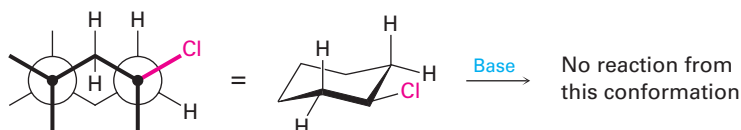
Figure 11.19 The geometric requirement for an E2 reaction in a substituted cyclohexane. The leaving group and the hydrogen must both be axial for anti periplanar elimination to occur.

The elimination of HCl from the isomeric menthyl and neomenthyl chlorides shown in **Figure 11.20** gives a good illustration of this trans-diaxial requirement. Neomenthyl chloride undergoes elimination of HCl on reaction with ethoxide ion 200 times as fast as menthyl chloride. Furthermore, neomenthyl chloride yields 3-menthene as the major alkene product, whereas menthyl chloride yields 2-menthene.
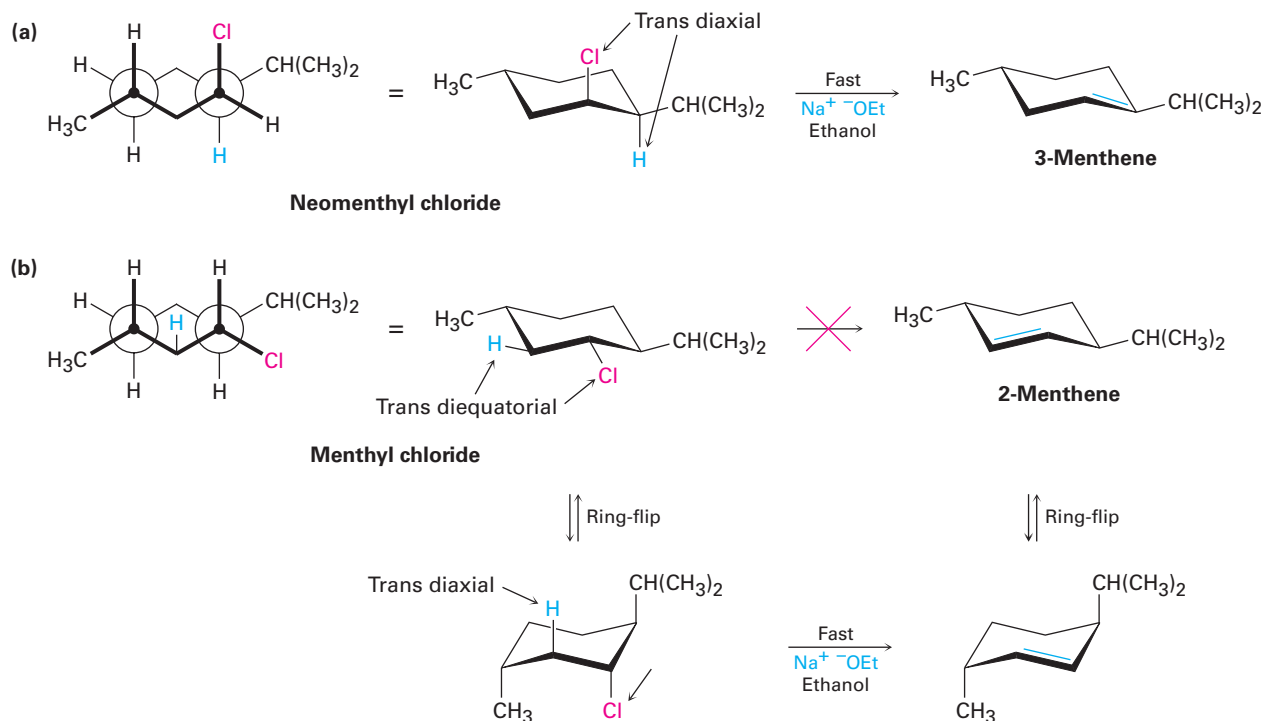
Figure 11.20 Dehydrochlorination of menthyl and neomenthyl chlorides. **(a)** Neomenthyl chloride loses HCl directly from its more stable conformation, but **(b)** menthyl chloride must first ring-flip to a higher energy conformation before HCl loss can occur. The abbreviation "Et" represents an ethyl group.

The difference in reactivity between the isomeric menthyl chlorides is due to the difference in their conformations. Neomenthyl chloride has the conformation shown in Figure 11.20a, with the methyl and isopropyl groups equatorial and the chlorine axial—a perfect geometry for E2 elimination. Loss of the hydrogen atom at C4 occurs easily to yield the more substituted alkene product, 3-menthene, as predicted by Zaitsev's rule.

Menthyl chloride, by contrast, has a conformation in which all three substituents are equatorial (Figure 11.20b). To achieve the necessary geometry for elimination, menthyl chloride must first ring-flip to a higher-energy chair conformation, in which all three substituents are axial. E2 elimination then occurs with loss of the only trans-diaxial hydrogen available, leading to the non-Zaitsev product 2-menthene. The net effect of the simple change in chlorine stereochemistry is a 200-fold change in reaction rate and a complete change of product. The chemistry of the molecule is controlled by its conformation.

Problem 11.19

Which isomer would you expect to undergo E2 elimination faster, *trans*-1-bromo-4-*tert*-butylcyclohexane or *cis*-1-bromo-4-*tert*-butylcyclohexane? Draw each molecule in its more stable chair conformation, and explain your answer.

11.10 The E1 and E1cB Reactions

The E1 Reaction

Just as the E2 reaction is analogous to the S$_N$2 reaction, the S$_N$1 reaction has a close analog called the **E1 reaction** (for *elimination, unimolecular*). The E1 reaction can be formulated as shown in **Figure 11.21** for the elimination of HCl from 2-chloro-2-methylpropane.

1 Spontaneous dissociation of the tertiary alkyl chloride yields an intermediate carbocation in a slow, rate-limiting step.
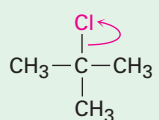
Carbocation
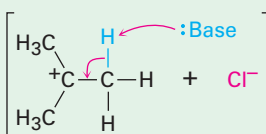
2 Loss of a neighboring H$^+$ in a fast step yields the neutral alkene product. The electron pair from the C–H bond goes to form the alkene π bond.
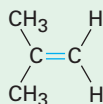
Figure 11.21 | MECHANISM

Mechanism of the E1 reaction. Two steps are involved, the first of which is rate-limiting, and a carbocation intermediate is present.

© John McMurry

E1 eliminations begin with the same unimolecular dissociation to give a carbocation that we saw in the S$_N$1 reaction, but the dissociation is followed by loss of H$^+$ from the adjacent carbon rather than by substitution. In fact, the E1 and S$_N$1 reactions normally occur together whenever an alkyl halide is treated in a protic solvent with a nonbasic nucleophile. Thus, the best E1 substrates are also the best S$_N$1 substrates, and mixtures of substitution and elimination products are usually obtained. For example, when 2-chloro-2-methylpropane is warmed to 65 °C in 80% aqueous ethanol, a 64:36 mixture of 2-methyl-2-propanol (S$_N$1) and 2-methylpropene (E1) results.

2-Chloro-2-methylpropane

2-Methyl-2-propanol (64%)   **2-Methylpropene (36%)**
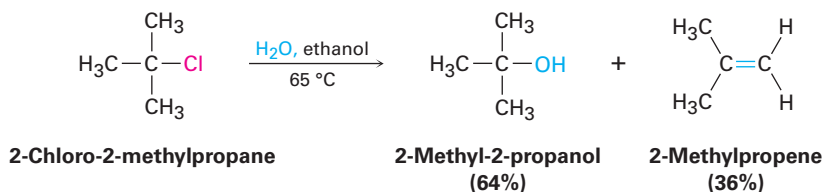
Much evidence has been obtained in support of the E1 mechanism. For example, E1 reactions show first-order kinetics, consistent with a rate-limiting, unimolecular dissociation process. Furthermore, E1 reactions show no deuterium isotope effect because rupture of the C−H (or C−D) bond occurs after the rate-limiting step rather than during it. Thus, we can't measure a rate difference between a deuterated and nondeuterated substrate.

A final piece of evidence involves the stereochemistry of elimination. Unlike the E2 reaction, where anti periplanar geometry is required, there is no geometric requirement on the E1 reaction because the halide and the hydrogen are lost in separate steps. We might therefore expect to obtain the more stable (Zaitsev's rule) product from E1 reaction, which is just what we find. To return to a familiar example, menthyl chloride loses HCl under E1 conditions in a polar solvent to give a mixture of alkenes in which the Zaitsev product, 3-menthene, predominates **(Figure 11.22)**.
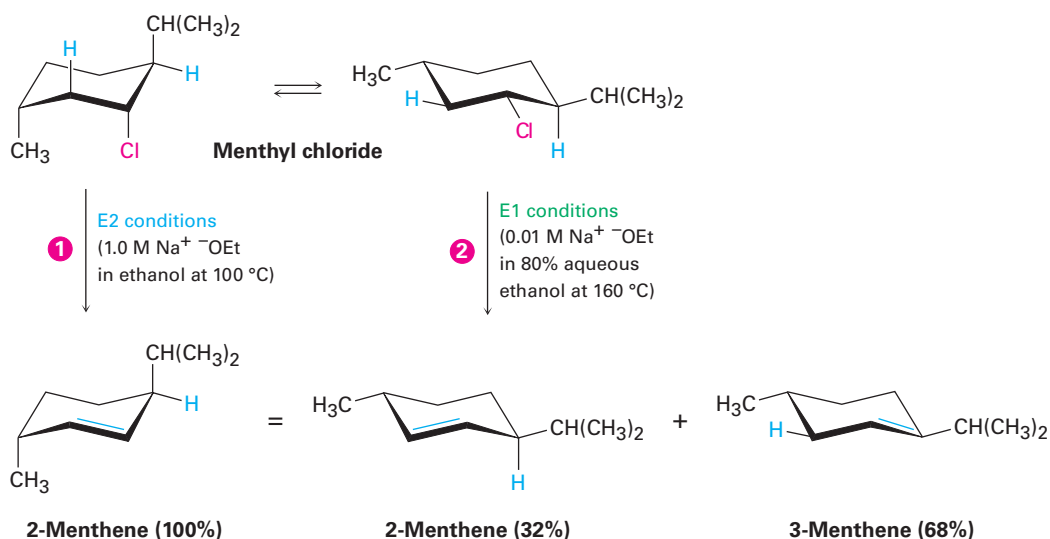
Figure 11.22 Elimination reactions of menthyl chloride. E2 conditions (**1**, strong base in 100% ethanol) lead to 2-menthene through an anti periplanar elimination, whereas E1 conditions (**2**, dilute base in 80% aqueous ethanol) lead to a mixture of 2-menthene and 3-menthene.

The E1cB Reaction

In contrast to the E1 reaction, which involves a carbocation intermediate, the **E1cB reaction** takes place through a carbanion intermediate. Base-induced abstraction of a proton in a slow, rate-limiting step gives an anion, which expels a leaving group on the adjacent carbon. The reaction is particularly common in substrates that have a poor leaving group, such as −OH, two carbons removed from a carbonyl group, HO—C—CH—C=O. The poor leaving group disfavors the alternative E1 and E2 possibilities, and the carbonyl group makes the adjacent hydrogen unusually acidic by resonance stabilization of

the anion intermediate. We'll look at this acidifying effect of a carbonyl group in **Section 22.5**.

Resonance-stabilized anion
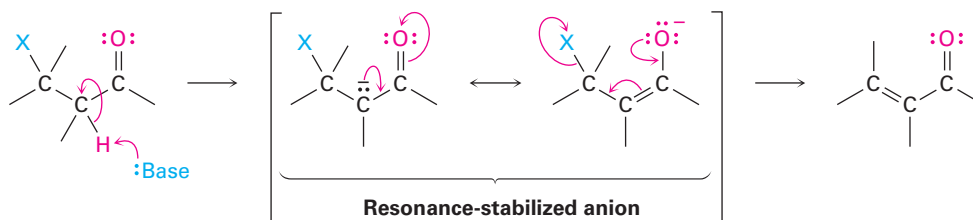
11.11 Biological Elimination Reactions

All three elimination reactions—E2, E1, and E1cB—occur in biological pathways, but the E1cB mechanism is particularly common. The substrate is usually an alcohol rather than an alkyl halide, and the H atom removed is usually adjacent to a carbonyl group, just as in laboratory reactions. Thus, 3-hydroxy carbonyl compounds are frequently converted to unsaturated carbonyl compounds by elimination reactions. A typical example occurs during the biosynthesis of fats when a 3-hydroxybutyryl thioester is dehydrated to the corresponding unsaturated (crotonyl) thioester. The base in this reaction is a histidine amino acid in the enzyme, and loss of the −OH group is assisted by simultaneous protonation.

Crotonyl thioester

3-Hydroxybutyryl thioester
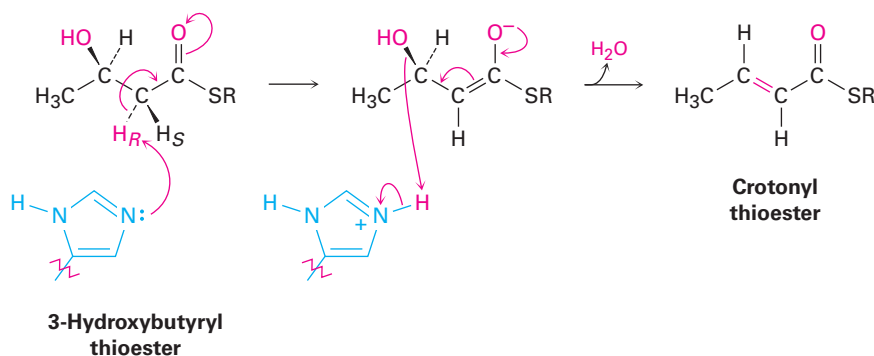
11.12 A Summary of Reactivity: S$_N$1, S$_N$2, E1, E1cB, and E2

S$_N$1, S$_N$2, E1, E1cB, E2—how can you keep it all straight and predict what will happen in any given case? Will substitution or elimination occur? Will the reaction be bimolecular or unimolecular? There are no rigid answers to these questions, but it's possible to recognize some trends and make some generalizations.

- **Primary alkyl halides**   S$_N$2 substitution occurs if a good nucleophile is used, E2 elimination occurs if a strong, sterically hindered base is used, and E1cB elimination occurs if the leaving group is two carbons away from a carbonyl group.

- **Secondary alkyl halides** S_N2 substitution occurs if a weakly basic nucleophile is used in a polar aprotic solvent, E2 elimination predominates if a strong base is used, and E1cB elimination takes place if the leaving group is two carbons away from a carbonyl group. Secondary allylic and benzylic alkyl halides can also undergo S_N1 and E1 reactions if a weakly basic nucleophile is used in a protic solvent.

- **Tertiary alkyl halides** E2 elimination occurs when a base is used, but S_N1 substitution and E1 elimination occur together under neutral conditions, such as in pure ethanol or water. E1cB elimination takes place if the leaving group is two carbons away from a carbonyl group.

Worked Example 11.5

Predicting the Product and Mechanism of Reactions

Tell whether each of the following reactions is likely to be S_N1, S_N2, E1, E1cB, or E2, and predict the product of each:

(a)

(b)
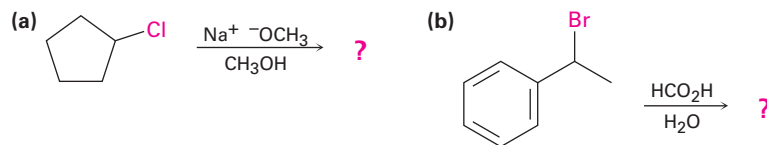
Strategy

Look carefully in each reaction at the structure of the substrate, the leaving group, the nucleophile, and the solvent. Then decide from the preceding summary which kind of reaction is likely to be favored.

Solution

(a) A secondary, nonallylic substrate can undergo an S_N2 reaction with a good nucleophile in a polar aprotic solvent but will undergo an E2 reaction on treatment with a strong base in a protic solvent. In this case, E2 reaction is likely to predominate.
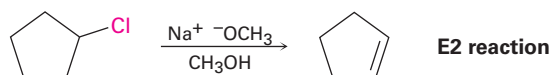
E2 reaction

(b) A secondary benzylic substrate can undergo an S_N2 reaction on treatment with a nonbasic nucleophile in a polar aprotic solvent and will undergo an E2 reaction on treatment with a base. Under protic conditions, such as aqueous formic acid (HCO_2H), an S_N1 reaction is likely, along with some E1 reaction.

S_N1 E1
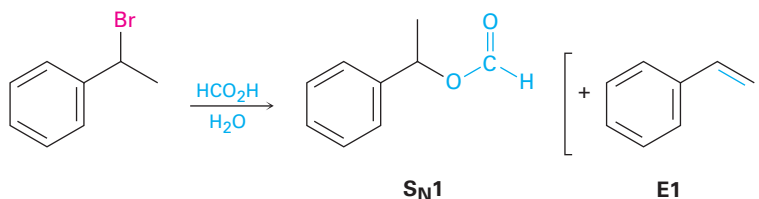
Problem 11.20

Tell whether each of the following reactions is likely to be S_N1, S_N2, E1, E1cB, or E2:

(a) $CH_3CH_2CH_2CH_2Br \xrightarrow[\text{THF}]{\text{NaN}_3} CH_3CH_2CH_2CH_2N{=}N{=}N$

(b)

$$CH_3CH_2\underset{\underset{Cl}{|}}{CH}CH_2CH_3 \xrightarrow[\text{Ethanol}]{\text{KOH}} CH_3CH_2CH{=}CHCH_3$$

(c)

$\xrightarrow{CH_3CO_2H}$

(d)

$\xrightarrow[\text{Ethanol}]{\text{NaOH}}$
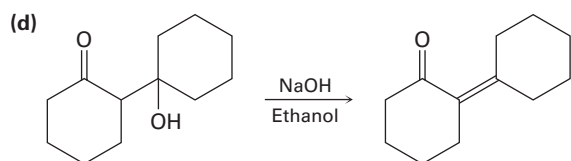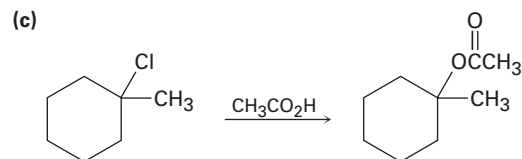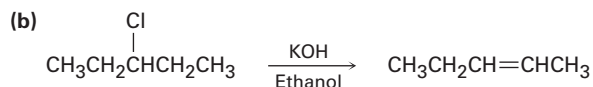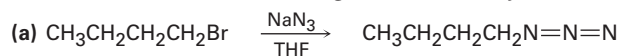
| A DEEPER LOOK | ## Green Chemistry

Organic chemistry in the 20th century changed the world, giving us new medicines, insecticides, adhesives, textiles, dyes, building materials, composites, and all manner of polymers. But these advances did not come without a cost: every chemical process produces wastes that must be dealt with, including reaction solvents and toxic by-products that might evaporate into the air or be leached into groundwater if not disposed of properly. Even apparently harmless by-products must be safely buried or otherwise sequestered. As always, there's no such thing as a free lunch; with the good also comes the bad.

It may never be possible to make organic chemistry completely benign, but awareness of the environmental problems caused by many chemical processes has grown dramatically in recent years, giving rise to a movement called *green chemistry*. Green chemistry is the design and implementation of chemical products and processes that reduce waste and attempt to eliminate the generation of hazardous substances. There are 12 principles of green chemistry:

Prevent waste – Waste should be prevented rather than treated or cleaned up after it has been created.

Maximize atom economy – Synthetic methods should maximize the incorporation of all materials used in a process into the final product so that waste is minimized.

Use less hazardous processes – Synthetic methods should use reactants and generate wastes with minimal toxicity to health and the environment.

Let's hope disasters like this are never repeated.

(continued)

Design safer chemicals – Chemical products should be designed to have minimal toxicity.

Use safer solvents – Minimal use should be made of solvents, separation agents, and other auxiliary substances in a reaction.

Design for energy efficiency – Energy requirements for chemical processes should be minimized, with reactions carried out at room temperature if possible.

Use renewable feedstocks – Raw materials should come from renewable sources when feasible.

Minimize derivatives – Syntheses should be designed with minimal use of protecting groups to avoid extra steps and reduce waste.

Use catalysis – Reactions should be catalytic rather than stoichiometric.

Design for degradation – Products should be designed to be biodegradable at the end of their useful lifetimes.

Monitor pollution in real time – Processes should be monitored in real time for the formation of hazardous substances.

Prevent accidents – Chemical substances and processes should minimize the potential for fires, explosions, or other accidents.

The foregoing 12 principles won't all be met in most real-world applications, but they provide a worthy goal to aim for and they can make chemists think more carefully about the environmental implications of their work. Real success stories are already occurring, and more are in progress. Approximately 7 million pounds per year of ibuprofen (6 billion tablets!) is now made by a "green" process that produces approximately 99% less waste than the process it replaces. Only three steps are needed, the anhydrous HF solvent used in the first step is recovered and reused, and the second and third steps are catalytic.

Isobutylbenzene → **Ibuprofen**
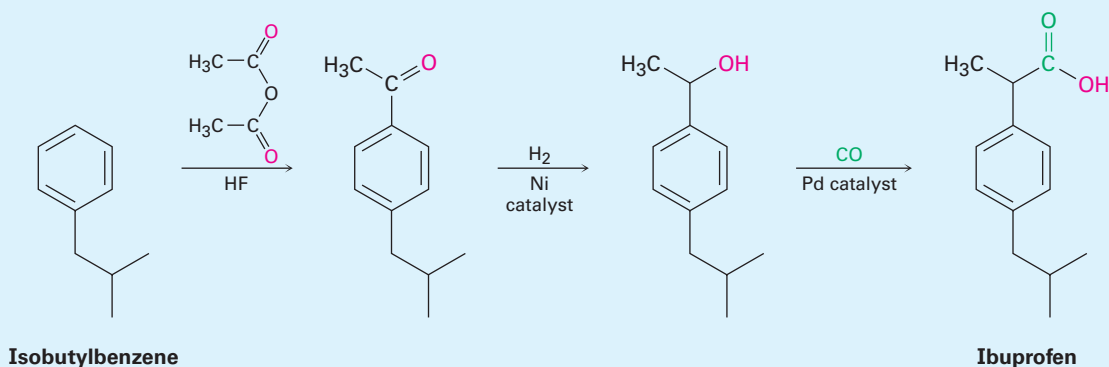
Summary

The reaction of an alkyl halide or tosylate with a nucleophile/base results either in *substitution* or in *elimination*. The resultant nucleophilic substitution and base-induced elimination reactions are two of the most widely occurring and versatile reaction types in organic chemistry, both in the laboratory and in biological pathways.

Nucleophilic substitutions are of two types: **S_N2 reactions** and **S_N1 reactions**. In the S_N2 reaction, the entering nucleophile approaches the halide from a direction 180° away from the leaving group, resulting in an umbrella-like inversion of configuration at the carbon atom. The reaction is kinetically **second-order** and is strongly inhibited by increasing steric bulk of the reactants. Thus, S_N2 reactions are favored for primary and secondary substrates.

In the S_N1 reaction, the substrate spontaneously dissociates to a carbocation in a slow **rate-limiting step**, followed by a rapid reaction with the nucleophile. As a result, S_N1 reactions are kinetically **first-order** and take place with substantial racemization of configuration at the carbon atom. They are most favored for tertiary substrates. Both S_N1 and S_N2 reactions occur in biological pathways, although the leaving group is typically a diphosphate ion rather than a halide.

Eliminations of alkyl halides to yield alkenes occur by three mechanisms: **E2 reactions**, **E1 reactions**, and **E1cB reactions**, which differ in the timing of C—H and C—X bond-breaking. In the E2 reaction, C—H and C—X bond-breaking occur simultaneously when a base abstracts H^+ from one carbon at the same time the leaving group departs from the neighboring carbon. The reaction takes place preferentially through an **anti periplanar** transition state in which the four reacting atoms—hydrogen, two carbons, and leaving group—are in the same plane. The reaction shows second-order kinetics and a **deuterium isotope effect**, and occurs when a secondary or tertiary substrate is treated with a strong base. These elimination reactions usually give a mixture of alkene products in which the more highly substituted alkene predominates (**Zaitsev's rule**).

In the E1 reaction, C—X bond-breaking occurs first. The substrate dissociates to yield a carbocation in the slow rate-limiting step before losing H^+ from an adjacent carbon in a second step. The reaction shows first-order kinetics and no deuterium isotope effect and occurs when a tertiary substrate reacts in polar, nonbasic solution.

In the E1cB reaction, C—H bond-breaking occurs first. A base abstracts a proton to give a carbanion, followed by loss of the leaving group from the adjacent carbon in a second step. The reaction is favored when the leaving group is two carbons removed from a carbonyl, which stabilizes the intermediate anion by resonance. Biological elimination reactions typically occur by this E1cB mechanism.

In general, substrates react in the following way:

RCH$_2$X   ⟶   Mostly S$_N$2 substitution
(primary)

R$_2$CHX   ⟶   S$_N$2 substitution with nonbasic nucleophiles
(secondary)   E2 elimination with strong bases

R$_3$CX   ⟶   Mostly E2 elimination
(tertiary)   (S$_N$1 substitution and E1 elimination in nonbasic solvents)

Key words

anti periplanar, 401
benzylic, 390
deuterium isotope effect, 400
E1 reaction, 405
E1cB reaction, 406
E2 reaction, 399
first-order reaction, 386
kinetics, 375
nucleophilic substitution reaction, 373
second-order reaction, 376
S_N1 reaction, 386
S_N2 reaction, 376
solvation, 383
syn periplanar, 401
Zaitsev's rule, 397

Summary of Reactions

1. Nucleophilic substitutions
   (a) S_N1 reaction of 3°, allylic, and benzylic halides (Sections 11.4 and 11.5)
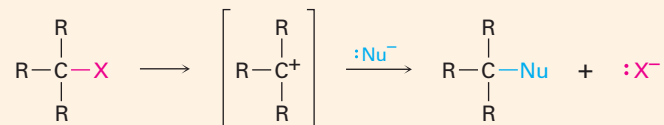
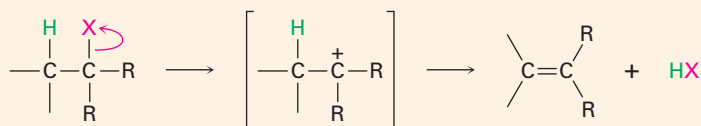

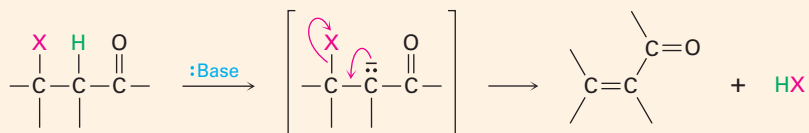   (b) S_N2 reaction of 1° and simple 2° halides (Sections 11.2 and 11.3)
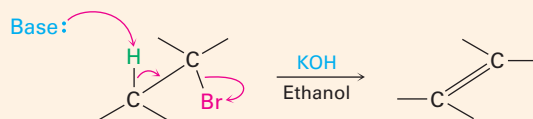

2. Eliminations
   (a) E1 reaction (Section 11.10)

   (b) E1cB reaction (Section 11.10)

   (c) E2 reaction (Section 11.8)

Exercises

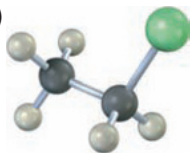## Visualizing Chemistry
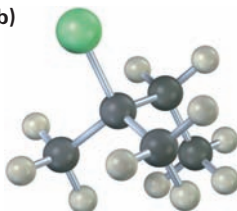
(Problems 11.1–11.20 appear within the chapter.)

11.21 Write the product you would expect from reaction of each of the following alkyl halides with (1) Na^+ $^-SCH_3$ and (2) Na^+ ^-OH (green = Cl):

(a)   **(b)**   **(c)**
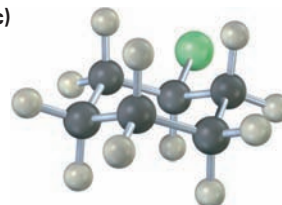
11.22 From what alkyl bromide was the following alkyl acetate made by S_N2 reaction? Write the reaction, showing all stereochemistry.
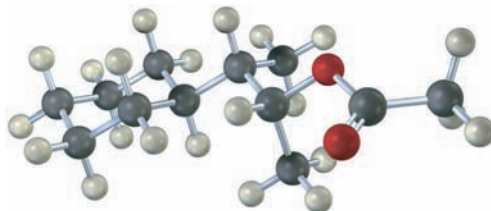
11.23 Assign *R* or *S* configuration to the following molecule, write the product you would expect from S_N2 reaction with NaCN, and assign *R* or *S* configuration to the product (green = Cl):
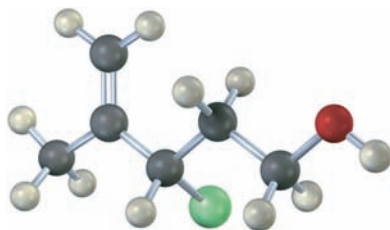
11.24 Draw the structure and assign *Z* or *E* stereochemistry to the product you expect from E2 reaction of the following molecule with NaOH (green = Cl):
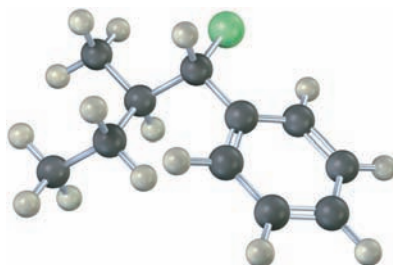
▲ Problems linked to Key Ideas in this chapter

Additional Problems

Nucleophilic Substitution Reactions

11.25 Draw all isomers of C_4H_9Br, name them, and arrange them in order of decreasing reactivity in the S_N2 reaction.

11.26 The following Walden cycle has been carried out. Explain the results, and indicate where Walden inversion is occurring.
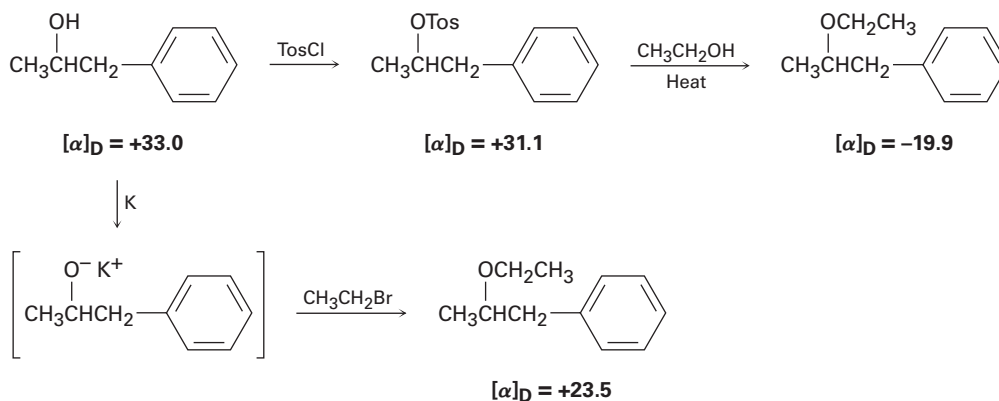
11.27 ▲ Which compound in each of the following pairs will react faster in an S_N2 reaction with OH^-?
(a) CH_3Br or CH_3I
(b) CH_3CH_2I in ethanol or in dimethyl sulfoxide
(c) $(CH_3)_3CCl$ or CH_3Cl
(d) $H_2C=CHBr$ or $H_2C=CHCH_2Br$

11.28 Which reactant in each of the following pairs is more nucleophilic? Explain.
(a) $^-NH_2$ or NH_3 **(b)** H_2O or $CH_3CO_2^-$
(c) BF_3 or F^- **(d)** $(CH_3)_3P$ or $(CH_3)_3N$
(e) I^- or Cl^- **(f)** $^-C\equiv N$ or $^-OCH_3$

11.29 What effect would you expect the following changes to have on the rate of the S_N2 reaction of 1-iodo-2-methylbutane with cyanide ion?
(a) The CN^- concentration is halved, and the 1-iodo-2-methylbutane concentration is doubled.
(b) Both the CN^- and the 1-iodo-2-methylbutane concentrations are tripled.

11.30 What effect would you expect the following changes to have on the rate of the reaction of ethanol with 2-iodo-2-methylbutane?
(a) The concentration of the halide is tripled.
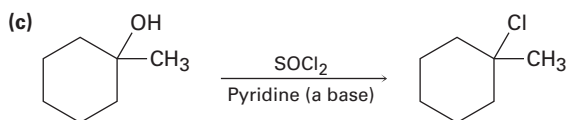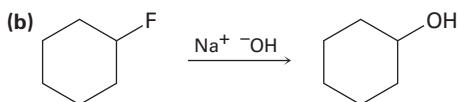**(b)** The concentration of the ethanol is halved by adding diethyl ether as an inert solvent.

▲ Problems linked to Key Ideas in this chapter

11.31 How might you prepare each of the following molecules using a nucleophilic substitution reaction at some step?

(a)   CH$_3$
CH$_3$C≡CCHCH$_3$

(b)   CH$_3$
CH$_3$—O—CCH$_3$
            CH$_3$

(c) CH$_3$CH$_2$CH$_2$CH$_2$CN

(d) CH$_3$CH$_2$CH$_2$NH$_2$
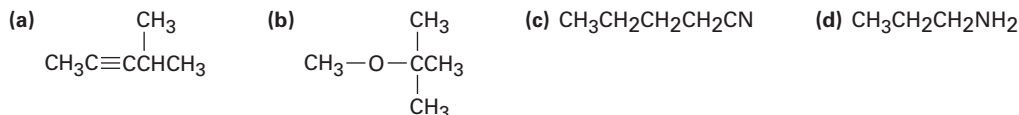
11.32 ▲ Which reaction in each of the following pairs would you expect to be faster?
(a) The S$_N$2 displacement by I⁻ on CH$_3$Cl or on CH$_3$OTos
(b) The S$_N$2 displacement by CH$_3$CO$_2$⁻ on bromoethane or on bromocyclohexane
(c) The S$_N$2 displacement on 2-bromopropane by CH$_3$CH$_2$O⁻ or by CN⁻
(d) The S$_N$2 displacement by HC≡C⁻ on bromomethane in benzene or in acetonitrile

11.33 Predict the product and give the stereochemistry resulting from reaction of each of the following nucleophiles with (R)-2-bromooctane:
(a) ⁻CN   (b) CH$_3$CO$_2$⁻   (c) CH$_3$S⁻

11.34 (R)-2-Bromooctane undergoes racemization to give (±)-2-bromooctane when treated with NaBr in dimethyl sulfoxide. Explain.

Elimination Reactions

11.35 Propose structures for compounds that fit the following descriptions:
(a) An alkyl halide that gives a mixture of three alkenes on E2 reaction
(b) An organohalide that will not undergo nucleophilic substitution
(c) An alkyl halide that gives the non-Zaitsev product on E2 reaction
(d) An alcohol that reacts rapidly with HCl at 0 °C

11.36 What products would you expect from the reaction of 1-bromopropane with each of the following?
(a) NaNH$_2$ (b) KOC(CH$_3$)$_3$ (c) NaI
(d) NaCN   (e) NaC≡CH   (f) Mg, then H$_2$O

11.37 1-Chloro-1,2-diphenylethane can undergo E2 elimination to give either cis- or trans-1,2-diphenylethylene (stilbene). Draw Newman projections of the reactive conformations leading to both possible products, and suggest a reason why the trans alkene is the major product.

1-Chloro-1,2-diphenylethane   **trans-1,2-Diphenylethylene**
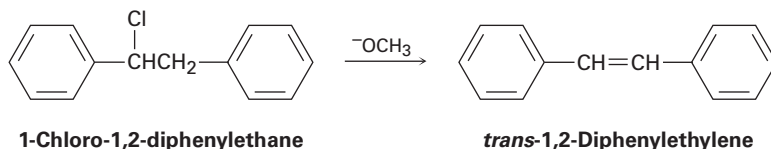
11.38 Predict the major alkene product of the following E1 reaction:
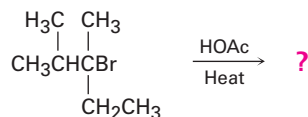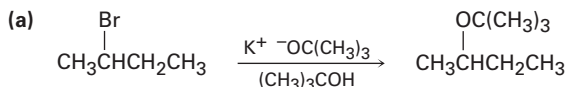

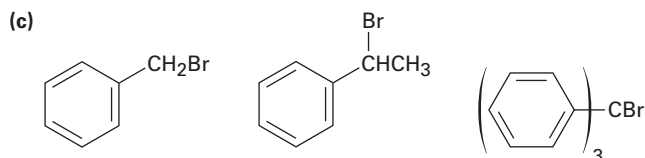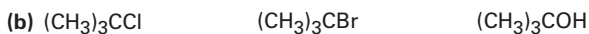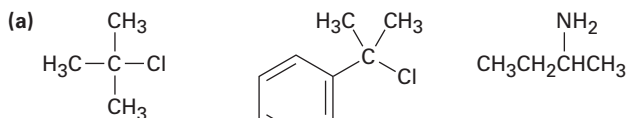▲ Problems linked to Key Ideas in this chapter

11.39 There are eight diastereomers of 1,2,3,4,5,6-hexachlorocyclohexane. Draw each in its more stable chair conformation. One isomer loses HCl in an E2 reaction nearly 1000 times more slowly than the others. Which isomer reacts so slowly, and why?

General Problems

11.40 The reactions shown below are unlikely to occur as written. Tell what is wrong with each, and predict the actual product.

(a)
$$CH_3\overset{\displaystyle Br}{\underset{\displaystyle |}{CH}}CH_2CH_3 \xrightarrow[\text{(CH}_3\text{)}_3\text{COH}]{K^+ \ ^-OC(CH_3)_3} CH_3\overset{\displaystyle OC(CH_3)_3}{\underset{\displaystyle |}{CH}}CH_2CH_3$$

(b)

(c)

11.41 ▲ Order each of the following sets of compounds with respect to S_N1 reactivity:

(a)

(b) $(CH_3)_3CCl$ $(CH_3)_3CBr$ $(CH_3)_3COH$

(c)

11.42 ▲ Order each of the following sets of compounds with respect to S_N2 reactivity:

(a)

(b)

(c) $CH_3CH_2CH_2OCH_3$ $CH_3CH_2CH_2OTos$ $CH_3CH_2CH_2Br$
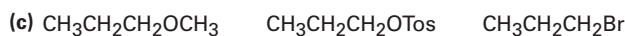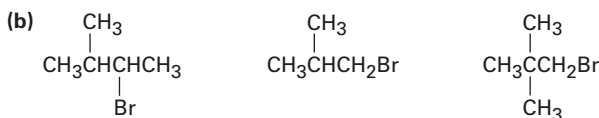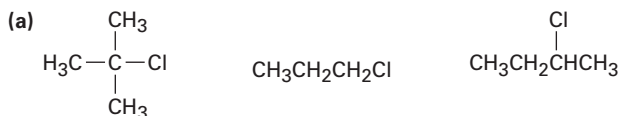

▲ Problems linked to Key Ideas in this chapter

**11.43** Reaction of the following *S* tosylate with cyanide ion yields a nitrile product that also has *S* stereochemistry. Explain.

H OTos
C
H₃C   CH₂OCH₃ $\xrightarrow{\text{NaCN}}$ **?**

(S stereochemistry)
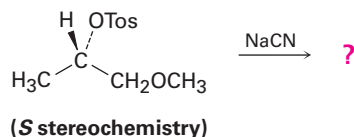
11.44 Ethers can often be prepared by S_N2 reaction of alkoxide ions, RO⁻, with alkyl halides. Suppose you wanted to prepare cyclohexyl methyl ether. Which of the two possible routes shown below would you choose? Explain.

O⁻   +   CH₃I

or

I   +   CH₃O⁻

$\longrightarrow$ OCH₃
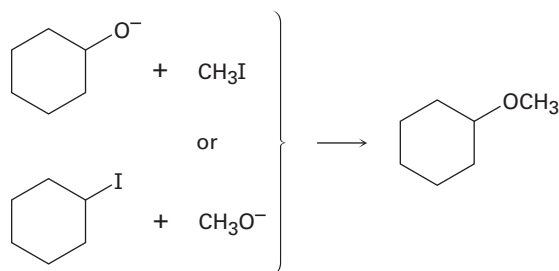
11.45 We saw in Section 8.7 that bromohydrins are converted into epoxides when treated with base. Propose a mechanism, using curved arrows to show the electron flow.

HO   Br
H   C—C   CH₃ $\xrightarrow[\text{Ethanol}]{\text{NaOH}}$ H   C—C   H
     CH₃ H   CH₃   CH₃
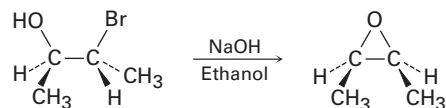
11.46 Show the stereochemistry of the epoxide (see Problem 11.45) you would obtain by formation of a bromohydrin from *trans*-2-butene, followed by treatment with base.

11.47 In light of your answer to Problem 11.45, what product might you expect from treatment of 4-bromo-1-butanol with base?

BrCH₂CH₂CH₂CH₂OH $\xrightarrow{\text{Base}}$ **?**
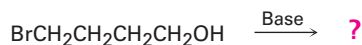
11.48 ▲ The following tertiary alkyl bromide does not undergo a nucleophilic substitution reaction by either S_N1 or S_N2 mechanisms. Explain.

Br

▲ Problems linked to Key Ideas in this chapter

11.49 In addition to not undergoing substitution reactions, the alkyl bromide shown in Problem 11.48 also fails to undergo an elimination reaction when treated with base. Explain.

11.50 The tosylate of (2R,3S)-3-phenyl-2-butanol undergoes E2 elimination on treatment with sodium ethoxide to yield (Z)-2-phenyl-2-butene. Explain, using Newman projections.


$$Na^+\ {}^-OCH_2CH_3$$

CH₃CHCHCH₃
  |
 OTos

CH₃C=CHCH₃
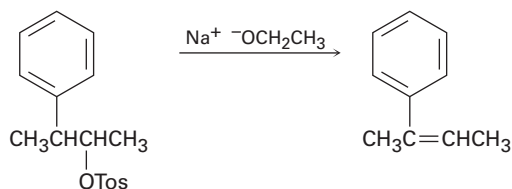
11.51 In light of your answer to Problem 11.50, which alkene, *E* or *Z,* would you expect from an E2 reaction on the tosylate of (2R,3R)-3-phenyl-2-butanol? Which alkene would result from E2 reaction on the (2S,3R) and (2S,3S) tosylates? Explain.

11.52 How can you explain the fact that *trans*-1-bromo-2-methylcyclohexane yields the non-Zaitsev elimination product 3-methylcyclohexene on treatment with base?

KOH

***trans*-1-Bromo-2-methylcyclohexane**   **3-Methylcyclohexene**
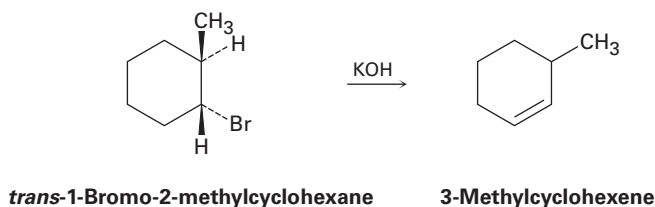
11.53 Predict the product(s) of the following reaction, indicating stereochemistry where necessary:

$$\xrightarrow[\text{Ethanol}]{\text{H}_2\text{O}}$$ **?**

▲ Problems linked to Key Ideas in this chapter
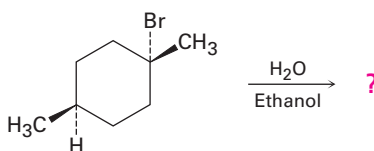
**11.54** Metabolism of *S*-adenosylhomocysteine (Section 11.6) involves the following sequence. Propose a mechanism for the second step.


S-Adenosylhomocysteine
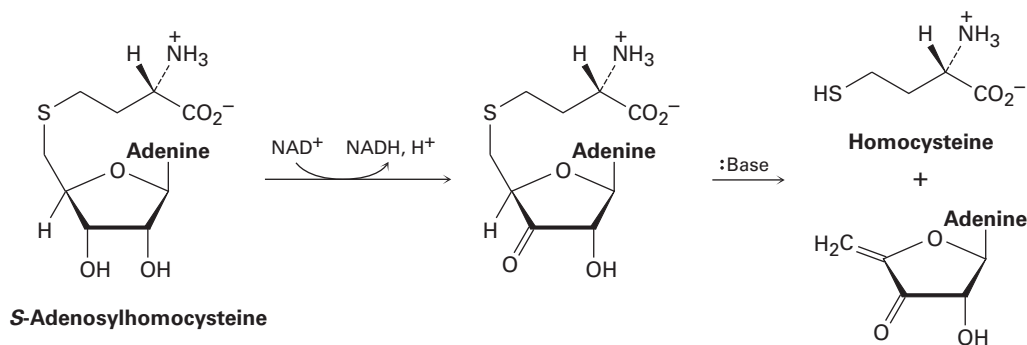
11.55 Reaction of iodoethane with CN^- yields a small amount of *isonitrile,* $CH_3CH_2N\equiv C$, along with the nitrile $CH_3CH_2C\equiv N$ as the major product. Write electron-dot structures for both products, assign formal charges as necessary, and propose mechanisms to account for their formation.

11.56 ▲ Alkynes can be made by dehydrohalogenation of vinylic halides in a reaction that is essentially an E2 process. In studying the stereochemistry of this elimination, it was found that (*Z*)-2-chloro-2-butenedioic acid reacts 50 times as fast as the corresponding *E* isomer. What conclusion can you draw about the stereochemistry of eliminations in vinylic halides? How does this result compare with eliminations of alkyl halides?
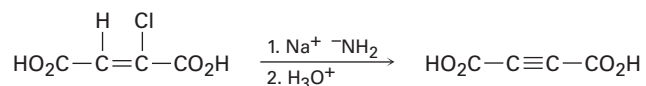
**11.57** (*S*)-2-Butanol slowly racemizes on standing in dilute sulfuric acid. Explain.
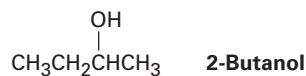
11.58 Reaction of HBr with (*R*)-3-methyl-3-hexanol leads to racemic 3-bromo-3-methylhexane. Explain.

▲ Problems linked to Key Ideas in this chapter
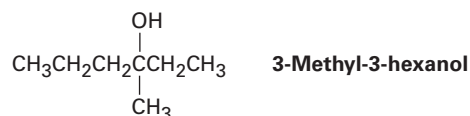
11.59 Treatment of 1-bromo-2-deuterio-2-phenylethane with strong base leads to a mixture of deuterated and nondeuterated phenylethylenes in an approximately 7 : 1 ratio. Explain.


7 : 1 ratio
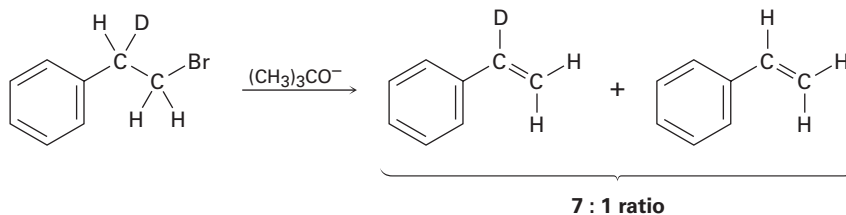
11.60 ▲ Propose a structure for an alkyl halide that gives only (*E*)-3-methyl-2-phenyl-2-pentene on E2 elimination. Make sure you indicate the stereochemistry.

11.61 One step in the urea cycle for ridding the body of ammonia is the conversion of argininosuccinate to the amino acid arginine plus fumarate. Propose a mechanism for the reaction, and show the structure of arginine.


Argininosuccinate   **Fumarate**
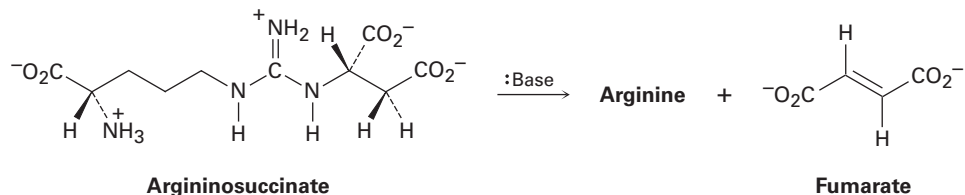
11.62 Although anti periplanar geometry is preferred for E2 reactions, it isn't absolutely necessary. The deuterated bromo compound shown here reacts with strong base to yield an undeuterated alkene. Clearly, a syn elimination has occurred. Make a molecular model of the reactant, and explain the result.

▲ Problems linked to Key Ideas in this chapter
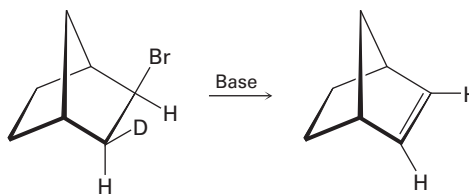
11.63 In light of your answer to Problem 11.62, explain why one of the following isomers undergoes E2 reaction approximately 100 times as fast as the other. Which isomer is more reactive, and why?

(a)

(b)
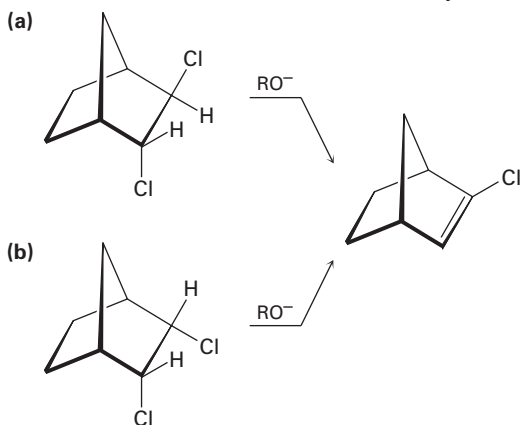
11.64 Methyl esters (RCO_2CH_3) undergo a cleavage reaction to yield carboxylate ions plus iodomethane on heating with LiI in dimethylformamide:
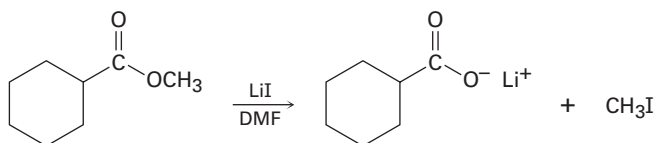

The following evidence has been obtained: (1) The reaction occurs much faster in DMF than in ethanol. (2) The corresponding ethyl ester ($RCO_2CH_2CH_3$) cleaves approximately 10 times more slowly than the methyl ester. Propose a mechanism for the reaction. What other kinds of experimental evidence could you gather to support your hypothesis?

11.65 The reaction of 1-chlorooctane with $CH_3CO_2{}^-$ to give octyl acetate is greatly accelerated by adding a small quantity of iodide ion. Explain.

11.66 Compound **X** is optically inactive and has the formula $C_{16}H_{16}Br_2$. On treatment with strong base, **X** gives hydrocarbon **Y**, $C_{16}H_{14}$. Compound **Y** absorbs 2 equivalents of hydrogen when reduced over a palladium catalyst and reacts with ozone to give two fragments. One fragment, **Z**, is an aldehyde with formula C_7H_6O. The other fragment is glyoxal, $(CHO)_2$. Write the reactions involved, and suggest structures for **X**, **Y**, and **Z**. What is the stereochemistry of **X**?

▲ Problems linked to Key Ideas in this chapter

11.67 When a primary alcohol is treated with *p*-toluenesulfonyl chloride at room temperature in the presence of an organic base such as pyridine, a tosylate is formed. When the same reaction is carried out at higher temperature, an alkyl chloride is often formed. Explain.
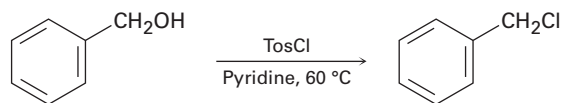

11.68 S_N2 reactions take place with inversion of configuration, and S_N1 reactions take place with racemization. The following substitution reaction, however, occurs with complete *retention* of configuration. Propose a mechanism.
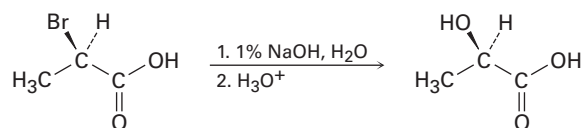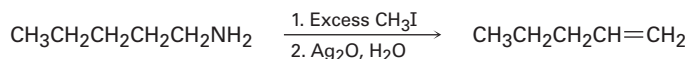

11.69 Propose a mechanism for the following reaction, an important step in the laboratory synthesis of proteins:
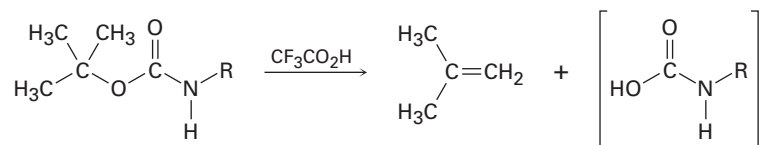

11.70 The amino acid methionine is formed by a methylation reaction of homocysteine with *N*-methyltetrahydrofolate. The stereochemistry of the reaction has been probed by carrying out the transformation using a donor with a "chiral methyl group" that contains protium (H), deuterium (D), and tritium (T) isotopes of hydrogen. Does the methylation reaction occur with inversion or retention of configuration?

Homocysteine   **Methionine**

N-**Methyltetrahydrofolate**   **Tetrahydrofolate**

▲ Problems linked to Key Ideas in this chapter
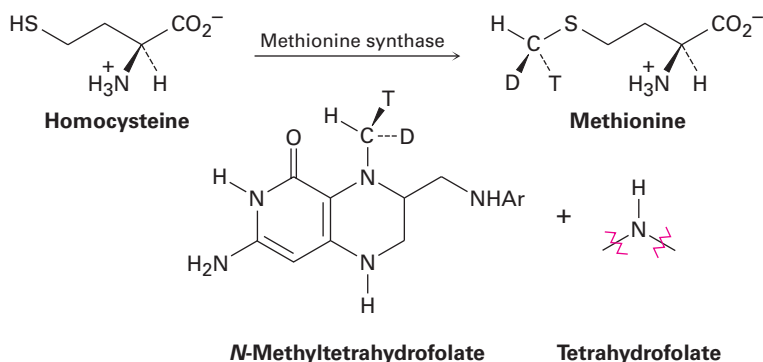
11.71 Amines are converted into alkenes by a two-step process called the *Hofmann elimination.* S_N2 reaction of the amine with an excess of CH_3I in the first step yields an intermediate that undergoes E2 reaction when treated with silver oxide as base. Pentylamine, for example, yields 1-pentene. Propose a structure for the intermediate, and explain why it undergoes ready elimination.

$$CH_3CH_2CH_2CH_2CH_2NH_2 \xrightarrow[\text{2. Ag}_2\text{O, H}_2\text{O}]{\text{1. Excess CH}_3\text{I}} CH_3CH_2CH_2CH=CH_2$$

11.72 The antipsychotic drug flupentixol is prepared by the following scheme:
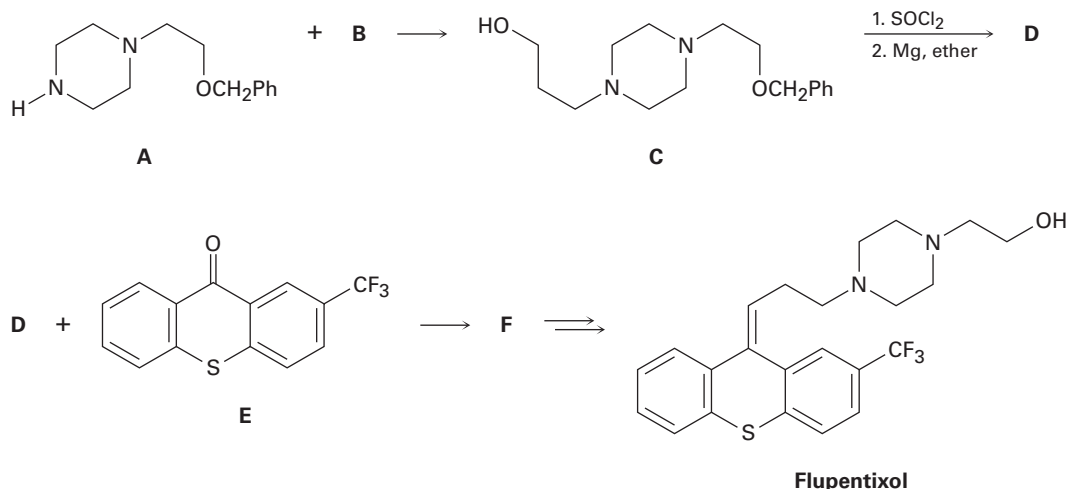
(a) What alkyl chloride **B** reacts with amine **A** to form **C**?
(b) Compound **C** is treated with $SOCl_2$, and the product is allowed to react with magnesium metal to give a Grignard reagent **D**. What is the structure of **D**?
(c) We'll see in Section 19.7 that Grignard reagents add to ketones, such as **E**, to give tertiary alcohols, such as **F**. Because of the newly formed chirality center, compound **F** exists as a pair of enantiomers. Draw both, and assign *R,S* configuration.
(d) Two stereoisomers of flupentixol are subsequently formed from **F**, but only one is shown. Draw the other isomer, and identify the type of stereoisomerism.

▲ Problems linked to Key Ideas in this chapter

12

More than a thousand different chemical compounds have been isolated from coffee. Their structures were determined using various spectroscopic techniques. © webphotographeer/iStockphoto

Structure Determination: Mass Spectrometry and Infrared Spectroscopy

Every time a reaction is run, the products must be identified, and every time a new compound is found in nature, its structure must be determined. Determining the structure of an organic compound was a difficult and time-consuming process until the mid-20th century, but powerful techniques and specialized instruments are now routinely available to simplify the problem. In this and the next two chapters, we'll look at four such techniques—mass spectrometry (MS), infrared (IR) spectroscopy, ultraviolet spectroscopy (UV), and nuclear magnetic resonance spectroscopy (NMR)—and we'll see the kind of information that can be obtained from each.

Mass spectrometry	What is the size and formula?
Infrared spectroscopy	What functional groups are present?
Ultraviolet spectroscopy	Is a conjugated π electron system present?
Nuclear magnetic resonance spectroscopy	What is the carbon–hydrogen framework?

Why This Chapter? Finding the structures of new molecules, whether small ones synthesized in the laboratory or large proteins and nucleic acids found in living organisms, is central to progress in chemistry and biochemistry. We can only scratch the surface of structure determination in this book, but after reading this and the following two chapters, you should have a good idea of the range of structural techniques available and of how and when each is used.
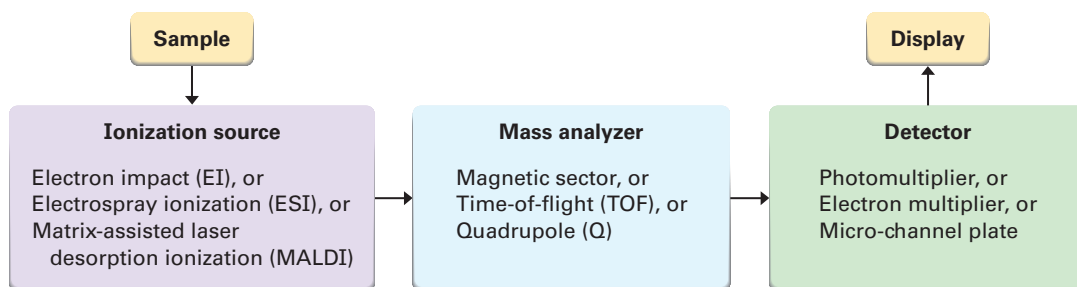
12.1 Mass Spectrometry of Small Molecules: Magnetic-Sector Instruments

At its simplest, **mass spectrometry (MS)** is a technique for measuring the mass, and therefore the molecular weight (MW), of a molecule. In addition,

it's often possible to gain structural information about a molecule by measuring the masses of the fragments produced when molecules are broken apart.

More than 20 different kinds of commercial mass spectrometers are available depending on the intended application, but all have three basic parts: an *ionization source* in which sample molecules are given an electrical charge, a *mass analyzer* in which ions are separated by their mass-to-charge ratio, and a *detector* in which the separated ions are observed and counted.

| Sample		
Ionization source	**Mass analyzer**	**Detector**
Electron impact (EI), or Electrospray ionization (ESI), or Matrix-assisted laser desorption ionization (MALDI)	Magnetic sector, or Time-of-flight (TOF), or Quadrupole (Q)	Photomultiplier, or Electron multiplier, or Micro-channel plate

Display

Among the most common mass spectrometers used for routine purposes in the laboratory is the electron-impact, magnetic-sector instrument shown schematically in **Figure 12.1**. A small amount of sample is vaporized into the ionization source, where it is bombarded by a stream of high-energy electrons. The energy of the electron beam can be varied but is commonly around 70 electron volts (eV), or 6700 kJ/mol. When a high-energy electron strikes an organic molecule, it dislodges a valence electron from the molecule, producing a *cation radical—cation* because the molecule has lost an electron and now has a positive charge; *radical* because the molecule now has an odd number of electrons.

$$RH \xrightarrow{\ e^- \ } RH^{+\cdot} \ + \ e^-$$

| **Organic molecule** | **Cation radical** |
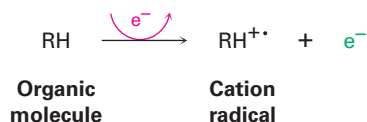
Electron bombardment transfers so much energy that most of the cation radicals fragment after formation. They fly apart into smaller pieces, some of which retain the positive charge and some of which are neutral. The fragments then flow through a curved pipe in a strong magnetic field, which deflects them into different paths according to their mass-to-charge ratio (m/z). Neutral fragments are not deflected by the magnetic field and are lost on the walls of the pipe, but positively charged fragments are sorted by the mass spectrometer onto a detector, which records them as peaks at the various m/z ratios. Since the number of charges z on each ion is usually 1, the value of m/z for each ion is simply its mass m. Masses up to approximately 2500 atomic mass units (amu) can be analyzed.

Figure 12.1 A representation of an electron-ionization, magnetic-sector mass spectrometer. Molecules are ionized by collision with high-energy electrons, causing some of the molecules to fragment. Passage of the charged fragments through a magnetic field then sorts them according to their mass.
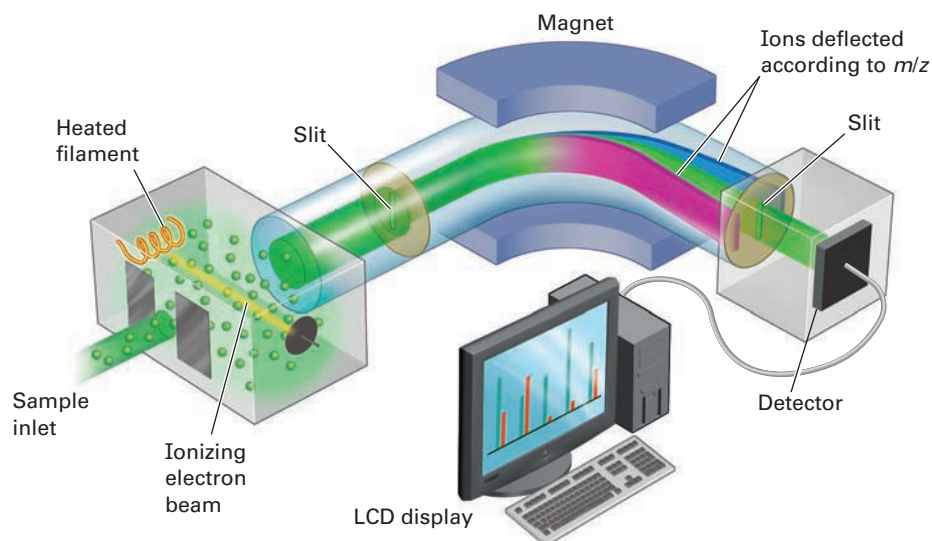
The **mass spectrum** of a compound is typically presented as a bar graph, with masses (m/z values) on the x axis and intensity, or relative abundance of ions of a given m/z striking the detector, on the y axis. The tallest peak, assigned an intensity of 100%, is called the **base peak**, and the peak that corresponds to the unfragmented cation radical is called the **parent peak**, or the *molecular ion* (M^+). **Figure 12.2** shows the mass spectrum of propane.
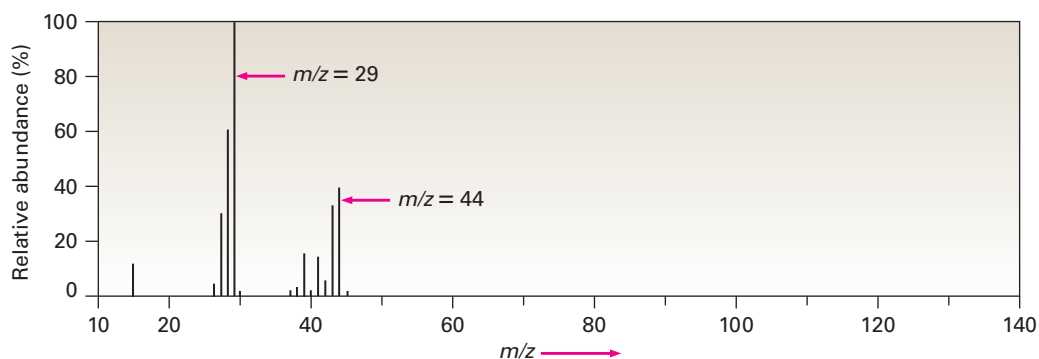
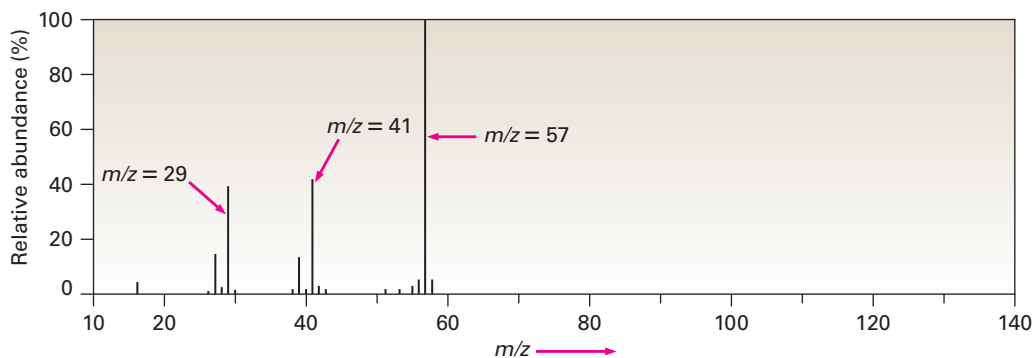**Figure 12.2** Mass spectrum of propane (C_3H_8; MW = 44).

Mass spectral fragmentation patterns are usually complex, and the molecular ion is often not the base peak. The mass spectrum of propane in Figure 12.2, for instance, shows a molecular ion at m/z = 44 that is only about 30% as high as the base peak at m/z = 29. In addition, many other fragment ions are present.

12.2 Interpreting Mass Spectra

What kinds of information can we get from a mass spectrum? The most obvious information is the molecular weight of the sample, which in itself can be invaluable. If we were given samples of hexane (MW = 86), 1-hexene (MW = 84), and 1-hexyne (MW = 82), for example, mass spectrometry would easily distinguish them.

Some instruments, called *double-focusing mass spectrometers,* have such high resolution that they provide exact mass measurements accurate to 5 ppm, or about 0.0005 amu, making it possible to distinguish between two formulas with the same nominal mass. For example, both C_5H_{12} and C_4H_8O have MW=72, but they differ slightly beyond the decimal point: C_5H_{12} has an exact mass of 72.0939 amu, whereas C_4H_8O has an exact mass of 72.0575 amu. A high-resolution instrument can easily distinguish between them. Note, however, that exact mass measurements refer to molecules with specific isotopic compositions. Thus, the sum of the exact atomic masses of the specific isotopes in a molecule is measured—1.00783 amu for ^1H, 12.00000 amu for ^{12}C, 14.00307 amu for ^{14}N, 15.99491 amu for ^{16}O, and so on—rather than the sum of the average atomic masses of elements as found on a periodic table.

Unfortunately, not every compound shows a molecular ion in its electron-impact mass spectrum. Although M^+ is usually easy to identify if it's abundant, some compounds, such as 2,2-dimethylpropane, fragment so easily that no molecular ion is observed **(Figure 12.3)**. In such cases, alternative "soft" ionization methods that do not use electron bombardment can prevent or minimize fragmentation.

Figure 12.3 Mass spectrum of 2,2-dimethylpropane (C_5H_{12}; MW = 72). No molecular ion is observed when electron-impact ionization is used. What do you think is the formula and structure of the M^+ peak at m/z = 57?

Knowing the molecular weight makes it possible to narrow greatly the choices of molecular formula. For example, if the mass spectrum of an unknown compound shows a molecular ion at $m/z = 110$, the molecular formula is likely to be C_8H_{14}, $C_7H_{10}O$, $C_6H_6O_2$, or $C_6H_{10}N_2$. There are always a number of molecular formulas possible for all but the lowest molecular weights, and a computer can easily generate a list of choices.

A further point about mass spectrometry, noticeable in the spectra of both propane (Figure 12.2) and 2,2-dimethylpropane (Figure 12.3), is that the peak for the molecular ion is not at the highest m/z value. There is also a small peak at M+1 because of the presence of different isotopes in the molecules. Although ^{12}C is the most abundant carbon isotope, a small amount (1.10% natural abundance) of ^{13}C is also present. Thus, a certain percentage of the molecules analyzed in the mass spectrometer are likely to contain a ^{13}C atom, giving rise to the observed M+1 peak. In addition, a small amount of ^2H (deuterium; 0.015% natural abundance) is present, making a further contribution to the M+1 peak.

Mass spectrometry would be useful even if molecular weight and formula were the only information that could be obtained, but in fact we can get much more. For one thing, the mass spectrum of a compound serves as a kind of "molecular fingerprint." Each organic compound fragments in a unique way depending on its structure, and the likelihood of two compounds having identical mass spectra is small. Thus, it's sometimes possible to identify an unknown by computer-based matching of its mass spectrum to one of the more than 592,000 spectra recorded in a data base called the *Registry of Mass Spectral Data*.

It's also possible to derive structural information about a molecule by interpreting its fragmentation pattern. Fragmentation occurs when the high-energy cation radical flies apart by spontaneous cleavage of a chemical bond. One of the two fragments retains the positive charge and is a carbocation, while the other fragment is a neutral radical.

Not surprisingly, the positive charge often remains with the fragment that is best able to stabilize it. In other words, a relatively stable carbocation is often formed during fragmentation. For example, 2,2-dimethylpropane tends to fragment in such a way that the positive charge remains with the *tert*-butyl group. 2,2-Dimethylpropane therefore has a base peak at $m/z = 57$, corresponding to $C_4H_9^+$ (Figure 12.3).
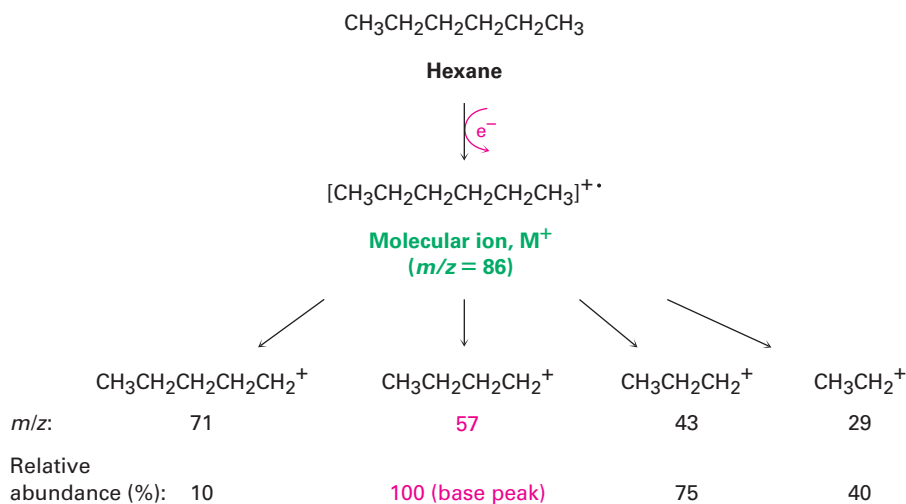

$m/z = 57$
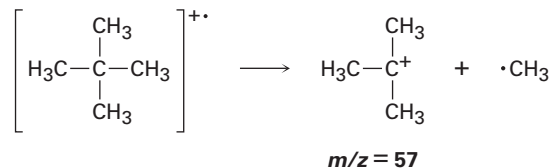
Because mass-spectral fragmentation patterns are usually complex, it's often difficult to assign structures to fragment ions. Most hydrocarbons fragment in many ways, as the mass spectrum of hexane shown in **Figure 12.4** demonstrates. The hexane spectrum shows a moderately abundant molecular ion at $m/z = 86$ and fragment ions at $m/z = 71, 57, 43,$ and 29. Since all the carbon–carbon bonds of hexane are electronically similar, all break to a similar extent, giving rise to the observed mixture of ions.
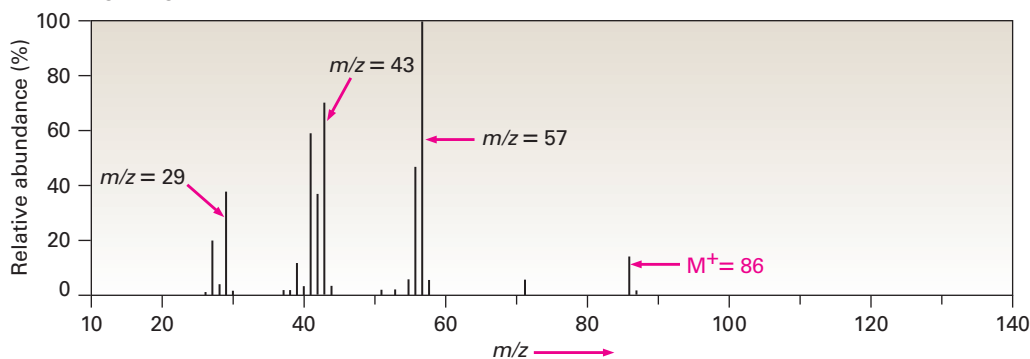
Figure 12.4 Mass spectrum of hexane (C_6H_{14}; MW = 86). The base peak is at $m/z = 57$, and numerous other ions are present.

Figure 12.5 shows how the hexane fragments might arise. The loss of a methyl radical from the hexane cation radical ($M^+ = 86$) gives rise to a fragment of mass 71; the loss of an ethyl radical accounts for a fragment of mass 57; the loss of a propyl radical accounts for a fragment of mass 43; and the loss of a butyl radical accounts for a fragment of mass 29. With practice, it's sometimes

possible to analyze the fragmentation pattern of an unknown compound and work backward to a structure that is compatible with the data.

$$CH_3CH_2CH_2CH_2CH_2CH_3$$

Hexane

e^-

$$[CH_3CH_2CH_2CH_2CH_2CH_3]^{+\cdot}$$

Molecular ion, M$^+$
($m/z = 86$)

	$CH_3CH_2CH_2CH_2CH_2^+$	$CH_3CH_2CH_2CH_2^+$	$CH_3CH_2CH_2^+$	$CH_3CH_2^+$
m/z:	71	57	43	29
Relative abundance (%):	10	100 (base peak)	75	40

Figure 12.5 Fragmentation of hexane in a mass spectrometer.

We'll see in the next section and in later chapters that specific functional groups, such as alcohols, ketones, aldehydes, and amines, show specific kinds of mass spectral fragmentations that can be interpreted to provide structural information.

Worked Example 12.1

Using Mass Spectra to Identify Compounds

Assume that you have two unlabeled samples, one of methylcyclohexane and the other of ethylcyclopentane. How could you use mass spectrometry to tell them apart? The mass spectra of both are shown in **Figure 12.6**.
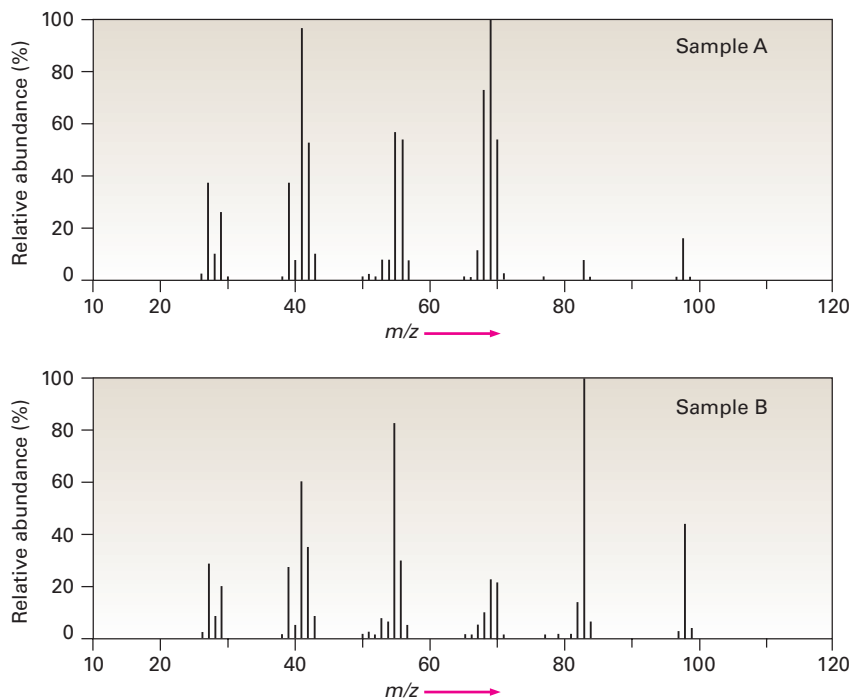
Figure 12.6 Mass spectra of unlabeled samples **A** and **B** for Worked Example 12.1.

Strategy

Look at the possible structures and decide on how they differ. Then think about how any of these differences in structure might give rise to differences in mass spectra. Methylcyclohexane, for instance, has a $-CH_3$ group, and ethylcyclopentane has a $-CH_2CH_3$ group, which should affect the fragmentation patterns.

Solution

Both mass spectra show molecular ions at $M^+ = 98$, corresponding to C_7H_{14}, but they differ in their fragmentation patterns. Sample **A** has its base peak at $m/z = 69$, corresponding to the loss of a CH_2CH_3 group (29 mass units), but **B** has a rather small peak at $m/z = 69$. Sample **B** shows a base peak at $m/z = 83$, corresponding to the loss of a CH_3 group (15 mass units), but sample **A** has only a small peak at $m/z = 83$. We can therefore be reasonably certain that **A** is ethylcyclopentane and **B** is methylcyclohexane.

Problem 12.1

The male sex hormone testosterone contains only C, H, and O and has a mass of 288.2089 amu as determined by high-resolution mass spectrometry. What is the likely molecular formula of testosterone?

Problem 12.2

Two mass spectra are shown in **Figure 12.7**. One spectrum is that of 2-methyl-2-pentene; the other is of 2-hexene. Which is which? Explain.
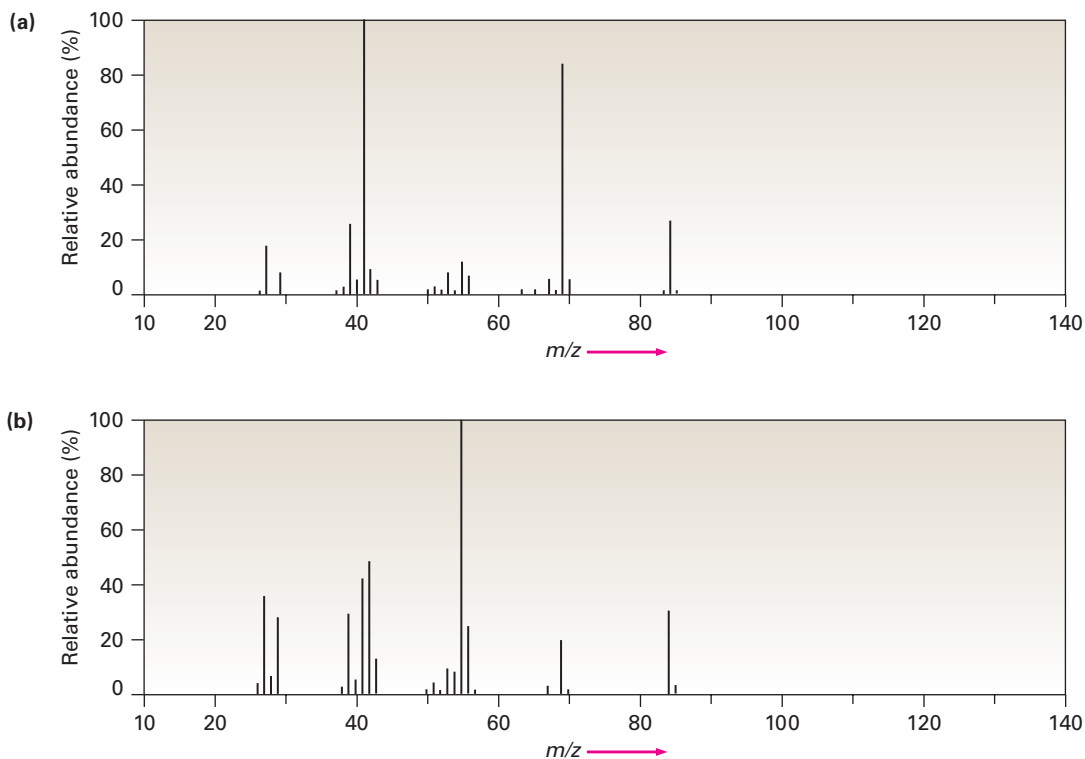
Figure 12.7 Mass spectra for Problem 12.2.

12.3 Mass Spectrometry of Some Common Functional Groups

As each functional group is discussed in future chapters, mass-spectral fragmentations characteristic of that group will be described. As a preview, though, we'll point out some distinguishing features of several common functional groups.

Alcohols

Alcohols undergo fragmentation in the mass spectrometer by two pathways: *alpha cleavage* and *dehydration*. In the α-cleavage pathway, a C—C bond nearest the hydroxyl group is broken, yielding a neutral radical plus a resonance-stabilized, oxygen-containing cation.
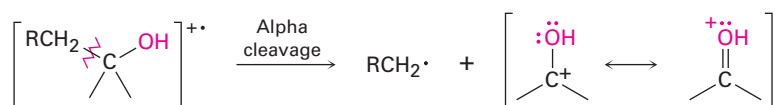
In the dehydration pathway, water is eliminated, yielding an alkene radical cation with a mass 18 units less than M^+.
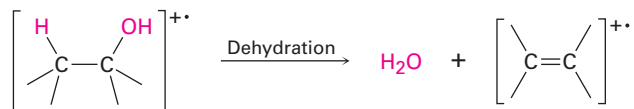
Amines

Aliphatic amines undergo a characteristic α cleavage in the mass spectrometer, similar to that observed for alcohols. A C—C bond nearest the nitrogen atom is broken, yielding an alkyl radical and a resonance-stabilized, nitrogen-containing cation.
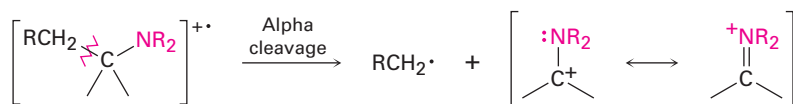
Carbonyl Compounds

Ketones and aldehydes that have a hydrogen on a carbon three atoms away from the carbonyl group undergo a characteristic mass-spectral cleavage called the *McLafferty rearrangement*. The hydrogen atom is transferred to the carbonyl oxygen, a C—C bond is broken, and a neutral alkene fragment is produced. The charge remains with the oxygen-containing fragment.
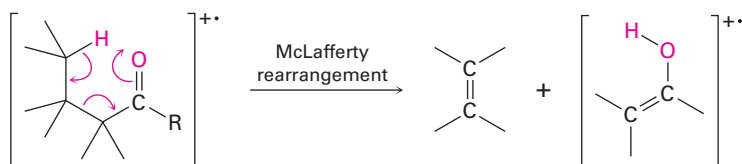
In addition, ketones and aldehydes frequently undergo α cleavage of the bond between the carbonyl group and the neighboring carbon. Alpha cleavage yields a neutral radical and a resonance-stabilized acyl cation.
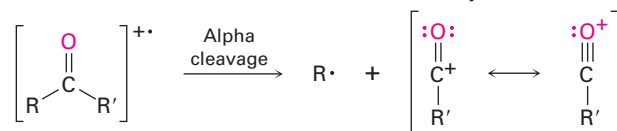
Worked Example 12.2

Identifying Fragmentation Patterns in a Mass Spectrum

The mass spectrum of 2-methyl-3-pentanol is shown in **Figure 12.8**. What fragments can you identify?
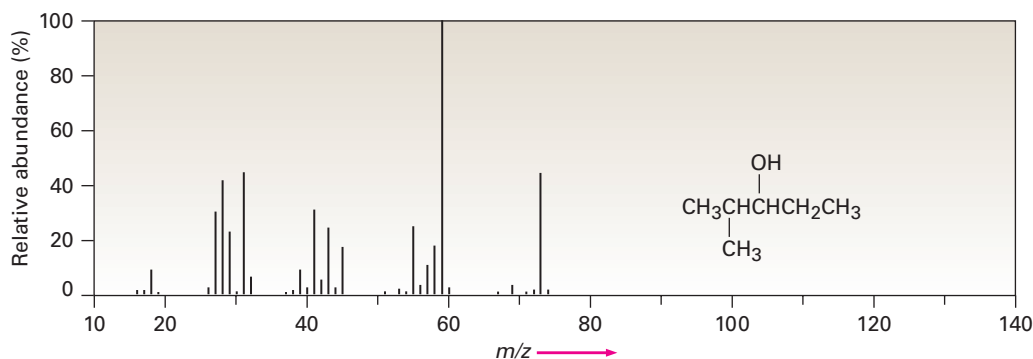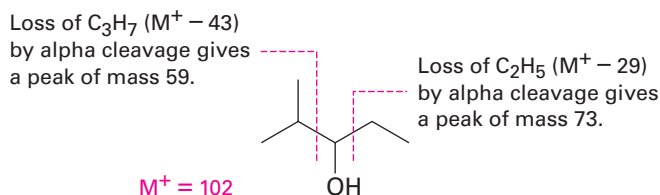

Figure 12.8 Mass spectrum of 2-methyl-3-pentanol, Worked Example 12.2.

Strategy

Calculate the mass of the molecular ion, and identify the functional groups in the molecule. Then write the fragmentation processes you might expect, and compare the masses of the resultant fragments with those peaks present in the spectrum.

Solution

2-Methyl-3-pentanol, an open-chain alcohol, has $M^+ = 102$ and might be expected to fragment by α cleavage and by dehydration. These processes would lead to fragment ions of $m/z = 84$, 73, and 59. Of the three expected fragments, dehydration is not observed (no $m/z = 84$ peak), but both α cleavages take place ($m/z = 73$, 59).


Loss of C_3H_7 ($M^+ - 43$) by alpha cleavage gives a peak of mass 59.

Loss of C_2H_5 ($M^+ - 29$) by alpha cleavage gives a peak of mass 73.

$M^+ = 102$

Problem 12.3

What are the masses of the charged fragments produced in the following cleavage pathways?

(a) Alpha cleavage of 2-pentanone ($CH_3COCH_2CH_2CH_3$)
(b) Dehydration of cyclohexanol (hydroxycyclohexane)
(c) McLafferty rearrangement of 4-methyl-2-pentanone [$CH_3COCH_2CH(CH_3)_2$]
(d) Alpha cleavage of triethylamine [$(CH_3CH_2)_3N$]

Problem 12.4

List the masses of the parent ion and of several fragments you might expect to find in the mass spectrum of the following molecule:
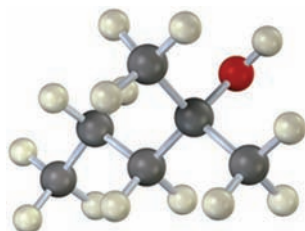
12.4 Mass Spectrometry in Biological Chemistry: Time-of-Flight (TOF) Instruments

Most biochemical analyses by MS use either electrospray ionization (ESI) or matrix-assisted laser desorption ionization (MALDI), typically linked to a time-of-flight (TOF) mass analyzer. Both ESI and MALDI are soft ionization methods that produce charged molecules with little fragmentation, even with biological samples of very high molecular weight.

In an ESI source, the sample is dissolved in a polar solvent and sprayed through a steel capillary tube. As it exits the tube, it is subjected to a high voltage that causes it to become protonated by removing one or more H^+ ions from the solvent. The volatile solvent is then evaporated, giving variably protonated sample molecules ($M+H_n^{n+}$). In a MALDI source, the sample is adsorbed onto a suitable matrix compound, such as 2,5-dihydroxybenzoic acid, which is ionized by a short burst of laser light. The matrix compound then transfers the energy to the sample and protonates it, forming $M+H_n^{n+}$ ions.

Following ion formation, the variably protonated sample molecules are electrically focused into a small packet with a narrow spatial distribution, and the packet is given a sudden kick of energy by an accelerator electrode. Since each molecule in the packet is given the same energy, $E = mv^2/2$, it begins moving with a velocity that depends on the square root of its mass, $v = \sqrt{2E/m}$. Lighter molecules move faster, and heavier molecules move slower. The analyzer itself—the *drift tube*—is simply an electrically grounded metal tube inside which the different charged molecules become separated as they move along at different velocities and take different amounts of time to complete their flight.

The TOF technique is considerably more sensitive than the magnetic sector alternative, and protein samples of up to 100 kilodaltons (100,000 amu) can be separated with a mass accuracy of 3 ppm. **Figure 12.9** shows a MALDI–TOF spectrum of chicken egg-white lysozyme, MW = 14,306.7578 daltons. (Biochemists generally use the unit *dalton,* abbreviated Da, instead of amu.)
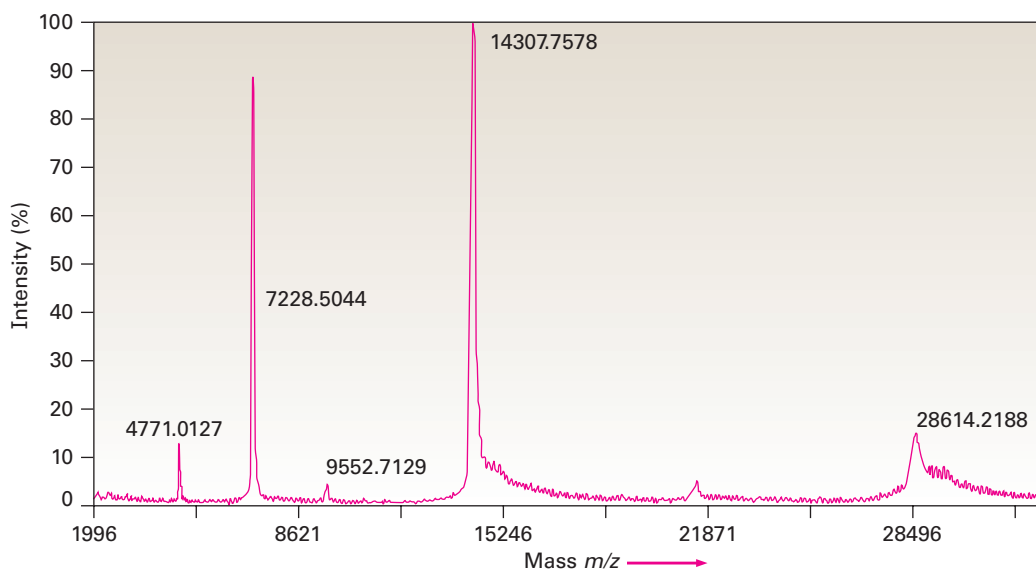
Figure 12.9 MALDI–TOF mass spectrum of chicken egg-white lysozyme. The peak at 14,307.7578 daltons (amu) is due to the monoprotonated protein, $M+H^+$, and the peak at 28,614.2188 daltons is due to an impurity formed by dimerization of the protein. Other peaks are various protonated species, $M+H_n^{n+}$.

12.5 Spectroscopy and the Electromagnetic Spectrum

Infrared, ultraviolet, and nuclear magnetic resonance spectroscopies differ from mass spectrometry in that they are nondestructive and involve the interaction of molecules with electromagnetic energy rather than with an ionizing source. Before beginning a study of these techniques, however, let's briefly review the nature of radiant energy and the electromagnetic spectrum.

Visible light, X rays, microwaves, radio waves, and so forth are all different kinds of *electromagnetic radiation*. Collectively, they make up the **electromagnetic spectrum**, shown in **Figure 12.10**. The electromagnetic spectrum is arbitrarily divided into regions, with the familiar visible region accounting for only a small portion, from 3.8×10^{-7} m to 7.8×10^{-7} m in wavelength. The visible region is flanked by the infrared and ultraviolet regions.

Figure 12.10 The electromagnetic spectrum covers a continuous range of wavelengths and frequencies, from radio waves at the low-frequency end to gamma (γ) rays at the high-frequency end. The familiar visible region accounts for only a small portion near the middle of the spectrum.
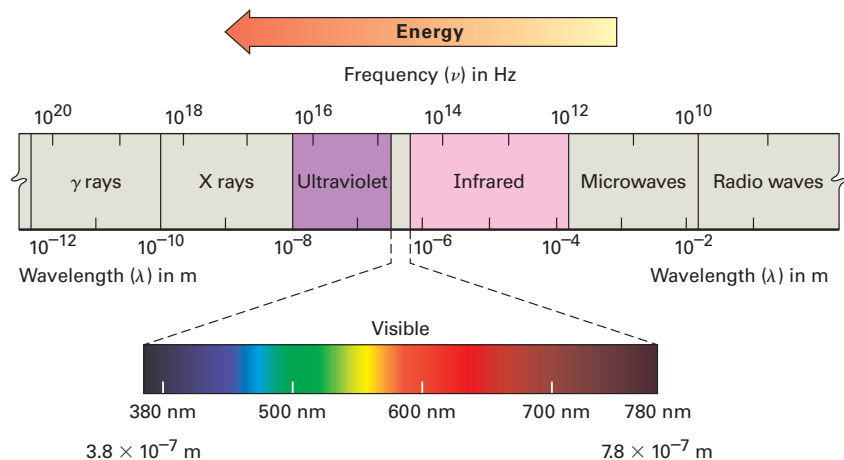
Electromagnetic radiation is often said to have dual behavior. In some respects, it has the properties of a particle, called a *photon,* yet in other respects it behaves as an energy wave. Like all waves, electromagnetic radiation is characterized by a *wavelength,* a *frequency,* and an *amplitude* **(Figure 12.11)**. The **wavelength, λ** (Greek lambda), is the distance from one wave maximum to the next. The **frequency, ν** (Greek nu), is the number of waves that pass by a fixed point per unit time, usually given in reciprocal seconds (s^{-1}), or **hertz, Hz** ($1\ Hz = 1\ s^{-1}$). The **amplitude** is the height of a wave, measured from midpoint to peak. The intensity of radiant energy, whether a feeble glow or a blinding glare, is proportional to the square of the wave's amplitude.

(a)

(b) Violet light
($\nu = 7.50 \times 10^{14}\ s^{-1}$)

(c) Infrared radiation
($\nu = 3.75 \times 10^{14}\ s^{-1}$)
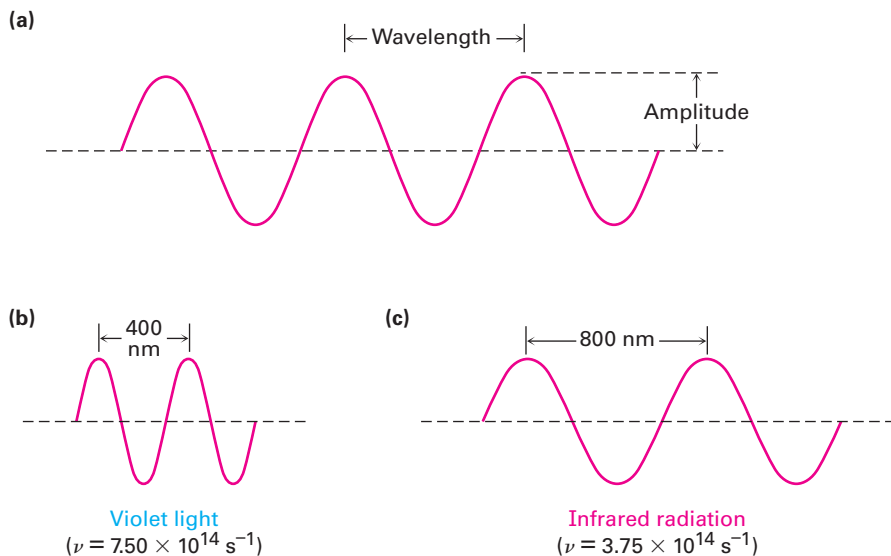
Figure 12.11 Electromagnetic waves are characterized by a wavelength, a frequency, and an amplitude. **(a)** Wavelength (λ) is the distance between two successive wave maxima. Amplitude is the height of the wave measured from the center. **(b)–(c)** What we perceive as different kinds of electromagnetic radiation are simply waves with different wavelengths and frequencies.

Multiplying the wavelength of a wave in meters (m) by its frequency in reciprocal seconds (s^{-1}) gives the speed of the wave in meters per second (m/s). The rate of travel of all electromagnetic radiation in a vacuum is a constant value, commonly called the "speed of light" and abbreviated c. Its numerical value is defined as exactly $2.997\ 924\ 58 \times 10^{8}$ m/s, usually rounded off to 3.00×10^{8} m/s.

$$\text{Wavelength} \times \text{Frequency} = \text{Speed}$$
$$\lambda\ (m) \times \nu\ (s^{-1}) = c\ (m/s)$$
$$\lambda = \frac{c}{\nu}\ \text{ or }\ \nu = \frac{c}{\lambda}$$

Just as matter comes only in discrete units called atoms, electromagnetic energy is transmitted only in discrete amounts called *quanta.* The amount of energy ϵ corresponding to 1 quantum of energy (1 photon) of a given frequency ν is expressed by the Planck equation

$$\varepsilon = h\nu = \frac{hc}{\lambda}$$

where h = Planck's constant ($6.62 \times 10^{-34}\ J \cdot s = 1.58 \times 10^{-34}\ cal \cdot s$).

The Planck equation says that the energy of a given photon varies directly with its frequency ν but inversely with its wavelength λ. High frequencies and short wavelengths correspond to high-energy radiation such as gamma rays; low frequencies and long wavelengths correspond to low-energy radiation such as radio waves. Multiplying ϵ by Avogadro's number N_A gives the same equation in more familiar units, where E represents the energy of Avogadro's number (one "mole") of photons of wavelength λ:

$$E = \frac{N_A h c}{\lambda} = \frac{1.20 \times 10^{-4} \text{ kJ/mol}}{\lambda \text{ (m)}} \quad \text{or} \quad \frac{2.86 \times 10^{-5} \text{ kcal/mol}}{\lambda \text{ (m)}}$$

When an organic compound is exposed to a beam of electromagnetic radiation, it absorbs energy of some wavelengths but passes, or transmits, energy of other wavelengths. If we irradiate the sample with energy of many different wavelengths and determine which are absorbed and which are transmitted, we can measure the **absorption spectrum** of the compound.

An example of an absorption spectrum—that of ethanol exposed to infrared radiation—is shown in **Figure 12.12**. The horizontal axis records the wavelength, and the vertical axis records the intensity of the various energy absorptions in percent transmittance. The baseline corresponding to 0% absorption (or 100% transmittance) runs along the top of the chart, so a downward spike means that energy absorption has occurred at that wavelength.
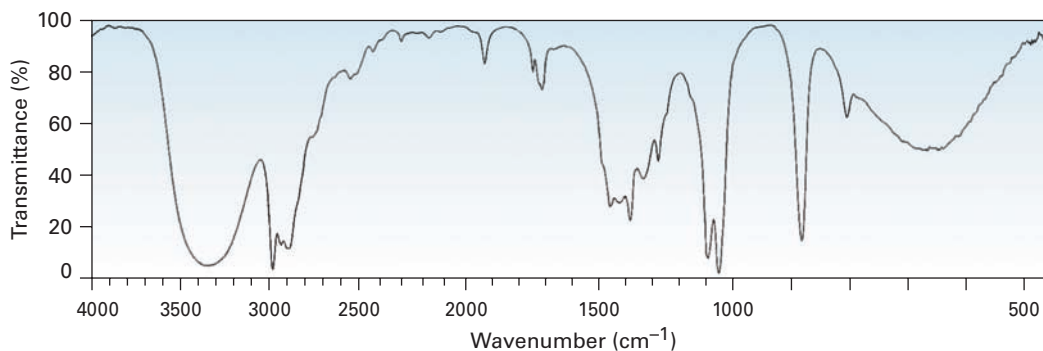
Figure 12.12 An infrared absorption spectrum of ethanol, CH_3CH_2OH. A transmittance of 100% means that all the energy is passing through the sample, whereas a lower transmittance means that some energy is being absorbed. Thus, each downward spike corresponds to an energy absorption.

The energy a molecule gains when it absorbs radiation must be distributed over the molecule in some way. With infrared radiation, the absorbed energy causes bonds to stretch and bend more vigorously. With ultraviolet radiation, the energy causes an electron to jump from a lower-energy orbital to a higher-energy one. Different radiation frequencies affect molecules in different ways, but each provides structural information when the results are interpreted.

There are many kinds of spectroscopies, which differ according to the region of the electromagnetic spectrum used. We'll look at three: infrared spectroscopy, ultraviolet spectroscopy, and nuclear magnetic resonance spectroscopy. Let's begin by seeing what happens when an organic sample absorbs infrared energy.

| Correlating Energy and Frequency of Radiation | Worked Example 12.3 |

Which is higher in energy, FM radio waves with a frequency of 1.015×10^8 Hz (101.5 MHz) or visible green light with a frequency of 5×10^{14} Hz?

Strategy
Remember the equations $\epsilon = h\nu$ and $\epsilon = hc/\lambda$, which say that energy increases as frequency increases and as wavelength decreases.

Solution
Since visible light has a higher frequency than radio waves, it is higher in energy.

Problem 12.5
Which has higher energy, infrared radiation with $\lambda = 1.0 \times 10^{-6}$ m or an X ray with $\lambda = 3.0 \times 10^{-9}$ m? Radiation with $\nu = 4.0 \times 10^9$ Hz or with $\lambda = 9.0 \times 10^{-6}$ m?

Problem 12.6
It's useful to develop a feeling for the amounts of energy that correspond to different parts of the electromagnetic spectrum. Calculate the energies in kJ/mol of each of the following kinds of radiation:

(a) A gamma ray with $\lambda = 5.0 \times 10^{-11}$ m   (b) An X ray with $\lambda = 3.0 \times 10^{-9}$ m
(c) Ultraviolet light with $\nu = 6.0 \times 10^{15}$ Hz   (d) Visible light with $\nu = 7.0 \times 10^{14}$ Hz
(e) Infrared radiation with $\lambda = 2.0 \times 10^{-5}$ m   (f) Microwave radiation with $\nu = 1.0 \times 10^{11}$ Hz

12.6 Infrared Spectroscopy

The **infrared (IR)** region of the electromagnetic spectrum covers the range from just above the visible (7.8×10^{-7} m) to approximately 10^{-4} m, but only the midportion from 2.5×10^{-6} m to 2.5×10^{-5} m is used by organic chemists **(Figure 12.13)**. Wavelengths within the IR region are usually given in micrometers (1 μm $= 10^{-6}$ m), and frequencies are given in wavenumbers rather than in hertz. The **wavenumber** ($\tilde{\nu}$) is the reciprocal of the wavelength in centimeters and is therefore expressed in units of cm^{-1}.

$$\text{Wavenumber:} \quad \tilde{\nu}\,(\text{cm}^{-1}) = \frac{1}{\lambda\,(\text{cm})}$$

Thus, the useful IR region is from 4000 to 400 cm^{-1}, corresponding to energies of 48.0 kJ/mol to 4.80 kJ/mol (11.5–1.15 kcal/mol).
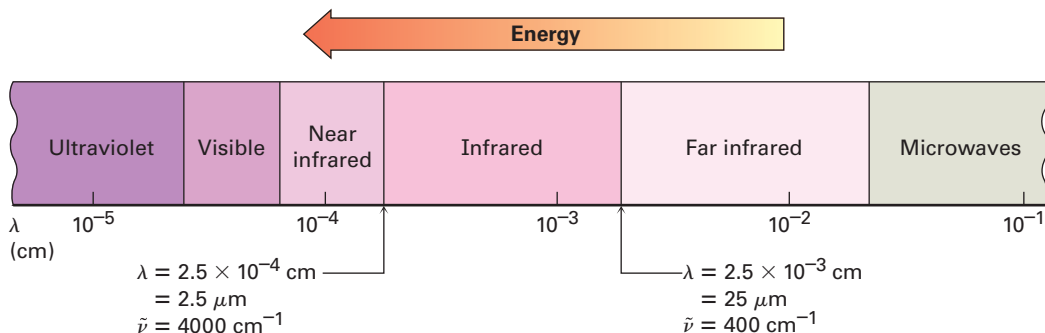
Figure 12.13 The infrared and adjacent regions of the electromagnetic spectrum.

Why does an organic molecule absorb some wavelengths of IR radiation but not others? All molecules have a certain amount of energy and are in constant motion. Their bonds stretch and contract, atoms wag back and forth, and other molecular vibrations occur. Some of the kinds of allowed vibrations are shown below:

| **Symmetric stretching** | **Antisymmetric stretching** | **In-plane bending** | **Out-of-plane bending** |
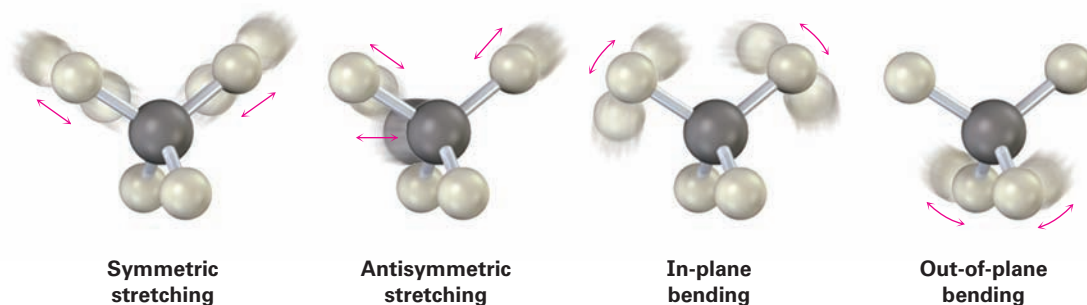
The amount of energy a molecule contains is not continuously variable but is *quantized*. That is, a molecule can stretch or bend only at specific frequencies corresponding to specific energy levels. Take bond stretching, for example. Although we usually speak of bond lengths as if they were fixed, the numbers given are really averages. In fact, a typical C−H bond with an average bond length of 110 pm is actually vibrating at a specific frequency, alternately stretching and contracting as if there were a spring connecting the two atoms.

When a molecule is irradiated with electromagnetic radiation, energy is absorbed if the frequency of the radiation matches the frequency of the vibration. The result of this energy absorption is an increased amplitude for the vibration; in other words, the "spring" connecting the two atoms stretches and compresses a bit further. Since each frequency absorbed by a molecule corresponds to a specific molecular motion, we can find what kinds of motions a molecule has by measuring its IR spectrum. By then interpreting those motions, we can find out what kinds of bonds (functional groups) are present in the molecule.

IR spectrum → What molecular motions? → What functional groups?

12.7 Interpreting Infrared Spectra

The complete interpretation of an IR spectrum is difficult because most organic molecules have dozens of different bond stretching and bending motions, and thus have dozens of absorptions. On the one hand, this complexity is a problem because it generally limits the laboratory use of IR spectroscopy to pure samples of fairly small molecules—little can be learned from IR spectroscopy

about large, complex biomolecules. On the other hand, the complexity is useful because an IR spectrum acts as a unique fingerprint of a compound. In fact, the complex region of the IR spectrum from 1500 cm^{-1} to around 400 cm^{-1} is called the *fingerprint region*. If two samples have identical IR spectra, they are almost certainly identical compounds.

Fortunately, we don't need to interpret an IR spectrum fully to get useful structural information. Most functional groups have characteristic IR absorption bands that don't change from one compound to another. The C=O absorption of a ketone is almost always in the range 1680 to 1750 cm^{-1}; the O−H absorption of an alcohol is almost always in the range 3400 to 3650 cm^{-1}; the C=C absorption of an alkene is almost always in the range 1640 to 1680 cm^{-1}; and so forth. By learning where characteristic functional-group absorptions occur, it's possible to get structural information from IR spectra. Table 12.1 lists the characteristic IR bands of some common functional groups.

Table 12.1 Characteristic IR Absorptions of Some Functional Groups

Functional Group	Absorption (cm^{-1})	Intensity	Functional Group	Absorption (cm^{-1})	Intensity
Alkane			Amine		
C−H	2850–2960	Medium	N−H	3300–3500	Medium
Alkene			C−N	1030–1230	Medium
=C−H	3020–3100	Medium	Carbonyl compound		
C=C	1640–1680	Medium	C=O	1670–1780	Strong
Alkyne			Aldehyde	1730	Strong
≡C−H	3300	Strong	Ketone	1715	Strong
C≡C	2100–2260	Medium	Ester	1735	Strong
Alkyl halide			Amide	1690	Strong
C−Cl	600–800	Strong	Carboxylic acid	1710	Strong
C−Br	500–600	Strong	Carboxylic acid		
Alcohol			O−H	2500–3100	Strong, broad
O−H	3400–3650	Strong, broad	Nitrile		
C−O	1050–1150	Strong	C≡N	2210–2260	Medium
Arene			Nitro		
C−H	3030	Weak	NO$_2$	1540	Strong
Aromatic ring	1660–2000	Weak			
	1450–1600	Medium			

Look at the IR spectra of hexane, 1-hexene, and 1-hexyne in **Figure 12.14** to see an example of how IR spectroscopy can be used. Although all three IR spectra contain many peaks, there are characteristic absorptions of the C=C and C≡C functional groups that allow the three compounds to be distinguished. Thus, 1-hexene shows a characteristic C=C absorption at 1660 cm^{-1} and a vinylic =C−H absorption at 3100 cm^{-1}, whereas 1-hexyne has a C≡C absorption at 2100 cm^{-1} and a terminal alkyne ≡C−H absorption at 3300 cm^{-1}.
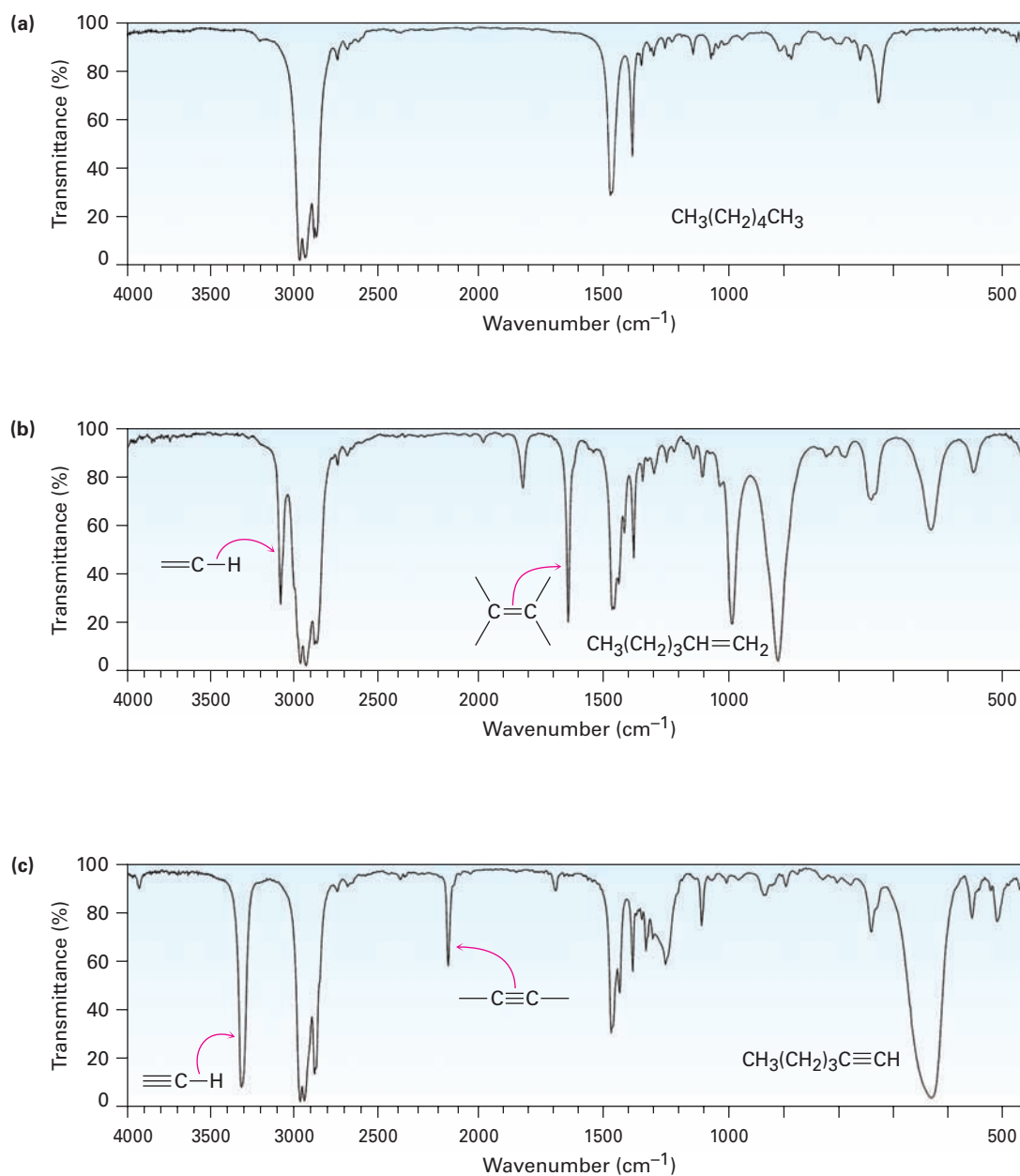
Figure 12.14 IR spectra of **(a)** hexane, **(b)** 1-hexene, and **(c)** 1-hexyne. Spectra like these are easily obtained on submilligram amounts of material in a few minutes using commercially available instruments.

It helps in remembering the position of specific IR absorptions to divide the IR region from 4000 cm^{-1} to 400 cm^{-1} into four parts, as shown in **Figure 12.15**.

- The region from 4000 to 2500 cm^{-1} corresponds to absorptions caused by N–H, C–H, and O–H single-bond stretching motions. N–H and O–H bonds absorb in the 3300 to 3600 cm^{-1} range; C–H bond stretching occurs near 3000 cm^{-1}.

- The region from 2500 to 2000 cm^{-1} is where triple-bond stretching occurs. Both C≡N and C≡C bonds absorb here.
- The region from 2000 to 1500 cm^{-1} is where double bonds (C=O, C=N, and C=C) absorb. Carbonyl groups generally absorb in the range 1680 to 1750 cm^{-1}, and alkene stretching normally occurs in the narrow range 1640 to 1680 cm^{-1}.
- The region below 1500 cm^{-1} is the fingerprint portion of the IR spectrum. A large number of absorptions due to a variety of C−C, C−O, C−N, and C−X single-bond vibrations occur here.
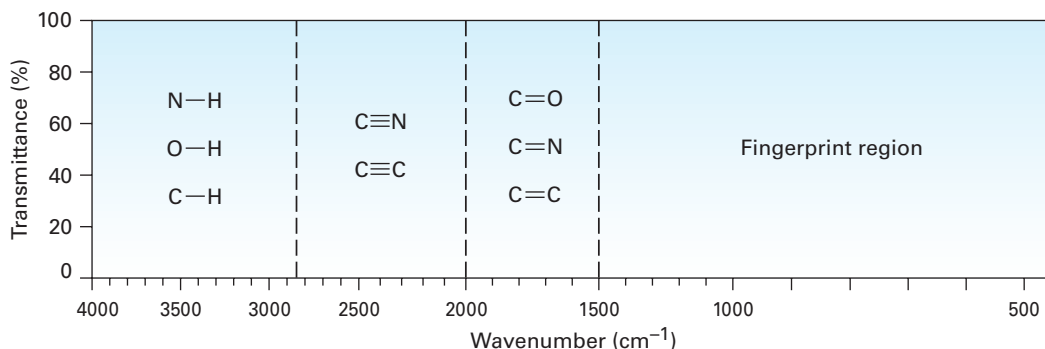
Figure 12.15 The four regions of the infrared spectrum: single bonds to hydrogen, triple bonds, double bonds, and fingerprint.

Why do different functional groups absorb where they do? As noted previously, a good analogy is that of two weights (atoms) connected by a spring (a bond). Short, strong bonds vibrate at a higher energy and higher frequency than do long, weak bonds, just as a short, strong spring vibrates faster than a long, weak spring. Thus, triple bonds absorb at a higher frequency than double bonds, which in turn absorb at a higher frequency than single bonds. In addition, springs connecting small weights vibrate faster than springs connecting large weights. Thus, C−H, O−H, and N−H bonds vibrate at a higher frequency than bonds between heavier C, O, and N atoms.

| **Distinguishing Isomeric Compounds by IR Spectroscopy** | **Worked Example 12.4** |

Acetone (CH_3COCH_3) and 2-propen-1-ol ($H_2C=CHCH_2OH$) are isomers. How could you distinguish them by IR spectroscopy?

Strategy
Identify the functional groups in each molecule, and refer to Table 12.1.

Solution
Acetone has a strong C=O absorption at 1715 cm^{-1}, while 2-propen-1-ol has an −OH absorption at 3500 cm^{-1} and a C=C absorption at 1660 cm^{-1}.

Problem 12.7

What functional groups might the following molecules contain?

(a) A compound with a strong absorption at 1710 cm^{-1}
(b) A compound with a strong absorption at 1540 cm^{-1}
(c) A compound with strong absorptions at 1720 cm^{-1} and at 2500–3100 cm^{-1}

Problem 12.8

How might you use IR spectroscopy to distinguish between the following pairs of isomers?

(a) CH_3CH_2OH and CH_3OCH_3 **(b)** Cyclohexane and 1-hexene
(c) $CH_3CH_2CO_2H$ and $HOCH_2CH_2CHO$

12.8 Infrared Spectra of Some Common Functional Groups

As each functional group is discussed in future chapters, the spectroscopic properties of that group will be described. For the present, we'll point out some distinguishing features of the hydrocarbon functional groups already studied and briefly preview some other common functional groups. We should also point out, however, that in addition to interpreting absorptions that *are* present in an IR spectrum, it's also possible to get structural information by noticing which absorptions are *not* present. If the spectrum of a compound has no absorptions at 3300 and 2150 cm^{-1}, the compound is not a terminal alkyne; if the spectrum has no absorption near 3400 cm^{-1}, the compound is not an alcohol; and so on.

Alkanes

The IR spectrum of an alkane is fairly uninformative because no functional groups are present and all absorptions are due to C–H and C–C bonds. Alkane C–H bonds show a strong absorption from 2850 to 2960 cm^{-1}, and saturated C–C bonds show a number of bands in the 800 to 1300 cm^{-1} range. Since most organic compounds contain saturated alkane-like portions, most organic compounds have these characteristic IR absorptions. The C–H and C–C bands are clearly visible in the three spectra shown in Figure 12.14.

Alkanes   C–H   2850–2960 cm^{-1}

   C–C   800–1300 cm^{-1}
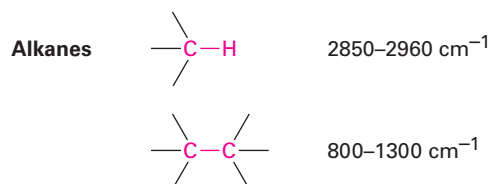
Alkenes

Alkenes show several characteristic stretching absorptions. Vinylic =C–H bonds absorb from 3020 to 3100 cm^{-1}, and alkene C=C bonds usually absorb near 1650 cm^{-1}, although in some cases the peaks can be rather small and difficult to see clearly. Both absorptions are visible in the 1-hexene spectrum in Figure 12.14b.

Monosubstituted and disubstituted alkenes have characteristic =C—H out-of-plane bending absorptions in the 700 to 1000 cm^{-1} range, thereby allowing the substitution pattern on a double bond to be determined. Monosubstituted alkenes such as 1-hexene show strong characteristic bands at 910 and 990 cm^{-1}, and 2,2-disubstituted alkenes (R$_2$C=CH$_2$) have an intense band at 890 cm^{-1}.

Alkenes	=C—H	3020–3100 cm^{-1}
	C=C	1640–1680 cm^{-1}
	RCH=CH$_2$	910 and 990 cm^{-1}
	R$_2$C=CH$_2$	890 cm^{-1}

Alkynes

Alkynes show a C≡C stretching absorption at 2100 to 2260 cm^{-1}, an absorption that is much more intense for terminal alkynes than for internal alkynes. In fact, symmetrically substituted triple bonds like that in 3-hexyne show no absorption at all, for reasons we won't go into. Terminal alkynes such as 1-hexyne also have a characteristic ≡C—H stretch at 3300 cm^{-1} (Figure 12.14c). This band is diagnostic for terminal alkynes because it is fairly intense and quite sharp.

Alkynes	—C≡C—	2100–2260 cm^{-1}
	≡C—H	3300 cm^{-1}

Aromatic Compounds

Aromatic compounds, such as benzene, have a weak C—H stretching absorption at 3030 cm^{-1}, just to the left of a typical saturated C—H band. In addition, they have a series of weak absorptions in the 1660 to 2000 cm^{-1} range and a series of medium-intensity absorptions in the 1450 to 1600 cm^{-1} region. These latter absorptions are due to complex molecular motions of the entire ring. The IR spectrum of phenylacetylene, shown in Figure 12.17 at the end of this section, gives an example.

| Aromatic compounds	C—H	3030 cm^{-1} (weak)
	(benzene ring)	1660–2000 cm^{-1} (weak)
		1450–1600 cm^{-1} (medium)

Alcohols

The O—H functional group of alcohols is easy to spot. Alcohols have a characteristic band in the range 3400 to 3650 cm^{-1} that is usually broad and intense. If present, it's hard to miss this band or to confuse it with anything else.

| Alcohols	—O—H	3400–3650 cm^{-1} (broad, intense)

Amines

The N−H functional group of amines is also easy to spot in the IR, with a characteristic absorption in the 3300 to 3500 cm^{-1} range. Although alcohols absorb in the same range, an N−H absorption is much sharper and less intense than an O−H band.

**Amines**   —N—H   3300–3500 cm^{-1} (sharp, medium intensity)
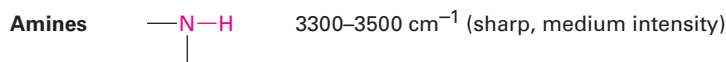
Carbonyl Compounds

Carbonyl functional groups are the easiest to identify of all IR absorptions because of their sharp, intense peak in the range 1670 to 1780 cm^{-1}. Most important, the exact position of absorption within the range can often be used to identify the exact kind of carbonyl functional group—aldehyde, ketone, ester, and so forth.

Aldehydes   Saturated aldehydes absorb at 1730 cm^{-1}; aldehydes next to either a double bond or an aromatic ring absorb at 1705 cm^{-1}.

Aldehydes CH_3CH_2CH $CH_3CH{=}CHCH$

1730 cm^{-1} 1705 cm^{-1} 1705 cm^{-1}
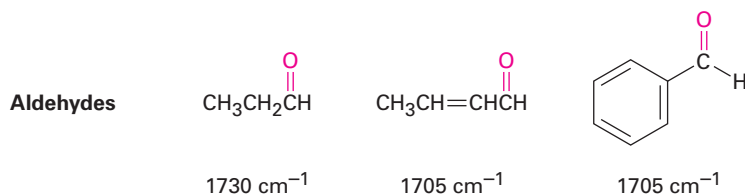
Ketones   Saturated open-chain ketones and six-membered cyclic ketones absorb at 1715 cm^{-1}, five-membered cyclic ketones absorb at 1750 cm^{-1}, and ketones next to a double bond or an aromatic ring absorb at 1690 cm^{-1}.

Ketones CH_3CCH_3 $CH_3CH{=}CHCCH_3$

1715 cm^{-1} 1750 cm^{-1} 1690 cm^{-1} 1690 cm^{-1}
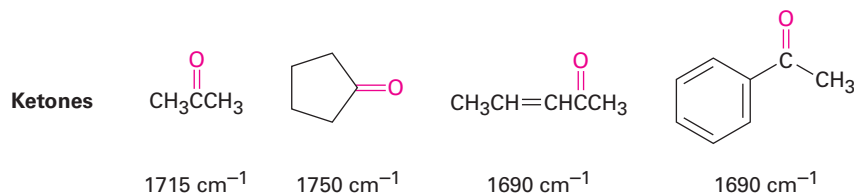
Esters   Saturated esters absorb at 1735 cm^{-1}; esters next to either an aromatic ring or a double bond absorb at 1715 cm^{-1}.

Esters CH_3COCH_3 $CH_3CH{=}CHCOCH_3$

1735 cm^{-1} 1715 cm^{-1} 1715 cm^{-1}
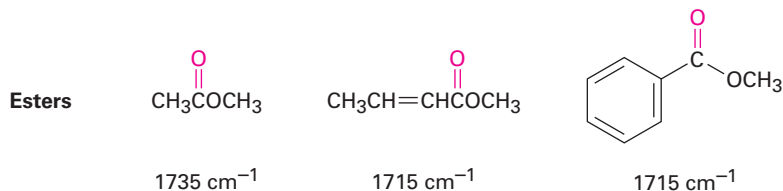
| Predicting IR Absorptions of Compounds | Worked Example 12.5 |

Where might the following compounds have IR absorptions?

(a) [structure: cyclohexene ring with CH₂OH substituent] (b)
$$HC\equiv CCH_2CHCH_2COCH_3$$
with CH_3 and O groups labeled above
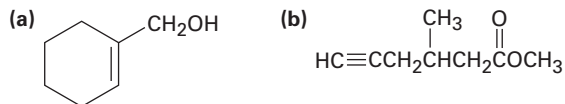
Strategy

Identify the functional groups in each molecule, and then check Table 12.1 to see where those groups absorb.

Solution

(a) *Absorptions:* 3400–3650 cm^{-1} (O−H), 3020–3100 cm^{-1} (=C−H), 1640–1680 cm^{-1} (C=C). This molecule has an alcohol O−H group and an alkene double bond.

(b) *Absorptions:* 3300 cm^{-1} (≡C−H), 2100–2260 cm^{-1} (C≡C), 1735 cm^{-1} (C=O). This molecule has a terminal alkyne triple bond and a saturated ester carbonyl group.

| Identifying Functional Groups from an IR Spectrum | Worked Example 12.6 |

The IR spectrum of an unknown compound is shown in **Figure 12.16**. What functional groups does the compound contain?
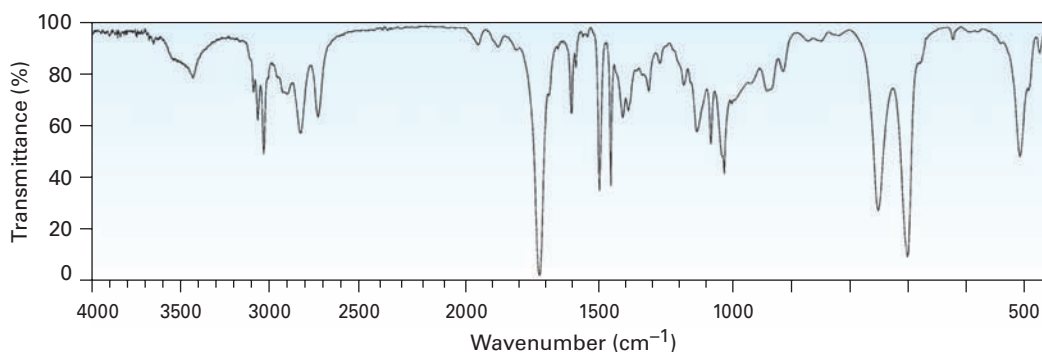
Figure 12.16 IR spectrum for Worked Example 12.6.

Strategy

All IR spectra have many absorptions, but those useful for identifying specific functional groups are usually found in the region from 1500 cm^{-1} to 3300 cm^{-1}. Pay particular attention to the carbonyl region (1670 to 1780 cm^{-1}), the aromatic region (1660 to 2000 cm^{-1}), the triple-bond region (2000 to 2500 cm^{-1}), and the C−H region (2500 to 3500 cm^{-1}).

Solution

The spectrum shows an intense absorption at 1725 cm^{-1} due to a carbonyl group (perhaps an aldehyde, −CHO), a series of weak absorptions from 1800 to 2000 cm^{-1} characteristic

of aromatic compounds, and a C—H absorption near 3030 cm^{-1}, also characteristic of aromatic compounds. In fact, the compound is phenylacetaldehyde.

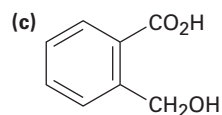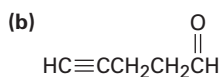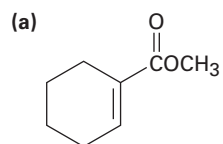**Phenylacetaldehyde**
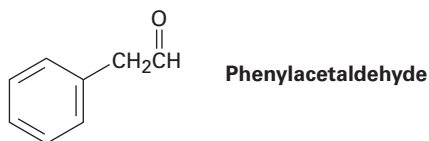
Problem 12.9

The IR spectrum of phenylacetylene is shown in **Figure 12.17**. What absorption bands can you identify?
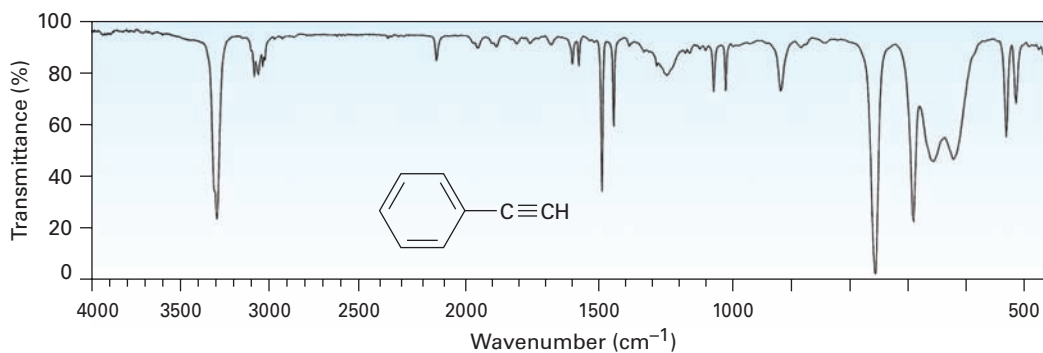
Figure 12.17   The IR spectrum of phenylacetylene, Problem 12.9.
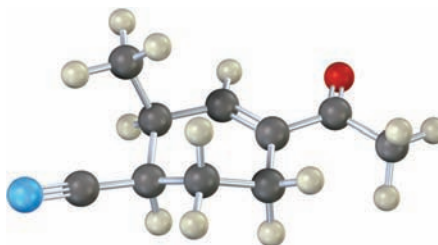
Problem 12.10

Where might the following compounds have IR absorptions?

(a)

(b)

$$HC\equiv CCH_2CH_2CH$$

(c)

Problem 12.11

Where might the following compound have IR absorptions?

X-Ray Crystallography

The various spectroscopic techniques described in this and the next two chapters are enormously important in chemistry and have been fine-tuned to such a degree that the structure of almost any molecule can be found. Nevertheless, wouldn't it be nice if you could simply look at a molecule and "see" its structure with your eyes?

Determining the three-dimensional shape of an object around you is easy—you just look at it, let your eyes focus the light rays reflected from the object, and let your brain assemble the data into a recognizable image. If the object is small, you use a microscope and let the microscope lens focus the visible light. Unfortunately, there is a limit to what you can see, even with the best optical microscope. Called the diffraction limit, you can't see anything smaller than the wavelength of light you are using for the observation. Visible light has wavelengths of several hundred nanometers, but atoms in molecules have dimension on the order of 0.1 nm. Thus, to "see" a molecule—whether a small one in the laboratory or a large, complex enzyme with a molecular weight in the tens of thousands—you need wavelengths in the 0.1 nm range, which corresponds to X rays.

The structure of human muscle fructose-1,6-bisphosphate aldolase, as determined by X-ray crystallography and downloaded from the Protein Data Bank, 1ALD.

Let's say that we want to determine the structure and shape of an enzyme or other biological molecule. The technique used is called *X-ray crystallography*. First, the molecule is crystallized (which often turns out to be the most difficult and time-consuming part of the entire process) and a small crystal with a dimension of 0.4 to 0.5 mm on its longest axis is glued to the end of a glass fiber. The fiber and attached crystal are then mounted in an instrument called an X-ray diffractometer, which consists of a radiation source, a sample positioning and orienting device that can rotate the crystal in any direction, a detector, and a controlling computer.

Once mounted in the diffractometer, the crystal is irradiated with X rays, usually so-called CuK_α radiation with a wavelength of 0.154 nm. When the X rays strike the enzyme crystal, they interact with electrons in the molecule and are scattered into a diffraction pattern which, when detected and visualized, appears as a series of intense spots against a null background.

Manipulation of the diffraction pattern to extract three-dimensional molecular data is a complex process, but the final result is that an electron-density map of the molecule is produced. Because electrons are largely localized around atoms, any two centers of electron density located within bonding distance of each other are assumed to represent bonded atoms, leading to a recognizable chemical structure. So important is this structural information for biochemistry that an online database of more than 66,000 biological substances has been created. Operated by Rutgers University and funded by the U.S. National Science Foundation, the Protein Data Bank (PDB) is a worldwide repository for processing and distributing three-dimensional structural data for biological macromolecules. We'll see how to access the PDB in the Chapter 26 *A Deeper Look*.

Summary

Finding the structure of a new molecule, whether a small one synthesized in the laboratory or a large protein found in living organisms, is central to progress in chemistry and biochemistry. The structure of an organic molecule is usually determined using spectroscopic methods, including mass spectrometry and infrared spectroscopy. **Mass spectrometry (MS)** tells the molecular weight and formula of a molecule; **infrared (IR) spectroscopy** identifies the functional groups present in the molecule.

In small-molecule mass spectrometry, molecules are first ionized by collision with a high-energy electron beam. The ions then fragment into smaller pieces, which are magnetically sorted according to their mass-to-charge ratio (m/z). The ionized sample molecule is called the *molecular ion, M^+*, and measurement of its mass gives the molecular weight of the sample. Structural clues about unknown samples can be obtained by interpreting the fragmentation pattern of the molecular ion. Mass-spectral fragmentations are usually complex, however, and interpretation is often difficult. In biological mass spectrometry, molecules are protonated using either electrospray ionization (ESI) or matrix-assisted laser desorption ionization (MALDI), and the protonated molecules are separated by time-of-flight (TOF).

Infrared spectroscopy involves the interaction of a molecule with **electromagnetic radiation**. When an organic molecule is irradiated with infrared energy, certain **frequencies** are absorbed by the molecule. The frequencies absorbed correspond to the amounts of energy needed to increase the amplitude of specific molecular vibrations such as bond stretchings and bendings. Since every functional group has a characteristic combination of bonds, every functional group has a characteristic set of infrared absorptions. For example, the terminal alkyne $\equiv$C–H bond absorbs IR radiation of 3300 cm^{-1} frequency, and the alkene C=C bond absorbs in the range 1640 to 1680 cm^{-1}. By observing which frequencies of infrared radiation are absorbed by a molecule and which are not, it's possible to determine the functional groups a molecule contains.
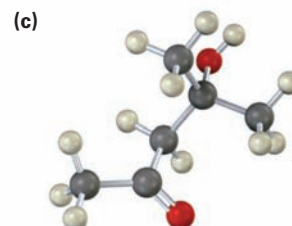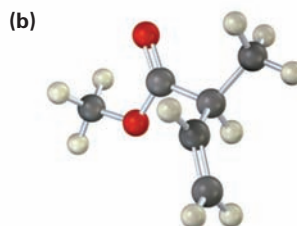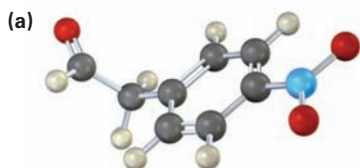
| Exercises

ⓌWL Interactive versions of these problems are assignable in OWL for Organic Chemistry.

Visualizing Chemistry

(Problems 12.1–12.11 appear within the chapter.)

12.12 Where in the IR spectrum would you expect each of the following molecules to absorb?

(a)   (b)   (c)

12.13 Show the structures of the likely fragments you would expect in the mass spectra of the following molecules:

(a)

(b)
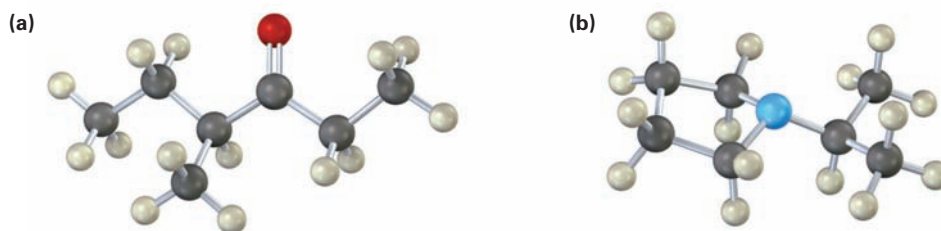
Additional Problems

Mass Spectrometry

12.14 Propose structures for compounds that fit the following mass-spectral data:
  (a) A hydrocarbon with $M^+ = 132$ **(b)** A hydrocarbon with $M^+ = 166$
  (c) A hydrocarbon with $M^+ = 84$

12.15 Write molecular formulas for compounds that show the following molecular ions in their high-resolution mass spectra, assuming that C, H, N, and O might be present. The exact atomic masses are: 1.007 83 (^1H) 12.000 00 (^{12}C), 14.003 07 (^{14}N), 15.994 91 (^{16}O).
  (a) $M^+ = 98.0844$ **(b)** $M^+ = 123.0320$

12.16 Camphor, a saturated monoketone from the Asian camphor tree, is used among other things as a moth repellent and as a constituent of embalming fluid. If camphor has $M^+ = 152.1201$ by high-resolution mass spectrometry, what is its molecular formula? How many rings does camphor have?

12.17 The *nitrogen rule* of mass spectrometry says that a compound containing an odd number of nitrogens has an odd-numbered molecular ion. Conversely, a compound containing an even number of nitrogens has an even-numbered M^+ peak. Explain.

12.18 In light of the nitrogen rule mentioned in Problem 12.17, what is the molecular formula of pyridine, $M^+ = 79$?

12.19 Nicotine is a diamino compound isolated from dried tobacco leaves. Nicotine has two rings and $M^+ = 162.1157$ by high-resolution mass spectrometry. Give a molecular formula for nicotine, and calculate the number of double bonds.

12.20 The hormone cortisone contains C, H, and O, and shows a molecular ion at $M^+ = 360.1937$ by high-resolution mass spectrometry. What is the molecular formula of cortisone? (The degree of unsaturation of cortisone is 8.)

12.21 Halogenated compounds are particularly easy to identify by their mass spectra because both chlorine and bromine occur naturally as mixtures of two abundant isotopes. Chlorine occurs as ^{35}Cl (75.8%) and ^{37}Cl (24.2%); bromine occurs as ^{79}Br (50.7%) and ^{81}Br (49.3%). At what masses do the molecular ions occur for the following formulas? What are the relative percentages of each molecular ion?

(a) Bromomethane, CH_3Br (b) 1-Chlorohexane, $C_6H_{13}Cl$

12.22 By knowing the natural abundances of minor isotopes, it's possible to calculate the relative heights of M^+ and $M+1$ peaks. If ^{13}C has a natural abundance of 1.10%, what are the relative heights of the M^+ and $M+1$ peaks in the mass spectrum of benzene, C_6H_6?

12.23 Propose structures for compounds that fit the following data:

(a) A ketone with $M^+ = 86$ and fragments at $m/z = 71$ and $m/z = 43$

(b) An alcohol with $M^+ = 88$ and fragments at $m/z = 73$, $m/z = 70$, and $m/z = 59$

12.24 2-Methylpentane (C_6H_{14}) has the mass spectrum shown. Which peak represents M^+? Which is the base peak? Propose structures for fragment ions of $m/z = 71$, 57, 43, and 29. Why does the base peak have the mass it does?
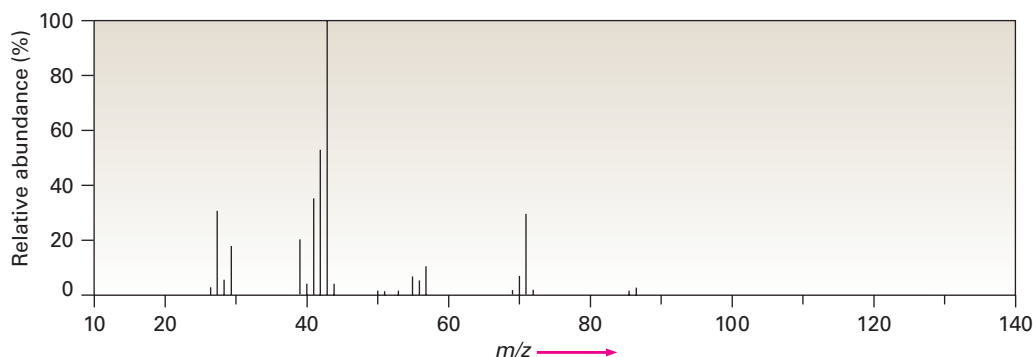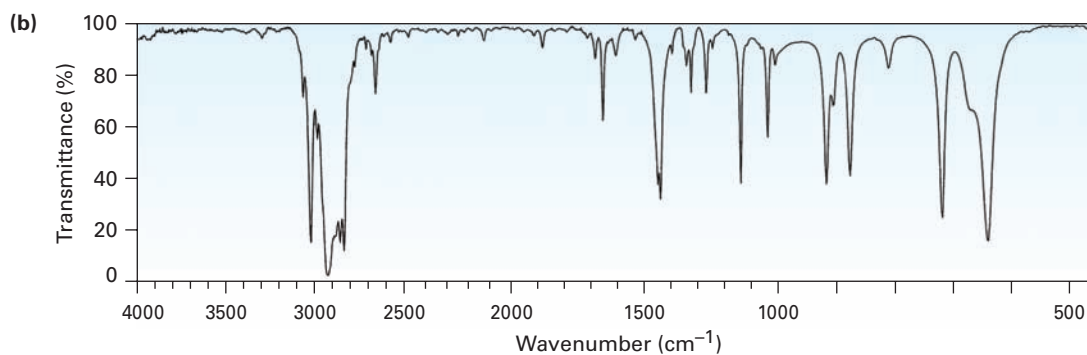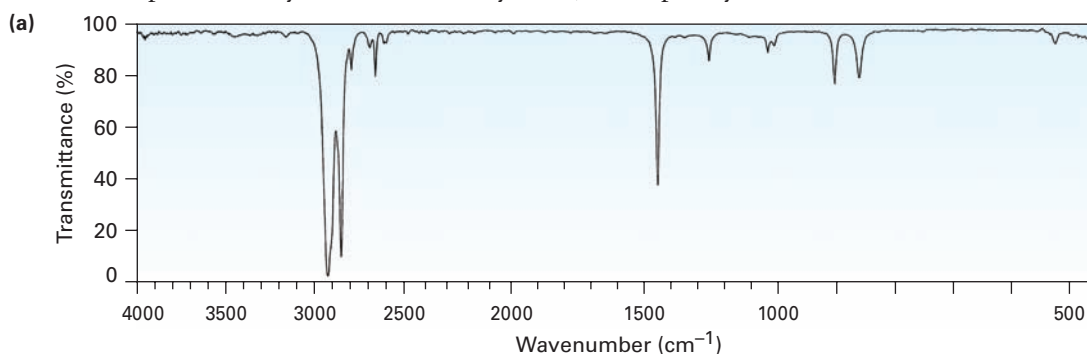

12.25 Assume that you are in a laboratory carrying out the catalytic hydrogenation of cyclohexene to cyclohexane. How could you use a mass spectrometer to determine when the reaction is finished?

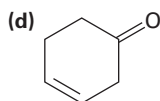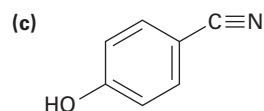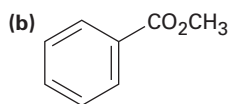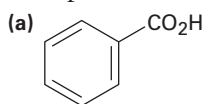**12.26** What fragments might you expect in the mass spectra of the following compounds?

(a)

(b)

(c)
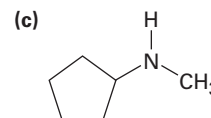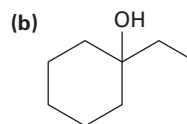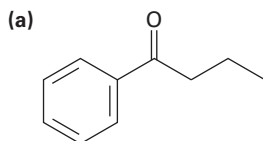
Infrared Spectroscopy

12.27 How might you use IR spectroscopy to distinguish among the three isomers 1-butyne, 1,3-butadiene, and 2-butyne?

12.28 Would you expect two enantiomers such as (R)-2-bromobutane and (S)-2-bromobutane to have identical or different IR spectra? Explain.

12.29 Would you expect two diastereomers such as *meso*-2,3-dibromobutane and (2R,3R)-dibromobutane to have identical or different IR spectra? Explain.

12.30 Propose structures for compounds that meet the following descriptions:
(a) C_5H_8, with IR absorptions at 3300 and 2150 cm^{-1}
(b) C_4H_8O, with a strong IR absorption at 3400 cm^{-1}
(c) C_4H_8O, with a strong IR absorption at 1715 cm^{-1}
(d) C_8H_{10}, with IR absorptions at 1600 and 1500 cm^{-1}

12.31 How could you use infrared spectroscopy to distinguish between the following pairs of isomers?
(a) $HC{\equiv}CCH_2NH_2$ and $CH_3CH_2C{\equiv}N$
(b) CH_3COCH_3 and CH_3CH_2CHO

12.32 Two infrared spectra are shown. One is the spectrum of cyclohexane, and the other is the spectrum of cyclohexene. Identify them, and explain your answer.
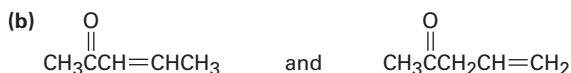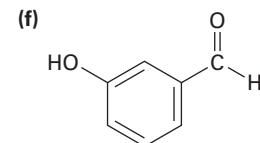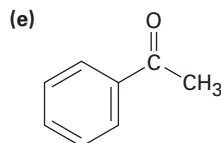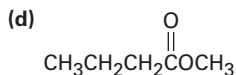
(a)

(b)

12.33 At what approximate positions might the following compounds show IR absorptions?

(a) [benzene ring with CO₂H] (b) [benzene ring with CO₂CH₃] (c) [benzene ring with C≡N and HO]

(d) [cyclohexenone structure with O] (e) $CH_3CCH_2CH_2COCH_3$ (with two O double bonds)

12.34 How would you use infrared spectroscopy to distinguish between the following pairs of constitutional isomers?

(a) $CH_3C\equiv CCH_3$ and $CH_3CH_2C\equiv CH$

(b) $CH_3CCH=CHCH_3$ (with O) and $CH_3CCH_2CH=CH_2$ (with O)

(c) $H_2C=CHOCH_3$ and CH_3CH_2CHO

12.35 At what approximate positions might the following compounds show IR absorptions?

(a) $CH_3CH_2CCH_3$ (with O)

(b) $CH_3CHCH_2C\equiv CH$ (with CH₃)

(c) $CH_3CHCH_2CH=CH_2$ (with CH₃)

(d) $CH_3CH_2CH_2COCH_3$ (with O)

(e) [benzene ring with C=O and CH₃]

(f) [HO benzene ring with C=O and H]
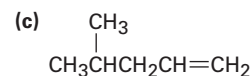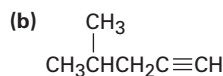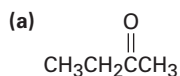
12.36 Assume that you are carrying out the dehydration of 1-methylcyclohexanol to yield 1-methylcyclohexene. How could you use infrared spectroscopy to determine when the reaction is complete?

12.37 Assume that you are carrying out the base-induced dehydrobromination of 3-bromo-3-methylpentane (Section 11.7) to yield an alkene. How could you use IR spectroscopy to tell which of two possible elimination products is formed?

General Problems

12.38 Which is stronger, the C=O bond in an ester (1735 cm^{-1}) or the C=O bond in a saturated ketone (1715 cm^{-1})? Explain.

12.39 Carvone is an unsaturated ketone responsible for the odor of spearmint. If carvone has M$^+$ = 150 in its mass spectrum and contains three double bonds and one ring, what is its molecular formula?

12.40 Carvone (Problem 12.39) has an intense infrared absorption at 1690 cm^{-1}. What kind of ketone does carvone contain?

12.41 The mass spectrum **(a)** and the infrared spectrum **(b)** of an unknown hydro-
carbon are shown. Propose as many structures as you can.

(a)

(b)
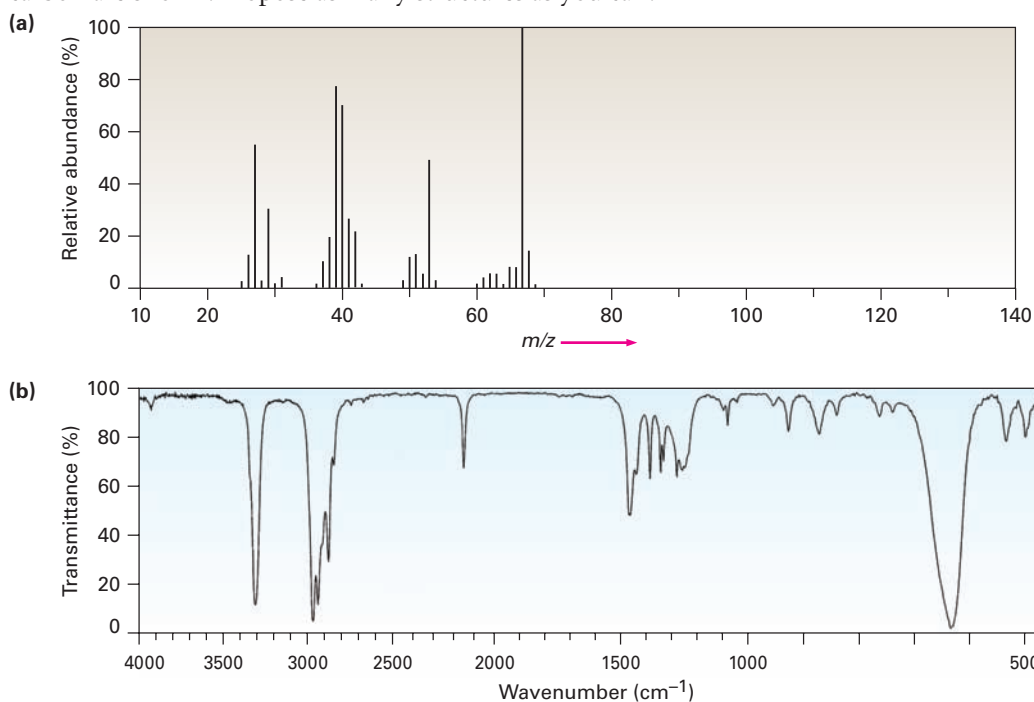
12.42 The mass spectrum **(a)** and the infrared spectrum **(b)** of another unknown
hydrocarbon are shown. Propose as many structures as you can.

(a)

(b)
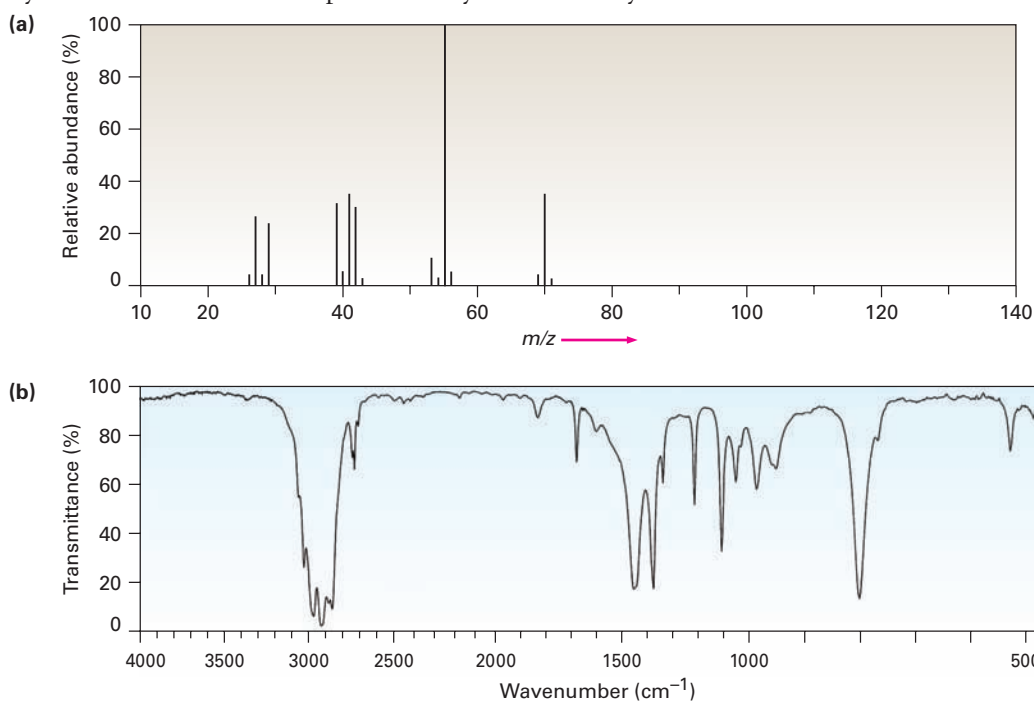
12.43 Propose structures for compounds that meet the following descriptions:
   (a) An optically active compound $C_5H_{10}O$ with an IR absorption at 1730 cm^{-1}
   (b) A non–optically active compound C_5H_9N with an IR absorption at 2215 cm^{-1}

12.44 4-Methyl-2-pentanone and 3-methylpentanal are isomers. Explain how you could tell them apart, both by mass spectrometry and by infrared spectroscopy.
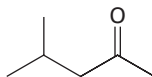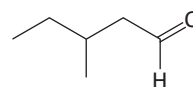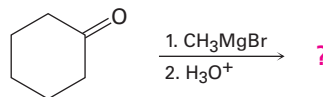

4-Methyl-2-pentanone   **3-Methylpentanal**

12.45 Grignard reagents undergo a general and very useful reaction with ketones. Methylmagnesium bromide, for example, reacts with cyclohexanone to yield a product with the formula $C_7H_{14}O$. What is the structure of this product if it has an IR absorption at 3400 cm^{-1}?

                    1. CH$_3$MgBr
                  ─────────────→   **?**
                    2. H$_3$O$^+$

Cyclohexanone

12.46 Ketones undergo a reduction when treated with sodium borohydride, $NaBH_4$. What is the structure of the compound produced by reaction of 2-butanone with $NaBH_4$ if it has an IR absorption at 3400 cm^{-1} and $M^+ = 74$ in the mass spectrum?

$$CH_3CH_2\overset{\overset{\textstyle O}{\|}}{C}CH_3 \quad \xrightarrow[\text{2. } H_3O^+]{\text{1. } NaBH_4} \quad \textbf{?}$$

2-Butanone
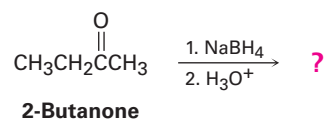
12.47 Nitriles, $R-C\equiv N$, undergo a hydrolysis reaction when heated with aqueous acid. What is the structure of the compound produced by hydrolysis of propanenitrile, $CH_3CH_2C\equiv N$, if it has IR absorptions at 2500–3100 cm^{-1} and 1710 cm^{-1} and has $M^+ = 74$?

13

NMR spectroscopy is an invaluable aid in carrying out the design and synthesis of new drugs.
Image copyright Jakub Pavlinec, 2010. Used under license from Shutterstock.com

Structure Determination: Nuclear Magnetic Resonance Spectroscopy

OWL Sign in to OWL for Organic Chemistry at **www.cengage.com/owl** to view tutorials and simulations, develop problem-solving skills, and complete online homework assigned by your professor.

Nuclear magnetic resonance (NMR) spectroscopy is the most valuable spectroscopic technique available to organic chemists. It's the method of structure determination that organic chemists turn to first.

We saw in Chapter 12 that mass spectrometry gives a molecule's formula and infrared spectroscopy identifies a molecule's functional groups. Nuclear magnetic resonance spectroscopy complements these other techniques by mapping a molecule's carbon–hydrogen framework. Taken together, mass spectrometry, IR, and NMR make it possible to determine the structures of even very complex molecules.

|	
Mass spectrometry	Molecular size and formula
Infrared spectroscopy	Functional groups
NMR spectroscopy	Map of carbon–hydrogen framework

Why This Chapter? The opening sentence in this chapter says it all: NMR is by far the most valuable spectroscopic technique for structure determination. Although we'll just give an overview of the subject in this chapter, focusing on NMR applications to small molecules, more advanced NMR techniques are also used in biological chemistry to study protein structure and folding.

13.1 Nuclear Magnetic Resonance Spectroscopy

Many kinds of nuclei behave as if they were spinning about an axis, much as the earth spins daily. Because they're positively charged, these spinning nuclei act like tiny magnets and interact with an external magnetic field, denoted B_0. Not all nuclei act this way, but fortunately for organic chemists, both the proton (^{1}H) and the ^{13}C nucleus do have spins. (In speaking about NMR, the words *proton* and *hydrogen* are often used interchangeably, since a hydrogen nucleus is just a proton.) Let's see what the consequences of nuclear spin are and how we can use the results.

In the absence of an external magnetic field, the spins of magnetic nuclei are oriented randomly. When a sample containing these nuclei is placed between the poles of a strong magnet, however, the nuclei adopt specific orientations, much as a compass needle orients in the earth's magnetic field. A spinning ^{1}H or ^{13}C nucleus can orient so that its own tiny magnetic field is aligned either with (parallel to) or against (antiparallel to) the external field. The two orientations don't have the same energy, however, and aren't equally likely. The parallel orientation is slightly lower in energy by an amount that depends on the strength of the external field, making this spin state very slightly favored over the antiparallel orientation **(Figure 13.1)**.
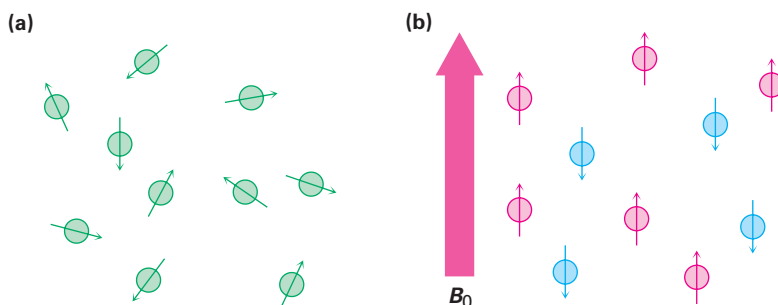
Figure 13.1 (a) Nuclear spins are oriented randomly in the absence of an external magnetic field but **(b)** have a specific orientation in the presence of an external field, B_0. Some of the spins (red) are aligned parallel to the external field while others (blue) are antiparallel. The parallel spin state is slightly lower in energy and therefore favored.

If the oriented nuclei are irradiated with electromagnetic radiation of the proper frequency, energy absorption occurs and the lower-energy state "spin-flips" to the higher-energy state. When this spin-flip occurs, the magnetic nuclei are said to be in resonance with the applied radiation—hence the name *nuclear magnetic resonance*.

The exact frequency necessary for resonance depends both on the strength of the external magnetic field and on the identity of the nuclei. If a very strong magnetic field is applied, the energy difference between the two spin states is larger and higher-frequency (higher-energy) radiation is required for a spin-flip. If a weaker magnetic field is applied, less energy is required to effect the transition between nuclear spin states **(Figure 13.2)**.
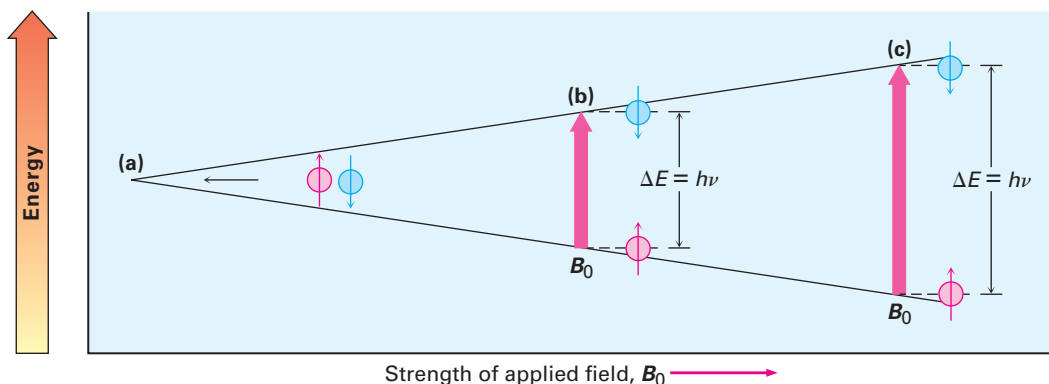
Figure 13.2 The energy difference ΔE between nuclear spin states depends on the strength of the applied magnetic field. Absorption of energy with frequency ν converts a nucleus from a lower spin state to a higher spin state. **(a)** Spin states have equal energies in the absence of an applied magnetic field but **(b)** have unequal energies in the presence of a magnetic field. At $\nu = 200$ MHz, $\Delta E = 8.0 \times 10^{-5}$ kJ/mol (1.9×10^{-5} kcal/mol). **(c)** The energy difference between spin states is greater at larger applied fields. At $\nu = 500$ MHz, $\Delta E = 2.0 \times 10^{-4}$ kJ/mol.

Table 13.1 The NMR Behavior of Some Common Nuclei

Magnetic nuclei	Nonmagnetic nuclei
^{1}H	^{12}C
^{13}C	^{16}O
^{2}H	^{32}S
^{14}N	
^{19}F	
^{31}P	

In practice, superconducting magnets that produce enormously powerful fields up to 21.2 tesla (T) are sometimes used, but field strengths in the range of 4.7 to 7.0 T are more common. At a magnetic field strength of 4.7 T, so-called radiofrequency (rf) energy in the 200 MHz range (1 MHz = 10^6 Hz) brings a ^{1}H nucleus into resonance, and rf energy of 50 MHz brings a ^{13}C nucleus into resonance. At the highest field strength currently available in commercial instruments (21.2 T), 900 MHz energy is required for ^{1}H spectroscopy. These energies needed for NMR are much smaller than those required for IR spectroscopy; 200 MHz rf energy corresponds to only 8.0×10^{-5} kJ/mol versus the 4.8 to 48 kJ/mol needed for IR spectroscopy.

^{1}H and ^{13}C nuclei are not unique in their ability to exhibit the NMR phenomenon. All nuclei with an odd number of protons (^{1}H, ^{2}H, ^{14}N, ^{19}F, ^{31}P, for example) and all nuclei with an odd number of neutrons (^{13}C, for example) show magnetic properties. Only nuclei with even numbers of both protons and neutrons (^{12}C, ^{16}O, ^{32}S) do not give rise to magnetic phenomena (Table 13.1).

Problem 13.1

The amount of energy required to spin-flip a nucleus depends both on the strength of the external magnetic field and on the nucleus. At a field strength of 4.7 T, rf energy of 200 MHz is required to bring a ^{1}H nucleus into resonance, but energy of only 187 MHz will bring a ^{19}F nucleus into resonance. Calculate the amount of energy required to spin-flip a ^{19}F nucleus. Is this amount greater or less than that required to spin-flip a ^{1}H nucleus?

Problem 13.2

Calculate the amount of energy required to spin-flip a proton in a spectrometer operating at 300 MHz. Does increasing the spectrometer frequency from 200 to 300 MHz increase or decrease the amount of energy necessary for resonance?

13.2 The Nature of NMR Absorptions

From the description thus far, you might expect all ^{1}H nuclei in a molecule to absorb energy at the same frequency and all ^{13}C nuclei to absorb at the same frequency. If so, we would observe only a single NMR absorption band in the ^{1}H or ^{13}C spectrum of a molecule, a situation that would be of little use. In fact, the absorption frequency is not the same for all ^{1}H or all ^{13}C nuclei.

All nuclei in molecules are surrounded by electrons. When an external magnetic field is applied to a molecule, the electrons moving around nuclei set up tiny local magnetic fields of their own. These local magnetic fields act in opposition to the applied field so that the effective field actually felt by the nucleus is a bit weaker than the applied field.

$$\boldsymbol{B}_{\text{effective}} = \boldsymbol{B}_{\text{applied}} - \boldsymbol{B}_{\text{local}}$$

In describing this effect of local fields, we say that nuclei are **shielded** from the full effect of the applied field by the surrounding electrons. Because each chemically distinct nucleus in a molecule is in a slightly different electronic environment, each nucleus is shielded to a slightly different extent and the effective magnetic field felt by each is slightly different. These tiny differences in the effective magnetic fields experienced by different nuclei can be detected,

and we thus see a distinct NMR signal for each chemically distinct ^{13}C or ^{1}H nucleus in a molecule. As a result, an NMR spectrum effectively maps the carbon–hydrogen framework of an organic molecule. With practice, it's possible to read the map and derive structural information.

Figure 13.3 shows both the ^{1}H and the ^{13}C NMR spectra of methyl acetate, $CH_3CO_2CH_3$. The horizontal axis shows the effective field strength felt by the nuclei, and the vertical axis indicates the intensity of absorption of rf energy. Each peak in the NMR spectrum corresponds to a chemically distinct ^{1}H or ^{13}C nucleus in the molecule. Note that NMR spectra are formatted with the zero absorption line at the bottom, whereas IR spectra are formatted with the zero absorption line at the top; **Section 12.5**. Note also that ^{1}H and ^{13}C spectra can't be observed simultaneously on the same spectrometer because different amounts of energy are required to spin-flip the different kinds of nuclei. The two spectra must be recorded separately.
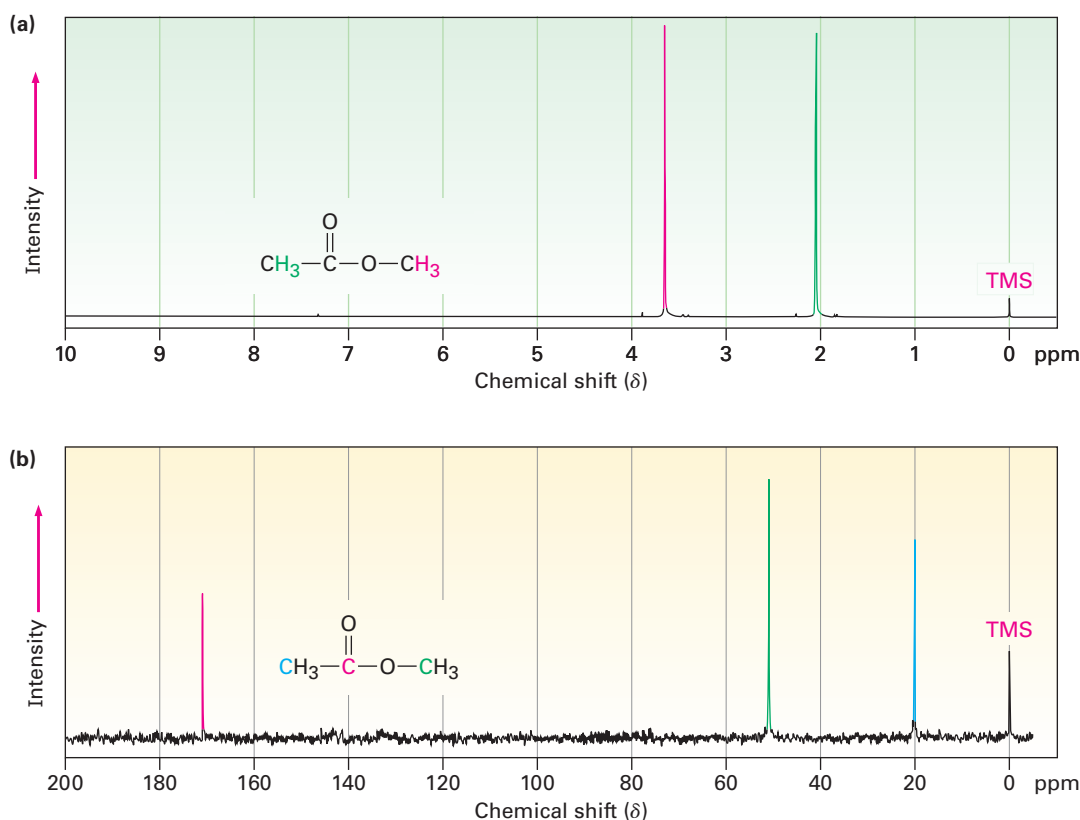
Figure 13.3 **(a)** The ^{1}H NMR spectrum and **(b)** the ^{13}C NMR spectrum of methyl acetate, $CH_3CO_2CH_3$. The small peak labeled "TMS" at the far right of each spectrum is a calibration peak, as explained in the next section.

The ^{13}C spectrum of methyl acetate in Figure 13.3b shows three peaks, one for each of the three chemically distinct carbon atoms in the molecule. The ^{1}H NMR spectrum in Figure 13.3a shows only two peaks, however, even though methyl acetate has six hydrogens. One peak is due to the $CH_3C{=}O$ hydrogens, and the other to the $-OCH_3$ hydrogens. Because the three hydrogens in each

methyl group have the same electronic environment, they are shielded to the same extent and are said to be equivalent. Chemically equivalent nuclei always show a single absorption. The two methyl groups themselves, however, are nonequivalent, so the two sets of hydrogens absorb at different positions.

The operation of a basic NMR spectrometer is illustrated in **Figure 13.4**. An organic sample is dissolved in a suitable solvent (usually deuteriochloroform, $CDCl_3$, which has no hydrogens) and placed in a thin glass tube between the poles of a magnet. The strong magnetic field causes the ^1H and ^{13}C nuclei in the molecule to align in one of the two possible orientations, and the sample is irradiated with rf energy. If the frequency of the rf irradiation is held constant and the strength of the applied magnetic field is varied, each nucleus comes into resonance at a slightly different field strength. A sensitive detector monitors the absorption of rf energy, and the electronic signal is then amplified and displayed as a peak.

Figure 13.4 Schematic operation of a basic NMR spectrometer. A thin glass tube containing the sample solution is placed between the poles of a strong magnet and irradiated with rf energy.
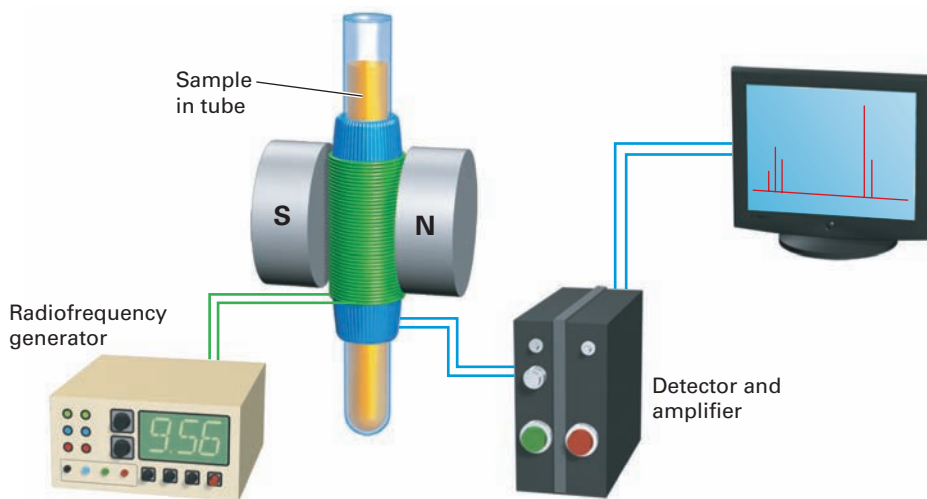
NMR spectroscopy differs from IR spectroscopy **(Sections 12.6–12.8)** in that the timescales of the two techniques are quite different. The absorption of infrared energy by a molecule giving rise to a change in vibrational amplitude is an essentially instantaneous process (about 10^{-13} s), but the NMR process is much slower (about 10^{-3} s). This difference in timescales between IR and NMR spectroscopy is analogous to the difference between cameras operating at very fast and very slow shutter speeds. The fast camera (IR) takes an instantaneous picture and freezes the action. If two rapidly interconverting species are present, IR spectroscopy records the spectrum of both. The slow camera (NMR), however, takes a blurred, time-averaged picture. If two species interconverting faster than 10^3 times per second are present in a sample, NMR records only a single, averaged spectrum, rather than separate spectra of the two discrete species.

Because of this blurring effect, NMR spectroscopy can be used to measure the rates and activation energies of very fast processes. In cyclohexane, for example, a ring-flip **(Section 4.6)** occurs so rapidly at room temperature that axial

and equatorial hydrogens can't be distinguished by NMR; only a single, aver-
aged ^{1}H NMR absorption is seen for cyclohexane at 25 °C. At −90 °C, however,
the ring-flip is slowed down enough that two absorption peaks are seen, one for
the six axial hydrogens and one for the six equatorial hydrogens. Knowing the
temperature and the rate at which signal blurring begins to occur, it's possible
to calculate that the activation energy for the cyclohexane ring-flip is 45 kJ/mol
(10.8 kcal/mol).

$$E_{act} = 45 \text{ kJ/mol}$$

^{1}H NMR: 1 peak at 25 °C
2 peaks at −90 °C
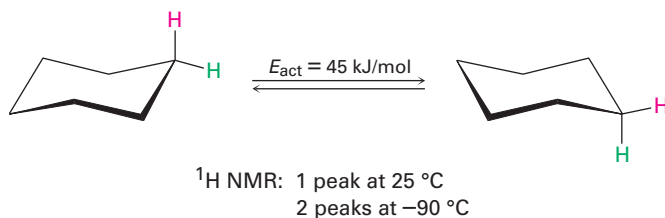
Problem 13.3
2-Chloropropene shows signals for three kinds of protons in its ^{1}H NMR spectrum. Explain.

13.3 Chemical Shifts

NMR spectra are displayed on charts that show the applied field strength
increasing from left to right **(Figure 13.5)**. Thus, the left part of the chart is the
low-field, or **downfield**, side, and the right part is the high-field, or **upfield**,
side. Nuclei that absorb on the downfield side of the chart require a lower field
strength for resonance, implying that they have less shielding. Nuclei that
absorb on the upfield side require a higher field strength for resonance, imply-
ing that they have more shielding.
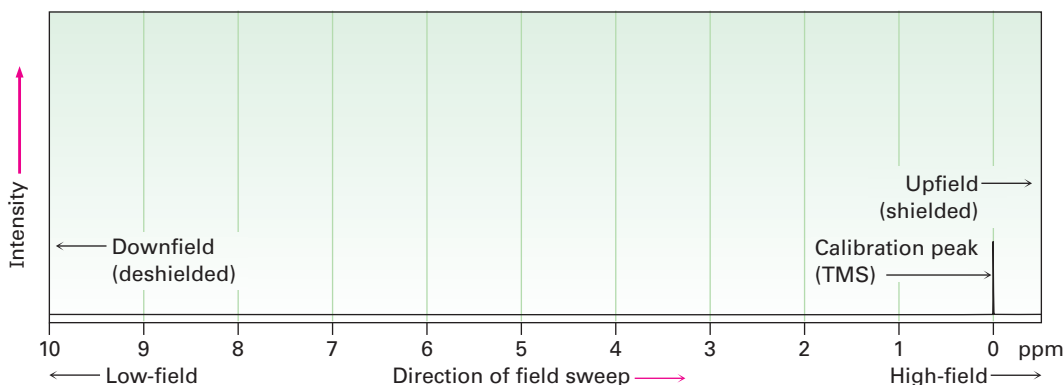
Figure 13.5 The NMR chart. The downfield, deshielded side is on the left, and the upfield, shielded side is on
the right. The tetramethylsilane (TMS) absorption is used as reference point.

To define the position of an absorption, the NMR chart is calibrated and a reference point is used. In practice, a small amount of tetramethylsilane [TMS; $(CH_3)_4Si$] is added to the sample so that a reference absorption peak is produced when the spectrum is run. TMS is used as reference for both ^1H and ^{13}C measurements because it produces in both a single peak that occurs upfield of other absorptions normally found in organic compounds. The ^1H and ^{13}C spectra of methyl acetate in Figure 13.3 have the TMS reference peak indicated.

The position on the chart at which a nucleus absorbs is called its **chemical shift**. The chemical shift of TMS is set as the zero point, and other absorptions normally occur downfield, to the left on the chart. NMR charts are calibrated using an arbitrary scale called the **delta (δ) scale**, where $1\,\delta$ equals 1 part-per-million (1 ppm) of the spectrometer operating frequency. For example, if we were measuring the ^1H NMR spectrum of a sample using an instrument operating at 200 MHz, $1\,\delta$ would be 1 millionth of 200,000,000 Hz, or 200 Hz. If we were measuring the spectrum using a 500 MHz instrument, $1\,\delta = 500$ Hz. The following equation can be used for any absorption:

$$\delta = \frac{\text{Observed chemical shift (number of Hz away from TMS)}}{\text{Spectrometer frequency in MHz}}$$

Although this method of calibrating NMR charts may seem complex, there's a good reason for it. As we saw earlier, the rf frequency required to bring a given nucleus into resonance depends on the spectrometer's magnetic field strength. But because there are many different kinds of spectrometers with many different magnetic field strengths available, chemical shifts given in frequency units (Hz) vary from one instrument to another. Thus, a resonance that occurs at 120 Hz downfield from TMS on one spectrometer might occur at 600 Hz downfield from TMS on another spectrometer with a more powerful magnet.

By using a system of measurement in which NMR absorptions are expressed in relative terms (parts per million relative to spectrometer frequency) rather than absolute terms (Hz), it's possible to compare spectra obtained on different instruments. *The chemical shift of an NMR absorption in δ units is constant, regardless of the operating frequency of the spectrometer.* A ^1H nucleus that absorbs at $2.0\,\delta$ on a 200 MHz instrument also absorbs at $2.0\,\delta$ on a 500 MHz instrument.

The range in which most NMR absorptions occur is quite narrow. Almost all ^1H NMR absorptions occur from 0 to $10\,\delta$ downfield from the proton absorption of TMS, and almost all ^{13}C absorptions occur from 1 to $220\,\delta$ downfield from the carbon absorption of TMS. Thus, there is a likelihood that accidental overlap of nonequivalent signals will occur. The advantage of using an instrument with higher field strength (say, 500 MHz) rather than lower field strength (200 MHz) is that different NMR absorptions are more widely separated at the higher field strength. The chances that two signals will accidentally overlap are therefore lessened, and interpretation of spectra becomes easier. For example, two signals that are only 20 Hz apart at 200 MHz (0.1 ppm) are 50 Hz apart at 500 MHz (still 0.1 ppm).

Problem 13.4

The following ^1H NMR peaks were recorded on a spectrometer operating at 200 MHz. Convert each into δ units.

(a) $CHCl_3$; 1454 Hz   **(b)** CH_3Cl; 610 Hz
(c) CH_3OH; 693 Hz   **(d)** CH_2Cl_2; 1060 Hz

Problem 13.5

When the ^1H NMR spectrum of acetone, CH_3COCH_3, is recorded on an instrument operating at 200 MHz, a single sharp resonance at 2.1 δ is seen.

(a) How many hertz downfield from TMS does the acetone resonance correspond to?
(b) If the ^1H NMR spectrum of acetone were recorded at 500 MHz, what would the position of the absorption be in δ units?
(c) How many hertz downfield from TMS does this 500 MHz resonance correspond to?

13.4 ^{13}C NMR Spectroscopy: Signal Averaging and FT–NMR

Everything we've said thus far about NMR spectroscopy applies to both ^1H and ^{13}C spectra. Now, though, let's focus only on ^{13}C spectroscopy because it's much easier to interpret. What we learn now about interpreting ^{13}C spectra will simplify the subsequent discussion of ^1H spectra.

In some ways, it's surprising that carbon NMR is even possible. After all, ^{12}C, the most abundant carbon isotope, has no nuclear spin and can't be seen by NMR. Carbon-13 is the only naturally occurring carbon isotope with a nuclear spin, but its natural abundance is only 1.1%. Thus, only about 1 of every 100 carbons in an organic sample is observable by NMR. The problem of low abundance has been overcome, however, by the use of *signal averaging* and *Fourier-transform NMR* (**FT–NMR**). Signal averaging increases instrument sensitivity, and FT–NMR increases instrument speed.

The low natural abundance of ^{13}C means that any individual NMR spectrum is extremely "noisy." That is, the signals are so weak that they are cluttered with random background electronic noise, as shown in **Figure 13.6a** on the next page. If, however, hundreds or thousands of individual runs are added together by a computer and then averaged, a greatly improved spectrum results (Figure 13.6b). Background noise, because of its random nature, averages to zero, while the nonzero signals stand out clearly. Unfortunately, the value of signal averaging is limited when using the method of NMR spectrometer operation described in **Section 13.2**, because it takes about 5 to 10 minutes to obtain a single spectrum. Thus, a faster way to obtain spectra is needed if signal averaging is to be used.

In the method of NMR spectrometer operation described in **Section 13.2**, the rf frequency is held constant while the strength of the magnetic field is varied so that all signals in the spectrum are recorded sequentially. In the FT–NMR technique used by modern spectrometers, however, all the signals are recorded simultaneously. A sample is placed in a magnetic field of constant strength and is irradiated with a short pulse of rf energy that covers the entire range of useful frequencies. All ^1H or ^{13}C nuclei in the sample resonate at once, giving a complex, composite signal that is mathematically manipulated using

so-called Fourier transforms and then displayed in the usual way. Because all resonance signals are collected at once, it takes only a few seconds rather than a few minutes to record an entire spectrum.
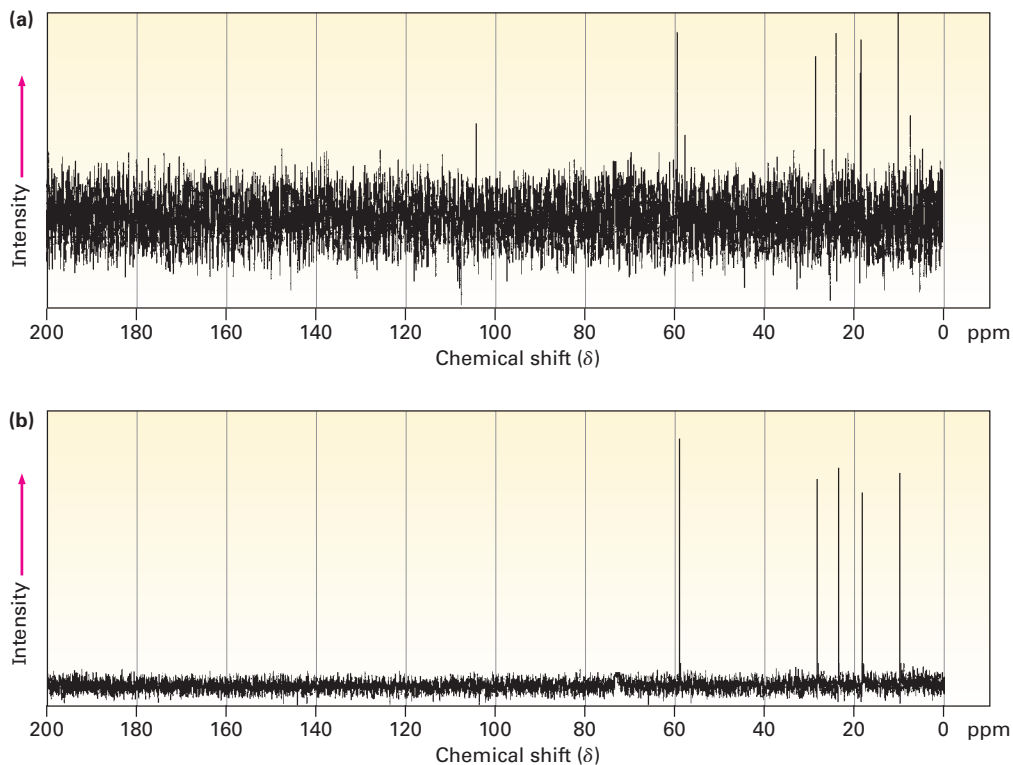

Figure 13.6 Carbon-13 NMR spectra of 1-pentanol, $CH_3CH_2CH_2CH_2CH_2OH$. Spectrum **(a)** is a single run, showing the large amount of background noise. Spectrum **(b)** is an average of 200 runs.

Combining the speed of FT–NMR with the sensitivity enhancement of signal averaging is what gives modern NMR spectrometers their power. Literally thousands of spectra can be taken and averaged in a few hours, resulting in sensitivity so high that a ^{13}C NMR spectrum can be obtained on less than 0.1 mg of sample and a ^1H spectrum can be recorded on only a few *micro*grams.

13.5 Characteristics of ^{13}C NMR Spectroscopy

At its simplest, ^{13}C NMR makes it possible to count the number of different carbon atoms in a molecule. Look at the ^{13}C NMR spectra of methyl acetate and 1-pentanol shown previously in Figures 13.3b and 13.6b. In each case, a single sharp resonance line is observed for each different carbon atom.

Most ^{13}C resonances are between 0 and 220 ppm downfield from the TMS reference line, with the exact chemical shift of each ^{13}C resonance dependent on that carbon's electronic environment within the molecule. **Figure 13.7** shows the correlation of chemical shift with environment.
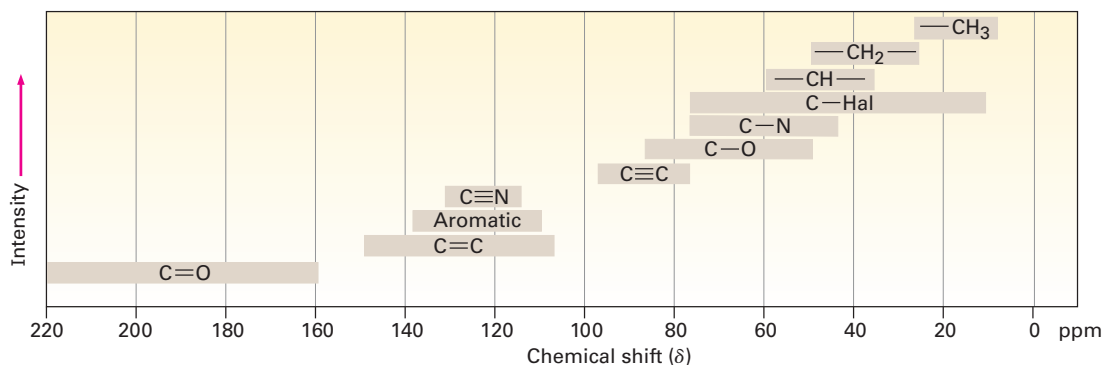
Figure 13.7 Chemical shift correlations for ^{13}C NMR.

The factors that determine chemical shifts are complex, but it's possible to make some generalizations from the data in Figure 13.7. One trend is that a carbon's chemical shift is affected by the electronegativity of nearby atoms. Carbons bonded to oxygen, nitrogen, or halogen absorb downfield (to the left) of typical alkane carbons. Because electronegative atoms attract electrons, they pull electrons away from neighboring carbon atoms, causing those carbons to be deshielded and to come into resonance at a lower field.

Another trend is that sp^3-hybridized carbons generally absorb from 0 to 90 δ, while sp^2 carbons absorb from 110 to 220 δ. Carbonyl carbons (C=O) are particularly distinct in ^{13}C NMR and are always found at the low-field end of the spectrum, from 160 to 220 δ. **Figure 13.8** shows the ^{13}C NMR spectra of 2-butanone and *para*-bromoacetophenone and indicates the peak assignments. Note that the C=O carbons are at the left edge of the spectrum in each case.
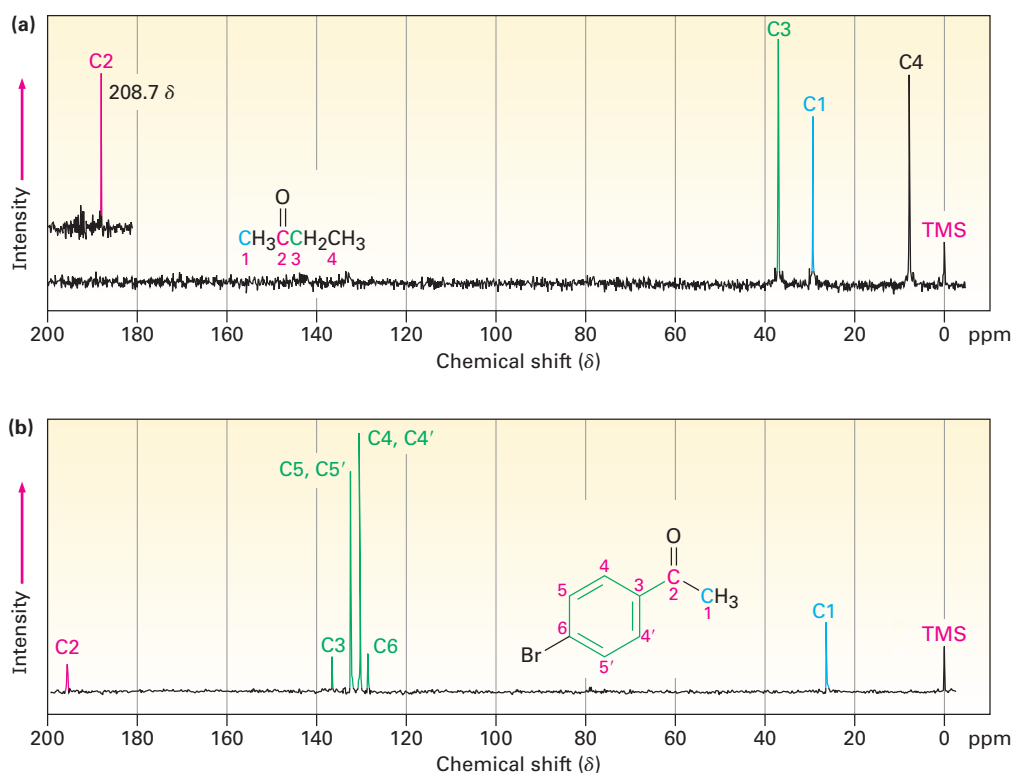
Figure 13.8 Carbon-13 NMR spectra of **(a)** 2-butanone and **(b)** *para*-bromoacetophenone.

The ^{13}C NMR spectrum of *para*-bromoacetophenone is interesting in several ways. Note particularly that only six carbon absorptions are observed, even though the molecule contains eight carbons. *para*-Bromoacetophenone has a symmetry plane that makes ring carbons 4 and 4′, and ring carbons 5 and 5′ equivalent. (Remember from **Section 2.4** that aromatic rings have two resonance forms.) Thus, the six ring carbons show only four absorptions in the range 128 to 137 δ.

***para*-Bromoacetophenone**
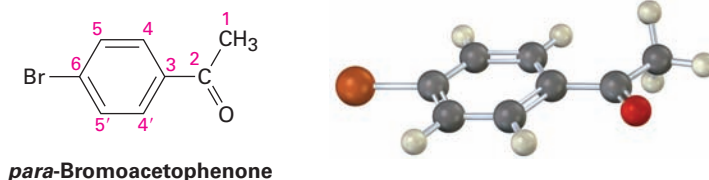
A second interesting point about both spectra in Figure 13.8 is that the peaks aren't uniform in size. Some peaks are larger than others even though they are one-carbon resonances (except for the two 2-carbon peaks of *para*-bromoacetophenone). This difference in peak size is a general feature of ^{13}C NMR spectra.

Worked Example 13.1

Predicting Chemical Shifts in ^{13}C NMR Spectra

At what approximate positions would you expect ethyl acrylate, $H_2C=CHCO_2CH_2CH_3$, to show ^{13}C NMR absorptions?

Strategy

Identify the distinct carbons in the molecule, and note whether each is alkyl, vinylic, aromatic, or in a carbonyl group. Then predict where each absorbs, using Figure 13.7 as necessary.

Solution

Ethyl acrylate has five chemically distinct carbons: two different C=C, one C=O, one O—C, and one alkyl C. From Figure 13.7, the likely absorptions are
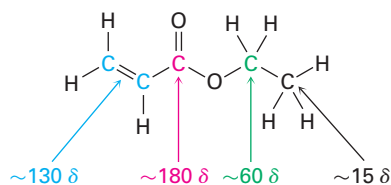
The actual absorptions are at 14.1, 60.5, 128.5, 130.3, and 166.0 δ.

Problem 13.6

Predict the number of carbon resonance lines you would expect in the ^{13}C NMR spectra of the following compounds:

(a) Methylcyclopentane **(b)** 1-Methylcyclohexene
(c) 1,2-Dimethylbenzene **(d)** 2-Methyl-2-butene
(e) **(f)**
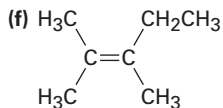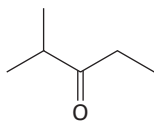
Problem 13.7

Propose structures for compounds that fit the following descriptions:
(a) A hydrocarbon with seven lines in its ^{13}C NMR spectrum
(b) A six-carbon compound with only five lines in its ^{13}C NMR spectrum
(c) A four-carbon compound with three lines in its ^{13}C NMR spectrum

Problem 13.8

Assign the resonances in the ^{13}C NMR spectrum of methyl propanoate, $CH_3CH_2CO_2CH_3$ **(Figure 13.9)**.
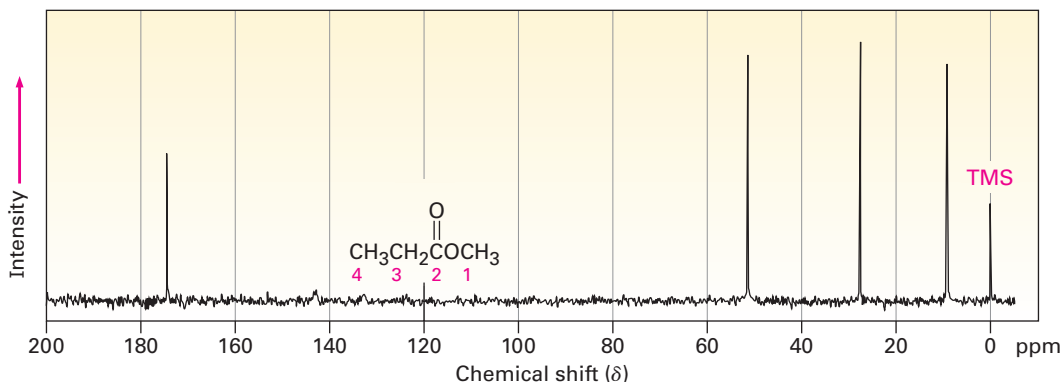
Figure 13.9 ^{13}C NMR spectrum of methyl propanoate, Problem 13.8.

13.6 DEPT ^{13}C NMR Spectroscopy

Numerous techniques developed in recent years have made it possible to obtain enormous amounts of information from ^{13}C NMR spectra. Among these techniques is one called DEPT–NMR, for *distortionless enhancement by polarization transfer,* which makes it possible to distinguish among signals due to CH$_3$, CH$_2$, CH, and quaternary carbons. That is, the number of hydrogens attached to each carbon in a molecule can be determined.

A DEPT experiment is usually done in three stages, as shown in **Figure 13.10** for 6-methyl-5-hepten-2-ol. The first stage is to run an ordinary spectrum (called a broadband-decoupled spectrum) to locate the chemical shifts of all carbons. Next, a second spectrum called a DEPT-90 is run, using special conditions under which only signals due to CH carbons appear. Signals due

to CH_3, CH_2, and quaternary carbons are absent. Finally, a third spectrum called a DEPT-135 is run, using conditions under which CH_3 and CH resonances appear as positive signals, CH_2 resonances appear as *negative* signals—that is, as peaks below the baseline—and quaternary carbons are again absent.
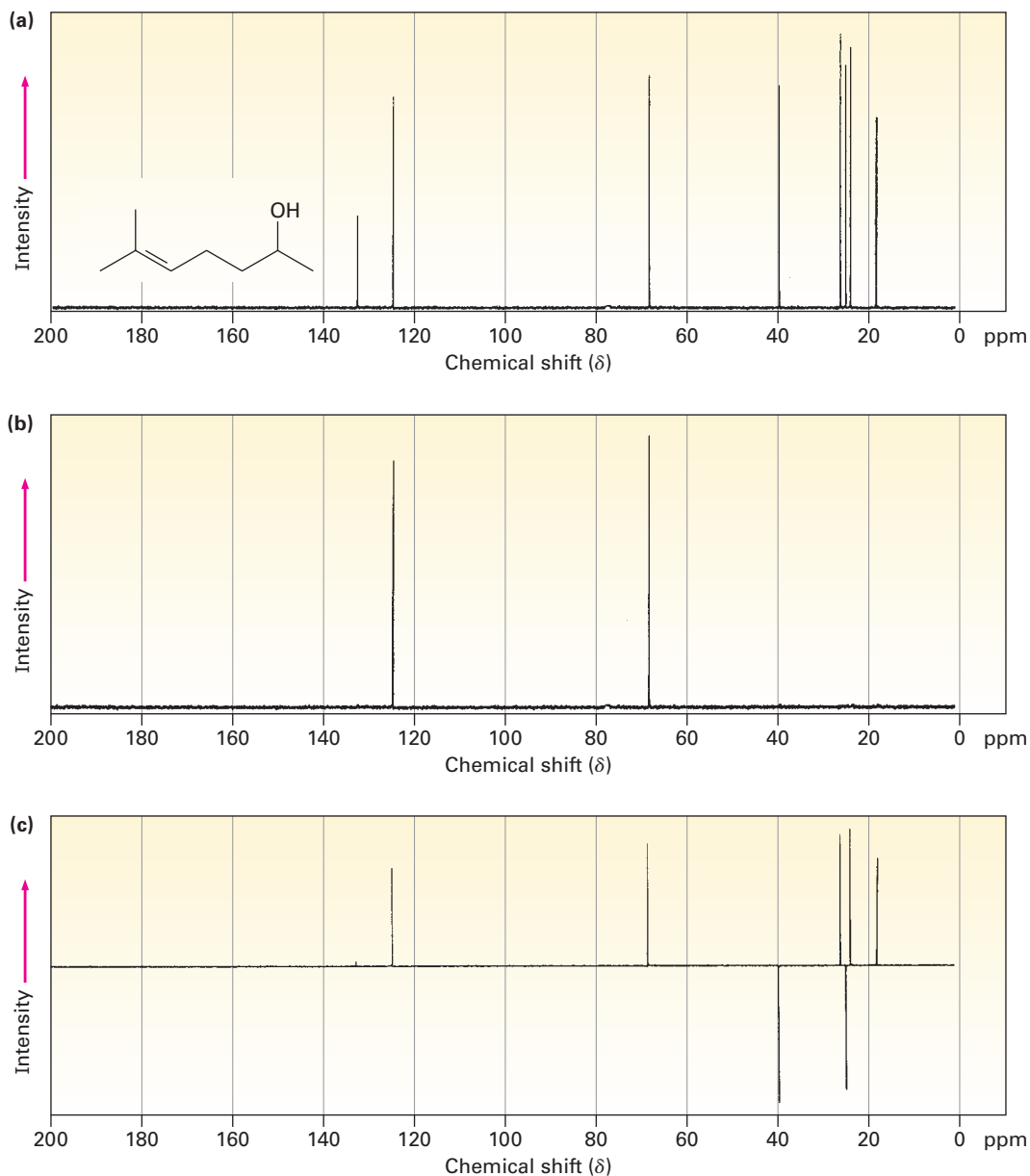
Figure 13.10 DEPT–NMR spectra for 6-methyl-5-hepten-2-ol. Part **(a)** is an ordinary broadband-decoupled spectrum, which shows signals for all eight carbons. Part **(b)** is a DEPT-90 spectrum, which shows only signals for the two CH carbons. Part **(c)** is a DEPT-135 spectrum, which shows positive signals for the two CH and three CH_3 carbons and negative signals for the two CH_2 carbons.

Putting together the information from all three spectra makes it possible to tell the number of hydrogens attached to each carbon. The CH carbons are identified in the DEPT-90 spectrum, the CH$_2$ carbons are identified as the negative peaks in the DEPT-135 spectrum, the CH$_3$ carbons are identified by subtracting the CH peaks from the positive peaks in the DEPT-135 spectrum, and quaternary carbons are identified by subtracting all peaks in the DEPT-135 spectrum from the peaks in the broadband-decoupled spectrum.

Broadband-decoupled	DEPT-90	DEPT-135
C, CH, CH$_2$, CH$_3$	CH	CH$_3$, CH are positive CH$_2$ is negative

C	Subtract DEPT-135 from broadband-decoupled spectrum
CH	DEPT-90
CH$_2$	Negative DEPT-135
CH$_3$	Subtract DEPT-90 from positive DEPT-135

Assigning a Chemical Structure from a ^{13}C NMR Spectrum

Worked Example 13.2

Propose a structure for an alcohol, C$_4$H$_{10}$O, that has the following ^{13}C NMR spectral data:

Broadband decoupled ^{13}C NMR: 19.0, 31.7, 69.5 δ;
DEPT-90: 31.7 δ;
DEPT-135: positive peak at 19.0 δ, negative peak at 69.5 δ.

Strategy

As noted in **Section 7.2**, it usually helps with compounds of known formula but unknown structure to calculate the compound's degree of unsaturation. In the present instance, a formula of C$_4$H$_{10}$O corresponds to a saturated, open-chain molecule.

To gain information from the ^{13}C data, let's begin by noting that the unknown alcohol has four carbon atoms, yet has only three NMR absorptions, which implies that two of the carbons must be equivalent. Looking at chemical shifts, two of the absorptions are in the typical alkane region (19.0 and 31.7 δ), while one is in the region of a carbon bonded to an electronegative atom (69.5 δ)—oxygen in this instance. The DEPT-90 spectrum tells us that the alkyl carbon at 31.7 δ is tertiary (CH); the DEPT-135 spectrum tells us that the alkyl carbon at 19.0 δ is a methyl (CH$_3$) and that the carbon bonded to oxygen (69.5 δ) is secondary (CH$_2$). The two equivalent carbons are probably both methyls bonded to the same tertiary carbon, (CH$_3$)$_2$CH—. We can now put the pieces together to propose a structure: 2-methyl-1-propanol.

Solution

2-Methyl-1-propanol
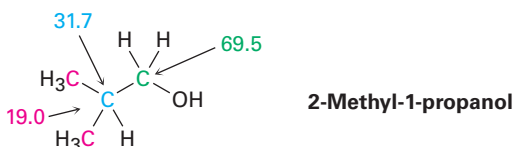
Problem 13.9

Assign a chemical shift to each carbon in 6-methyl-5-hepten-2-ol (Figure 13.10).

Problem 13.10

Estimate the chemical shift of each carbon in the following molecule. Predict which carbons will appear in the DEPT-90 spectrum, which will give positive peaks in the DEPT-135 spectrum, and which will give negative peaks in the DEPT-135 spectrum.
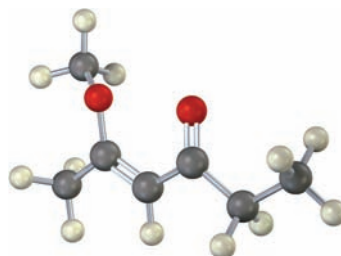
Problem 13.11

Propose a structure for an aromatic hydrocarbon, $C_{11}H_{16}$, that has the following ^{13}C NMR spectral data:

Broadband decoupled: 29.5, 31.8, 50.2, 125.5, 127.5, 130.3, 139.8 δ

DEPT-90: 125.5, 127.5, 130.3 δ

DEPT-135: positive peaks at 29.5, 125.5, 127.5, 130.3 δ; negative peak at 50.2 δ

13.7 Uses of ^{13}C NMR Spectroscopy

The information derived from ^{13}C NMR spectroscopy is extraordinarily useful for structure determination. Not only can we count the number of nonequivalent carbon atoms in a molecule, we can also get information about the electronic environment of each carbon and find how many protons each is attached to. As a result, we can answer many structural questions that go unanswered by IR spectroscopy or mass spectrometry.

Here's an example: how do we know that the E2 reaction of an alkyl halide follows Zaitsev's rule **(Section 11.7)**? Does treatment of 1-chloro-1-methyl-cyclohexane with a strong base give predominantly the trisubstituted alkene 1-methylcyclohexene or the disubstituted alkene methylenecyclohexane?
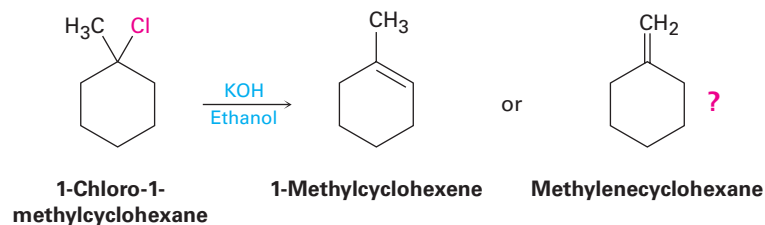
1-Methylcyclohexene will have five sp^3-carbon resonances in the 20 to 50 δ range and two sp^2-carbon resonances in the 100 to 150 δ range. Methylene-cyclohexane, however, because of its symmetry, will have only three sp^3-carbon

resonance peaks and two sp^2-carbon peaks. The spectrum of the actual reaction product, shown in **Figure 13.11**, clearly identifies 1-methylcyclohexene as the product of this E2 reaction.
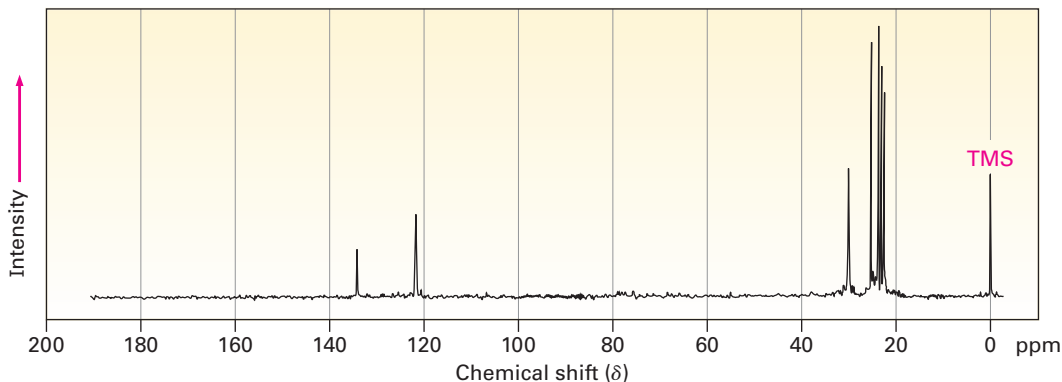
Figure 13.11 The ¹³C NMR spectrum of 1-methylcyclohexene, the E2 reaction product from treatment of 1-chloro-1-methylcyclohexane with base.

Problem 13.12

We saw in **Section 9.3** that addition of HBr to a terminal alkyne leads to the Markovnikov addition product, with the Br bonding to the more highly substituted carbon. How could you use ¹³C NMR to identify the product of the addition of 1 equivalent of HBr to 1-hexyne?

13.8 ¹H NMR Spectroscopy and Proton Equivalence

Having looked at ¹³C spectra, let's now focus on ¹H NMR spectroscopy. Because each electronically distinct hydrogen in a molecule has its own unique absorption, one use of ¹H NMR is to find out how many kinds of electronically non-equivalent hydrogens are present. In the ¹H NMR spectrum of methyl acetate shown previously in Figure 13.3a on page 459, for instance, there are two signals, corresponding to the two kinds of nonequivalent protons present, $CH_3C=O$ protons and $-OCH_3$ protons.

For relatively small molecules, a quick look at the structure is often enough to decide how many kinds of protons are present and thus how many NMR absorptions might appear. If in doubt, though, the equivalence or nonequivalence of two protons can be determined by comparing the structures that would be formed if each hydrogen were replaced by an X group. There are four possibilities.

- One possibility is that the protons are chemically unrelated and thus nonequivalent. If so, the products formed on substitution of H by X would be different constitutional isomers. In butane, for instance, the $-CH_3$ protons are different from the $-CH_2-$ protons. They therefore

give different products on substitution by X than the −CH$_2$ protons and would likely show different NMR absorptions.

The −CH$_2$− and −CH$_3$
hydrogens are unrelated and
have different NMR absorptions.

Replace either
H or H with X

or

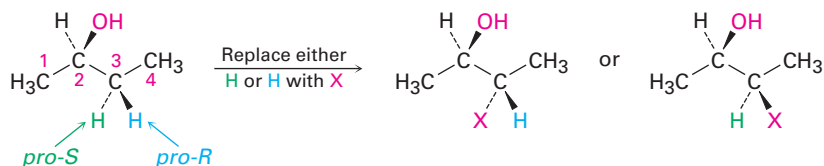The two substitution products
are constitutional isomers.
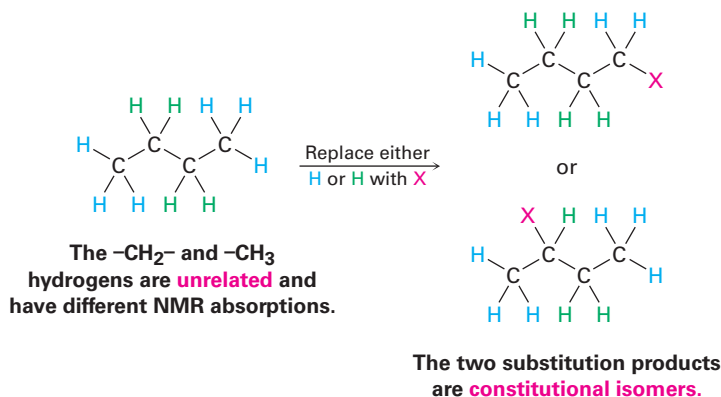
- A second possibility is that the protons are chemically identical and thus electronically equivalent. If so, the same product would be formed regardless of which H is substituted by X. In butane, for instance, the six −CH$_3$ hydrogens on C1 and C4 are identical, would give the identical structure on substitution by X, and would show the identical NMR absorption. Such protons are said to be **homotopic**.

The six −CH$_3$ hydrogens
are homotopic and have
the same NMR absorption.

Replace one H
with X

Only one substitution
product is possible.
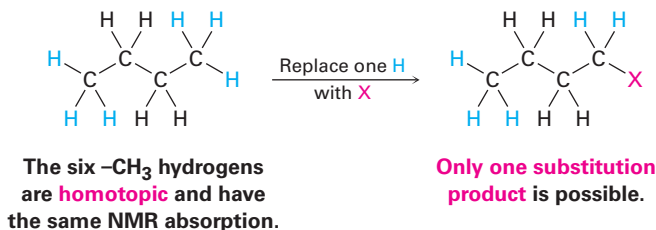
- The third possibility is a bit more subtle. Although they might at first seem homotopic, the two −CH$_2$− hydrogens on C2 in butane (and the two −CH$_2$− hydrogens on C3) are in fact not identical. Substitution by X of a hydrogen at C2 (or C3) would form a new chirality center, so different enantiomers **(Section 5.1)** would result depending on whether the *pro-R* or *pro-S* hydrogen were substituted for **(Section 5.11)**. Such hydrogens, whose substitution by X would lead to different enantiomers, are said to be **enantiotopic**. Enantiotopic hydrogens, even though not identical, are nevertheless electronically equivalent and thus have the same NMR absorption.

The two hydrogens on C2 (and
on C3) are enantiotopic and
have the same NMR absorption.

Replace either
H or H with X

or

The two possible substitution
products are enantiomers.
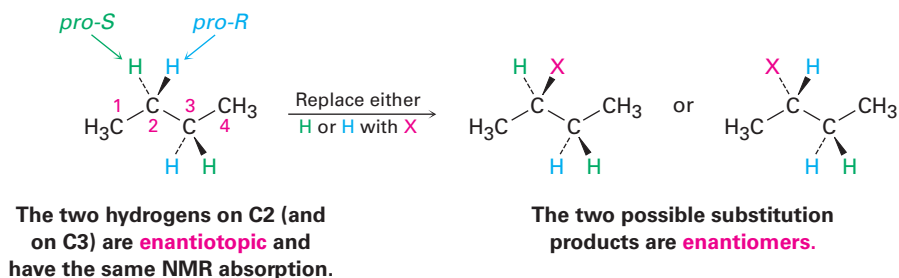
- The fourth possibility arises in chiral molecules, such as (*R*)-2-butanol. The two −CH$_2$− hydrogens at C3 are neither homotopic nor enantiotopic. Since substitution of a hydrogen at C3 would form a second chirality center, different diastereomers **(Section 5.6)** would result depending on whether the *pro-R* or *pro-S* hydrogen were substituted for. Such hydrogens, whose substitution by X leads to different diastereomers, are said to be **diastereotopic**. Diastereotopic hydrogens are neither chemically nor electronically equivalent. They are completely different and would likely show different NMR absorptions.

The two hydrogens on C3 are diastereotopic and have different NMR absorptions.

The two possible substitution products are diastereomers.

Problem 13.13

Identify the indicated sets of protons as unrelated, homotopic, enantiotopic, or diastereotopic:

(a)

(b)

(c)

(d)

(e)

(f)
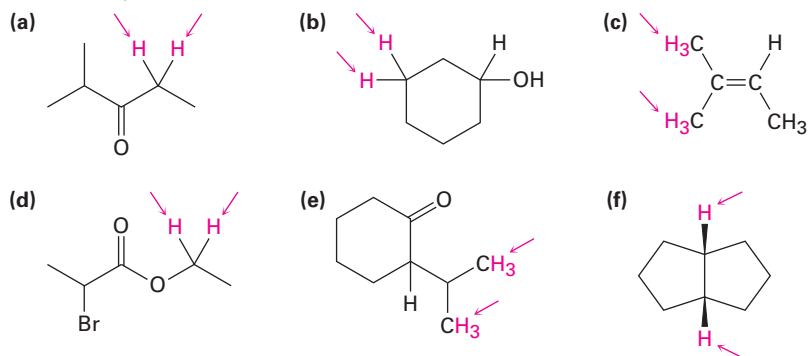
Problem 13.14

How many kinds of electronically nonequivalent protons are present in each of the following compounds, and thus how many NMR absorptions might you expect in each?
(a) CH_3CH_2Br **(b)** $CH_3OCH_2CH(CH_3)_2$ **(c)** $CH_3CH_2CH_2NO_2$
(d) Methylbenzene   **(e)** 2-Methyl-1-butene   **(f)** *cis*-3-Hexene

Problem 13.15

How many absorptions would you expect (*S*)-malate, an intermediate in carbohydrate metabolism, to have in its ¹H NMR spectrum? Explain.
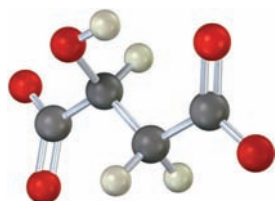
(*S*)-Malate

13.9 Chemical Shifts in ^{1}H NMR Spectroscopy

As we said previously, differences in chemical shifts are caused by the small local magnetic fields of electrons surrounding the different nuclei. Nuclei that are more strongly shielded by electrons require a higher applied field to bring them into resonance and therefore absorb on the right side of the NMR chart. Nuclei that are less strongly shielded need a lower applied field for resonance and therefore absorb on the left of the NMR chart.

Most ^{1}H chemical shifts fall within the range 0 to 10 δ, which can be divided into the five regions shown in Table 13.2. By remembering the positions of these regions, it's often possible to tell at a glance what kinds of protons a molecule contains.

Table 13.2 Regions of the ^{1}H NMR Spectrum
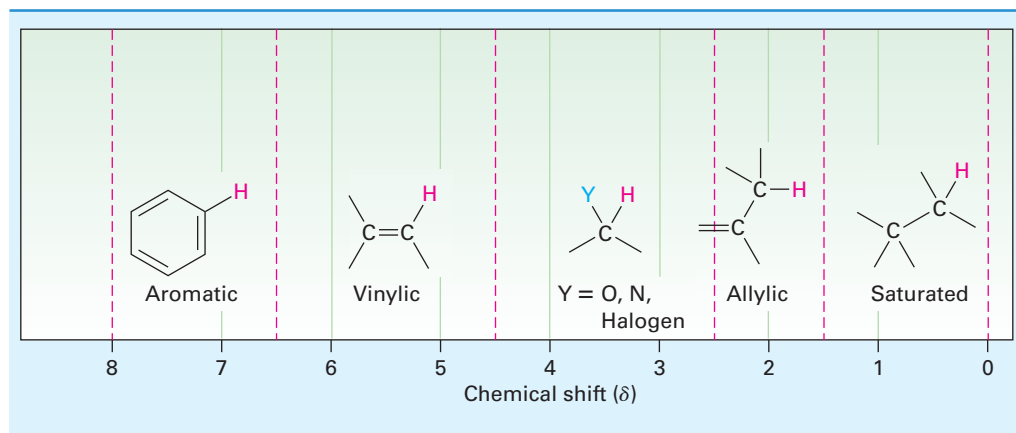
Table 13.3 shows the correlation of ^{1}H chemical shift with electronic environment in more detail. In general, protons bonded to saturated, sp^3-hybridized carbons absorb at higher fields, whereas protons bonded to sp^2-hybridized carbons absorb at lower fields. Protons on carbons that are bonded to electronegative atoms, such as N, O, or halogen, also absorb at lower fields.

Worked Example 13.3

Predicting Chemical Shifts in ^{1}H NMR Spectra

Methyl 2,2-dimethylpropanoate $(CH_3)_3CCO_2CH_3$ has two peaks in its ^{1}H NMR spectrum. What are their approximate chemical shifts?

Strategy

Identify the types of hydrogens in the molecule, and note whether each is alkyl, vinylic, or next to an electronegative atom. Then predict where each absorbs, using Table 13.3 if necessary.

Solution

The $-OCH_3$ protons absorb around 3.5 to 4.0 δ because they are on carbon bonded to oxygen. The $(CH_3)_3C-$ protons absorb near 1.0 δ because they are typical alkane-like protons.

Table 13.3 Correlation of ¹H Chemical Shift with Environment

| Type of hydrogen		Chemical shift (δ)	Type of hydrogen		Chemical shift (δ)
Reference	$Si(CH_3)_4$	0	Alcohol	$-\overset{\|}{\underset{\|}{C}}-O-H$	2.5–5.0
Alkyl (primary)	$-CH_3$	0.7–1.3			
Alkyl (secondary)	$-CH_2-$	1.2–1.6			
Alkyl (tertiary)	$-\overset{\|}{C}H-$	1.4–1.8	Alcohol, ether	$-\overset{H}{\underset{\|}{C}}-O-$	3.3–4.5
Allylic	$C=C-\overset{H}{\underset{\|}{C}}-$	1.6–2.2			
			Vinylic	$\overset{H}{C=C}$	4.5–6.5
Methyl ketone	$-\overset{O}{\overset{\|\|}{C}}-CH_3$	2.0–2.4			
Aromatic methyl	$Ar-CH_3$	2.4–2.7	Aryl	$Ar-H$	6.5–8.0
Alkynyl	$-C\equiv C-H$	2.5–3.0	Aldehyde	$-\overset{O}{\overset{\|\|}{C}}-H$	9.7–10.0
Alkyl halide	$-\overset{H}{\underset{\|}{C}}-Hal$	2.5–4.0	Carboxylic acid	$-\overset{O}{\overset{\|\|}{C}}-O-H$	11.0–12.0

Problem 13.16

Each of the following compounds has a single ¹H NMR peak. Approximately where would you expect each compound to absorb?

(a) [cyclohexane structure]

(b) $H_3C-\overset{O}{\overset{\|\|}{C}}-CH_3$

(c) [benzene structure]

(d) CH_2Cl_2

(e) [glyoxal structure: O=C(H)-C(H)=O]

(f) $\overset{H_3C}{\underset{H_3C}{>}}N-CH_3$
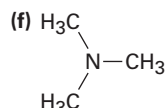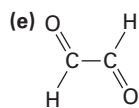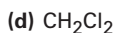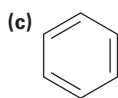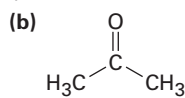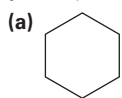
Problem 13.17

Identify the different kinds of nonequivalent protons in the following molecule, and tell where you would expect each to absorb:

[substituted benzene structure with CH₃O and C=C-CH₂CH₃ substituents]
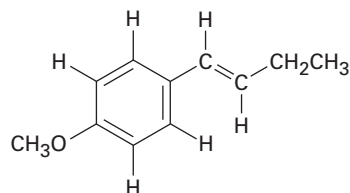
13.10 Integration of ^{1}H NMR Absorptions: Proton Counting

Look at the ^{1}H NMR spectrum of methyl 2,2-dimethylpropanoate in **Figure 13.12**. There are two peaks, corresponding to the two kinds of protons, but the peaks aren't the same size. The peak at 1.2 δ, due to the $(CH_3)_3C-$ protons, is larger than the peak at 3.7 δ, due to the $-OCH_3$ protons.

| Chem. shift	Rel. area
1.20	3.00
3.65	1.00
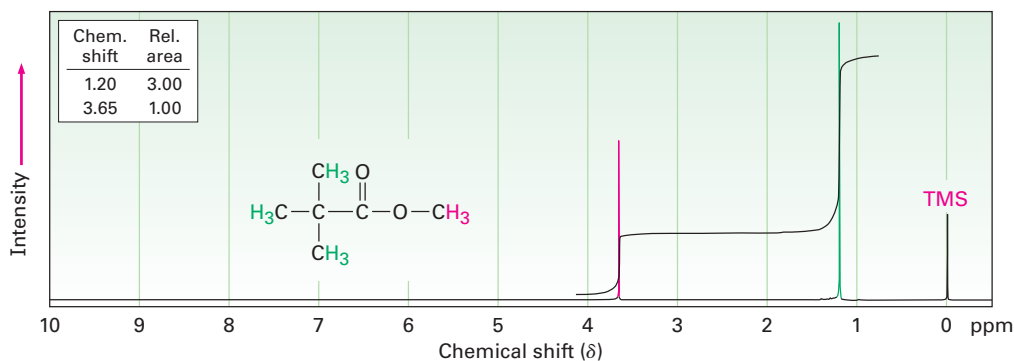
Figure 13.12 The ^{1}H NMR spectrum of methyl 2,2-dimethylpropanoate. Integrating the peaks in a stair-step manner shows that they have a 1:3 ratio, corresponding to the ratio of the numbers of protons (3:9) responsible for each peak. Modern instruments give a direct digital readout of relative peak areas.

The area under each peak is proportional to the number of protons causing that peak. By electronically measuring, or **integrating**, the area under each peak, it's possible to measure the relative numbers of the different kinds of protons in a molecule.

Modern NMR instruments provide a digital readout of relative peak areas, but an older, more visual method displays the integrated peak areas as a stair-step line, with the height of each step proportional to the area under the peak, and therefore proportional to the relative number of protons causing the peak. For example, the two steps for the peaks in methyl 2,2-dimethylpropanoate are found to have a 1:3 (or 3:9) height ratio when integrated—exactly what we expect since the three $-OCH_3$ protons are equivalent and the nine $(CH_3)_3C-$ protons are equivalent.


Problem 13.18

How many peaks would you expect in the ^{1}H NMR spectrum of 1,4-dimethylbenzene (*para*-xylene, or *p*-xylene)? What ratio of peak areas would you expect on integration of the spectrum? Refer to Table 13.3 for approximate chemical shifts, and sketch what the spectrum would look like. (Remember from **Section 2.4** that aromatic rings have two resonance forms.)

p-Xylene
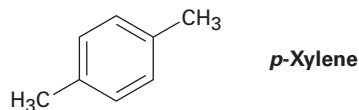
13.11 Spin–Spin Splitting in ^{1}H NMR Spectra

In the ^{1}H NMR spectra we've seen thus far, each different kind of proton in a molecule has given rise to a single peak. It often happens, though, that the absorption of a proton splits into multiple peaks, called a **multiplet**. For example, in the ^{1}H NMR spectrum of bromoethane shown in **Figure 13.13**,

the $-CH_2Br$ protons appear as four peaks (a *quartet*) centered at 3.42 δ and the $-CH_3$ protons appear as three peaks (a *triplet*) centered at 1.68 δ.

Chem. shift	Rel. area
1.68	1.50
3.42	1.00
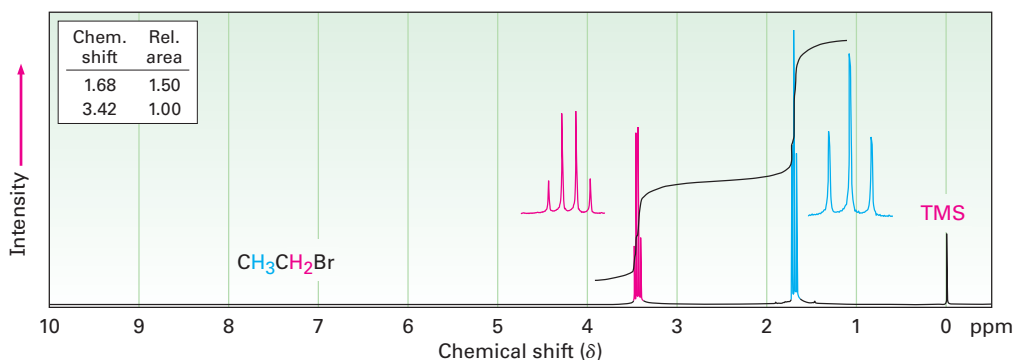
Figure 13.13 The ^{1}H NMR spectrum of bromoethane, CH_3CH_2Br. The $-CH_2Br$ protons appear as a quartet at 3.42 δ, and the $-CH_3$ protons appear as a triplet at 1.68 δ.

Called **spin–spin splitting**, multiple absorptions of a nucleus are caused by the interaction, or **coupling**, of the spins of nearby nuclei. In other words, the tiny magnetic field produced by one nucleus affects the magnetic field felt by a neighboring nucleus. Look at the $-CH_3$ protons in bromoethane, for example. The three equivalent $-CH_3$ protons are neighbored by two other magnetic nuclei—the two protons on the adjacent $-CH_2Br$ group. Each of the neighboring $-CH_2Br$ protons has its own nuclear spin, which can align either with or against the applied field, producing a tiny effect that is felt by the $-CH_3$ protons.

There are three ways in which the spins of the two $-CH_2Br$ protons can align, as shown in **Figure 13.14**. If both proton spins align with the applied field, the total effective field felt by the neighboring $-CH_3$ protons is slightly larger than it would otherwise be. Consequently, the applied field necessary to cause resonance is slightly reduced. Alternatively, if one of the $-CH_2Br$ proton spins aligns with the field and one aligns against the field, there is no effect on the neighboring $-CH_3$ protons. (This arrangement can occur in two ways, depending on which of the two proton spins aligns which way.) Finally, if both $-CH_2Br$ proton spins align against the applied field, the effective field felt by the $-CH_3$ protons is slightly smaller than it would otherwise be and the applied field needed for resonance is slightly increased.
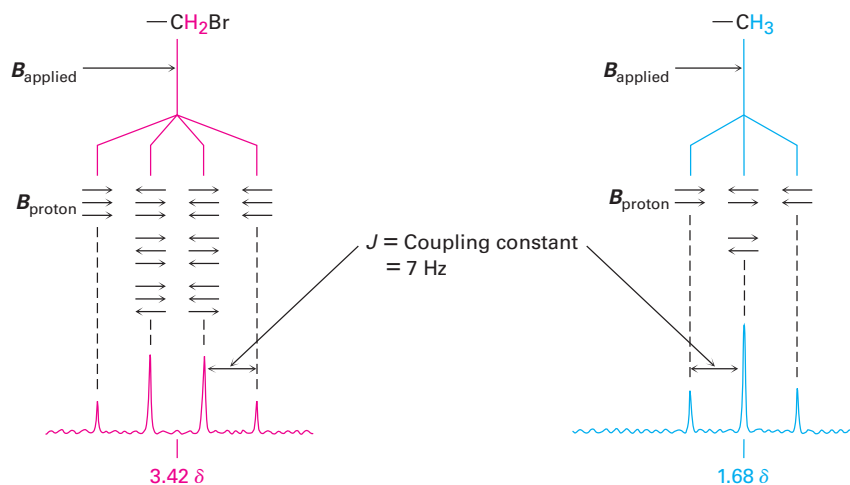

Figure 13.14 The origin of spin–spin splitting in bromoethane. The nuclear spins of neighboring protons, indicated by horizontal arrows, align either with or against the applied field, causing the splitting of absorptions into multiplets.

Any given molecule has only one of the three possible alignments of $-CH_2Br$ spins, but in a large collection of molecules, all three spin states are represented in a 1:2:1 statistical ratio. We therefore find that the neighboring $-CH_3$ protons come into resonance at three slightly different values of the applied field, and we see a 1:2:1 triplet in the NMR spectrum. One resonance is a little above where it would be without coupling, one is at the same place it would be without coupling, and the third resonance is a little below where it would be without coupling.

In the same way that the $-CH_3$ absorption of bromoethane is split into a triplet, the $-CH_2Br$ absorption is split into a quartet. The three spins of the neighboring $-CH_3$ protons can align in four possible combinations: all three with the applied field, two with and one against (three ways), one with and two against (three ways), or all three against. Thus, four peaks are produced for the $-CH_2Br$ protons in a 1:3:3:1 ratio.

As a general rule, called the **n + 1** rule, protons that have *n* equivalent neighboring protons show $n + 1$ peaks in their NMR spectrum. For example, the spectrum of 2-bromopropane in **Figure 13.15** shows a doublet at 1.71 δ and a seven-line multiplet, or septet, at 4.28 δ. The septet is caused by splitting of the $-CHBr-$ proton signal by six equivalent neighboring protons on the two methyl groups ($n = 6$ leads to $6 + 1 = 7$ peaks). The doublet is due to signal splitting of the six equivalent methyl protons by the single $-CHBr-$ proton ($n = 1$ leads to 2 peaks). Integration confirms the expected 6:1 ratio.

Chem. shift	Rel. area
1.71	6.00
4.28	1.00

Br
|
CH_3CHCH_3
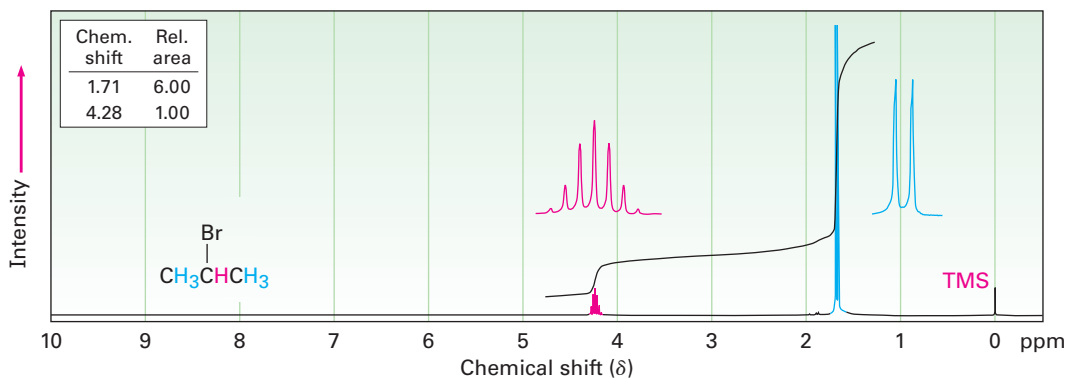
Figure 13.15 The ^1H NMR spectrum of 2-bromopropane. The $-CH_3$ proton signal at 1.71 δ is split into a doublet, and the $-CHBr-$ proton signal at 4.28 δ is split into a septet. Note that the distance between peaks—the *coupling constant*—is the same in both multiplets. Note also that the outer two peaks of the septet are so small as to be nearly lost.

The distance between peaks in a multiplet is called the **coupling constant** and is denoted *J.* Coupling constants are measured in hertz and generally fall in the range 0 to 18 Hz. The exact value of the coupling constant between two neighboring protons depends on the geometry of the molecule, but a typical value for an open-chain alkane is $J = 6$ to 8 Hz. The same coupling constant is shared by both groups of hydrogens whose spins are coupled and is independent of spectrometer field strength. In bromoethane, for instance, the $-CH_2Br$ protons are coupled to the $-CH_3$ protons and appear as a quartet with $J = 7$ Hz. The $-CH_3$ protons appear as a triplet with the same $J = 7$ Hz coupling constant.

Because coupling is a reciprocal interaction between two adjacent groups of protons, it's sometimes possible to tell which multiplets in a complex NMR spectrum are related to each other. If two multiplets have the same coupling

constant, they are probably related, and the protons causing those multiplets are therefore adjacent in the molecule.

The most commonly observed coupling patterns and the relative intensities of lines in their multiplets are listed in Table 13.4. Note that it's not possible for a given proton to have five equivalent neighboring protons. (Why not?) A six-line multiplet, or sextet, is therefore found only when a proton has five non-equivalent neighboring protons that coincidentally happen to be coupled with an identical coupling constant J.

Table 13.4 Some Common Spin Multiplicities

Number of equivalent adjacent protons	Multiplet	Ratio of intensities
0	Singlet	1
1	Doublet	1:1
2	Triplet	1:2:1
3	Quartet	1:3:3:1
4	Quintet	1:4:6:4:1
6	Septet	1:6:15:20:15:6:1

Spin–spin splitting in ^{1}H NMR can be summarized in three rules.

RULE 1

Chemically equivalent protons don't show spin–spin splitting. The equivalent protons may be on the same carbon or on different carbons, but their signals don't split.
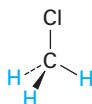
Three C–H protons are chemically equivalent; no splitting occurs.
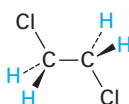
Four C–H protons are chemically equivalent; no splitting occurs.

RULE 2

The signal of a proton with n equivalent neighboring protons is split into a multiplet of $n + 1$ peaks with coupling constant J. Protons that are farther than two carbon atoms apart don't usually couple, although they sometimes show small coupling when they are separated by a π bond.
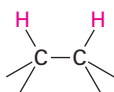
Splitting observed
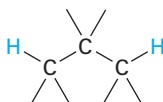
Splitting not usually observed

RULE 3

Two groups of protons coupled to each other have the same coupling constant, J.

The spectrum of *para*-methoxypropiophenone in **Figure 13.16** further illustrates the three rules. The downfield absorptions at 6.91 and 7.93 δ are due to the four aromatic ring protons. There are two kinds of aromatic protons, each of which gives a signal that is split into a doublet by its neighbor. The $-OCH_3$ signal is unsplit and appears as a sharp singlet at 3.84 δ. The $-CH_2-$ protons next to the carbonyl group appear at 2.93 δ in the region expected for protons on carbon next to an unsaturated center, and their signal is split into a quartet by coupling with the protons of the neighboring methyl group. The methyl protons appear as a triplet at 1.20 δ in the usual upfield region.

Chem. shift	Rel. area
1.20	1.50
2.93	1.00
3.84	1.50
6.91	1.00
7.93	1.00
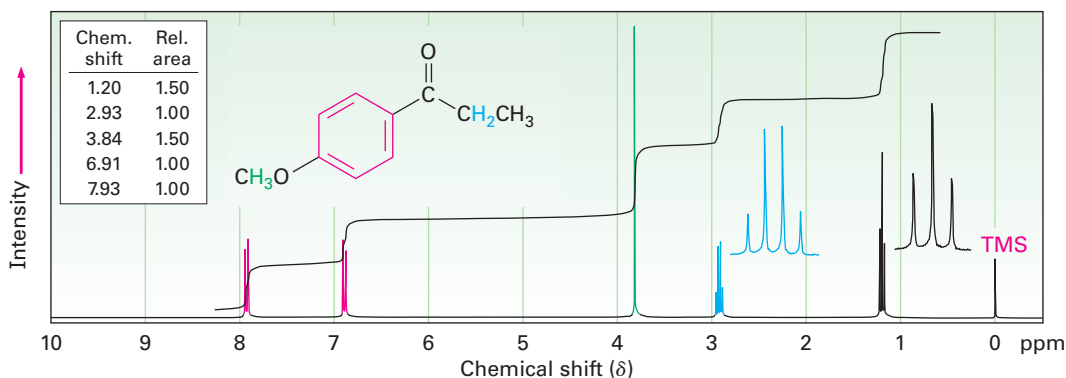
Figure 13.16 The ^{1}H NMR spectrum of *para*-methoxypropiophenone.

One further question needs to be answered before leaving the topic of spin–spin splitting. Why is spin–spin splitting seen only for ^{1}H NMR? Why is there no splitting of *carbon* signals into multiplets in ^{13}C NMR? After all, you might expect that the spin of a given ^{13}C nucleus would couple with the spin of an adjacent magnetic nucleus, either ^{13}C or ^{1}H.

No coupling of a ^{13}C nucleus with nearby carbons is seen because their low natural abundance makes it unlikely that two ^{13}C nuclei will be adjacent. No coupling of a ^{13}C nucleus with nearby hydrogens is seen because ^{13}C spectra, as previously noted **(Section 13.6)**, are normally recorded using broadband decoupling. At the same time that the sample is irradiated with a pulse of rf energy to cover the carbon resonance frequencies, it is also irradiated by a second band of rf energy covering all the hydrogen resonance frequencies. This second irradiation makes the hydrogens spin-flip so rapidly that their local magnetic fields average to zero and no coupling with carbon spins occurs.

Worked Example 13.4

### Assigning a Chemical Structure from a ^{1}H NMR Spectrum

Propose a structure for a compound, $C_5H_{12}O$, that fits the following ^{1}H NMR data: 0.92 δ (3 H, triplet, $J = 7$ Hz), 1.20 δ (6 H, singlet), 1.50 δ (2 H, quartet, $J = 7$ Hz), 1.64 δ (1 H, broad singlet).

Strategy

As noted in Worked Example 13.2, it's best to begin solving structural problems by calculating a molecule's degree of unsaturation. In the present instance, a formula of $C_5H_{12}O$ corresponds to a saturated, open-chain molecule, either an alcohol or an ether.
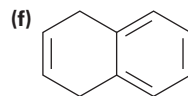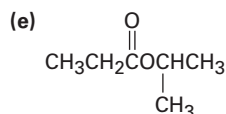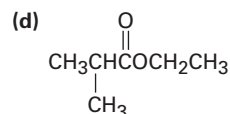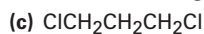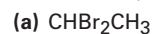
To interpret the NMR information, let's look at each absorption individually. The three-proton absorption at 0.92 δ is due to a methyl group in an alkane-like environment, and the triplet splitting pattern implies that the CH_3 is next to a CH_2. Thus, our molecule contains an ethyl group, CH_3CH_2-. The six-proton singlet at 1.20 δ is due to two equivalent alkane-like methyl groups attached to a carbon with no hydrogens, $(CH_3)_2C$, and the two-proton quartet at 1.50 δ is due to the CH_2 of the ethyl group. All 5 carbons and 11 of the 12 hydrogens in the molecule are now accounted for. The remaining hydrogen, which appears as a broad one-proton singlet at 1.64 δ, is probably due to an OH group, since there is no other way to account for it. Putting the pieces together gives the structure: 2-methyl-2-butanol.
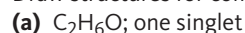
Solution

2-Methyl-2-butanol
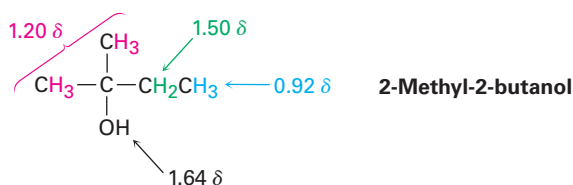
Problem 13.19

Predict the splitting patterns you would expect for each proton in the following molecules:

(a) $CHBr_2CH_3$

(b) $CH_3OCH_2CH_2Br$

(c) $ClCH_2CH_2CH_2Cl$

(d)
$$CH_3CHCOCH_2CH_3$$
with O double bond above, and CH_3 below

(e)
$$CH_3CH_2COCHCH_3$$
with O double bond above, and CH_3 below

(f)

Problem 13.20

Draw structures for compounds that meet the following descriptions:

(a) C_2H_6O; one singlet

(b) C_3H_7Cl; one doublet and one septet

(c) $C_4H_8Cl_2O$; two triplets

(d) $C_4H_8O_2$; one singlet, one triplet, and one quartet
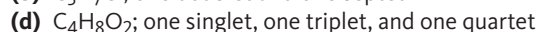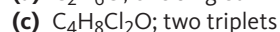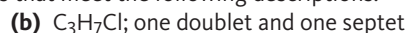
Problem 13.21

The integrated ^{1}H NMR spectrum of a compound of formula $C_4H_{10}O$ is shown in **Figure 13.17**. Propose a structure.

Chem. shift	Rel. area
1.22	1.50
3.49	1.00
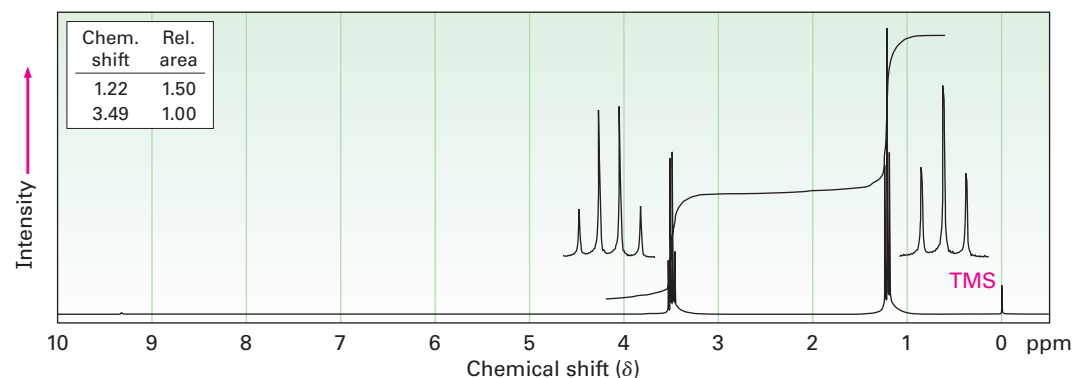
Figure 13.17 An integrated ^{1}H NMR spectrum for Problem 13.21.

13.12 More Complex Spin–Spin Splitting Patterns

In the ^{1}H NMR spectra we've seen so far, the chemical shifts of different protons have been distinct and the spin–spin splitting patterns have been straightforward. It often happens, however, that different kinds of hydrogens in a molecule have accidentally overlapping signals. The spectrum of toluene (methylbenzene) in **Figure 13.18**, for example, shows that the five aromatic ring protons give a complex, overlapping pattern, even though they aren't all equivalent.

Chem. shift	Rel. area
2.35	1.50
7.15	1.50
7.23	1.00
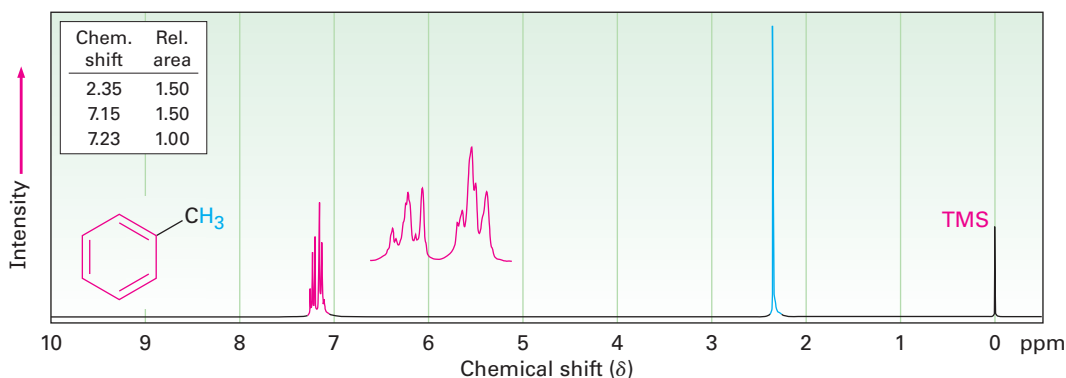
Figure 13.18 The ^{1}H NMR spectrum of toluene, showing the accidental overlap of the five nonequivalent aromatic ring protons.

Yet another complication in ^{1}H NMR spectroscopy arises when a signal is split by two or more *nonequivalent* kinds of protons, as is the case with *trans*-cinnamaldehyde, isolated from oil of cinnamon **(Figure 13.19)**. Although the *n* + 1 rule predicts splitting caused by equivalent protons, splittings caused by nonequivalent protons are more complex.

Chem. shift	Rel. area
6.73	1.00
7.42	3.00
7.49	1.00
7.57	2.00
9.69	1.00
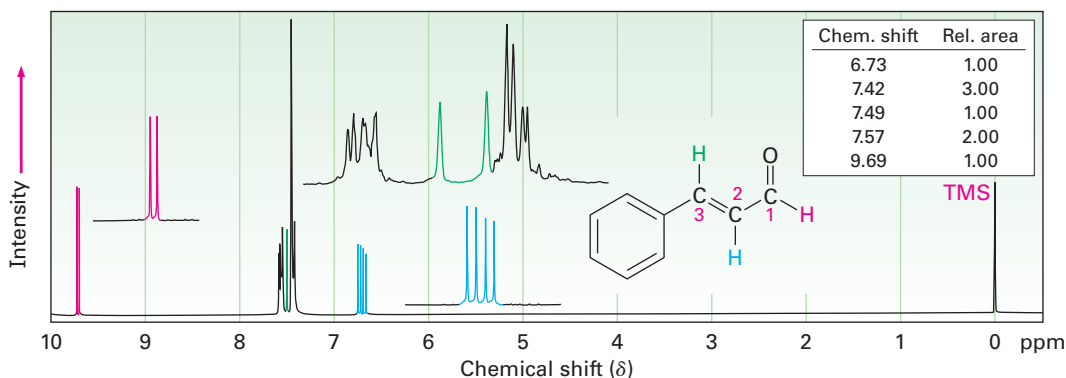
Figure 13.19 The ^{1}H NMR spectrum of *trans*-cinnamaldehyde. The signal of the proton at C2 (blue) is split into four peaks—a doublet of doublets—by the two nonequivalent neighboring protons.

To understand the ^{1}H NMR spectrum of *trans*-cinnamaldehyde, we have to isolate the different parts and look at the signal of each proton individually.

- The five aromatic proton signals (black in Figure 13.19) overlap into a complex pattern with a large peak at 7.42 δ and a broad absorption at 7.57 δ.

- The aldehyde proton signal at C1 (red) appears in the normal downfield position at 9.69 δ and is split into a doublet with J = 6 Hz by the adjacent proton at C2.

- The vinylic proton at C3 (green) is next to the aromatic ring and is therefore shifted downfield from the normal vinylic region. This C3 proton signal appears as a doublet centered at 7.49 δ. Because it has one neighbor proton at C2, its signal is split into a doublet, with J = 12 Hz.

- The C2 vinylic proton signal (blue) appears at 6.73 δ and shows an interesting, four-line absorption pattern. It is coupled to the two non-equivalent protons at C1 and C3 with two different coupling constants: $J_{1\text{-}2}$ = 6 Hz and $J_{2\text{-}3}$ = 12 Hz.

A good way to understand the effect of multiple coupling such as occurs for the C2 proton of *trans*-cinnamaldehyde is to draw a *tree diagram*, like that in **Figure 13.20**. The diagram shows the individual effect of each coupling constant on the overall pattern. Coupling with the C3 proton splits the signal of the C2 proton in *trans*-cinnamaldehyde into a doublet with J =12 Hz. Further coupling with the aldehyde proton then splits each peak of the doublet into new doublets with J = 6 Hz, and we therefore observe a four-line spectrum for the C2 proton.
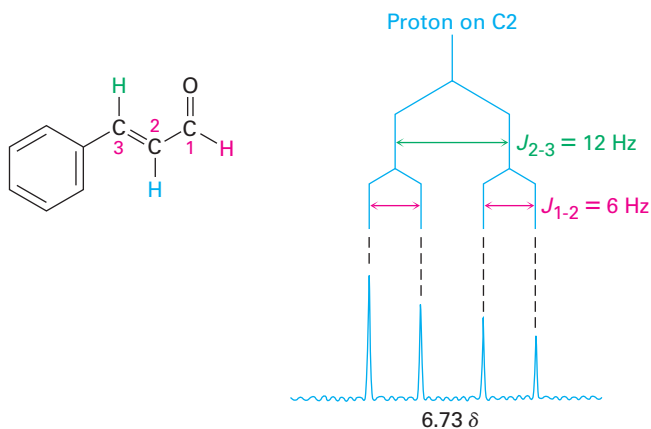
Figure 13.20 A tree diagram for the C2 proton of *trans*-cinnamaldehyde shows how it is coupled to the C1 and C3 protons with different coupling constants.

One further point evident in the cinnamaldehyde spectrum is that the four peaks of the C2 proton signal are not all the same size. The two left-hand peaks are somewhat larger than the two right-hand peaks. Such a size difference occurs whenever coupled nuclei have similar chemical shifts—in this case, 7.49 δ for the C3 proton and 6.73 δ for the C2 proton. The peaks nearer the signal of the coupled partner are always larger, and the peaks farther from the signal of the coupled partner are always smaller. Thus, the

left-hand peaks of the C2 proton multiplet at 6.73 δ are closer to the C3 proton absorption at 7.49 δ and are larger than the right-hand peaks. At the same time, the right-hand peak of the C3 proton doublet at 7.49 δ is larger than the left-hand peak because it is closer to the C2 proton multiplet at 6.73 δ. This skewing effect on multiplets can often be useful because it tells where to look in the spectrum to find the coupled partner: look in the direction of the larger peaks.

Problem 13.22

3-Bromo-1-phenyl-1-propene shows a complex NMR spectrum in which the vinylic proton at C2 is coupled with both the C1 vinylic proton ($J = 16$ Hz) and the C3 methylene protons ($J = 8$ Hz). Draw a tree diagram for the C2 proton signal, and account for the fact that a five-line multiplet is observed.
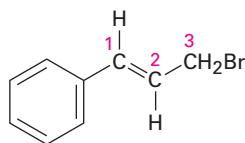
3-Bromo-1-phenyl-1-propene

13.13 Uses of ^{1}H NMR Spectroscopy

NMR is used to help identify the product of nearly every reaction run in the laboratory. For example, we said in **Section 8.5** that hydroboration–oxidation of alkenes occurs with non-Markovnikov regiochemistry to yield the less highly substituted alcohol. With the help of NMR, we can now prove this statement.

Does hydroboration–oxidation of methylenecyclohexane yield cyclohexylmethanol or 1-methylcyclohexanol?

Methylenecyclohexane   **Cyclohexylmethanol**   **1-Methylcyclohexanol**
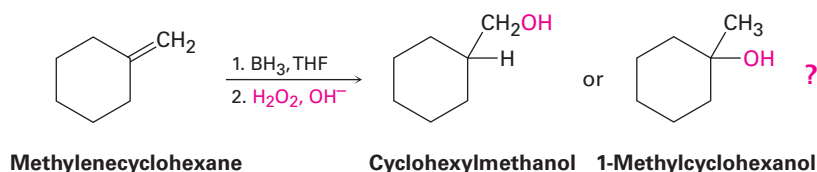
The ^{1}H NMR spectrum of the reaction product is shown in **Figure 13.21a**. The spectrum shows a 2-proton peak at 3.40 δ, indicating that the product has a $-CH_2-$ group bonded to an electronegative oxygen atom ($-CH_2OH$). Furthermore, the spectrum shows no large three-proton singlet absorption near 1 δ, where we would expect the signal of a quaternary $-CH_3$ group to appear. (Figure 13.21b gives the spectrum of 1-methylcyclohexanol, the alternative product.) Thus, it's clear that cyclohexylmethanol is the reaction product.

(a)

Chem. shift	Rel. area
0.93	2.00
1.21	3.00
1.44	1.00
1.72	5.00
2.82	1.00
3.40	2.00

CH₂OH

TMS

(b)

Chem. shift	Rel. area
1.19	1.00
1.46	3.67

CH₃
OH

TMS
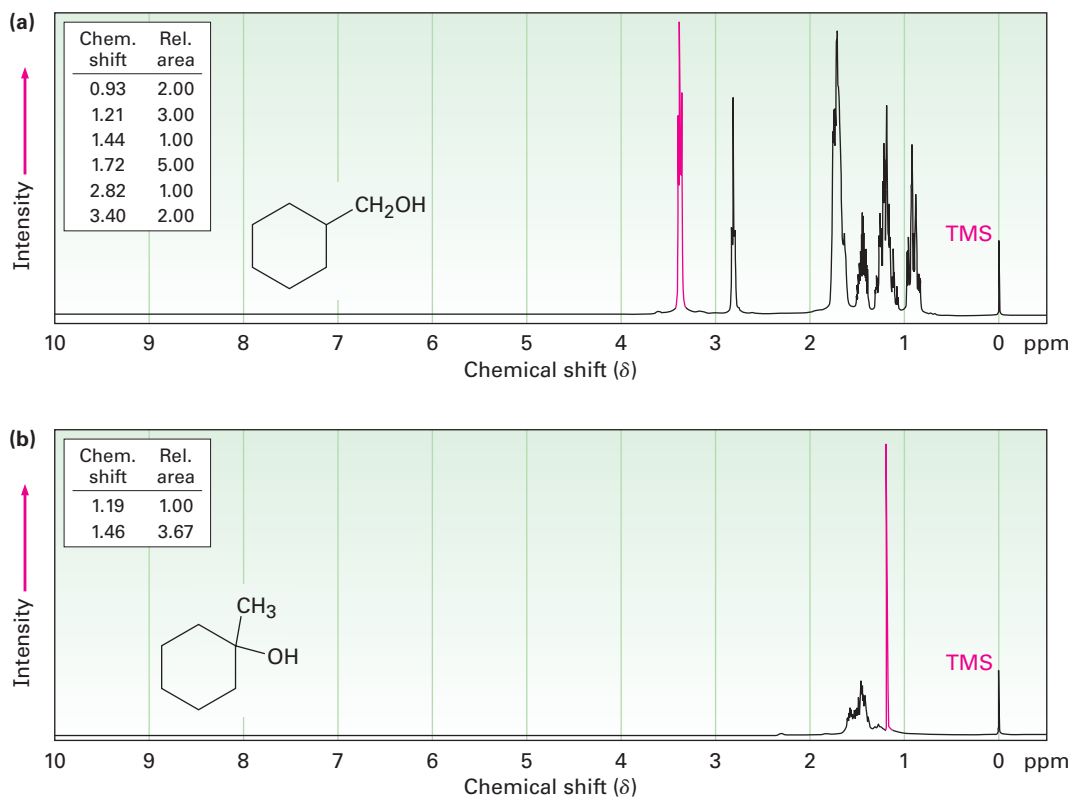
Figure 13.21 **(a)** The ¹H NMR spectrum of cyclohexylmethanol, the product from hydroboration–oxidation of methylenecyclohexane, and **(b)** the ¹H NMR spectrum of 1-methylcyclohexanol, the possible alternative reaction product.

Problem 13.23

How could you use ¹H NMR to determine the regiochemistry of electrophilic addition to alkenes? For example, does addition of HCl to 1-methylcyclohexene yield 1-chloro-1-methyl-cyclohexane or 1-chloro-2-methylcyclohexane?

If you're a runner, you really don't want this to happen to you. The MRI of this left knee shows the presence of a ganglion cyst.

Magnetic Resonance Imaging (MRI) | A DEEPER LOOK

As practiced by organic chemists, NMR spectroscopy is a powerful method of structure determination. A small amount of sample, typically a few milligrams or less, is dissolved in a small amount of solvent, the solution is placed in a thin glass tube, and the tube is placed into the narrow (1–2 cm) gap between the poles of a strong magnet. Imagine, though, that a much larger NMR instrument were available. Instead of a few milligrams, the sample size could be tens of kilograms; instead of a narrow gap between magnet poles, the gap could be large enough for a whole person to climb into so that an NMR spectrum of body parts could be obtained. That large instrument is exactly what's used for *magnetic resonance imaging (MRI)*, a diagnostic technique of enormous value to the medical community.

Like NMR spectroscopy, MRI takes advantage of the magnetic properties of certain nuclei, typically hydrogen, and of the signals emitted when those nuclei are stimulated by radiofrequency energy. Unlike what happens in NMR spectroscopy, though, MRI instruments use data manipulation techniques to look at the three-dimensional *location* of magnetic nuclei in the body rather than at the chemical nature of the nuclei. As noted, most MRI instruments currently look at hydrogen, present in abundance wherever there is water or fat in the body.

The signals detected by MRI vary with the density of hydrogen atoms and with the nature of their surroundings, allowing identification of different types of tissue and even allowing the visualization of motion. For example, the volume of blood leaving the heart in a single stroke can be measured, and heart motion can be observed. Soft tissues that don't show up well on X rays can be seen clearly, allowing diagnosis of brain tumors, strokes, and other conditions. The technique is also valuable in diagnosing damage to knees or other joints and is a noninvasive alternative to surgical explorations.

Several types of atoms in addition to hydrogen can be detected by MRI, and the applications of images based on ^{31}P atoms are being explored. The technique holds great promise for studies of metabolism.

Summary

Key words

chemical shift, 462
coupling, 477
coupling constant (*J*), 478
delta (*δ*) scale, 462
diastereotopic, 473
downfield, 461
enantiotopic, 472
FT–NMR, 463
homotopic, 472
integration, 476
multiplet, 476
n + 1 rule, 478

Nuclear magnetic resonance spectroscopy, or **NMR**, is the most valuable of the numerous spectroscopic techniques used for structure determination. Although we focused in this chapter on NMR applications to small molecules, more advanced NMR techniques are also used in biological chemistry to study protein structure and folding.

When magnetic nuclei, such as ^1H and ^{13}C, are placed in a strong magnetic field, their spins orient either with or against the field. On irradiation with radiofrequency (rf) waves, energy is absorbed and the nuclei "spin-flip" from the lower energy state to the higher energy state. This absorption of rf energy is detected, amplified, and displayed as an NMR spectrum.

Each electronically distinct ^1H or ^{13}C nucleus in a molecule comes into resonance at a slightly different value of the applied field, thereby producing a unique absorption signal. The exact position of each peak is called the **chemical shift**. Chemical shifts are caused by electrons setting up tiny local magnetic fields that **shield** a nearby nucleus from the applied field.

The NMR chart is calibrated in **delta units (δ)**, where $1\ \delta = 1$ ppm of spectrometer frequency. Tetramethylsilane (TMS) is used as a reference point because it shows both ^{1}H and ^{13}C absorptions at unusually high values of the applied magnetic field. The TMS absorption occurs at the right-hand (**upfield**) side of the chart and is arbitrarily assigned a value of $0\ \delta$.

^{13}C spectra are run on Fourier-transform NMR (**FT–NMR**) spectrometers using broadband decoupling of proton spins so that each chemically distinct carbon shows a single unsplit resonance line. As with ^{1}H NMR, the chemical shift of each ^{13}C signal provides information about a carbon's chemical environment in the sample. In addition, the number of protons attached to each carbon can be determined using the DEPT–NMR technique.

In ^{1}H NMR spectra, the area under each absorption peak can be electronically **integrated** to determine the relative number of hydrogens responsible for each peak. In addition, neighboring nuclear spins can **couple**, causing the **spin–spin splitting** of NMR peaks into **multiplets**. The NMR signal of a hydrogen neighbored by n equivalent adjacent hydrogens splits into $n + 1$ peaks (the ***n* + 1 rule**) with **coupling constant *J***.

Key words—cont'd

nuclear magnetic resonance (NMR) spectroscopy, 456
shielding, 458
spin–spin splitting, 477
upfield, 461

| Exercises

Visualizing Chemistry

(Problems 13.1–13.23 appear within the chapter.)

OWL Interactive versions of these problems are assignable in OWL for Organic Chemistry.

13.24 Into how many peaks would you expect the ^{1}H NMR signals of the indicated protons to be split? (Green = Cl.)

(a)

(b)
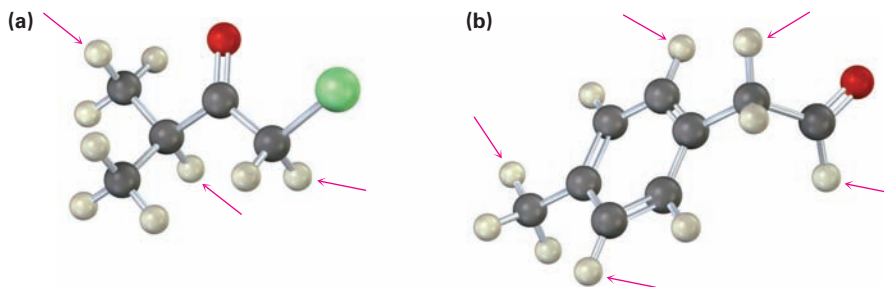
13.25 How many absorptions would you expect the following compound to have in its ^{1}H and ^{13}C NMR spectra?
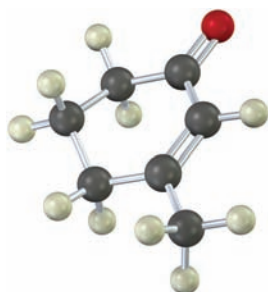
13.26 Sketch what you might expect the ^{1}H and ^{13}C NMR spectra of the following compound to look like (green = Cl):
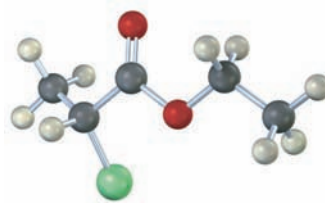
13.27 How many electronically nonequivalent kinds of protons and how many kinds of carbons are present in the following compound? Don't forget that cyclohexane rings can ring-flip.
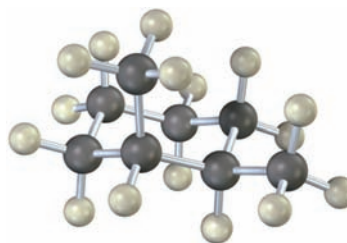
13.28 Identify the indicated protons in the following molecules as unrelated, homotopic, enantiotopic, or diastereotopic.

(a)   **(b)**

Cysteine
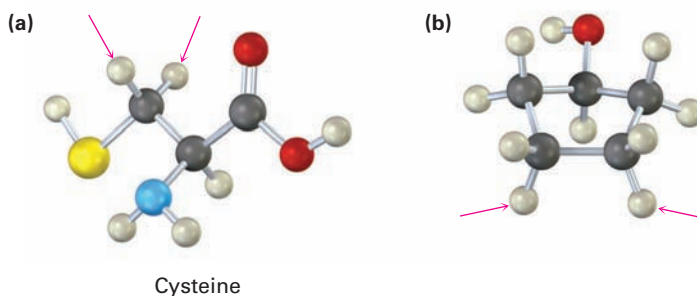
Additional Problems

Chemical Shifts and NMR Spectroscopy

13.29 The following ^{1}H NMR absorptions were obtained on a spectrometer operating at 200 MHz and are given in hertz downfield from the TMS standard. Convert the absorptions to δ units.
(a) 436 Hz   (b) 956 Hz   (c) 1504 Hz

13.30 The following ^{1}H NMR absorptions were obtained on a spectrometer operating at 300 MHz. Convert the chemical shifts from δ units to hertz downfield from TMS.
(a) 2.1 δ   (b) 3.45 δ   (c) 6.30 δ   (d) 7.70 δ

13.31 When measured on a spectrometer operating at 200 MHz, chloroform ($CHCl_3$) shows a single sharp absorption at 7.3 δ.

    (a) How many parts per million downfield from TMS does chloroform absorb?

    (b) How many hertz downfield from TMS would chloroform absorb if the measurement were carried out on a spectrometer operating at 360 MHz?

    (c) What would be the position of the chloroform absorption in δ units when measured on a 360 MHz spectrometer?

13.32 Why do you suppose accidental overlap of signals is much more common in ^1H NMR than in ^{13}C NMR?

13.33 Is a nucleus that absorbs at 6.50 δ more shielded or less shielded than a nucleus that absorbs at 3.20 δ? Does the nucleus that absorbs at 6.50 δ require a stronger applied field or a weaker applied field to come into resonance than the nucleus that absorbs at 3.20 δ?

^1H NMR Spectroscopy

13.34 How many types of nonequivalent protons are present in each of the following molecules?

    (a) H_3C CH_3

    (b) $CH_3CH_2CH_2OCH_3$

    (c)

    Naphthalene

    (d)
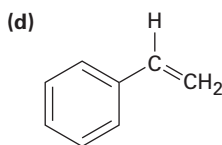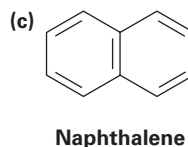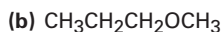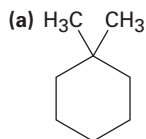
    Styrene

    (e)
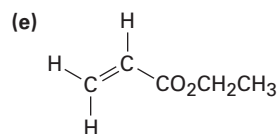
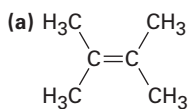   **Ethyl acrylate**

13.35 The following compounds all show a single line in their ^1H NMR spectra. List them in expected order of increasing chemical shift:

$$CH_4, CH_2Cl_2, \text{cyclohexane}, CH_3COCH_3, H_2C=CH_2, \text{benzene}$$

13.36 How many signals would you expect each of the following molecules to have in its ^1H and ^{13}C spectra?

    (a) H_3C CH_3 C=C H_3C CH_3

    (b) CH_3 —CH_3

    (c) CH_3CCH_3 (with O)

    (d) H_3C O CH_3C—C—OCH_3 H_3C

    (e) CH_3 H_3C

    (f) CH_3 CH_3
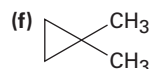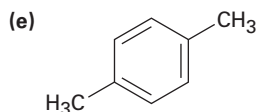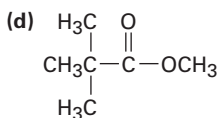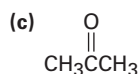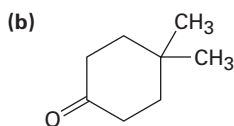
13.37 Propose structures for compounds with the following formulas that show only one peak in their ^{1}H NMR spectra:
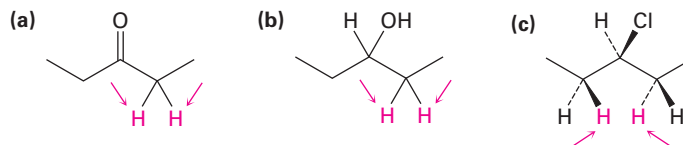**(a)** C_5H_{12} **(b)** C_5H_{10} **(c)** $C_4H_8O_2$

13.38 Predict the splitting pattern for each kind of hydrogen in the following molecules:
(a) $(CH_3)_3CH$ **(b)** $CH_3CH_2CO_2CH_3$ **(c)** *trans*-2-Butene

13.39 Predict the splitting pattern for each kind of hydrogen in isopropyl propanoate, $CH_3CH_2CO_2CH(CH_3)_2$.

13.40 Identify the indicated sets of protons as unrelated, homotopic, enantiotopic, or diastereotopic:

13.41 Identify the indicated sets of protons as unrelated, homotopic, enantiotopic, or diastereotopic:
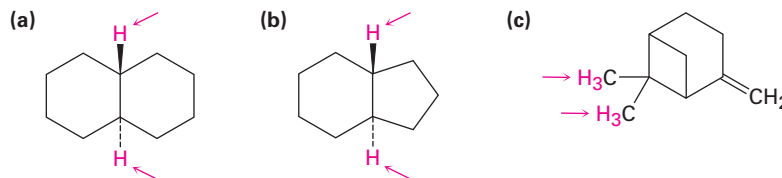
13.42 The acid-catalyzed dehydration of 1-methylcyclohexanol yields a mixture of two alkenes. How could you use ^{1}H NMR to help you decide which was which?
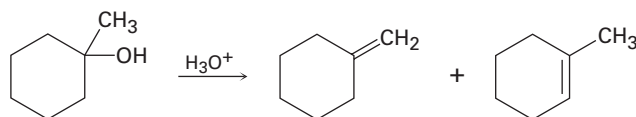
13.43 How could you use ^{1}H NMR to distinguish between the following pairs of isomers?

(a) $CH_3CH{=}CHCH_2CH_3$ and

(b) $CH_3CH_2OCH_2CH_3$ and $CH_3OCH_2CH_2CH_3$

(c)

(d)
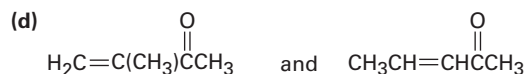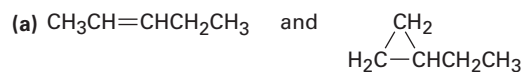
13.44 Propose structures for compounds that fit the following ^{1}H NMR data:

(a) $C_5H_{10}O$
0.95 δ (6 H, doublet, J = 7 Hz)
2.10 δ (3 H, singlet)
2.43 δ (1 H, multiplet)

(b) C_3H_5Br
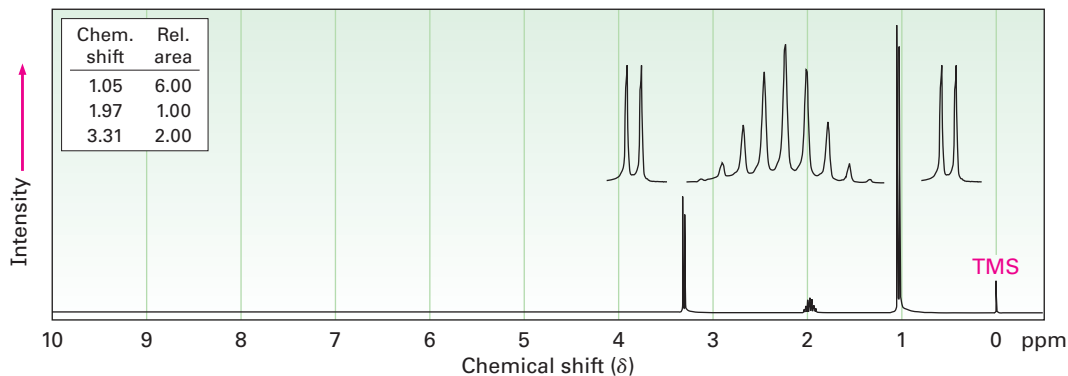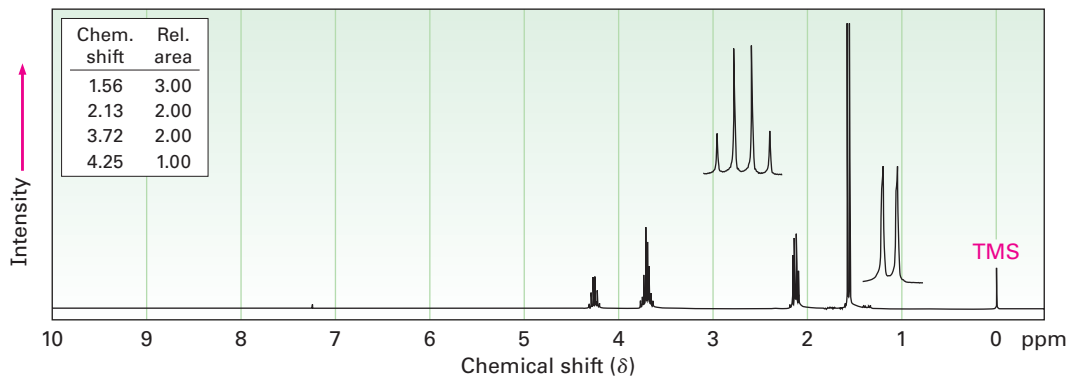2.32 δ (3 H, singlet)
5.35 δ (1 H, broad singlet)
5.54 δ (1 H, broad singlet)

13.45 Propose structures for the two compounds whose ^{1}H NMR spectra are shown.

(a) C_4H_9Br

Chem. shift	Rel. area
1.05	6.00
1.97	1.00
3.31	2.00

(b) $C_4H_8Cl_2$

Chem. shift	Rel. area
1.56	3.00
2.13	2.00
3.72	2.00
4.25	1.00

^{13}C NMR Spectroscopy

13.46 How many ^{13}C NMR absorptions would you expect for *cis*-1,3-dimethyl-cyclohexane? For *trans*-1,3-dimethylcyclohexane? Explain.

13.47 How many absorptions would you expect to observe in the ^{13}C NMR spectra of the following compounds?
(a) 1,1-Dimethylcyclohexane
(b) $CH_3CH_2OCH_3$
(c) *tert*-Butylcyclohexane
(d) 3-Methyl-1-pentyne
(e) *cis*-1,2-Dimethylcyclohexane
(f) Cyclohexanone

13.48 Suppose you ran a DEPT-135 spectrum for each substance in Problem 13.47. Which carbon atoms in each molecule would show positive peaks, and which would show negative peaks?
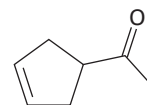
13.49 How could you use ^1H and ^{13}C NMR to help you distinguish among the following isomeric compounds of formula C_4H_8?

$$CH_2-CH_2 \atop CH_2-CH_2 \qquad H_2C=CHCH_2CH_3 \qquad CH_3CH=CHCH_3 \qquad CH_3 \atop CH_3C=CH_2$$
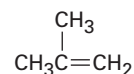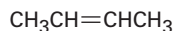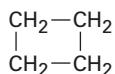
13.50 How could you use ^1H NMR, ^{13}C NMR, and IR spectroscopy to help you distinguish between the following structures?
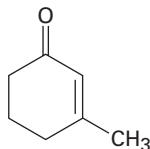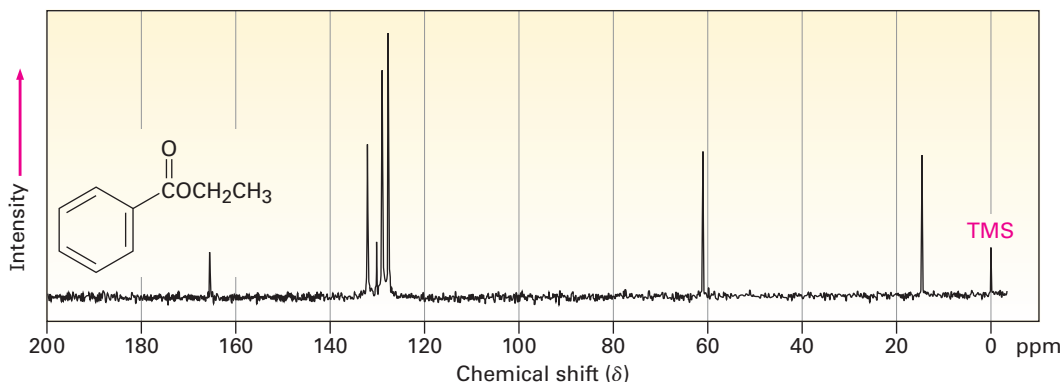
**3-Methyl-2-cyclohexenone**   **3-Cyclopentenyl methyl ketone**

13.51 Assign as many of the resonances as you can to specific carbon atoms in the ^{13}C NMR spectrum of ethyl benzoate.


General Problems

13.52 Assume that you have a compound with formula C_3H_6O.
   (a) How many double bonds and/or rings does your compound contain?
   (b) Propose as many structures as you can that fit the molecular formula.
   (c) If your compound shows an infrared absorption peak at 1715 cm^{-1}, what functional group does it have?
   (d) If your compound shows a single ^1H NMR absorption peak at 2.1 δ, what is its structure?

13.53 The compound whose ^1H NMR spectrum is shown has the molecular formula $C_3H_6Br_2$. Propose a structure.

| Chem. shift	Rel. area
2.33	1.00
3.56	2.00
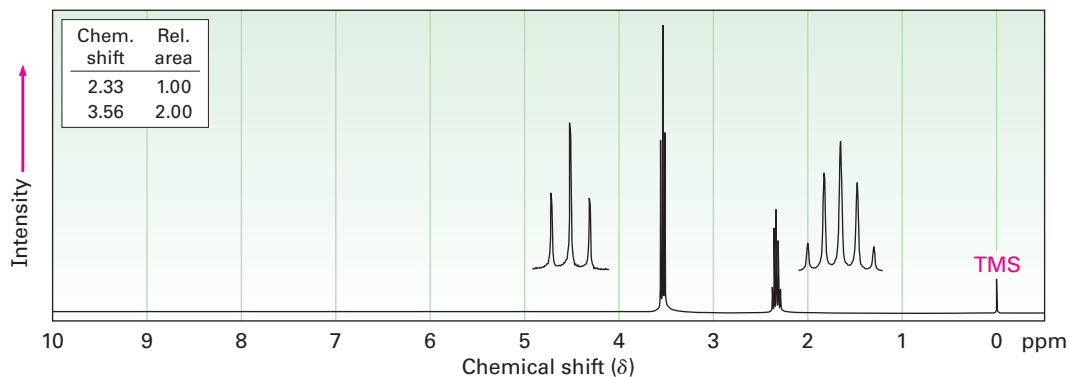
13.54 The compound whose ^1H NMR spectrum is shown has the molecular formula $C_4H_7O_2Cl$ and has an infrared absorption peak at 1740 cm^{-1}. Propose a structure.

Chem. shift	Rel. area
1.32	1.50
4.08	1.00
4.26	1.00
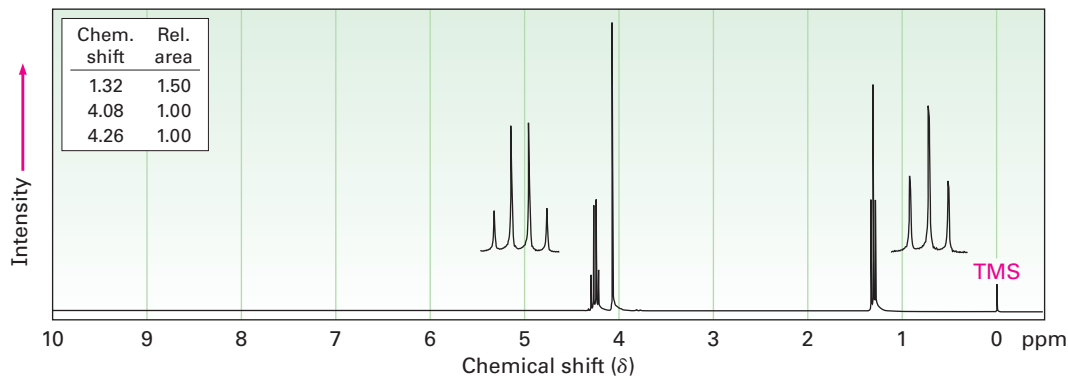
13.55 Propose structures for compounds that fit the following ^1H NMR data:

(a) $C_4H_6Cl_2$
 2.18 δ (3 H, singlet)
 4.16 δ (2 H, doublet, J = 7 Hz)
 5.71 δ (1 H, triplet, J = 7 Hz)

(b) $C_{10}H_{14}$
 1.30 δ (9 H, singlet)
 7.30 δ (5 H, singlet)

(c) C_4H_7BrO
 2.11 δ (3 H, singlet)
 3.52 δ (2 H, triplet, J = 6 Hz)
 4.40 δ (2 H, triplet, J = 6 Hz)

(d) $C_9H_{11}Br$
 2.15 δ (2 H, quintet, J = 7 Hz)
 2.75 δ (2 H, triplet, J = 7 Hz)
 3.38 δ (2 H, triplet, J = 7 Hz)
 7.22 δ (5 H, singlet)

13.56 Long-range coupling between protons more than two carbon atoms apart is sometimes observed when π bonds intervene. An example is found in 1-methoxy-1-buten-3-yne. Not only does the acetylenic proton, H_a, couple with the vinylic proton H_b, it also couples with the vinylic proton H_c, *four* carbon atoms away. The data are:

$$CH_3O$$

H_a (3.08 δ) H_b (4.52 δ) H_c (6.35 δ)

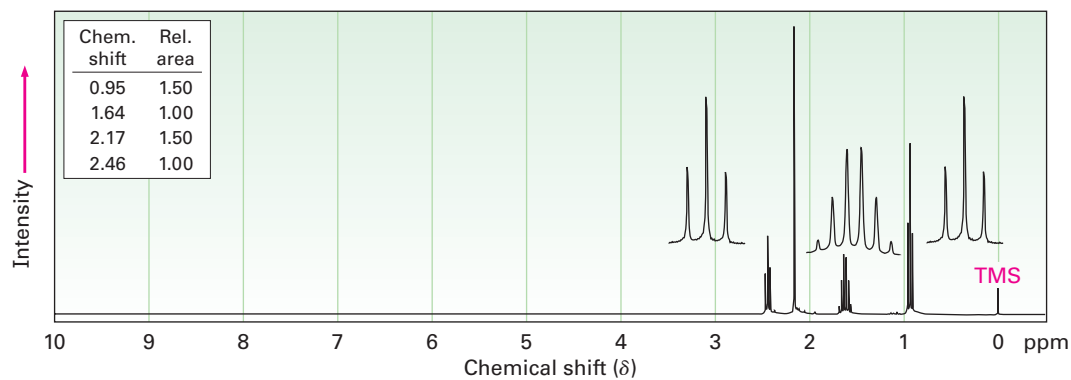J_{a-b} = 3 Hz J_{a-c} = 1 Hz J_{b-c} = 7 Hz
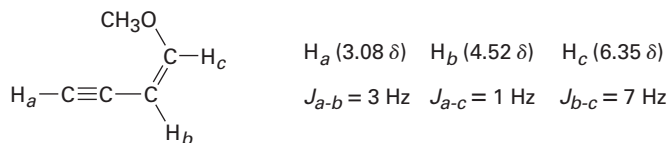
1-Methoxy-1-buten-3-yne

Construct tree diagrams that account for the observed splitting patterns of H_a, H_b, and H_c.

13.57 The ^1H and ^{13}C NMR spectra of compound **A**, C_8H_9Br, are shown. Propose a structure for **A**, and assign peaks in the spectra to your structure.
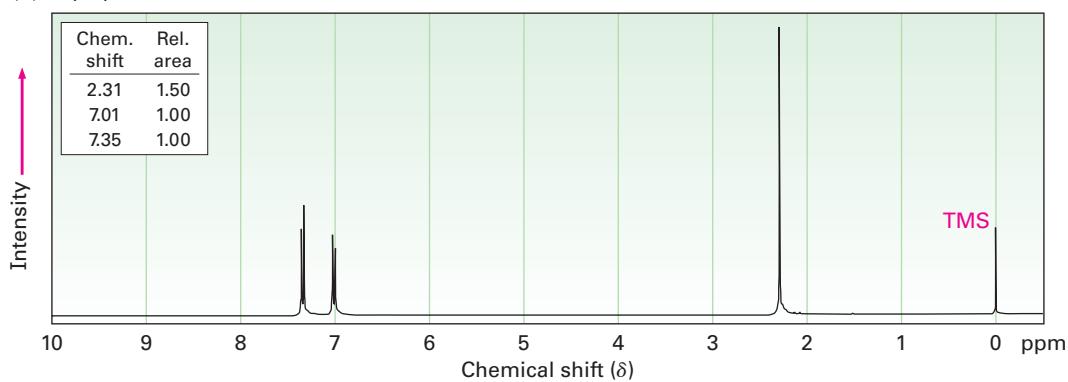
Chem. shift	Rel. area
1.20	3.00
2.58	2.00
7.07	2.00
7.39	2.00
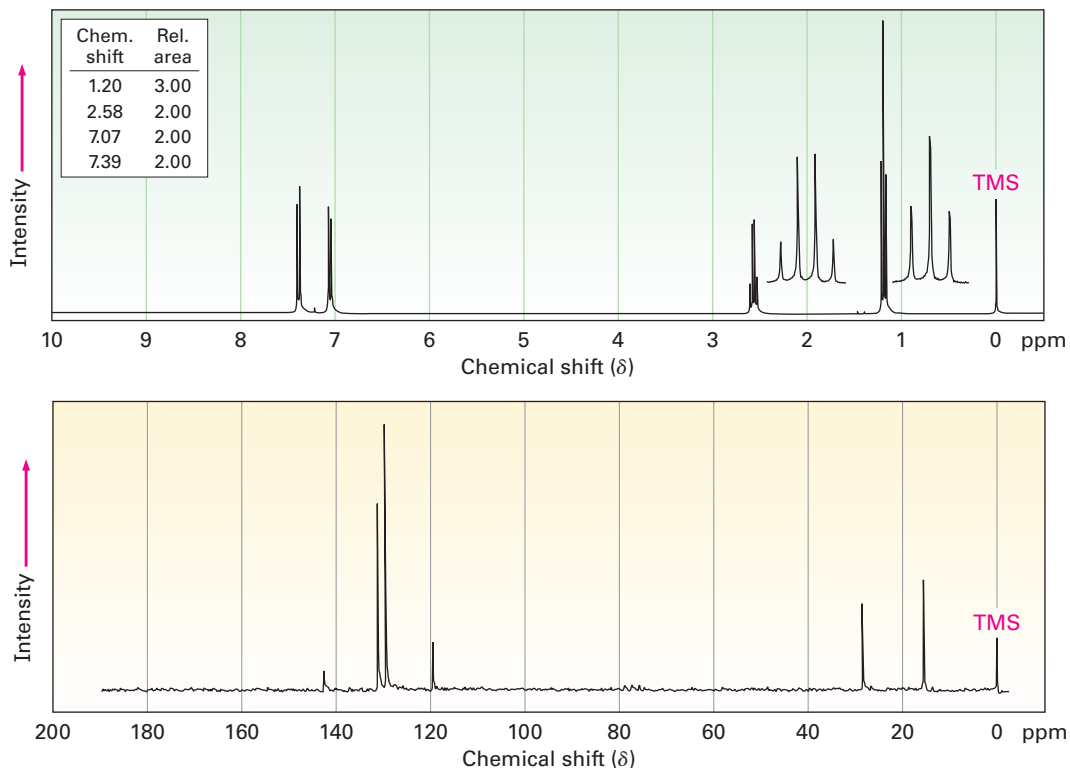
13.58 Propose structures for the three compounds whose ^1H NMR spectra are shown.

(a) $C_5H_{10}O$

Chem. shift	Rel. area
0.95	1.50
1.64	1.00
2.17	1.50
2.46	1.00

(b) C_7H_7Br

Chem. shift	Rel. area
2.31	1.50
7.01	1.00
7.35	1.00

(c) C_8H_9Br

Chem. shift	Rel. area
3.16	1.00
3.56	1.00
7.18	1.00
7.29	1.50
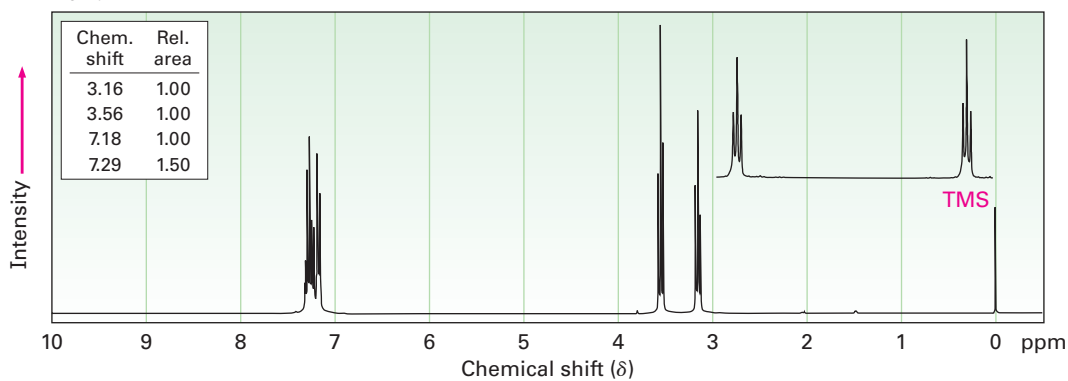
13.59 The mass spectrum and ^{13}C NMR spectrum of a hydrocarbon are shown. Propose a structure for this hydrocarbon, and explain the spectral data.
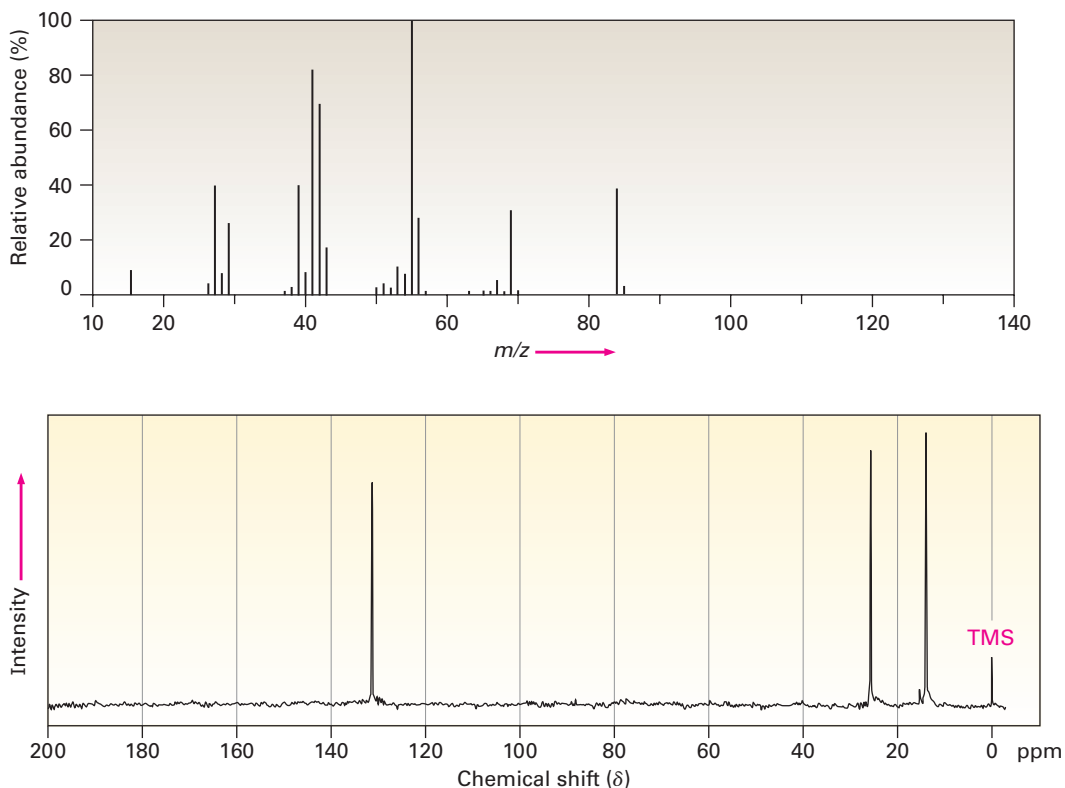
13.60 Compound **A**, a hydrocarbon with $M^+ = 96$ in its mass spectrum, has the ^{13}C spectral data given below. On reaction with BH_3 followed by treatment with basic H_2O_2, **A** is converted into **B**, whose ^{13}C spectral data are also given below. Propose structures for **A** and **B**.

Compound A

Broadband-decoupled ^{13}C NMR: 26.8, 28.7, 35.7, 106.9, 149.7 δ
DEPT-90: no peaks
DEPT-135: no positive peaks; negative peaks at 26.8, 28.7, 35.7, 106.9 δ

Compound B

Broadband-decoupled ^{13}C NMR: 26.1, 26.9, 29.9, 40.5, 68.2 δ
DEPT-90: 40.5 δ
DEPT-135: positive peak at 40.5 δ; negative peaks at 26.1, 26.9, 29.9, 68.2 δ

13.61 Propose a structure for compound **C**, which has $M^+ = 86$ in its mass spectrum, an IR absorption at 3400 cm^{-1}, and the following ^{13}C NMR spectral data:

Compound C
Broadband-decoupled ^{13}C NMR: 30.2, 31.9, 61.8, 114.7, 138.4 δ
DEPT-90: 138.4 δ
DEPT-135: positive peak at 138.4 δ; negative peaks at 30.2, 31.9, 61.8, 114.7 δ

13.62 Compound **D** is isomeric with compound **C** (Problem 13.61) and has the following ^{13}C NMR spectral data. Propose a structure.

Compound D
Broadband-decoupled ^{13}C NMR: 9.7, 29.9, 74.4, 114.4, 141.4 δ
DEPT-90: 74.4, 141.4 δ
DEPT-135: positive peaks at 9.7, 74.4, 141.4 δ; negative peaks at 29.9, 114.4 δ

13.63 Propose a structure for compound **E**, $C_7H_{12}O_2$, which has the following ^{13}C NMR spectral data:

Compound E
Broadband-decoupled ^{13}C NMR: 19.1, 28.0, 70.5, 129.0, 129.8, 165.8 δ
DEPT-90: 28.0, 129.8 δ
DEPT-135: positive peaks at 19.1, 28.0, 129.8 δ; negative peaks at 70.5, 129.0 δ

13.64 Compound **F**, a hydrocarbon with $M^+ = 96$ in its mass spectrum, undergoes reaction with HBr to yield compound **G**. Propose structures for **F** and **G**, whose ^{13}C NMR spectral data are given below.

Compound F
Broadband-decoupled ^{13}C NMR: 27.6, 29.3, 32.2, 132.4 δ
DEPT-90: 132.4 δ
DEPT-135: positive peak at 132.4 δ; negative peaks at 27.6, 29.3, 32.2 δ

Compound G
Broadband-decoupled ^{13}C NMR: 25.1, 27.7, 39.9, 56.0 δ
DEPT-90: 56.0 δ
DEPT-135: positive peak at 56.0 δ; negative peaks at 25.1, 27.7, 39.9 δ

13.65 3-Methyl-2-butanol has five signals in its ^{13}C NMR spectrum at 17.90, 18.15, 20.00, 35.05, and 72.75 δ. Why are the two methyl groups attached to C3 nonequivalent? Making a molecular model should be helpful.

$$H_3C \quad OH$$
$$CH_3CHCHCH_3 \quad \textbf{3-Methyl-2-butanol}$$
$$4 \quad 3 \quad 2 \quad 1$$

13.66 A ^{13}C NMR spectrum of commercially available 2,4-pentanediol, shows *five* peaks at 23.3, 23.9, 46.5, 64.8, and 68.1 δ. Explain.

$$OH \quad OH$$
$$CH_3CHCH_2CHCH_3 \quad \textbf{2,4-Pentanediol}$$
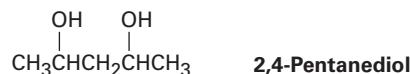
13.67 Carboxylic acids (RCO_2H) react with alcohols (R′OH) in the presence of an acid catalyst. The reaction product of propanoic acid with methanol has the following spectroscopic properties. Propose a structure.
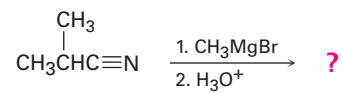
$$CH_3CH_2\overset{\overset{\displaystyle O}{\|}}{C}OH \xrightarrow[\text{H}^+ \text{ catalyst}]{CH_3OH} \quad ?$$

Propanoic acid
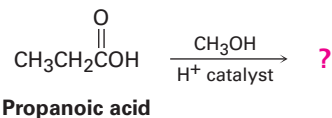
MS: $M^+ = 88$
IR: 1735 cm^{-1}
^{1}H NMR: 1.11 δ (3 H, triplet, J = 7 Hz); 2.32 δ (2 H, quartet, J = 7 Hz); 3.65 δ (3 H, singlet)
^{13}C NMR: 9.3, 27.6, 51.4, 174.6 δ

13.68 Nitriles (RC≡N) react with Grignard reagents (R′MgBr). The reaction product from 2-methylpropanenitrile with methylmagnesium bromide has the following spectroscopic properties. Propose a structure.

$$CH_3CHC≡N \quad \xrightarrow[\text{2. } H_3O^+]{\text{1. } CH_3MgBr} \quad ?$$

with CH₃ substituent on the central carbon:

$$\underset{\overset{|}{CH_3}}{CH_3CHC≡N}$$

2-Methylpropanenitrile

MS: M$^+$ = 86
IR: 1715 cm^{-1}
^{1}H NMR: 1.05 δ (6 H, doublet, J = 7 Hz); 2.12 δ (3 H, singlet);
2.67 δ (1 H, septet, J = 7 Hz)
^{13}C NMR: 18.2, 27.2, 41.6, 211.2 δ

14

Saffron, derived from stigmas of the saffron crocus, is the world's most expensive spice. Its color is caused by the presence of alternating single and double bonds. Image copyright Demark, 2010. Used under license from Shutterstock.com

Conjugated Compounds and Ultraviolet Spectroscopy

OWL Sign in to OWL for Organic Chemistry at **www.cengage.com/owl** to view tutorials and simulations, develop problem-solving skills, and complete online homework assigned by your professor.

The unsaturated compounds we looked at in Chapters 7 and 8 had only one double bond, but many compounds have numerous sites of unsaturation. If the different unsaturations are well separated in a molecule, they react independently, but if they're close together, they may interact with one another. In particular, compounds that have alternating single and double bonds—so-called **conjugated** compounds—have some distinctive characteristics. The conjugated diene 1,3-butadiene, for instance, has some properties quite different from those of the nonconjugated 1,4-pentadiene.
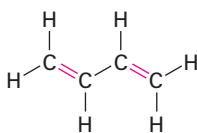
1,3-Butadiene
(conjugated; alternating double and single bonds)
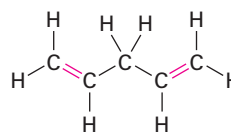
1,4-Pentadiene
(nonconjugated; nonalternating double and single bonds)

Why This Chapter? Conjugated compounds of many different sorts are common in nature. Many of the pigments responsible for the brilliant colors of fruits and flowers have numerous alternating single and double bonds. Lycopene, for instance, the red pigment found in tomatoes and thought to protect against prostate cancer, is a conjugated *polyene.* Conjugated *enones* (alkene + ketone) are common structural features of many biologically important molecules such as progesterone, the hormone that prepares the uterus for implantation of a fertilized ovum. Cyclic conjugated molecules such as benzene are a major field of study in themselves. In this chapter, we'll look at some of the

distinctive properties of conjugated molecules and at the reasons for those properties.
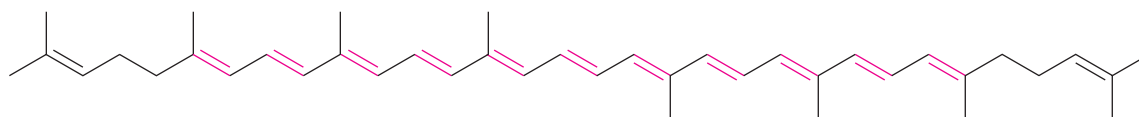

Lycopene, a conjugated polyene
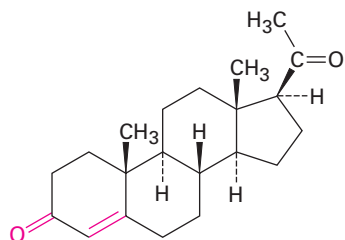
Progesterone, a conjugated enone

**Benzene,
a cyclic conjugated molecule**

14.1 Stability of Conjugated Dienes: Molecular Orbital Theory

Conjugated dienes can be prepared by some of the methods previously discussed for preparing alkenes **(Sections 11.7–11.10)**. The base-induced elimination of HX from an allylic halide is one such reaction.
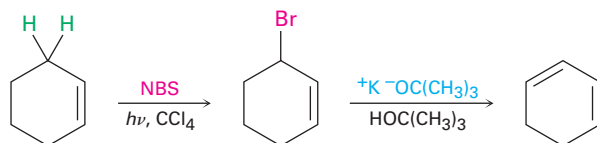
Cyclohexene   3-Bromocyclohexene   1,3-Cyclohexadiene (76%)

Simple conjugated dienes used in polymer synthesis include 1,3-butadiene, chloroprene (2-chloro-1,3-butadiene), and isoprene (2-methyl-1,3-butadiene). Isoprene has been prepared industrially by several methods, including the acid-catalyzed double dehydration of 3-methyl-1,3-butanediol.
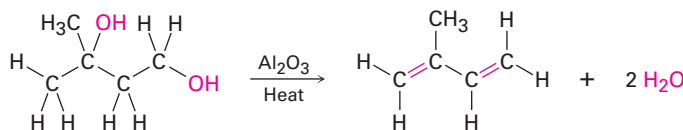

**3-Methyl-1,3-butanediol   Isoprene
2-Methyl-1,3-butadiene**

One of the properties that distinguishes conjugated from nonconjugated dienes is that the central single bond in shorter than might be expected. The

C2–C3 single bond in 1,3-butadiene, for instance, has a length of 147 pm, some 6 pm shorter than the C2–C3 bond in butane (153 pm).

147 pm

153 pm

$H_2C=CH-CH=CH_2$ $CH_3-CH_2-CH_2-CH_3$

1,3-Butadiene   **Butane**
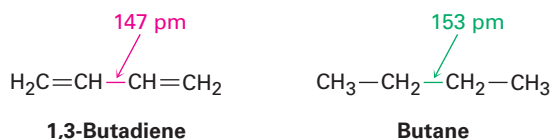
Another distinctive property of conjugated dienes is their unusual stability, as evidenced by their heats of hydrogenation (Table 14.1). We saw in **Section 7.6** that monosubstituted alkenes, such as 1-butene, have $\Delta H°_{hydrog}$ near −126 kJ/mol (−30.1 kcal/mol), whereas disubstituted alkenes, such as 2-methylpropene, have $\Delta H°_{hydrog}$ near −119 kJ/mol (−28.4 kcal/mol), approximately 7 kJ/mol less negative. We concluded from these data that more highly substituted alkenes are more stable than less substituted ones. That is, more highly substituted alkenes release less heat on hydrogenation because they contain less energy to start with. A similar conclusion can be drawn for conjugated dienes.

**Table 14.1** Heats of Hydrogenation for Some Alkenes and Dienes

Alkene or diene	Product	$\Delta H°_{hydrog}$ (kJ/mol)	(kcal/mol)
$CH_3CH_2CH=CH_2$	$CH_3CH_2CH_2CH_3$	−126	−30.1
$CH_3\overset{\overset{\displaystyle CH_3}{\mid}}{C}=CH_2$	$CH_3\overset{\overset{\displaystyle CH_3}{\mid}}{C}HCH_3$	−119	−28.4
$H_2C=CHCH_2CH=CH_2$	$CH_3CH_2CH_2CH_2CH_3$	−253	−60.5
$H_2C=CH-CH=CH_2$	$CH_3CH_2CH_2CH_3$	−236	−56.4
$H_2C=CH-\overset{\overset{\displaystyle CH_3}{\mid}}{C}=CH_2$	$CH_3CH_2\overset{\overset{\displaystyle CH_3}{\mid}}{C}HCH_3$	−229	−54.7

Because a monosubstituted alkene has a $\Delta H°_{hydrog}$ of approximately −126 kJ/mol, we might expect that a compound with two monosubstituted double bonds would have a $\Delta H°_{hydrog}$ approximately twice that value, or −252 kJ/mol. Nonconjugated dienes, such as 1,4-pentadiene ($\Delta H°_{hydrog}$ = −253 kJ/mol), meet this expectation, but the conjugated diene 1,3-butadiene ($\Delta H°_{hydrog}$ = −236 kJ/mol) does not. 1,3-Butadiene is approximately 16 kJ/mol (3.8 kcal/mol) more stable than expected.

$\Delta H°_{hydrog}$ **(kJ/mol)**

$H_2C=CHCH_2CH=CH_2$	−126 + (−126) = −252	Expected
	−253	Observed
1,4-Pentadiene	1	Difference
$H_2C=CHCH=CH_2$	−126 + (−126) = −252	Expected
	−236	Observed
1,3-Butadiene	−16	Difference

What accounts for the stability of conjugated dienes? According to valence bond theory **(Sections 1.5 and 1.8)**, the stability is due to orbital hybridization. Typical C−C single bonds like those in alkanes result from σ overlap of sp^3 orbitals on both carbons, but in a conjugated diene, the central C−C single bond results from σ overlap of sp^2 orbitals on both carbons. Since sp^2 orbitals have more s character (33% s) than sp^3 orbitals (25% s), the electrons in sp^2 orbitals are closer to the nucleus and the bonds they form are somewhat shorter and stronger. Thus, the "extra" stability of a conjugated diene results in part from the greater amount of s character in the orbitals forming the C−C single bond.

$$CH_3-CH_2-CH_2-CH_3 \qquad H_2C=CH-CH=CH_2$$

Bonds formed by overlap   **Bond formed by overlap**
of sp^3 orbitals   **of sp^2 orbitals**

According to molecular orbital theory **(Section 1.11)**, the stability of a conjugated diene arises because of an interaction between the π orbitals of the two double bonds. To review briefly, when two p atomic orbitals combine to form a π bond, two π molecular orbitals (MOs) result. One is lower in energy than the starting p orbitals and is therefore bonding; the other is higher in energy, has a node between nuclei, and is antibonding. The two π electrons occupy the low-energy, bonding orbital, resulting in formation of a stable bond between atoms **(Figure 14.1)**.

Figure 14.1 Two p orbitals combine to form two π molecular orbitals. Both electrons occupy the low-energy, bonding orbital, leading to a net lowering of energy and formation of a stable bond. The asterisk on ψ_2^* indicates an antibonding orbital.

Now let's combine four adjacent p atomic orbitals, as occurs in a conjugated diene. In so doing, we generate a set of four π molecular orbitals, two of which are bonding and two of which are antibonding **(Figure 14.2)**. The four π electrons occupy the two bonding orbitals, leaving the antibonding orbitals vacant.

Figure 14.2 Four π molecular orbitals in 1,3-butadiene. Note that the number of nodes between nuclei increases as the energy level of the orbital increases.

Antibonding (3 nodes)

Antibonding (2 nodes)

Bonding (1 node)
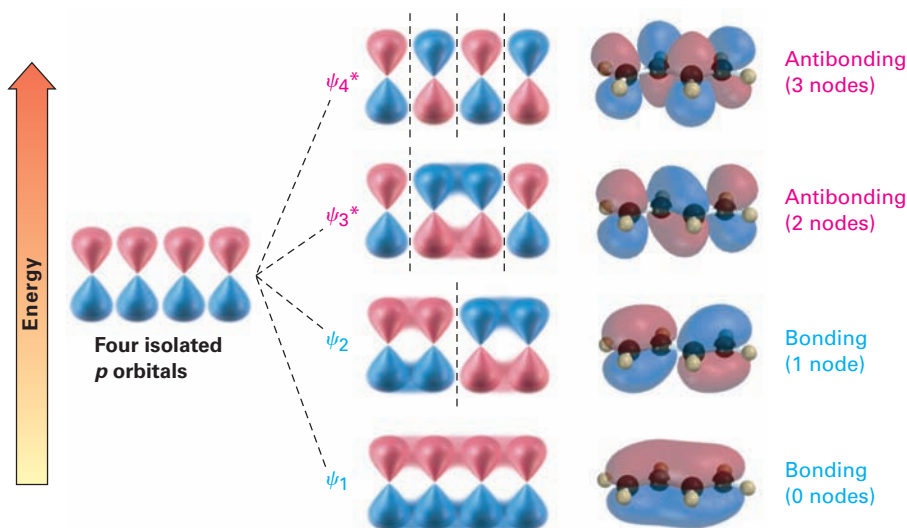
Bonding (0 nodes)

The lowest-energy π molecular orbital (denoted ψ_1, Greek psi) has no nodes between the nuclei and is therefore bonding. The π MO of next lowest energy, ψ_2, has one node between nuclei and is also bonding. Above ψ_1 and ψ_2 in energy are the two antibonding π MOs, ψ_3^* and ψ_4^*. (The asterisks indicate antibonding orbitals.) Note that the number of nodes between nuclei increases as the energy level of the orbital increases. The ψ_3^* orbital has two nodes between nuclei, and ψ_4^*, the highest-energy MO, has three nodes between nuclei.

Comparing the π molecular orbitals of 1,3-butadiene (two conjugated double bonds) with those of 1,4-pentadiene (two isolated double bonds) shows why the conjugated diene is more stable. In a conjugated diene, the lowest-energy π MO (ψ_1) has a favorable bonding interaction between C2 and C3 that is absent in a nonconjugated diene. As a result, there is a certain amount of double-bond character to the C2–C3 bond, making that bond both stronger and shorter than a typical single bond. Electrostatic potential maps show clearly the additional electron density in the central bond **(Figure 14.3)**.

Figure 14.3 Electrostatic potential maps of 1,3-butadiene (conjugated) and 1,4-pentadiene (nonconjugated) show additional **electron density** in the central C—C bond of 1,3-butadiene, corresponding to partial double-bond character.

Partial double-bond character

**1,3-Butadiene
(conjugated)**

**1,4-Pentadiene
(nonconjugated)**
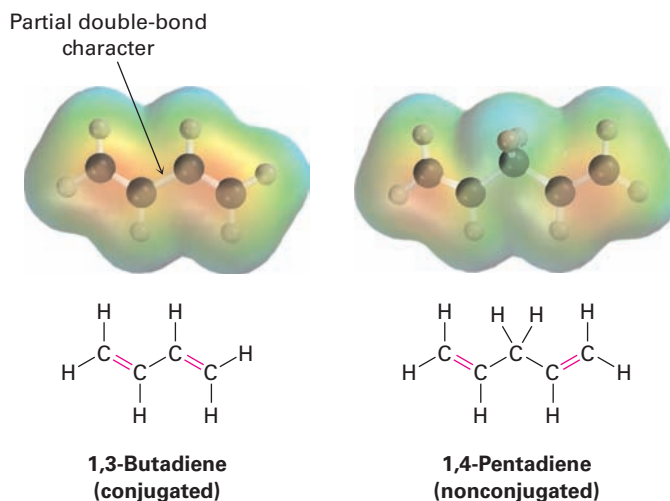
In describing 1,3-butadiene, we say that the π electrons are spread out, or *delocalized,* over the entire π framework rather than localized between two

specific nuclei. Delocalization allows the bonding electrons to be closer to more nuclei, thus leading to lower energy and greater stability.


Problem 14.1
Allene, $H_2C=C=CH_2$, has a heat of hydrogenation of -298 kJ/mol (-71.3 kcal/mol). Rank a conjugated diene, a nonconjugated diene, and an allene in order of stability.

## 14.2 Electrophilic Additions to Conjugated Dienes: Allylic Carbocations

One of the most striking differences between conjugated dienes and typical alkenes is their behavior in electrophilic addition reactions. To review briefly, the addition of an electrophile to a carbon–carbon double bond is a general reaction of alkenes **(Section 7.7)**. Markovnikov regiochemistry is found because the more stable carbocation is formed as an intermediate. Thus, addition of HCl to 2-methylpropene yields 2-chloro-2-methylpropane rather than 1-chloro-2-methylpropane, and addition of 2 mol equiv of HCl to the nonconjugated diene 1,4-pentadiene yields 2,4-dichloropentane.

2-Methylpropene   **Tertiary carbocation**   **2-Chloro-2-methylpropane**

1,4-Pentadiene (nonconjugated)   **2,4-Dichloropentane**
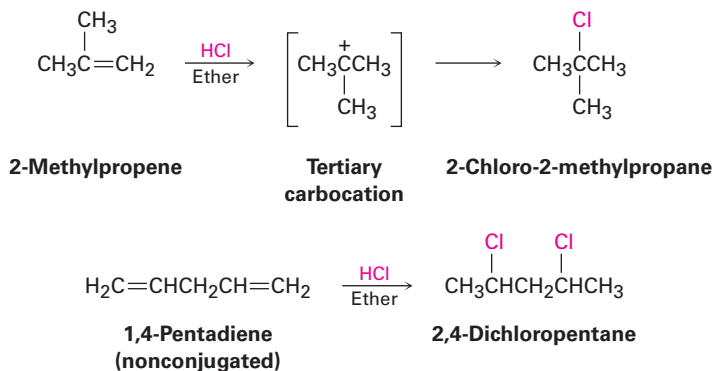
Conjugated dienes also undergo electrophilic addition reactions readily, but mixtures of products are invariably obtained. Addition of HBr to 1,3-butadiene, for instance, yields a mixture of two products (not counting cis–trans isomers). 3-Bromo-1-butene is the typical Markovnikov product of **1,2 addition** to a double bond, but 1-bromo-2-butene appears unusual. The double bond in this product has moved to a position between carbons 2 and 3, and HBr has added to carbons 1 and 4, a result described as **1,4 addition**.

3-Bromo-1-butene (71%; 1,2-addition)

1,3-Butadiene

1-Bromo-2-butene (29%; 1,4-addition)
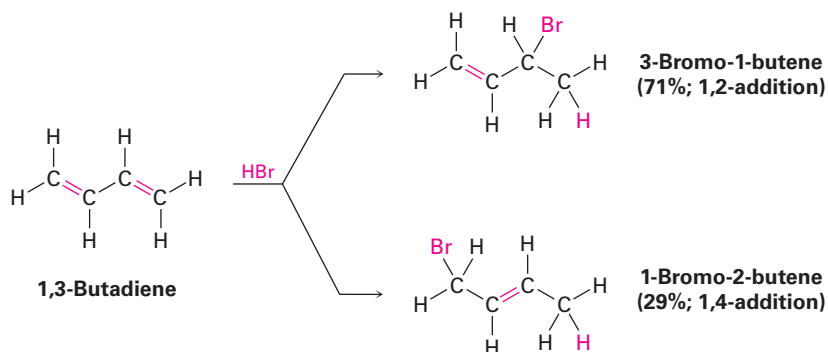
Many other electrophiles besides HBr add to conjugated dienes, and mixtures of products are usually formed. For example, Br_2 adds to 1,3-butadiene to give a mixture of 3,4-dibromo-1-butene and 1,4-dibromo-2-butene.


1,3-Butadiene

3,4-Dibromo-1-butene
(55%; 1,2-addition)

1,4-Dibromo-2-butene
(45%; 1,4-addition)
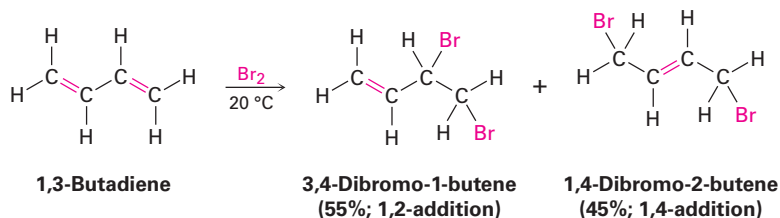
How can we account for the formation of 1,4-addition products? The answer is that allylic carbocations are involved as intermediates (recall that the word *allylic* means "next to a double bond"). When 1,3-butadiene reacts with an electrophile such as H^+, two carbocation intermediates are possible—a primary nonallylic carbocation and a secondary allylic cation. Because an allylic cation is stabilized by resonance between two forms **(Section 11.5)**, it is more stable and forms faster than a nonallylic carbocation.

Secondary, allylic

1,3-Butadiene

Primary, nonallylic
(not formed)
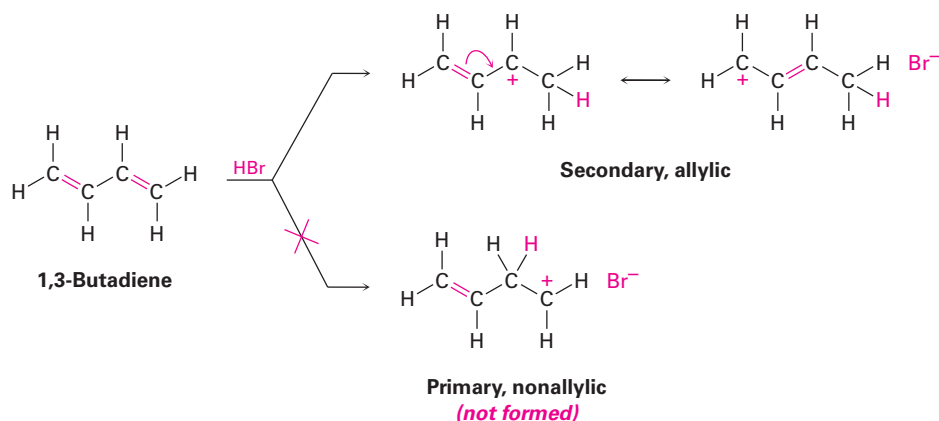
When the allylic cation reacts with Br^- to complete the electrophilic addition, reaction can occur either at C1 or at C3 because both carbons share the positive charge **(Figure 14.4)**. Thus, a mixture of 1,2- and 1,4-addition products results. You might recall that a similar product mixture was seen for NBS bromination of alkenes in **Section 10.3**, a reaction that proceeds through an allylic *radical*.

Figure 14.4 An electrostatic potential map of the allylic carbocation produced by protonation of 1,3-butadiene shows that the **positive charge** is shared by carbons 1 and 3. Reaction of Br^- with the more positive carbon **(C3)** gives predominantly the 1,2-addition product.

1,4-Addition
(29%)
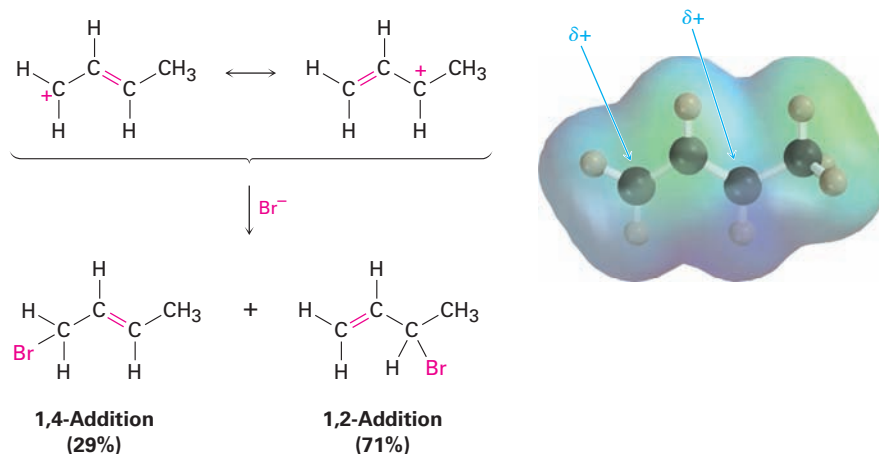
1,2-Addition
(71%)

| Predicting the Product of an Electrophilic Addition Reaction of a Conjugated Diene	Worked Example 14.1

Give the structures of the likely products from reaction of 1 equivalent of HCl with 2-methyl-1,3-cyclohexadiene. Show both 1,2 and 1,4 adducts.

Strategy

Electrophilic addition of HCl to a conjugated diene involves the formation of allylic carbocation intermediates. Thus, the first step is to protonate the two ends of the diene and draw the resonance forms of the two allylic carbocations that result. Then allow each resonance form to react with Cl⁻, generating a maximum of four possible products.

In the present instance, protonation of the C1–C2 double bond gives a carbocation that can react further to give the 1,2 adduct 3-chloro-3-methylcyclohexene and the 1,4 adduct 3-chloro-1-methylcyclohexene. Protonation of the C3–C4 double bond gives a symmetrical carbocation, whose two resonance forms are equivalent. Thus, the 1,2 adduct and the 1,4 adduct have the same structure: 6-chloro-1-methylcyclohexene. Of the two possible modes of protonation, the first is more likely because it yields a more stable, tertiary allylic cation rather than a less-stable, secondary allylic cation.

Solution

2-Methyl-1,3-cyclo-hexadiene

3-Chloro-3-methyl-cyclohexene	3-Chloro-1-methyl-cyclohexene	6-Chloro-1-methyl-cyclohexene
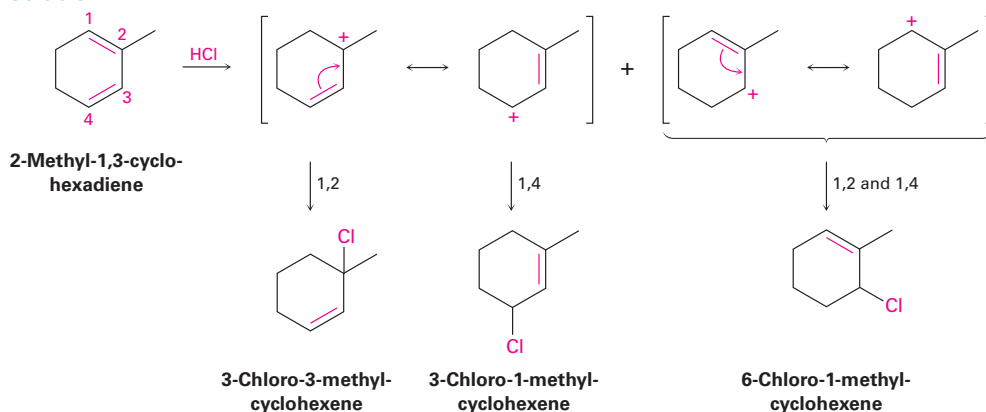
Problem 14.2

Give the structures of both 1,2 and 1,4 adducts resulting from reaction of 1 equivalent of HCl with 1,3-pentadiene.

Problem 14.3

Look at the possible carbocation intermediates produced during addition of HCl to 1,3-pentadiene (Problem 14.2), and predict which 1,2 adduct predominates. Which 1,4 adduct predominates?

Problem 14.4

Give the structures of both 1,2 and 1,4 adducts resulting from reaction of 1 equivalent of HBr with the following compound:
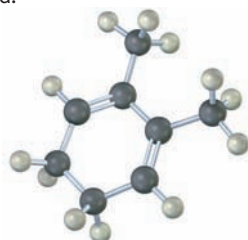
14.3 Kinetic versus Thermodynamic Control of Reactions

Electrophilic addition to a conjugated diene at or below room temperature normally leads to a mixture of products in which the 1,2 adduct predominates over the 1,4 adduct. When the same reaction is carried out at higher temperatures, though, the product ratio often changes and the 1,4 adduct predominates. For example, addition of HBr to 1,3-butadiene at 0 °C yields a 71:29 mixture of 1,2 and 1,4 adducts, but the same reaction carried out at 40 °C yields a 15:85 mixture. Furthermore, when the product mixture formed at 0 °C is heated to 40 °C in the presence of HBr, the ratio of adducts slowly changes from 71:29 to 15:85. Why?

1,3-Butadiene   **1,2-Adduct**   **1,4-Adduct**

	1,2-Adduct	1,4-Adduct
At 0 °C:	71%	29%
At 40 °C:	15%	85%
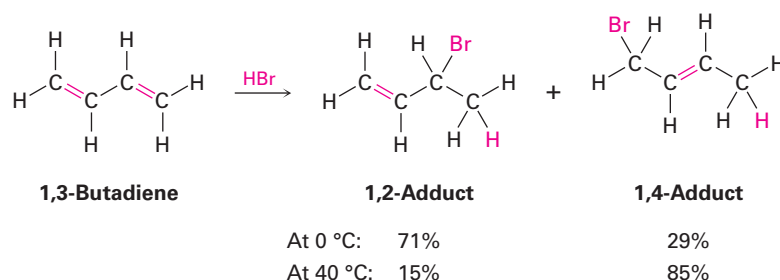
To understand the effect of temperature on product distribution, let's briefly review what we said in **Section 6.7** about rates and equilibria. Imagine a reaction that can give either or both of two products, **B** and **C**.

$$A \diagdown \diagup$$

B   **C**
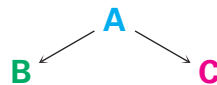
Let's assume that **B** forms faster than **C** (in other words, $\Delta G^{\ddagger}_B < \Delta G^{\ddagger}_C$) but that **C** is more stable than **B** (in other words, $\Delta G^{\circ}_C > \Delta G^{\circ}_B$). An energy diagram for the two processes might look like that shown in **Figure 14.5**.

Figure 14.5 An energy diagram for two competing reactions in which the less stable product **B** forms faster than the more stable product **C**.
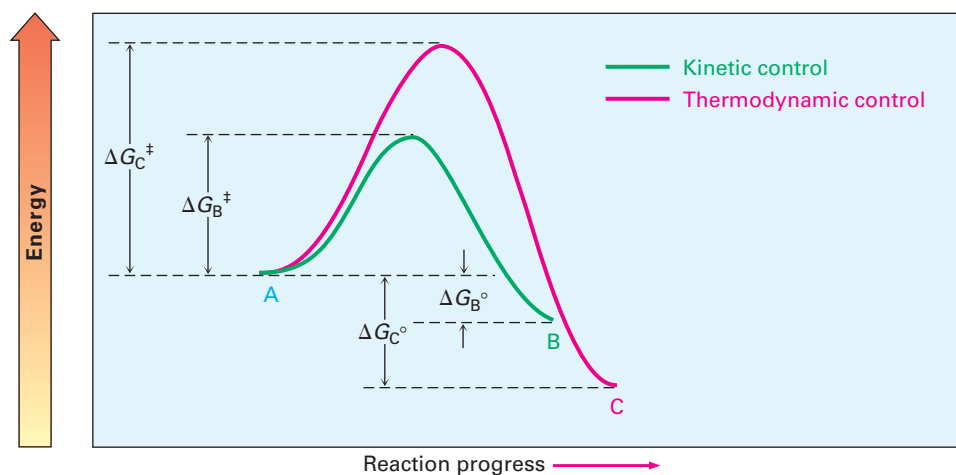
Let's first carry out the reaction at a lower temperature so that both processes are irreversible and no equilibrium is reached. Since **B** forms faster than **C**, **B** is the major product. It doesn't matter that **C** is more stable than **B**, because the two

the *intramolecular* Diels–Alder reaction of a triene, in which the diene and dienophile components are within the same molecule.
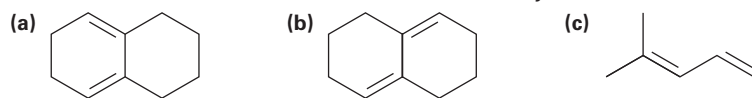

Lovastatin
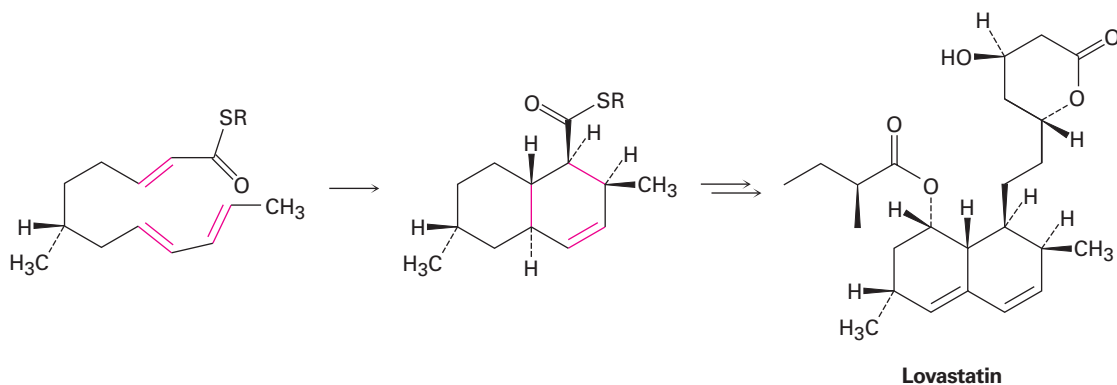
Problem 14.8
Which of the following alkenes would you expect to be good Diels–Alder dienophiles?

(a)

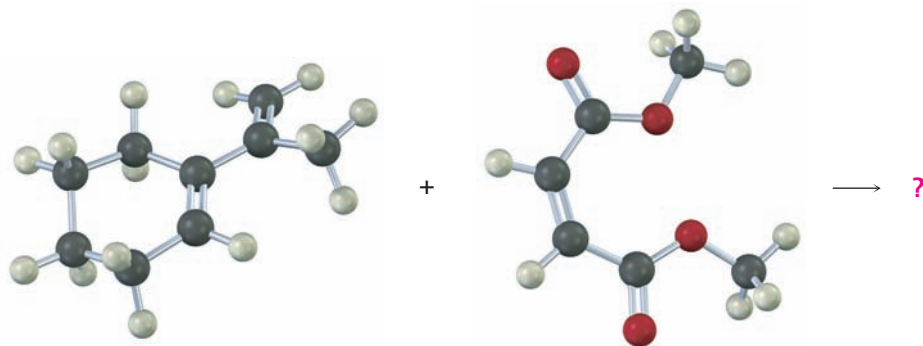$$H_2C=CHCCl$$

(b)

$$H_2C=CHCH_2CH_2COCH_3$$

(c)

(d)

(e)
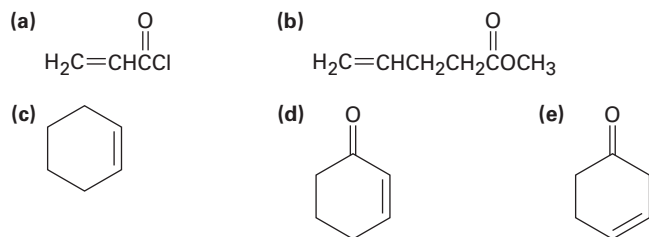
Problem 14.9
Which of the following dienes have an *s*-cis conformation, and which have an *s*-trans conformation? Of the *s*-trans dienes, which can readily rotate to *s*-cis?

(a)

(b)

(c)

Problem 14.10
Predict the product of the following Diels–Alder reaction:

$+$ $\longrightarrow$ **?**

14.6 Diene Polymers: Natural and Synthetic Rubbers

Conjugated dienes can be polymerized just as simple alkenes can **(Section 8.10)**. Diene polymers are structurally more complex than simple alkene polymers, though, because double bonds remain every four carbon atoms along the chain, leading to the possibility of cis–trans isomers. The initiator (In) for the reaction can be either a radical, as occurs in ethylene polymerization, or an acid. Note that the polymerization is a 1,4 addition of the growing chain to a conjugated diene monomer.

1,3-Butadiene

cis-**Polybutadiene**

trans-**Polybutadiene**
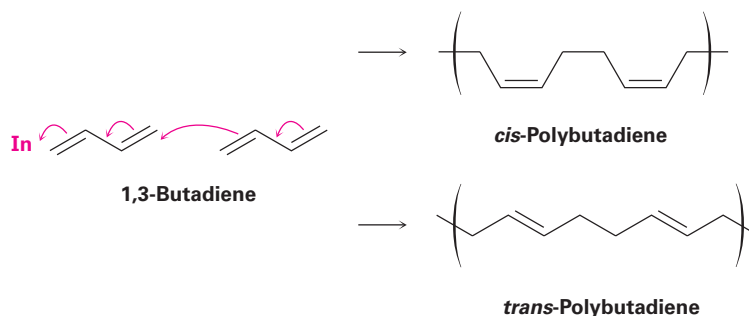
Rubber is a naturally occurring diene polymer of isoprene (2-methyl-1,3-butadiene) and is produced by more than 400 different plants. The major source is the so-called rubber tree, *Hevea brasiliensis,* from which the crude material, called *latex,* is harvested as it drips from a slice made through the bark. The double bonds of rubber have *Z* stereochemistry, but gutta-percha, the *E* isomer of rubber, also occurs naturally. Harder and more brittle than rubber, gutta-percha has a variety of minor applications, including occasional use in dentistry and as the covering on golf balls.

**Isoprene
(2-methyl-1,3-butadiene)**

Natural rubber (*Z*)

Gutta-percha (*E*)
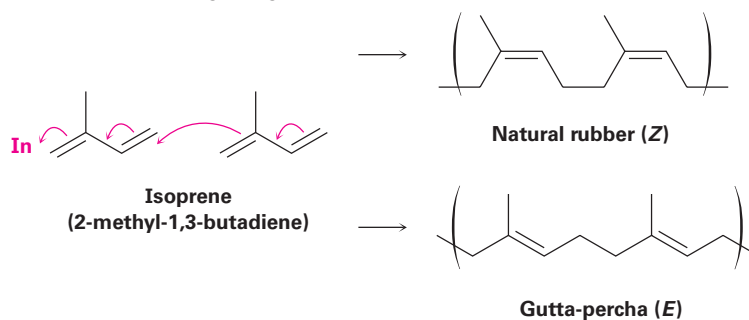
A number of different synthetic rubbers are produced commercially by diene polymerization. Both *cis*- and *trans*-polyisoprene can be made, and the synthetic rubber thus produced is similar to the natural material. Chloroprene (2-chloro-1,3-butadiene) is polymerized to yield neoprene, an excellent, although expensive, synthetic rubber with good weather resistance. Neoprene is used in the production of industrial hoses and gloves, among other things.

**Chloroprene
(2-chloro-1,3-butadiene)**

Neoprene (*Z*)
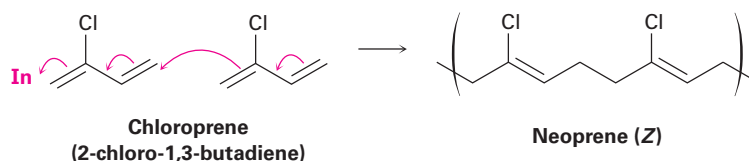
Both natural and synthetic rubbers are too soft and tacky to be useful until they are hardened by heating with elemental sulfur, a process called *vulcanization*. Vulcanization cross-links the rubber chains together by forming carbon–sulfur bonds between them, thereby hardening and stiffening the polymer. The exact degree of hardening can be varied, yielding material soft enough for automobile tires or hard enough for bowling balls *(ebonite)*.

The unusual ability of rubber to stretch and then contract to its original shape is due to the irregular shapes of the polymer chains caused by the double bonds. These double bonds introduce bends and kinks into the polymer chains, thereby preventing neighboring chains from nestling together. When stretched, the randomly coiled chains straighten out and orient along the direction of the pull but are kept from sliding over one another by the cross-links. When the stretch is released, the polymer reverts to its original random state.

Problem 14.11
Draw a segment of the polymer that might be prepared from 2-phenyl-1,3-butadiene.

Problem 14.12
Show the mechanism of the acid-catalyzed polymerization of 1,3-butadiene.

14.7 Structure Determination in Conjugated Systems: Ultraviolet Spectroscopy

Mass spectrometry, infrared spectroscopy, and nuclear magnetic resonance spectroscopy are techniques of structure determination applicable to all organic molecules. In addition to these three generally useful methods, there is a fourth—**ultraviolet (UV) spectroscopy**—that is applicable only to conjugated compounds. UV is less commonly used than the other three spectroscopic techniques because of the specialized information it gives, so we'll mention it only briefly.

Mass spectrometry	Molecular size and formula
IR spectroscopy	Functional groups present
NMR spectroscopy	Carbon–hydrogen framework
UV spectroscopy	**Nature of conjugated π electron system**

The ultraviolet region of the electromagnetic spectrum extends from the short-wavelength end of the visible region (4×10^{-7} m) to the long-wavelength end of the X-ray region (10^{-8} m), but the narrow range from 2×10^{-7} m to 4×10^{-7} m is the part of greatest interest to organic chemists. Absorptions in this region are usually measured in nanometers (nm), where 1 nm = 10^{-9} m. Thus, the ultraviolet range of interest is from 200 to 400 nm **(Figure 14.10)**.
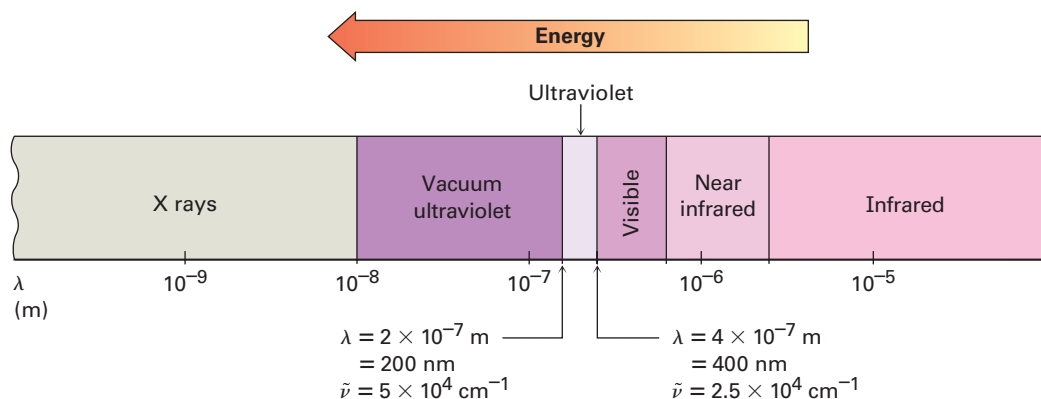
Figure 14.10 The ultraviolet (UV) and neighboring regions of the electromagnetic spectrum.

We saw in **Section 12.5** that when an organic molecule is irradiated with electromagnetic energy, the radiation either passes through the sample or is absorbed, depending on its energy. With IR irradiation, the energy absorbed corresponds to the amount necessary to increase molecular vibrations. With UV radiation, the energy absorbed corresponds to the amount necessary to promote an electron from a lower-energy orbital to a higher-energy one in a conjugated molecule. The conjugated diene 1,3-butadiene, for instance, has four π molecular orbitals, as shown previously in Figure 14.2 on page 504. The two lower-energy, bonding MOs are occupied in the ground state, and the two higher-energy, antibonding MOs are unoccupied.

On irradiation with ultraviolet light ($h\nu$), 1,3-butadiene absorbs energy and a π electron is promoted from the **highest occupied molecular orbital**, or **HOMO**, to the **lowest unoccupied molecular orbital**, or **LUMO**. Since the electron is promoted from a bonding π molecular orbital to an antibonding π^* molecular orbital, we call this a $\pi \rightarrow \pi^*$ excitation (read as "pi to pi star"). The energy gap between the HOMO and the LUMO of 1,3-butadiene is such that UV light of 217 nm wavelength is required to accomplish the $\pi \rightarrow \pi^*$ electronic transition **(Figure 14.11)**.

Figure 14.11 Ultraviolet excitation of 1,3-butadiene results in the promotion of an electron from ψ_2, the highest occupied molecular orbital (HOMO), to ψ_3^*, the lowest unoccupied molecular orbital (LUMO).
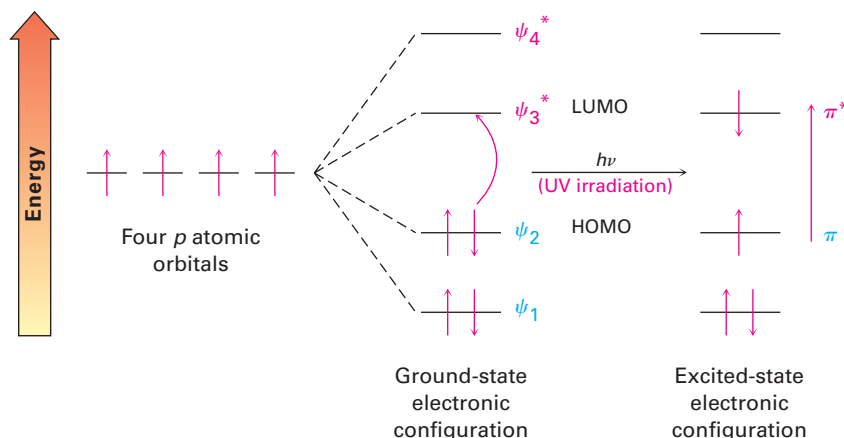
An ultraviolet spectrum is recorded by irradiating the sample with UV light of continuously changing wavelength. When the wavelength corresponds to the energy level required to excite an electron to a higher level, energy is

absorbed. This absorption is detected and displayed on a chart that plots wavelength versus *absorbance (A),* defined as

$$A = \log \frac{I_0}{I}$$

where I_0 is the intensity of the incident light and I is the intensity of the light transmitted through the sample.

Note that UV spectra differ from IR spectra in the way they are presented. For historical reasons, IR spectra are usually displayed so that the baseline corresponding to zero absorption runs across the top of the chart and a valley indicates an absorption, whereas UV spectra are displayed with the baseline at the bottom of the chart so that a peak indicates an absorption **(Figure 14.12)**.
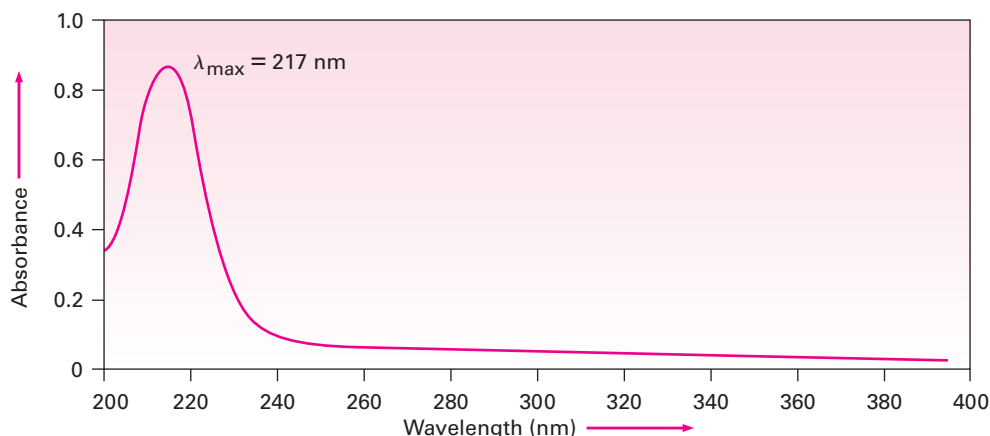
Figure 14.12 The ultraviolet spectrum of 1,3-butadiene, $\lambda_{max} = 217$ nm.

The amount of UV light absorbed is expressed as the sample's **molar absorptivity (ϵ)**, defined by the equation

$$\varepsilon = \frac{A}{c \times l}$$

where
A = Absorbance
c = Concentration in mol/L
l = Sample pathlength in cm

Molar absorptivity is a physical constant, characteristic of the particular substance being observed and thus characteristic of the particular π electron system in the molecule. Typical values for conjugated dienes are in the range ϵ = 10,000 to 25,000. The units for molar absorptivity, L/(mol · cm), are usually dropped.

A particularly important use of this equation comes from rearranging it to the form $c = A/(\epsilon \cdot l)$, which lets us measure the concentration of a sample in solution when A, ϵ, and l are known. As an example, β-carotene, the pigment responsible for the orange color of carrots, has ϵ = 138,000 L/(mol · cm). If a sample of β-carotene is placed in a cell with a pathlength of 1.0 cm and the UV absorbance reads 0.37, then the concentration of β-carotene in the sample is

$$c = \frac{A}{\varepsilon l} = \frac{0.37}{\left(1.38 \times 10^5 \dfrac{L}{mol \cdot cm}\right)(1.00 \text{ cm})}$$

$$= 2.7 \times 10^{-6} \text{ mol/L}$$

Unlike IR and NMR spectra, which show many absorptions for a given molecule, UV spectra are usually quite simple—often only a single peak. The peak is usually broad, and we identify its position by noting the wavelength at the very top of the peak—λ_{max}, read as "lambda max."

Problem 14.13

Calculate the energy range of electromagnetic radiation in the UV region of the spectrum from 200 to 400 nm (see **Section 12.5**). How does this value compare with the values calculated previously for IR and NMR spectroscopy?

Problem 14.14

If pure vitamin A has $\lambda_{max} = 325$ ($\epsilon = 50{,}100$), what is the vitamin A concentration in a sample whose absorbance at 325 nm is $A = 0.735$ in a cell with a pathlength of 1.00 cm?

14.8 Interpreting Ultraviolet Spectra: The Effect of Conjugation

The wavelength necessary to effect the $\pi \rightarrow \pi^*$ transition in a conjugated molecule depends on the energy gap between HOMO and LUMO, which in turn depends on the nature of the conjugated system. Thus, by measuring the UV spectrum of an unknown, we can derive structural information about the nature of any conjugated π electron system present in a molecule.

One of the most important factors affecting the wavelength of UV absorption by a molecule is the extent of conjugation. Molecular orbital calculations show that the energy difference between HOMO and LUMO decreases as the extent of conjugation increases. Thus, 1,3-butadiene absorbs at $\lambda_{max} = 217$ nm, 1,3,5-hexatriene absorbs at $\lambda_{max} = 258$ nm, and 1,3,5,7-octatetraene absorbs at $\lambda_{max} = 290$ nm. (Remember: longer wavelength means lower energy.)

Other kinds of conjugated systems, such as conjugated enones and aromatic rings, also have characteristic UV absorptions that are useful in structure determination. The UV absorption maxima of some representative conjugated molecules are given in Table 14.2.

Table 14.2 Ultraviolet Absorptions of Some Conjugated Molecules

Name	Structure	λ_{max} (nm)
2-Methyl-1,3-butadiene	CH_3 $\mid$ $H_2C{=}C{-}CH{=}CH_2$	220
1,3-Cyclohexadiene		256
1,3,5-Hexatriene	$H_2C{=}CH{-}CH{=}CH{-}CH{=}CH_2$	258
1,3,5,7-Octatetraene	$H_2C{=}CH{-}CH{=}CH{-}CH{=}CH{-}CH{=}CH_2$	290
3-Buten-2-one	$\quad\quad\quad O$ $\quad\quad\quad \|\|$ $H_2C{=}CH{-}C{-}CH_3$	219
Benzene		203

Problem 14.15

Which of the following compounds would you expect to show ultraviolet absorptions in the 200 to 400 nm range?

(a)

(b)

(c) CN

(d)

Aspirin

(e) CH$_3$

(f)

Indole
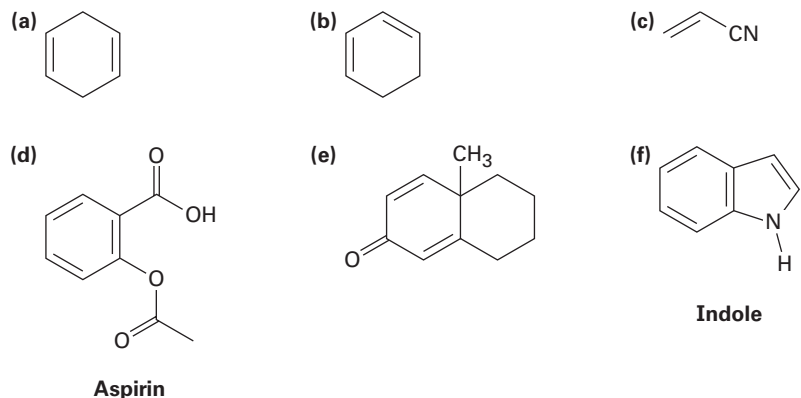
14.9 Conjugation, Color, and the Chemistry of Vision

Why are some organic compounds colored while others aren't? β-Carotene, the pigment in carrots, is purple-orange, for instance, while cholesterol is colorless. The answer involves both the chemical structures of colored molecules and the way we perceive light.

The visible region of the electromagnetic spectrum is adjacent to the ultraviolet region, extending from approximately 400 to 800 nm. Colored compounds have such extended systems of conjugation that their "UV" absorptions extend into the visible region. β-Carotene, for example, has 11 double bonds in conjugation, and its absorption occurs at λ$_{max}$ = 455 nm **(Figure 14.13)**.

λ_{max} = 455 nm
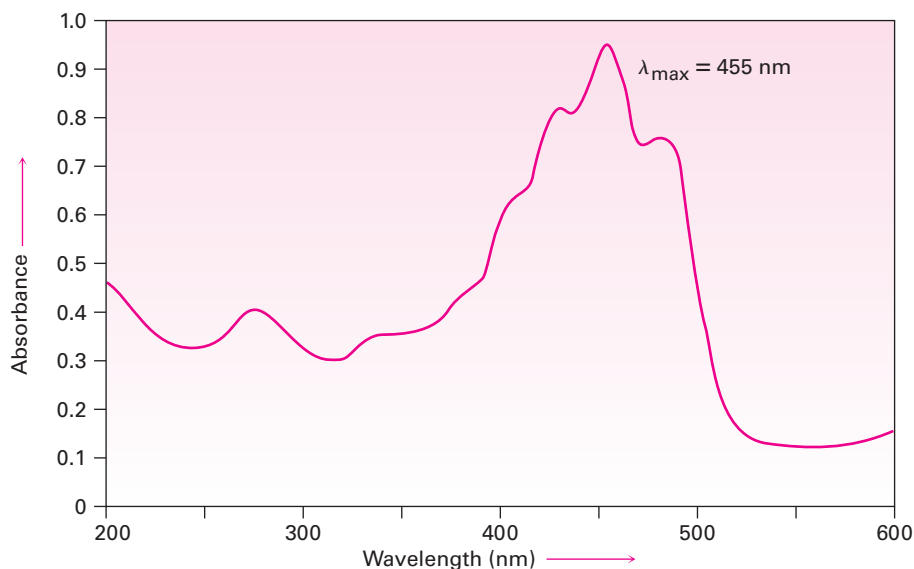
Figure 14.13 Ultraviolet spectrum of β-carotene, a conjugated molecule with 11 double bonds. The absorption occurs in the visible region.

"White" light from the sun or from a lamp consists of all wavelengths in the visible region. When white light strikes β-carotene, the wavelengths from 400 to 500 nm (blue) are absorbed while all other wavelengths are transmitted and can reach our eyes. We therefore see the white light with the blue removed, and we perceive a yellow-orange color for β-carotene.

Conjugation is crucial not only for the colors we see in organic molecules but also for the light-sensitive molecules on which our visual system is based. The key substance for vision is dietary β-carotene, which is converted to vitamin A by enzymes in the liver, oxidized to an aldehyde called 11-*trans*-retinal, and then isomerized by a change in geometry of the C11–C12 double bond to produce 11-*cis*-retinal.

β-Carotene

Vitamin A

11-*cis*-Retinal
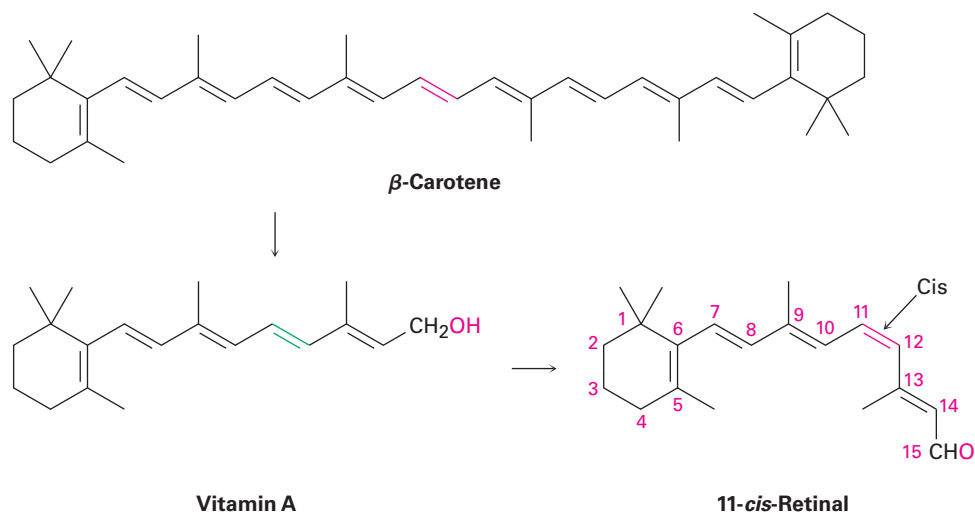
There are two main types of light-sensitive receptor cells in the retina of the human eye, *rod* cells and *cone* cells. The 3 million or so rod cells are primarily responsible for seeing in dim light, whereas the 100 million cone cells are responsible for seeing in bright light and for the perception of bright colors. In the rod cells of the eye, 11-*cis*-retinal is converted into rhodopsin, a light-sensitive substance formed from the protein opsin and 11-*cis*-retinal. When light strikes the rod cells, isomerization of the C11–C12 double bond occurs and *trans*-rhodopsin, called metarhodopsin II, is produced. In the absence of light, this cis–trans isomerization takes approximately 1100 years, but in the presence of light, it occurs within 200 femtoseconds, or 2×10^{-13} seconds! Isomerization of rhodopsin is accompanied by a change in molecular geometry, which in turn causes a nerve impulse to be sent through the optic nerve to the brain, where it is perceived as vision.

Rhodopsin
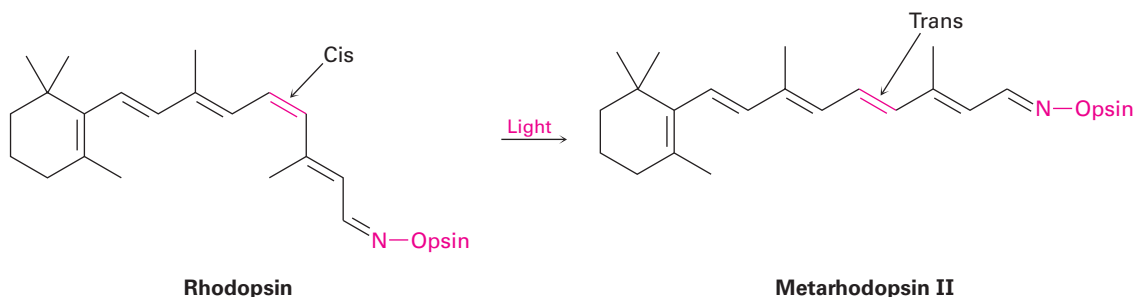
Metarhodopsin II

Metarhodopsin II is then recycled back into rhodopsin by a multistep sequence involving cleavage to all-*trans*-retinal and cis–trans isomerization back to 11-*cis*-retinal.

A DEEPER LOOK Photolithography

Manufacturing the ultrathin circuitry on this computer chip depends on the organic chemical reactions of special polymers.

Fifty years ago, someone interested in owning a computer would have paid approximately $150,000 for 16 megabytes of random-access memory that would have occupied a volume the size of a small desk. Today, anyone can buy 60 times as much computer memory for $20 and fit the small chip into their shirt pocket. The difference between then and now is due to improvements in *photolithography*, the process by which integrated-circuit chips are made.

Photolithography begins by coating a layer of SiO_2 onto a silicon wafer and further coating with a thin (0.5–1.0 μm) film of a light-sensitive organic polymer called a *resist*. A *mask* is then used to cover those parts of the chip that will become a circuit, and the wafer is irradiated with UV light. The nonmasked sections of the polymer undergo a chemical change when irradiated that makes them more soluble than the masked, unirradiated sections. On washing the irradiated chip with solvent, solubilized polymer is selectively removed from the irradiated areas, exposing the SiO_2 underneath. This SiO_2 is then chemically etched away by reaction with hydrofluoric acid, leaving behind a pattern of polymer-coated SiO_2. Further washing removes the remaining polymer, leaving a positive image of the mask in the form of exposed ridges of SiO_2 **(Figure 14.14)**. Additional cycles of coating, masking, and etching then produce the completed chips.

Figure 14.14 Outline of the photolithography process for producing integrated circuit chips.

The polymer resist currently used in chip manufacturing is based on the two-component *diazoquinone–novolac system*. Novolac resin is a soft, relatively low-molecular-weight polymer made from methylphenol and formaldehyde, while the diazoquinone is a bicyclic (two-ring) molecule containing a diazo group (=N=N) adjacent to a ketone carbonyl (C=O). The diazoquinone–novolac mix is relatively insoluble when fresh, but on exposure to ultraviolet light and water vapor, the diazoquinone component undergoes reaction to yield N_2 and a carboxylic acid, which can be washed away with dilute base. Novolac–diazoquinone

technology is capable of producing features as small as 0.5 μm (5×10^{-7} m), but still further improvements in miniaturization are being developed.

Diazonaphthoquinone

Novolac resin

$h\nu$
H_2O

CO_2H

+ N$_2$
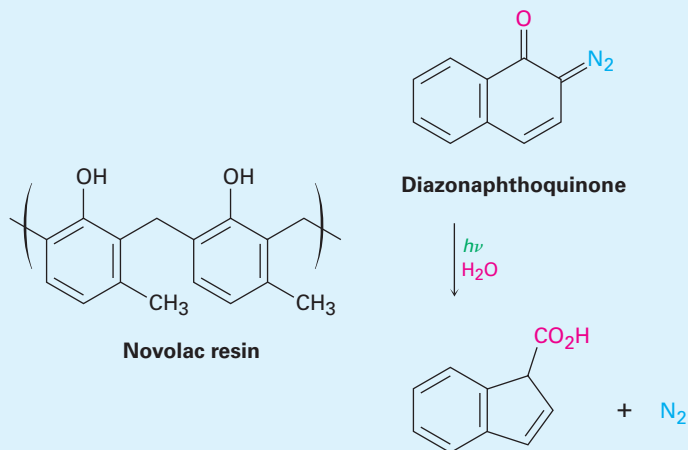
Summary

Key words

1,2 addition, 505
1,4 addition, 505
conjugated, 500
Diels–Alder cycloaddition reaction, 510
dienophile, 511
highest occupied molecular orbital (HOMO), 518
kinetic control, 509
lowest unoccupied molecular orbital (LUMO), 518
molar absorptivity (ϵ), 519
thermodynamic control, 509
ultraviolet (UV) spectroscopy, 517

The unsaturated compounds we've looked at previously have had only one double bond, but many compounds have numerous sites of unsaturation, which gives them some distinctive properties. Many such compounds are common in nature, including pigments and hormones.

A **conjugated** diene or other compound is one that contains alternating double and single bonds. One characteristic of conjugated dienes is that they are more stable than their nonconjugated counterparts. This stability can be explained by a molecular orbital description in which four p atomic orbitals combine to form four π molecular orbitals. Only the two bonding orbitals are occupied; the two antibonding orbitals are unoccupied. A π bonding interaction in the lowest-energy MO introduces some partial double-bond character between carbons 2 and 3, thereby strengthening the C2–C3 bond and stabilizing the molecule.

Conjugated dienes undergo several reactions not observed for nonconjugated dienes. One is the 1,4 addition of electrophiles. When a conjugated diene is treated with an electrophile such as HCl, **1,2-** and **1,4-addition** products are formed. Both are formed from the same resonance-stabilized allylic carbocation intermediate and are produced in varying amounts depending on the reaction conditions. The 1,2 adduct is usually formed faster and is said to be the product of **kinetic control**. The 1,4 adduct is usually more stable and is said to be the product of **thermodynamic control**.

Another reaction unique to conjugated dienes is the **Diels–Alder cycloaddition**. Conjugated dienes react with electron-poor alkenes (**dienophiles**) in a single step through a cyclic transition state to yield a cyclohexene product. The reaction is stereospecific, meaning that only a single product stereoisomer is formed, and can occur only if the diene is able to adopt an s-cis conformation.

Ultraviolet (UV) spectroscopy is a method of structure determination applicable specifically to conjugated π-electron systems. When a conjugated molecule is irradiated with ultraviolet light, energy absorption occurs and a π electron is promoted from the **highest occupied molecular orbital (HOMO)** to the **lowest unoccupied molecular orbital (LUMO)**. For 1,3-butadiene, radiation of $\lambda_{max} = 217$ nm is required. The greater the extent of conjugation, the less the energy needed and the longer the wavelength of radiation required.

Summary of Reactions

1. Electrophilic addition reactions (Sections 14.2 and 14.3)
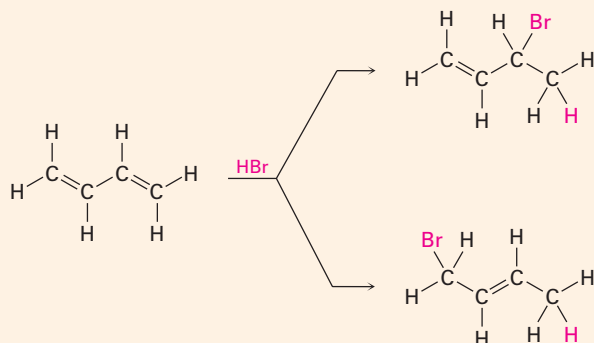
2. Diels–Alder cycloaddition reaction (Sections 14.4 and 14.5)

A diene   **A dienophile**   **A cyclohexene**
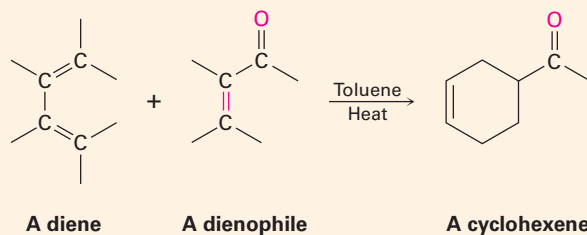
| Exercises

Visualizing Chemistry

(Problems 14.1–14.15 appear within the chapter.)

14.16 Show the structures of all possible adducts of the following diene with 1 equivalent of HCl:
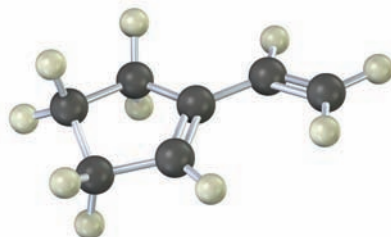
▲ Problems linked to Key Ideas in this chapter

14.17 Show the product of the Diels–Alder reaction of the following diene with 3-buten-2-one, H_2C=$CHCOCH_3$. Make sure you show the full stereochemistry of the reaction product.
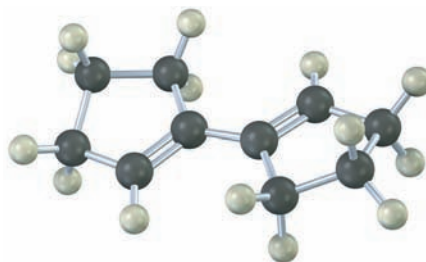
14.18 The following diene does not undergo Diels–Alder reactions. Explain.
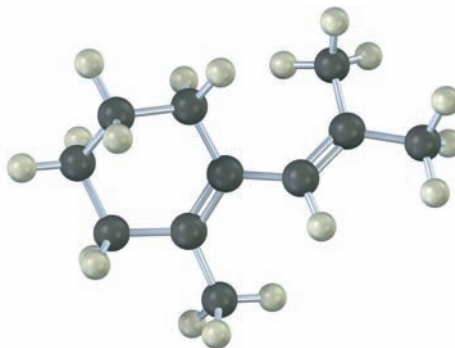
14.19 The following model is that of an allylic carbocation intermediate formed by protonation of a conjugated diene with HBr. Show the structure of the diene and the structures of the final reaction products.
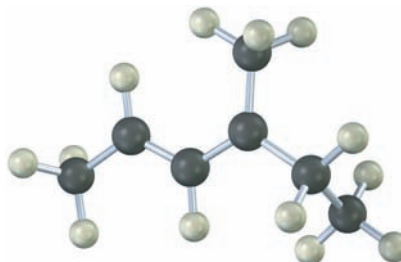
Additional Problems

Conjugated Dienes

14.20 Give IUPAC names for the following compounds:

(a)

$$CH_3$$
$$|$$
$$CH_3CH=CCH=CHCH_3$$

(b) H_2C=$CHCH$=$CHCH$=$CHCH_3$

(c) CH_3CH=C=$CHCH$=$CHCH_3$

(d)

$$CH_2CH_2CH_3$$
$$|$$
$$CH_3CH=CCH=CH_2$$
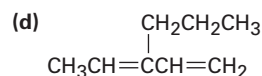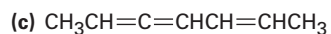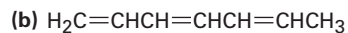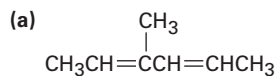
▲ Problems linked to Key Ideas in this chapter

14.21 Draw and name the six possible diene isomers of formula C_5H_8. Which of the six are conjugated dienes?

14.22 What product(s) would you expect to obtain from reaction of 1,3-cyclohexadiene with each of the following?
  (a) 1 mol Br_2 in CH_2Cl_2
  (b) O_3 followed by Zn
  (c) 1 mol HCl in ether
  (d) 1 mol DCl in ether
  (e) 3-Buten-2-one ($H_2C=CHCOCH_3$)
  (f) Excess OsO_4, followed by $NaHSO_3$

14.23 Electrophilic addition of Br_2 to isoprene (2-methyl-1,3-butadiene) yields the following product mixture:

(3%)   **(21%)**   **(76%)**
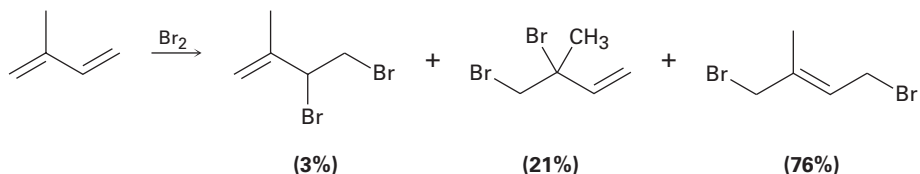
Of the 1,2-addition products, explain why 3,4-dibromo-3-methyl-1-butene (21%) predominates over 3,4-dibromo-2-methyl-1-butene (3%).

14.24 Propose a structure for a conjugated diene that gives the same product from both 1,2 and 1,4 addition of HBr.

14.25 Draw the possible products resulting from addition of 1 equivalent of HCl to 1-phenyl-1,3-butadiene. Which would you expect to predominate, and why?

1-Phenyl-1,3-butadiene
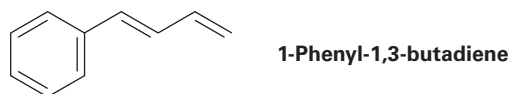
Diels–Alder Reactions

14.26 Predict the products of the following Diels–Alder reactions:

(a)

(b)
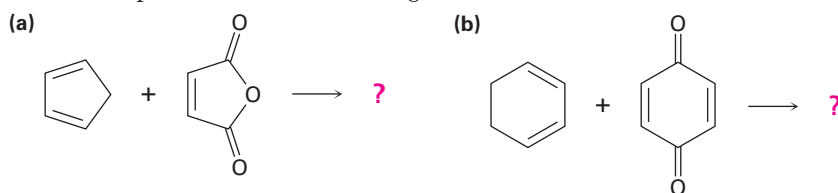
14.27 2,3-Di-*tert*-butyl-1,3-butadiene does not undergo Diels–Alder reactions. Explain.

2,3-Di-*tert*-butyl-1,3-butadiene

▲ Problems linked to Key Ideas in this chapter

14.28 Show the structure, including stereochemistry, of the product from the following Diels–Alder reaction:
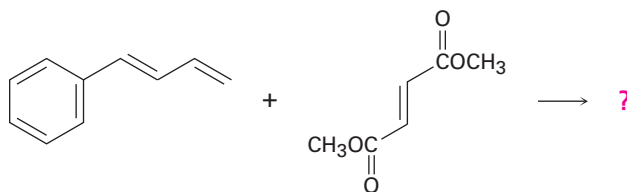
14.29 How can you account for the fact that *cis*-1,3-pentadiene is much less reactive than *trans*-1,3-pentadiene in the Diels–Alder reaction?

14.30 Would you expect a conjugated diyne such as 1,3-butadiyne to undergo Diels–Alder reaction with a dienophile? Explain.

14.31 Reaction of isoprene (2-methyl-1,3-butadiene) with ethyl propenoate gives a mixture of two Diels–Alder adducts. Show the structure of each, and explain why a mixture is formed.
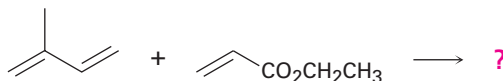
14.32 Rank the following dienophiles in order of their expected reactivity in the Diels–Alder reaction.
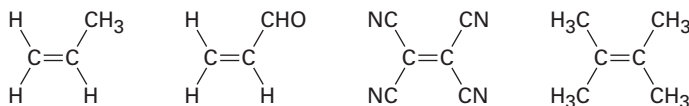
14.33 1,3-Cyclopentadiene is very reactive in Diels–Alder cycloaddition reactions, but 1,3-cyclohexadiene is less reactive and 1,3-cycloheptadiene is nearly inert. Explain. (Molecular models are helpful.)

14.34 1,3-Pentadiene is much more reactive in Diels–Alder reactions than 2,4-pentadienal. Why might this be?

1,3-Pentadiene   **2,4-Pentadienal**

▲ Problems linked to Key Ideas in this chapter

14.35 How could you use Diels–Alder reactions to prepare the following products? Show the starting diene and dienophile in each case.

(a)

(b)

(c)

(d)
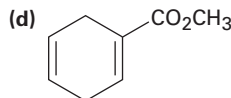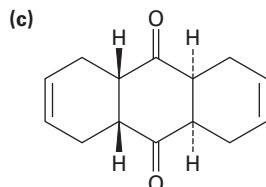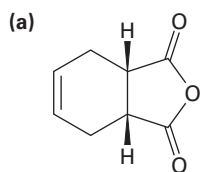
Diene Polymers

14.36 Diene polymers contain occasional vinyl branches along the chain. How do you think these branches might arise?
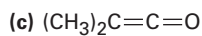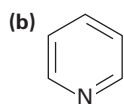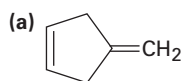
A vinyl branch
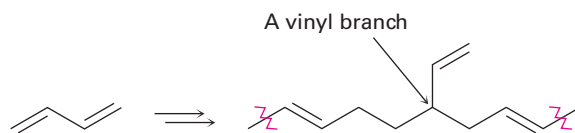
14.37 Tires whose sidewalls are made of natural rubber tend to crack and weather rapidly in areas around cities where high levels of ozone and other industrial pollutants are found. Explain.

14.38 ▲ 1,3-Cyclopentadiene polymerizes slowly at room temperature to yield a polymer that has no double bonds except on the ends. On heating, the polymer breaks down to regenerate 1,3-cyclopentadiene. Propose a structure for the product.

UV Spectroscopy

14.39 Which of the following compounds would you expect to have a $\pi \rightarrow \pi^*$ UV absorption in the 200 to 400 nm range?

(a)

(b)

Pyridine

(c) $(CH_3)_2C=C=O$

A ketene

▲ Problems linked to Key Ideas in this chapter

**14.40** Would you expect allene, $H_2C=C=CH_2$, to show a UV absorption in the 200 to 400 nm range? Explain.

14.41 The following ultraviolet absorption maxima have been measured:

1,3-Butadiene	217 nm
2-Methyl-1,3-butadiene	220 nm
1,3-Pentadiene	223 nm
2,3-Dimethyl-1,3-butadiene	226 nm
2,4-Hexadiene	227 nm
2,4-Dimethyl-1,3-pentadiene	232 nm
2,5-Dimethyl-2,4-hexadiene	240 nm

What conclusion can you draw about the effect of alkyl substitution on UV absorption maxima? Approximately what effect does each added alkyl group have?

14.42 1,3,5-Hexatriene has λ_{max} = 258 nm. In light of your answer to Problem 14.41, approximately where would you expect 2,3-dimethyl-1,3,5-hexatriene to absorb?

14.43 β-Ocimene is a pleasant-smelling hydrocarbon found in the leaves of certain herbs. It has the molecular formula $C_{10}H_{16}$ and a UV absorption maximum at 232 nm. On hydrogenation with a palladium catalyst, 2,6-dimethyloctane is obtained. Ozonolysis of β-ocimene, followed by treatment with zinc and acetic acid, produces the following four fragments:
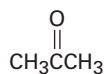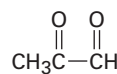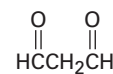

|			
CH_3CCH_3	HCH	CH_3C-CH	$HCCH_2CH$
Acetone	**Formaldehyde**	**Pyruvaldehyde**	**Malonaldehyde**

(a) How many double bonds does β-ocimene have?
(b) Is β-ocimene conjugated or nonconjugated?
(c) Propose a structure for β-ocimene.
(d) Write the reactions, showing starting material and products.

General Problems

14.44 Treatment of 3,4-dibromohexane with strong base leads to loss of 2 equivalents of HBr and formation of a product with formula C_6H_{10}. Three products are possible. Name each of the three, and tell how you would use ^{1}H and ^{13}C NMR spectroscopy to help identify them. How would you use UV spectroscopy?

14.45 Addition of HCl to 1-methoxycyclohexene yields 1-chloro-1-methoxycyclohexane as the sole product. Use resonance structures to explain why none of the other regioisomer is formed.
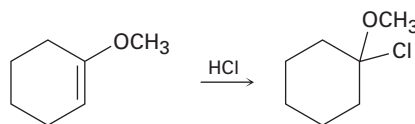
14.46 Aldrin, a chlorinated insecticide now banned for use in the United States, can be made by Diels–Alder reaction of hexachloro-1,3-cyclopentadiene with norbornadiene. What is the structure of aldrin?


Norbornadiene

14.47 Norbornadiene (Problem 14.46) can be prepared by reaction of chloro-ethylene with 1,3-cyclopentadiene, followed by treatment of the product with sodium ethoxide. Write the overall scheme, and identify the two kinds of reactions.

14.48 ▲ We've seen that the Diels–Alder cycloaddition reaction is a one-step, peri-cyclic process that occurs through a cyclic transition state. Propose a mecha-nism for the following reaction:
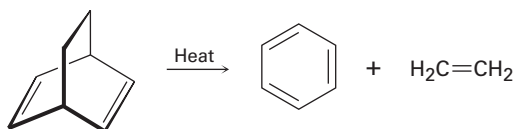
14.49 In light of your answer to Problem 14.48, propose a mechanism for the following reaction:

α-Pyrone
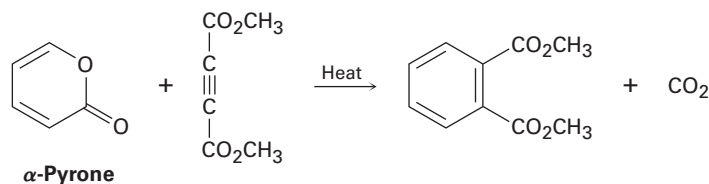
14.50 The triene shown here reacts with 2 equivalents of maleic anhydride to yield a product with the formula $C_{17}H_{16}O_6$. Predict a structure for the product.
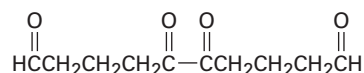

▲ Problems linked to Key Ideas in this chapter
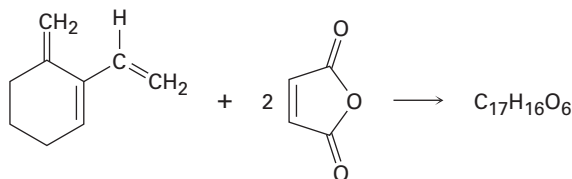
14.51 Myrcene, $C_{10}H_{16}$, is found in oil of bay leaves and is isomeric with β-ocimene (Problem 14.43). It has an ultraviolet absorption at 226 nm and can be catalytically hydrogenated to yield 2,6-dimethyloctane. On ozonolysis followed by zinc/acetic acid treatment, myrcene yields formaldehyde, acetone, and 2-oxopentanedial:
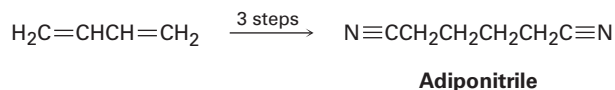
$$\underset{\text{HCCH}_2\text{CH}_2\text{C}-\text{CH}}{\overset{\text{O}\qquad\quad\text{O}\;\;\text{O}}{\| \qquad\quad \| \;\; \|}}\qquad \textbf{2-Oxopentanedial}$$

Propose a structure for myrcene, and write the reactions, showing starting material and products.

14.52 Hydrocarbon **A**, $C_{10}H_{14}$, has a UV absorption at $\lambda_{max} = 236$ nm and gives hydrocarbon **B**, $C_{10}H_{18}$, on catalytic hydrogenation. Ozonolysis of **A** followed by zinc/acetic acid treatment yields the following diketo dialdehyde:

$$\underset{\text{HCCH}_2\text{CH}_2\text{CH}_2\text{C}-\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}}{\overset{\text{O}\qquad\qquad\qquad\text{O}\;\;\text{O}\qquad\qquad\quad\text{O}}{\|\qquad\qquad\qquad\|\;\;\|\qquad\qquad\quad\|}}$$

(a) Propose two possible structures for **A**.
(b) Hydrocarbon **A** reacts with maleic anhydride to yield a Diels–Alder adduct. Which of your structures for **A** is correct?
(c) Write the reactions, showing starting material and products.

14.53 Adiponitrile, a starting material used in the manufacture of nylon, can be prepared in three steps from 1,3-butadiene. How would you carry out this synthesis?

$$\text{H}_2\text{C}=\text{CHCH}=\text{CH}_2 \quad \xrightarrow{\text{3 steps}} \quad \text{N}\equiv\text{CCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{C}\equiv\text{N}$$

Adiponitrile

14.54 Ergosterol, a precursor of vitamin D, has $\lambda_{max} = 282$ nm and molar absorptivity $\epsilon = 11{,}900$. What is the concentration of ergosterol in a solution whose absorbance $A = 0.065$ with a sample pathlength $l = 1.00$ cm?


Ergosterol $(C_{28}H_{44}O)$

▲ Problems linked to Key Ideas in this chapter
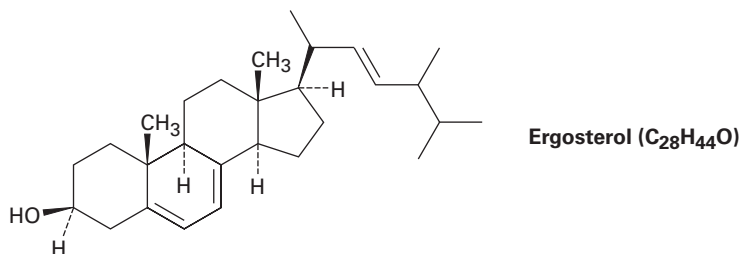
14.55 ▲ Dimethyl butynedioate undergoes a Diels–Alder reaction with (2*E*,4*E*)-hexadiene. Show the structure and stereochemistry of the product.

$$CH_3O\overset{\displaystyle O}{\overset{\displaystyle \|}{C}}-C\equiv C-\overset{\displaystyle O}{\overset{\displaystyle \|}{C}}OCH_3 \qquad \textbf{Dimethyl butynedioate}$$
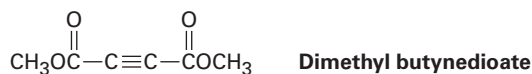
14.56 Dimethyl butynedioate also undergoes a Diels–Alder reaction with (2*E*,4*Z*)-hexadiene, but the stereochemistry of the product is different from that of the (2*E*,4*E*) isomer (Problem 14.55). Explain.

14.57 How would you carry out the following synthesis (more than one step is required)? What stereochemical relationship between the $-CO_2CH_3$ group attached to the cyclohexane ring and the $-CHO$ groups would your synthesis produce?
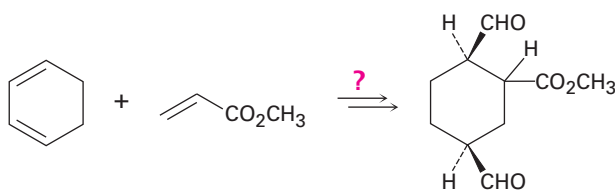
14.58 The double bond of an *enamine* (alk*ene* + *amine*) is much more nucleophilic than a typical alkene double bond. Assuming that the nitrogen atom in an enamine is *sp*^{2}-hybridized, draw an orbital picture of an enamine, and explain why the double bond is electron-rich.

An enamine
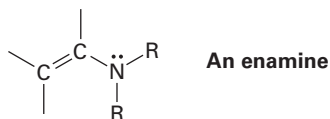
14.59 Benzene has an ultraviolet absorption at $\lambda_{max} = 204$ nm, and para-toluidine has $\lambda_{max} = 235$ nm. How do you account for this difference?

Benzene
($\lambda_{max} = 204$ nm)

p-Toluidine
($\lambda_{max} = 235$ nm)

▲ Problems linked to Key Ideas in this chapter
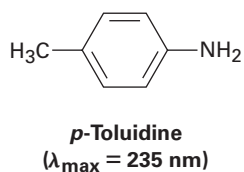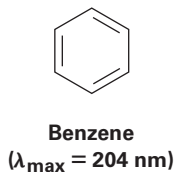
15

A fennel plant is an aromatic herb used in cooking. A phenyl group—pronounced exactly the same way—is the characteristic structural unit of "aromatic" organic compounds. Image copyright Lukiyanova Natalia/frenta, 2010. Used under license from Shutterstock.com

Benzene and Aromaticity

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

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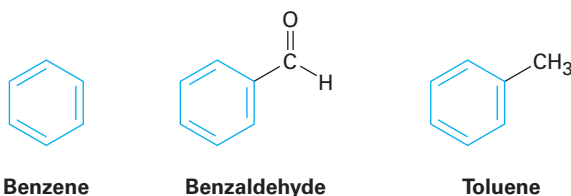
Today, the association of aromaticity with fragrance has long been lost, and we now use the word **aromatic** to refer to the class of compounds that contain six-membered benzene-like rings with three double bonds. Many naturally occurring compounds are aromatic in part, including steroids such as estrone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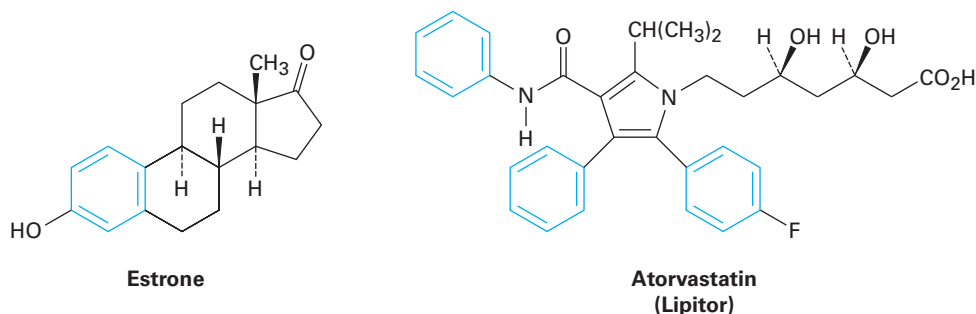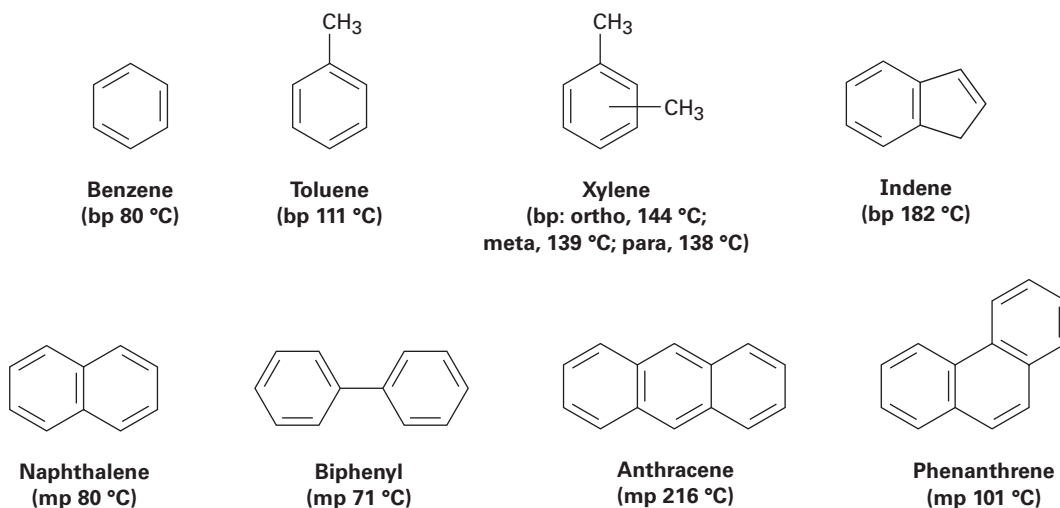

Estrone

Atorvastatin (Lipitor)

OWL Sign in to OWL for Organic Chemistry at **www.cengage.com/owl** to view tutorials and simulations, develop problem-solving skills, and complete online homework assigned by your professor.

534

Why This Chapter? The reactivity of substituted aromatic compounds, more than that of any other class of substances, is intimately tied to their exact structure. As a result, aromatic compounds provide an extraordinarily sensitive probe for studying the relationship between structure and reactivity. We'll examine that relationship in this and the next chapter, and we'll find that the lessons learned are applicable to all other organic compounds, including such particularly important substances as the nucleic acids that control our genetic makeup.

15.1 Sources and Names of Aromatic Compounds

Simple aromatic hydrocarbons come from two main sources: coal and petroleum. Coal is an enormously complex mixture made up primarily of large arrays of benzene-like rings joined together. Thermal breakdown of coal occurs when it is heated to 1000 °C in the absence of air, and a mixture of volatile products called *coal tar* boils off. Fractional distillation of coal tar yields benzene, toluene, xylene (dimethylbenzene), naphthalene, and a host of other aromatic compounds **(Figure 15.1)**.
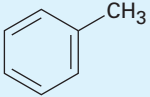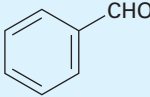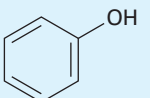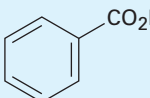

Benzene
(bp 80 °C)

Toluene
(bp 111 °C)

Xylene
**(bp: ortho, 144 °C;
meta, 139 °C; para, 138 °C)**

Indene
(bp 182 °C)

Naphthalene
(mp 80 °C)

Biphenyl
(mp 71 °C)
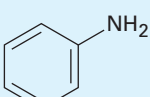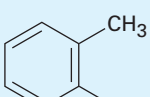
Anthracene
(mp 216 °C)
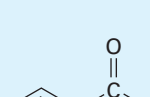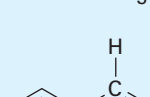
Phenanthrene
(mp 101 °C)

**Figure 15.1** Some aromatic hydrocarbons found in coal tar.

Unlike coal, petroleum contains few aromatic compounds and consists largely of alkanes (Chapter 3 *A Deeper Look*). During petroleum refining, however, aromatic molecules are formed when alkanes are passed over a catalyst at about 500 °C under high pressure.

Aromatic substances, more than any other class of organic compounds, have acquired a large number of nonsystematic names. IUPAC rules discourage the use of most such names but do allow for some of the more widely used ones to be retained (Table 15.1). Thus, methylbenzene is known commonly as *toluene;* hydroxybenzene, as *phenol;* aminobenzene, as *aniline;* and so on.
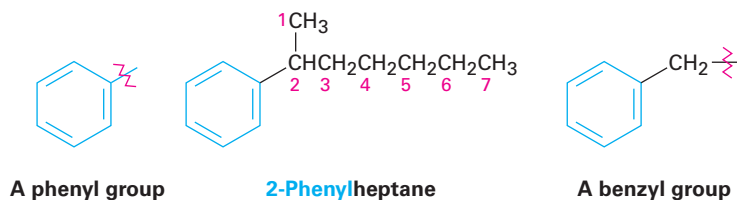
Table 15.1 Common Names of Some Aromatic Compounds

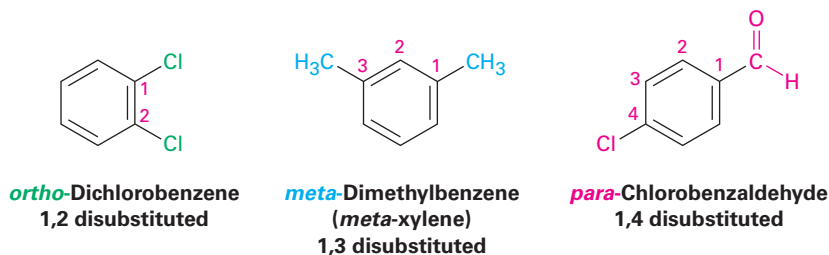| Structure	Name	Structure	Name
CH$_3$	Toluene (bp 111 °C)	CHO	Benzaldehyde (bp 178 °C)
OH	Phenol (mp 43 °C)	CO$_2$H	Benzoic acid (mp 122 °C)
NH$_2$	Aniline (bp 184 °C)	CH$_3$ CH$_3$	ortho-Xylene (bp 144 °C)
O C CH$_3$	Acetophenone (mp 21 °C)	H C C H H	Styrene (bp 145 °C)

Monosubstituted benzenes are named systematically in the same manner as other hydrocarbons, with -*benzene* as the parent name. Thus, C$_6$H$_5$Br is bromo-benzene, C$_6$H$_5$NO$_2$ is nitrobenzene, and C$_6$H$_5$CH$_2$CH$_2$CH$_3$ is propylbenzene.

**Bromo**benzene   **Nitro**benzene   **Propyl**benzene
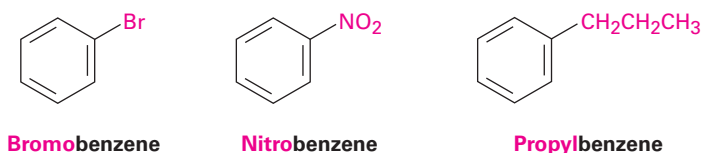
Alkyl-substituted benzenes are sometimes referred to as **arenes** and are named in different ways depending on the size of the alkyl group. If the alkyl substituent is smaller than the ring (six or fewer carbons), the arene is named as an alkyl-substituted benzene. If the alkyl substituent is larger than the ring (seven or more carbons), the compound is named as a phenyl-substituted alkane. The name **phenyl**, pronounced **fen**-nil and sometimes abbreviated as Ph or *Φ* (Greek *phi*), is used for the −C$_6$H$_5$ unit when the benzene ring is considered as a substituent. The word is derived from the Greek *pheno* ("I bear light"), commemorating the discovery of benzene by Michael Faraday in 1825 from the oily residue left by the illuminating gas used in London street lamps. In addition, the name **benzyl** is used for the C$_6$H$_5$CH$_2$− group.

^{1}CH$_3$
CHCH$_2$CH$_2$CH$_2$CH$_2$CH$_3$
2   3   4   5   6   7

CH$_2$

A phenyl group   **2-Phenyl**heptane   **A benzyl group**

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

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

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

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

The ortho, meta, para system of nomenclature is also useful when discussing reactions. For example, we might describe the reaction of bromine with toluene by saying, "Reaction occurs at the para position"—in other words, at the position para to the methyl group already present on the ring.

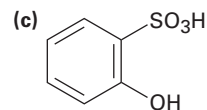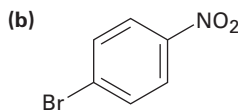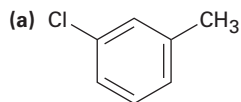**Toluene**   ***p*-Bromotoluene**
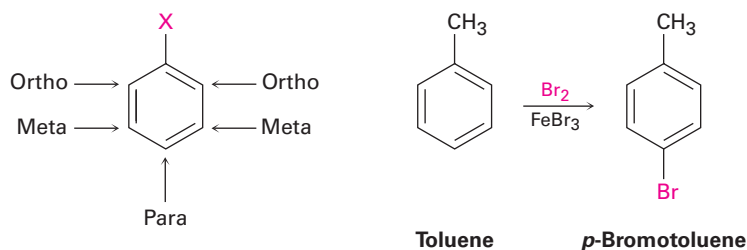
As with cycloalkanes **(Section 4.1)**, benzenes with more than two substituents are named by choosing a point of attachment as carbon 1 and numbering the substituents on the ring so that the second substituent has as low a number as possible. If ambiguity still exists, number so that the third or fourth substituent has as low a number as possible, until a point of difference is found. The substituents are listed alphabetically when writing the name.
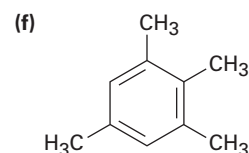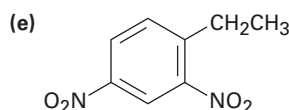

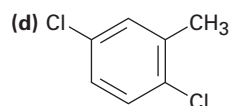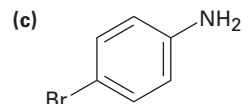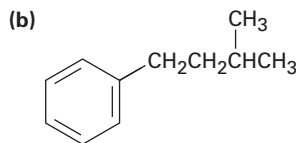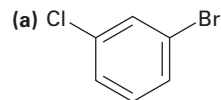**4-Bromo-1,2-dimethylbenzene**   **2,5-Dimethylphenol**   **2,4,6-Trinitrotoluene (TNT)**
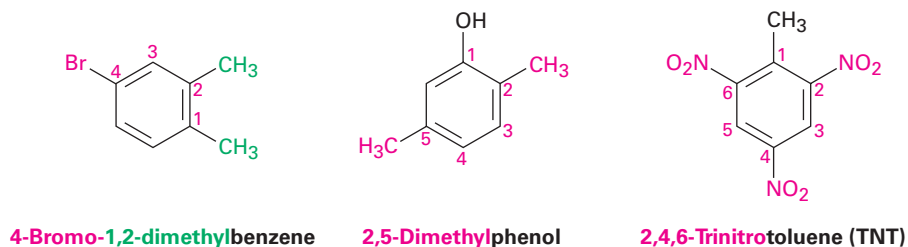
Note in the second and third examples shown that *-phenol* and *-toluene* are used as the parent names rather than *-benzene*. Any of the monosubstituted aromatic compounds shown in Table 15.1 can serve as a parent name, with the principal substituent ($-OH$ in phenol or $-CH_3$ in toluene) attached to C1 on the ring.

Problem 15.1
Tell whether the following compounds are ortho-, meta-, or para-disubstituted:

(a) Cl, CH₃

(b) NO₂, Br

(c) SO₃H, OH

Problem 15.2
Give IUPAC names for the following compounds:

(a) Cl, Br

(b) CH₃, CH₂CH₂CHCH₃

(c) NH₂, Br

(d) Cl, CH₃, Cl

(e) CH₂CH₃, O₂N, NO₂

(f) CH₃, CH₃, H₃C, CH₃

Problem 15.3
Draw structures corresponding to the following IUPAC names:
(a) *p*-Bromochlorobenzene   **(b)** *p*-Bromotoluene
(c) *m*-Chloroaniline   **(d)** 1-Chloro-3,5-dimethylbenzene

15.2 Structure and Stability of Benzene

Benzene (C_6H_6) has six fewer hydrogens than the corresponding six-carbon cycloalkane (C_6H_{12}) and is clearly unsaturated, usually being represented as a six-membered ring with alternating double and single bonds. Yet it has been known since the mid-1800s that benzene is much less reactive than typical alkenes and fails to undergo typical alkene addition reactions. Cyclohexene, for instance, reacts rapidly with Br_2 and gives the addition product 1,2-dibromocyclohexane, but benzene reacts only slowly with Br_2 and gives the *substitution* product C_6H_5Br.

Benzene $+$ Br_2 $\xrightarrow[\text{catalyst}]{\text{Fe}}$ Bromobenzene (substitution product) $+$ HBr   [(Addition product) ***not* formed**]
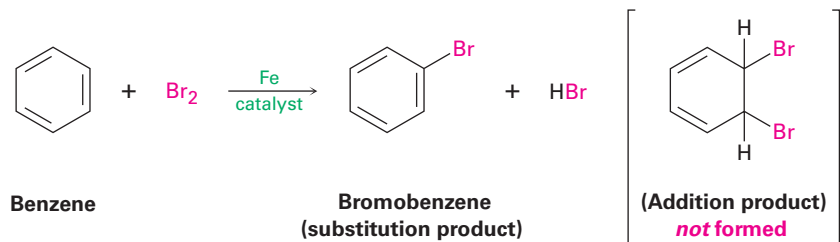
We can get a quantitative idea of benzene's stability by measuring heats of hydrogenation **(Section 7.6)**. Cyclohexene, an isolated alkene, has $\Delta H°_{\text{hydrog}} = -118$ kJ/mol (-28.2 kcal/mol), and 1,3-cyclohexadiene, a conjugated diene, has $\Delta H°_{\text{hydrog}} = -230$ kJ/mol (-55.0 kcal/mol). As noted in **Section 14.1**, this value for 1,3-cyclohexadiene is a bit less than twice that for cyclohexene because conjugated dienes are more stable than isolated dienes.

Carrying the process one step further, we might expect $\Delta H°_{\text{hydrog}}$ for "cyclohexatriene" (benzene) to be a bit less than -356 kJ/mol, or three times the

cyclohexene value. The actual value, however, is -206 kJ/mol, some 150 kJ/mol (36 kcal/mol) less than expected. Since 150 kJ/mol less heat than expected is released during hydrogenation of benzene, benzene must have 150 kJ/mol less energy to begin with. In other words, benzene is more stable than expected by 150 kJ/mol **(Figure 15.2)**.
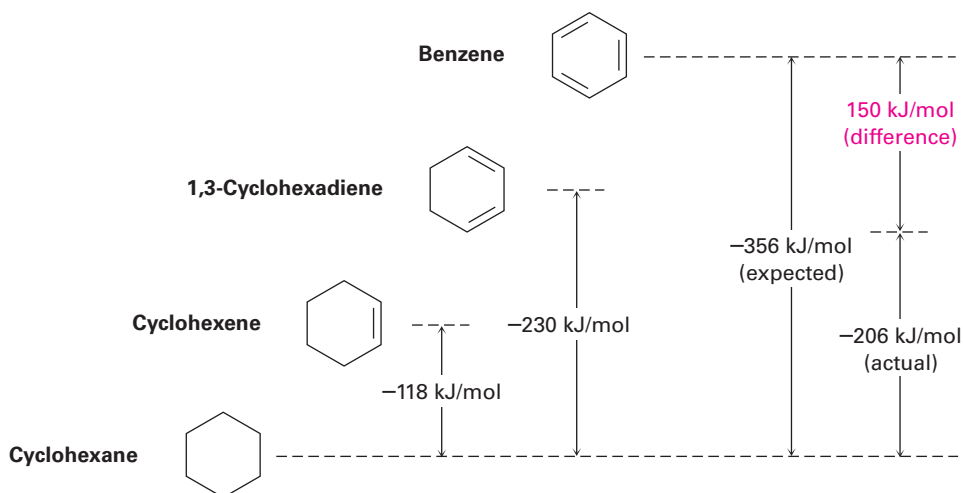

Figure 15.2 A comparison of the heats of hydrogenation for cyclohexene, 1,3-cyclohexadiene, and benzene. Benzene is 150 kJ/mol (36 kcal/mol) more stable than might be expected for "cyclohexatriene."

Further evidence for the unusual nature of benzene is that all its carbon–carbon bonds have the same length—139 pm—intermediate between typical single (154 pm) and double (134 pm) bonds. In addition, an electrostatic potential map shows that the electron density in all six C–C bonds is identical. Thus, benzene is a planar molecule with the shape of a regular hexagon. All C–C–C bond angles are 120°, all six carbon atoms are sp^2-hybridized, and each carbon has a p orbital perpendicular to the plane of the six-membered ring.
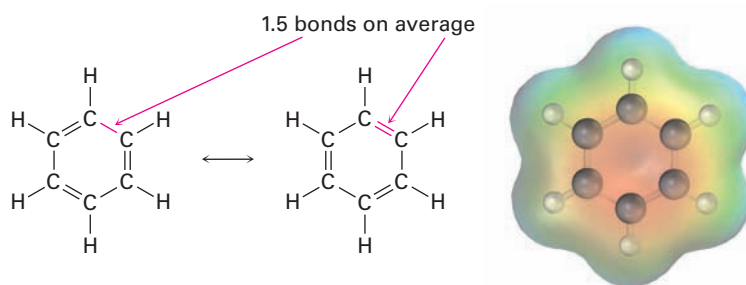
Because all six carbon atoms and all six p orbitals in benzene are equivalent, it's impossible to define three localized π bonds in which a given p orbital overlaps only one neighboring p orbital. Rather, each p orbital overlaps equally well with both neighboring p orbitals, leading to a picture of benzene in which all six π electrons are free to move about the entire ring **(Figure 15.3b)**. In resonance terms **(Sections 2.4 and 2.5)**, benzene is a hybrid of two equivalent forms. Neither form is correct by itself; the true structure of benzene is somewhere in between the two resonance forms but is impossible to draw with our usual conventions. Because of this resonance, benzene is more stable and less reactive than a typical alkene.

(a)

(b)
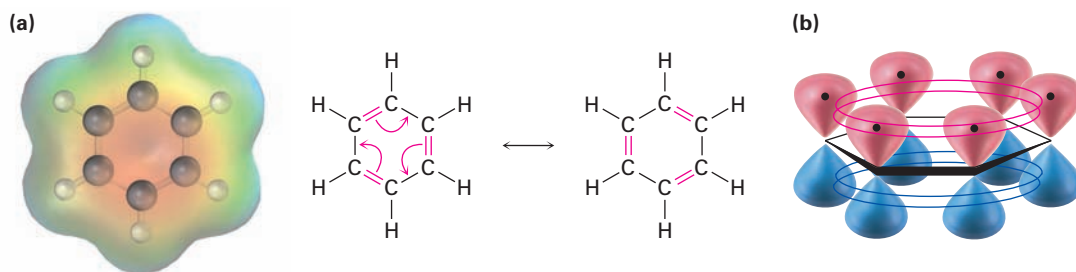
Figure 15.3 **(a)** An electrostatic potential map of benzene and **(b)** an orbital picture. Each of the six carbon atoms has a *p* orbital that can overlap equally well with neighboring *p* orbitals on both sides. As a result, all C—C bonds are equivalent and benzene must be represented as a hybrid of two resonance forms.

Chemists sometimes represent the two benzene resonance forms by using a circle to indicate the equivalence of the carbon–carbon bonds. This kind of representation has to be used carefully, however, because it doesn't indicate the number of π electrons in the ring. (How many electrons does a circle represent?) In this book, benzene and other aromatic compounds will be represented by a single line-bond structure. We'll be able to keep count of π electrons this way but must be aware of the limitations of the drawings.

Alternative representations of benzene. The "circle" representation must be used carefully since it doesn't indicate the number of π electrons in the ring.

Having just seen a resonance description of benzene, let's now look at the alternative molecular orbital description. We can construct π molecular orbitals for benzene just as we did for 1,3-butadiene in **Section 14.1**. If six *p* atomic orbitals combine in a cyclic manner, six benzene molecular orbitals result, as shown in **Figure 15.4**. The three low-energy molecular orbitals, denoted ψ_1, ψ_2, and ψ_3, are bonding combinations, and the three high-energy orbitals are antibonding.

Figure 15.4 The six benzene π molecular orbitals. The bonding orbitals ψ_2 and ψ_3 have the same energy and are said to be degenerate, as are the antibonding orbitals $\psi_4{}^*$ and $\psi_5{}^*$. The orbitals ψ_3 and $\psi_4{}^*$ have no π electron density on two carbons because of a node passing through these atoms.

Energy

Six *p* atomic orbitals

$\psi_6{}^*$

$\psi_4{}^*$ $\psi_5{}^*$

ψ_2 ψ_3

ψ_1

Antibonding

Nonbonding

Bonding

Six benzene molecular orbitals
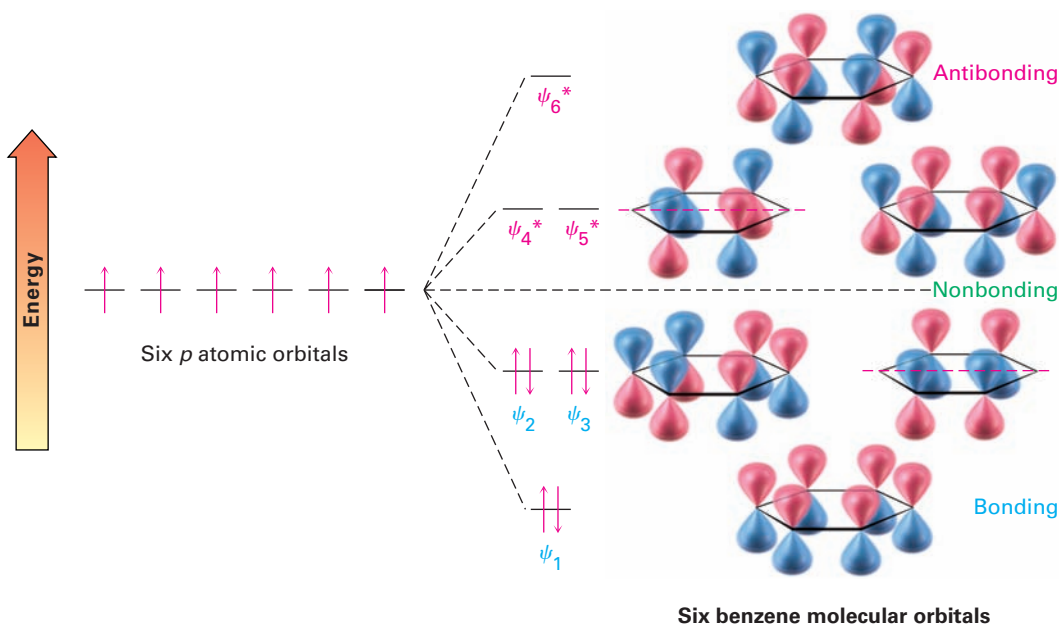
Note that the two bonding orbitals ψ_2 and ψ_3 have the same energy, as do the two antibonding orbitals $\psi_4{}^*$ and $\psi_5{}^*$. Such orbitals with the same energy are said to be *degenerate*. Note also that the two orbitals ψ_3 and $\psi_4{}^*$ have nodes passing through ring carbon atoms, thereby leaving no π electron density on these carbons. The six p electrons of benzene occupy the three bonding molecular orbitals and are delocalized over the entire conjugated system, leading to the observed 150 kJ/mol stabilization of benzene.

Problem 15.4

Pyridine is a flat, hexagonal molecule with bond angles of 120°. It undergoes substitution rather than addition and generally behaves like benzene. Draw a picture of the π orbitals of pyridine to explain its properties. Check your answer by looking ahead to **Section 15.5**.

Pyridine
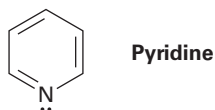

15.3 Aromaticity and the Hückel 4*n* + 2 Rule

Let's list what we've said thus far about benzene and, by extension, about other benzene-like aromatic molecules.

- Benzene is cyclic and conjugated.

- Benzene is unusually stable, having a heat of hydrogenation 150 kJ/mol less negative than we might expect for a conjugated cyclic triene.

- Benzene is planar and has the shape of a regular hexagon. All bond angles are 120°, all carbon atoms are sp^2-hybridized, and all carbon–carbon bond lengths are 139 pm.

- Benzene undergoes substitution reactions that retain the cyclic conjugation rather than electrophilic addition reactions that would destroy the conjugation.

- Benzene can be described as a resonance hybrid whose structure is intermediate between two line-bond structures.

This list would seem to be a good description of benzene and other aromatic molecules, but it isn't enough. Something else, called the **Hückel 4*n* + 2 rule**, is needed to complete a description of aromaticity. According to a theory devised in 1931 by the German physicist Erich Hückel, a molecule is aromatic only if it has a planar, monocyclic system of conjugation and contains a total of $4n + 2$ π *electrons*, where n is an integer ($n = 0, 1, 2, 3, \ldots$). In other words, only molecules with 2, 6, 10, 14, 18, . . . π electrons can be aromatic. Molecules with $4n$ π electrons (4, 8, 12, 16, . . .) can't be aromatic, even though they may be cyclic, planar, and apparently conjugated. In fact, planar, conjugated molecules with $4n$ π electrons are said to be **antiaromatic** because delocalization of their π electrons would lead to their destabilization.

Let's look at several examples to see how the Hückel $4n + 2$ rule works.

- **Cyclobutadiene** has four π electrons and is antiaromatic. The π electrons are localized in two double bonds rather than delocalized around the ring, as indicated by an electrostatic potential map.

**Cyclobutadiene**

Two double bonds;
four π electrons
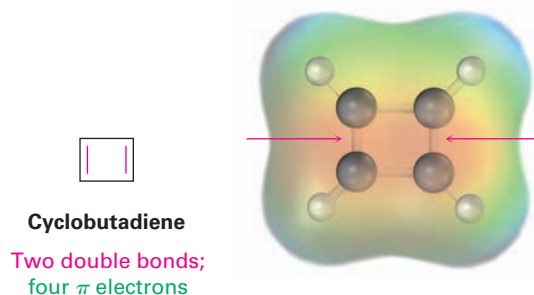
Cyclobutadiene is highly reactive and shows none of the properties associated with aromaticity. In fact, it was not even prepared until 1965, when Rowland Pettit of the University of Texas was able to make it at low temperature. Even at $-78\ ^\circ$C, however, cyclobutadiene is so reactive that it dimerizes by a Diels–Alder reaction. One molecule behaves as a diene and the other as a dienophile.
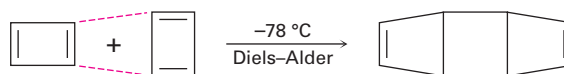
- **Benzene** has six π electrons ($4n + 2 = 6$ when $n = 1$) and is aromatic.

Benzene

Three double bonds;
six π electrons
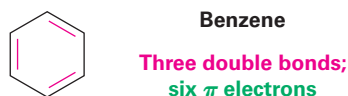
- **Cyclooctatetraene** has eight π electrons and is not aromatic. The π electrons are localized into four double bonds rather than delocalized around the ring, and the molecule is tub-shaped rather than planar.

Cyclooctatetraene

Four double bonds;
eight π electrons
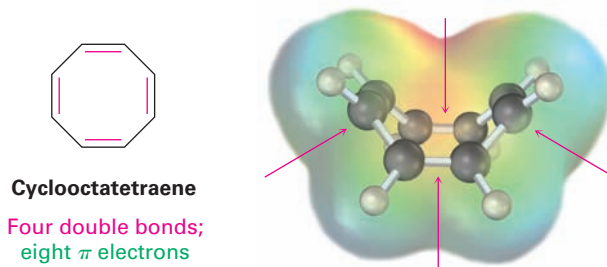
Chemists in the early 1900s believed that the only requirement for aromaticity was the presence of a cyclic conjugated system. It was therefore expected that cyclooctatetraene, as a close analog of benzene, would also prove to be unusually stable. The facts, however, proved otherwise. When cyclooctatetraene was first prepared in 1911 by the German chemist Richard Willstätter, it was found not to be particularly stable but to resemble an open-chain polyene in its reactivity.

In fact, cyclooctatetraene is not even conjugated because neighboring *p* orbitals don't have the necessary parallel alignment for overlap. The π electrons are localized in four discrete C=C bonds rather than delocalized around the ring. X-ray studies show that the C−C single bonds are 147 pm long and the double bonds are 134 pm long. In addition, the ^{1}H NMR spectrum shows a single sharp resonance line at 5.7 δ, a value characteristic of an alkene rather than an aromatic molecule.

What's so special about 4*n* + 2 π electrons? Why do 2, 6, 10, 14 . . . π electrons lead to aromatic stability, while other numbers of electrons do not? The answer comes from molecular orbital theory. When the energy levels of molecular orbitals for cyclic conjugated molecules are calculated, it turns out that there is always a single lowest-lying MO, above which the MOs come in degenerate pairs. Thus, when electrons fill the various molecular orbitals, it takes two electrons, or one pair, to fill the lowest-lying orbital and four electrons, or two pairs, to fill each of *n* succeeding energy levels—a total of 4*n* + 2. Any other number would leave an energy level partially filled.

The six π molecular orbitals of benzene were shown previously in Figure 15.4, and their relative energies are shown again in **Figure 15.5**. The lowest-energy MO, ψ_1, occurs singly and contains two electrons. The next two lowest-energy orbitals, ψ_2 and ψ_3, are degenerate, and it therefore takes four electrons to fill both. The result is a stable six-π-electron aromatic molecule with filled bonding orbitals.
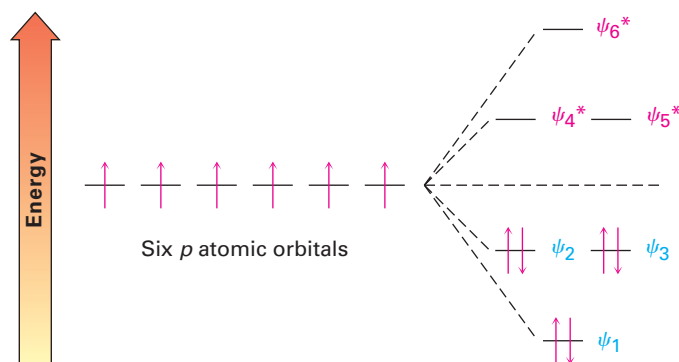
Figure 15.5 Energy levels of the six benzene π molecular orbitals. There is a single, lowest-energy orbital, above which the orbitals come in degenerate pairs.

Problem 15.5

To be aromatic, a molecule must have 4*n* + 2 π electrons and must have cyclic conjugation. 1,3,5,7,9-Cyclodecapentaene fulfills one of these criteria but not the other and has resisted all attempts at synthesis. Explain.
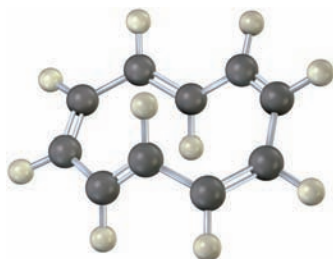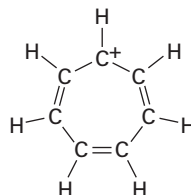
15.4 Aromatic Ions

According to the Hückel criteria for aromaticity, a molecule must be cyclic, conjugated (nearly planar with a p orbital on each atom), and have $4n + 2$ π electrons. Nothing in this definition says that the number of π electrons must be the same as the number of atoms in the ring or that the substance must be neutral. In fact, the numbers can be different and the substance can be an ion. Thus, both the cyclopentadienyl anion and the cycloheptatrienyl cation are aromatic even though both are ions and neither contains a six-membered ring.
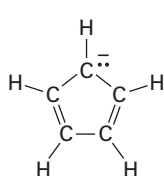
Cyclopentadienyl anion   Cycloheptatrienyl cation

Six π electrons; aromatic ions

To see why the cyclopentadienyl anion and the cycloheptatrienyl cation are aromatic, imagine starting from the related neutral hydrocarbons, 1,3-cyclopentadiene and 1,3,5-cycloheptatriene, and removing one hydrogen from the saturated CH_2 carbon in each. If that carbon then rehybridizes from sp^3 to sp^2, the resultant products would be fully conjugated, with a p orbital on every carbon. There are three ways in which the hydrogen might be removed.

- The hydrogen can be removed with *both* electrons (H:$^-$) from the C—H bond, leaving a carbocation as product.

- The hydrogen can be removed with *one* electron (H·) from the C—H bond, leaving a carbon radical as product.

- The hydrogen can be removed with *no* electrons (H$^+$) from the C—H bond, leaving a carbanion as product.

All the potential products formed by removing a hydrogen from 1,3-cyclopentadiene and from 1,3,5-cycloheptatriene can be drawn with numerous resonance structures, but Hückel's rule predicts that only the six-π-electron cyclopentadienyl anion and cycloheptatrienyl cation should be aromatic. The other products are predicted by the $4n + 2$ rule to be unstable and antiaromatic **(Figure 15.6)**.

In practice, both the four-π-electron cyclopentadienyl cation and the five-π-electron cyclopentadienyl radical are highly reactive and difficult to prepare. Neither shows any sign of the stability expected for an aromatic system. The six-π-electron cyclopentadienyl anion, by contrast, is easily prepared and remarkably stable **(Figure 15.7a)**. In fact, the anion is so stable and easily formed that 1,3-cyclopentadiene is one of the most acidic hydrocarbons known, with $pK_a = 16$, a value comparable to that of water!

In the same way, the seven-π-electron cycloheptatrienyl radical and eight-π-electron anion are reactive and difficult to prepare, while the six-π-electron cycloheptatrienyl cation is extraordinarily stable **(Figure 15.7b)**. In fact, the cycloheptatrienyl cation was first prepared more than a century ago by reaction of 1,3,5-cycloheptatriene with Br_2, although its structure was not recognized at the time.
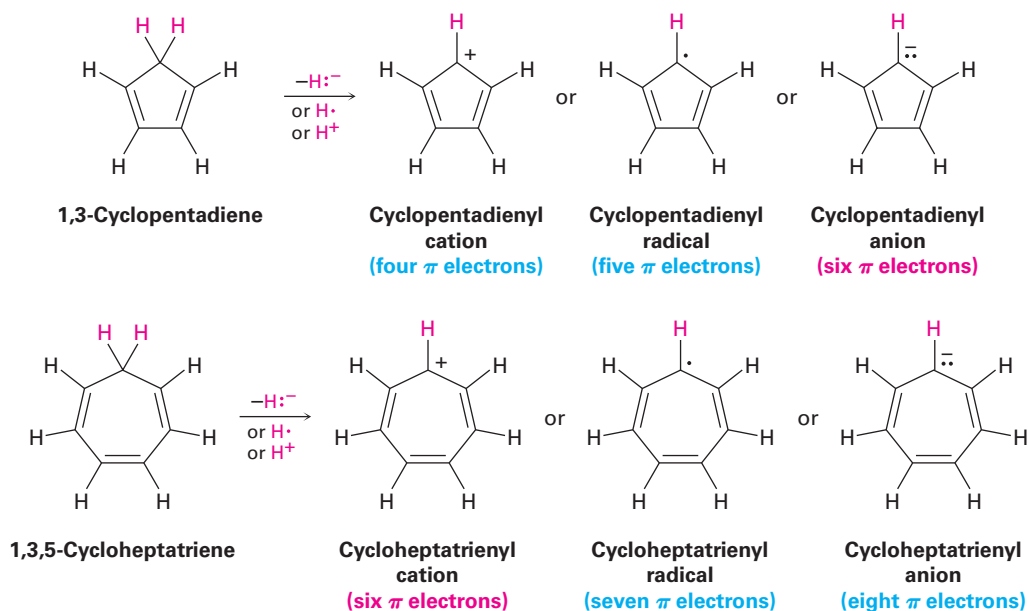
Figure 15.6 The aromatic six-π-electron cyclopentadienyl anion can be formed by removing a hydrogen ion (H$^+$) from the CH$_2$ group of 1,3-cyclopentadiene. Similarly, the aromatic six-π-electron cycloheptatrienyl cation can be generated by removing a hydride ion (H:$^-$) from the CH$_2$ group of 1,3-cycloheptatriene.
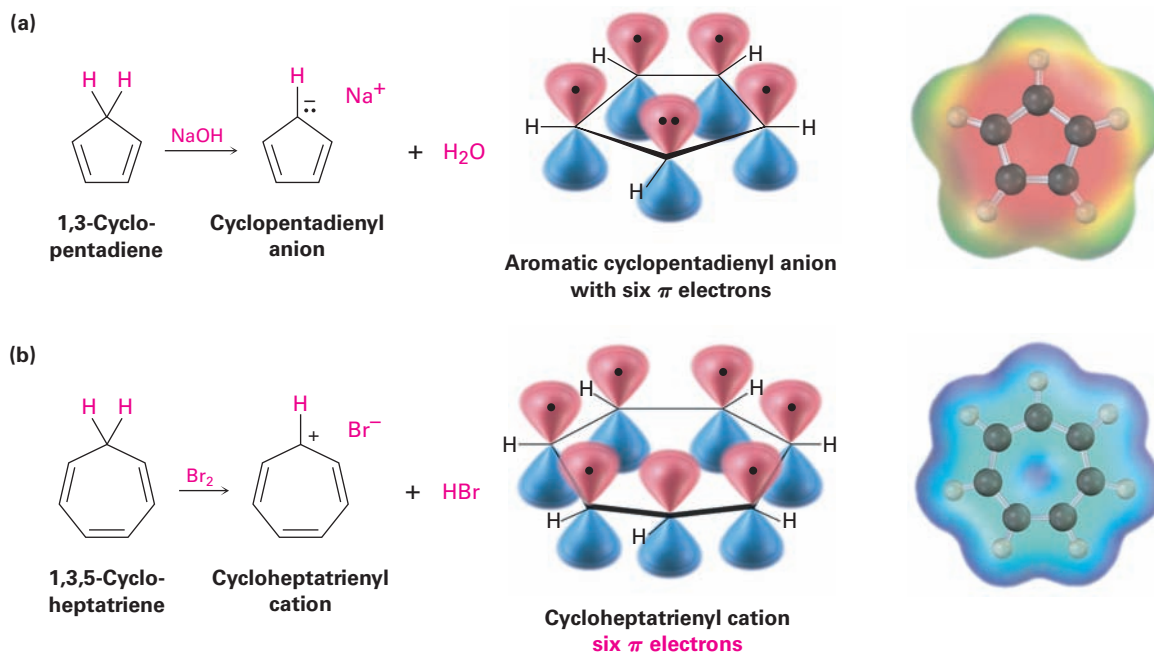
**Figure 15.7** **(a)** The aromatic cyclopentadienyl anion, showing the cyclic conjugation and six π electrons in five *p* orbitals, and **(b)** the aromatic cycloheptatrienyl cation, showing the cyclic conjugation and six π electrons in seven *p* orbitals. Electrostatic potential maps indicate that both ions are symmetrical, with the charge equally shared among all atoms in each ring.

Problem 15.6

Draw the five resonance structures of the cyclopentadienyl anion. Are all carbon–carbon bonds equivalent? How many absorption lines would you expect to see in the ^{1}H NMR and ^{13}C NMR spectra of the anion?

Problem 15.7

Cyclooctatetraene readily reacts with potassium metal to form the stable cyclooctatetraene dianion, $C_8H_8^{2-}$. Why do you suppose this reaction occurs so easily? What geometry do you expect for the cyclooctatetraene dianion?
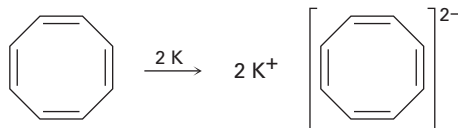
Problem 15.8

The relative energy levels of the five π molecular orbitals of the cyclopentadienyl system are similar to those in benzene. That is, there is a single lowest-energy MO, above which the orbitals come in degenerate pairs. Draw a diagram like that in Figure 15.5, and tell which of the five orbitals are occupied in the cation, radical, and anion.

## 15.5 Aromatic Heterocycles: Pyridine and Pyrrole

Look back once again at the definition of aromaticity in **Section 15.3**: . . . a cyclic, conjugated molecule containing $4n + 2$ π electrons. Nothing in this definition says that the atoms in the ring must be *carbon*. In fact, *heterocyclic* compounds can also be aromatic. A **heterocycle** is a cyclic compound that contains atoms of two or more elements in its ring, usually carbon along with nitrogen, oxygen, or sulfur. Pyridine and pyrimidine, for example, are six-membered heterocycles with nitrogen in their rings **(Figure 15.8)**.
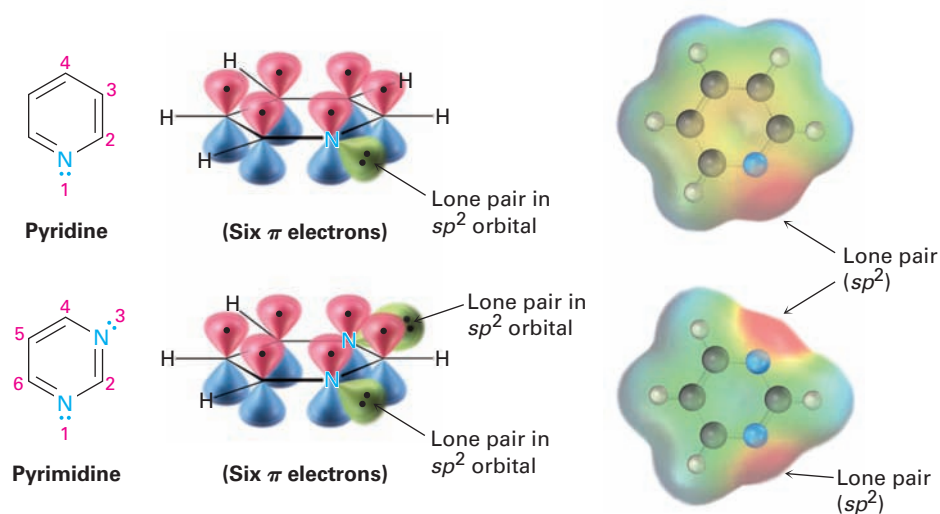
Figure 15.8 Pyridine and pyrimidine are nitrogen-containing aromatic heterocycles with π electron arrangements like that of benzene. Both have a lone pair of electrons on nitrogen in an sp^2 orbital in the plane of the ring.

Pyridine is much like benzene in its π electron structure. Each of the five sp^2-hybridized carbons has a p orbital perpendicular to the plane of the ring, and each p orbital contains one π electron. The nitrogen atom is also sp^2-hybridized and has one electron in a p orbital, bringing the total to six π electrons. The nitrogen lone-pair electrons (red in an electrostatic potential map) are in an sp^2 orbital in the plane of the ring and are not part of the aromatic π system. Pyrimidine, also shown in Figure 15.8, is a benzene analog that has two nitrogen atoms in a six-membered, unsaturated ring. Both nitrogens are sp^2-hybridized, and each contributes one electron to the aromatic π system.

Pyrrole (spelled with two r's and one l) and imidazole are *five*-membered heterocycles, yet both have *six* π electrons and are aromatic. In pyrrole, each of the four sp^2-hybridized carbons contributes one π electron and the sp^2-hybridized nitrogen atom contributes the two from its lone pair, which occupies a p orbital **(Figure 15.9)**. Imidazole, also shown in Figure 15.9, is an analog of pyrrole that has two nitrogen atoms in a five-membered, unsaturated ring. Both nitrogens are sp^2-hybridized, but one is in a double bond and contributes only one electron to the aromatic π system while the other is not in a double bond and contributes two from its lone pair.
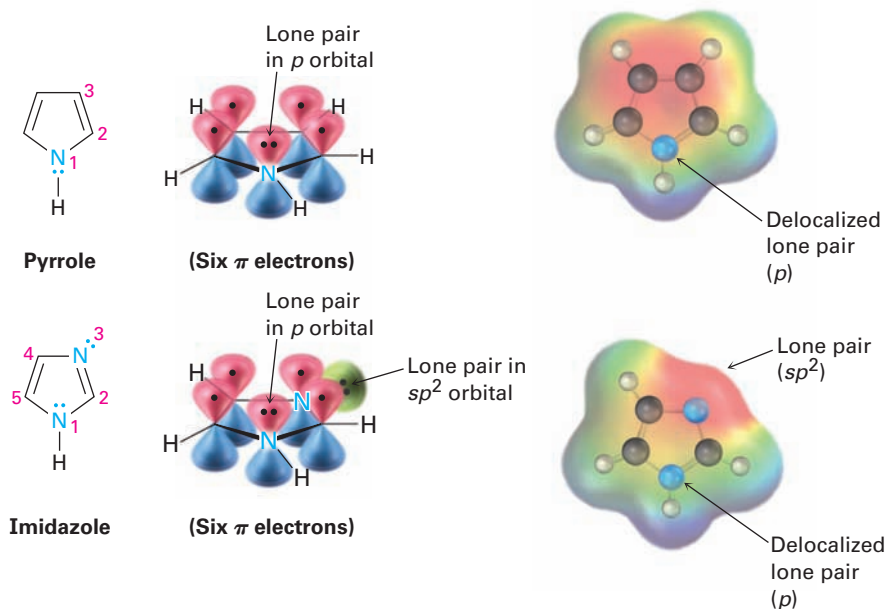

Figure 15.9 Pyrrole and imidazole are five-membered, nitrogen-containing heterocycles but have six π electron arrangements like that of the cyclopentadienyl anion. Both have a lone pair of electrons on nitrogen in a p orbital perpendicular to the ring.

Note that nitrogen atoms have different roles depending on the structure of the molecule. The nitrogen atoms in pyridine and pyrimidine are both in double bonds and contribute only one π electron to the aromatic sextet, just as a carbon atom in benzene does. The nitrogen atom in pyrrole, however, is not in a double bond and contributes two π electrons (its lone pair) to the aromatic sextet. In imidazole, both kinds of nitrogen are present in the same molecule—a double-bonded "pyridine-like" nitrogen that contributes one π electron and a "pyrrole-like" nitrogen that contributes two.

Pyrimidine and imidazole rings are particularly important in biological chemistry. Pyrimidine, for instance, is the parent ring system in cytosine, thymine, and uracil, three of the five heterocyclic amine bases found in nucleic acids. An aromatic imidazole ring is present in histidine, one of the twenty amino acids found in proteins.

Cytosine (in DNA and RNA)   **Thymine** (in DNA)   **Uracil** (in RNA)   **Histidine** (an amino acid)
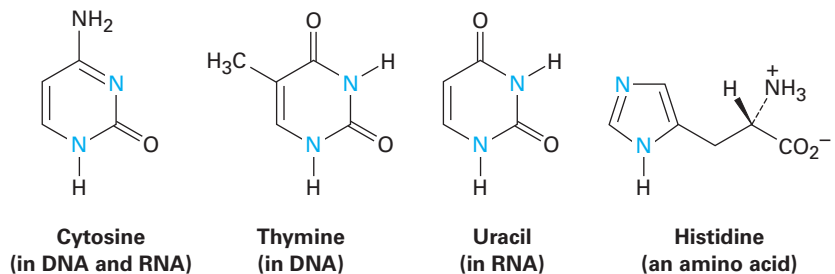
Worked Example 15.1 — Accounting for the Aromaticity of a Heterocycle

Thiophene, a sulfur-containing heterocycle, undergoes typical aromatic substitution reactions rather than addition reactions. Why is thiophene aromatic?

Thiophene

Strategy

Recall the requirements for aromaticity—a planar, cyclic, conjugated molecule with $4n + 2$ π electrons—and see how these requirements apply to thiophene.

Solution

Thiophene is the sulfur analog of pyrrole. The sulfur atom is sp^2-hybridized and has a lone pair of electrons in a p orbital perpendicular to the plane of the ring. Sulfur also has a second lone pair of electrons in the ring plane.
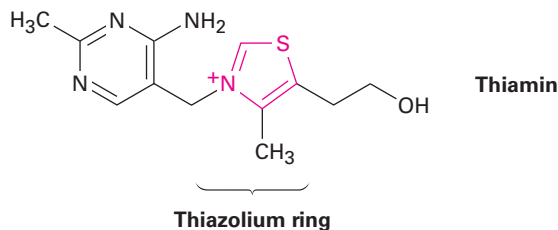

sp^2-hybridized

Thiophene
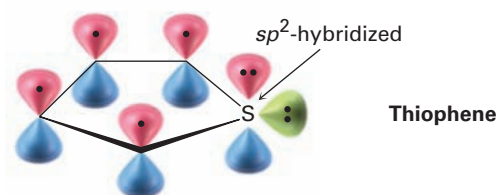
Problem 15.9

Draw an orbital picture of furan to show how the molecule is aromatic.


Furan
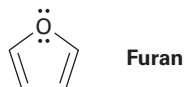
Problem 15.10

Thiamin, or vitamin B_1, contains a positively charged five-membered nitrogen–sulfur heterocycle called a *thiazolium* ring. Explain why the thiazolium ring is aromatic.


Thiamin

Thiazolium ring

# 15.6 Polycyclic Aromatic Compounds

The Hückel rule is strictly applicable only to monocyclic compounds, but the general concept of aromaticity can be extended to include *polycyclic* aromatic compounds. Naphthalene, with two benzene-like rings fused together; anthracene, with three rings; benzo[a]pyrene, with five rings; and coronene, with six rings, are all well-known aromatic hydrocarbons. Benzo[a]pyrene is particularly interesting because it is one of the cancer-causing substances found in tobacco smoke.

Naphthalene   **Anthracene**   **Benzo[a]pyrene**   **Coronene**
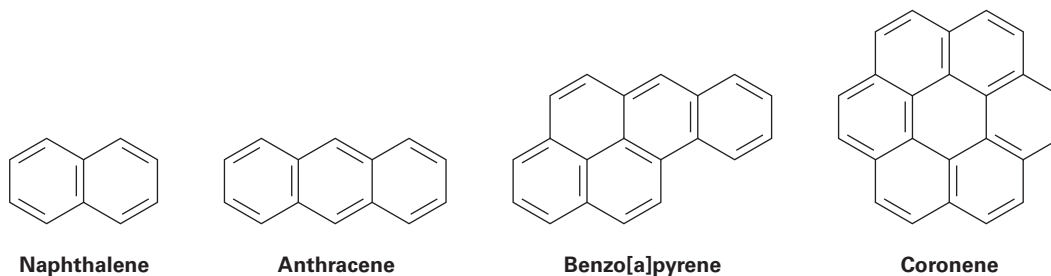
All polycyclic aromatic hydrocarbons can be represented by a number of different resonance forms. Naphthalene, for instance, has three.
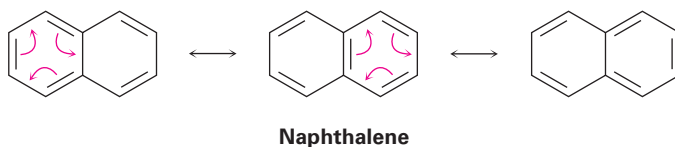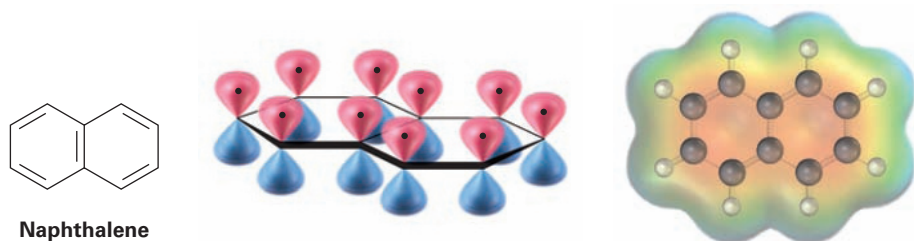

Naphthalene

Naphthalene and other polycyclic aromatic hydrocarbons show many of the chemical properties associated with aromaticity. Thus, measurement of its heat of hydrogenation shows an aromatic stabilization energy of approximately 250 kJ/mol (60 kcal/mol). Furthermore, naphthalene reacts slowly with electrophiles such as Br_2 to give substitution products rather than double-bond addition products.

**Naphthalene**   **1-Bromonaphthalene (75%)**
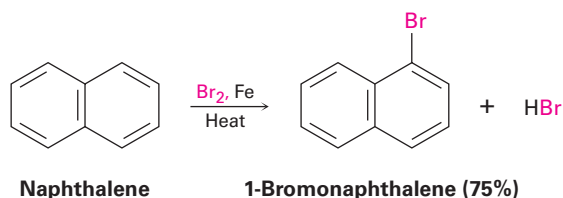
The aromaticity of naphthalene is explained by the orbital picture in **Figure 15.10**. Naphthalene has a cyclic, conjugated π electron system, with p orbital overlap both around the ten-carbon periphery of the molecule and across the central bond. Since ten π electrons is a Hückel number, there is π electron delocalization and consequent aromaticity in naphthalene.

Figure 15.10 An orbital picture and electrostatic potential map of naphthalene, showing that the ten π electrons are fully delocalized throughout both rings.

Naphthalene

Just as there are heterocyclic analogs of benzene, there are also many heterocyclic analogs of naphthalene. Among the most common are quinoline, isoquinoline, indole, and purine. Quinoline, isoquinoline, and purine all contain pyridine-like nitrogens that are part of a double bond and contribute one electron to the aromatic π system. Indole and purine both contain pyrrole-like nitrogens that contribute two π electrons.

Quinoline   **Isoquinoline**   **Indole**   **Purine**
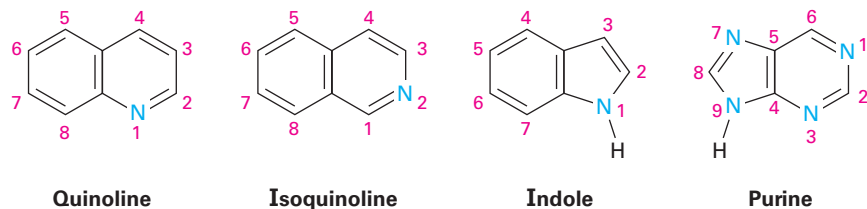
Among the many biological molecules that contain polycyclic aromatic rings, the amino acid tryptophan contains an indole ring and the antimalarial drug quinine contains a quinoline ring. Adenine and guanine, two of the five heterocyclic amine bases found in nucleic acids, have rings based on purine.

Tryptophan
(an amino acid)

Adenine
(in DNA and RNA)

Guanine
(in DNA and RNA)

Quinine
(an antimalarial agent)
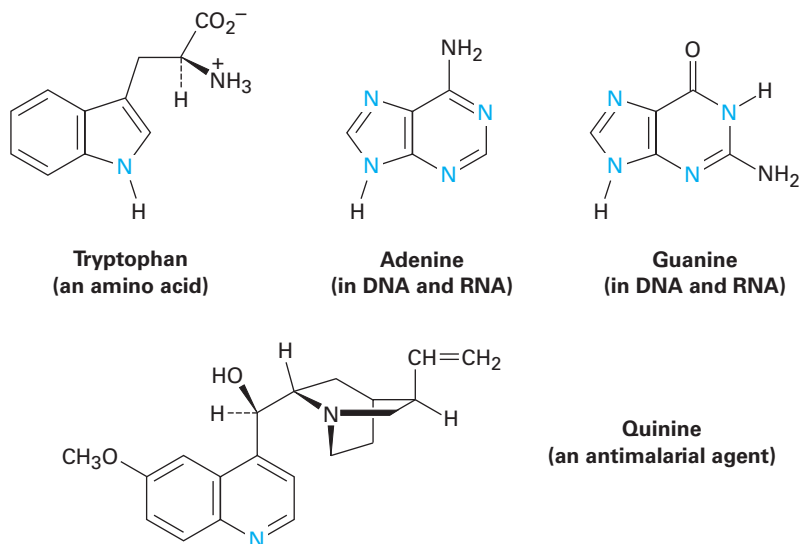
Problem 15.11

Azulene, a beautiful blue hydrocarbon, is an isomer of naphthalene. Is azulene aromatic? Draw a second resonance form of azulene in addition to that shown.

Azulene
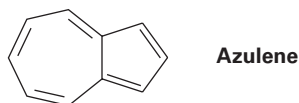
Problem 15.12

How many electrons does each of the four nitrogen atoms in purine contribute to the aromatic π system?

Purine
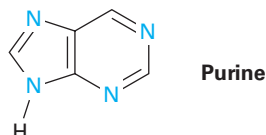
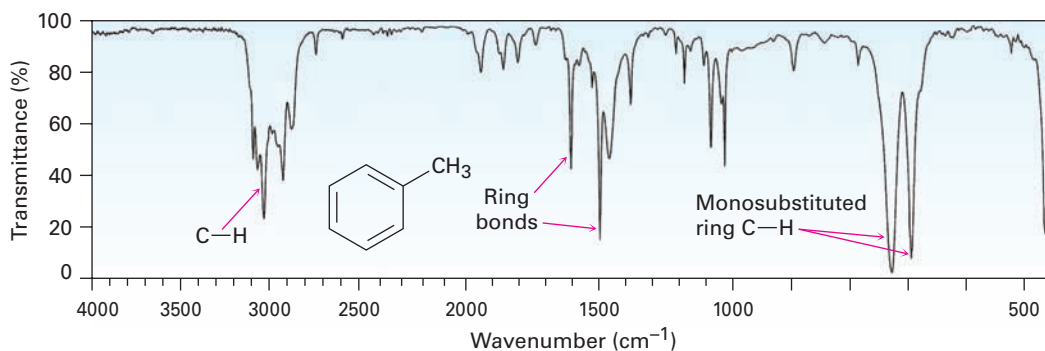## 15.7 Spectroscopy of Aromatic Compounds

Infrared Spectroscopy

Aromatic rings show a characteristic C—H stretching absorption at 3030 cm^{-1} and a series of peaks in the 1450 to 1600 cm^{-1} range of the infrared spectrum. The aromatic C—H band at 3030 cm^{-1} generally has low intensity and occurs just to the left of a typical saturated C—H band.

As many as four absorptions are sometimes observed in the 1450 to 1600 cm^{-1} region because of complex molecular motions of the ring itself. Two bands, one at 1500 cm^{-1} and one at 1600 cm^{-1}, are usually the most intense. In addition, aromatic compounds show weak absorptions in the 1660 to 2000 cm^{-1} region and strong absorptions in the 690 to 900 cm^{-1} range due to C—H out-of-plane bending. The exact position of both sets of absorptions is diagnostic of the substitution pattern of the aromatic ring.

Monosubstituted:	690–710 cm^{-1}	**m-Disubstituted:**	690–710 cm^{-1}
	730–770 cm^{-1}		810–850 cm^{-1}
o-Disubstituted:	735–770 cm^{-1}	**p-Disubstituted:**	810–840 cm^{-1}

The IR spectrum of toluene in **Figure 15.11** shows these characteristic absorptions.

Figure 15.11 The infrared spectrum of toluene.

Ultraviolet Spectroscopy

Aromatic rings are detectable by ultraviolet spectroscopy because they contain a conjugated π electron system. In general, aromatic compounds show a series of bands, with a fairly intense absorption near 205 nm and a less intense absorption in the 255 to 275 nm range. The presence of these bands in the ultraviolet spectrum of a molecule is a sure indication of an aromatic ring.

Nuclear Magnetic Resonance Spectroscopy

Hydrogens directly bonded to an aromatic ring are easily identifiable in the ^{1}H NMR spectrum. Aromatic hydrogens are strongly deshielded by the ring and absorb between 6.5 and 8.0 δ. The spins of nonequivalent aromatic protons on substituted rings often couple with each other, giving rise to spin–spin splitting patterns that can identify the substitution of the ring.

Much of the difference in chemical shift between aromatic protons (6.5–8.0 δ) and vinylic protons (4.5–6.5 δ) is due to a property of aromatic rings called *ring-current*. When an aromatic ring is oriented perpendicular to a strong magnetic field, the delocalized π electrons circulate around the ring, producing a small local magnetic field. This induced field opposes the applied field in the middle of the ring but reinforces the applied field outside the ring **(Figure 15.12)**. Aromatic protons therefore experience an effective magnetic field greater than the applied field and come into resonance at a lower applied field.

Figure 15.12 The origin of aromatic ring-current. Aromatic protons are deshielded by the induced magnetic field caused by delocalized π electrons circulating around the aromatic ring.

Circulating π electrons (ring current)

Proton deshielded by induced field

Induced magnetic field because of ring current

H   H

Applied magnetic field
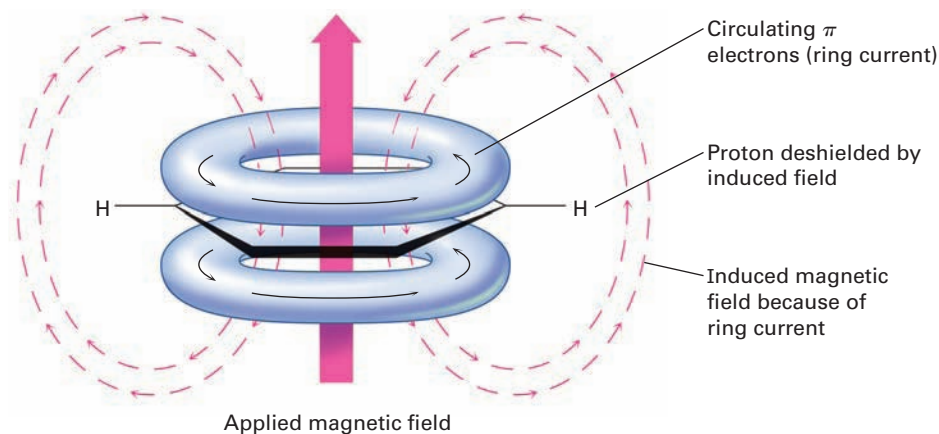
Note that the aromatic ring-current produces different effects inside and outside the ring. If a ring were large enough to have both "inside" and "outside" protons, those protons on the outside would be deshielded and absorb at a field lower than normal but those protons on the inside would be shielded and absorb at a field higher than normal. This prediction has been strikingly verified by studies on [18]annulene, an 18-π-electron cyclic conjugated polyene that contains a Hückel number of electrons (4*n* + 2 = 18 when n = 4). The 6 inside protons of [18]annulene are strongly shielded by the aromatic ring-current and absorb at −3.0 δ (that is, 3.0 ppm *upfield* from TMS, off the normal chart), while the 12 outside protons are

strongly deshielded and absorb in the typical aromatic region at 9.3 ppm downfield from TMS.
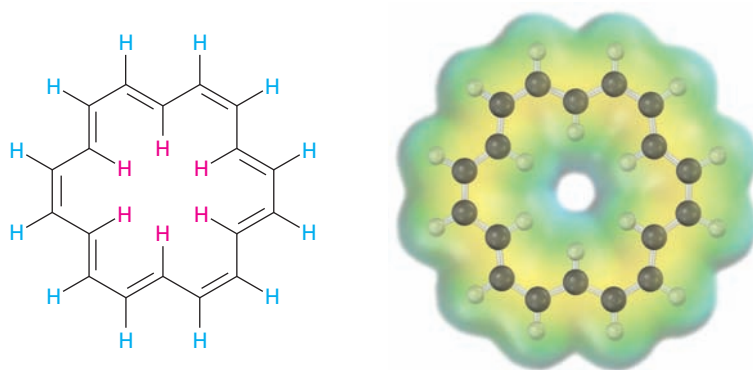

[18]Annulene

Inside H: −3.0 δ
Outside H: 9.3 δ

The presence of a ring-current is characteristic of all Hückel aromatic molecules and is a good test of aromaticity. For example, benzene, a six-π-electron aromatic molecule, absorbs at 7.37 δ because of its ring-current, but cyclooctatetraene, an eight-π-electron nonaromatic molecule, absorbs at 5.78 δ.

Hydrogens on carbon next to aromatic rings—*benzylic* hydrogens—also show distinctive absorptions in the NMR spectrum. Benzylic protons normally absorb downfield from other alkane protons in the region from 2.3 to 3.0 δ.
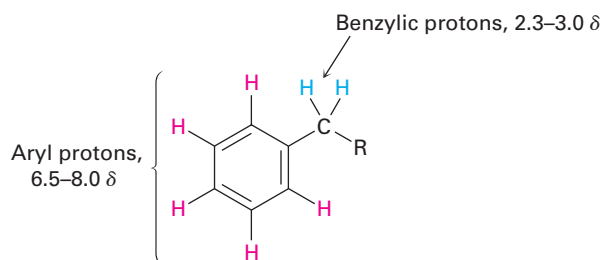
The ¹H NMR spectrum of *p*-bromotoluene, shown in **Figure 15.13**, displays many of the features just discussed. The aromatic protons appear as two doublets at 7.02 and 7.45 δ, and the benzylic methyl protons absorb as a sharp singlet at 2.29 δ. Integration of the spectrum shows the expected 2:2:3 ratio of peak areas.

Chem. shift	Rel. area
2.26	1.50
7.04	1.00
7.37	1.00
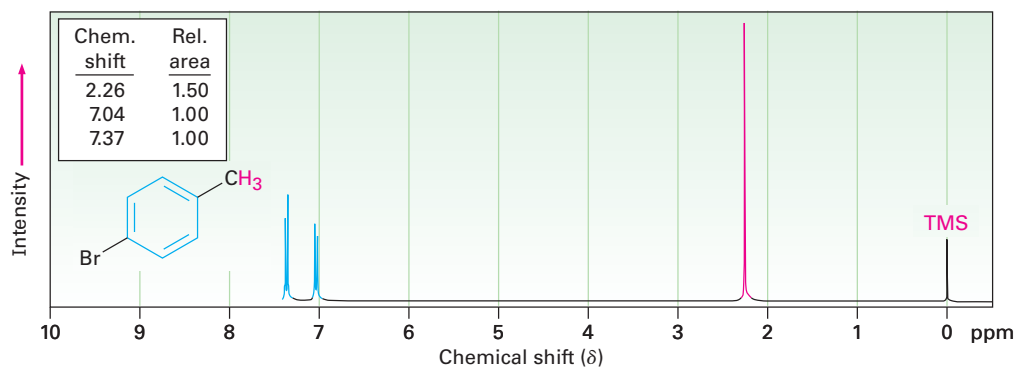
Figure 15.13 The ¹H NMR spectrum of *p*-bromotoluene.

The carbon atoms in an aromatic ring absorb in the range 110 to 140 δ in the ^{13}C NMR spectrum, as indicated by the examples in **Figure 15.14**. These resonances are easily distinguished from those of alkane carbons but occur in the same range as alkene carbons. Thus, the presence of ^{13}C absorptions at 110 to 140 δ does not in itself establish the presence of an aromatic ring. Confirming evidence from infrared, ultraviolet, or ^{1}H NMR is needed.

Figure 15.14 Some ^{13}C NMR absorptions of aromatic compounds (δ units).
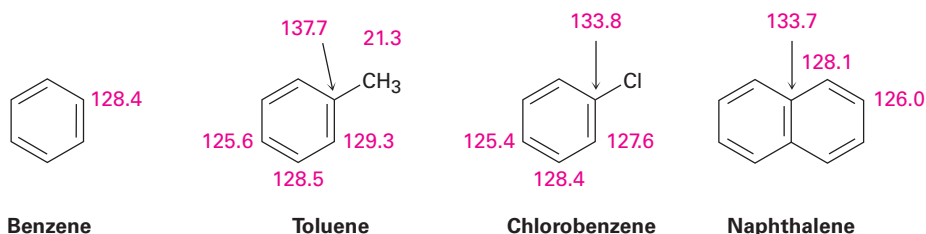
Benzene — 128.4

Toluene — 137.7, 21.3, CH₃, 125.6, 129.3, 128.5

Chlorobenzene — 133.8, Cl, 125.4, 127.6, 128.4

Naphthalene — 133.7, 128.1, 126.0

Benzene   **Toluene**   **Chlorobenzene**   **Naphthalene**

Aspirin, NSAIDs, and COX-2 Inhibitors

| A DEEPER LOOK

Many athletes rely on NSAIDs to help with pain and soreness.

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

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

CH₂OH, OH

Salicyl alcohol

CO₂H, OH

Salicylic acid

CO₂H, OCCH₃, O

Acetylsalicylic acid (aspirin)
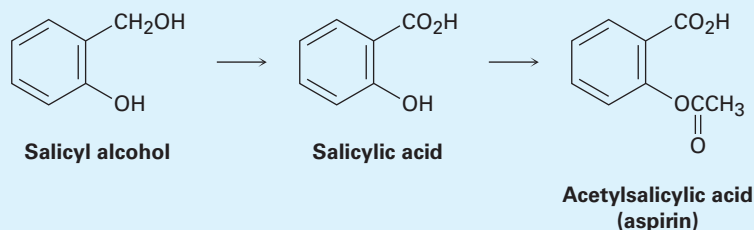
(continued)

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

Like aspirin, both ibuprofen and naproxen are relatively simple aromatic compounds containing a side-chain carboxylic acid group. Ibuprofen, sold under the names Advil, Nuprin, Motrin, and others, has roughly the same potency as aspirin but is less prone to cause stomach upset. Naproxen, sold under the names Aleve and Naprosyn, also has about the same potency as aspirin but remains active in the body six times longer.
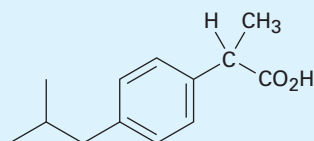
**Ibuprofen**
(Advil, Nuprin, Motrin)
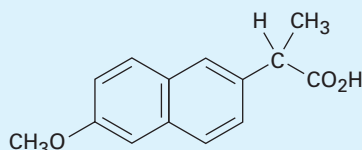
Naproxen
(Aleve, Naprosyn)

Aspirin and other NSAIDs function by blocking the cyclooxygenase (COX) enzymes that carry out the body's synthesis of prostaglandins **(Sections 8.11 and 27.4)**. There are two forms of the enzyme: COX-1, which carries out the normal physiological production of prostaglandins, and COX-2, which mediates the body's response to arthritis and other inflammatory conditions. Unfortunately, both COX-1 and COX-2 enzymes are blocked by aspirin, ibuprofen, and other NSAIDs, thereby shutting down not only the response to inflammation but also various protective functions, including the control mechanism for production of acid in the stomach.

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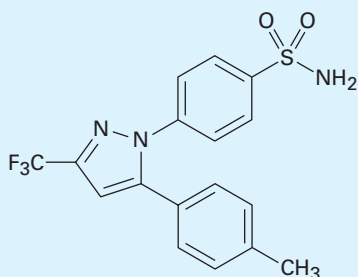
Celecoxib
(Celebrex)
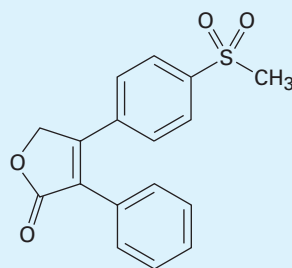
Rofecoxib
(Vioxx)

Summary

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

The word **aromatic** is used for historical reasons to refer to the class of compounds related structurally to benzene. Aromatic compounds are systematically named according to IUPAC rules, but many common names are also used. Disubstituted benzenes are named as **ortho** (1,2 disubstituted), **meta** (1,3 disubstituted), or **para** (1,4 disubstituted) derivatives. The C_6H_5- unit itself is referred to as a **phenyl** group, and the $C_6H_5CH_2-$ unit is a **benzyl** group.

Benzene is described by valence-bond theory as a resonance hybrid of two equivalent structures and is described by molecular orbital theory as a planar, cyclic, conjugated molecule with six π electrons. According to the **Hückel rule**, a molecule must have **$4n + 2$ π electrons**, where n = 0, 1, 2, 3, and so on, to be aromatic. Planar, cyclic, conjugated molecules with other numbers of π electrons are **antiaromatic**.

Other kinds of substances besides benzene-like compounds can also be aromatic. The cyclopentadienyl anion and the cycloheptatrienyl cation, for instance, are aromatic ions. Pyridine and pyrimidine are six-membered, nitrogen-containing, aromatic **heterocycles**. Pyrrole and imidazole are five-membered, nitrogen-containing heterocycles. Naphthalene, quinoline, indole, and many others are polycyclic aromatic compounds.

Aromatic compounds have the following characteristics:

- Aromatic compounds are cyclic, planar, and conjugated.

- Aromatic compounds are unusually stable. Benzene, for instance, has a heat of hydrogenation 150 kJ/mol less than we might expect for a cyclic triene.

- Aromatic compounds react with electrophiles to give substitution products, in which cyclic conjugation is retained, rather than addition products, in which conjugation is destroyed.

- Aromatic compounds have $4n + 2$ π electrons, which are delocalized over the ring.
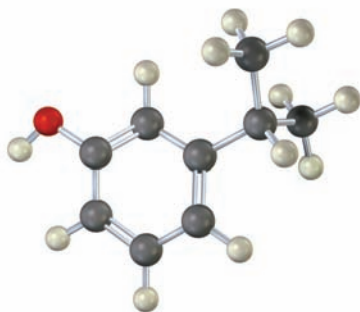
Key words

antiaromatic, 541
arene, 536
aromatic, 534
benzyl, 536
heterocycle, 546
Hückel $4n + 2$ rule, 541
meta (*m*), 537
ortho (*o*), 537
para (*p*), 537
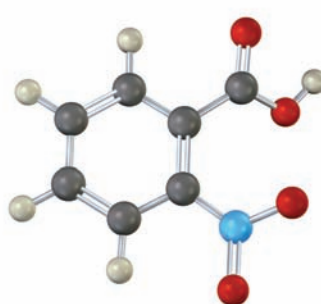**phenyl, 536**

Exercises

Visualizing Chemistry

(Problems 15.1–15.12 appear within the chapter.)

15.13 Give IUPAC names for the following substances (red = O, blue = N):
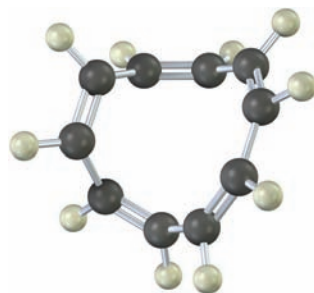
(a)

(b)

15.14 ▲ All-cis cyclodecapentaene is a stable molecule that shows a single absorption in its ^{1}H NMR spectrum at 5.67 δ. Tell whether it is aromatic, and explain its NMR spectrum.


15.15 ▲ 1,6-Methanonaphthalene has an interesting ^{1}H NMR spectrum in which the eight hydrogens around the perimeter absorb at 6.9 to 7.3 δ, while the two CH$_2$ protons absorb at −0.5 δ. Tell whether it is aromatic, and explain its NMR spectrum.
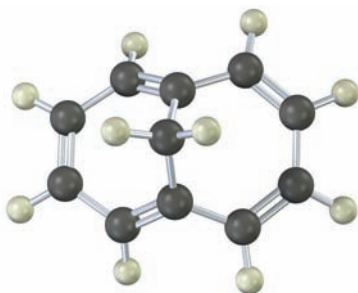
1,6-Methanonaphthalene

▲ Problems linked to Key Ideas in this chapter

15.16 The following molecular model is that of a carbocation. Draw two resonance structures for the carbocation, indicating the positions of the double bonds.
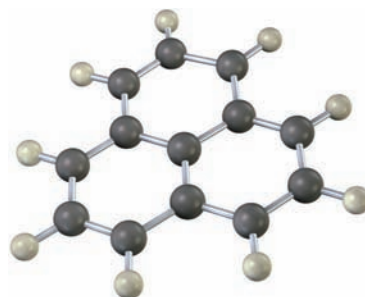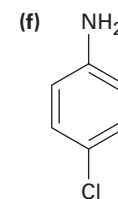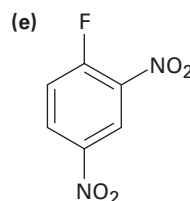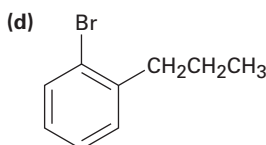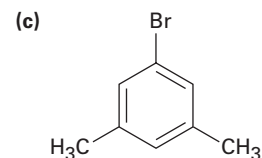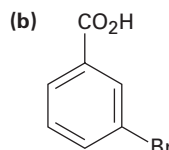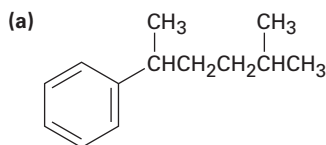

15.17 Azulene, an isomer of naphthalene, has a remarkably large dipole moment for a hydrocarbon (μ = 1.0 D). Explain, using resonance structures.

Azulene
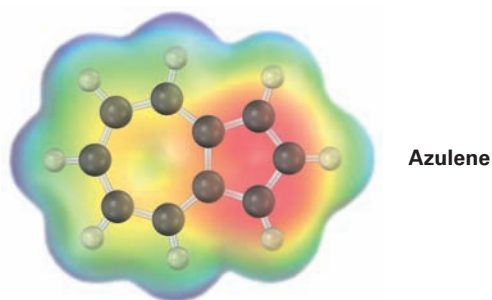
Additional Problems

Naming Aromatic Compounds

15.18 Give IUPAC names for the following compounds:

(a) CH_3 CH_3 CHCH$_2$CH$_2$CHCH$_3$

(b) CO_2H ... Br

(c) Br ... H_3C ... CH_3

(d) Br ... $CH_2CH_2CH_3$

(e) F ... NO_2 ... NO_2

(f) NH_2 ... Cl

15.19 Draw structures corresponding to the following names:
   (a) 3-Methyl-1,2-benzenediamine   (b) 1,3,5-Benzenetriol
   (c) 3-Methyl-2-phenylhexane   (d) *o*-Aminobenzoic acid
   (e) *m*-Bromophenol   (f) 2,4,6-Trinitrophenol (picric acid)

▲ Problems linked to Key Ideas in this chapter

15.20 Draw and name all possible isomers of the following:
  (a) Dinitrobenzene   **(b)** Bromodimethylbenzene   **(c)** Trinitrophenol

15.21 Draw and name all possible aromatic compounds with the formula C_7H_7Cl.

15.22 Draw and name all possible aromatic compounds with the formula C_8H_9Br. (There are 14.)

Structure of Aromatic Compounds

15.23 ▲ Propose structures for aromatic hydrocarbons that meet the following descriptions:
  (a) C_9H_{12}; gives only one $C_9H_{11}Br$ product on substitution of a hydrogen on the aromatic ring with bromine
  (b) $C_{10}H_{14}$; gives only one $C_{10}H_{13}Cl$ product on substitution of a hydrogen on the aromatic ring with chlorine
  (c) C_8H_{10}; gives three C_8H_9Br products on substitution of a hydrogen on the aromatic ring with bromine
  (d) $C_{10}H_{14}$; gives two $C_{10}H_{13}Cl$ products on substitution of a hydrogen on the aromatic ring with chlorine

15.24 Look at the three resonance structures of naphthalene shown in Section 15.6, and account for the fact that not all carbon–carbon bonds have the same length. The C1–C2 bond is 136 pm long, whereas the C2–C3 bond is 139 pm long.

**15.25** Anthracene has four resonance structures, one of which is shown. Draw the other three.
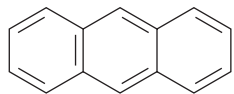
Anthracene

15.26 Phenanthrene has five resonance structures, one of which is shown. Draw the other four.
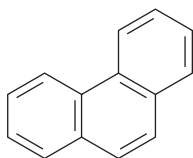
Phenanthrene

15.27 Look at the five resonance structures for phenanthrene (Problem 15.26), and predict which of its carbon–carbon bonds is shortest.

15.28 In 1932, A. A. Levine and A. G. Cole studied the ozonolysis of *o*-xylene and isolated three products: glyoxal, 2,3-butanedione, and pyruvaldehyde:
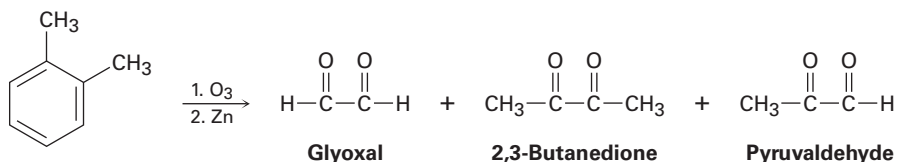

▲ Problems linked to Key Ideas in this chapter

In what ratio would you expect the three products to be formed if *o*-xylene is a resonance hybrid of two structures? The actual ratio found was 3 parts glyoxal, 1 part 2,3-butanedione, and 2 parts pyruvaldehyde. What conclusions can you draw about the structure of *o*-xylene?

Aromaticity and Hückel's Rule

15.29 3-Chlorocyclopropene, on treatment with $AgBF_4$, gives a precipitate of AgCl and a stable solution of a product that shows a single ^1H NMR absorption at 11.04 δ. What is a likely structure for the product, and what is its relation to Hückel's rule?

3-Chlorocyclopropene
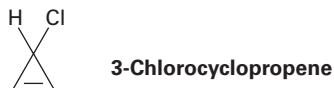
15.30 Draw an energy diagram for the three molecular orbitals of the cyclopropenyl system (C_3H_3). How are these three molecular orbitals occupied in the cyclopropenyl anion, cation, and radical? Which of the three substances is aromatic according to Hückel's rule?

15.31 Cyclopropanone is highly reactive because of its large amount of angle strain. but methylcyclopropenone, although even more strained than cyclopropanone, is nevertheless quite stable and can even be distilled. Explain, taking the polarity of the carbonyl group into account.

Cyclopropanone   **Methylcyclopropenone**
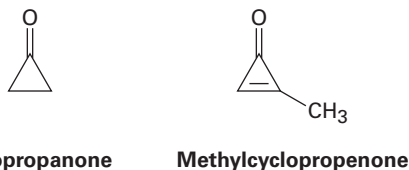
15.32 Cycloheptatrienone is stable, but cyclopentadienone is so reactive that it can't be isolated. Explain, taking the polarity of the carbonyl group into account.

Cycloheptatrienone   **Cyclopentadienone**
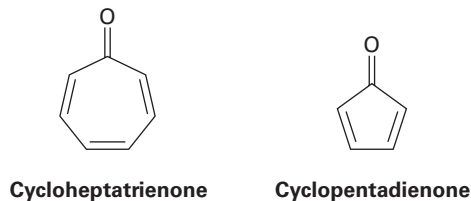
15.33 Which would you expect to be most stable, cyclononatetraenyl radical, cation, or anion?

**15.34** How might you convert 1,3,5,7-cyclononatetraene to an aromatic substance?

▲ Problems linked to Key Ideas in this chapter

15.35 Calicene, like azulene (Problem 15.17), has an unusually large dipole moment for a hydrocarbon. Explain, using resonance structures.


Calicene
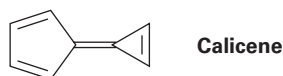
15.36 Pentalene is a most elusive molecule that has been isolated only at liquid-nitrogen temperature. The pentalene dianion, however, is well known and quite stable. Explain.

Pentalene   **Pentalene dianion**

15.37 Indole is an aromatic heterocycle that has a benzene ring fused to a pyrrole ring. Draw an orbital picture of indole.
 (a) How many π electrons does indole have?
 (b) What is the electronic relationship of indole to naphthalene?

Indole
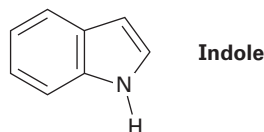
15.38 Ribavirin, an antiviral agent used against hepatitis C and viral pneumonia, contains a 1,2,4-triazole ring. Why is the ring aromatic?

1,2,4-Triazole ring

Ribavirin
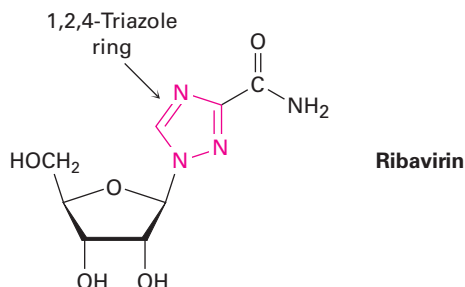
Spectroscopy

15.39 Compound **A**, C_8H_{10}, yields three substitution products, C_8H_9Br, on reaction with Br_2. Propose two possible structures for **A**. The ^1H NMR spectrum of **A** shows a complex four-proton multiplet at 7.0 δ and a six-proton singlet at 2.30 δ. What is the structure of **A**?

15.40 What is the structure of a hydrocarbon that has $M^+ = 120$ in its mass spectrum and has the following ^1H NMR spectrum?

7.25 δ (5 H, broad singlet); 2.90 δ (1 H, septet, $J = 7$ Hz); 1.22 δ (6 H, doublet, $J = 7$ Hz)

▲ Problems linked to Key Ideas in this chapter

15.41 Propose structures for compounds that fit the following descriptions:

(a) $C_{10}H_{14}$
^1H NMR: 7.18 δ (4 H, broad singlet); 2.70 δ (4 H, quartet, $J = 7$ Hz); 1.20 δ (6 H, triplet, $J = 7$ Hz)
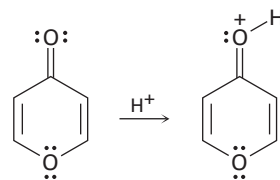IR: 745 cm^{-1}

(b) $C_{10}H_{14}$
^1H NMR: 7.0 δ (4 H, broad singlet); 2.85 δ (1 H, septet, $J = 8$ Hz); 2.28 δ (3 H, singlet); 1.20 δ (6 H, doublet, $J = 8$ Hz)
IR: 825 cm^{-1}

General Problems

15.42 On reaction with acid, 4-pyrone is protonated on the carbonyl-group oxygen to give a stable cationic product. Using resonance structures and the Hückel $4n + 2$ rule, explain why the protonated product is so stable.
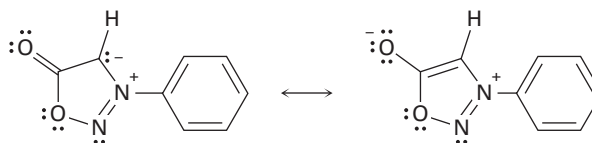

4-Pyrone

15.43 Bextra, a COX-2 inhibitor used in the treatment of arthritis, contains an isoxazole ring. Why is the ring aromatic?

Isoxazole ring
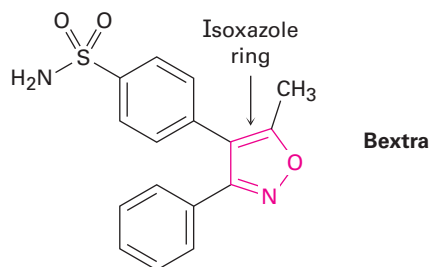
Bextra

15.44 *N*-Phenylsydnone, so-named because it was first studied at the University of Sydney, Australia, behaves like a typical aromatic molecule. Explain, using the Hückel $4n + 2$ rule.
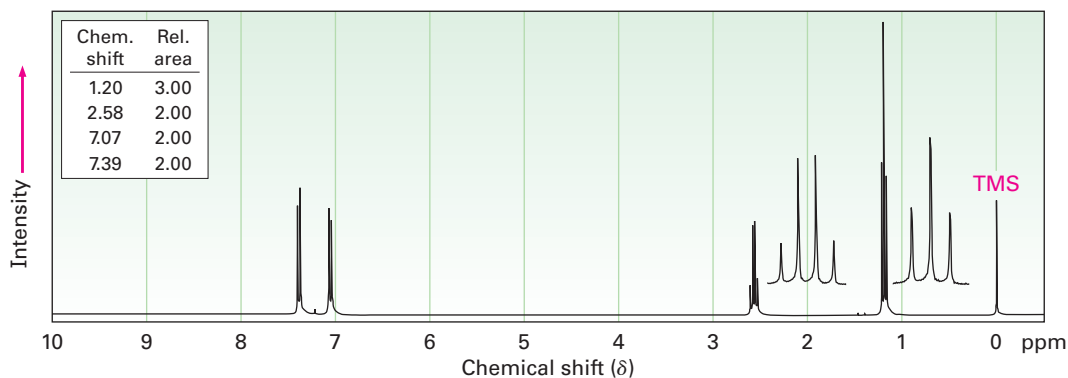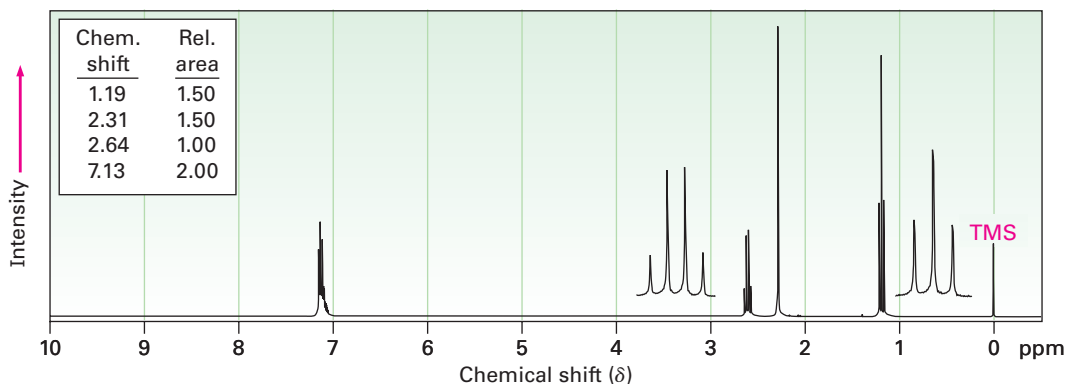

N-Phenylsydnone

▲ Problems linked to Key Ideas in this chapter

15.45 Show the relative energy levels of the seven π molecular orbitals of the cycloheptatrienyl system. Tell which of the seven orbitals are filled in the cation, radical, and anion, and account for the aromaticity of the cycloheptatrienyl cation.

15.46 1-Phenyl-2-butene has an ultraviolet absorption at λ_{max} = 208 nm (ϵ = 8000). On treatment with a small amount of strong acid, isomerization occurs and a new substance with λ_{max} = 250 nm (ϵ = 15,800) is formed. Propose a structure for this isomer, and suggest a mechanism for its formation.

15.47 Propose structures for aromatic compounds that have the following ^{1}H NMR spectra:

(a) C_8H_9Br
IR: 820 cm^{-1}

Chem. shift	Rel. area
1.20	3.00
2.58	2.00
7.07	2.00
7.39	2.00

(b) C_9H_{12}
IR: 750 cm^{-1}

Chem. shift	Rel. area
1.19	1.50
2.31	1.50
2.64	1.00
7.13	2.00

(c) $C_{11}H_{16}$
IR: 820 cm^{-1}

Chem. shift	Rel. area
1.31	4.50
2.30	1.50
7.06	1.00
7.27	1.00
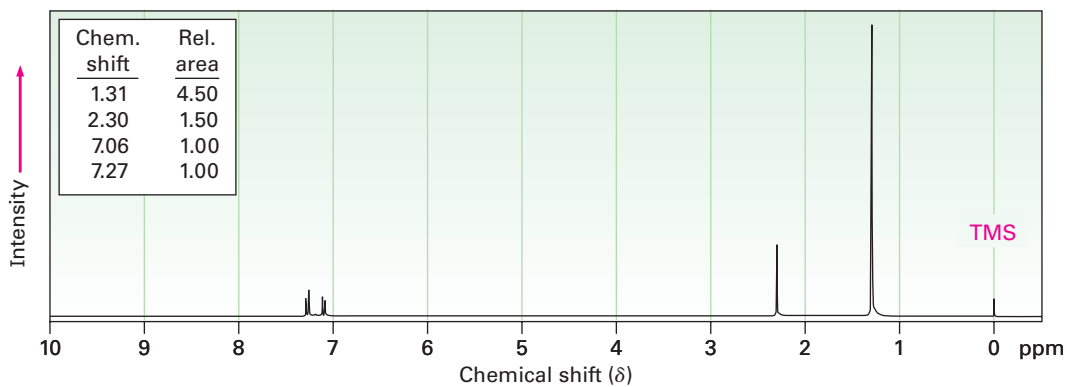
15.48 Propose a structure for a molecule $C_{14}H_{12}$ that has the following ^{1}H NMR spectrum and has IR absorptions at 700, 740, and 890 cm^{-1}:

Chem. shift	Rel. area
5.41	1.00
7.31	5.00
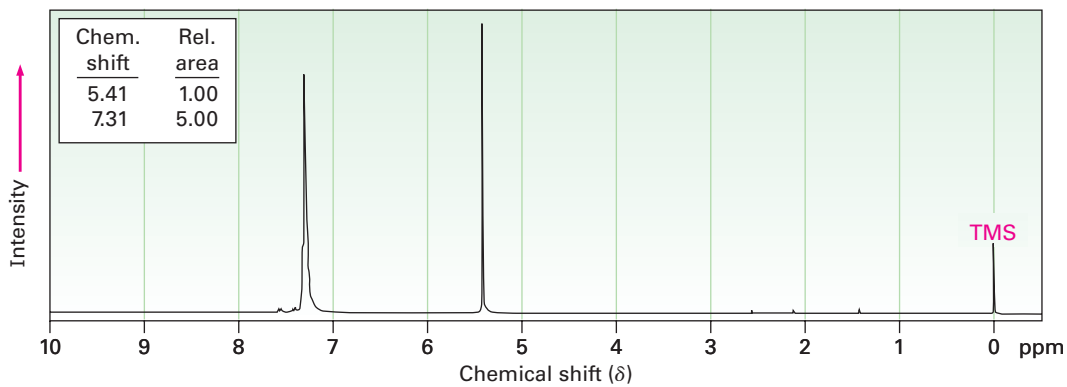
▲ Problems linked to Key Ideas in this chapter

15.49 Aromatic substitution reactions occur by addition of an electrophile such as Br^+ to the aromatic ring to yield an allylic carbocation intermediate, followed by loss of H^+. Show the structure of the intermediate formed by reaction of benzene with Br^+.

15.50 The substitution reaction of toluene with Br_2 can, in principle, lead to the formation of three isomeric bromotoluene products. In practice, however, only *o*- and *p*-bromotoluene are formed in substantial amounts. The meta isomer is not formed. Draw the structures of the three possible carbocation intermediates (Problem 15.49), and explain why ortho and para products predominate over meta.

▲ Problems linked to Key Ideas in this chapter