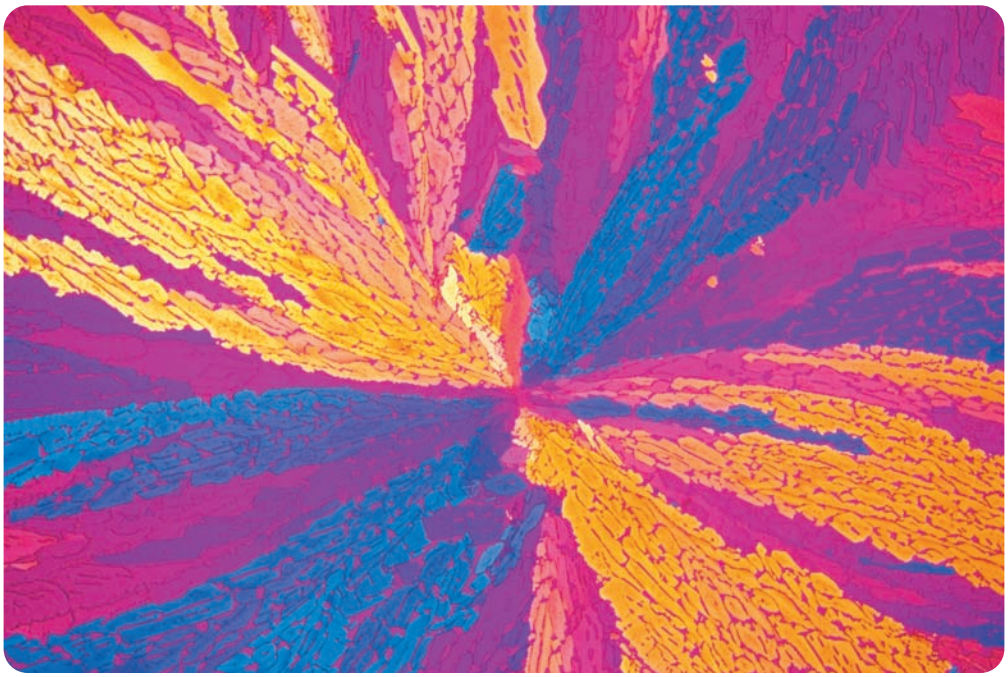
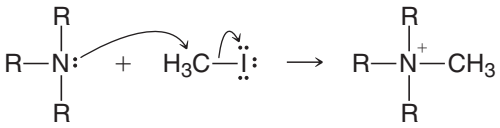
6

Ionic Reactions

Nucleophilic Substitution and Elimination Reactions of Alkyl Halides



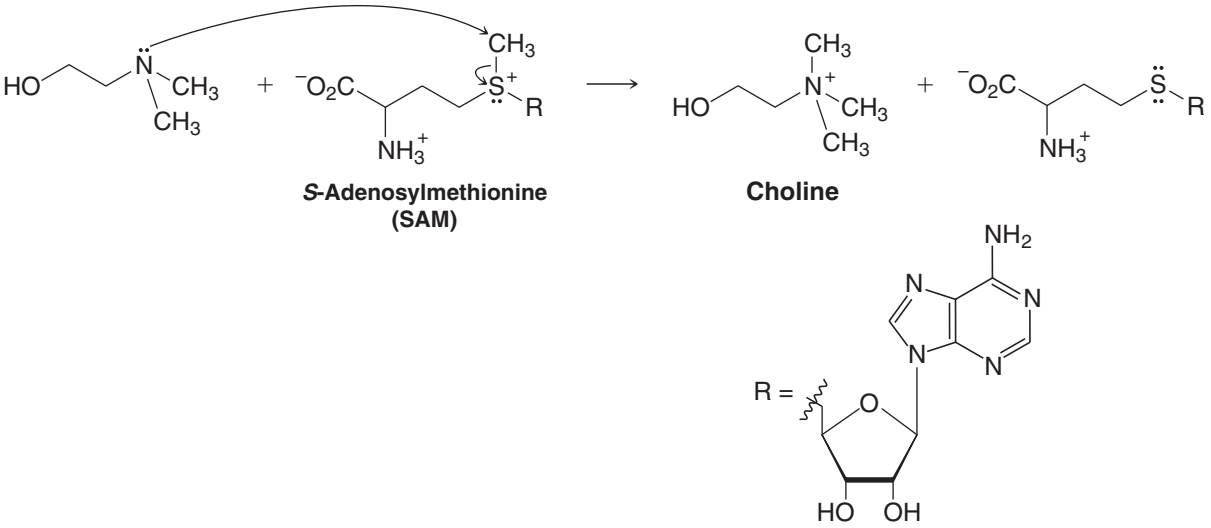
Organic syntheses, whether they take place in the glassware of the laboratory or in the cells of a living organism, often involve fairly simple processes, such as the installation of a methyl group in just the right place. For example, we may want to install a methyl group on the nitrogen atom of a tertiary amine, a reaction that has an important counterpart in biochemistry. To do this we often employ a reaction like the following:



If we wanted to describe this reaction to an organic chemist we would describe it as a ***nucleophilic substitution reaction***, a kind of reaction we describe in detail in this chapter.

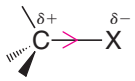
On the other hand, if we wanted to describe this reaction to a biochemist, we might call it a ***methyl transfer reaction***. Biochemists have described many similar reactions this way, for example, the reaction below that transfers a methyl group from *S-adenosylmethionine* (SAM) to a tertiary amine to make choline. Choline is incorporated into the phospholipids of our cell membranes, and it is the hydrolysis product of acetylcholine, an important neurotransmitter. (Crystals of acetylcholine are shown in the polarized light microscopy image above.)

Now, the biological reaction may seem more complicated, but its essence is similar to many nucleophilic substitution reactions we shall study in this chapter. First we consider alkyl halides, one of the most important types of reactants in nucleophilic substitution reactions.



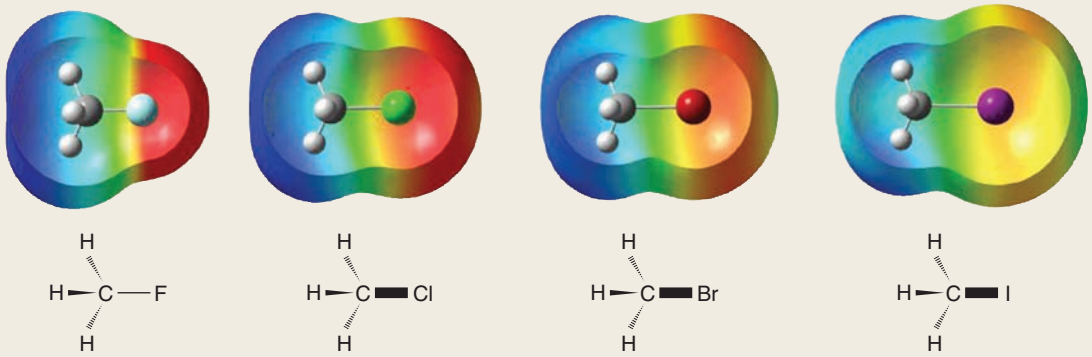
6.1 Organic Halides

The halogen atom of an alkyl halide is attached to an sp^3-hybridized carbon. The arrangement of groups around the carbon atom, therefore, is generally tetrahedral. Because halogen atoms are more electronegative than carbon, the carbon–halogen bond of alkyl halides is *polarized*; the carbon atom bears a partial positive charge, the halogen atom a partial negative charge:



Halogen atom size increases as we go down the periodic table: fluorine atoms are the smallest and iodine atoms the largest. Consequently, the carbon–halogen *bond length increases* and carbon–halogen *bond strength decreases* as we go down the periodic table (Table 6.1). Maps of electrostatic potential (see Table 6.1) at the van der Waals surface for the four methyl

TABLE 6.1 Carbon–Halogen Bond Lengths and Bond Strengths



C—X Bond length (Å)	1.39	1.78	1.93	2.14
C—X Bond strength (kJ mol^{-1})	472	350	293	239

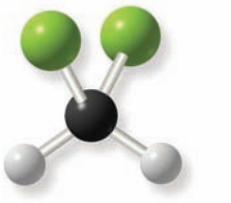
halides, with ball-and-stick models inside, illustrate the trend in polarity, C—X bond length, and halogen atom size as one progresses from fluorine to iodine substitution. Fluoromethane is highly polar and has the shortest C—X bond length and the strongest C—X bond. Iodomethane is much less polar and has the longest C—X bond length and the weakest C—X bond.

In the laboratory and in industry, alkyl halides are used as solvents for relatively nonpolar compounds, and they are used as the starting materials for the synthesis of many compounds. As we shall learn in this chapter, the halogen atom of an alkyl halide can be easily replaced by other groups, and the presence of a halogen atom on a carbon chain also affords us the possibility of introducing a multiple bond.

Alkyl halides are classified as primary (1°), secondary (2°), or tertiary (3°) according to the number of carbon atoms directly bonded to the carbon bearing the halogen (Section 2.5). Compounds in which a halogen atom is bonded to an sp^2-hybridized carbon are called **vinylic halides** or **phenyl halides**. The compound $CH_2{=}CHCl$ has the common name **vinyl chloride**, and the group $CH_2{=}CH{-}$ is commonly called the **vinyl group**. *Vinylic halide*, therefore, is a general term that refers to a compound in which a halogen is attached to a carbon atom that is also forming a double bond to another carbon atom. *Phenyl halides* are compounds in which a halogen is attached to a benzene ring (Section 2.4B). Phenyl halides belong to a larger group of compounds that we shall study later, called **aryl halides**.

A vinylic halide **A phenyl halide or aryl halide**

Together with alkyl halides, these compounds comprise a larger group of compounds known simply as **organic halides** or **organohalogen compounds**. The chemistry of vinylic and aryl halides is, as we shall also learn later, quite different from that of alkyl halides, and it is on alkyl halides that we shall focus most of our attention in this chapter.



Dichloromethane (CH_2Cl_2), a common laboratory solvent

6.1A Physical Properties of Organic Halides

Most alkyl and aryl halides have very low solubilities in water, but as we might expect, they are miscible with each other and with other relatively nonpolar solvents. Dichloromethane (CH_2Cl_2, also called *methylene chloride*), trichloromethane ($CHCl_3$, also called *chloroform*), and tetrachloromethane (CCl_4, also called *carbon tetrachloride*) are sometimes used as solvents for nonpolar and moderately polar compounds. Many chloroalkanes, including CH_2Cl_2, $CHCl_3$, and CCl_4, have a cumulative toxicity and are carcinogenic, however, and should therefore be used only in fume hoods and with great care.

Table 6.2 lists the physical properties of some common organic halides.

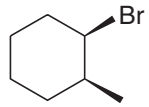
TABLE 6.2 Organic Halides

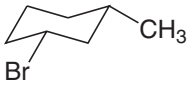
	Fluoride		Chloride		Bromide		Iodide	
Group	bp (°C)	Density[a] (g mL^{-1})	bp (°C)	Density[a] (g mL^{-1})	bp (°C)	Density[a] (g mL^{-1})	bp (°C)	Density[a] (g mL^{-1})
Methyl	−78.4	0.84^{-60}	−23.8	0.92^{20}	3.6	1.73^{0}	42.5	2.28^{20}
Ethyl	−37.7	0.72^{20}	13.1	0.91^{15}	38.4	1.46^{20}	72	1.95^{20}
Propyl	−2.5	0.78^{-3}	46.6	0.89^{20}	70.8	1.35^{20}	102	1.74^{20}
Isopropyl	−9.4	0.72^{20}	34	0.86^{20}	59.4	1.31^{20}	89.4	1.70^{20}
Butyl	32	0.78^{20}	78.4	0.89^{20}	101	1.27^{20}	130	1.61^{20}
sec-Butyl	—	—	68	0.87^{20}	91.2	1.26^{20}	120	1.60^{20}
Isobutyl	—	—	69	0.87^{20}	91	1.26^{20}	119	1.60^{20}
tert-Butyl	12	0.75^{12}	51	0.84^{20}	73.3	1.22^{20}	100 dec[b]	1.57^{0}

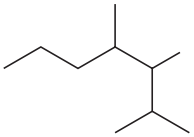
[a]Densities were measured at temperature (°C) indicated in superscript.
[b]Decomposes is abbreviated dec.

Give IUPAC names for each of the following.

Review Problem 6.1

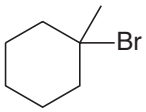
(a) 

(b) 

(c) 

Classify each of the following organic halides as primary, secondary, tertiary, vinylic, or aryl.

Review Problem 6.2

(a) 

(b) 

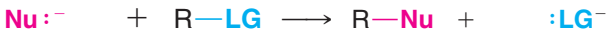
(c) 

(d) 

(e) 

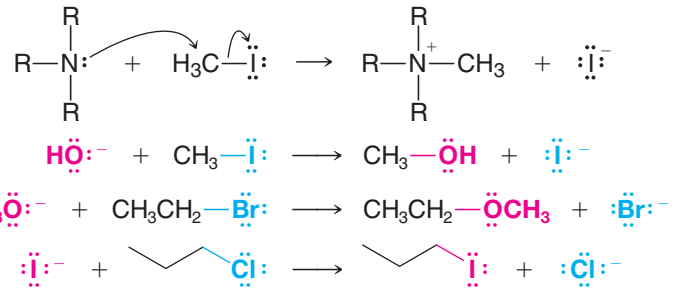
6.2 Nucleophilic Substitution Reactions

Nucleophilic substitution reactions, like the examples mentioned at the beginning of this chapter, are among the most fundamental types of organic reactions. In general, we can depict nucleophilic substitution reactions in the following way:



Nucleophile **Substrate** **Product** **Leaving group**

In this type of reaction a **nucleophile** (Nu:) replaces a **leaving group** (LG) in the molecule that undergoes substitution (called the **substrate**). The nucleophile is always a Lewis base, and it may be negatively charged or neutral. The leaving group is always a species that takes a pair of electrons with it when it departs. Often the substrate is an alkyl halide (R—$\ddot{X}$:) and the leaving group is a halide anion (:$\ddot{X}$:⁻), as in the examples of **nucleophilic substitution** below.



Helpful Hint

In Section 6.14 we shall see examples of biological nucleophilic substitution.

Later we shall see examples of leaving groups other than halide anions. Some of these leaving groups depart as neutral species. For the time being, however, our examples will involve alkyl halides, which we represent generally as R—$\ddot{X}$:.

In nucleophilic substitution reactions the bond between the substrate carbon and the leaving group undergoes *heterolytic* bond cleavage, and the unshared electron pair of the nucleophile forms a new bond to the carbon atom.

The nucleophile donates an electron pair to the substrate.

The bond between the carbon and the leaving group breaks, giving both electrons from the bond to the leaving group.

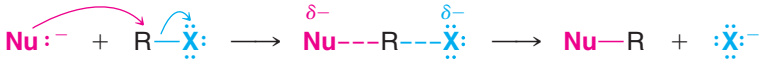
The nucleophile uses its electron pair to form a new covalent bond with the substrate carbon.

The leaving group gains the pair of electrons that originally bonded it in the substrate.

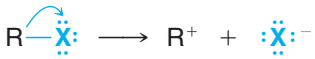
Helpful Hint

In color-coded reactions of this chapter, we will use red to indicate a nucleophile and blue to indicate a leaving group.

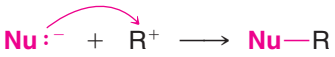
A key question we shall want to address later in this chapter is this: When does the bond between the leaving group and the carbon break? Does it break at the same time that the new bond between the nucleophile and carbon forms, as shown below?



Or, does the bond to the leaving group break first?



Followed by



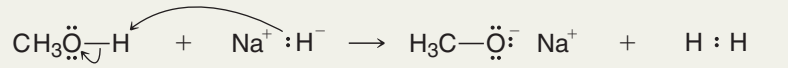
We shall find that the answer depends greatly on the structure of the substrate.

Solved Problem 6.1

(a) A solution containing methoxide ions, CH_3O^- ions (as $NaOCH_3$), in methanol can be prepared by adding sodium hydride (NaH) to methanol (CH_3OH). A flammable gas is the other product. Write the acid–base reaction that takes place. **(b)** Write the nucleophilic substitution that takes place when CH_3I is added and the resulting solution is heated.

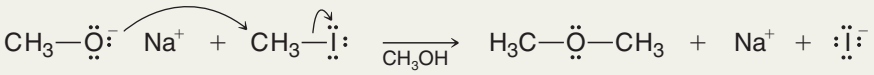
STRATEGY AND ANSWER

(a) We recall from Section 3.15 that sodium hydride consists of Na^+ ions and hydride ions ($H:^-$ ions), and that the hydride ion is a very strong base. [It is the conjugate base of H_2, a very weak acid ($pK_a = 35$, see Table 3.1).] The acid–base reaction that takes place is



Methanol (stronger acid)	**Sodium hydride** (stronger base)	**Sodium methoxide** (weaker base)	**Hydrogen** (weaker acid)

(b) The methoxide ion reacts with the alkyl halide (CH_3I) in a nucleophilic substitution:



6.3 Nucleophiles

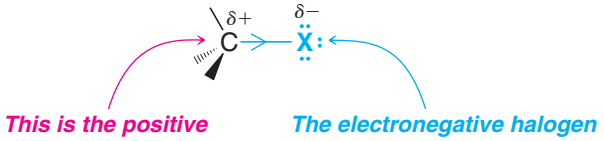
A nucleophile is a reagent that seeks a positive center.

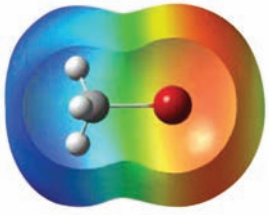
- Any negative ion or uncharged molecule with an unshared electron pair is a potential nucleophile.

Helpful Hint

You may wish to review Section 3.3A, "Opposite Charges Attract."

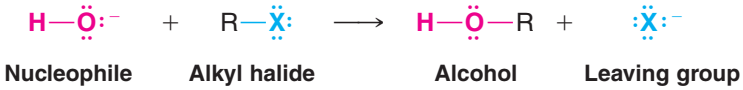
When a nucleophile reacts with an alkyl halide, the carbon atom bearing the halogen atom is the positive center that attracts the nucleophile. This carbon carries a partial positive charge because the electronegative halogen pulls the electrons of the carbon–halogen bond in its direction.





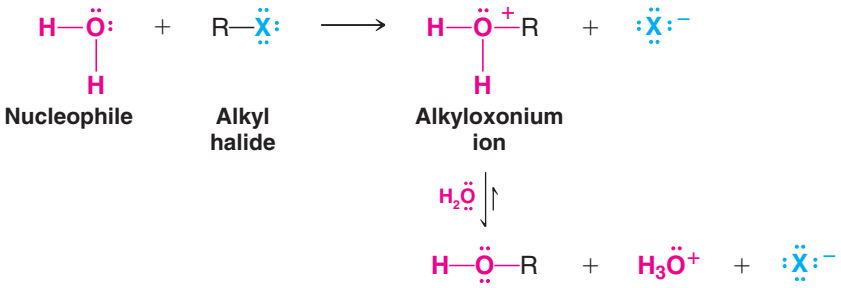
Let us look at two examples, one in which **the nucleophile (a hydroxide ion) bears a negative charge**, and one in which **the nucleophile (water) is uncharged**. In the first example below involving a negative nucleophile, the reaction produces an alcohol directly. This is because the formal negative charge of the nucleophile is neutralized when the nucleophile uses one of its unshared electron pairs to form a covalent bond.

General Reaction for Nucleophilic Substitution of an Alkyl Halide by Hydroxide Ion



In the second example, involving a neutral nucleophile (water), the reaction leads to a product that initially bears a formal positive charge. This is because use of an unshared electron pair from the neutral nucleophile leaves the nucleophilic atom with a formal positive charge after the bond is formed. The initial product in this case is called an alkyloxonium ion. In a subsequent step a proton is removed from the alkyloxonium ion to form the neutral alcohol.

General Reaction for Nucleophilic Substitution of an Alkyl Halide by Water

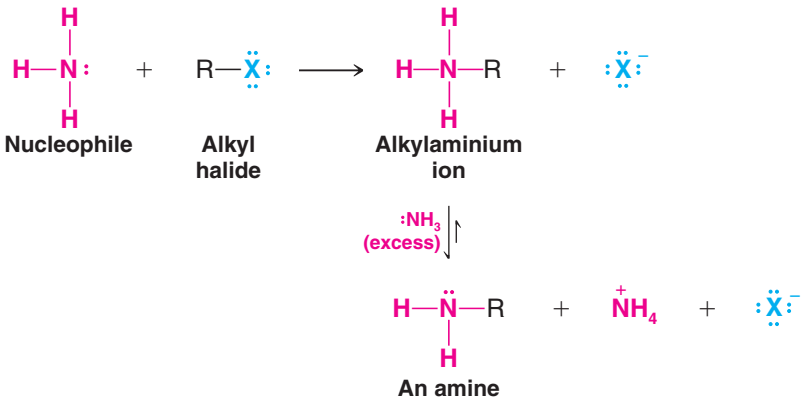


Helpful Hint

A deprotonation step is always required to complete the reaction when the nucleophile was a neutral atom that bore a proton.

In a reaction like this the nucleophile is a solvent molecule (as is often the case when neutral nucleophiles are involved). Since solvent molecules are present in great excess, the equilibrium favors transfer of a proton from the alkyloxonium ion to a water molecule. (This type of reaction is an example of solvolysis, which we shall discuss further in Section 6.12B.)

The reaction of ammonia (NH_3) with an alkyl halide, as shown below, provides another example where the nucleophile is uncharged. An excess of ammonia favors equilibrium removal of a proton from the alkylaminium ion to form the neutral amine.



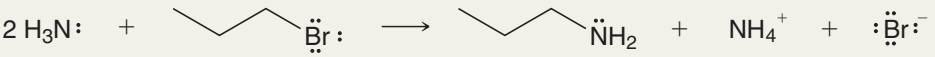
Solved Problem 6.2

Write the following as net ionic equations and designate the nucleophile, substrate, and leaving group in each case.

(a)

(b)

(c)



STRATEGY A net ionic equation does not include spectator ions but is still balanced in terms of charges and the remaining species. Spectator ions are those ions which have not been involved in covalent bonding changes during a reaction, and which appear on both sides of a chemical equation. In reactions (a) and (b) the sodium ion is a spectator ion, thus the net ionic equation would not include them, and their net ionic equations would have a net negative charge on each side of the arrow. Equation (c) has no ions present among the reactants, and thus the ions found with the products are not spectator ions—they have resulted from covalent bonding changes. Equation (c) cannot be simplified to a net ionic equation.

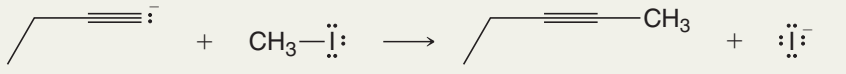
Nucleophiles use a pair of electrons to form a covalent bond that is present in a product molecule. In all of the above reactions we can identify a species that used a pair of electrons in this way. These are the nucleophiles. **Leaving groups** depart from one of the reactant molecules and take a pair of electrons with them. In each reaction above we can identify such a species. Lastly, the reactant to which the nucleophile became bonded and from which the leaving groups departed is the **substrate**.

ANSWER The net ionic equations are as follows for (a) and (b), and there is no abbreviated equation possible for (c). Nucleophiles, substrates, and leaving groups are labeled accordingly.

(a)

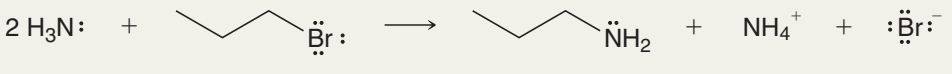
Nucleophile **Substrate** **Leaving group**

(b)



Nucleophile **Substrate** **Leaving group**

(c)



Nucleophile **Substrate** **Leaving group**

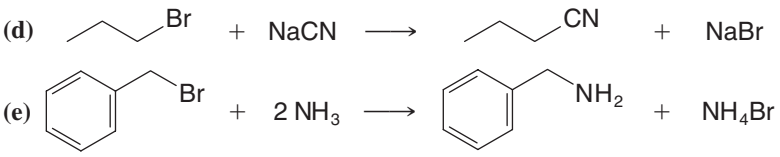
Review Problem 6.3

Write the following as net ionic equations and designate the nucleophile, substrate, and leaving group in each reaction:

(a) $CH_3I + CH_3CH_2ONa \longrightarrow CH_3OCH_2CH_3 + NaI$

(b) $NaI + CH_3CH_2Br \longrightarrow CH_3CH_2I + NaBr$

(c) $2\ CH_3OH + (CH_3)_3CCl \longrightarrow (CH_3)_3COCH_3 + CH_3OH_2^+ + Cl^-$



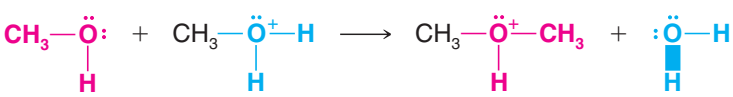
6.4 Leaving Groups

To act as the substrate in a nucleophilic substitution reaction, a molecule must have a good leaving group.

- A good **leaving group** is a substituent that can leave as a relatively stable, weakly basic molecule or ion.

In the examples shown above (Sections 6.2 and 6.3) the leaving group has been a halogen. Halide anions are weak bases (they are the conjugate bases of strong acids, HX), and therefore halogens are good leaving groups.

Some leaving groups depart as neutral molecules, such as a molecule of water or an alcohol. For this to be possible, the leaving group must have a formal positive charge while it is bonded to the substrate. When this group departs with a pair of electrons the leaving group's formal charge goes to zero. The following is an example where the leaving group departs as a water molecule.



Helpful Hint

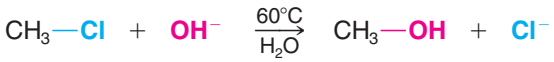
Note that the net charge is the same on each side of a properly written chemical equation.

As we shall see later, the positive charge on a leaving group (like that above) usually results from protonation of the substrate by an acid. However, use of an acid to protonate the substrate and make a positively charged leaving group is feasible only when the nucleophile itself is not strongly basic, and when the nucleophile is present in abundance (such as in solvolysis).

Let us now begin to consider the mechanisms of nucleophilic substitution reactions. How does the nucleophile replace the leaving group? Does the reaction take place in one step or is more than one step involved? If more than one step is involved, what kinds of intermediates are formed? Which steps are fast and which are slow? In order to answer these questions, we need to know something about the rates of chemical reactions.

6.5 Kinetics of a Nucleophilic Substitution Reaction: An S_N2 Reaction

To understand how the rate of a reaction (**kinetics**) might be measured, let us consider an actual example: the reaction that takes place between chloromethane and hydroxide ion in aqueous solution:



Although chloromethane is not highly soluble in water, it is soluble enough to carry out our kinetic study in an aqueous solution of sodium hydroxide. Because reaction rates are known to be temperature dependent (Section 6.7), we carry out the reaction at a constant temperature.

6.5A How Do We Measure the Rate of This Reaction?

The rate of the reaction can be determined experimentally by measuring the rate at which chloromethane or hydroxide ion *disappears* from the solution or the rate at which methanol or chloride ion *appears* in the solution. We can make any of these measurements by withdrawing a small sample from the reaction mixture soon after the reaction begins and analyzing it

for the concentrations of CH_3Cl or OH^- and CH_3OH or Cl^-. We are interested in what are called *initial rates*, because as time passes the concentrations of the reactants change. Since we also know the initial concentrations of reactants (because we measured them when we made up the solution), it will be easy to calculate the rate at which the reactants are disappearing from the solution or the products are appearing in the solution.

We perform several such experiments keeping the temperature the same but varying the initial concentrations of the reactants. The results that we might get are shown in Table 6.3.

TABLE 6.3 Rate Study of Reaction of CH_3Cl with OH^- at 60°C

Experiment Number	Initial $[CH_3Cl]$	Initial $[OH^-]$	Initial Rate (mol L^{-1} s^{-1})
1	0.0010	1.0	4.9×10^{-7}
2	0.0020	1.0	9.8×10^{-7}
3	0.0010	2.0	9.8×10^{-7}
4	0.0020	2.0	19.6×10^{-7}

Notice that the experiments show that the rate depends on the concentration of chloromethane *and* on the concentration of hydroxide ion. When we doubled the concentration of chloromethane in experiment 2, the rate *doubled*. When we doubled the concentration of hydroxide ion in experiment 3, the rate *doubled*. When we doubled both concentrations in experiment 4, the rate increased by a factor of *four*.

We can express these results as a proportionality,

$$\text{Rate} \propto [CH_3Cl][OH^-]$$

and this proportionality can be expressed as an equation through the introduction of a proportionality constant (k) called the rate constant:

$$\text{Rate} = k[CH_3Cl][OH^-]$$

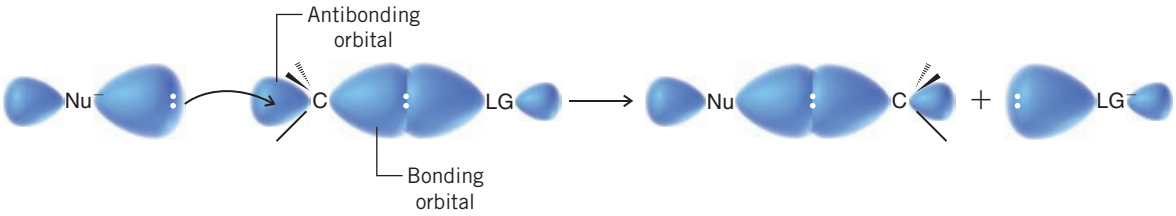
For this reaction at this temperature we find that $k = 4.9 \times 10^{-4}$ L mol^{-1} s^{-1}. (Verify this for yourself by doing the calculation.)

6.5B What Is the Order of This Reaction?

This reaction is said to be **second order overall**.* It is reasonable to conclude, therefore, that *for the reaction to take place a hydroxide ion and a chloromethane molecule must collide*. We also say that the reaction is **bimolecular**. (By *bimolecular* we mean that two species are involved in the step whose rate is being measured. In general the number of species involved in a reaction step is called the **molecularity** of the reaction.) We call this kind of reaction an **S_N2 reaction**, meaning **substitution, nucleophilic, bimolecular**.

6.6 A Mechanism for the S_N2 Reaction

A schematic representation of orbitals involved in an S_N2 reaction—based on ideas proposed by Edward D. Hughes and Sir Christopher Ingold in 1937—is outlined below.



*In general, the overall order of a reaction is equal to the sum of the exponents a and b in the rate equation Rate $= k[A]^a [B]^b$. If in some other reaction, for example, we found that Rate $= k[A]^2 [B]$, then we would say that the reaction is second order with respect to [A], first order with respect to [B], and third order overall.

According to this mechanism:

- The nucleophile approaches the carbon bearing the leaving group from the **back side**, that is, from the side directly opposite the leaving group.

The orbital that contains the electron pair of the nucleophile (its highest occupied molecular orbital, or HOMO) begins to overlap with an empty orbital (the lowest unoccupied molecular orbital, or LUMO) of the carbon atom bearing the leaving group. As the reaction progresses, the bond between the nucleophile and the carbon atom strengthens, and the bond between the carbon atom and the leaving group weakens.

- As the nucleophile forms a bond and the leaving group departs, the substrate carbon atom undergoes **inversion*** —its tetrahedral bonding configuration is turned inside out.

The formation of the bond between the nucleophile and the carbon atom provides most of the energy necessary to break the bond between the carbon atom and the leaving group. We can represent this mechanism with chloromethane and hydroxide ion as shown in the box "Mechanism for the S_N2 Reaction" below.

- The S_N2 reaction proceeds in a single step (without any intermediates) through an unstable arrangement of atoms called the **transition state**.

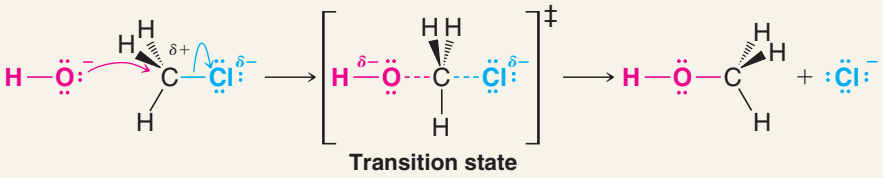
A MECHANISM FOR THE REACTION

Mechanism for the S_N2 Reaction

REACTION

$$HO^- + CH_3Cl \longrightarrow CH_3OH + Cl^-$$

MECHANISM



The negative hydroxide ion brings a pair of electrons to the partially positive carbon from the back side with respect to the leaving group. The chlorine begins to move away with the pair of electrons that bonded it to the carbon.

In the transition state, a bond between oxygen and carbon is partially formed and the bond between carbon and chlorine is partially broken. The configuration of the carbon atom begins to invert.

Now the bond between the oxygen and carbon has formed and the chloride ion has departed. The configuration of the carbon has inverted.

*Considerable evidence had appeared in the years prior to Hughes and Ingold's 1937 publication indicating that in reactions like this an inversion of configuration of the carbon bearing the leaving group takes place. The first observation of such an inversion was made by the Latvian chemist Paul Walden in 1896, and such inversions are called **Walden inversions** in his honor. We shall study this aspect of the S_N2 reaction further in Section 6.8.

The transition state is a fleeting arrangement of the atoms in which the nucleophile and the leaving group are both partially bonded to the carbon atom undergoing substitution. Because the transition state involves both the nucleophile (e.g., a hydroxide ion) and the substrate (e.g., a molecule of chloromethane), this mechanism accounts for the second-order reaction kinetics that we observe.

- The S_N2 reaction is said to be a **concerted reaction**, because bond forming and bond breaking occur in concert (*simultaneously*) through a single transition state.

The transition state has an extremely brief existence. It lasts only as long as the time required for one molecular vibration, about 10^{-12} s. The structure and energy of the transition state are highly important aspects of any chemical reaction. We shall, therefore, examine this subject further in Section 6.7.

6.7 Transition State Theory: Free-Energy Diagrams

- A reaction that proceeds with a negative free-energy change (releases energy to its surroundings) is said to be **exergonic**; one that proceeds with a positive free-energy change (absorbs energy from its surroundings) is said to be **endergonic**.

The reaction between chloromethane and hydroxide ion in aqueous solution is highly exergonic; at 60°C (333 K), $\Delta G^\circ = -100$ kJ mol^{-1}. (The reaction is also exothermic, $\Delta H^\circ = -75$ kJ mol^{-1}.)

$$CH_3{-}Cl + OH^- \longrightarrow CH_3{-}OH + Cl^- \qquad \Delta G^\circ = -100 \text{ kJ mol}^{-1}$$

The equilibrium constant for the reaction is extremely large, as we show by the following calculation:

$$\Delta G^\circ = -RT \ln K_{eq}$$

$$\ln K_{eq} = \frac{-\Delta G^\circ}{RT}$$

$$\ln K_{eq} = \frac{-(-100 \text{ kJ mol}^{-1})}{0.00831 \text{ kJ K}^{-1} \text{ mol}^{-1} \times 333 \text{ K}}$$

$$\ln K_{eq} = 36.1$$

$$K_{eq} = 5.0 \times 10^{15}$$

An equilibrium constant as large as this means that the reaction goes to completion.

Because the free-energy change is negative, we can say that in energy terms the reaction goes **downhill**. The products of the reaction are at a lower level of free energy than the reactants. However, if covalent bonds are broken in a reaction, the reactants must go up an energy hill first, before they can go downhill. This will be true even if the reaction is exergonic.

We can represent the energy changes in a reaction using a graph called a **free-energy diagram**, where we plot the free energy of the reacting particles (*y*-axis) against the reaction coordinate (*x*-axis). Figure 6.1 is an example for a generalized S_N2 reaction.

- The **reaction coordinate** indicates the progress of the reaction, in terms of the conversion of reactants to products.
- The top of the energy curve corresponds to the **transition state** for the reaction.
- The **free energy of activation** ($\Delta G^\ddagger$) for the reaction is the difference in energy between the reactants and the transition state.
- The **free energy change for the reaction** (ΔG°) is the difference in energy between the reactants and the products.

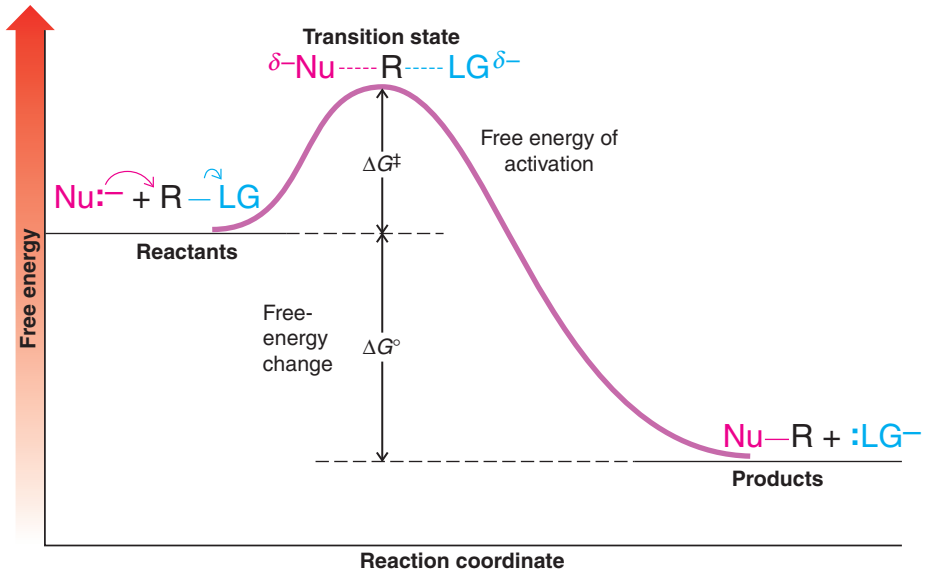


Figure 6.1 A free-energy diagram for a hypothetical exergonic S_N2 reaction (i.e., that takes place with a negative $\Delta G°$, releasing energy to the surroundings).

The top of the energy hill corresponds to the transition state. *The difference in free energy between the reactants and the transition state is the free energy of activation,* $\Delta G^{\ddagger}$. *The difference in free energy between the reactants and products is the free-energy change for the reaction,* $\Delta G°$. For our example in Fig. 6.1, the free-energy level of the products is lower than that of the reactants. In terms of our analogy, we can say that the reactants in one energy valley must surmount an energy hill (the transition state) in order to reach the lower energy valley of the products.

If a reaction in which covalent bonds are broken proceeds with a positive free-energy change (Fig. 6.2), there will still be a free energy of activation. That is, if the products have greater free energy than reactants, the free energy of activation will be even higher. ($\Delta G^{\ddagger}$ will be larger than $\Delta G°$.) In other words, in the **uphill** (endergonic) reaction an even larger energy hill lies between the reactants in one valley and the products in a higher one.

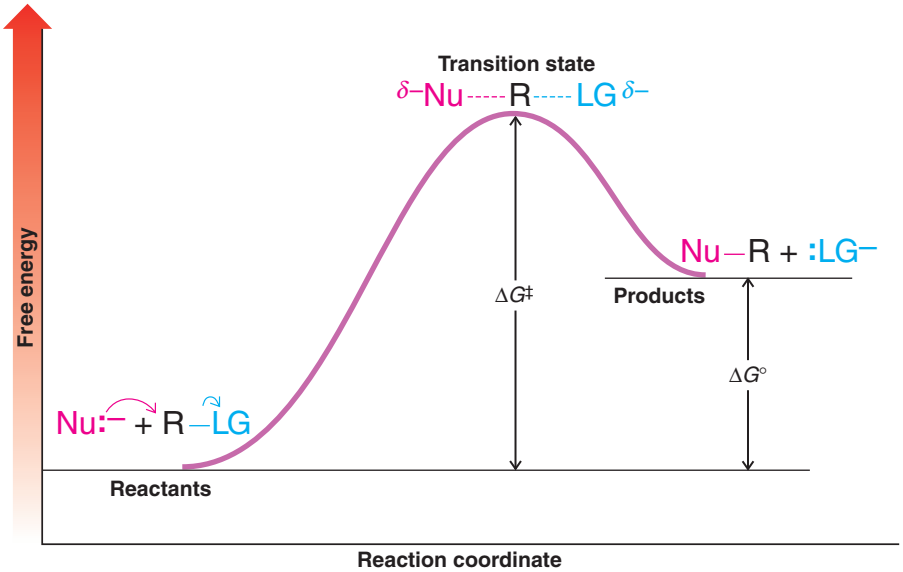


Figure 6.2 A free-energy diagram for a hypothetical endergonic S_N2 reaction (i.e., that takes place with a positive $\Delta G°$, absorbing energy from the surroundings).

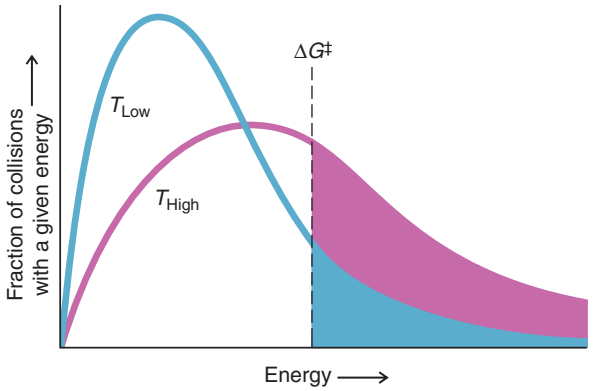


Figure 6.3 The distribution of energies at two different temperatures, T_{Low} and T_{High}. The number of collisions with energies greater than the free energy of activation is indicated by the corresponding shaded area under each curve.

6.7A Temperature, Reaction Rate, and the Equilibrium Constant

Most chemical reactions occur much more rapidly at higher temperatures. The increase in reaction rate for S_N2 reactions relates to the fact that at higher temperatures the number of collisions between reactants with sufficient energy to surmount the activation energy ($\Delta G^{\ddagger}$) increases significantly (see Fig. 6.3).

- A 10°C increase in temperature will cause the reaction rate to double for many reactions taking place near room temperature.

This dramatic increase in reaction rate results from a large increase in the number of collisions between reactants that together have sufficient energy to surmount the barrier at the higher temperature. The kinetic energies of molecules at a given temperature are not all the same. Figure 6.3 shows the distribution of energies brought to collisions at two temperatures (that do not differ greatly), labeled T_{Low} and T_{High}. Because of the way energies are distributed at different temperatures (as indicated by the shapes of the curves), increasing the temperature by only a small amount causes a large increase in the number of collisions with larger energies. In Fig. 6.3 we have designated an arbitrary minimum free energy of activation as being required to bring about a reaction between colliding molecules.

There is also an important relationship between the rate of a reaction and the magnitude of the free energy of activation. The relationship between the rate constant (k) and $\Delta G^{\ddagger}$ is an *exponential one*:

$$k = k_0 e^{-\Delta G^{\ddagger}/RT}$$

In this equation, $e = 2.718$, the base of natural logarithms, and k_0 is the absolute rate constant, which equals the rate at which all transition states proceed to products. At 25°C, $k_0 = 6.2 \times 10^{12}\ s^{-1}$.

- A reaction with a lower free energy of activation ($\Delta G^{\ddagger}$) will occur exponentially faster than a reaction with a higher free energy of activation, as dictated by $k = k_0 e^{-\Delta G^{\ddagger}/RT}$.

Generally speaking, if a reaction has a $\Delta G^{\ddagger}$ less than 84 kJ mol^{-1}, it will take place readily at room temperature or below. If $\Delta G^{\ddagger}$ is greater than 84 kJ mol^{-1}, heating will be required to cause the reaction to occur at a reasonable rate.

A free-energy diagram for the reaction of chloromethane with hydroxide ion is shown in Fig. 6.4. At 60°C, $\Delta G^{\ddagger} = 103$ kJ mol^{-1}, which means that at this temperature the reaction reaches completion in a matter of a few hours.

Review Problem 6.4

Draw a hypothetical free-energy diagram for the S_N2 reaction of iodide anion with 1-chlorobutane. Label the diagram as in Fig. 6.4, and assume it is exergonic but without specific values for $\Delta G^{\ddagger}$ and $\Delta G°$.

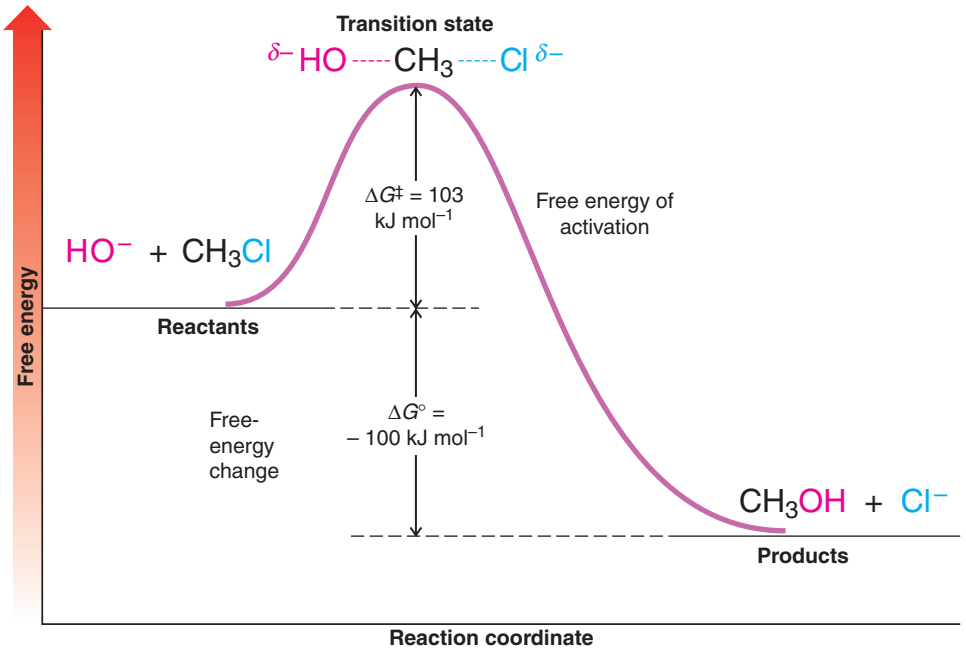


Figure 6.4 A free-energy diagram for the reaction of chloromethane with hydroxide ion at 60°C.

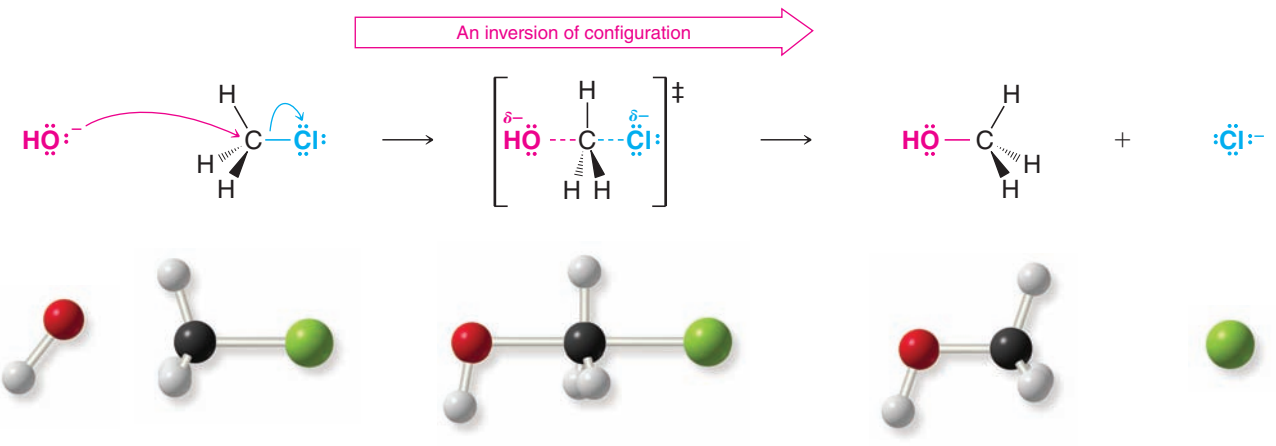
6.8 *The Stereochemistry of S_N2 Reactions*

The stereochemistry of S_N2 reactions is directly related to key features of the mechanism that we learned earlier:

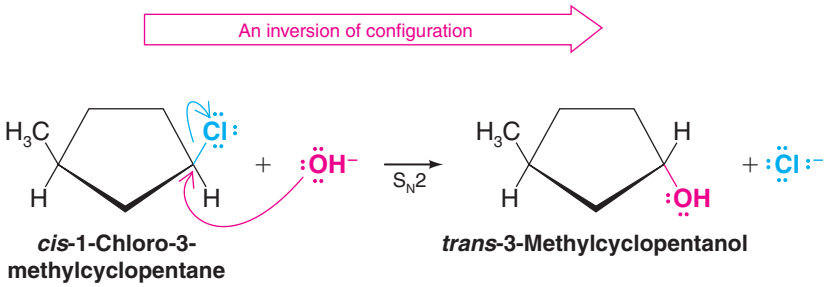
- **The nucleophile approaches the substrate carbon from the back side with respect to the leaving group**. In other words, the bond to the nucleophile that is forming is opposite (at 180°) to the bond to the leaving group that is breaking.
- Nucleophilic displacement of the leaving group in an S_N2 reaction causes **inversion of configuration** at the substrate carbon.

We depict the inversion process as follows. It is much like the way an umbrella is inverted in a strong wind.

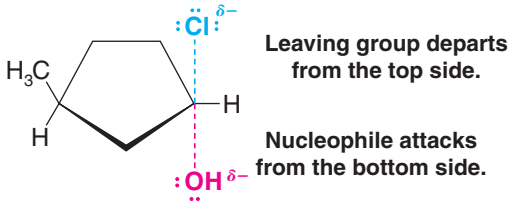
Transition state for an S_N2 reaction.



With a molecule such as chloromethane, however, there is no way to prove that attack by the nucleophile has involved inversion of configuration of the carbon atom because one form of methyl chloride is identical to its inverted form. With a molecule containing chirality centers such as *cis*-1-chloro-3-methylcyclopentane, however, we can observe the results of an inversion of configuration by the change in stereochemistry that occurs. When *cis*-1-chloro-3-methylcyclopentane reacts with hydroxide ion in an S_N2 reaction, the product is *trans*-3-methylcyclopentanol. *The hydroxide ion ends up being bonded on the opposite side of the ring from the chlorine it replaces*:



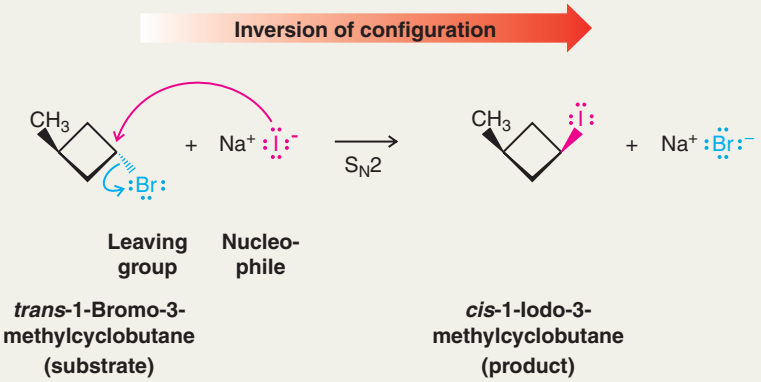
Presumably, the transition state for this reaction is like that shown here.



Solved Problem 6.3

Give the structure of the product that would be formed when *trans*-1-bromo-3-methylcyclobutane undergoes an S_N2 reaction with NaI.

STRATEGY AND ANSWER First, write the formulas for the reactants and identify the nucleophile, the substrate, and the leaving group. Then, recognizing that the nucleophile will attack the back side of the substrate carbon atom that bears the leaving group, causing an inversion of configuration at that carbon, write the structure of the product.

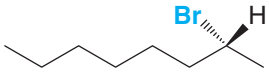


Review Problem 6.5

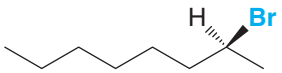
Using chair conformational structures (Section 4.11), show the nucleophilic substitution reaction that would take place when *trans*-1-bromo-4-*tert*-butylcyclohexane reacts with iodide ion. (Show the most stable conformation of the reactant and the product.)

- **S_N2 reactions always occur with inversion of configuration.**

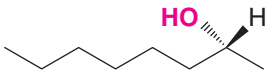
We can also observe inversion of configuration when an S_N2 reaction occurs at a chirality center in an acyclic molecule. The reaction of (*R*)-(−)-2-bromooctane with sodium hydroxide provides an example. We can determine whether or not inversion of configuration occurs in this reaction because the configurations and optical rotations for both enantiomers of 2-bromooctane and the expected product, 2-octanol, are known.



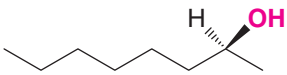
(*R*)-(−)-2-Bromooctane
$[\alpha]_D^{25} = -34.25$



(*S*)-(+)-2-Bromooctane
$[\alpha]_D^{25} = +34.25$



(*R*)-(−)-2-Octanol
$[\alpha]_D^{25} = -9.90$



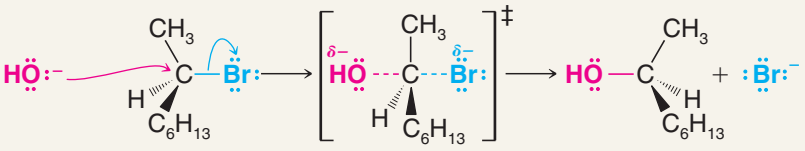
(*S*)-(+)-2-Octanol
$[\alpha]_D^{25} = +9.90$

When the reaction is carried out, we find that enantiomerically pure (*R*)-(−)-2-bromooctane ($[\alpha]_D^{25} = -34.25$) has been converted to enantiomerically pure (*S*)-(+)-2-octanol ($[\alpha]_D^{25} = +9.90$).

A MECHANISM FOR THE REACTION

The Stereochemistry of an S_N2 Reaction

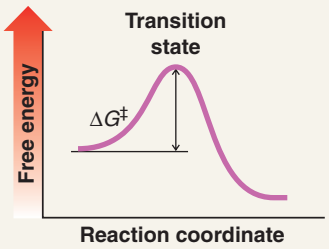
The reaction of (*R*)–(−)–2-bromooctane with hydroxide is an S_N2 reaction and takes place with *complete inversion of configuration*:



An inversion of configuration

(*R*)-(−)-2-Bromooctane
$[\alpha]_D^{25} = -34.25°$
Enantiomeric purity = 100%

(*S*)-(+)-2-Octanol
$[\alpha]_D^{25} = +9.90°$
Enantiomeric purity = 100%



An S_N2 reaction has one transition state.

Review Problem 6.6

S_N2 reactions that involve breaking a bond to a chirality center can be used to relate configurations of molecules because the *stereochemistry* of the reaction is known.

(a) Illustrate how this is true by assigning configurations to the 2-chlorobutane enantiomers based on the following data. [The configuration of (−)-2-butanol is given in Section 5.8C.]

(+)-2-Chlorobutane $\xrightarrow[S_N2]{OH^-}$ (−)-2-Butanol

$[\alpha]_D^{25} = +36.00$
Enantiomerically pure

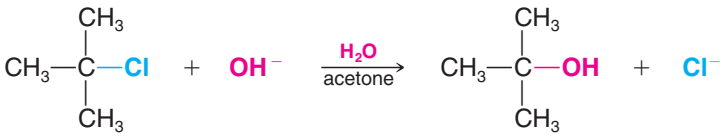
$[\alpha]_D^{25} = -13.52$
Enantiomerically pure

(b) When optically pure (+)-2-chlorobutane is allowed to react with potassium iodide in acetone in an S_N2 reaction, the 2-iodobutane that is produced has a minus rotation. What is the configuration of (−)-2-iodobutane? Of (+)-2-iodobutane?

6.9 The Reaction of tert-Butyl Chloride with Hydroxide Ion: An S_N1 Reaction

Let us now consider another mechanism for nucleophilic substitution: the S_N1 reaction. When *tert*-butyl chloride reacts with sodium hydroxide in a mixture of water and acetone, the kinetic results are quite different than for the reaction of chloromethane with hydroxide. The rate of formation of *tert*-butyl alcohol is dependent on the concentration of *tert*-butyl chloride, but it is *independent of the concentration of hydroxide ion*. Doubling the *tert*-butyl chloride concentration *doubles* the rate of the substitution reaction, but changing the hydroxide ion concentration (within limits) has no appreciable effect. *tert*-Butyl chloride reacts by substitution at virtually the same rate in pure water (where the hydroxide ion is 10^{-7} *M*) as it does in 0.05*M* aqueous sodium hydroxide (where the hydroxide ion concentration is 500,000 times larger). (We shall see in Section 6.10 that the important nucleophile in this reaction is a molecule of water.)

Thus, the rate equation for this substitution reaction is first order with respect to *tert*-butyl chloride and *first order overall*:



$$\text{Rate} \propto [(CH_3)_3CCl]$$

$$\text{Rate} = k[(CH_3)_3CCl]$$

We can conclude, therefore, that hydroxide ions do not participate in the transition state of the step that controls the rate of the reaction and that only molecules of *tert*-butyl chloride are involved. This reaction is said to be **unimolecular** (first order) in the rate-determining step. We call this type of reaction an **S_N1 reaction** (**substitution, nucleophilic, unimolecular**). (In Section 6.15 we shall see that elimination reactions can compete with S_N1 reactions, leading to the formation of alkenes, but in the case of *tert*-butyl chloride in the absence of base and at room temperature, S_N1 is the dominant process.)

How can we explain an S_N1 reaction in terms of a mechanism? To do so, we shall need to consider the possibility that the mechanism involves more than one step. But what kind of kinetic results should we expect from a multistep reaction? Let us consider this point further.

6.9A Multistep Reactions and the Rate-Determining Step

- If a reaction takes place in a series of steps, and if one step is intrinsically slower than all the others, then the rate of the overall reaction will be essentially the same as the rate of this slow step. This slow step, consequently, is called the **rate-limiting step** or the **rate-determining step**.

Consider a multistep reaction such as the following:

$$\text{Reactant} \xrightarrow[\text{(slow)}]{k_1} \text{intermediate 1} \xrightarrow[\text{(fast)}]{k_2} \text{intermediate 2} \xrightarrow[\text{(fast)}]{k_3} \text{product}$$

Step 1 *Step 2* *Step 3*

When we say that the first step in this example is intrinsically slow, we mean that the rate constant for step 1 is very much smaller than the rate constant for step 2 or for step 3. That is, $k_1 << k_2$ or k_3. When we say that steps 2 and 3 are *fast*, we mean that because their rate constants are larger, they could (in theory) take place rapidly if the concentrations of the two intermediates ever became high. In actuality, the concentrations of the intermediates are always very small because of the slowness of step 1.

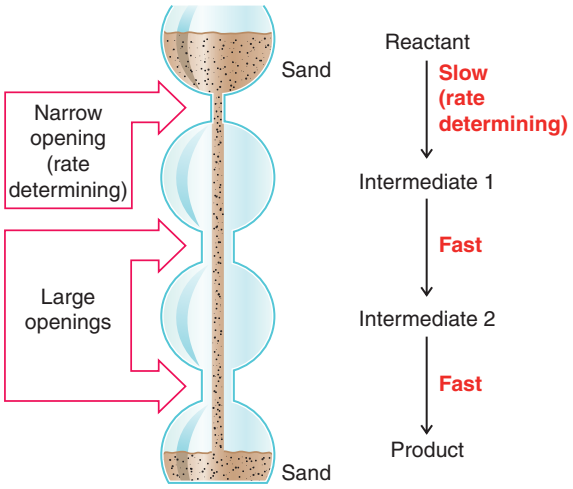
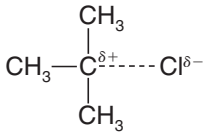


Figure 6.5 A modified hourglass that serves as an analogy for a multistep reaction. The overall rate is limited by the rate of the slow step.

As an analogy, imagine an hourglass modified in the way shown in Fig. 6.5. The opening between the top chamber and the one just below is considerably smaller than the other two. The overall rate at which sand falls from the top to the bottom of the hourglass is limited by the rate at which sand passes through the small orifice. This step, in the passage of sand, is analogous to the rate-determining step of the multistep reaction.

6.10 *A Mechanism for the S_N1 Reaction*

The mechanism for the reaction of *tert*-butyl chloride with water (Section 6.9) can be described in three steps. See the box "Mechanism for the S_N1 Reaction" below, with a schematic free-energy diagram highlighted for each step. Two distinct **intermediates** are formed. The first step is the slow step—it is the rate-determining step. In it a molecule of *tert*-butyl chloride ionizes and becomes a *tert*-butyl cation and a chloride ion. In the transition state for this step the carbon–chlorine bond of *tert*-butyl chloride is largely broken and ions are beginning to develop:



The solvent (water) stabilizes these developing ions by solvation. Carbocation formation, in general, takes place slowly because it is usually a highly endothermic process and is uphill in terms of free energy.

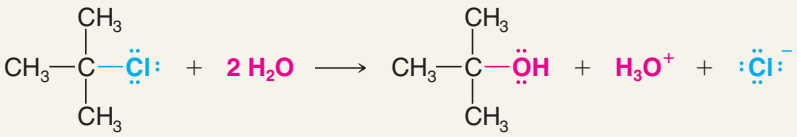
The first step requires heterolytic cleavage of the carbon–chlorine bond. Because no other bonds are formed in this step, it should be highly endothermic and it should have a high free energy of activation, as we see in the free-energy diagram. **That departure of the halide takes place at all is largely because of the ionizing ability of the solvent, water**. Experiments indicate that in the gas phase (i.e., in the absence of a solvent), the free energy of activation is about 630 kJ mol^{-1}! In aqueous solution, however, the free energy of activation is much lower—about 84 kJ mol^{-1}. **Water molecules surround and stabilize the cation and anion that are produced** (cf. Section 2.13D).

In the second step the intermediate *tert*-butyl cation reacts rapidly with water to produce a *tert*-butyloxonium ion, $(CH_3)_3COH_2^+$, which in the third step, rapidly transfers a proton to a molecule of water producing *tert*-butyl alcohol.

A MECHANISM FOR THE REACTION

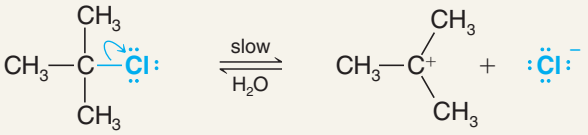
Mechanism for the S_N1 Reaction

REACTION



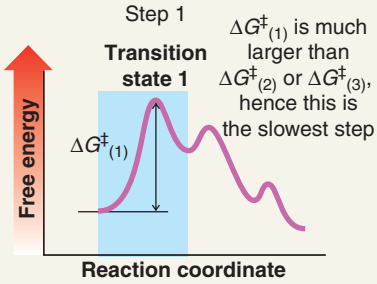
MECHANISM

Step 1

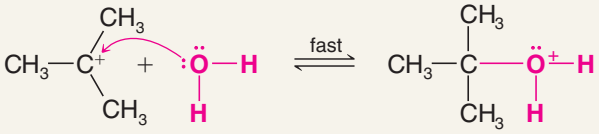


Aided by the polar solvent, a chlorine departs with the electron pair that bonded it to the carbon.

This slow step produces the 3° carbocation intermediate and a chloride ion. Although not shown here, the ions are solvated (and stabilized) by water molecules.

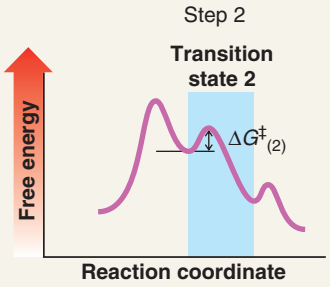


Step 2

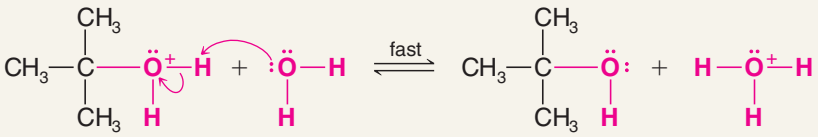


A water molecule acting as a Lewis base donates an electron pair to the carbocation (a Lewis acid). This gives the cationic carbon eight electrons.

The product is a *tert*-butyloxonium ion (or protonated *tert*-butyl alcohol).

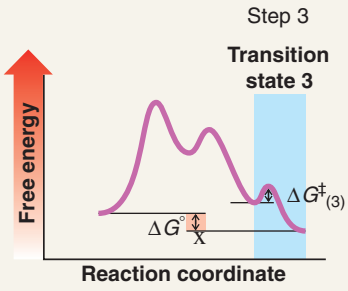


Step 3



A water molecule acting as a Brønsted base accepts a proton from the *tert*-butyloxonium ion.

The products are *tert*-butyl alcohol and a hydronium ion.



6.11 *Carbocations*

Beginning in the 1920s much evidence began to accumulate implicating simple alkyl cations as intermediates in a variety of ionic reactions. However, because alkyl cations are highly unstable and highly reactive, they were, in all instances studied before 1962, very short-lived,

transient species that could not be observed directly.* However, in 1962 George A. Olah (University of Southern California) and co-workers published the first of a series of papers describing experiments in which alkyl cations were prepared in an environment in which they were reasonably stable and in which they could be observed by a number of spectroscopic techniques.

Olah was awarded the 1994 Nobel Prize in Chemistry.

6.11A The Structure of Carbocations

- Carbocations are trigonal planar.

Just as the trigonal planar structure of BF_3 (Section 1.16D) can be accounted for on the basis of sp^2 hybridization, so, too (Fig. 6.6), can the trigonal planar structure of carbocations.

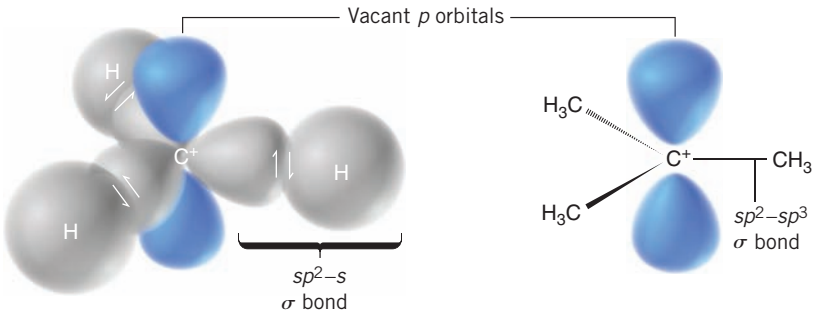


Figure 6.6 *(a)* A stylized orbital structure of the methyl cation. The bonds are sigma (σ) bonds formed by overlap of the carbon atom's three sp^2 orbitals with the 1*s* orbitals of the hydrogen atoms. The *p* orbital is vacant. *(b)* A dashed line–wedge representation of the *tert*-butyl cation. The bonds between carbon atoms are formed by overlap of sp^3 orbitals of the methyl groups with sp^2 orbitals of the central carbon atom.

- The central carbon atom in a carbocation is electron deficient; it has only six electrons in its valence shell.

In our model (Fig. 6.6) these six electrons are used to form three sigma covalent bonds to hydrogen atoms or alkyl groups.

- The *p* orbital of a carbocation contains no electrons, but it can accept an electron pair when the carbocation undergoes further reaction.

Not all types of carbocations have the same relative stability as we shall learn in the next section.

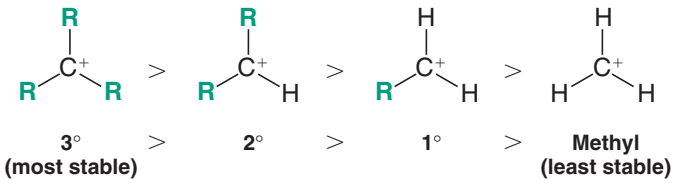
6.11B The Relative Stabilities of Carbocations

Helpful Hint

An understanding of carbocation structure and relative stability is important for learning a variety of reaction processes.

The relative stabilities of carbocations are related to the number of alkyl groups attached to the positively charged trivalent carbon.

- Tertiary carbocations are the most stable, and the methyl carbocation is the least stable.
- The overall order of stability is as follows:



This order of carbocation stability can be explained on the basis of hyperconjugation.

- **Hyperconjugation** involves electron delocalization (via partial orbital overlap) from a filled bonding orbital to an adjacent unfilled orbital (Section 4.8).

*As we shall learn later, carbocations bearing aromatic groups can be much more stable; one of these had been studied as early as 1901.

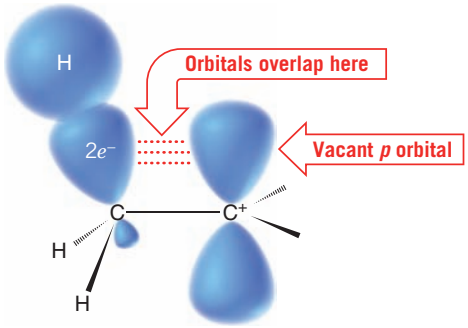


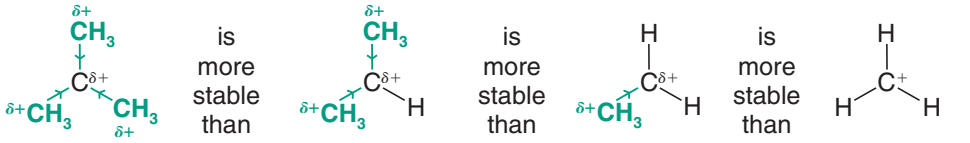
Figure 6.7 *How a methyl group helps stabilize the positive charge of a carbocation.* Electron density from one of the carbon–hydrogen sigma bonds of the methyl group flows into the vacant *p* orbital of the carbocation because the orbitals can partly overlap. Shifting electron density in this way makes the sp^2-hybridized carbon of the carbocation somewhat less positive, and the hydrogens of the methyl group assume some of the positive charge. Delocalization (dispersal) of the charge in this way leads to greater stability. This interaction of a bond orbital with a *p* orbital is called hyperconjugation.

In the case of a carbocation, the unfilled orbital is the vacant *p* orbital of the carbocation, and the filled orbitals are C—H or C—C sigma bonds at the carbons *adjacent* to the *p* orbital of the carbocation. Sharing of electron density from adjacent C—H or C—C sigma bonds with the carbocation *p* orbital delocalizes the positive charge.

- Any time a charge can be dispersed or delocalized by hyperconjugation, inductive effects, or resonance, a system will be stabilized.

Figure 6.7 shows a stylized representation of hyperconjugation between a sigma bonding orbital and an adjacent carbocation *p* orbital.

Tertiary carbocations have three carbons with C—H bonds (or, depending on the specific example, C—C bonds instead of C—H) adjacent to the carbocation that can overlap partially with the vacant *p* orbital. Secondary carbocations have only two adjacent carbons with C—H or C—C bonds to overlap with the carbocation; hence, the possibility for hyperconjugation is less and the secondary carbocation is less stable. Primary carbocations have only one adjacent carbon from which to derive hyperconjugative stabilization, and so they are even less stable. A methyl carbocation has no possibility for hyperconjugation, and it is the least stable of all in this series. The following are specific examples:

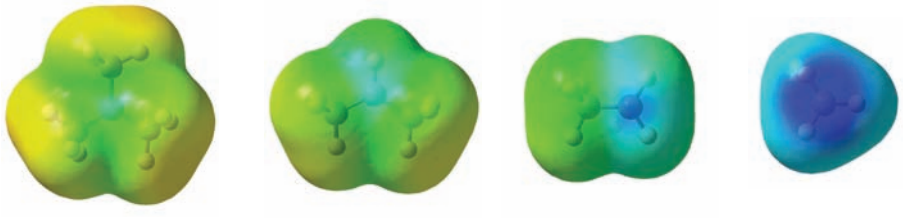


***tert*-Butyl cation (3°) (most stable)** — **Isopropyl cation (2°)** — **Ethyl cation (1°)** — **Methyl cation (least stable)**

In summary:

- **The relative stability of carbocations is 3° > 2° > 1° > methyl.**

This trend is also readily seen in electrostatic potential maps for these carbocations (Fig. 6.8).

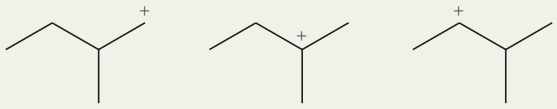


(*a*) *tert*-Butyl (3°) **(*b*) Isopropyl (2°)** **(*c*) Ethyl (1°)** **(*d*) Methyl**

Figure 6.8 Maps of electrostatic potential for *(a) tert*-butyl (3°), *(b)* isopropyl (2°), *(c)* ethyl (1°), and *(d)* methyl carbocations show the trend from greater to lesser delocalization (stabilization) of the positive charge in these structures. Less blue color indicates greater delocalization of the positive charge. (The structures are mapped on the same scale of electrostatic potential to allow direct comparison.)

Solved Problem 6.4

Rank the following carbocations in order of increasing stability:

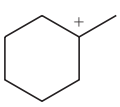
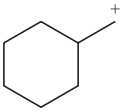
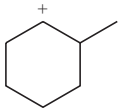


A **B** **C**

STRATEGY AND ANSWER Structure **A** is a primary carbocation, **B** is tertiary, and **C** is secondary. Therefore, in order of increasing stability, **A** < **C** < **B**.

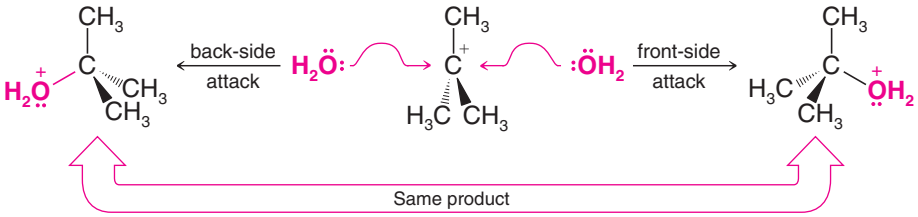
Review Problem 6.7

Rank the following carbocations in order of increasing stability:

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

6.12 The Stereochemistry of S_N1 Reactions

Because the carbocation formed in the first step of an S_N1 reaction has a trigonal planar structure (Section 6.11A), when it reacts with a nucleophile, it may do so from either the front side or the back side (see below). With the *tert*-butyl cation this makes no difference; since the *tert*-butyl group is not a chirality center, the same product is formed by either mode of attack. (Convince yourself of this result by examining models.)



With some cations, however, stereoisomeric products arise from the two reaction possibilities. We shall study this point next.

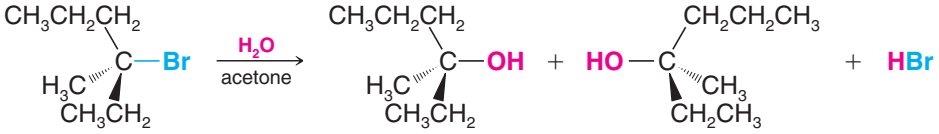
6.12A Reactions That Involve Racemization

A reaction that transforms an optically active compound into a racemic form is said to proceed with **racemization**. If the original compound loses all of its optical activity in the course of the reaction, chemists describe the reaction as having taken place with *complete* racemization. If the original compound loses only part of its optical activity, as would be the case if an enantiomer were only partially converted to a racemic form, then chemists describe this as proceeding with *partial* racemization.

- Racemization takes place whenever the reaction causes chiral molecules to be converted to an achiral intermediate.

Examples of this type of reaction are S_N1 reactions in which the leaving group departs from a chirality center. These reactions almost always result in extensive and sometimes complete racemization. For example, heating optically active (*S*)-3-bromo-3-methylhexane

with aqueous acetone results in the formation of 3-methyl-3-hexanol as a mixture of 50% (*R*) and 50% (*S*).



(*S*)-3-Bromo-3-methylhexane
(optically active)

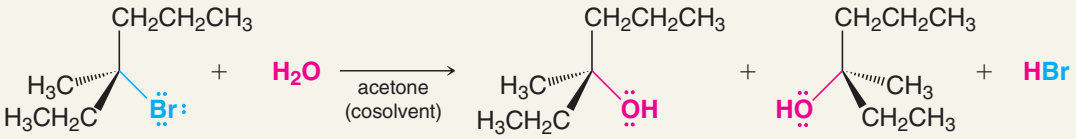
50% (*S*)-3-Methyl-3-hexanol
50% (*R*)-3-Methyl-3-hexanol
(optically inactive, a racemic form)

The reason: The S_N1 reaction proceeds through the formation of an intermediate carbocation and the carbocation, because of its trigonal planar configuration, *is achiral*. It reacts with water at equal rates from either side to form the enantiomers of 3-methyl-3-hexanol in equal amounts.

A MECHANISM FOR THE REACTION

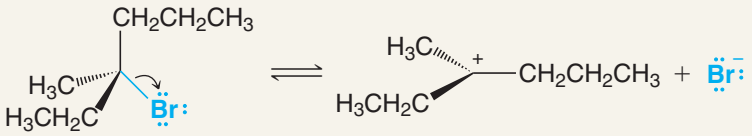
The Stereochemistry of an S_N1 Reaction

REACTION



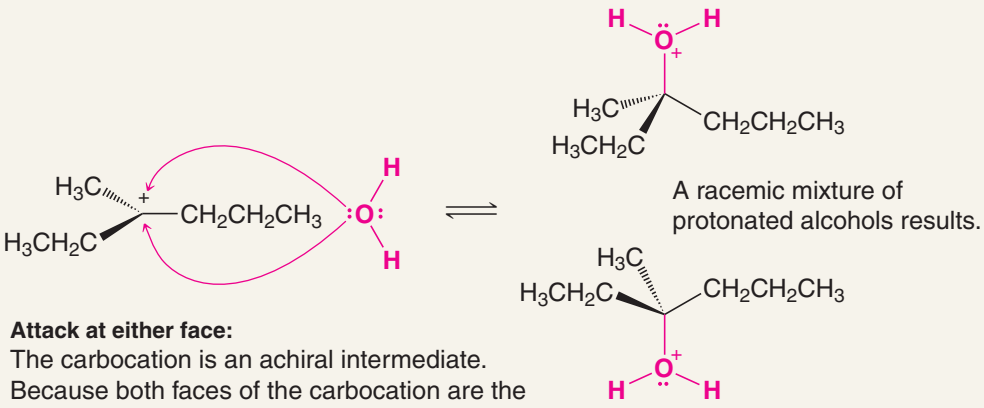
MECHANISM

Step 1



Departure of the leaving group (assisted by hydrogen bonding with solvent) leads to the carbocation.

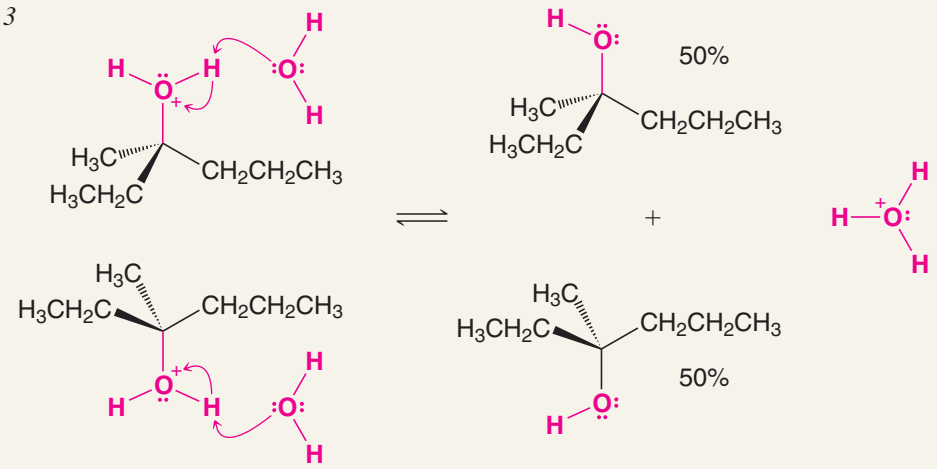
Step 2



Attack at either face:
The carbocation is an achiral intermediate. Because both faces of the carbocation are the same, the nucleophile can bond with either face to form a mixture of stereoisomers.

(mechanism continues on the next page)

Step 3



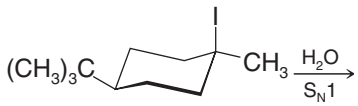
Additional solvent molecules (water) deprotonate the alkyloxonium ion.

The product is a racemic mixture.

The S_N1 reaction of (*S*)-3-bromo-3-methylhexane proceeds with racemization because the intermediate carbocation is achiral and attack by the nucleophile can occur from either side.

Review Problem 6.8

Keeping in mind that carbocations have a trigonal planar structure, **(a)** write a structure for the carbocation intermediate and **(b)** write structures for the alcohol (or alcohols) that you would expect from the following reaction:



6.12B Solvolysis

The S_N1 reaction of an alkyl halide with water is an example of **solvolysis**. A solvolysis reaction is a nucleophilic substitution in which *the nucleophile is a molecule of the solvent* (*solvent* + *lysis*: cleavage by the solvent). Since the solvent in this instance is water, we could also call the reaction a **hydrolysis**. If the reaction had taken place in methanol, we would call it a **methanolysis**.

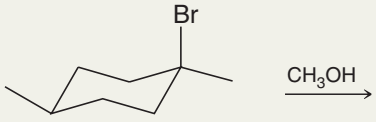
Examples of Solvolysis

$$(CH_3)_3C{-}Br + H_2O \longrightarrow (CH_3)_3C{-}OH + HBr$$

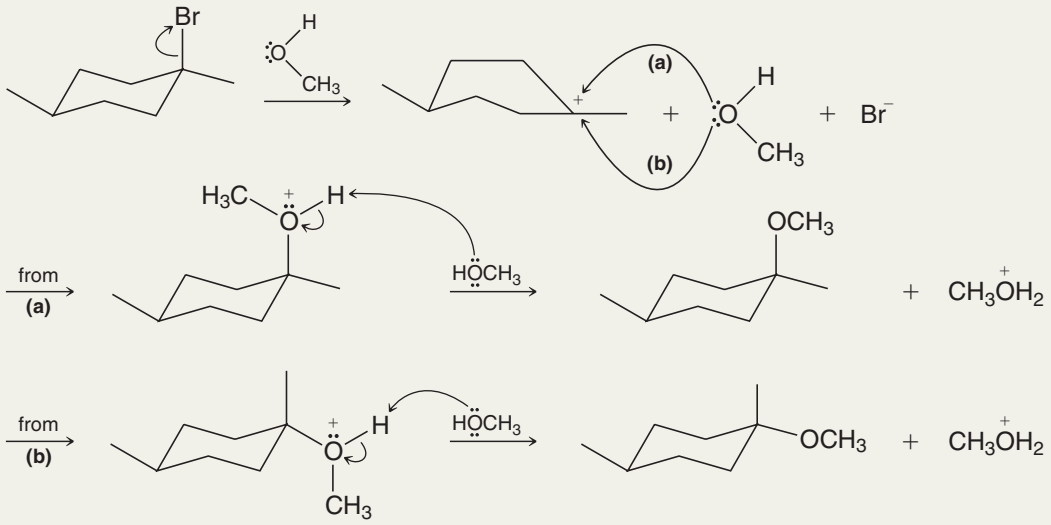
$$(CH_3)_3C{-}Cl + CH_3OH \longrightarrow (CH_3)_3C{-}OCH_3 + HCl$$

Solved Problem 6.5

What product(s) would you expect from the following solvolysis?



STRATEGY AND ANSWER We observe that this cyclohexyl bromide is tertiary, and therefore in methanol it should lose a bromide ion to form a tertiary carbocation. Because the carbocation is trigonal planar at the positive carbon, it can react with a solvent molecule (methanol) to form two products.



Review Problem 6.9 What product(s) would you expect from the methanolysis of the iodocyclohexane derivative given as the reactant in Review Problem 6.8?

6.13 Factors Affecting the Rates of S_N1 and S_N2 Reactions

Now that we have an understanding of the mechanisms of S_N2 and S_N1 reactions, our next task is to explain why chloromethane reacts by an S_N2 mechanism and *tert*-butyl chloride by an S_N1 mechanism. We would also like to be able to predict which pathway—S_N1 or S_N2—would be followed by the reaction of any alkyl halide with any nucleophile under varying conditions.

The answer to this kind of question is to be found in the *relative rates of the reactions that occur*. If a given alkyl halide and nucleophile react *rapidly* by an S_N2 mechanism but *slowly* by an S_N1 mechanism under a given set of conditions, then an S_N2 pathway will be followed by most of the molecules. On the other hand, another alkyl halide and another nucleophile may react very slowly (or not at all) by an S_N2 pathway. If they react rapidly by an S_N1 mechanism, then the reactants will follow an S_N1 pathway.

- A number of factors affect the relative rates of S_N1 and S_N2 reactions. The most important factors are
  1. the structure of the substrate,
  2. the concentration and reactivity of the nucleophile (for bimolecular reactions only),
  3. the effect of the solvent, and
  4. the nature of the leaving group.

6.13A The Effect of the Structure of the Substrate

S_N2 Reactions Simple alkyl halides show the following general order of reactivity in S_N2 reactions:

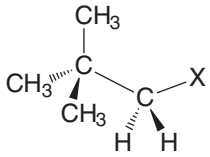
Methyl > **primary** > **secondary** >> **(tertiary—unreactive)**

Methyl halides react most rapidly and tertiary halides react so slowly as to be unreactive by the S_N2 mechanism. Table 6.4 gives the relative rates of typical S_N2 reactions.

TABLE 6.4 Relative Rates of Reactions of Alkyl Halides in S_N2 Reactions

Substituent	Compound	Approximate Relative Rate
Methyl	CH_3X	30
1°	CH_3CH_2X	1
2°	$(CH_3)_2CHX$	0.03
Neopentyl	$(CH_3)_3CCH_2X$	0.00001
3°	$(CH_3)_3CX$	~0

Neopentyl halides, even though they are primary halides, are very unreactive:



A neopentyl halide

The important factor behind this order of reactivity is a steric effect, and in this case, steric hindrance.

- A **steric effect** is an effect on the relative rates caused by the space-filling properties of those parts of a molecule attached at or near the reacting site.
- **Steric hindrance** is when the spatial arrangement of atoms or groups at or near a reacting site of a molecule hinders or retards a reaction.

For particles (molecules and ions) to react, their reactive centers must be able to come within bonding distance of each other. Although most molecules are reasonably flexible, very large and bulky groups can often hinder the formation of the required transition state. In some cases they can prevent its formation altogether.

An S_N2 reaction requires an approach by the nucleophile to a distance within the bonding range of the carbon atom bearing the leaving group. Because of this, bulky substituents on *or near* that carbon atom have a dramatic inhibiting effect (Fig. 6.9). They cause the free energy of the required transition state to be increased and, consequently, they increase the free energy of activation for the reaction. Of the simple alkyl halides, methyl halides react most rapidly in S_N2 reactions because only three small hydrogen atoms interfere with the approaching nucleophile. Neopentyl and tertiary halides are the least reactive because bulky groups present a strong hindrance to the approaching nucleophile. (Tertiary substrates, for all practical purposes, do not react by an S_N2 mechanism.)

Helpful Hint

You can best appreciate the steric effects in these structures by building models.

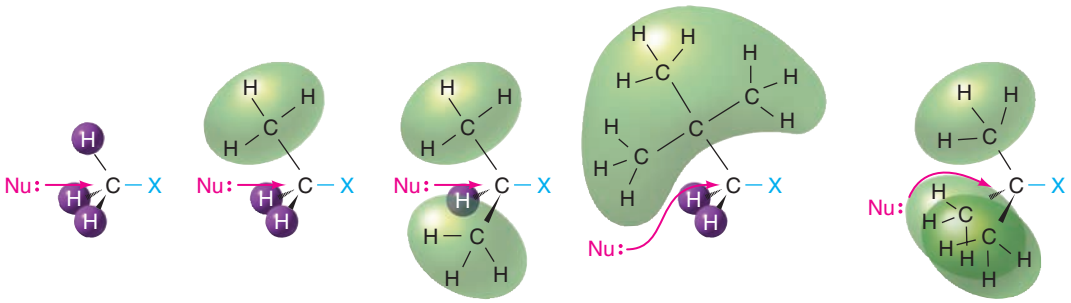
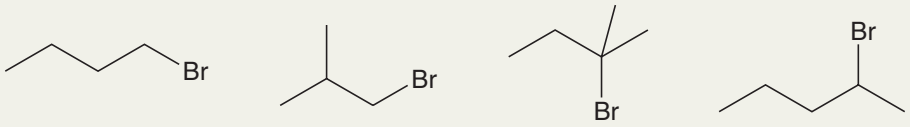


Figure 6.9 Steric effects and relative rates in the S_N2 reaction.

Solved Problem 6.6

Rank the following alkyl bromides in order of decreasing reactivity (from fastest to slowest) as a substrate in an S_N2 reaction.



A **B** **C** **D**

STRATEGY AND ANSWER We examine the carbon bearing the leaving group in each instance to assess the steric hindrance to an S_N2 reaction at that carbon. In **C** it is 3°; therefore, three groups would hinder the approach of a nucleophile, so this alkyl bromide would react most slowly. In **D** the carbon bearing the leaving group is 2° (two groups hinder the approach of the nucleophile), while in both **A** and **B** it is 1° (one group hinders the nucleophile's approach). Therefore, **D** would react faster than **C**, but slower than either **A** or **B**. But, what about **A** and **B**? They are both 1° alkyl bromides, but **B** has a methyl group on the carbon adjacent to the one bearing the bromine, which would provide hindrance to the approaching nucleophile that would not be present in **A**. The order of reactivity, therefore, is **A** > **B** > **D** >> **C**.

Helpful Hint

The primary factor that determines the reactivity of organic substrates in an S_N1 reaction is the relative stability of the carbocation that is formed.

S_N1 Reactions

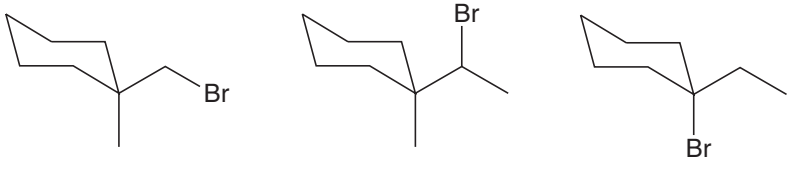
- Except for those reactions that take place in strong acids, which we shall study later, **the only organic compounds that undergo reaction by an S_N1 path at a reasonable rate are *those that are capable of forming relatively stable carbocations***.

Of the simple alkyl halides that we have studied so far, this means (for all practical purposes) that only tertiary halides react by an S_N1 mechanism. (Later we shall see that certain organic halides, called *allylic halides* and *benzylic halides*, can also react by an S_N1 mechanism because they can form relatively stable carbocations; see Sections 13.4 and 15.15.)

Tertiary carbocations are stabilized because sigma bonds at three adjacent carbons contribute electron density to the carbocation *p* orbital by hyperconjugation (Section 6.11B). Secondary and primary carbocations have less stabilization by hyperconjugation. A methyl carbocation has no stabilization. Formation of a relatively stable carbocation is important in an S_N1 reaction because it means that the free energy of activation for the slow step of the reaction (e.g., $R{-}L \longrightarrow R^+ + L^-$) will be low enough for the reaction to take place at a reasonable rate.

Review Problem 6.10

Which of the following alkyl halides is most likely to undergo substitution by an S_N1 mechanism?

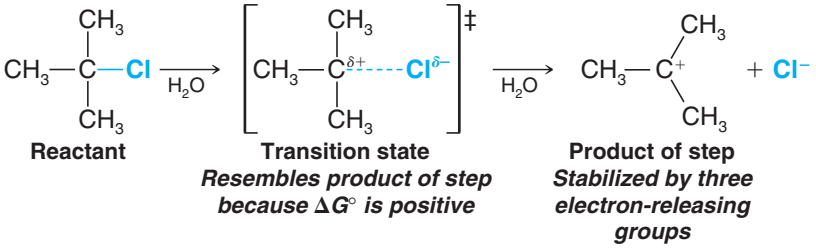


(a) **(b)** **(c)**

The Hammond–Leffler Postulate If you review the free-energy diagrams that accompany the mechanism for the S_N1 reaction of *tert*-butyl chloride and water (Section 6.10), you will see that step 1, the ionization of the leaving group to form the carbocation, is *uphill in terms of free energy* ($\Delta G°$ for this step is positive). It is also uphill in terms of enthalpy ($\Delta H°$ is also positive), and, therefore, this step is *endothermic*. According to the **Hammond–Leffler postulate**, **the transition-state structure for a step that is uphill in energy should show**

a strong resemblance to the structure of the product of that step. Since the product of this step (actually an intermediate in the overall reaction) is a carbocation, any factor that stabilizes the carbocation—such as dispersal of the positive charge by electron-releasing groups—should also stabilize the transition state in which the positive charge is developing.

Ionization of the Leaving Group



Reactant

Transition state
Resembles product of step because ΔG° is positive

Product of step
Stabilized by three electron-releasing groups

A methyl, primary, or secondary alkyl halide would have to ionize to form a methyl, primary, or secondary carbocation to react by an S_N1 mechanism. These carbocations, however, are much higher in energy than a tertiary carbocation, and the transition states leading to these carbocations are even higher in energy. The activation energy for an S_N1 reaction of a simple methyl, primary, or secondary halide, consequently, is so large (therefore the reaction is so slow) that, for all practical purposes, an S_N1 reaction with a methyl, primary, or secondary halide does not compete with the corresponding S_N2 reaction.

The Hammond–Leffler postulate is quite general and can be better understood through consideration of Fig. 6.10. One way that the postulate can be stated is to say that *the structure of a transition state resembles the stable species that is nearest it in free energy*. For example, in a highly **endergonic** step (blue curve) the transition state lies close to the products in free energy, and we assume, therefore, that **it resembles the products of that step in structure**. Conversely, in a highly exergonic step (red curve) the transition state lies close to the reactants in free energy, and we assume **it resembles the reactants in structure** as well. The great value of the Hammond–Leffler postulate is that it gives us an intuitive way of visualizing those important, but fleeting, species that we call transition states. We shall make use of it in many future discussions.

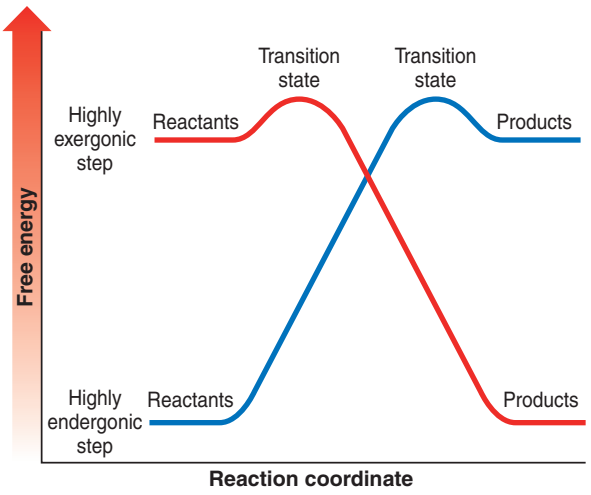


Figure 6.10 The transition state for a highly exergonic step (red curve) lies close to and resembles the reactants. The transition state for an endergonic step (blue curve) lies close to and resembles the products of a reaction. (Reprinted with permission of The McGraw-Hill Companies from Pryor, *Free Radicals*, p. 156, Copyright 1966.)

Review Problem 6.11

The relative rates of ethanolysis of four primary alkyl halides are as follows: CH_3CH_2Br, 1.0; $CH_3CH_2CH_2Br$, 0.28; $(CH_3)_2CHCH_2Br$, 0.030; $(CH_3)_3CCH_2Br$, 0.00000042.

(a) Is each of these reactions likely to be S_N1 or S_N2?

(b) Provide an explanation for the relative reactivities that are observed.

6.13B The Effect of the Concentration and Strength of the Nucleophile

Since the nucleophile does not participate in the rate-determining step of an S_N1 reaction, the rates of S_N1 reactions are unaffected by either the concentration or the identity of the nucleophile. The rates of S_N2 reactions, however, depend on *both* the concentration *and* the identity of the attacking nucleophile. We saw in Section 6.5 how increasing the concentration of the nucleophile increases the rate of an S_N2 reaction. We can now examine how the rate of an S_N2 reaction depends on the identity of the nucleophile.

- The relative strength of a nucleophile (its **nucleophilicity**) is measured in terms of the relative rate of its S_N2 reaction with a given substrate.

A good nucleophile is one that reacts rapidly in an S_N2 reaction with a given substrate. A poor nucleophile is one that reacts slowly in an S_N2 reaction with the same substrate under comparable reaction conditions. (As mentioned above, we cannot compare nucleophilicities with regard to S_N1 reactions because the nucleophile does not participate in the rate-determining step of an S_N1 reaction.)

Methoxide anion, for example, is a good nucleophile for a substitution reaction with iodomethane. It reacts rapidly by an S_N2 mechanism to form dimethyl ether:

$$CH_3O^- + CH_3I \xrightarrow{\text{rapid}} CH_3OCH_3 + I^-$$

Methanol, on the other hand, is a poor nucleophile for reaction with iodomethane. Under comparable conditions it reacts very slowly. It is not a sufficiently powerful Lewis base (i.e., nucleophile) to cause displacement of the iodide leaving group at a significant rate:

$$CH_3OH + CH_3I \xrightarrow{\text{very slow}} CH_3\overset{+}{O}(H)CH_3 + I^-$$

The relative strengths of nucleophiles can be correlated with three structural features:

1. **A negatively charged nucleophile is always a more reactive nucleophile than its conjugate acid**. Thus HO^- is a better nucleophile than H_2O and RO^- is better than ROH.
2. **In a group of nucleophiles in which the nucleophilic atom is the same, nucleophilicities parallel basicities**. Oxygen compounds, for example, show the following order of reactivity:

   $$RO^- > HO^- >> RCO_2^- > ROH > H_2O$$

   This is also their order of basicity. An alkoxide ion (RO^-) is a slightly stronger base than a hydroxide ion (HO^-), a hydroxide ion is a much stronger base than a carboxylate ion (RCO_2^-), and so on.
3. **When the nucleophilic atoms are different, nucleophilicities may not parallel basicities**. For example, in protic solvents HS^-, CN^-, and I^- are all weaker bases than HO^-, yet they are **stronger nucleophiles** than HO^-.

   $$HS^- > CN^- > I^- > HO^-$$

Nucleophilicity versus Basicity While nucleophilicity and basicity are related, they are not measured in the same way. Basicity, as expressed by pK_a, is measured *by the position of an equilibrium* involving an electron pair donor (base), a proton, the conjugate acid, and the conjugate base. Nucleophilicity is measured *by relative rates of reaction*, by how rapidly an electron pair donor reacts at an atom (usually carbon) bearing a leaving group. For example, the hydroxide ion (OH^-) is a stronger base than a cyanide ion (CN^-); at equilibrium it has the greater affinity for a proton (the pK_a of H_2O is ~16, while the pK_a of HCN is ~10). Nevertheless, cyanide ion is a stronger nucleophile; it reacts more rapidly with a carbon bearing a leaving group than does hydroxide ion.

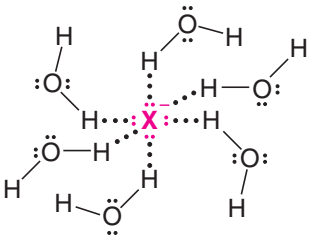
Review Problem 6.12

Rank the following in terms of *decreasing* nucleophilicity:

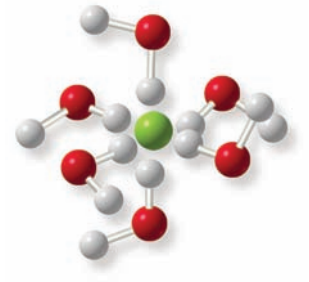
$CH_3CO_2^-$ CH_3OH CH_3O^- CH_3CO_2H CN^-

6.13C Solvent Effects on S_N2 Reactions: Polar Protic and Aprotic Solvents

A molecule of a solvent such as water or an alcohol—called a **protic solvent** (Section 3.12)—has a hydrogen atom attached to a strongly electronegative element (oxygen). Molecules of protic solvents can, therefore, form hydrogen bonds to nucleophiles in the following way.



Molecules of the protic solvent, water, solvate a halide ion by forming hydrogen bonds to it.



- Hydrogen bonding encumbers a nucleophile and hinders its reactivity in a substitution reaction.

For a strongly solvated nucleophile to react, it must shed some of its solvent molecules so that it can approach the carbon of the substrate that bears the leaving group. This is one type of important **solvent effect** in nucleophilic reactions.

- Hydrogen bonds to a small nucleophilic atom are stronger than those to larger nucleophilic atoms among elements in the same group (column) of the periodic table.

For example, fluoride anion is more strongly solvated than the other halides because it is the smallest halide anion and its charge is the most concentrated. Hence, in a protic solvent fluoride is not as effective a nucleophile as the other halide anions. Iodide is the largest halide anion and it is the most weakly solvated in a protic solvent; hence, it is the strongest nucleophile among the halide anions.

- In a protic solvent, the general trend in *nucleophilicity* among the halide anions is as follows:

$$I^- > Br^- > Cl^- > F^-$$

Halide nucleophilicity in protic solvents

The same effect holds true when we compare sulfur nucleophiles with oxygen nucleophiles. Sulfur atoms are larger than oxygen atoms and hence they are not solvated as strongly in a protic solvent. Thus, thiols (R—SH) are stronger nucleophiles than alcohols, and RS^- anions are better nucleophiles than RO^- anions.

The greater reactivity of nucleophiles with large nucleophilic atoms is not entirely related to solvation. Larger atoms have greater **polarizability** (their electron clouds are more easily distorted); therefore, a larger nucleophilic atom can donate a greater degree of electron density to the substrate than a smaller nucleophile whose electrons are more tightly held.

The relative nucleophilicities of some common nucleophiles in protic solvents are as follows:

$$SH^- > CN^- > I^- > OH^- > N_3^- > Br^- > CH_3CO_2^- > Cl^- > F^- > H_2O$$

Relative nucleophilicity in protic solvents

Review Problem 6.13

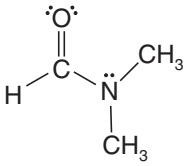
Rank the following in terms of decreasing nucleophilicity:

$CH_3CO_2^-$ CH_3O^- CH_3S^- CH_3SH CH_3OH

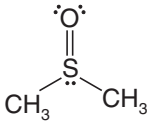
Polar Aprotic Solvents

- **Aprotic solvents** do not have a hydrogen atom bonded to an electronegative atom, and therefore do not hinder nucleophiles through hydrogen bonding.

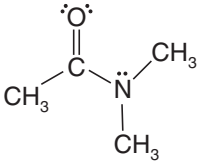
A number of **polar aprotic solvents** have come into wide use by chemists *because they are especially useful in S_N2 reactions*. Several examples are the following:



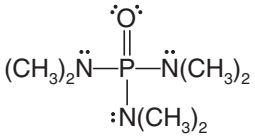
DMF
(*N,N*-dimethylformamide)



DMSO
(dimethyl sulfoxide)

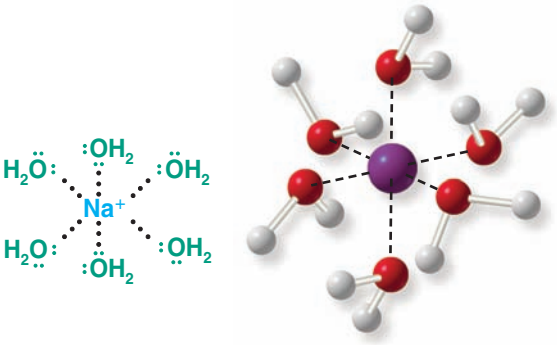


DMA
(dimethylacetamide)

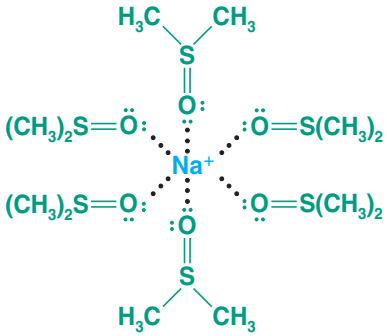


HMPA
(hexamethylphosphoramide)

All of these solvents (DMF, DMSO, DMA, and HMPA) dissolve ionic compounds, and they solvate cations very well. They do so in the same way that protic solvents solvate cations: by orienting their negative ends around the cation and by donating unshared electron pairs to vacant orbitals of the cation:



A sodium ion solvated by molecules of the protic solvent water



A sodium ion solvated by molecules of the aprotic solvent DMSO

However, because they cannot form hydrogen bonds and because their positive centers are well shielded by steric effects from any interaction with anions, **aprotic solvents do not solvate anions to any appreciable extent**. In these solvents anions are unencumbered by a layer of solvent molecules and they are therefore poorly stabilized by solvation. These "naked" anions are highly reactive both *as bases and nucleophiles*. In DMSO, for example, the relative order of reactivity of halide ions is opposite to that in protic solvents, and it follows the same trend as their relative basicity:

$$F^- > Cl^- > Br^- > I^-$$

Halide nucleophilicity in aprotic solvents

Helpful Hint

Polar aprotic solvents increase S_N2 rates.

- *The rates of S_N2 reactions generally are vastly increased when they are carried out in polar aprotic solvents*. The increase in rate can be as large as a millionfold.

Review Problem 6.14 Classify the following solvents as being protic or aprotic: formic acid, HCO_2H; acetone, CH_3COCH_3; acetonitrile, $CH_3C{\equiv}N$; formamide, $HCONH_2$; sulfur dioxide, SO_2; ammonia, NH_3; trimethylamine, $N(CH_3)_3$; ethylene glycol, $HOCH_2CH_2OH$.

Review Problem 6.15 Would you expect the reaction of propyl bromide with sodium cyanide (NaCN), that is,

$$CH_3CH_2CH_2Br + NaCN \longrightarrow CH_3CH_2CH_2CN + NaBr$$

to occur faster in DMF or in ethanol? Explain your answer.

Which would you expect to be the stronger nucleophile in a polar aprotic solvent? **(a)** $CH_3CO_2^-$ or CH_3O^-; **(b)** H_2O or H_2S; **(c)** $(CH_3)_3P$ or $(CH_3)_3N$

Review Problem 6.16

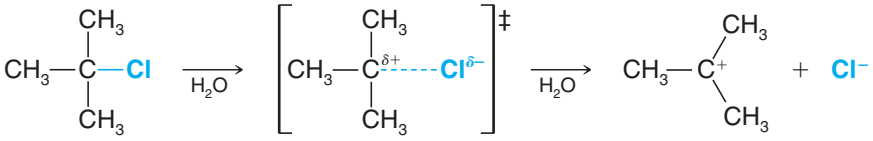
6.13D Solvent Effects on S_N1 Reactions: The Ionizing Ability of the Solvent

- Use of a **polar protic solvent** will greatly increase the rate of carbocation formation of an alkyl halide *in any S_N1 reaction* because of its ability to solvate cations *and* anions so effectively.

Helpful Hint

Polar protic solvents favor S_N1 reactions.

Solvation stabilizes the transition state leading to the intermediate carbocation and halide ion more than it does the reactants; thus the free energy of activation is lower. The transition state for this endothermic step is one in which separated charges are developing, and thus it resembles the ions that are ultimately produced:



Reactant | **Transition state** *Separated charges are developing.* | **Carbocation intermediate**

A rough indication of a solvent's polarity is a quantity called the **dielectric constant**. The dielectric constant is a measure of the solvent's ability to insulate opposite charges (or separate ions) from each other. Electrostatic attractions and repulsions between ions are smaller in solvents with higher dielectric constants. Table 6.5 gives the dielectric constants of some common solvents.

TABLE 6.5 Dielectric Constants of Common Solvents

	Solvent	Formula	Dielectric Constant
↑ Increasing solvent polarity ↓	Water	H_2O	80
	Formic acid	HCO_2H	59
	Dimethyl sulfoxide (DMSO)	CH_3SOCH_3	49
	N,N-Dimethylformamide (DMF)	$HCON(CH_3)_2$	37
	Acetonitrile	$CH_3C{\equiv}N$	36
	Methanol	CH_3OH	33
	Hexamethylphosphoramide (HMPA)	$[(CH_3)_2N]_3P{=}O$	30
	Ethanol	CH_3CH_2OH	24
	Acetone	CH_3COCH_3	21
	Acetic acid	CH_3CO_2H	6

Water is the most effective solvent for promoting ionization, but most organic compounds do not dissolve appreciably in water. They usually dissolve, however, in alcohols, and quite often mixed solvents are used. Methanol–water and ethanol–water are common mixed solvents for nucleophilic substitution reactions.

When *tert*-butyl bromide undergoes solvolysis in a mixture of methanol and water, the rate of solvolysis (measured by the rate at which bromide ions form in the mixture) *increases* when the percentage of water in the mixture is increased. **(a)** Explain this occurrence. **(b)** Provide an explanation for the observation that the rate of the S_N2 reaction of ethyl chloride with potassium iodide in methanol and water *decreases* when the percentage of water in the mixture is increased.

Review Problem 6.17

6.13E The Nature of the Leaving Group

- Leaving groups depart with the electron pair that was used to bond them to the substrate.

Helpful Hint

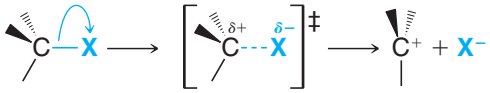
Good leaving groups are weak bases.

The best leaving groups are those that become either a relatively stable anion or a neutral molecule when they depart. First, let us consider leaving groups that become anions when they separate from the substrate. Because weak bases stabilize a negative charge effectively, leaving groups that become weak bases are good leaving groups.

- In general, the best leaving groups are those that can be classified as weak bases after they depart.

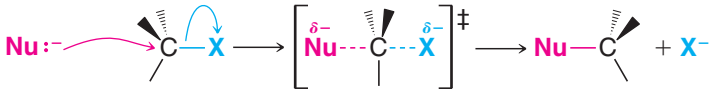
The reason that stabilization of the negative charge is important can be understood by considering the structure of the transition states. In either an S_N1 or S_N2 reaction the leaving group begins to acquire a negative charge as the transition state is reached:

S_N1 Reaction (Rate-Limiting Step)



Transition state

S_N2 Reaction



Transition state

Stabilization of this developing negative charge at the leaving group stabilizes the transition state (lowers its free energy); this lowers the free energy of activation and thereby increases the rate of the reaction.

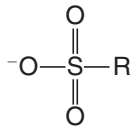
- Among the halogens, an iodide ion is the best leaving group and a fluoride ion is the poorest:

$$I^- > Br^- > Cl^- >> F^-$$

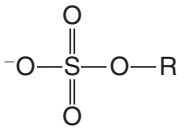
The order is the opposite of the basicity:

$$F^- >> Cl^- > Br^- > I^-$$

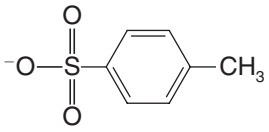
Other weak bases that are good leaving groups, which we shall study later, are alkanesulfonate ions, alkyl sulfate ions, and the *p*-toluenesulfonate ion:



An alkanesulfonate ion



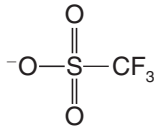
An alkyl sulfate ion



***p*-Toluenesulfonate ion**

These anions are all the conjugate bases of very strong acids.

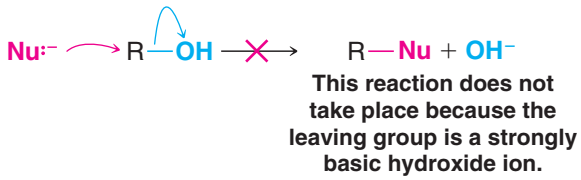
The trifluoromethanesulfonate ion ($CF_3SO_3^-$, commonly called the **triflate ion**) is one of the best leaving groups known to chemists. It is the conjugate base of CF_3SO_3H, an exceedingly strong acid ($pK_a \sim -5$ to -6):



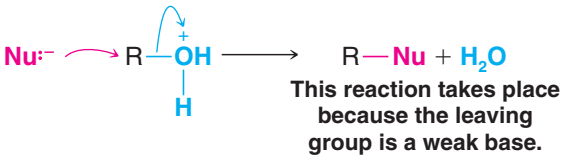
Triflate ion
(a "super" leaving group)

- Strongly basic ions rarely act as leaving groups.

The hydroxide ion, for example, is a strong base and thus reactions like the following do not take place:



However, when an alcohol is dissolved in a strong acid, it can undergo substitution by a nucleophile. Because the acid protonates the —OH group of the alcohol, the leaving group no longer needs to be a hydroxide ion; it is now a molecule of water—a much weaker base than a hydroxide ion and a good leaving group:

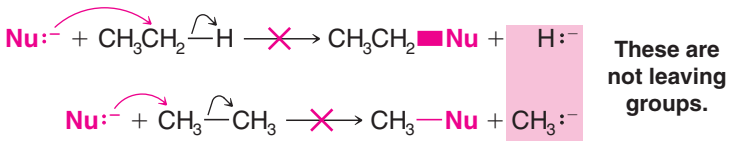


Review Problem 6.18

List the following compounds in order of decreasing reactivity toward CH_3O^- in an S_N2 reaction carried out in CH_3OH: CH_3F, CH_3Cl, CH_3Br, CH_3I, $CH_3OSO_2CF_3$, $^{14}CH_3OH$.

- Very powerful bases such as hydride ions ($H:^-$) and alkanide ions ($R:^-$) virtually never act as leaving groups.

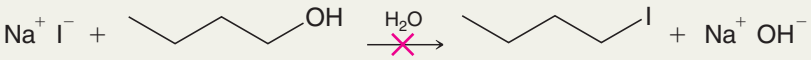
Therefore, **reactions such as the following are not feasible**:



Remember: The best leaving groups are weak bases after they depart.

Solved Problem 6.7

Explain why the following reaction is not feasible as a synthesis of butyl iodide.



STRATEGY AND ANSWER The strongly basic OH^- ion (hydroxide ion) virtually never acts as a leaving group, something this reaction would require. This reaction would be feasible under acidic conditions, in which case the leaving group would be a water molecule.

Summary of S_N1 versus S_N2 Reactions

S_N1: The Following Conditions Favor an S_N1 Reaction:

Helpful Hint

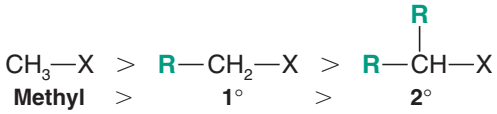
S_N1 versus S_N2

1. A substrate that can form a relatively stable carbocation (such as a substrate with a leaving group at a tertiary position)
2. A relatively weak nucleophile
3. A polar, protic solvent

The S_N1 mechanism is, therefore, important in solvolysis reactions of tertiary alkyl halides, especially when the solvent is highly polar. In a solvolysis reaction the nucleophile is weak because it is a neutral molecule (of the polar protic solvent) rather than an anion.

S_N2: The Following Conditions Favor an S_N2 Reaction:

1. A substrate with a relatively unhindered leaving group (such as a methyl, primary, or secondary alkyl halide). The order of reactivity is



   Tertiary halides do not react by an S_N2 mechanism.
2. A strong nucleophile (usually negatively charged)
3. High concentration of the nucleophile
4. A polar, aprotic solvent

The trend in reaction rate among halogens as the leaving group is the same in S_N1 and S_N2 reactions:

$$R - I > R - Br > R - Cl \qquad S_N1 \text{ or } S_N2$$

Because alkyl fluorides react so slowly, they are seldom used in nucleophilic substitution reactions.

These factors are summarized in Table 6.6.

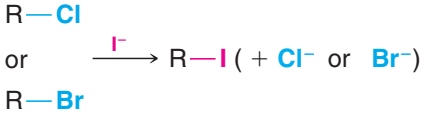
TABLE 6.6 Factors Favoring S_N1 versus S_N2 Reactions

Factor	S_N1	S_N2
Substrate	3° (requires formation of a relatively stable carbocation)	Methyl > 1° > 2° (requires unhindered substrate)
Nucleophile	Weak Lewis base, neutral molecule, nucleophile may be the solvent (solvolysis)	Strong Lewis base, rate increased by high concentration of nucleophile
Solvent	Polar protic (e.g., alcohols, water)	Polar aprotic (e.g., DMF, DMSO)
Leaving group	I > Br > Cl > F for both S_N1 and S_N2 (the weaker the base after the group departs, the better the leaving group)	

6.14 *Organic Synthesis: Functional Group Transformations Using S_N2 Reactions*

S_N2 reactions are highly useful in organic synthesis because they enable us to convert one functional group into another—a process that is called a **functional group transformation** or a **functional group interconversion**. With the S_N2 reactions shown in Fig. 6.11, methyl, primary, or secondary alkyl halides can be transformed into alcohols, ethers, thiols, thioethers, nitriles, esters, and so on. (*Note*: The use of the prefix *thio-* in a name means that a sulfur atom has replaced an oxygen atom in the compound.)

Alkyl chlorides and bromides are also easily converted to alkyl iodides by nucleophilic substitution reactions.



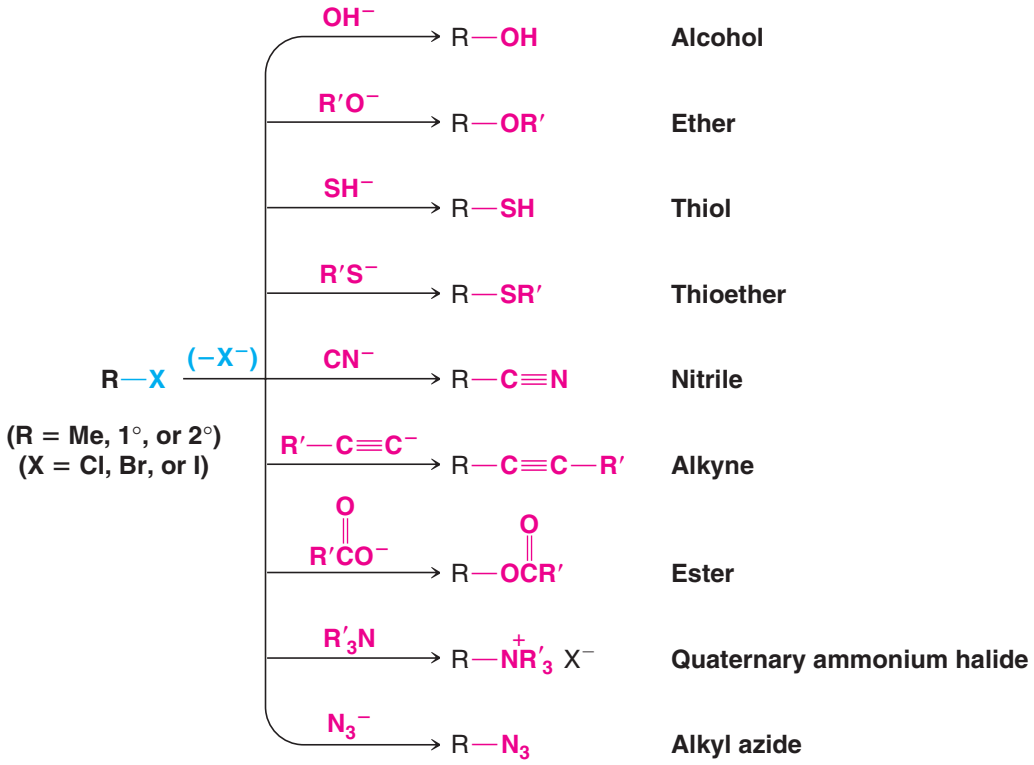
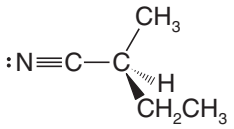


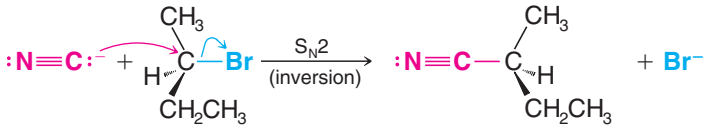
Figure 6.11 Functional group interconversions of methyl, primary, and secondary alkyl halides using S_N2 reactions.

One other aspect of the S_N2 reaction that is of great importance is **stereochemistry** (Section 6.8). S_N2 reactions always occur with **inversion of configuration** at the atom that bears the leaving group. This means that when we use S_N2 reactions in syntheses we can be sure of the configuration of our product if we know the configuration of our reactant. For example, suppose we need a sample of the following nitrile with the (*S*) configuration:



(*S*)-2-Methylbutanenitrile

If we have available (*R*)-2-bromobutane, we can carry out the following synthesis:



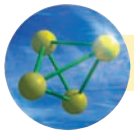
(*R*)-2-Bromobutane **(*S*)-2-Methylbutanenitrile**

Review Problem 6.19

Starting with (*S*)-2-bromobutane, outline syntheses of each of the following compounds:

(a) (*R*)-$CH_3CH(OCH_2CH_3)CH_2CH_3$ **(c)** (*R*)-$CH_3CH(SH)CH_2CH_3$

(b) (*R*)-$CH_3CH(OCCH_3{=}O)CH_2CH_3$ **(d)** (*R*)-$CH_3CH(SCH_3)CH_2CH_3$

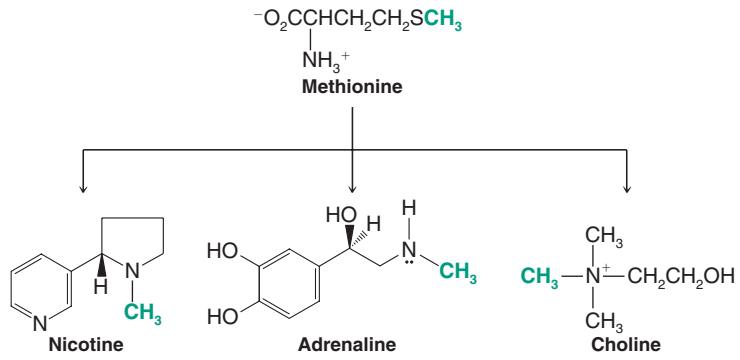


THE CHEMISTRY OF . . .

Biological Methylation: A Biological Nucleophilic Substitution Reaction

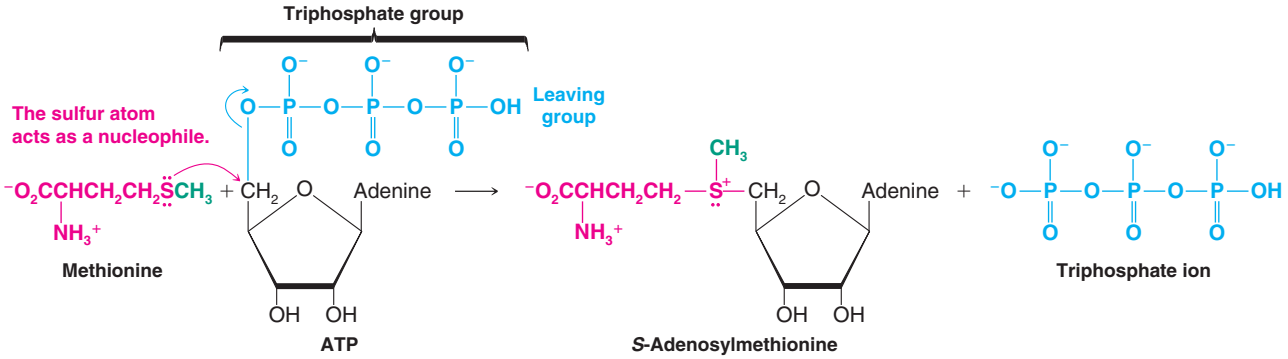
The cells of living organisms synthesize many of the compounds they need from smaller molecules. Often these biosyntheses resemble the syntheses organic chemists carry out in their laboratories. Let us examine one example now.

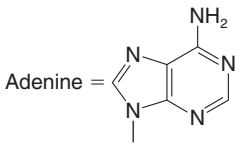
Many reactions taking place in the cells of plants and animals involve the transfer of a methyl group from an amino acid called methionine to some other compound. That this transfer takes place can be demonstrated experimentally by feeding a plant or animal methionine containing an isotopically labeled carbon atom (e.g., ^{13}C or ^{14}C) in its methyl group. Later, other compounds containing the "labeled" methyl group can be isolated from the organism. Some of the compounds that get their methyl groups from methionine are the following. The isotopically labeled carbon atom is shown in green.



Choline is important in the transmission of nerve impulses, adrenaline causes blood pressure to increase, and nicotine is the compound contained in tobacco that makes smoking tobacco addictive. (In large doses nicotine is poisonous.)

The transfer of the methyl group from methionine to these other compounds does not take place directly. The actual methylating agent is not methionine; it is *S*-adenosylmethionine,* a compound that results when methionine reacts with adenosine triphosphate (ATP):

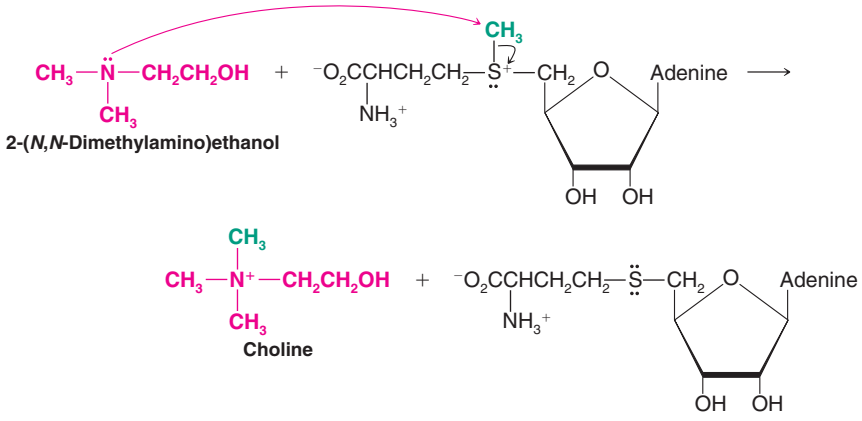




*The prefix *S* is a locant meaning "on the sulfur atom" and should not be confused with the (*S*) used to define absolute configuration. Another example of this kind of locant is *N*, meaning "on the nitrogen atom."

This reaction is a nucleophilic substitution reaction. The nucleophilic atom is the sulfur atom of methionine. The leaving group is the weakly basic triphosphate group of ATP. The product, *S*-adenosylmethionine, contains a methyl-sulfonium group, $CH_3—\overset{|}{\underset{\cdot\cdot}{S^+}}—$.

S-Adenosylmethionine then acts as the substrate for other nucleophilic substitution reactions. In the biosynthesis of choline, for example, it transfers its methyl group to a nucleophilic nitrogen atom of 2-(*N*,*N*-dimethylamino)ethanol:



These reactions appear complicated only because the structures of the nucleophiles and substrates are complex. Yet conceptually they are simple, and they illustrate many of the principles we have encountered thus far in Chapter 6. In them we see how nature makes use of the high nucleophilicity of sulfur atoms. We also see how a weakly basic group (e.g., the triphosphate group of ATP) functions as a leaving group. In the reaction of 2-(*N*,*N*-dimethylamino) ethanol we see that the more basic $(CH_3)_2N—$ group acts as the nucleophile rather than the less basic —OH group. And when a nucleophile attacks *S*-adenosylmethionine, we see that the attack takes place at the less hindered $CH_3—$ group rather than at one of the more hindered $—CH_2—$ groups.

Study Problem

(a) What is the leaving group when 2-(*N*,*N*-dimethylamino)ethanol reacts with *S*-adenosylmethionine?

(b) What would the leaving group have to be if methionine itself were to react with 2-(*N*,*N*-dimethylamino)ethanol?

(c) Of what special significance is this difference?

6.14A The Unreactivity of Vinylic and Phenyl Halides

As we learned in Section 6.1, compounds that have a halogen atom attached to one carbon atom of a double bond are called **vinylic halides**; those that have a halogen atom attached to a benzene ring are called **aryl** or **phenyl halides**:

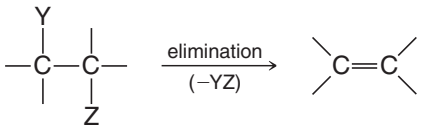
A vinylic halide **A phenyl halide**

- Vinylic and phenyl halides are generally unreactive in S_N1 or S_N2 reactions.

They are unreactive in S_N1 reactions because vinylic and phenyl cations are relatively unstable and do not form readily. They are unreactive in S_N2 reactions because the carbon–halogen bond of a vinylic or phenyl halide is stronger than that of an alkyl halide (we shall see why later), and the electrons of the double bond or benzene ring repel the approach of a nucleophile from the back side.

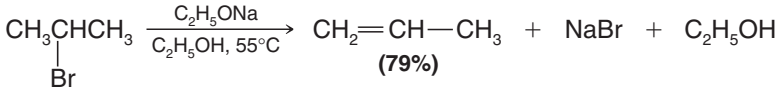
6.15 Elimination Reactions of Alkyl Halides

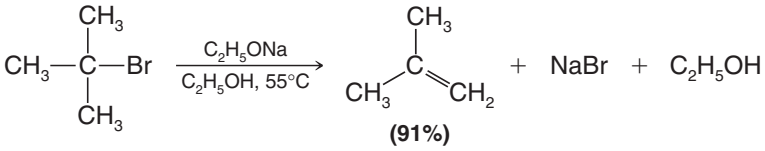
Elimination reactions of alkyl halides are important reactions that compete with substitution reactions. In an **elimination reaction** the fragments of some molecule (YZ) are removed (eliminated) from adjacent atoms of the reactant. This elimination leads to the creation of a multiple bond:



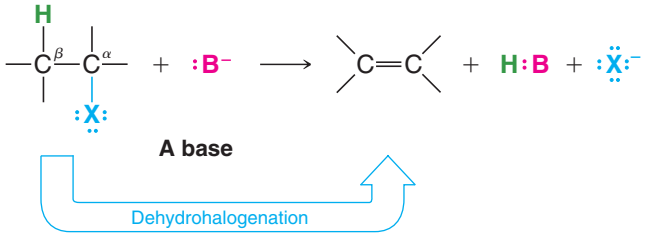
6.15A Dehydrohalogenation

A widely used method for synthesizing alkenes is the elimination of HX from adjacent atoms of an alkyl halide. Heating the alkyl halide with a strong base causes the reaction to take place. The following are two examples:



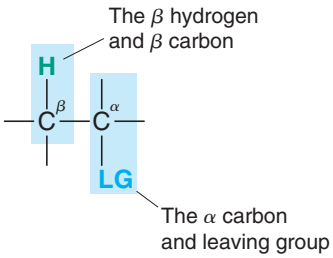


Reactions like these are not limited to the elimination of hydrogen bromide. Chloroalkanes also undergo the elimination of hydrogen chloride, iodoalkanes undergo the elimination of hydrogen iodide, and, in all cases, alkenes are produced. When the elements of a hydrogen halide are eliminated from a haloalkane in this way, the reaction is often called **dehydrohalogenation**:



In these eliminations, as in S_N1 and S_N2 reactions, there is a leaving group and an attacking Lewis base that possesses an electron pair.

Chemists often call the carbon atom that bears the leaving group (e.g., the halogen atom in the previous reaction) the **alpha (α) carbon atom** and any carbon atom adjacent to it a **beta (β) carbon atom**. A hydrogen atom attached to the β carbon atom is called a ***β* hydrogen atom**. Since the hydrogen atom that is eliminated in dehydrohalogenation is from the β carbon atom, these reactions are often called ***β* eliminations**. They are also often referred to as **1,2 eliminations**.

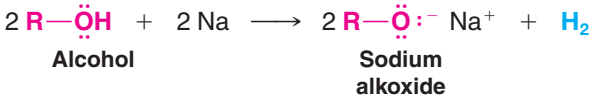


We shall have more to say about dehydrohalogenation in Chapter 7, but we can examine several important aspects here.

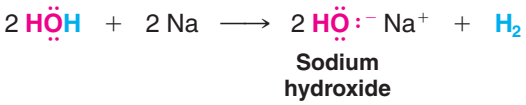
6.15B Bases Used in Dehydrohalogenation

Various strong bases have been used for dehydrohalogenations. Potassium hydroxide dissolved in ethanol (KOH/EtOH) is a reagent sometimes used, but the conjugate bases of alcohols, such as sodium ethoxide (EtONa), often offer distinct advantages.

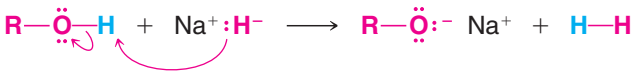
The conjugate base of an alcohol (an alkoxide) can be prepared by treating an alcohol with an alkali metal. For example:



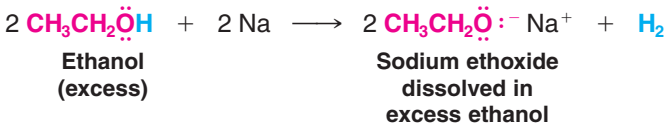
This reaction is an **oxidation–reduction reaction**. Metallic sodium reacts with hydrogen atoms that are bonded to oxygen atoms to generate hydrogen gas, sodium cations, and the alkoxide anion. The reaction with water is vigorous and at times explosive.



Sodium alkoxides can also be prepared by allowing an alcohol to react with sodium hydride (NaH). The hydride ion ($H:^-$) is a very strong base. (The pK_a of H_2 is 35.)



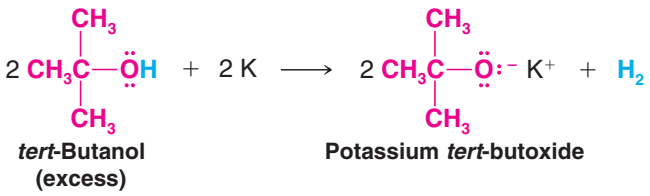
Sodium (and potassium) alkoxides are usually prepared by using an excess of the alcohol, and the excess alcohol becomes the solvent for the reaction. Sodium ethoxide is frequently prepared in this way using excess ethanol.



Helpful Hint

EtONa/EtOH is a common abbreviation for sodium ethoxide dissolved in ethanol.

Potassium *tert*-butoxide (*t*-BuOK) is another highly effective dehydrohalogenating reagent. It can be made by the reaction below, or purchased as a solid.



Helpful Hint

t-BuOK/*t*-BuOH represents potassium *tert*-butoxide dissolved in *tert*-butanol.

6.15C Mechanisms of Dehydrohalogenations

Elimination reactions occur by a variety of mechanisms. With alkyl halides, two mechanisms are especially important because they are closely related to the S_N2 and S_N1 reactions that we have just studied. One mechanism, called the **E2 reaction**, is bimolecular in the rate-determining step; the other mechanism is the **E1 reaction**, which is unimolecular in the rate-determining step.

6.16 The E2 Reaction

When isopropyl bromide is heated with sodium ethoxide in ethanol to form propene, the reaction rate depends on the concentration of isopropyl bromide and the concentration of ethoxide ion. The rate equation is first order in each reactant and second order overall:

$$\text{Rate} = k[CH_3CHBrCH_3][C_2H_5O^-]$$

- From the reaction order we infer that the transition state for the rate-determining step must involve both the alkyl halide and the alkoxide ion: The reaction must be bimolecular.

Considerable experimental evidence indicates that the reaction takes place in the following way:

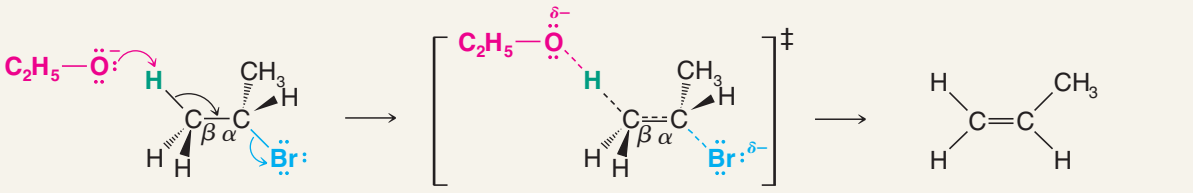
A MECHANISM FOR THE REACTION

Mechanism for the E2 Reaction

REACTION

$$C_2H_5O^- + CH_3CHBrCH_3 \longrightarrow CH_2{=}CHCH_3 + C_2H_5OH + Br^-$$

MECHANISM

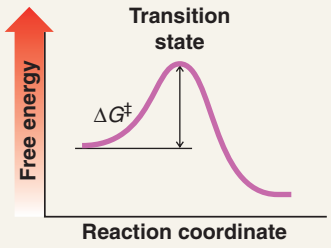


The basic ethoxide ion begins to remove a proton from the β carbon using its electron pair to form a bond to it. At the same time, the electron pair of the β C—H bond begins to move in to become the π bond of a double bond, and the bromine begins to depart with the electrons that bonded it to the α carbon.

Transition state

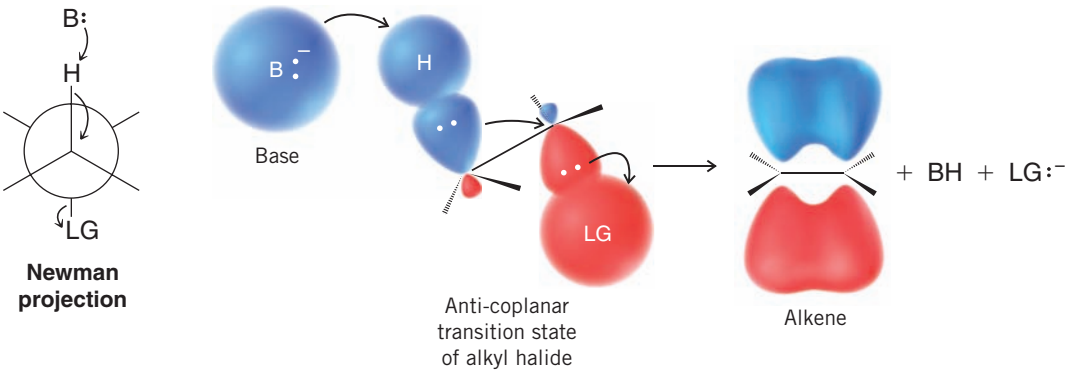
Partial bonds in the transition state extend from the oxygen atom that is removing the β hydrogen, through the carbon skeleton of the developing double bond, to the departing leaving group. The flow of electron density is from the base toward the leaving group as an electron pair fills the π bonding orbital of the alkene.

At completion of the reaction, the double bond is fully formed and the alkene has a trigonal planar geometry at each carbon atom. The other products are a molecule of ethanol and a bromide ion.



An E2 reaction has one transition state

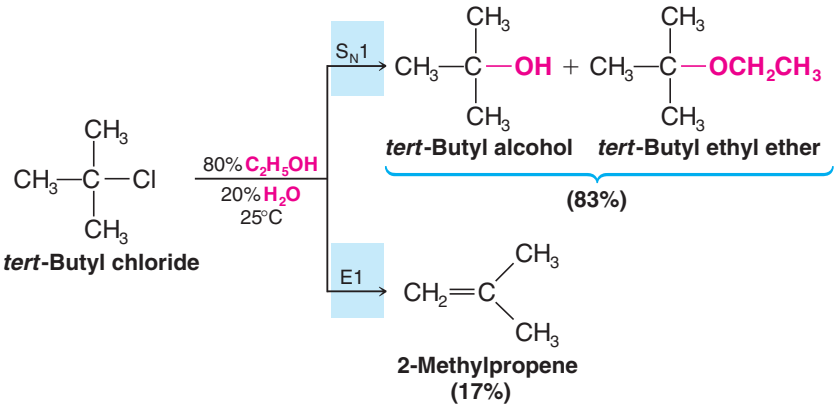
When we study the E2 reaction further in Section 7.6D, we shall find that the orientations of the hydrogen atom being removed and the leaving group are not arbitrary and that an orientation where they are all in the same plane, like that shown above and in the example that follows, is required.



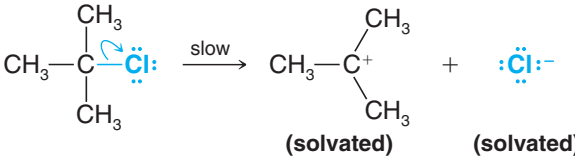
Notice that the geometry required here is similar to that of the S_N2 reaction. In the S_N2 reaction (Section 6.6) the nucleophile must push out the leaving group from the **opposite side**. In the E2 reaction the **electron pair of the C—H** bond pushes the leaving group away from the **opposite side** as the base removes the hydrogen. (We shall also find in Section 7.7C that a syn-coplanar E2 transition state is possible, though not as favorable.)

6.17 The E1 Reaction

Elimination reactions may follow a different pathway from that given in Section 6.16. Treating *tert*-butyl chloride with 80% aqueous ethanol at 25°C, for example, gives *substitution products* in 83% yield and an elimination product (2-methylpropene) in 17% yield:

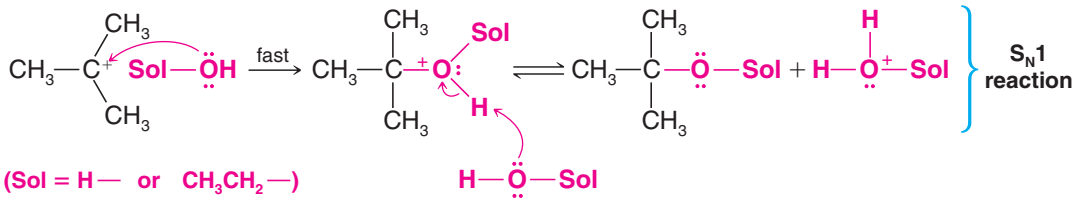


- The initial step for both reactions is the formation of a *tert*-butyl cation as a common intermediate. This is also the rate-determining step for both reactions; thus both reactions are unimolecular:

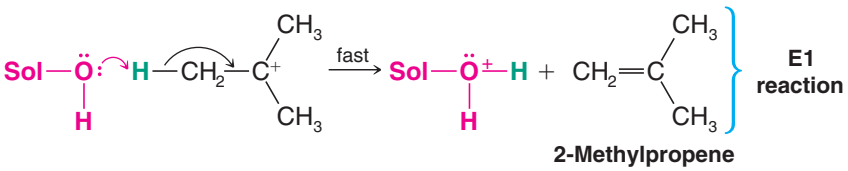


Whether substitution or elimination takes place depends on the next step (the fast step).

- If a solvent molecule reacts as a nucleophile at the positive carbon atom of the *tert*-butyl cation, the product is *tert*-butyl alcohol or *tert*-butyl ethyl ether and the reaction is S_N1:



- If, however, a solvent molecule acts as a base and removes one of the β hydrogen atoms as a proton, the product is 2-methylpropene and the reaction is E1.



E1 reactions almost always accompany S_N1 reactions.

A MECHANISM FOR THE REACTION

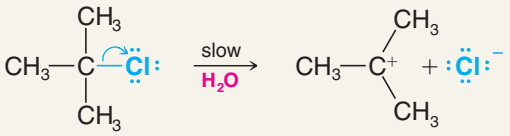
Mechanism for the E1 Reaction

REACTION

$$(CH_3)_3CCl + H_2O \longrightarrow CH_2{=}C(CH_3)_2 + H_3O^+ + Cl^-$$

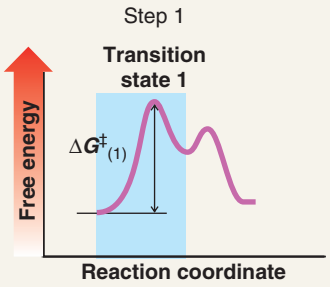
MECHANISM

Step 1



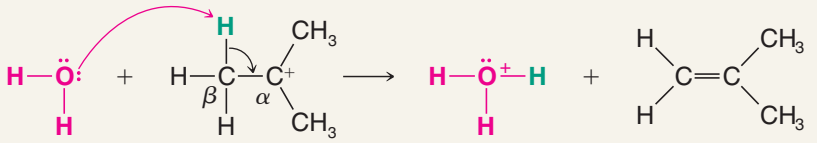
Aided by the polar solvent, a chlorine departs with the electron pair that bonded it to the carbon.

This slow step produces the relatively stable 3° carbocation and a chloride ion. The ions are solvated (and stabilized) by surrounding water molecules.



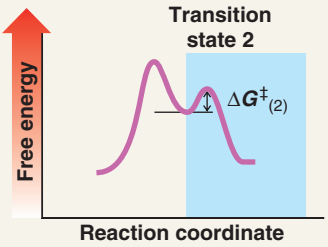
(mechanism continues on the next page)

Step 2



A molecule of water removes one of the hydrogens from the β carbon of the carbocation. These hydrogens are acidic due to the adjacent positive charge. At the same time an electron pair moves in to form a double bond between the α and β carbon atoms.

This step produces the alkene and a hydronium ion.



6.18 How to Determine Whether Substitution or Elimination Is Favored

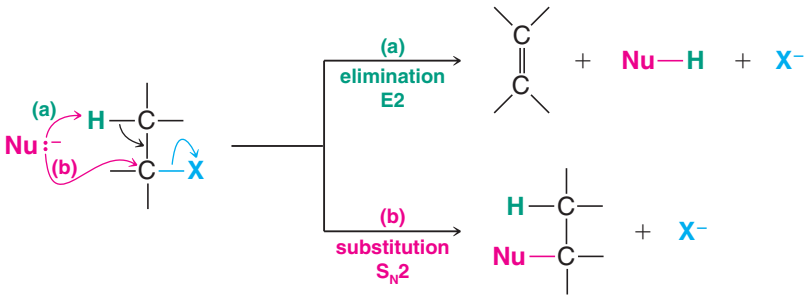
All nucleophiles are potential bases and all bases are potential nucleophiles. This is because the reactive part of both nucleophiles and bases is an unshared electron pair. It should not be surprising, then, that nucleophilic substitution reactions and elimination reactions often compete with each other. We shall now summarize factors that influence which type of reaction is favored, and provide some examples.

6.18A S_N2 versus E2

Helpful Hint

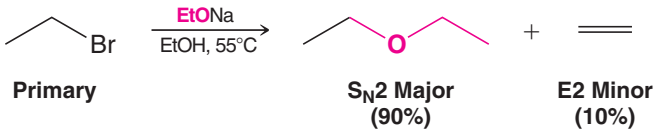
This section draws together the various factors that influence the competition between substitution and elimination.

S_N2 and E2 reactions are both favored by a high concentration of a strong nucleophile or base. When the nucleophile (base) attacks a β hydrogen atom, elimination occurs. When the nucleophile attacks the carbon atom bearing the leaving group, substitution results:

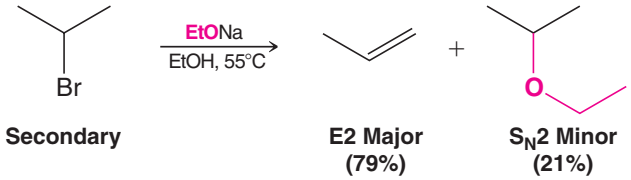


The following examples illustrate the effects of several parameters on substitution and elimination: relative steric hindrance in the substrate (class of alkyl halide), temperature, size of the base/nucleophile (EtONa versus *t*-BuOK), and the effects of basicity and polarizability. In these examples we also illustrate a very common way of writing organic reactions, where reagents are written over the reaction arrow, solvents and temperatures are written under the arrow, and only the substrate and major organic products are written to the left and right of the reaction arrow. We also employ typical shorthand notations of organic chemists, such as exclusive use of bond-line formulas and use of commonly accepted abbreviations for some reagents and solvents.

Primary Substrate When the substrate is a *primary* halide and the base is strong and unhindered, like ethoxide ion, substitution is highly favored because the base can easily approach the carbon bearing the leaving group:

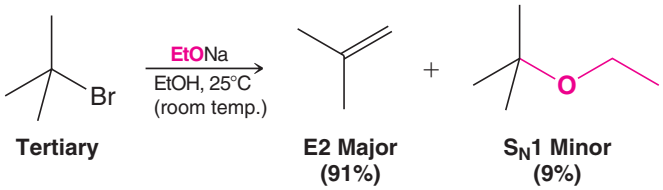


Secondary Substrate With *secondary* halides, however, a strong base favors elimination because steric hindrance in the substrate makes substitution more difficult:

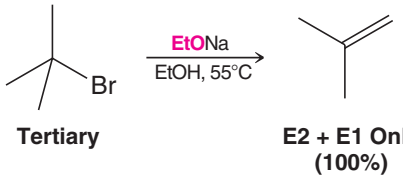


Tertiary Substrate With *tertiary* halides, steric hindrance in the substrate is severe and an S_N2 reaction cannot take place. Elimination is highly favored, especially when the reaction is carried out at higher temperatures. Any substitution that occurs must take place through an S_N1 mechanism:

Without Heating



With Heating

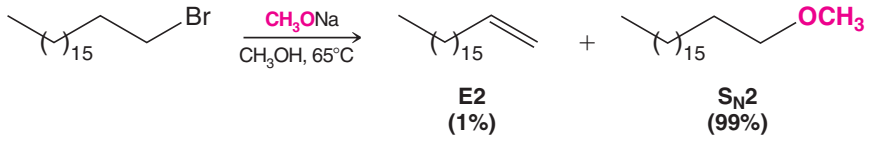


Temperature Increasing the reaction temperature favors elimination (E1 and E2) over substitution. Elimination reactions have greater free energies of activation than substitution reactions because more bonding changes occur during elimination. When higher temperature is used, the proportion of molecules able to surmount the energy of activation barrier for elimination increases more than the proportion of molecules able to undergo substitution, although the rate of both substitution and elimination will be increased. Furthermore, elimination reactions are entropically favored over substitution because the products of an elimination reaction are greater in number than the reactants. Additionally, because temperature is the coefficient of the entropy term in the Gibbs free-energy equation $\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$, an increase in temperature further enhances the entropy effect.

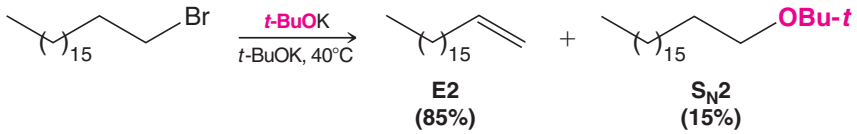
Size of the Base/Nucleophile Increasing the reaction temperature is one way of favorably influencing an elimination reaction of an alkyl halide. Another way is to use a **strong sterically hindered base** such as the *tert*-butoxide ion. The bulky methyl groups of the

tert-butoxide ion inhibit its reaction by substitution, allowing elimination reactions to take precedence. We can see an example of this effect in the following two reactions. The relatively unhindered methoxide ion reacts with octadecyl bromide primarily by *substitution*, whereas the bulky *tert*-butoxide ion gives mainly *elimination*.

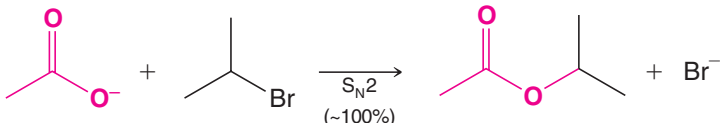
Unhindered (Small) Base/Nucleophile



Hindered Base/Nucleophile



Basicity and Polarizability Another factor that affects the relative rates of E2 and S_N2 reactions is the relative basicity and polarizability of the base/nucleophile. Use of a strong, slightly polarizable base such as hydroxide ion, amide ion (NH_2^-), or alkoxide ion (especially a hindered one) tends to increase the likelihood of elimination (E2). Use of a weakly basic ion such as a chloride ion (Cl^-) or an acetate ion ($CH_3CO_2^-$) or a weakly basic and highly polarizable one such as Br^-, I^-, or RS^- increases the likelihood of substitution (S_N2). Acetate ion, for example, reacts with isopropyl bromide almost exclusively by the S_N2 path:



The more strongly basic ethoxide ion (Section 6.15B) reacts with the same compound mainly by an E2 mechanism.

6.18B Tertiary Halides: S_N1 versus E1

Because E1 and S_N1 reactions proceed through the formation of a common intermediate, the two types respond in similar ways to factors affecting reactivities. E1 reactions are favored with substrates that can form stable carbocations (i.e., tertiary halides); they are also favored by the use of poor nucleophiles (weak bases) and they are generally favored by the use of polar solvents.

It is usually difficult to influence the relative partition between S_N1 and E1 products because the free energy of activation for either reaction proceeding from the carbocation (loss of a proton or combination with a molecule of the solvent) is very small.

In most unimolecular reactions the S_N1 reaction is favored over the E1 reaction, especially at lower temperatures. *In general, however, substitution reactions of tertiary halides do not find wide use as synthetic methods. Such halides undergo eliminations much too easily.*

Increasing the temperature of the reaction favors reaction by the E1 mechanism at the expense of the S_N1 mechanism.

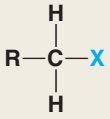
- **If an elimination product is desired from a tertiary substrate, it is advisable to use a strong base so as to encourage an E2 mechanism over the competing E1 and S_N1 mechanisms.**

6.19 Overall Summary

The most important reaction pathways for the substitution and elimination reactions of simple alkyl halides are summarized in Table 6.7.

Helpful Hint
Overall summary

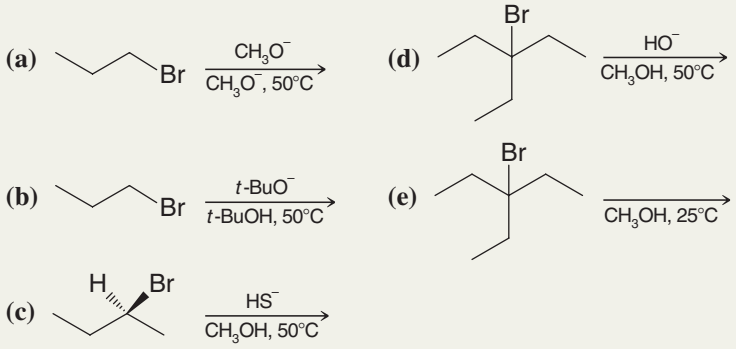
TABLE 6.7 Overall Summary of S_N1, S_N2, E1, and E2 Reactions

CH_3X			
Methyl	1°	2°	3°
	Bimolecular (S_N2/E2) Reactions Only		**S_N1/E1 or E2**
Gives S_N2 reactions	Gives mainly S_N2 except with a hindered strong base [e.g., $(CH_3)_3CO^-$] and then gives mainly E2.	Gives mainly S_N2 with weak bases (e.g., I^-, CN^-, RCO_2^-) and mainly E2 with strong bases (e.g., RO^-).	No S_N2 reaction. In solvolysis gives S_N1/E1, and at lower temperatures S_N1 is favored. When a strong base (e.g., RO^-) is used, E2 predominates.

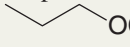
Let us examine several sample exercises that will illustrate how the information in Table 6.7 can be used.

Solved Problem 6.8

Give the product (or products) that you would expect to be formed in each of the following reactions. In each case give the mechanism (S_N1, S_N2, E1, or E2) by which the product is formed and predict the relative amount of each (i.e., would the product be the only product, the major product, or a minor product?).

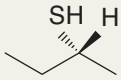


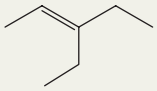
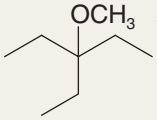
STRATEGY AND ANSWER

(a) The substrate is a 1° halide. The base/nucleophile is CH_3O^-, a strong base (but not a hindered one) and a good nucleophile. According to Table 6.7, we should expect an S_N2 reaction mainly, and the major product should be  . A minor product might be  by an E2 pathway.

(b) Again the substrate is a 1° halide, but the base/nucleophile, *t*-BuO^-, is a strong hindered base. We should expect, therefore, the major product to be  by an E2 pathway and a minor product to be   by an S_N2 pathway.

(c) The reactant is (*S*)-2-bromobutane, a 2° halide and one in which the leaving group is attached to a chirality center. The base/nucleophile is HS^-, a strong nucleophile but a weak base. We should expect mainly an S_N2 reaction, causing an inversion of configuration at the chirality center and producing the (*R*) stereoisomer:



(d) The base/nucleophile is OH^-, a strong base and a strong nucleophile. The substrate is a 3° halide; therefore, we should not expect an S_N2 reaction. The major product should be  via an E2 reaction. At this higher temperature and in the presence of a strong base, we should not expect an appreciable amount of the S_N1 solvolysis, product, 

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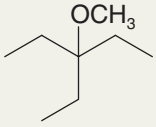
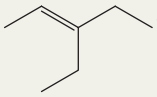
(e) This is solvolysis; the only base/nucleophile is the solvent, CH_3OH, which is a weak base (therefore, no E2 reaction) and a poor nucleophile. The substrate is tertiary (therefore, no S_N2 reaction). At this lower temperature we should expect mainly an S_N1 pathway leading to 

. A minor product, by an E1 pathway, would be 
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Key Terms and Concepts

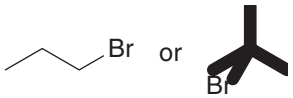
The key terms and concepts that are highlighted in **bold, blue text** within the chapter are defined in the glossary (at the back of the book) and have hyperlinked definitions in the accompanying ***WileyPLUS*** course (www.wileyplus.com).

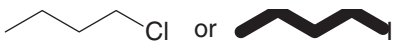
Problems

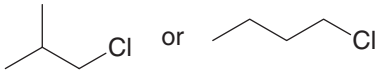
Note to Instructors: Many of the homework problems are available for assignment via ***WileyPLUS***, an online teaching and learning solution.

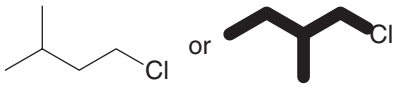
RELATIVE RATES OF NUCLEOPHILIC SUBSTITUTION

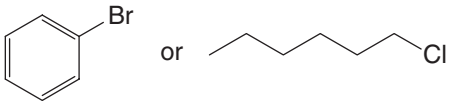
6.20 Which alkyl halide would you expect to react more rapidly by an S_N2 mechanism? Explain your answer.

(a) 

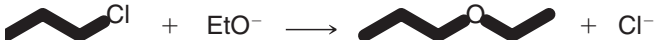
(b) 

(c) 

(d) 

(e) 

6.21 Which S_N2 reaction of each pair would you expect to take place more rapidly in a protic solvent?

(a) (1) 

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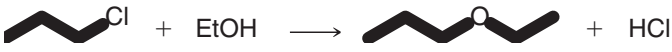
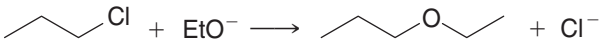
(2) 

(b) (1) 

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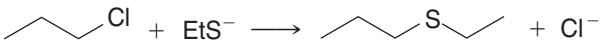
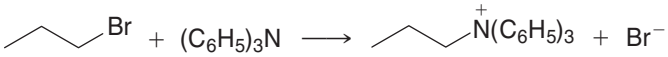
(2) 

(c) (1) 

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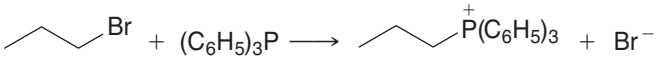
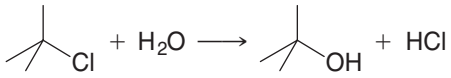
(2) 

(d) (1) 

or

(2) 

6.22 Which S_N1 reaction of each pair would you expect to take place more rapidly? Explain your answer.

(a) (1) 

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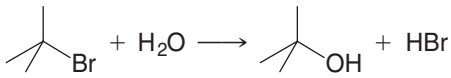
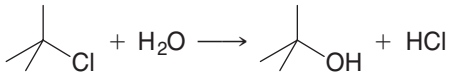
(2) 

(b) (1) 

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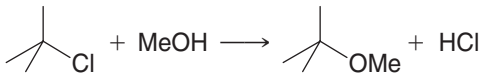
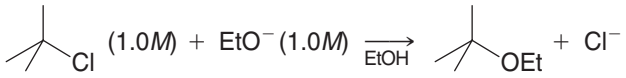
(2) 

(c) (1) 

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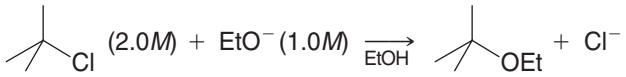
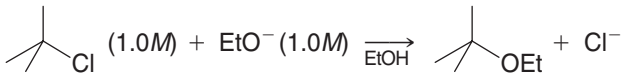
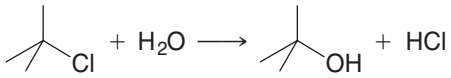
(2) 

(d) (1) 

or

(2) 

(e) (1) 

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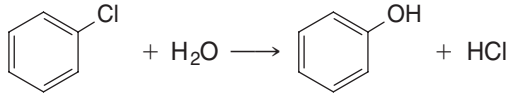
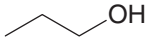
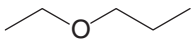
(2) 

SYNTHESIS

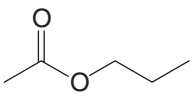
6.23 Show how you might use a nucleophilic substitution reaction of 1-bromopropane to synthesize each of the following compounds. (You may use any other compounds that are necessary.)

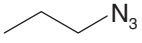
(a) 

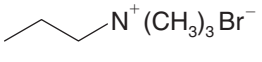
(b) 1-Iodopropane

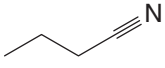
(c) 

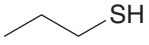
(d) $CH_3CH_2CH_2—S—CH_3$

(e) 

(f) 

(g) 

(h) 

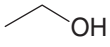
(i) 

6.24 With methyl, ethyl, or cyclopentyl halides as your organic starting materials and using any needed solvents or inorganic reagents, outline syntheses of each of the following. More than one step may be necessary and you need not repeat steps carried out in earlier parts of this problem.

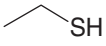
(a) CH_3I

(b) 

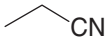
(c) CH_3OH

(d) 

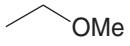
(e) CH_3SH

(f) 

(g) CH_3CN

(h) 

(i) CH_3OCH_3

(j) 

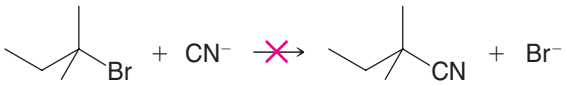
(k) 

6.25 Listed below are several hypothetical nucleophilic substitution reactions. None is synthetically useful because the product indicated is not formed at an appreciable rate. In each case provide an explanation for the failure of the reaction to take place as indicated.

(a) 

(b) 

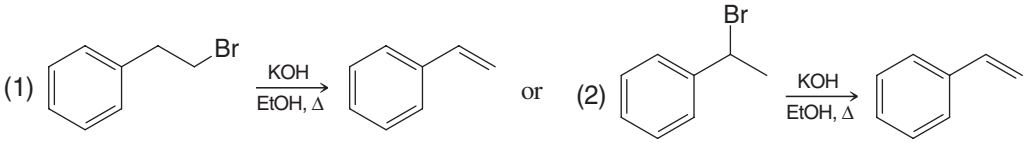
(c) 

(d) 

(e) $NH_3 + CH_3OCH_3 \not\longrightarrow CH_3NH_2 + CH_3OH$

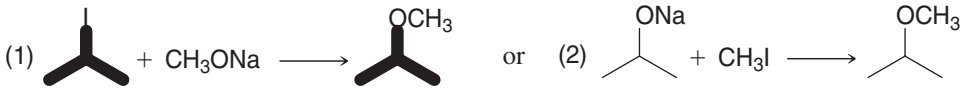
(f) $NH_3 + CH_3OH_2^+ \not\longrightarrow CH_3NH_3^+ + H_2O$

6.26 Your task is to prepare styrene by one of the following reactions. Which reaction would you choose to give the better yield of styrene? Explain your answer.



Styrene **Styrene**

6.27 Your task is to prepare isopropyl methyl ether by one of the following reactions. Which reaction would give the better yield? Explain your answer.



Isopropyl methyl ether **Isopropyl methyl ether**

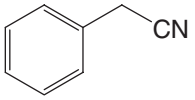
6.28 Starting with an appropriate alkyl halide and using any other needed reagents, outline syntheses of each of the following. When alternative possibilities exist for a synthesis, you should be careful to choose the one that gives the better yield.

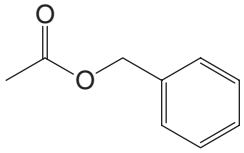
(a) Butyl *sec*-butyl ether

(b) 

(c) Methyl neopentyl ether

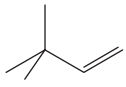
(d) Methyl phenyl ether

(e) 

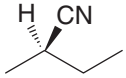
(f) 

(g) (*S*)-2-Pentanol

(h) (*R*)-2-Iodo-4-methylpentane

(i) 

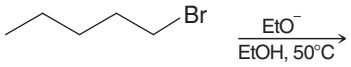
(j) *cis*-4-Isopropylcyclohexanol

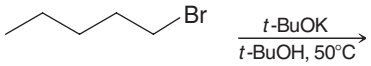
(k) 

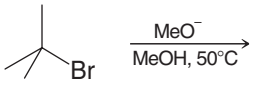
(l) *trans*-1-Iodo-4-methylcyclohexane

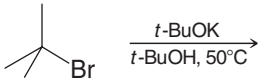
GENERAL S_N1, S_N2, AND ELIMINATION

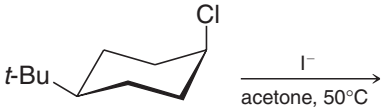
6.29 Which product (or products) would you expect to obtain from each of the following reactions? In each part give the mechanism (S_N1, S_N2, E1, or E2) by which each product is formed and predict the relative amount of each product (i.e., would the product be the only product, the major product, a minor product, etc.?).

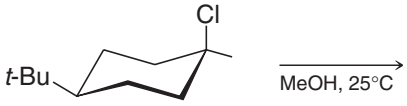
(a) 

(b) 

(c) 

(d) 

(e) 

(f) 

(g) 3-Chloropentane $\xrightarrow[\text{MeOH, 50°C}]{\text{MeO}^-}$

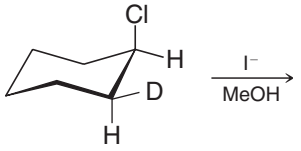
(h) 3-Chloropentane $\xrightarrow[\text{CH}_3\text{CO}_2\text{H, 50°C}]{\text{CH}_3\text{CO}_2^-}$

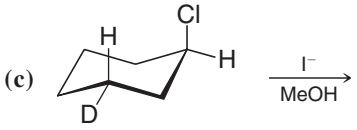
(i) (*R*)-2-bromobutane $\xrightarrow[\text{25°C}]{\text{HO}^-}$

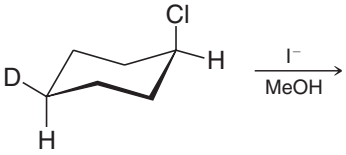
(j) (*S*)-3-Bromo-3-methylhexane $\xrightarrow[\text{MeOH}]{\text{25°C}}$

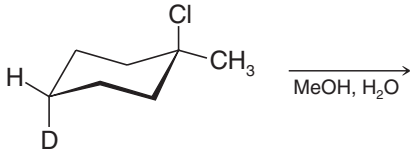
(k) (*S*)-2-Bromooctane $\xrightarrow[\text{MeOH, 50°C}]{\text{I}^-}$

6.30 Write conformational structures for the substitution products of the following deuterium-labeled compounds:

(a) 

(c) 

(b) 

(d) 

6.31 Although ethyl bromide and isobutyl bromide are both primary halides, ethyl bromide undergoes S_N2 reactions more than 10 times faster than isobutyl bromide does. When each compound is treated with a strong base/nucleophile (EtO^-), isobutyl bromide gives a greater yield of elimination products than substitution products, whereas with ethyl bromide this behavior is reversed. What factor accounts for these results?

6.32 Consider the reaction of I^- with CH_3CH_2Cl.

(a) Would you expect the reaction to be S_N1 or S_N2? The rate constant for the reaction at 60°C is 5×10^{-5} L mol^{-1} s^{-1}.

(b) What is the reaction rate if $[I^-] = 0.1$ mol L^{-1} and $[CH_3CH_2Cl] = 0.1$ mol L^{-1}?

(c) If $[I^-] = 0.1$ mol L^{-1} and $[CH_3CH_2Cl] = 0.2$ mol L^{-1}?

(d) If $[I^-] = 0.2$ mol L^{-1} and $[CH_3CH_2Cl] = 0.1$ mol L^{-1}?

(e) If $[I^-] = 0.2$ mol L^{-1} and $[CH_3CH_2Cl] = 0.2$ mol L^{-1}?

6.33 Which reagent in each pair listed here would be the more reactive nucleophile in a polar aprotic solvent?

(a) CH_3NH^- or CH_3NH_2

(b) CH_3O^- or $CH_3CO_2^-$ (^-OAc)

(c) CH_3SH or CH_3OH

(d) $(C_6H_5)_3N$ or $(C_6H_5)_3P$

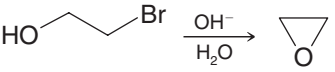
(e) H_2O or H_3O^+

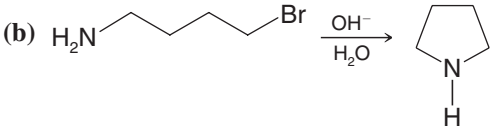
(f) NH_3 or NH_4^+

(g) H_2S or HS^-

(h) $CH_3CO_2^-$ (^-OAc) or OH^-

6.34 Write mechanisms that account for the products of the following reactions:

(a) 

(b) 

6.35 Draw a three-dimensional representation for the transition state structure in the S_N2 reaction of $N{\equiv}C:^-$ (cyanide anion) with bromoethane, showing all nonbonding electron pairs and full or partial charges.

6.36 Many S_N2 reactions of alkyl chlorides and alkyl bromides are catalyzed by the addition of sodium or potassium iodide. For example, the hydrolysis of methyl bromide takes place much faster in the presence of sodium iodide. Explain.

6.37 Explain the following observations: When *tert*-butyl bromide is treated with sodium methoxide in a mixture of methanol and water, the rate of formation of *tert*-butyl alcohol and *tert*-butyl methyl ether does not change appreciably as the concentration of sodium methoxide is increased. However, increasing the concentration of sodium methoxide causes a marked increase in the rate at which *tert*-butyl bromide disappears from the mixture.

6.38 **(a)** Consider the general problem of converting a tertiary alkyl halide to an alkene, for example, the conversion of *tert*-butyl chloride to 2-methylpropene. What experimental conditions would you choose to ensure that elimination is favored over substitution?

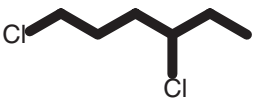
(b) Consider the opposite problem, that of carrying out a substitution reaction on a tertiary alkyl halide. Use as your example the conversion of *tert*-butyl chloride to *tert*-butyl ethyl ether. What experimental conditions would you employ to ensure the highest possible yield of the ether?

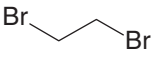
6.39 1-Bromobicyclo[2.2.1]heptane is extremely unreactive in either S_N2 or S_N1 reactions. Provide explanations for this behavior.

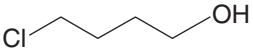
6.40 When ethyl bromide reacts with potassium cyanide in methanol, the major product is CH_3CH_2CN. Some CH_3CH_2NC is formed as well, however. Write Lewis structures for the cyanide ion and for both products and provide a mechanistic explanation of the course of the reaction.

6.41 Give structures for the products of each of the following reactions:

(a)  $\xrightarrow[\text{acetone}]{\text{NaI (1 mol)}}$ $C_5H_8FI + NaBr$

(b)  (1 mol) $\xrightarrow[\text{acetone}]{\text{NaI (1 mol)}}$ $C_6H_{12}ClI + NaCl$

(c)  (1 mol) $\xrightarrow{NaS\text{—}SNa}$ $C_4H_8S_2 + 2\ NaBr$

(d)  $\xrightarrow[Et_2O]{NaH\ (-H_2)}$ $C_4H_8ClONa \xrightarrow[Et_2O,\ heat]{}$ $C_4H_8O + NaCl$

(e)  $\xrightarrow[\text{liq. } NH_3]{NaNH_2\ (-NH_3)}$ $C_3H_3Na \xrightarrow{CH_3I}$ $C_4H_6 + NaI$

6.42 When *tert*-butyl bromide undergoes S_N1 hydrolysis, adding a "common ion" (e.g., NaBr) to the aqueous solution has no effect on the rate. On the other hand, when $(C_6H_5)_2CHBr$ undergoes S_N1 hydrolysis, adding NaBr retards the reaction. Given that the $(C_6H_5)_2CH^+$ cation is known to be much more stable than the $(CH_3)_3C^+$ cation (and we shall see why in Section 15.12A), provide an explanation for the different behavior of the two compounds.

6.43 When the alkyl bromides (listed here) were subjected to hydrolysis in a mixture of ethanol and water (80% EtOH/20% H_2O) at 55°C, the rates of the reaction showed the following order:

$$(CH_3)_3CBr > CH_3Br > CH_3CH_2Br > (CH_3)_2CHBr$$

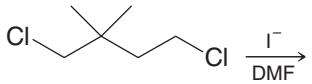
Provide an explanation for this order of reactivity.

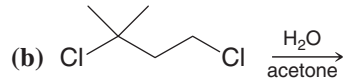
6.44 The reaction of 1° alkyl halides with nitrite salts produces both RNO_2 and RONO. Account for this behavior.

6.45 What would be the effect of increasing solvent polarity on the rate of each of the following nucleophilic substitution reactions?

(a) $Nu: + R\text{—}L \longrightarrow R\text{—}Nu^+ + :L^-$ **(b)** $R\text{—}L^+ \longrightarrow R^+ + :L$

6.46 Competition experiments are those in which two reactants at the same concentration (or one reactant with two reactive sites) compete for a reagent. Predict the major product resulting from each of the following competition experiments:

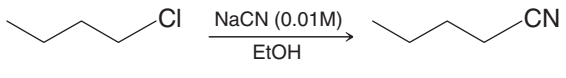
(a) 

(b) 

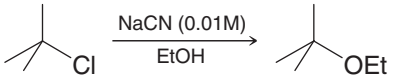
6.47 In contrast to S_N2 reactions, S_N1 reactions show relatively little nucleophile selectivity. That is, when more than one nucleophile is present in the reaction medium, S_N1 reactions show only a slight tendency to discriminate between weak nucleophiles and strong nucleophiles, whereas S_N2 reactions show a marked tendency to discriminate.

(a) Provide an explanation for this behavior.

(b) Show how your answer accounts for the following:



Major product



Major product

Challenge Problems

6.48 The reaction of chloroethane with water *in the gas phase* to produce ethanol and hydrogen chloride has $\Delta H^\circ = +26.6$ kJ mol^{-1} and $\Delta S^\circ = +4.81$ J K^{-1} mol^{-1} at 25°C.

(a) Which of these terms, if either, favors the reaction going to completion?

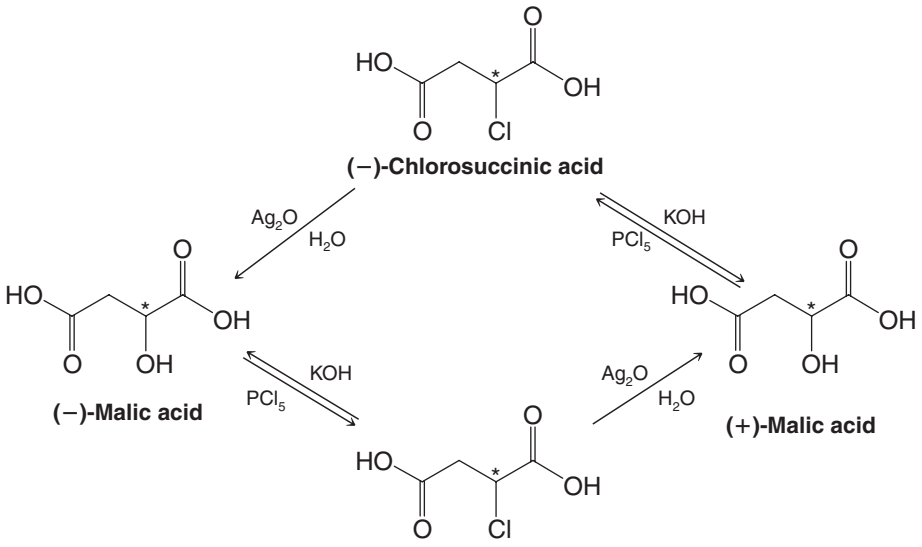
(b) Calculate ΔG° for the reaction. What can you now say about whether the reaction will proceed to completion?

(c) Calculate the equilibrium constant for the reaction.

(d) In aqueous solution the equilibrium constant is very much larger than the one you just calculated. How can you account for this fact?

6.49 When (*S*)-2-bromopropanoic acid [(*S*)-$CH_3CHBrCO_2H$] reacts with concentrated sodium hydroxide, the product formed (after acidification) is (*R*)-2-hydroxypropanoic acid [(*R*)-$CH_3CHOHCO_2H$, commonly known as (*R*)-lactic acid]. This is, of course, the normal stereochemical result for an S_N2 reaction. However, when the same reaction is carried out with a low concentration of hydroxide ion in the presence of Ag_2O (where Ag^+ acts as a Lewis acid), it takes place with overall *retention of configuration* to produce (*S*)-2-hydroxypropanoic acid. The mechanism of this reaction involves a phenomenon called **neighboring-group participation**. Write a detailed mechanism for this reaction that accounts for the net retention of configuration when Ag^+ and a low concentration of hydroxide are used.

6.50 The phenomenon of configuration inversion in a chemical reaction was discovered in 1896 by Paul Walden (Section 6.6). Walden's proof of configuration inversion was based on the following cycle:



The Walden Cycle

(a) Basing your answer on the preceding problem, which reactions of the Walden cycle are likely to take place with overall inversion of configuration and which are likely to occur with overall retention of configuration?

(b) Malic acid with a negative optical rotation is now known to have the (*S*) configuration. What are the configurations of the other compounds in the Walden cycle?

(c) Walden also found that when (+)-malic acid is treated with thionyl chloride (rather than PCl_5), the product of the reaction is (+)-chlorosuccinic acid. How can you explain this result?

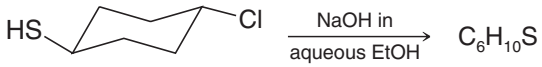
(d) Assuming that the reaction of (−)-malic acid and thionyl chloride has the same stereochemistry, outline a Walden cycle based on the use of thionyl chloride instead of PCl_5.

6.51 (*R*)-(3-Chloro-2-methylpropyl) methyl ether **(A)** on reaction with azide ion (N_3^-) in aqueous ethanol gives (*S*)-(3-azido-2-methylpropyl) methyl ether **(B)**. Compound **A** has the structure $ClCH_2CH(CH_3)CH_2OCH_3$.

(a) Draw wedge–dashed wedge–line formulas of both **A** and **B**.

(b) Is there a change of configuration during this reaction?

6.52 Predict the structure of the product of this reaction:



The product has no infrared absorption in the 1620–1680-cm^{-1} region.

6.53 *cis*-4-Bromocyclohexanol $\xrightarrow[t\text{-BuOH}]{t\text{-BuO}^-}$ racemic $C_6H_{10}O$ (compound **C**)

Compound **C** has infrared absorption in the 1620–1680-cm^{-1} and in the 3590–3650-cm^{-1} regions. Draw and label the (*R*) and (*S*) enantiomers of product **C**.

6.54 1-Bromo[2.2.1]bicycloheptane is unreactive toward both S_N2 and S_N1 reactions. Open the computer molecular model at the book's website titled "1-Bromo[2.2.1]bicycloheptane" and examine the structure. What barriers are there to substitution of 1-bromo[2.2.1]bicycloheptane by both S_N2 and S_N1 reaction mechanisms?

6.55 Open the computer molecular model titled "1-Bromo[2.2.1]bicycloheptane LUMO" at the book's website for the lowest unoccupied molecular orbital (LUMO) of this compound. Where is the lobe of the LUMO with which the HOMO of a nucleophile would interact in an S_N2 reaction?

6.56 In the previous problem and the associated molecular model at the book's website, you considered the role of HOMOs and LUMOs in an S_N2 reaction.

(a) What is the LUMO in an S_N1 reaction and in what reactant and species is it found?

(b) Open the molecular model at the book's website titled "Isopropyl Methyl Ether Carbocation LUMO." Identify the lobe of the LUMO in this carbocation model with which a nucleophile would interact.

(c) Open the model titled "Isopropyl Methyl Ether Carbocation HOMO." Why is there a large orbital lobe between the oxygen and the carbon of the carbocation?

Learning Group Problems

1. Consider the solvolysis reaction of (1*S*,2*R*)-1-bromo-1,2-dimethylcyclohexane in 80% H_2O/20% CH_3CH_2OH at room temperature.

(a) Write the structure of all chemically reasonable products from this reaction and predict which would be the major one.

(b) Write a detailed mechanism for formation of the major product.

(c) Write the structure of all transition states involved in formation of the major product.

2. Consider the following sequence of reactions, taken from the early steps in a synthesis of ω-fluorooleic acid, a toxic natural compound from an African shrub. (ω-Fluorooleic acid, also called "ratsbane," has been used to kill rats and also as an arrow poison in tribal warfare. Two more steps beyond those below are required to complete its synthesis.)

(i) 1-Bromo-8-fluorooctane + sodium acetylide (the sodium salt of ethyne) $\longrightarrow$ compound **A** ($C_{10}H_{17}F$)

(ii) Compound **A** + $NaNH_2$ $\longrightarrow$ compound **B** ($C_{10}H_{16}FNa$)

(iii) Compound **B** + $I{-}(CH_2)_7{-}Cl$ $\longrightarrow$ compound **C** ($C_{17}H_{30}ClF$)

(iv) Compound **C** + NaCN $\longrightarrow$ compound **D** ($C_{18}H_{30}NF$)

(a) Elucidate the structures of compounds **A**, **B**, **C**, and **D** above.

(b) Write the mechanism for each of the reactions above.

(c) Write the structure of the transition state for each reaction.

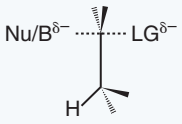
Summary and Review Tools

Mechanism Review: Substitution versus Elimination

S_N2

Primary substrate
Back side attack of Nu: with respect to LG
Strong/polarizable unhindered nucleophile

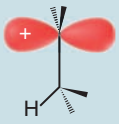
Bimolecular in rate-determining step
Concerted bond forming/bond breaking
Inversion of stereochemistry
Favored by polar aprotic solvent

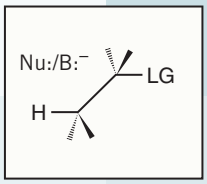


S_N1 and E1

Tertiary substrate
Carbocation intermediate
Weak nucleophile/base (e.g., solvent)

Unimolecular in rate-determining step
Racemization if S_N1
Removal of β-hydrogen if E1
Protic solvent assists ionization of LG
Low temperature (S_N1) / high temperature (E1)





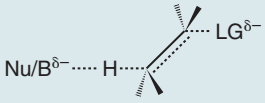
S_N2 and E2

Secondary or primary substrate
Strong unhindered base/nucleophile leads to S_N2
Strong hindered base/nucleophile leads to E2
Low temperature (S_N2) / high temperature (E2)

E2

Tertiary or secondary substrate
Concerted anti-coplanar transition state

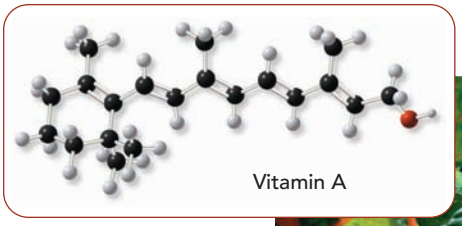
Bimolecular in rate-determining step
Strong hindered base
High temperature



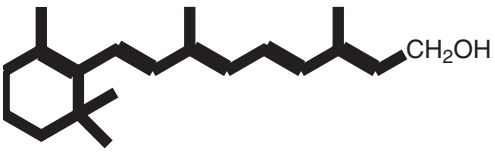
7

Alkenes and Alkynes I

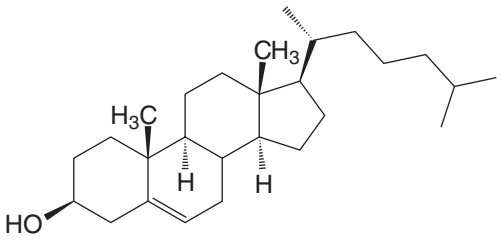
Properties and Synthesis. Elimination Reactions of Alkyl Halides



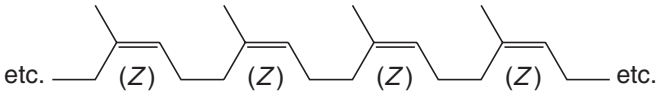
Three very dissimilar substances—vitamin A from sources including dark green leafy vegetables, cholesterol from animals, and rubber from certain trees—have something in common. Their molecules all have carbon–carbon double bonds—the alkene functional group.



Vitamin A

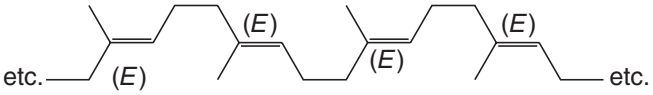


Cholesterol



Natural rubber

Gutta percha, another natural latex from the sap of some trees, is similar to natural rubber, yet also different in an important way.



Gutta percha

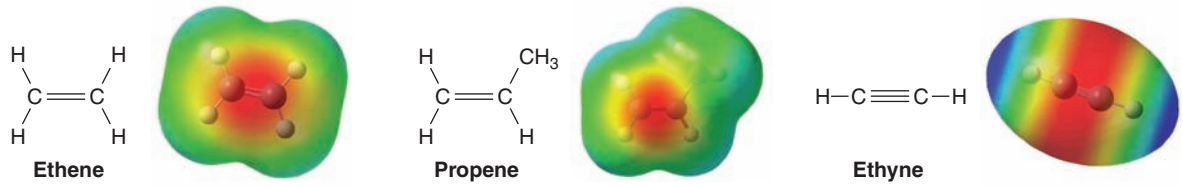
Natural rubber and gutta percha differ in the directions taken by the main chain at each double bond. As we learn in this chapter, according to the (*E*)–(*Z*) system, the double bonds of rubber are all designated (*Z*) and those of gutta percha are all (*E*). This seemingly slight difference in stereochemistry, however, renders gutta percha useless for many applications of rubber. For example, gutta percha is inelastic.

All four of these substances give characteristic reactions of alkenes that we will study in Chapter 8. Moreover, when nature puts these molecules together, the double bonds are made by a reaction that we have just studied and will study further in this chapter, the elimination reaction.

7.1 Introduction

Alkenes are hydrocarbons whose molecules contain the carbon–carbon double bond. An old name for this family of compounds that is still often used is the name **olefins.** Ethene (ethylene), the simplest olefin (alkene), was called olefiant gas (Latin: *oleum,* oil + *facere,* to make) because gaseous ethene (C_2H_4) reacts with chlorine to form $C_2H_4Cl_2$, a liquid (oil).

Hydrocarbons whose molecules contain the carbon–carbon triple bond are called alkynes. The common name for this family is **acetylenes,** after the simplest member, HC≡CH:

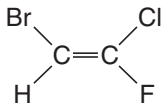


7.1A Physical Properties of Alkenes and Alkynes

Alkenes and alkynes have physical properties similar to those of corresponding alkanes. Alkenes and alkynes up to four carbons (except 2-butyne) are gases at room temperature. Being relatively nonpolar themselves, alkenes and alkynes dissolve in nonpolar solvents or in solvents of low polarity. Alkenes and alkynes are only *very slightly soluble* in water (with alkynes being slightly more soluble than alkenes). The densities of alkenes and alkynes are lower than that of water.

7.2 The (E)–(Z) System for Designating Alkene Diastereomers

In Section 4.5 we learned to use the terms **cis** and **trans** to designate the stereochemistry of alkene diastereomers. These terms are unambiguous, however, only when applied to disubstituted alkenes. If the alkene is trisubstituted or tetrasubstituted, the terms cis and trans are either ambiguous or do not apply at all. Consider the following alkene as an example:

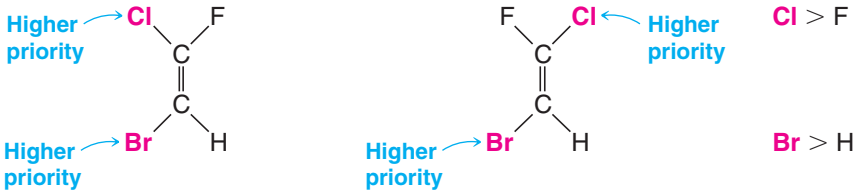


A

It is impossible to decide whether **A** is cis or trans since no two groups are the same.

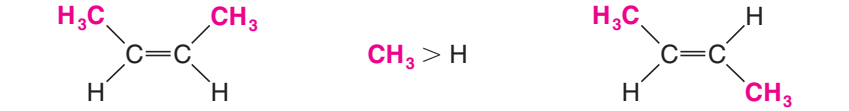
A system that works in all cases is based on the priorities of groups in the Cahn–Ingold–Prelog convention (Section 5.7). This system, called the **(*E*)–(*Z*) system**, applies to alkene diastereomers of all types. In the (*E*)–(*Z*) system, we examine the two

groups attached to one carbon atom of the double bond and decide which has higher priority. Then we repeat that operation at the other carbon atom:



(*Z*)-2-Bromo-1-chloro-1-fluoroethene **(*E*)-2-Bromo-1-chloro-1-fluoroethene**

We take the group of higher priority on one carbon atom and compare it with the group of higher priority on the other carbon atom. If the two groups of higher priority are on the same side of the double bond, the alkene is designated (*Z*) (from the German word *zusammen,* meaning together). If the two groups of higher priority are on opposite sides of the double bond, the alkene is designated (*E*) (from the German word *entgegen,* meaning opposite). The following example illustrates this:

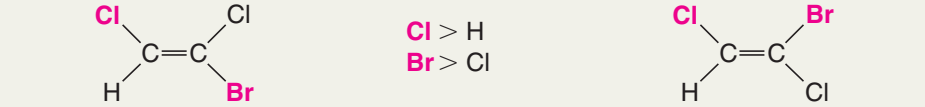


(*Z*)-2-Butene or (*Z*)-but-2-ene (*cis*-2-butene) **(*E*)-2-Butene or (*E*)-but-2-ene (*trans*-2-butene)**

Solved Problem 7.1

The two stereoisomers of 1-bromo-1,2-dichloroethene cannot be designated as cis and trans in the normal way because the double bond is trisubstituted. They can, however, be given (*E*) and (*Z*) designations. Write a structural formula for each isomer and give each the proper designation.

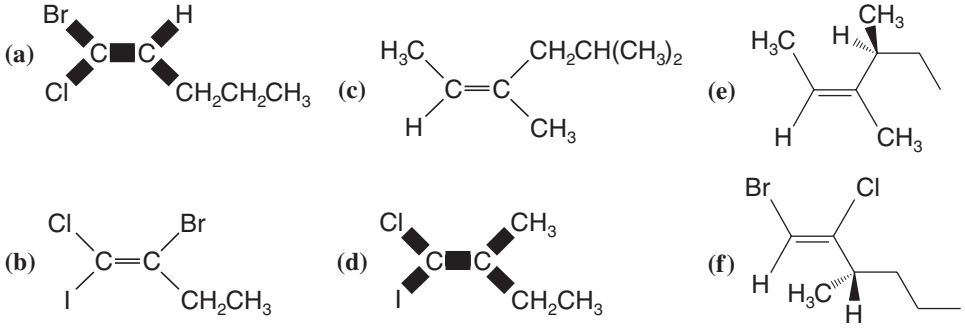
STRATEGY AND ANSWER We write the structures (below), then note that chlorine has a higher priority than hydrogen, and bromine has a higher priority than chlorine. The group with higher priority on C1 is bromine and the group with higher priority at C2 is chlorine. In the first structure the higher priority chlorine and bromine atoms are on opposite sides of the double bond, and therefore this isomer is (*E*). In the second structure those chlorine and bromine atoms are on the same side, so the latter isomer is (*Z*).



(*E*)-1-Bromo-1,2-dichloroethene **(*Z*)-1-Bromo-1,2-dichloroethene**

Review Problem 7.1

Using the (*E*)–(*Z*) designation [and in parts (e) and (f) the (*R*)–(*S*) designation as well] give IUPAC names for each of the following:



7.3 Relative Stabilities of Alkenes

Cis and trans isomers of alkenes do not have the same stability.

- Strain caused by crowding of two alkyl groups on the same side of a double bond makes cis isomers generally less stable than trans isomers (Fig. 7.1).

This effect can be measured quantitatively by comparing thermodynamic data from experiments involving alkenes with related structures, as we shall see below.

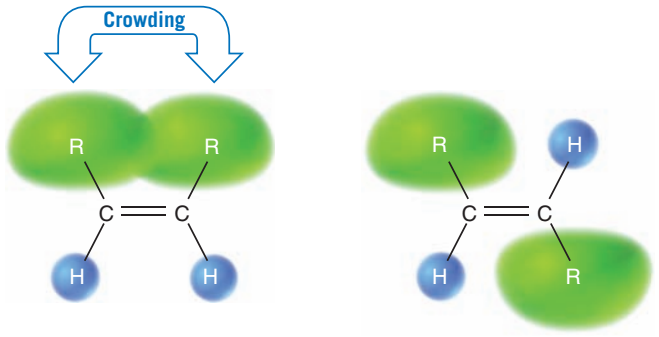
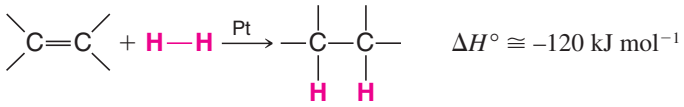


Figure 7.1 Cis and trans alkene isomers. The cis isomer is less stable due to greater strain from crowding by the adjacent alkyl groups.

7.3A Heat of Reaction

The addition of hydrogen to an alkene (**hydrogenation**, Sections 4.16A and 7.13) is an exothermic reaction; the enthalpy change involved is called the **heat of reaction** or, in this specific case, the **heat of hydrogenation**.



We can gain a quantitative measure of relative alkene stabilities by comparing the heats of hydrogenation for a family of alkenes that all become the same alkane product on hydrogenation. The results of such an experiment involving platinum-catalyzed hydrogenation of three butene isomers are shown in Fig. 7.2. All three isomers yield the same product—butane—but the heat of reaction is different in each case. On conversion to butane, 1-butene liberates the most heat (127 kJ mol^{-1}), followed by *cis*-2-butene (120 kJ mol^{-1}), with *trans*-2-butene producing the least heat (115 kJ mol^{-1}). These data indicate that the trans isomer

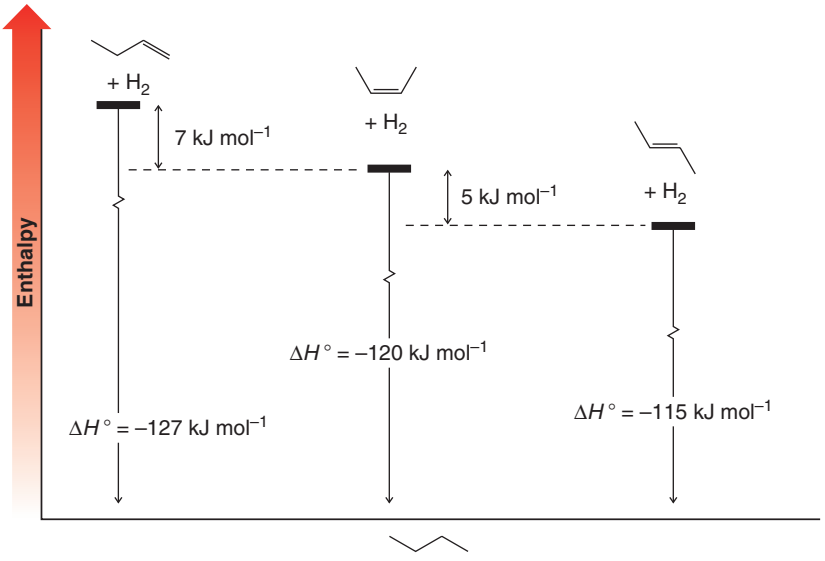


Figure 7.2 An energy diagram for platinum-catalyzed hydrogenation of the three butene isomers. The order of stability based on the differences in their heats of hydrogenation is *trans*-2-butene > *cis*-2-butene > 1-butene.

is more stable than the cis isomer, since less energy is released when the trans isomer is converted to butane. Furthermore, it shows that the terminal alkene, 1-butene, is less stable than either of the disubstituted alkenes, since its reaction is the most exothermic. Of course, alkenes that do not yield the same hydrogenation products cannot be compared on the basis of their respective heats of hydrogenation. In such cases it is necessary to compare other thermochemical data, such as heats of combustion, although we will not go into analyses of that type here.

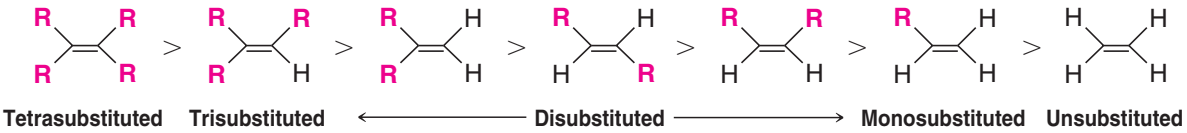
7.3B Overall Relative Stabilities of Alkenes

Studies of numerous alkenes reveal a pattern of stabilities that is related to the number of alkyl groups attached to the carbon atoms of the double bond.

- The greater the number of attached alkyl groups (i.e., the more highly substituted the carbon atoms of the double bond), the greater is the alkene's stability.

This order of stabilities can be given in general terms as follows:*

Relative Stabilities of Alkenes

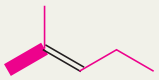


Solved Problem 7.2

Consider the two alkenes 2-methyl-1-pentene and 2-methyl-2-pentene and decide which would be most stable.

STRATEGY AND ANSWER First write the structures of the two alkenes, then decide how many substituents the double bond of each has.

2-Methyl-1-pentene (disubstituted, less stable)

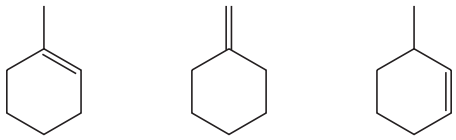


2-Methyl-2-pentene (trisubstituted, more stable)

2-Methyl-2-pentene has three substituents on its double bond, whereas 2-methyl-1-pentene has only one, and therefore it is the more stable.

Review Problem 7.2

Rank the following cycloalkenes in order of increasing stability.



*This order of stabilities may seem contradictory when compared with the explanation given for the relative stabilities of cis and trans isomers. Although a detailed explanation of the trend given here is beyond our scope, the relative stabilities of substituted alkenes can be rationalized. Part of the explanation can be given in terms of the electron-releasing effect of alkyl groups (Section 6.11B), an effect that satisfies the electron-withdrawing properties of the sp^2-hybridized carbon atoms of the double bond.

Review Problem 7.3

Heats of hydrogenation of three alkenes are as follows:

2-methyl-1-butene (-119 kJ mol^{-1})
3-methyl-1-butene (-127 kJ mol^{-1})
2-methyl-2-butene (-113 kJ mol^{-1})

(a) Write the structure of each alkene and classify it as to whether its doubly bonded atoms are monosubstituted, disubstituted, trisubstituted, or tetrasubstituted. **(b)** Write the structure of the product formed when each alkene is hydrogenated. **(c)** Can heats of hydrogenation be used to relate the relative stabilities of these three alkenes? **(d)** If so, what is the predicted order of stability? If not, why not? **(e)** What other alkene isomers are possible for these alkenes? Write their structures. **(f)** What are the relative stabilities among just these isomers?

Review Problem 7.4

Predict the more stable alkene of each pair: **(a)** 2-methyl-2-pentene or 2,3-dimethyl-2-butene; **(b)** *cis*-3-hexene or *trans*-3-hexene; **(c)** 1-hexene or *cis*-3-hexene; **(d)** *trans*-2-hexene or 2-methyl-2-pentene.

Review Problem 7.5

Reconsider the pairs of alkenes given in Review Problem 7.4. Explain how IR spectroscopy can be used to differentiate between the members of each pair.

7.4 Cycloalkenes

The rings of cycloalkenes containing five carbon atoms or fewer exist only in the cis form (Fig. 7.3). The introduction of a trans double bond into rings this small would, if it were possible, introduce greater strain than the bonds of the ring atoms could accommodate.

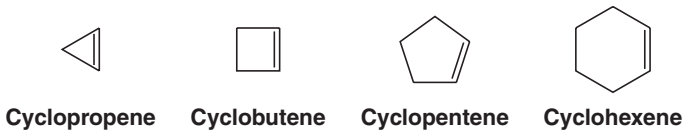


Figure 7.3 *cis*-Cycloalkenes.

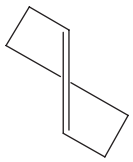


Figure 7.4 Hypothetical *trans*-cyclohexene. This molecule is apparently too highly strained to exist at room temperature.

(Verify this with handheld molecular models.) *trans*-Cyclohexene might resemble the structure shown in Fig. 7.4. There is evidence that it can be formed as a very reactive short-lived intermediate in some chemical reactions, but it is not isolable as a stable molecule.

trans-Cycloheptene has been observed spectroscopically, but it is a substance with a very short lifetime and has not been isolated.

trans-Cyclooctene (Fig. 7.5) has been isolated, however. Here the ring is large enough to accommodate the geometry required by a trans double bond and still be stable at room temperature. *trans*-Cyclooctene is chiral and exists as a pair of enantiomers. You may wish to verify this using handheld models.

Helpful Hint

Exploring all of these cycloalkenes with handheld molecular models, including both enantiomers of *trans*-cyclooctene, will help illustrate their structural differences.

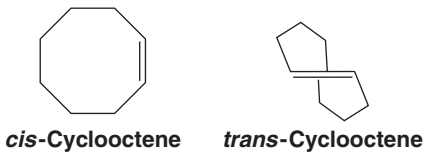
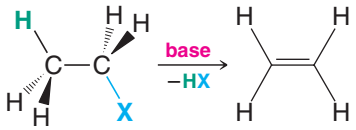


Figure 7.5 The cis and trans forms of cyclooctene.

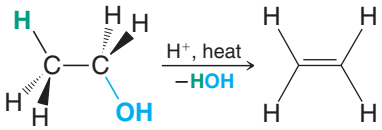
7.5 Synthesis of Alkenes via Elimination Reactions

Elimination reactions are the most important means for synthesizing alkenes. In this chapter we shall study two methods for alkene synthesis based on elimination reactions: dehydrohalogenation of alkyl halides and dehydration of alcohols.

Dehydrohalogenation of Alkyl Halides (Sections 6.15, 6.16, and 7.6)



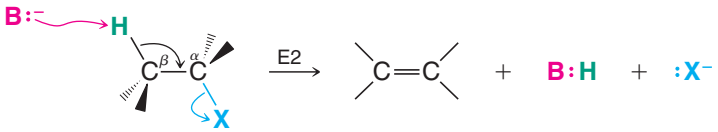
Dehydration of Alcohols (Sections 7.7 and 7.8)



7.6 Dehydrohalogenation of Alkyl Halides

- The best reaction conditions to use when synthesizing an alkene by **dehydrohalogenation** are those that promote an E2 mechanism.

In an E2 mechanism, a base removes a β hydrogen from the β carbon, as the double bond forms and a leaving group departs from the α carbon.



Reaction conditions that favor elimination by an E1 mechanism should be avoided because the results can be too variable. The carbocation intermediate that accompanies an E1 reaction can undergo rearrangement of the carbon skeleton, as we shall see in Section 7.8, and it can also undergo substitution by an S_N1 mechanism, which competes strongly with formation of products by an E1 path.

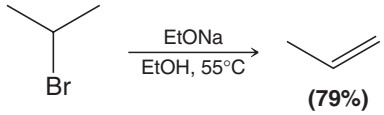
7.6A How to Favor an E2 Mechanism

1. **Use a secondary or tertiary alkyl halide if possible.**
   Why: Because steric hindrance in the substrate will inhibit substitution.
2. **When a synthesis must begin with a primary alkyl halide, use a bulky base.**
   Why: Because the steric bulk of the base will inhibit substitution.
3. **Use a high concentration of a strong and nonpolarizable base such as an alkoxide.**
   Why: Because a weak and polarizable base would not drive the reaction toward a bimolecular reaction, thereby allowing unimolecular processes (such as S_N1 or E1 reactions) to compete.
4. **Sodium ethoxide in ethanol (EtONa/EtOH) and potassium *tert*-butoxide in *tert*-butyl alcohol (*t*-BuOK/*t*-BuOH) are bases typically used to promote E2 reactions.**
   Why: Because they meet criterion 3 above. Note that in each case the alkoxide base is dissolved in its corresponding alcohol. (Potassium hydroxide dissolved in ethanol or *tert*-butyl alcohol is also sometimes used, in which case the active base includes both the alkoxide and hydroxide species present at equilibrium.)

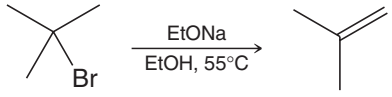
5. **Use elevated temperature because heat generally favors elimination over substitution.**
   Why: Because elimination reactions are entropically favored over substitution reactions (because the products are greater in number than the reactants). Hence $\Delta S°$ in the Gibbs free-energy equation, $\Delta G° = \Delta H° - T\,\Delta S°$ is significant, and $\Delta S°$ will be increased by higher temperature since T is a coefficient, leading to a more negative (favorable) $\Delta G°$.

7.6B Zaitsev's Rule: Formation of the More Substituted Alkene Is Favored with a Small Base

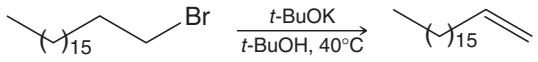
We showed examples in Sections 6.15–6.17 of dehydrohalogenations where only a single elimination product was possible. For example:



(79%)

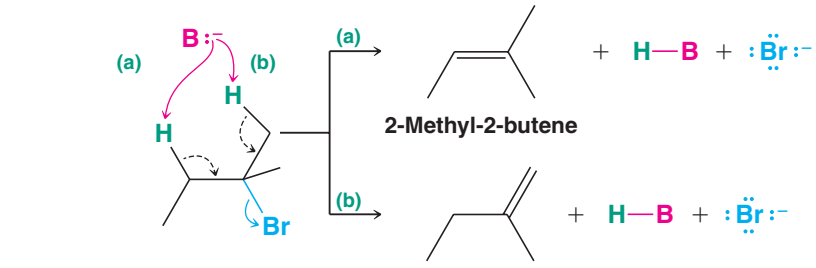


(91%)



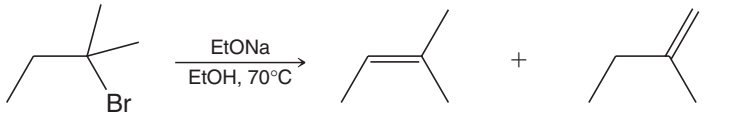
(85%)

Dehydrohalogenation of many alkyl halides, however, yields more than one product. For example, dehydrohalogenation of 2-bromo-2-methylbutane can yield two products: 2-methyl-2-butene and 2-methyl-1-butene, as shown here by pathways (a) and (b), respectively:



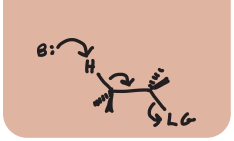
2-Bromo-2-methylbutane **2-Methyl-2-butene** **2-Methyl-1-butene**

- If we use a small base such as ethoxide or hydroxide, the major product of the reaction will be the more highly substituted alkene (which is also the more stable alkene).



2-Methyl-2-butene (69%) (more stable) **2-Methyl-1-butene (31%) (less stable)**

2-Methyl-2-butene is a trisubstituted alkene (three methyl groups are attached to carbon atoms of the double bond), whereas 2-methyl-1-butene is only disubstituted. 2-Methyl-2-butene is the major product.

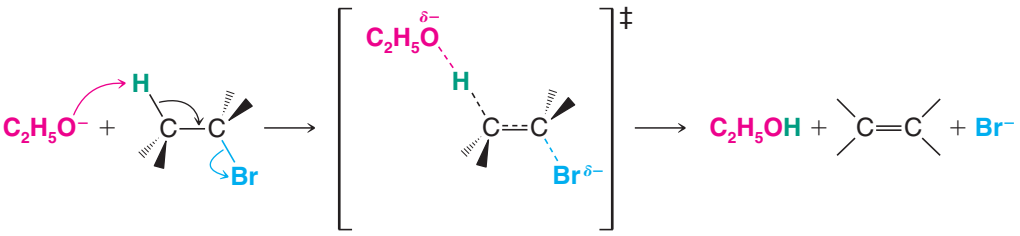


- Whenever an elimination occurs to give the more stable, more highly substituted alkene, chemists say that the elimination follows the **Zaitsev rule**, named for the nineteenth-century Russian chemist A. N. Zaitsev (1841–1910) who formulated it. (Zaitsev's name is also transliterated as Zaitzev, Saytzeff, Saytseff, or Saytzev.)

Helpful Hint

The Zaitsev product is that which is the more stable product.

The reason for this behavior is related to the double-bond character that develops in the transition state (cf. Section 6.16) for each reaction:



Transition state for an E2 reaction
The carbon–carbon bond has some of the character of a double bond.

The transition state for the reaction leading to 2-methyl-2-butene (Fig. 7.6) has the developing character of the double bond in a trisubstituted alkene. The transition state for the reaction leading to 2-methyl-1-butene has the developing character of a double bond in a disubstituted alkene. Because the transition state leading to 2-methyl-2-butene resembles a more stable alkene, this transition state is more stable (recall the Hammond–Leffler postulate, Fig. 6.10). Because this transition state is more stable (occurs at lower free energy), the free energy of activation for this reaction is lower and 2-methyl-2-butene is formed faster. This explains why 2-methyl-2-butene is the major product. In general, the preferential formation of one product because the free energy of activation leading to its formation is lower than that for another product, and therefore the rate of its formation faster, is called **kinetic control** of product formation. (See also Section 13.10A.)

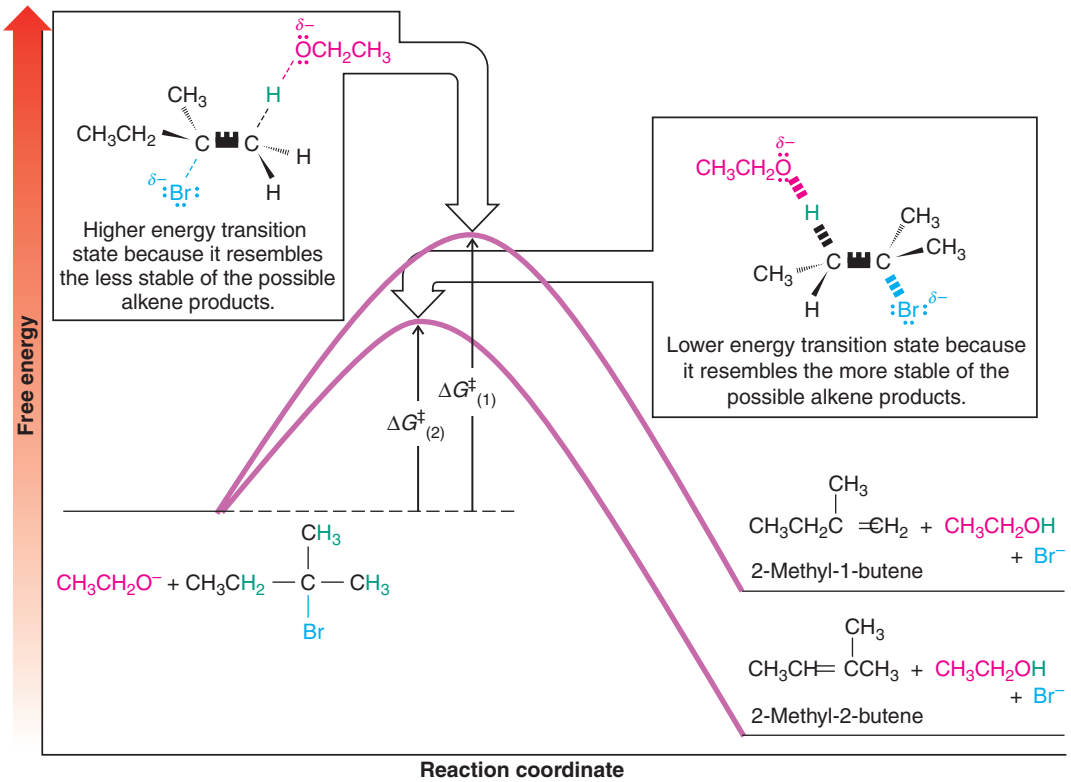
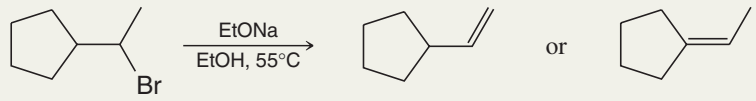


Figure 7.6 Reaction (2) leading to the more stable alkene occurs faster than reaction (1) leading to the less stable alkene; $\Delta G^{\ddagger}_{(2)}$ is less than $\Delta G^{\ddagger}_{(1)}$.

Solved Problem 7.3

Using Zaitsev's rule, predict which would be the major product of the following reaction:



A **B**

STRATEGY AND ANSWER Alkene **B** has a trisubstituted double bond whereas the double bond of **A** is only monosubstituted. Therefore, **B** is more stable and, according to Zaitsev's rule, would be the major product.

Review Problem 7.6

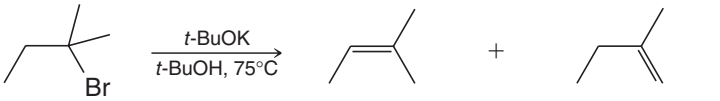
Predict the major product formed when 2-bromobutane is subjected to dehydrobromination using sodium ethoxide in ethanol at 55°C.

Review Problem 7.7

List the alkenes that would be formed when each of the following alkyl halides is subjected to dehydrohalogenation with potassium ethoxide in ethanol and use Zaitsev's rule to predict the major product of each reaction: **(a)** 2-bromo-3-methylbutane and **(b)** 2-bromo-2,3-dimethylbutane.

7.6C Formation of the Less Substituted Alkene Using a Bulky Base

- Carrying out dehydrohalogenations with a bulky base such as potassium *tert*-butoxide (*t*-BuOK) in *tert*-butyl alcohol (*t*-BuOH) favors the formation of the **less substituted alkene:**



2-Methyl-2-butene (27.5%) (more substituted) **2-Methyl-1-butene (72.5%) (less substituted)**

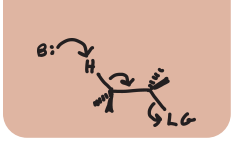
The reasons for this behavior are related in part to the steric bulk of the base and to the fact that in *tert*-butyl alcohol the base is associated with solvent molecules and thus made even larger. The large *tert*-butoxide ion appears to have difficulty removing one of the internal (2°) hydrogen atoms because of greater crowding at that site in the transition state. It removes one of the more exposed (1°) hydrogen atoms of the methyl group instead.

- When an elimination yields the less substituted alkene, we say that it follows the **Hofmann rule** (see also Section 20.12A).

Solved Problem 7.4

Your task is the following synthesis. Which base would you use to maximize the yield of this specific alkene?

STRATEGY AND ANSWER Here you want the Hofmann rule to apply (you want the less substituted alkene to be formed). Therefore, use a bulky base such as potassium *tert*-butoxide in *tert*-butyl alcohol.



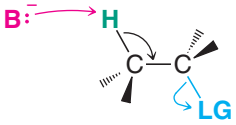
Review Problem 7.8

Examine Solved Problem 7.3. Your task is to prepare **A** in the highest possible yield by dehydrobromination. Which base would you use?

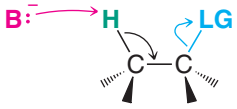
7.6D The Stereochemistry of E2 Reactions: The Orientation of Groups in the Transition State

- The five atoms involved in the transition state of an E2 reaction (including the base) must lie in the same plane.

The requirement for coplanarity of the H—C—C—LG unit arises from a need for proper overlap of orbitals in the developing π bond of the alkene that is being formed (see Section 6.16). There are two ways that this can happen:



Anti coplanar transition state (preferred)



Syn coplanar transition state (only with certain rigid molecules)

- The **anti coplanar** conformation is the preferred transition state geometry.

Helpful Hint

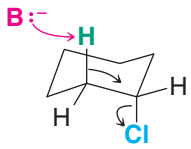
Be able to draw a three-dimensional representation of an anti coplanar E2 transition state.

The **syn coplanar** transition state occurs only with rigid molecules that are unable to assume the anti arrangement. The reason: The anti coplanar transition state is staggered (and therefore of lower energy), while the syn coplanar transition state is eclipsed. Review Problem 7.9 will help to illustrate this difference.

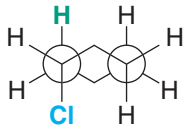
Review Problem 7.9

Consider a simple molecule such as ethyl bromide and show with Newman projection formulas how the anti coplanar transition state would be favored over the syn coplanar one.

Part of the evidence for the preferred anti coplanar arrangement of groups comes from experiments done with cyclic molecules. Two groups axially oriented on adjacent carbons in a chair conformation of cyclohexane are anti coplanar. If one of these groups is a hydrogen and the other a leaving group, the geometric requirements for an anti coplanar E2 transition state are met. Neither an axial–equatorial nor an equatorial–equatorial orientation of the groups allows formation of an anti coplanar transition state. (Note that there are no syn coplanar groups in a chair conformation, either.)

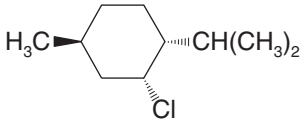


Here the hydrogen and the chlorine are both axial. This allows an anti coplanar transition state.

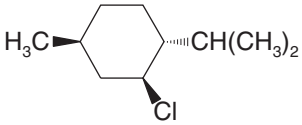


A Newman projection formula shows that the hydrogen and the chlorine are anti coplanar when they are both axial.

As examples, let us consider the different behavior in E2 reactions shown by two compounds containing cyclohexane rings, neomenthyl chloride and menthyl chloride:



Neomenthyl chloride



Menthyl chloride

In the more stable conformation of neomenthyl chloride (see the following mechanism), the alkyl groups are both equatorial and the chlorine is axial. There are also axial hydrogen

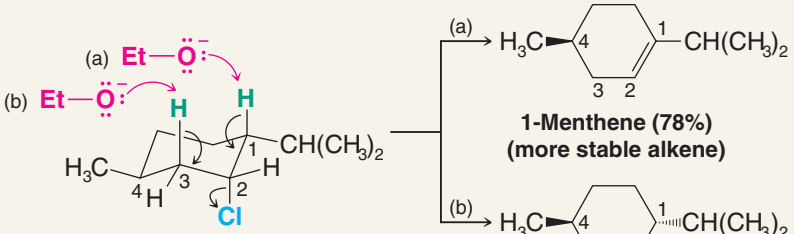
Helpful Hint

Examine the conformations of neomenthyl chloride using handheld models.

atoms on both C1 and C3. The base can attack either of these hydrogen atoms and achieve an anti coplanar transition state for an E2 reaction. Products corresponding to each of these transition states (2-menthene and 1-menthene) are formed rapidly. In accordance with Zaitsev's rule, 1-menthene (with the more highly substituted double bond) is the major product.

A MECHANISM FOR THE REACTION

E2 Elimination Where There Are Two Axial β Hydrogens



Neomenthyl chloride

Both green hydrogens are anti to the chlorine in this, the more stable conformation. Elimination by path (a) leads to 1-menthene; by path (b) to 2-menthene.

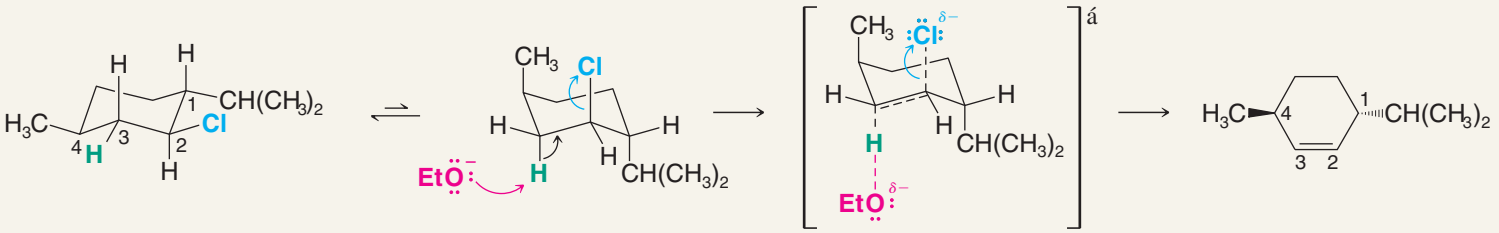
1-Menthene (78%) (more stable alkene)

2-Menthene (22%) (less stable alkene)

On the other hand, the more stable conformation of menthyl chloride has all three groups (including the chlorine) equatorial. For the chlorine to become axial, menthyl chloride has to assume a conformation in which the large isopropyl group and the methyl group are also axial. This conformation is of much higher energy, and the free energy of activation for the reaction is large because it includes the energy necessary for the conformational change. Consequently, menthyl chloride undergoes an E2 reaction very slowly, and the product is entirely 2-menthene because the hydrogen atom at C1 cannot be anti to the chlorine. This product (or any resulting from an elimination to yield the less substituted alkene) is sometimes called the *Hofmann product* (Sections 7.6C and 20.12A).

A MECHANISM FOR THE REACTION

E2 Elimination Where the Only Axial β Hydrogen Is from a Less Stable Conformer



Menthyl chloride (*more stable conformation*)

Elimination is not possible for this conformation because no hydrogen is anti to the leaving group.

Menthyl chloride (*less stable conformation*)

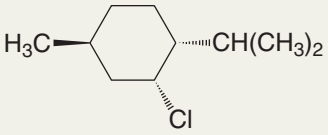
Elimination is possible from this conformation because the green hydrogen is anti to the chlorine.

The transition state for the E2 elimination is anti coplanar.

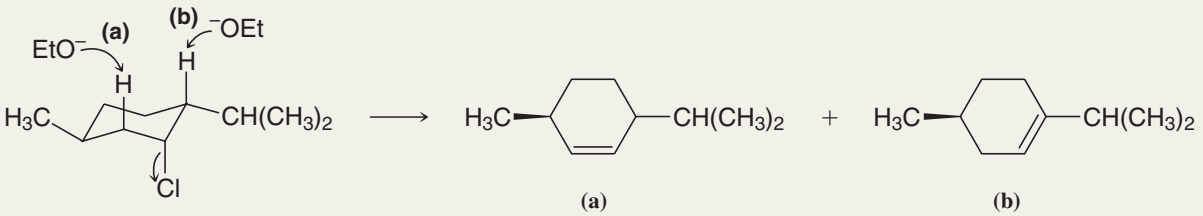
2-Menthene (100%)

Solved Problem 7.5

Predict the major product formed when the following compound is subjected to dehydrochlorination with sodium ethoxide in ethanol.



STRATEGY AND ANSWER We know that for an E2 dehydrochlorination to take place the chlorine will have to be axial. The following conformation has the chlorine axial and has two hydrogen atoms that are anti coplanar to the chlorine. Two products will be formed but (b) being more stable should be the major product.



Disubstituted, less stable (minor product)

Trisubstituted, more stable (major product)

Review Problem 7.10

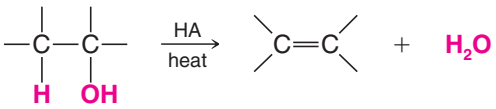
When *cis*-1-bromo-4-*tert*-butylcyclohexane is treated with sodium ethoxide in ethanol, it reacts rapidly; the product is 4-*tert*-butylcyclohexene. Under the same conditions, *trans*-1-bromo-4-*tert*-butylcyclohexane reacts very slowly. Write conformational structures and explain the difference in reactivity of these cis–trans isomers.

Review Problem 7.11

(a) When *cis*-1-bromo-2-methylcyclohexane undergoes an E2 reaction, two products (cycloalkenes) are formed. What are these two cycloalkenes, and which would you expect to be the major product? Write conformational structures showing how each is formed. **(b)** When *trans*-1-bromo-2-methylcyclohexane reacts in an E2 reaction, only one cycloalkene is formed. What is this product? Write conformational structures showing why it is the only product.

7.7 Acid-Catalyzed Dehydration of Alcohols

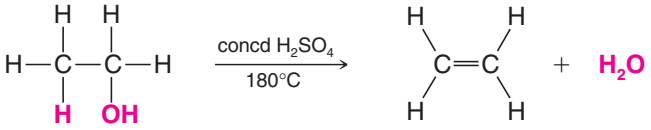
- Most alcohols undergo **dehydration** (lose a molecule of water) to form an alkene when heated with a strong acid.



The reaction is an **elimination** and is favored at higher temperatures (Section 6.18A). The most commonly used acids in the laboratory are Brønsted acids—proton donors such as sulfuric acid and phosphoric acid. Lewis acids such as alumina (Al_2O_3) are often used in industrial, gas-phase dehydrations.

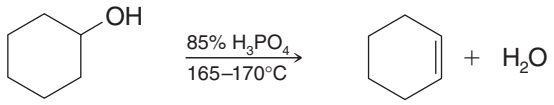
1. **The temperature and concentration of acid required to dehydrate an alcohol depend on the structure of the alcohol substrate.**

   (a) Primary alcohols are the most difficult to dehydrate. Dehydration of ethanol, for example, requires concentrated sulfuric acid and a temperature of 180°C:



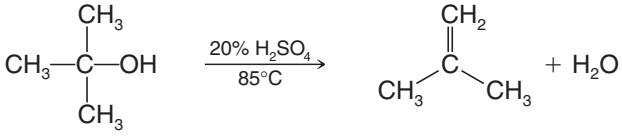
Ethanol (a 1° alcohol)

(b) Secondary alcohols usually dehydrate under milder conditions. Cyclohexanol, for example, dehydrates in 85% phosphoric acid at 165–170°C:



Cyclohexanol **Cyclohexene (80%)**

(c) Tertiary alcohols are usually so easily dehydrated that extremely mild conditions can be used. *tert*-Butyl alcohol, for example, dehydrates in 20% aqueous sulfuric acid at a temperature of 85°C:

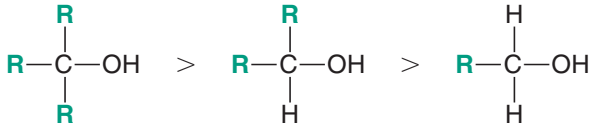


***tert*-Butyl alcohol** **2-Methylpropene (84%)**

Thus, overall, the relative ease with which alcohols undergo dehydration is in the following order:

Helpful Hint

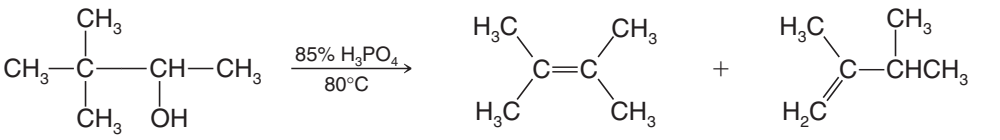
Be able to classify any alcohol as 1°, 2°, or 3°, and thereby compare its relative ease of dehydration.



3° Alcohol **2° Alcohol** **1° Alcohol**

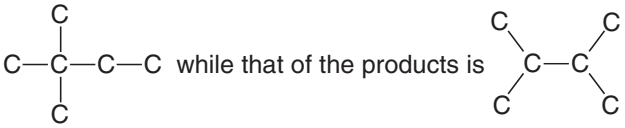
This behavior, as we shall see in Section 7.7B, is related to the relative stabilities of carbocations.

2. **Some primary and secondary alcohols also undergo rearrangements of their carbon skeletons during dehydration.** Such a rearrangement occurs in the dehydration of 3,3-dimethyl-2-butanol:



3,3-Dimethyl-2-butanol **2,3-Dimethyl-2-butene (80%)** **2,3-Dimethyl-1-butene (20%)**

Notice that the carbon skeleton of the reactant is



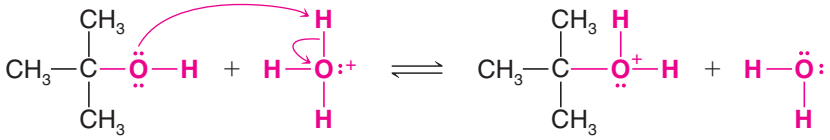
We shall see in Section 7.8 that this reaction involves the migration of a methyl group from one carbon to the next so as to form a more stable carbocation. (Rearrangements to carbocations of approximately equal energy may also be possible with some substrates.)

7.7A Mechanism for Dehydration of Secondary and Tertiary Alcohols: An E1 Reaction

Explanations for these observations can be based on a stepwise mechanism originally proposed by F. Whitmore (of Pennsylvania State University).

The mechanism is an E1 reaction in which the substrate is a protonated alcohol. Consider the dehydration of *tert*-butyl alcohol as an example:

Step 1

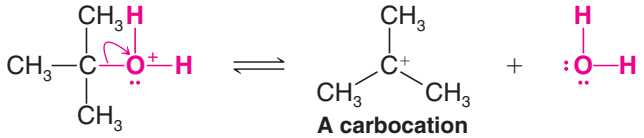


Protonated alcohol

In this step, an acid–base reaction, a proton is rapidly transferred from the acid to one of the unshared electron pairs of the alcohol. In dilute sulfuric acid the acid is a hydronium ion; in concentrated sulfuric acid the initial proton donor is sulfuric acid itself. This step is characteristic of all reactions of an alcohol with a strong acid.

The presence of the positive charge on the oxygen of the protonated alcohol weakens all bonds to oxygen, including the carbon–oxygen bond, and in step 2 the carbon–oxygen bond breaks. The leaving group is a molecule of water:

Step 2

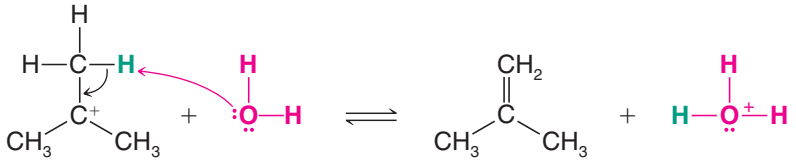


A carbocation

The carbon–oxygen bond breaks **heterolytically.** The bonding electrons depart with the water molecule and leave behind a carbocation. The carbocation is, of course, highly reactive because the central carbon atom has only six electrons in its valence level, not eight.

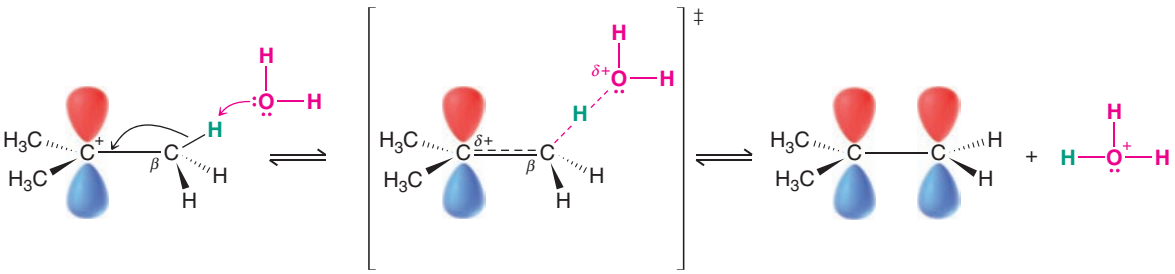
Finally, in step 3, a water molecule removes a proton from the β carbon of the carbocation by the process shown below. The result is the formation of a hydronium ion and an alkene:

Step 3



2-Methylpropene

In step 3, also an acid–base reaction, any one of the nine protons available at the three methyl groups can be transferred to a molecule of water. The electron pair left behind when a proton is removed becomes the second bond of the double bond of the alkene. Notice that this step restores an octet of electrons to the central carbon atom. An orbital representation of this process, with the transition state, is as follows.



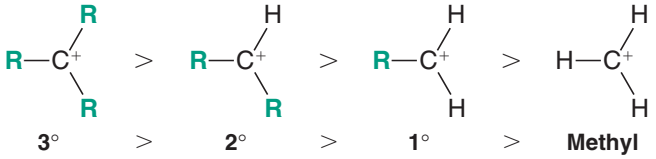
Transition state for removal of a proton from the β carbon of the carbocation

Review Problem 7.12

Dehydration of 2-propanol occurs in 14*M* H_2SO_4 at 100°C. **(a)** Using curved arrows, write all steps in a mechanism for the dehydration. **(b)** Explain the essential role performed in alcohol dehydrations by the acid catalyst. [*Hint:* Consider what would have to happen if no acid were present.]

7.7B Carbocation Stability and the Transition State

We saw in Section 6.11B that the order of stability of carbocations is tertiary > secondary > primary > methyl:



In the dehydration of secondary and tertiary alcohols the slowest step is formation of the carbocation as shown in step 2 of the "A Mechanism for the Reaction" box in this section. The first and third steps involve simple acid–base proton transfers, which occur very rapidly. The second step involves loss of the protonated hydroxyl as a leaving group, a highly endergonic process (Section 6.7), and hence it is the rate-determining step.

Because step 2 is the rate-determining step, it is this step that determines the overall reactivity of alcohols toward dehydration. With that in mind, we can now understand why tertiary alcohols are the most easily dehydrated. The formation of a tertiary carbocation is easiest because the free energy of activation for step 2 of a reaction leading to a tertiary carbocation is lowest (see Fig. 7.7). Secondary alcohols are not so easily dehydrated because the free energy of activation for their dehydration is higher—a secondary carbocation is less stable. The free energy of activation for dehydration of primary alcohols via a carbocation is so high that they undergo dehydration by another mechanism (Section 7.7C).

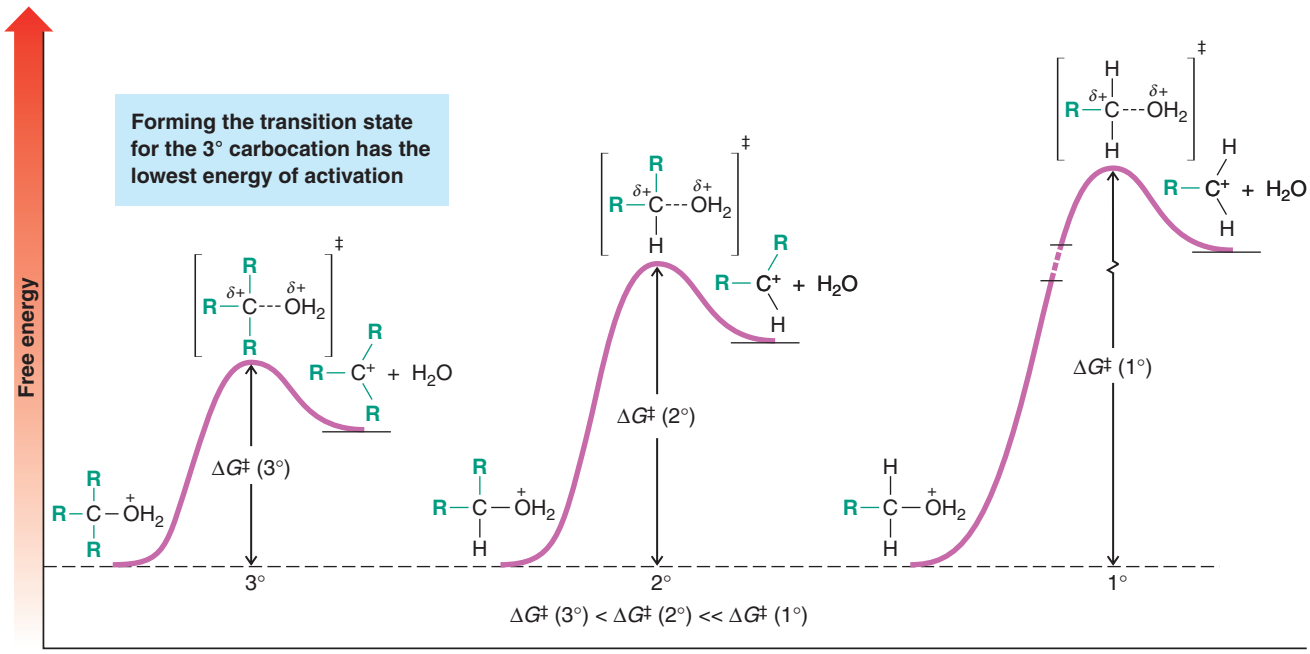
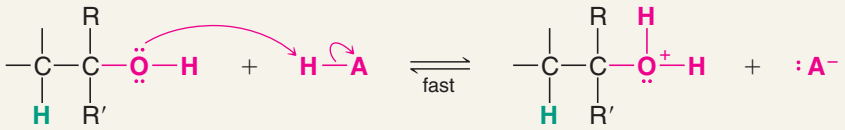


Figure 7.7 Free-energy diagrams for the formation of carbocations from protonated tertiary, secondary, and primary alcohols. The relative free energies of activation are tertiary < secondary << primary.

A MECHANISM FOR THE REACTION

Acid-Catalyzed Dehydration of Secondary or Tertiary Alcohols: An E1 Reaction

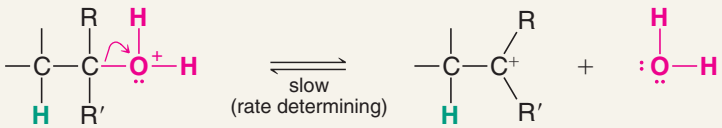
Step 1



2° or 3° Alcohol (R′ may be H) | **Acid catalyst (typically sulfuric or phosphoric acid)** | **Protonated alcohol** | **Conjugate base**

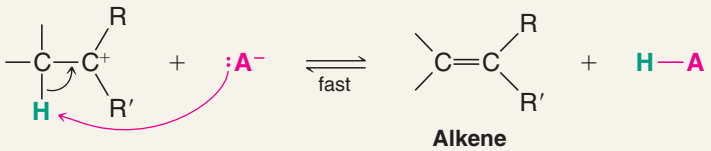
The alcohol accepts a proton from the acid in a fast step.

Step 2



The protonated alcohol loses a molecule of water to become a carbocation. This step is slow and rate determining.

Step 3



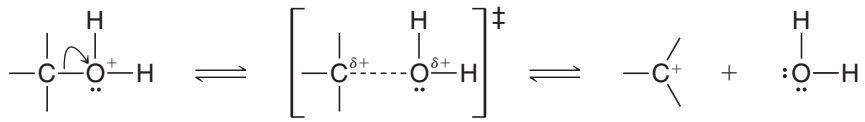
Alkene

The carbocation loses a proton to a base. In this step, the base may be another molecule of the alcohol, water, or the conjugate base of the acid. The proton transfer results in the formation of the alkene. Note that the overall role of the acid is catalytic (it is used in the reaction and regenerated).

The reactions by which carbocations are formed from protonated alcohols are all highly *endergonic*. Based on the Hammond–Leffler postulate (Section 6.13A), there should be a strong resemblance between the transition state and the carbocation in each case.

- ***The transition state that leads to the tertiary carbocation is lowest in free energy because it resembles the carbocation that is lowest in energy.***

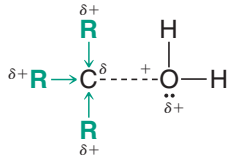
By contrast, the transition state that leads to the primary carbocation occurs at highest free energy because it resembles the carbocation that is highest in energy. In each instance, moreover, the same factor stabilizes the transition state that stabilizes the carbocation itself: **delocalization of the charge.** We can understand this if we examine the process by which the transition state is formed:



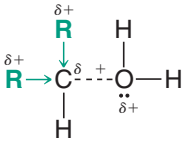
Protonated alcohol | **Transition state** | **Carbocation**

The oxygen atom of the protonated alcohol bears a full positive charge. As the transition state develops, this oxygen atom begins to separate from the carbon atom to which it is attached. The carbon atom begins to develop a partial positive charge because it is

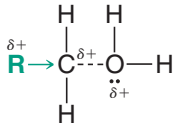
losing the electrons that bonded it to the oxygen atom. This developing positive charge ***is most effectively delocalized in the transition state leading to a tertiary carbocation because three alkyl groups are present to contribute electron density by hyperconjugation (Section 6.11B) to the developing carbocation.*** The positive charge is less effectively delocalized in the transition state leading to a secondary carbocation (*two* electron-releasing groups) and is least effectively delocalized in the transition state leading to a primary carbocation (*one* electron-releasing group). For this reason the dehydration of a primary alcohol proceeds through a different mechanism—an E2 mechanism.



Transition state leading to 3° carbocation (most stable)



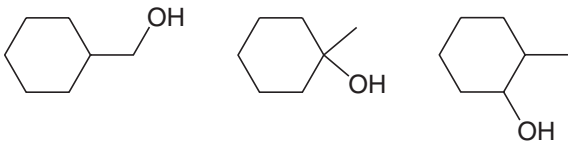
Transition state leading to 2° carbocation



Transition state leading to 1° carbocation (least stable)

Review Problem 7.13

Rank the following alcohols in order of increasing ease of acid-catalyzed dehydration.



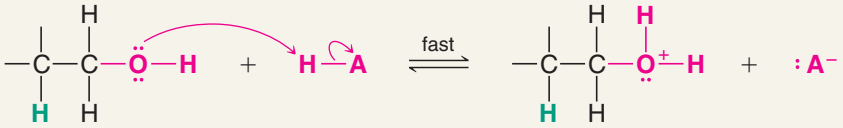
(a) **(b)** **(c)**

7.7C A Mechanism for Dehydration of Primary Alcohols: An E2 Reaction

Dehydration of primary alcohols apparently proceeds through an E2 mechanism because the primary carbocation required for dehydration by an E1 mechanism is relatively unstable. The first step in dehydration of a primary alcohol is protonation, just as in the E1 mechanism. Then, with the protonated hydroxyl as a good leaving group, a Lewis base in the reaction mixture removes a β hydrogen simultaneously with formation of the alkene double bond and departure of the protonated hydroxyl group (water).

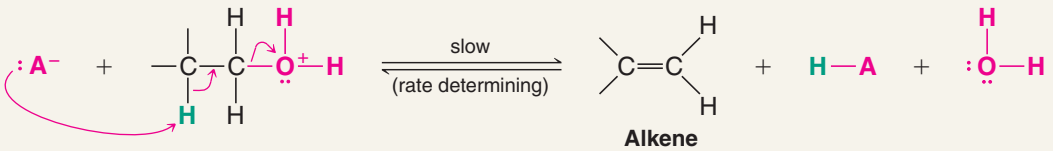
A MECHANISM FOR THE REACTION

Dehydration of a Primary Alcohol: An E2 Reaction



Primary alcohol — **Acid catalyst (typically sulfuric or phosphoric acid)** — **Protonated alcohol** — **Conjugate base**

The alcohol accepts a proton from the acid in a fast step.



Alkene

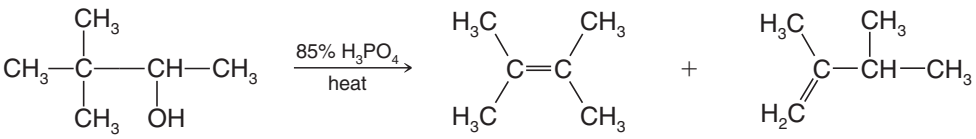
A base removes a hydrogen from the β carbon as the double bond forms and the protonated hydroxyl group departs. (The base may be another molecule of the alcohol or the conjugate base of the acid.)

7.8 Carbocation Stability and the Occurrence of Molecular Rearrangements

With an understanding of carbocation stability and its effect on transition states, we can now proceed to explain the rearrangements of carbon skeletons that occur in some alcohol dehydrations.

7.8A Rearrangements during Dehydration of Secondary Alcohols

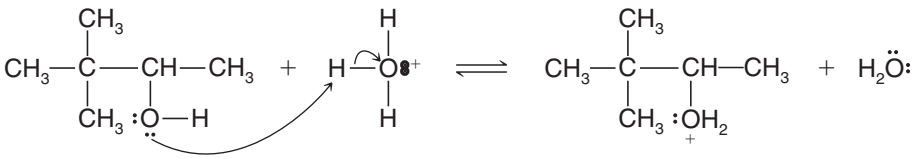
Consider again the rearrangement that occurs when 3,3-dimethyl-2-butanol is dehydrated:



3,3-Dimethyl-2-butanol → **2,3-Dimethyl-2-butene (major product)** + **2,3-Dimethyl-1-butene (minor product)**

The first step of this dehydration is the formation of the protonated alcohol in the usual way:

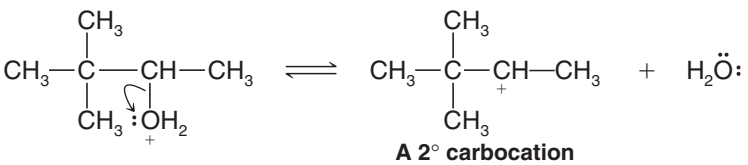
Step 1



Protonated alcohol

In the second step the protonated alcohol loses water and a secondary carbocation forms:

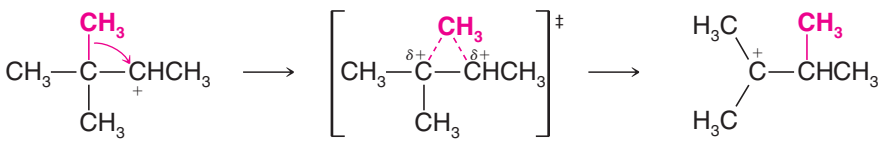
Step 2



A 2° carbocation

Now the rearrangement occurs. ***The less stable, secondary carbocation rearranges to a more stable tertiary carbocation:***

Step 3



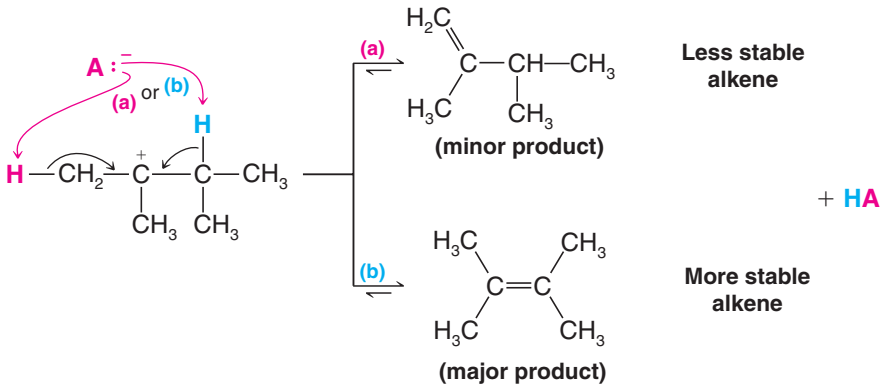
2° Carbocation (less stable) → **Transition state** → **3° Carbocation (more stable)**

The rearrangement occurs through the migration of an alkyl group (methyl) from the carbon atom adjacent to the one with the positive charge. The methyl group migrates **with its pair of electrons,** that is, as a methyl anion, $^{-}:CH_3$ (called a **methanide** ion). After the migration is complete, the carbon atom that the methyl anion left has become a carbocation, and the positive charge on the carbon atom to which it migrated has been neutralized. Because a group migrates from one carbon to the next, this kind of rearrangement is often called a **1,2 shift**.

In the transition state the shifting methyl is partially bonded to both carbon atoms by the pair of electrons with which it migrates. It never leaves the carbon skeleton.

The final step of the reaction is the removal of a proton from the new carbocation (by a Lewis base in the reaction mixture) and the formation of an alkene. This step, however, can occur in two ways:

Step 4



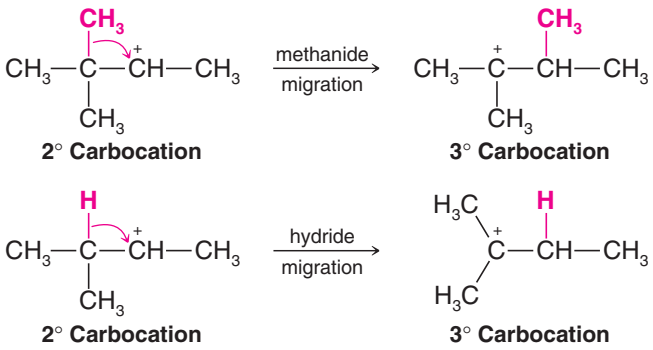
The more favored product is dictated by the stability of the alkene being formed. The conditions for the reaction (heat and acid) allow **equilibrium to be achieved** between the two forms of the alkene, and **the more stable alkene is the major product because it has lower potential energy**. Such a reaction is said to be **under equilibrium** or **thermodynamic control**. Path (b) leads to the highly stable tetrasubstituted alkene and this is the path followed by most of the carbocations. Path (a), on the other hand, leads to a less stable, disubstituted alkene, and because its potential energy is higher, it is the minor product of the reaction.

Helpful Hint

Alcohol dehydration follows Zaitsev's rule.

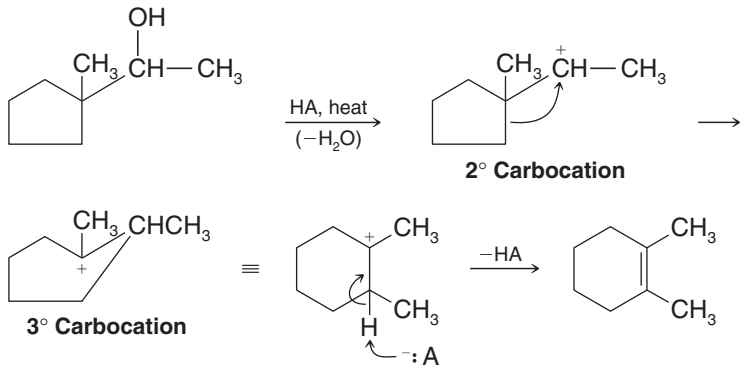
- **Formation of the more stable alkene is the general rule in acid-catalyzed dehydration of alcohols (Zaitsev's rule).**

Studies of many reactions involving carbocations show that rearrangements like those just described are general phenomena. ***They occur almost invariably when the migration of an alkanide ion or hydride ion can lead to a more stable carbocation.*** The following are examples:



We shall see biological examples of methanide and hydride migrations in "The Chemistry of . . . Cholesterol Biosynthesis" (Chapter 8).

Rearrangements of carbocations can also lead to a change in ring size, as the following example shows:

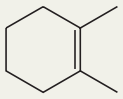


This process is especially favorable if a relief in ring strain occurs.

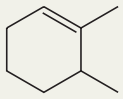
It is important to note that rearrangements to carbocations having approximately equal energy are also possible (e.g., from one secondary carbocation to another), and this can complicate the mixture of products that might be obtained from a reaction.

Solved Problem 7.6

Explain why the major product of the dehydration above is 1,2-dimethylcyclohexene (as shown) and not 2,3-dimethyl-1-cyclohexene.



1,2-Dimethylcyclohexene (major product)



2,3-Dimethyl-1-cyclohexene (minor product)

STRATEGY AND ANSWER We have just learned that dehydration leads mainly to the more stable alkene (when two are possible). We also know that the stability of an alkene is related to the number of alkyl groups that are attached to the carbons of the double bond. 1,2-Dimethylcyclohexene has a tetrasubstituted double bond (and is more stable), while in 2,3-dimethylcyclohexene the double bond is only trisubstituted.

Review Problem 7.14

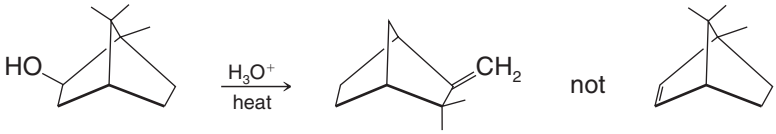
Acid-catalyzed dehydration of neopentyl alcohol, $(CH_3)_3CCH_2OH$, yields 2-methyl-2-butene as the major product. Outline a mechanism showing all steps in its formation.

Review Problem 7.15

Acid-catalyzed dehydration of either 2-methyl-1-butanol or 3-methyl-1-butanol gives 2-methyl-2-butene as the major product. Write plausible mechanisms that explain these results.

Review Problem 7.16

When the compound called *isoborneol* is heated with 9*M* sulfuric acid, the product of the reaction is the compound called camphene and not bornylene, as one might expect. Using models to assist you, write a step-by-step mechanism showing how camphene is formed.



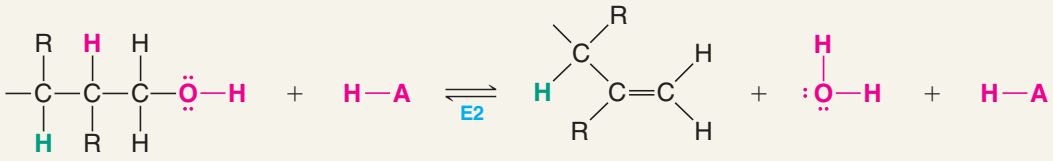
Isoborneol **Camphene** **Bornylene**

7.8B Rearrangement after Dehydration of a Primary Alcohol

Rearrangements also accompany the dehydration of primary alcohols. Since a primary carbocation is unlikely to be formed during dehydration of a primary alcohol, the alkene that is produced initially from a primary alcohol arises by an E2 mechanism, as described in Section 7.7C. However, an alkene can accept a proton to *generate* a carbocation in a process that is essentially the reverse of the *deprotonation* step in the E1 mechanism for dehydration of an alcohol (Section 7.7A). When a terminal alkene does this by using its π electrons to bond a proton at the terminal carbon, a carbocation forms at the second carbon of the chain.* This carbocation, since it is internal to the chain, will be secondary or tertiary, depending on the specific substrate. Various processes that you have already learned can now occur from this carbocation: (1) a different β hydrogen may be removed, leading to a more stable alkene than the initially formed terminal alkene; (2) a hydride or alkanide rearrangement may occur leading to a yet more stable carbocation (e.g., moving from a 2° to a 3° carbocation) or to a carbocation of approximately equal stability, after which the elimination may be completed; or (3) a nucleophile may attack any of these carbocations to form a substitution product. Under the high-temperature conditions for alcohol dehydration the principal products will be alkenes rather than substitution products.

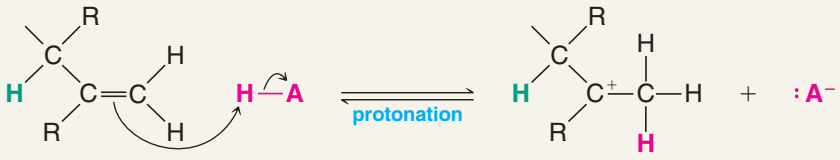
A MECHANISM FOR THE REACTION

Formation of a Rearranged Alkene during Dehydration of a Primary Alcohol



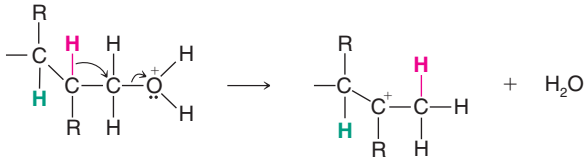
Primary alcohol (R may be H) **Initial alkene**

The primary alcohol initially undergoes acid-catalyzed dehydration by an E2 mechanism (Section 7.7C).



The π electrons of the initial alkene can then be used to form a bond with a proton at the terminal carbon, forming a secondary or tertiary carbocation.*

*The carbocation could also form directly from the primary alcohol by a hydride shift from its β carbon to the terminal carbon as the protonated hydroxyl group departs:

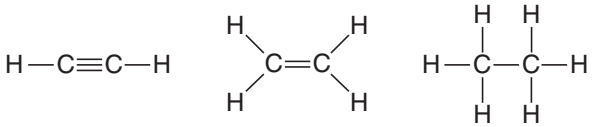


Final alkene

A different β hydrogen can be removed from the carbocation, so as to form a more highly substituted alkene than the initial alkene. This deprotonation step is the same as the usual completion of an E1 elimination. (This carbocation could experience other fates, such as further rearrangement before elimination or substitution by an S_N1 process.)

7.9 The Acidity of Terminal Alkynes

The hydrogen bonded to the carbon of a terminal alkyne, called an **acetylenic hydrogen atom**, is considerably more acidic than those bonded to carbons of an alkene or alkane (see Section 3.8A). The pK_a values for ethyne, ethene, and ethane illustrate this point:



pK_a = 25 **pK_a = 44** **pK_a = 50**

The order of basicity of their anions is opposite that of their relative acidity:

Relative Basicity

$$CH_3CH_2{:}^- > CH_2{=}CH{:}^- > HC{\equiv}C{:}^-$$

If we include in our comparison hydrogen compounds of other first-row elements of the periodic table, we can write the following orders of relative acidities and basicities:

Relative Acidity

H—ÖH	>	H—ÖR	>	H—C≡CR	>	H—N̈H$_2$	>	H—CH=CH$_2$	>	H—CH$_2$CH$_3$
pK_a 15.7		16–17		25		38		44		50

Relative Basicity

$$^-{:}\ddot{O}H < {}^-{:}\ddot{O}R < {}^-{:}C{\equiv}CR < {}^-{:}\ddot{N}H_2 < {}^-{:}CH{=}CH_2 < {}^-{:}CH_2CH_3$$

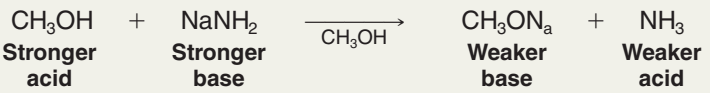
We see from the order just given that while terminal alkynes are more acidic than ammonia, they are less acidic than alcohols and are less acidic than water.

Solved Problem 7.7

As we shall soon see, sodium amide ($NaNH_2$) is useful, especially when a reaction requires a very strong base. Explain why a solvent such as methanol cannot be used to carry out a reaction in which you might want to use sodium amide as a base.

STRATEGY AND ANSWER An alcohol has pK_a = 16–17, and ammonia has pK_a = 38. This means that methanol is a significantly stronger acid than ammonia, and the conjugate base of ammonia (the NH_2^- ion) is a significantly stronger base than an alkoxide ion. Therefore, the following acid–base reaction would take place as soon as the sodium amide dissolves in the methanol.

(continues on next page)



With a pK_a difference this large, the methanol would convert all of the sodium amide to sodium methoxide, a much weaker base than sodium amide. (This is an example of what is called the leveling effect of a solvent.)

Review Problem 7.17

Predict the products of the following acid–base reactions. If the equilibrium would not result in the formation of appreciable amounts of products, you should so indicate. In each case label the stronger acid, the stronger base, the weaker acid, and the weaker base:

(a) $CH_3CH{=}CH_2 + NaNH_2 \longrightarrow$

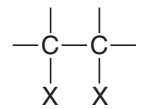
(b) $CH_3C{\equiv}CH + NaNH_2 \longrightarrow$

(c) $CH_3CH_2CH_3 + NaNH_2 \longrightarrow$

(d) $CH_3C{\equiv}C{:}^- + CH_3CH_2OH \longrightarrow$

(e) $CH_3C{\equiv}C{:}^- + NH_4Cl \longrightarrow$

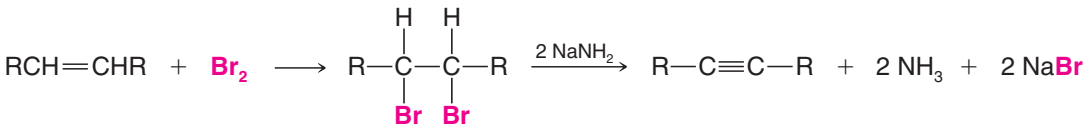
7.10 Synthesis of Alkynes by Elimination Reactions



A *vic*–dihalide

- Alkynes can be synthesized from alkenes via compounds called vicinal dihalides.

A vicinal dihalide (abbreviated ***vic*-dihalide**) is a compound bearing the halogens on adjacent carbons (*vicinus,* Latin: adjacent). A vicinal dibromide, for example, can be synthesized by addition of bromine to an alkene (Section 8.1). The *vic*-dibromide can then be subjected to a double dehydrohalogenation reaction with a strong base to yield an alkyne.

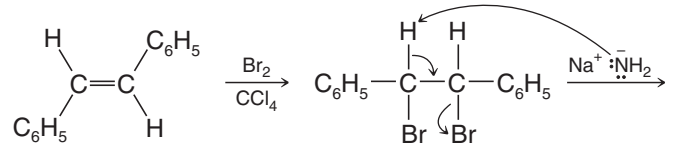


A *vic*-dibromide

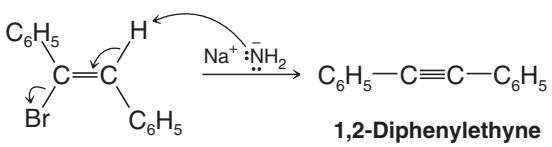
The dehydrohalogenations occur in two steps, the first yielding a bromoalkene, and the second, the alkyne.

7.10A Laboratory Application of This Alkyne Synthesis

The two dehydrohalogenations may be carried out as separate reactions, or they may be carried out consecutively in a single mixture. Sodium amide ($NaNH_2$), a very strong base, can be used to cause both reactions in a single mixture. At least two molar equivalents of sodium amide per mole of the dihalide must be used. For example (see below) adding bromine to 1,2-diphenylethene provides the starting material for a synthesis of 1,2-diphenylethyne.



1,2-Diphenylethene

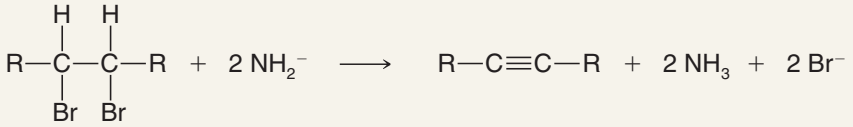


1,2-Diphenylethyne

A MECHANISM FOR THE REACTION

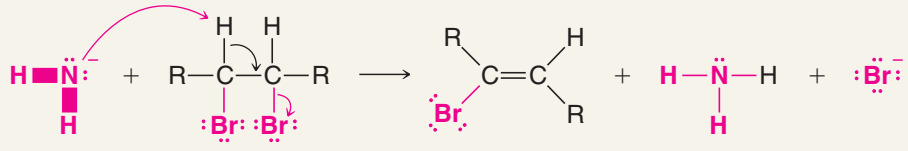
Dehydrohalogenation of *vic*-Dibromides to Form Alkynes

REACTION



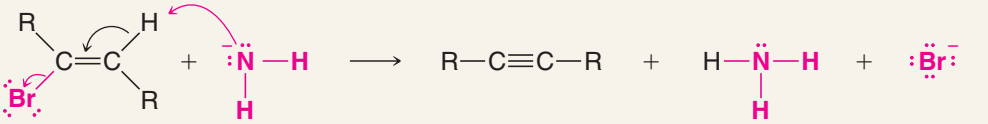
MECHANISM

Step 1



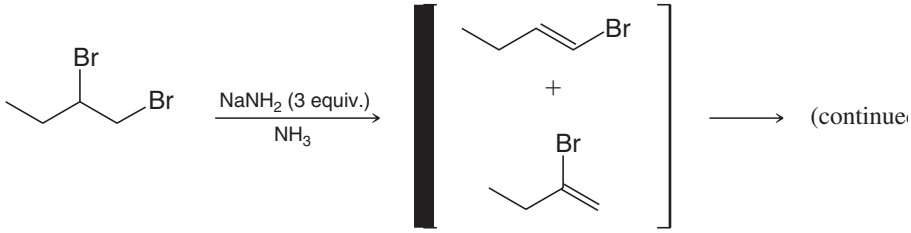
The strongly basic amide ion brings about an E2 reaction.

Step 2

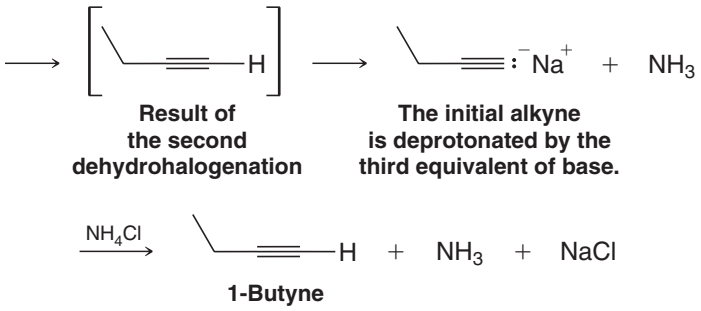


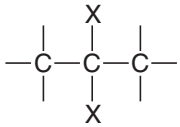
A second E2 reaction produces the alkyne.

If the product is to be an alkyne with a triple bond at the end of the chain (a terminal alkyne) as we show in the example below, then three molar equivalents of sodium amide are required. Initial dehydrohalogenation of the *vic*-dihalide produces a mixture of two bromoalkenes which are not isolated but which undergo a second dehydrohalogenation. The terminal alkyne that results from this step is deprotonated (because of its acidity) by the third mole of sodium amide (see Section 7.9). To complete the process, addition of ammonium chloride converts the sodium alkynide to the desired product, 1-butyne.



Result of the first dehydrohalogenation

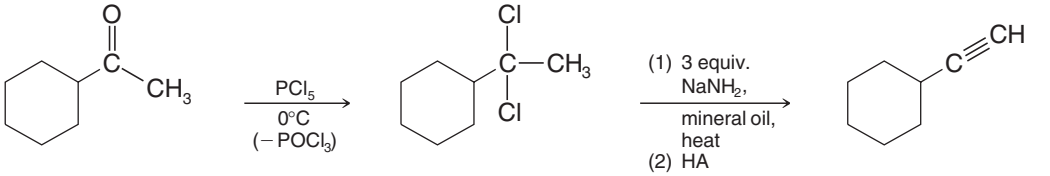




A *gem*–dihalide

- Geminal dihalides can also be converted to alkynes by dehydrohalogenation.

A geminal dihalide (abbreviated ***gem*-dihalide**) has two halogen atoms bonded to the same carbon (*geminus,* Latin: twins). Ketones can be converted to *gem*-dichlorides by reaction with phosphorus pentachloride, and the *gem*-dichlorides can be used to synthesize alkynes.



Cyclohexyl methyl ketone — **A *gem*-dichloride (70–80%)** — **Cyclohexylacetylene (46%)**

Review Problem 7.18 Show how you might synthesize ethynylbenzene from methyl phenyl ketone.

Review Problem 7.19 Outline all steps in a synthesis of propyne from each of the following:

(a) CH_3COCH_3 **(c)** $CH_3CHBrCH_2Br$

(b) $CH_3CH_2CHBr_2$ **(d)** $CH_3CH{=}CH_2$

7.11 *Substitution of the Acetylenic Hydrogen Atom of Terminal Alkynes*

Sodium ethynide and other sodium alkynides can be prepared by treating terminal alkynes with sodium amide in liquid ammonia:

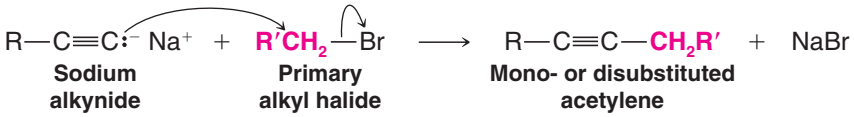
$$H{-}C{\equiv}C{-}H + NaNH_2 \xrightarrow[\text{liq. } NH_3]{} H{-}C{\equiv}C{:}^{-}Na^{+} + NH_3$$

$$CH_3C{\equiv}C{-}H + NaNH_2 \xrightarrow[\text{liq. } NH_3]{} CH_3C{\equiv}C{:}^{-}Na^{+} + NH_3$$

These are acid–base reactions. The amide ion, by virtue of its being the anion of a very weak acid, ammonia ($pK_a = 38$), is able to remove the acetylenic protons of terminal alkynes ($pK_a = 25$). These reactions, for all practical purposes, go to completion.

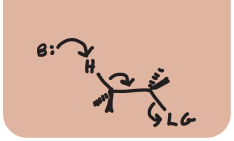
- Sodium alkynides are useful intermediates for the synthesis of other alkynes.

These syntheses can be accomplished by treating the sodium alkynide with a primary alkyl halide:

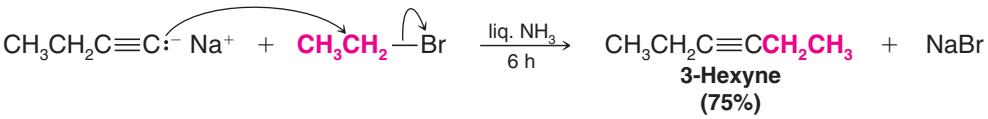


Sodium alkynide — **Primary alkyl halide** — **Mono- or disubstituted acetylene**

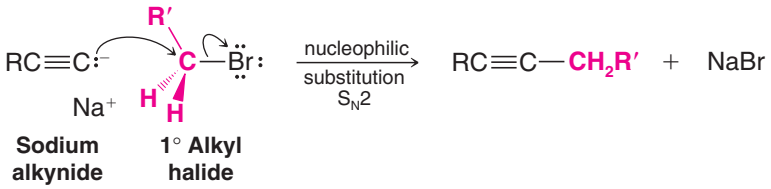
(R or R′ or both may be hydrogen.)



The following example illustrates this synthesis of higher alkyne homologues:



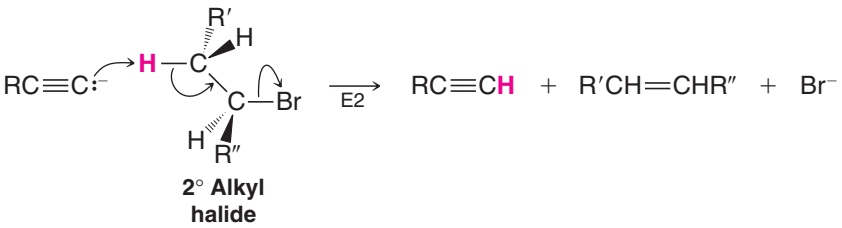
- The alkynide ion acts as a nucleophile and displaces a halide ion from the primary alkyl halide. We now recognize this as an **S_N2 reaction** (Section 6.5):



The unshared electron pair of the alkynide ion attacks the back side of the carbon atom that bears the halogen atom and forms a bond to it. The halogen atom departs as a halide ion.

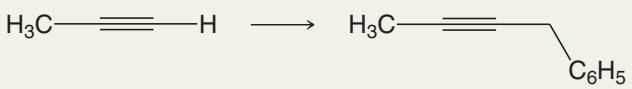
- This synthesis fails when secondary or tertiary halides are used because the alkynide ion acts as a base rather than as a nucleophile, and the major result is an **E2 elimination** (Section 6.16).

The products of the elimination are an alkene and the alkyne from which the sodium alkynide was originally formed:

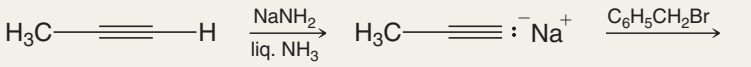


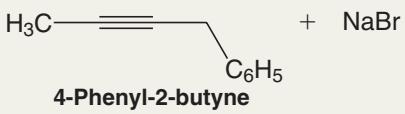
Solved Problem 7.8

Outline a synthesis of 4-phenyl-2-butyne from 1-propyne.



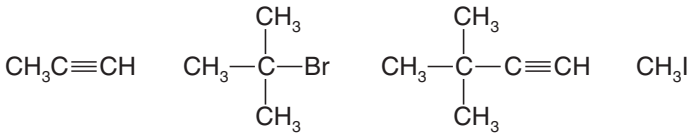
STRATEGY AND ANSWER Take advantage of the acidity of the acetylenic hydrogen of propyne and convert it to an alkynide anion using sodium amide, a base that is strong enough to remove the acetylenic hydrogen. Then use the akynide ion as a nucleophile in an S_N2 reaction with benzyl bromide.





Review Problem 7.20

Your goal is to synthesize 4,4-dimethyl-2-pentyne. You have a choice of beginning with any of the following reagents:



Assume that you also have available sodium amide and liquid ammonia. Outline the best synthesis of the required compound.

7.12 *Alkylation of Alkynide Anions: Some General Principles of Structure and Reactivity Illustrated*

The **alkylation** of alkynide anions has illustrated several essential aspects of structure and reactivity that we have just discussed. First, preparation of the alkynide anion involves simple **Brønsted–Lowry acid–base chemistry.** As you have seen (Sections 7.9 and 7.11), the hydrogen of a terminal alkyne is weakly acidic ($pK_a \cong 25$), and with a strong base such as sodium amide it can be removed. The reason for this acidity was explained in Section 3.8A. Once formed, the alkynide anion is a Lewis base (Section 3.3) with which the alkyl halide reacts as an electron pair acceptor (a **Lewis acid**). The alkynide anion can thus be called a ***nucleophile*** (Sections 3.4 and 6.3) because of the negative charge concentrated at its terminal carbon—it is a reagent that seeks positive charge. Conversely, the alkyl halide can be called an ***electrophile*** (Sections 3.4 and 8.1) because of the partial positive charge at the carbon bearing the halogen—it is a reagent that seeks negative charge. Polarity in the alkyl halide is the direct result of the difference in electronegativity between the halogen atom and carbon atom.

The electrostatic potential maps for ethynide (acetylide) anion and chloromethane in Fig. 7.8 illustrate the complementary nucleophilic and electrophilic character of a typical alkynide anion and alkyl halide. The ethynide anion has strong localization of negative charge at its terminal carbon, indicated by red in the electrostatic potential map. Conversely, chloromethane has partial positive charge at the carbon bonded to the electronegative chlorine atom. (The dipole moment for chloromethane is aligned directly along the carbon–chlorine bond.) Thus, acting as a Lewis base, the alkynide anion is attracted to the partially positive carbon of the alkyl halide. Assuming a collision between the two occurs with the proper orientation and sufficient kinetic energy, as the alkynide anion brings two electrons to the alkyl halide to form a new bond, it will displace the halogen from the alkyl halide. The halogen leaves as an anion with the pair of electrons that formerly bonded it to the carbon. This is an S_N2 reaction, of course, akin to others we discussed fully in Chapter 6.

Helpful Hint

You should pay attention to the bookkeeping of valence electrons and formal charges in the reaction shown in Fig. 7.8, just as with every other reaction you study in organic chemistry.

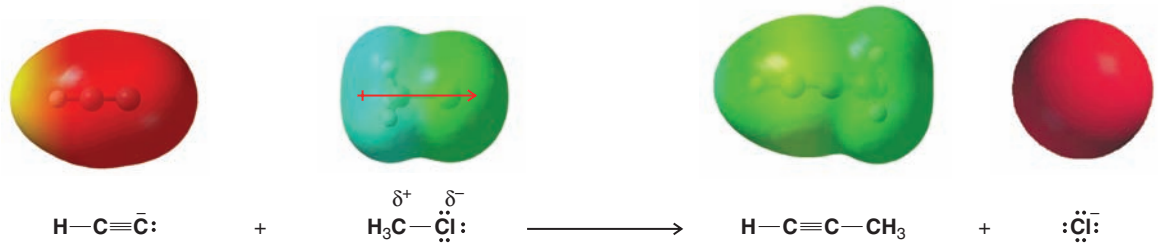


Figure 7.8 The reaction of ethynide (acetylide) anion and chloromethane. Electrostatic potential maps illustrate the complementary nucleophilic and electrophilic character of the alkynide anion and the alkyl halide. The dipole moment of chloromethane is shown by the red arrow.

7.13 Hydrogenation of Alkenes

Alkenes react with hydrogen in the presence of a variety of metal catalysts to add one hydrogen atom to each carbon atom of the double bond (Sections 4.16A, 5.10A). Hydrogenation reactions that involve finely divided *insoluble* platinum, palladium, or nickel catalysts (Section 4.16A) are said to proceed by **heterogeneous catalysis** because the substrate is soluble in the reaction mixture but the catalyst is not. Hydrogenation reactions where the catalyst is *soluble* in the reaction mixture involve **homogeneous catalysis.** Typical homogeneous hydrogenation catalysts include rhodium and ruthenium complexes that bear various phosphorus and other ligands. One of the most well-known homogeneous hydrogenation catalysts is Wilkinson's catalyst, tris(triphenylphosphine)rhodium chloride, $Rh[(C_6H_5)_3P]_3Cl$. The following are some examples of hydrogenation reactions under heterogeneous and homogeneous catalysis:

$$CH_2{=}CH_2 + H_2 \xrightarrow[\text{or Pt}]{\text{Ni, Pd,}} CH_3{-}CH_3 \quad (25^\circ C)$$

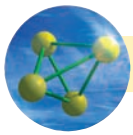
$$CH_3CH{=}CH_2 + H_2 \xrightarrow[\text{or Pt}]{\text{Ni, Pd,}} CH_3CH_2{-}CH_3 \quad (25^\circ C)$$

$$CH_3CH_2CH_2CH_2CH{=}CH_2 + H_2 \xrightarrow{Rh[(C_6H_5)_3P]_3Cl} CH_3CH_2CH_2CH_2CH_2CH_3$$

Helpful Hint

These are all addition reactions.

The type of reaction that takes place in these examples is an **addition reaction**. The product that results from the addition of hydrogen to an alkene is an alkane. Alkanes have only



THE CHEMISTRY OF . . .

Hydrogenation in the Food Industry

The food industry makes use of catalytic hydrogenation to convert liquid vegetable oils to semisolid fats in making margarine and solid cooking fats. Examine the labels of many prepared foods and you will find that they contain "partially hydrogenated vegetable oils." There are several reasons why foods contain these oils, but one is that partially hydrogenated vegetable oils have a longer shelf life.

Fats and oils (Section 23.2) are glyceryl esters of carboxylic acids with long carbon chains, called "fatty acids." Fatty acids are saturated (no double bonds), monounsaturated (one double bond), or polyunsaturated (more than one double bond). Oils typically contain a higher proportion of fatty acids with one or more double bonds than fats do. Hydrogenation of an oil converts some of its double bonds to single bonds, and this conversion has the effect of producing a fat with the consistency of margarine or a semisolid cooking fat.

A product used in baking that contains oils and mono- and diacylglycerols that are partially hydrogenated.

Our bodies are incapable of making polyunsaturated fats, and therefore, such fats must be present in our diets in moderate amounts in order to maintain health. Saturated fats can be made in the cells of our body from other food sources, for example, from carbohydrates (i.e., from sugars and starches). For this reason saturated fats in our diet are not absolutely necessary and, indeed, too much saturated fat has been implicated in the development of cardiovascular disease.

One potential problem that arises from using catalytic hydrogenation to produce partially hydrogenated vegetable oils is that the catalysts used for hydrogenation cause isomerization of some of the double bonds of the fatty acids (some of those that do not absorb hydrogen). In most natural fats and oils, the double bonds of the fatty acids have the cis configuration. The catalysts used for hydrogenation convert some of these cis double bonds to the unnatural trans configuration. The health effects of trans fatty acids are still under study, but experiments thus far indicate that they cause an increase in serum levels of cholesterol and triacylglycerols, which in turn increases the risk of cardiovascular disease.

No (or zero%) trans fatty acids.

single bonds and contain the maximum number of hydrogen atoms that a hydrocarbon can possess. For this reason, alkanes are said to be **saturated compounds**. Alkenes, because they contain a double bond and possess fewer than the maximum number of hydrogen atoms, are capable of adding hydrogen and are said to be **unsaturated**. The process of adding hydrogen to an alkene is sometimes described as being one of **reduction.** Most often, however, the term used to describe the addition of hydrogen is **catalytic hydrogenation**. Now let us see what the mechanism is for heterogeneous catalytic hydrogenation. (The mechanism of homogeneous catalysis is discussed in Special Topic H.)

7.14 Hydrogenation: The Function of the Catalyst

Hydrogenation of an alkene is an exothermic reaction ($\Delta H^\circ \cong -120$ kJ mol^{-1}):

$$\text{R—CH=CH—R} + \text{H}_2 \xrightarrow{\text{hydrogenation}} \text{R—CH}_2\text{—CH}_2\text{—R} + \text{heat}$$

Although the process is exothermic, there is usually a high free energy of activation for uncatalyzed alkene hydrogenation, and therefore, the uncatalyzed reaction does not take place at room temperature. However, hydrogenation will take place readily at room temperature in the presence of a catalyst because the catalyst provides a new pathway for the reaction that involves lower free energy of activation (Fig. 7.9).

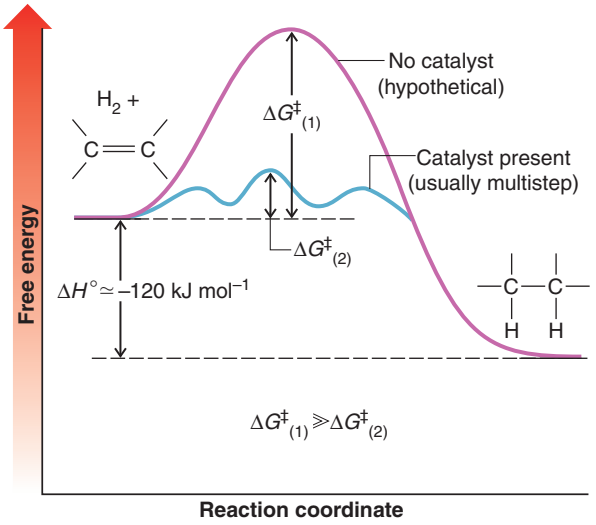


Figure 7.9 Free-energy diagram for the hydrogenation of an alkene in the presence of a catalyst and the hypothetical reaction in the absence of a catalyst. The free energy of activation for the uncatalyzed reaction ($\Delta G^\ddagger_{(1)}$) is very much larger than the largest free energy of activation for the catalyzed reaction ($\Delta G^\ddagger_{(2)}$) (the uncatalyzed hydrogenation reaction does not occur).

Heterogeneous hydrogenation catalysts typically involve finely divided platinum, palladium, nickel, or rhodium deposited on the surface of powdered carbon (charcoal). Hydrogen gas introduced into the atmosphere of the reaction vessel adsorbs to the metal by a chemical reaction where unpaired electrons on the surface of the metal *pair* with the electrons of hydrogen (Fig. 7.10*a*) and bind the hydrogen to the surface. The collision of an alkene with the surface bearing adsorbed hydrogen causes adsorption of the alkene as

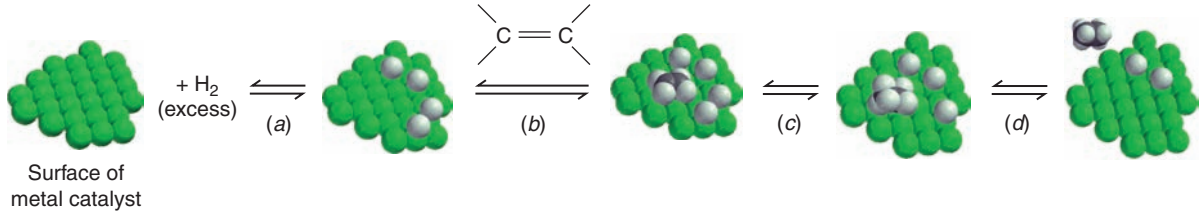
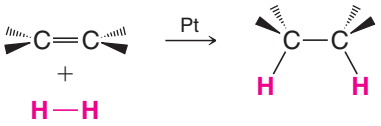


Figure 7.10 The mechanism for the hydrogenation of an alkene as catalyzed by finely divided platinum metal: *(a)* hydrogen adsorption; *(b)* adsorption of the alkene; *(c, d)* stepwise transfer of both hydrogen atoms to the same face of the alkene (syn addition).

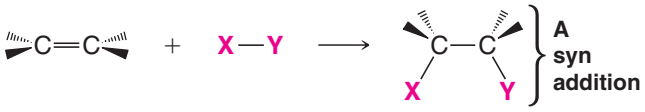
well (Fig. 7.10*b*). A stepwise transfer of hydrogen atoms takes place, and this produces an alkane before the organic molecule leaves the catalyst surface (Figs. 7.10*c,d*). As a consequence, *both hydrogen atoms usually add from the same side of the molecule.* This mode of addition is called a **syn** addition (Section 7.14A):



Catalytic hydrogenation is a syn addition.

7.14A Syn and Anti Additions

An addition that places the parts of the adding reagent on the same side (or face) of the reactant is called **syn addition.** We have just seen that the platinum-catalyzed addition of hydrogen (X = Y = H) is a syn addition:



The opposite of a syn addition is an **anti addition.** An anti addition places the parts of the adding reagent on opposite faces of the reactant.

In Chapter 8 we shall study a number of important syn and anti additions.

7.15 Hydrogenation of Alkynes

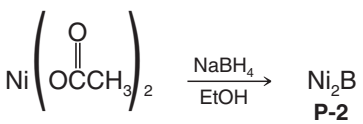
Depending on the conditions and the catalyst employed, one or two molar equivalents of hydrogen will add to a carbon–carbon triple bond. When a platinum catalyst is used, the alkyne generally reacts with two molar equivalents of hydrogen to give an alkane:

$$CH_3C{\equiv}CCH_3 \xrightarrow{Pt,\ H_2} [CH_3CH{=}CHCH_3] \xrightarrow{Pt,\ H_2} CH_3CH_2CH_2CH_3$$

However, hydrogenation of an alkyne to an alkene can be accomplished through the use of special catalysts or reagents. Moreover, these special methods allow the preparation of either (*E*)- or (*Z*)-alkenes from disubstituted alkynes.

7.15A Syn Addition of Hydrogen: Synthesis of *cis*-Alkenes

A heterogeneous catalyst that permits hydrogenation of an alkyne to an alkene is the nickel boride compound called P-2 catalyst. The P-2 catalyst can be prepared by the reduction of nickel acetate with sodium borohydride:

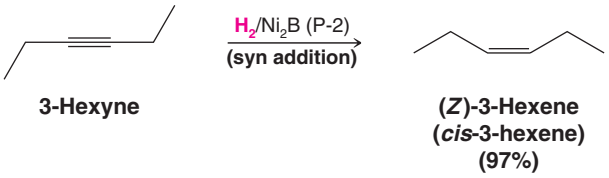


- Hydrogenation of alkynes in the presence of P-2 catalyst causes **syn addition of hydrogen**. The alkene formed from an internal alkyne has the (*Z*) or cis configuration.

The hydrogenation of 3-hexyne illustrates this method. The reaction takes place on the surface of the catalyst (Section 7.14), accounting for the syn addition:

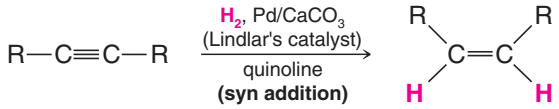
Helpful Hint

Syn addition of hydrogen to an alkyne.



3-Hexyne → **(*Z*)-3-Hexene (*cis*-3-hexene) (97%)**

Other specially conditioned catalysts can be used to prepare *cis*-alkenes from disubstituted alkynes. Metallic palladium deposited on calcium carbonate can be used in this way after it has been conditioned with lead acetate and quinoline (an amine, see Section 20.1B). This special catalyst is known as Lindlar's catalyst:



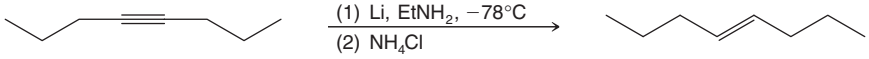
7.15B Anti Addition of Hydrogen: Synthesis of *trans*-Alkenes

- **Anti addition** of hydrogen to the triple bond of alkynes occurs when they are treated with lithium or sodium metal in ammonia or ethylamine at low temperatures.

This reaction, called a **dissolving metal reduction,** takes place in solution and produces an (*E*)- or *trans*-alkene. The mechanism involves radicals, which are molecules that have unpaired electrons (see Chapter 10).

Helpful Hint

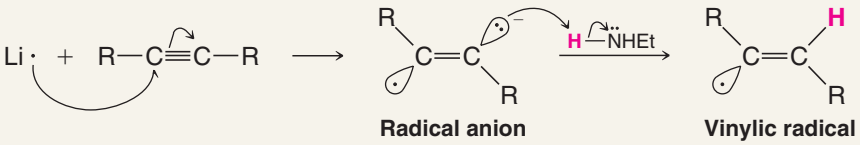
Anti addition of hydrogen to an alkyne.



4-Octyne → **(anti addition)** → **(*E*)-4-Octene (*trans*-4-octene) (52%)**

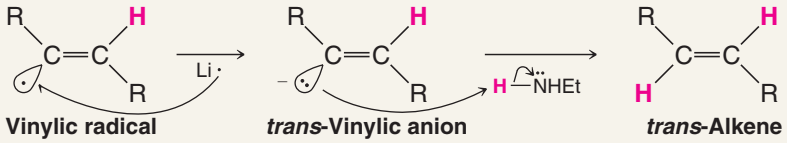
A MECHANISM FOR THE REACTION

The Dissolving Metal Reduction of an Alkyne



A lithium atom donates an electron to the π bond of the alkyne. An electron pair shifts to one carbon as the hybridization states change to sp^2.

The radical anion acts as a base and removes a proton from a molecule of ethylamine.

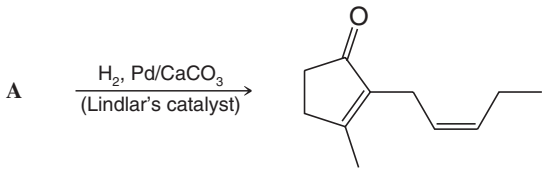


A second lithium atom donates an electron to the vinylic radical.

The anion acts as a base and removes a proton from a second molecule of ethylamine.

The mechanism for this reduction, shown in the preceding box, involves successive electron transfers from lithium (or sodium) atoms and proton transfers from amines (or ammonia). In the first step, a lithium atom transfers an electron to the alkyne to produce an intermediate that bears a negative charge and has an unpaired electron, called a **radical anion.** In the second step, an amine transfers a proton to produce a **vinylic radical.** Then, transfer of another electron gives a **vinylic anion.** It is this step that determines the stereochemistry of the reaction. The *trans*-vinylic anion is formed preferentially because it is more stable; the bulky alkyl groups are farther apart. Protonation of the *trans*-vinylic anion leads to the *trans*-alkene.

Write the structure of compound **A**, used in this synthesis of the perfume ingredient (Z)-jasmone. *Review Problem 7.21*



(*Z*)-Jasmone

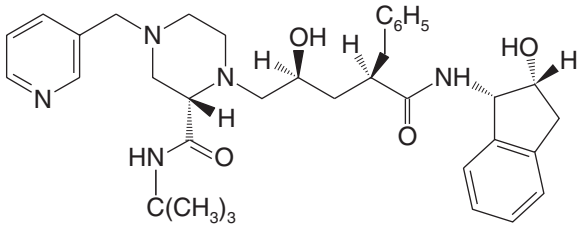
How would you convert 2-nonyne into (*E*)-2-nonene? *Review Problem 7.22*

7.16 An Introduction to Organic Synthesis

You have learned quite a few tools to this point that are useful for organic synthesis. Among them are nucleophilic substitution reactions, elimination reactions, and the hydrogenation reactions covered in Sections 7.13–7.15. Now we will consider the logic of organic synthesis and the important process of retrosynthetic analysis. Then we will apply nucleophilic substitution (in the specific case of alkylation of alkynide anions) and hydrogenation reactions to the synthesis of some simple target molecules.

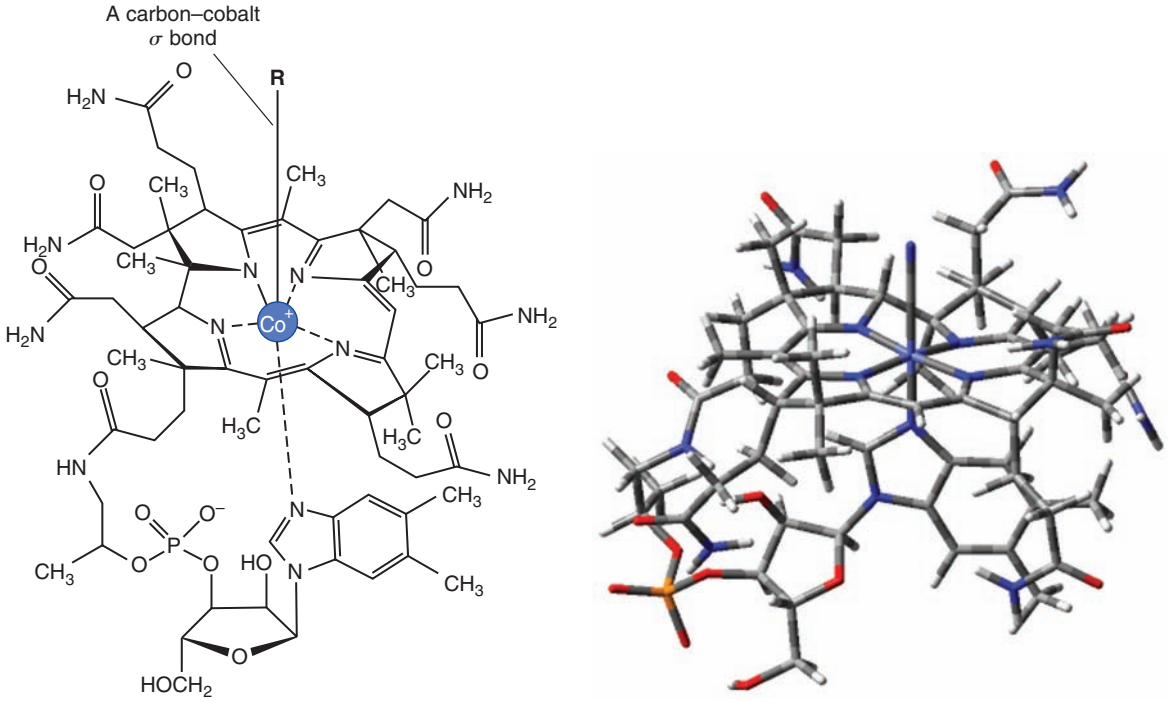
7.16A Why Do Organic Synthesis?

Organic synthesis is the process of building organic molecules from simpler precursors. Syntheses of organic compounds are carried out for many reasons. Chemists who develop new drugs carry out organic syntheses in order to discover molecules with structural attributes that enhance certain medicinal effects or reduce undesired side effects. Crixivan, whose structure is shown below, was designed by small-scale synthesis in a research laboratory and then quickly moved to large-scale synthesis after its approval as a drug. In other situations, organic synthesis may be needed to test a hypothesis about a reaction mechanism or about how a certain organism metabolizes a compound. In cases like these we often will need to synthesize a particular compound "labeled" at a certain position (e.g., with deuterium, tritium, or an isotope of carbon).



Crixivan (an HIV protease inhibitor)

A very simple organic synthesis may involve only one chemical reaction. Others may require from several to 20 or more steps. A landmark example of organic synthesis is that of vitamin B_{12}, announced in 1972 by R. B. Woodward (Harvard) and A. Eschenmoser (Swiss Federal Institute of Technology). Their synthesis of vitamin B_{12} took 11 years, required more than 90 steps, and involved the work of nearly 100 people. We will work with much simpler examples, however.



Vitamin B_{12}

An organic synthesis typically involves two types of transformations: reactions that convert functional groups from one to another and reactions that create new carbon–carbon bonds. You have studied examples of both types of reactions already—hydrogenation transforms the carbon–carbon double- or triple-bond functional groups in alkenes and alkynes to single bonds (actually removing a functional group in this case), and alkylation of alkynide anions forms carbon–carbon bonds. Ultimately, at the heart of organic synthesis is the orchestration of functional group interconversions and carbon–carbon bond-forming steps. Many methods are available to accomplish both of these things.

7.16B Retrosynthetic Analysis—Planning an Organic Synthesis

Sometimes it is possible to visualize from the start all the steps necessary to synthesize a desired (target) molecule from obvious precursors. Often, however, the sequence of transformations that would lead to the desired compound is too complex for us to "see" a path from the beginning to the end. In this case, since we know where we want to finish (the target molecule) but not where to start, we envision the sequence of steps that is required in a backward fashion, one step at a time. We begin by identifying immediate precursors that could react to make the target molecule. Once these have been chosen, they in turn become new intermediate target molecules, and we identify the next set of precursors that could react to form them, and so on, and so on. This process is repeated until we have

worked backward to compounds that are sufficiently simple that they are readily available in a typical laboratory:

- The process we have just described is called **retrosynthetic analysis**.
- The open arrow used in the example above is a **retrosynthetic arrow,** a symbol that relates the target molecule to its most immediate precursors; it signifies a **retro** or **backward** step.

Although organic chemists have used retrosynthetic analysis intuitively for many years, E. J. Corey originated the term retrosynthetic analysis and was the first person to state its principles formally. Once retrosynthetic analysis has been completed, to actually carry out the synthesis we conduct the sequence of reactions from the beginning, starting with the simplest precursors and working step by step until the target molecule is achieved.

Corey was awarded the Nobel Prize in Chemistry in 1990 for finding new ways of synthesizing organic compounds, which, in the words of the Nobel committee, "have contributed to the high standards of living and health enjoyed . . . in the Western world."

- When doing retrosynthetic analysis it is necessary to generate as many possible precursors, and hence different synthetic routes, as possible.

We evaluate all the possible advantages and disadvantages of each path and in so doing determine the most efficient route for synthesis. The prediction of which route is most feasible is usually based on specific restrictions or limitations of reactions in the sequence, the availability of materials, or other factors. We shall see an example of this in Section 7.16C. In actuality more than one route may work well. In other cases it may be necessary to try several approaches in the laboratory in order to find the most efficient or successful route.

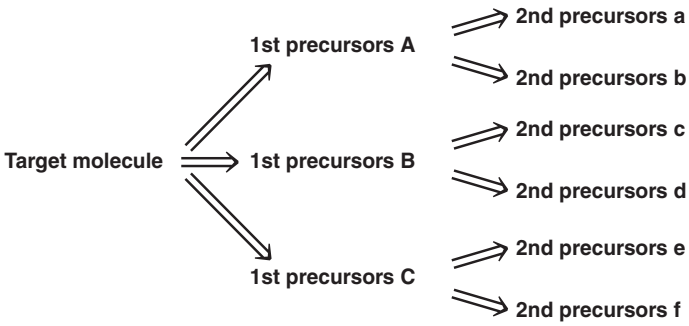


Figure 7.11 Retrosynthetic analysis often discloses several routes from the target molecule back to varied precursors.

7.16C Identifying Precursors

In the case of functional groups we need to have a toolbox of reactions from which to choose those we know can convert one given functional group into another. You will develop such a toolbox of reactions as you proceed through your study of organic chemistry. Similarly, with regard to making carbon–carbon bonds in synthesis, you will develop a repertoire of reactions for that purpose. In order to choose the appropriate reaction for either purpose, you will inevitably consider basic principles of structure and reactivity.

As we stated in Sections 3.3A and 7.12:

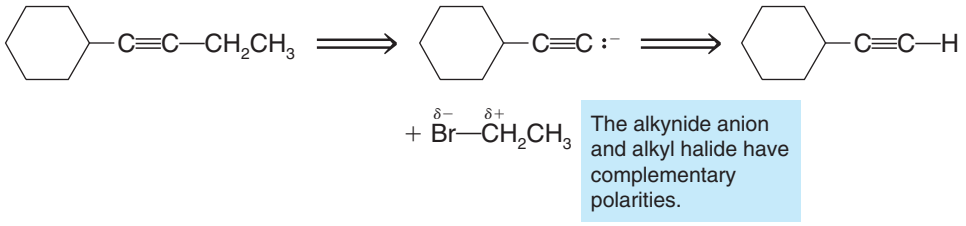
- Many organic reactions depend on the interaction of molecules that have complementary full or partial charges.

Helpful Hint

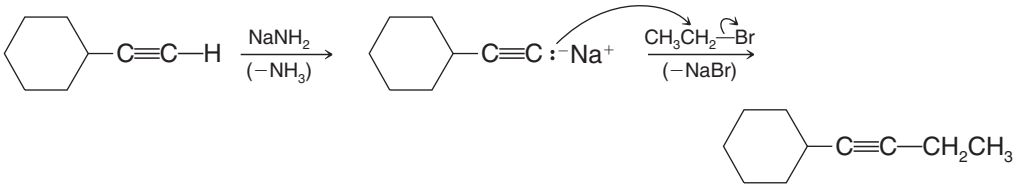
Over time you will add to your toolbox reactions for two major categories of synthetic operations: carbon–carbon bond formation and functional group interconversion.

One very important aspect of retrosynthetic analysis is being able to identify those atoms in a target molecule that could have had complementary (opposite) charges in synthetic precursors. Consider, for example, the synthesis of 1-cyclohexyl-1-butyne. On the basis of reactions learned in this chapter, you might envision an alkynide anion and an alkyl halide as precursors having complementary polarities that when allowed to react together would lead to this molecule:

Retrosynthetic Analysis



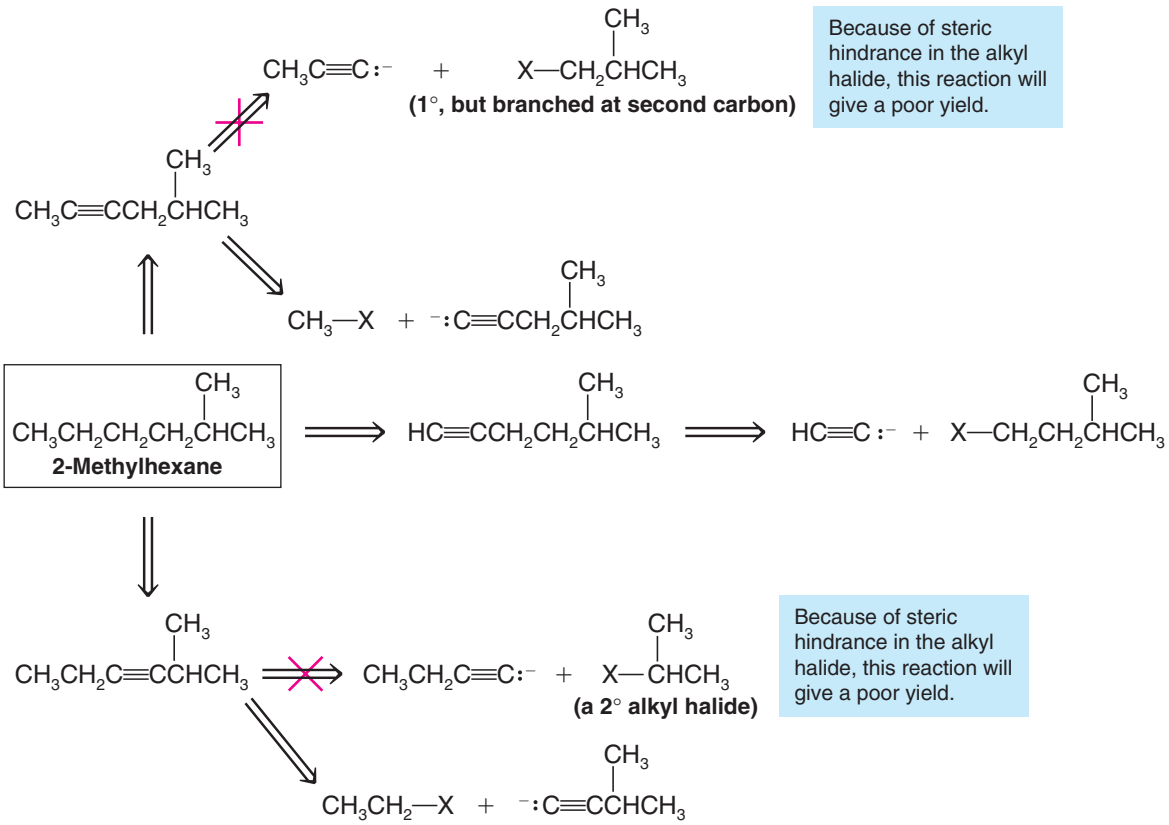
Synthesis



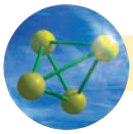
Sometimes, however, it will not at first be obvious where the retrosynthetic bond disconnections are in a target molecule that would lead to oppositely charged or complementary precursors. The synthesis of an alkane would be such an example. An alkane does not contain carbon atoms that could directly have had opposite charges in precursor molecules. However, if one supposes that certain carbon–carbon single bonds in the alkane could have arisen by hydrogenation of a corresponding alkyne (a functional group interconversion), then, in turn, two atoms of the alkyne could have been joined from precursor molecules that had complementary charges (i.e., an alkynide anion and an alkyl halide).

Consider the following retrosynthetic analysis for **2-methylhexane:**

Retrosynthetic Analysis



As indicated in the retrosynthetic analysis above, we must bear in mind the limitations that exist for the reactions that would be applied in the synthetic (forward) direction. In the example above, two of the pathways have to be discarded because they involve the use of a 2° alkyl halide or a primary halide branched at the second (beta) carbon (Sections 6.13A, 7.11).



THE CHEMISTRY OF . . .

From the Inorganic to the Organic

In 1862, Friedrich Wöhler discovered calcium carbide (CaC_2) by heating carbon with an alloy of zinc and calcium. He then synthesized acetylene by allowing the calcium carbide to react with water:

$$C \xrightarrow{\text{zinc–calcium alloy, heat}} CaC_2 \xrightarrow{2\,H_2O} HC{\equiv}CH + Ca(OH)_2$$

Acetylene produced this way burned in lamps of some lighthouses and in old-time miners' headlamps. From the standpoint of organic synthesis, it is theoretically possible to synthesize *anything* using reactions of alkynes to form carbon–carbon bonds and to prepare other functional groups. Thus, while Wöhler's 1828 conversion of ammonium cyanate to urea was the first synthesis of an organic compound from an inorganic precursor (Section 1.1A), his discovery of calcium carbide and its reaction with water to form acetylene gives us a formal link from inorganic materials to the entire realm of organic synthesis.

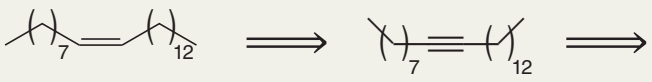
Solved Problem 7.9

Outline a retrosynthetic pathway that leads from 'muscalure', the sex attractant pheromone of the common housefly back to the simplest alkyne, ethyne (acetylene). Then show the synthesis. You may use any inorganic compounds, or solvents, you need and alkyl halides of any length necessary.

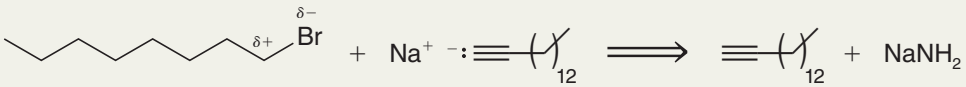
Muscalure

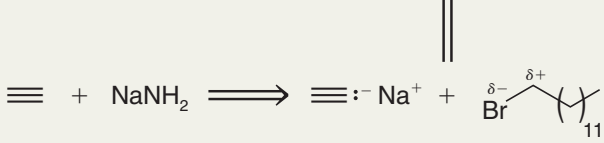
STRATEGY AND ANSWER We make use of two reactions that we have just studied in this chapter: syn addition of hydrogen to an alkyne, and alkylation of alkynide ions.

Retrosynthetic Analysis

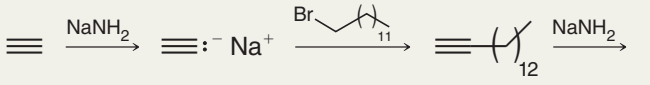


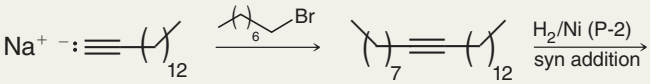
Muscalure **+ H_2, syn addition**

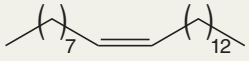




Synthesis







Muscalure

Review Problem 7.23 Referring to the retrosynthetic analysis for 2-methylhexane in this section, write reactions for those synthesis routes that are feasible.

Review Problem 7.24 **(a)** Devise retrosynthetic schemes for all conceivable alkynide anion alkylation syntheses of the insect pheromones undecane and 2-methylheptadecane (see "The Chemistry of . . . Pheromones" box in Chapter 4). **(b)** Write reactions for two feasible syntheses of each pheromone.

7.16D Raison d'Etre

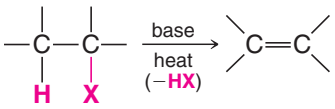
Solving synthetic puzzles by application of retrosynthetic analysis is one of the joys of learning organic chemistry. As you might imagine, there is skill and some artistry involved. Over the years many chemists have set their minds to organic synthesis, and because of this we have all prospered from the fruits of their endeavors.

Summary of Methods for the Preparation of Alkenes and Alkynes

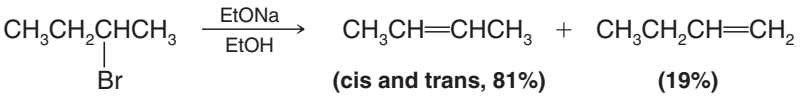
In this chapter we described four general methods for the preparation of alkenes.

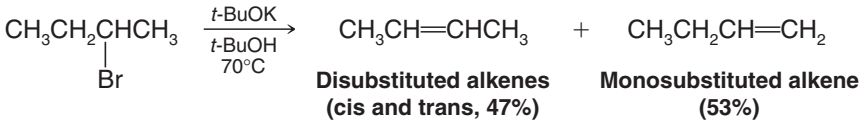
1. Dehydrohalogenation of alkyl halides (Section 7.6):

General Reaction



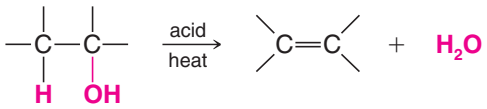
Specific Examples



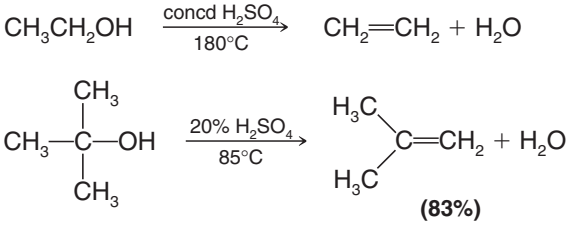


2. Dehydration of alcohols (Sections 7.7 and 7.8):

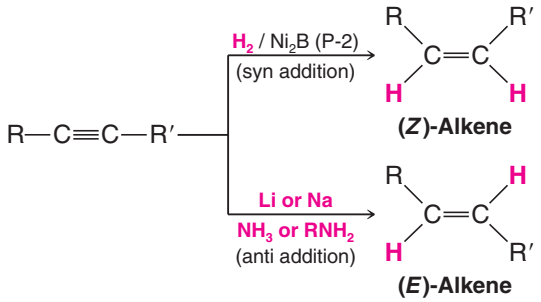
General Reaction



Specific Examples



3. Hydrogenation of alkynes (Section 7.15):
General Reaction



In subsequent chapters we shall see a number of other methods for alkene synthesis.

Key Terms and Concepts

The key terms and concepts that are highlighted in **bold, blue text** within the chapter are defined in the glossary (at the back of the book) and have hyperlinked definitions in the accompanying ***WileyPLUS*** course (www.wileyplus.com).

Problems

Note to Instructors: Many of the homework problems are available for assignment via ***WileyPLUS***, an online teaching and learning solution.

STRUCTURE AND NOMENCLATURE

7.25 Each of the following names is incorrect. Give the correct name and explain your reasoning.

(a) *trans*-3-Pentene
(b) 1,1-Dimethylethene
(c) 2-Methylcyclohexene
(d) 4-Methylcyclobutene
(e) (*Z*)-3-Chloro-2-butene
(f) 5,6-Dichlorocyclohexene

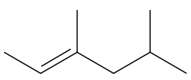
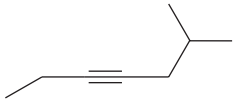
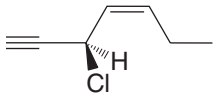
7.26 Write a structural formula for each of the following:

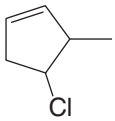
(a) 3-Methylcyclobutene
(b) 1-Methylcyclopentene
(c) 2,3-Dimethyl-2-pentene
(d) (*Z*)-3-Hexene
(e) (*E*)-2-Pentene
(f) 3,3,3-Tribromopropene
(g) (*Z*,4*R*)-4-Methyl-2-hexene
(h) (*E*,4*S*)-4-Chloro-2-pentene
(i) (*Z*)-1-Cyclopropyl-1-pentene
(j) 5-Cyclobutyl-1-pentene
(k) (*R*)-4-Chloro-2-pentyne
(l) (*E*)-4-Methylhex-4-en-1-yne

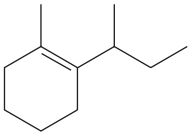
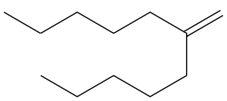
7.27 Write three-dimensional formulas for and give names using (*R*)–(*S*) and (*E*)–(*Z*) designations for the isomers of:

(a) 4-Bromo-2-hexene
(b) 3-Chloro-1,4-hexadiene
(c) 2,4-Dichloro-2-pentene
(d) 2-Bromo-4-chlorohex-2-en-5-yne

7.28 Give the IUPAC names for each of the following:

(a) 
(c) 
(e) 

(b) 

(d) 
(f) 

7.29 Without consulting tables, arrange the following compounds in order of decreasing acidity:

Pentane 1-Pentene 1-Pentyne 1-Pentanol

SYNTHESIS

7.30 Outline a synthesis of propene from each of the following:

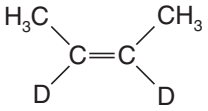
(a) Propyl chloride **(c)** Propyl alcohol **(e)** 1,2-Dibromopropane
(b) Isopropyl chloride **(d)** Isopropyl alcohol **(f)** Propyne

7.31 Outline a synthesis of cyclopentene from each of the following:

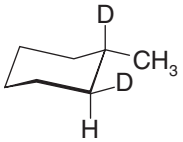
(a) Bromocyclopentane **(b)** 1,2-Dichlorocyclopentane **(c)** Cyclopentanol

7.32 Starting with ethyne, outline syntheses of each of the following. You may use any other needed reagents, and you need not show the synthesis of compounds prepared in earlier parts of this problem.

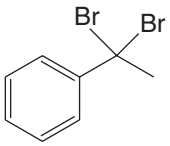
(a) Propyne **(f)** 1-Pentyne **(k)** $CH_3CH_2C{\equiv}CD$
(b) 1-Butyne **(g)** 2-Hexyne **(l)**
(c) 2-Butyne **(h)** (*Z*)-2-Hexene
(d) *cis*-2-Butene **(i)** (*E*)-2-Hexene
(e) *trans*-2-Butene **(j)** 3-Hexyne

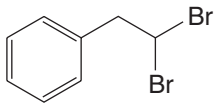


7.33 Starting with 1-methylcyclohexene and using any other needed reagents, outline a synthesis of the following deuterium-labeled compound:



7.34 Outline a synthesis of phenylethyne from each of the following:

(a)


(b)


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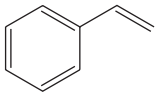

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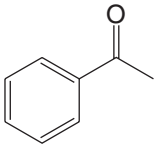
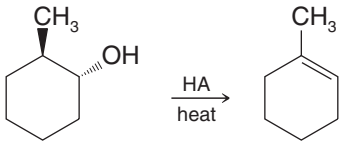


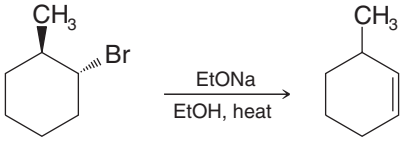
DEHYDROHALOGENATION AND DEHYDRATION

7.35 Write a three-dimensional representation for the transition state structure leading to formation of 2-methyl-2-butene from reaction of 2-bromo-2-methylbutane with sodium ethoxide.

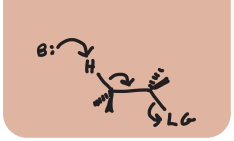
7.36 When *trans*-2-methylcyclohexanol (see the following reaction) is subjected to acid-catalyzed dehydration, the major product is 1-methylcyclohexene:



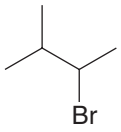
However, when *trans*-1-bromo-2-methylcyclohexane is subjected to dehydrohalogenation, the major product is 3-methylcyclohexene:

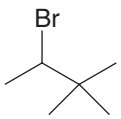


Account for the different products of these two reactions.

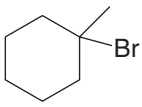


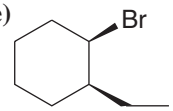
7.37 Write structural formulas for all the products that would be obtained when each of the following alkyl halides is heated with sodium ethoxide in ethanol. When more than one product results, you should indicate which would be the major product and which would be the minor product(s). You may neglect cis–trans isomerism of the products when answering this question.

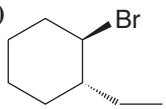
(a) 

(b) 

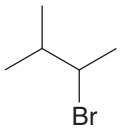
(c) 

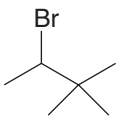
(d) 

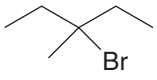
(e) 

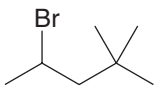
(f) 

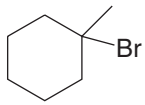
7.38 Write structural formulas for all the products that would be obtained when each of the following alkyl halides is heated with potassium *tert*-butoxide in *tert*-butyl alcohol. When more than one product results, you should indicate which would be the major product and which would be the minor product(s). You may neglect cis–trans isomerism of the products when answering this question.

(a) 

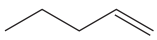
(b) 

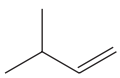
(c) 

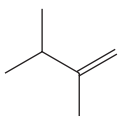
(d) 

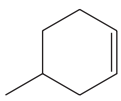
(e) 

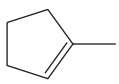
7.39 Starting with an appropriate alkyl halide and base, outline syntheses that would yield each of the following alkenes as the major (or only) product:

(a) 

(b) 

(c) 

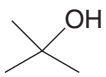
(d) 

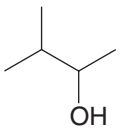
(e) 

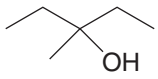
7.40 Arrange the following alcohols in order of their reactivity toward acid-catalyzed dehydration (with the most reactive first):

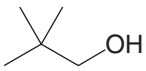
1-Pentanol 2-Methyl-2-butanol 3-Methyl-2-butanol

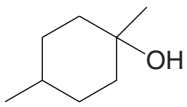
7.41 Give the products that would be formed when each of the following alcohols is subjected to acid-catalyzed dehydration. If more than one product would be formed, designate the alkene that would be the major product. (Neglect cis–trans isomerism.)

(a) 

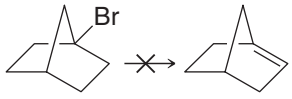
(b) 

(c) 

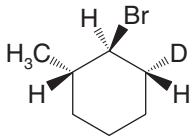
(d) 

(e) 

7.42 1-Bromobicyclo[2.2.1]heptane does not undergo elimination (below) when heated with a base. Explain this failure to react. (Construction of molecular models may help.)

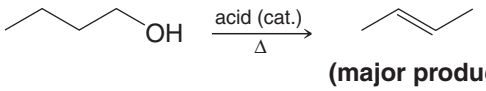


7.43 When the deuterium-labeled compound shown at right is subjected to dehydrohalogenation using sodium ethoxide in ethanol, the only alkene product is 3-methylcyclohexene. (The product contains no deuterium.) Provide an explanation for this result.



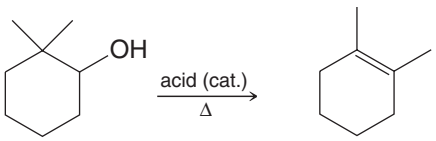
7.44 Provide a mechanistic explanation for each of the following reactions:

(a)



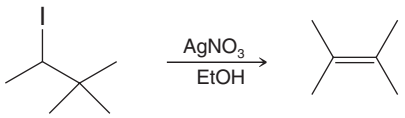
(major product)

(b)



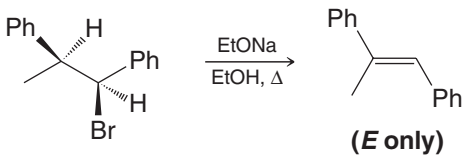
(major product)

(c)



(major product)

(d)



(*E* only)

INDEX OF HYDROGEN DEFICIENCY

7.45 Caryophyllene, a compound found in oil of cloves, has the molecular formula $C_{15}H_{24}$ and has no triple bonds. Reaction of caryophyllene with an excess of hydrogen in the presence of a platinum catalyst produces a compound with the formula $C_{15}H_{28}$. How many **(a)** double bonds and **(b)** rings does a molecule of caryophyllene have?

7.46 Squalene, an important intermediate in the biosynthesis of steroids, has the molecular formula $C_{30}H_{50}$ and has no triple bonds.

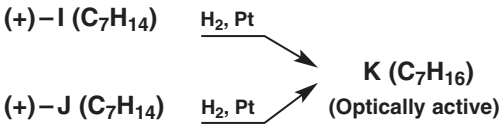
(a) What is the index of hydrogen deficiency of squalene?

(b) Squalene undergoes catalytic hydrogenation to yield a compound with the molecular formula $C_{30}H_{62}$. How many double bonds does a molecule of squalene have?

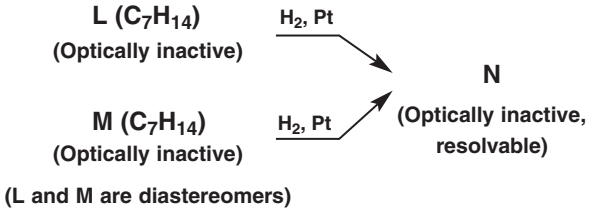
(c) How many rings?

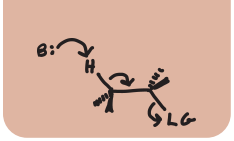
STRUCTURE ELUCIDATION

7.47 Compounds **I** and **J** both have the molecular formula C_7H_{14}. Compounds **I** and **J** are both optically active and both rotate plane-polarized light in the same direction. On catalytic hydrogenation **I** and **J** yield the same compound **K** (C_7H_{16}). Compound **K** is optically active. Propose possible structures for **I**, **J**, and **K**.



7.48 Compounds **L** and **M** have the molecular formula C_7H_{14}. Compounds **L** and **M** are optically inactive, are nonresolvable, and are diastereomers of each other. Catalytic hydrogenation of either **L** or **M** yields **N**. Compound **N** is optically inactive but can be resolved into separate enantiomers. Propose possible structures for **L**, **M**, and **N**.





Challenge Problems

7.49 Propose structures for compounds **E–H**. Compound **E** has the molecular formula C_5H_8 and is optically active. On catalytic hydrogenation **E** yields **F**. Compound **F** has the molecular formula C_5H_{10}, is optically inactive, and cannot be resolved into separate enantiomers. Compound **G** has the molecular formula C_6H_{10} and is optically active. Compound **G** contains no triple bonds. On catalytic hydrogenation **G** yields **H**. Compound **H** has the molecular formula C_6H_{14}, is optically inactive, and cannot be resolved into separate enantiomers.

7.50 Consider the interconversion of *cis*-2-butene and *trans*-2-butene.

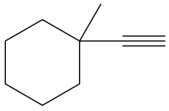
(a) What is the value of $\Delta H°$ for the reaction *cis*-2-butene $\longrightarrow$ *trans*-2-butene (see Section 7.3A)?

(b) Assume $\Delta H° \cong \Delta G°$. What minimum value of $\Delta G^{\ddagger}$ would you expect for this reaction (see Section 1.13A)?

(c) Sketch a free-energy diagram for the reaction and label $\Delta G°$ and $\Delta G^{\ddagger}$.

7.51 **(a)** Partial dehydrohalogenation of either (1*R*,2*R*)-1,2-dibromo-1,2-diphenylethane or (1*S*,2*S*)-1,2-dibromo-1,2-diphenylethane enantiomers (or a racemate of the two) produces (*Z*)-1-bromo-1,2-diphenylethene as the product, whereas **(b)** partial dehydrohalogenation of (1*R*,2*S*)-1,2-dibromo-1,2-diphenylethane (the meso compound) gives only (*E*)-1-bromo-1,2-diphenylethene. **(c)** Treating (1*R*,2*S*)-1,2-dibromo-1,2-diphenylethane with sodium iodide in acetone produces only (*E*)-1,2-diphenylethene. Explain these results.

7.52 **(a)** Using reactions studied in this chapter, show steps by which this alkyne could be converted to the seven-membered ring homolog of the product obtained in Problem 7.44(b).



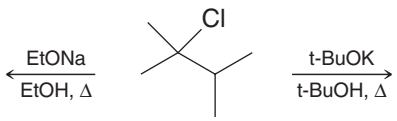
(b) Could the homologous products obtained in these two cases be relied upon to show infrared absorption in the 1620–1680-cm^{-1} region?

7.53 Predict the structures of compounds **A**, **B**, and **C**:
A is an unbranched C_6 alkyne that is also a primary alcohol.
B is obtained from **A** by use of hydrogen and nickel boride catalyst or dissolving metal reduction.
C is formed from **B** on treatment with aqueous acid at room temperature. Compound **C** has no infrared absorption in either the 1620–1680-cm^{-1} or the 3590–3650-cm^{-1} region. It has an index of hydrogen deficiency of 1 and has one chirality center but forms as the racemate.

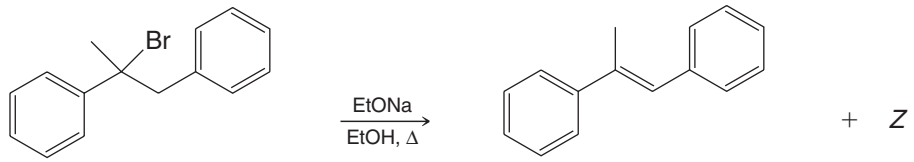
7.54 What is the index of hydrogen deficiency for **(a)** $C_7H_{10}O_2$ and **(b)** $C_5H_4N_4$?

Learning Group Problems

1. Write the structure(s) of the major product(s) obtained when 2-chloro-2,3-dimethylbutane (either enantiomer) reacts with **(a)** sodium ethoxide (EtONa) in ethanol (EtOH) at 80°C or (in a separate reaction) with **(b)** potassium *tert*-butoxide (*t*-BuOK) in *tert*-butyl alcohol (*t*-BuOH) at 80°C. If more than one product is formed, indicate which one would be expected to be the major product. **(c)** Provide a detailed mechanism for formation of the major product from each reaction, including a drawing of the transition state structures.

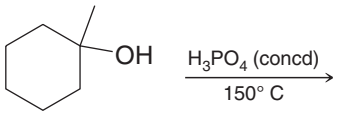


2. Explain using mechanistic arguments involving Newman projections or other three-dimensional formulas why the reaction of 2-bromo-1,2-diphenylpropane (either enantiomer) with sodium ethoxide (EtONa) in ethanol (EtOH) at 80°C produces mainly (*E*)-1,2-diphenylpropene [little of the (*Z*) diastereomer is formed].

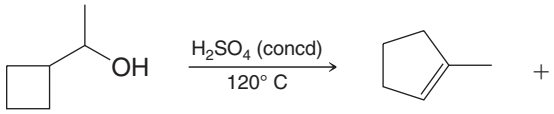


(major) **(minor)**

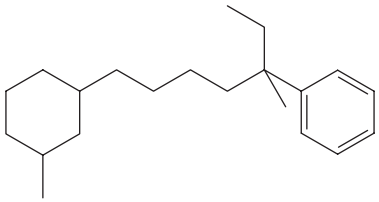
3. **(a)** Write the structure of the product(s) formed when 1-methylcyclohexanol reacts with 85% (coned) H_3PO_4 at 150°C. **(b)** Write a detailed mechanism for the reaction.



4. Consider the reaction of 1-cyclobutylethanol (1-hydroxyethylcyclobutane) with concentrated H_2SO_4 at 120°C. Write structures of all reasonable organic products. Assuming that methylcyclopentene is one product, write a mechanism that accounts for its formation. Write mechanisms that account for formation of all other products as well.



5. Consider the following compound:



(a) Develop all reasonable retrosynthetic analyses for this compound (any diastereomer) that, at some point, involve carbon–carbon bond formation by alkylation of an alkynide ion.

(b) Write reactions, including reagents and conditions, for syntheses of this compound that correspond to the retrosynthetic analyses you developed above.

(c) Infrared spectroscopy could be used to show the presence of certain impurities in your final product that would result from leftover intermediates in your syntheses. Which of your synthetic intermediates would show IR absorptions that are distinct from those in the final product, and in what regions of the IR spectrum would the absorptions occur?

(d) Draw a three-dimensional structure for either the cis or trans form of the target molecule. Use dashed and solid wedges where appropriate in the alkyl side chain and use a chair conformational structure for the ring. [*Hint:* Draw the structure so that the carbon chain of the most complicated substituent on the cyclohexane ring and the ring carbon where it is attached are all in the plane of the paper. In general, for three-dimensional structures choose an orientation that allows as many carbon atoms as possible to be in the plane of the paper.]

Summary and Review Tools

Reaction Summary of E2 and E1 Elimination

E2 via small base

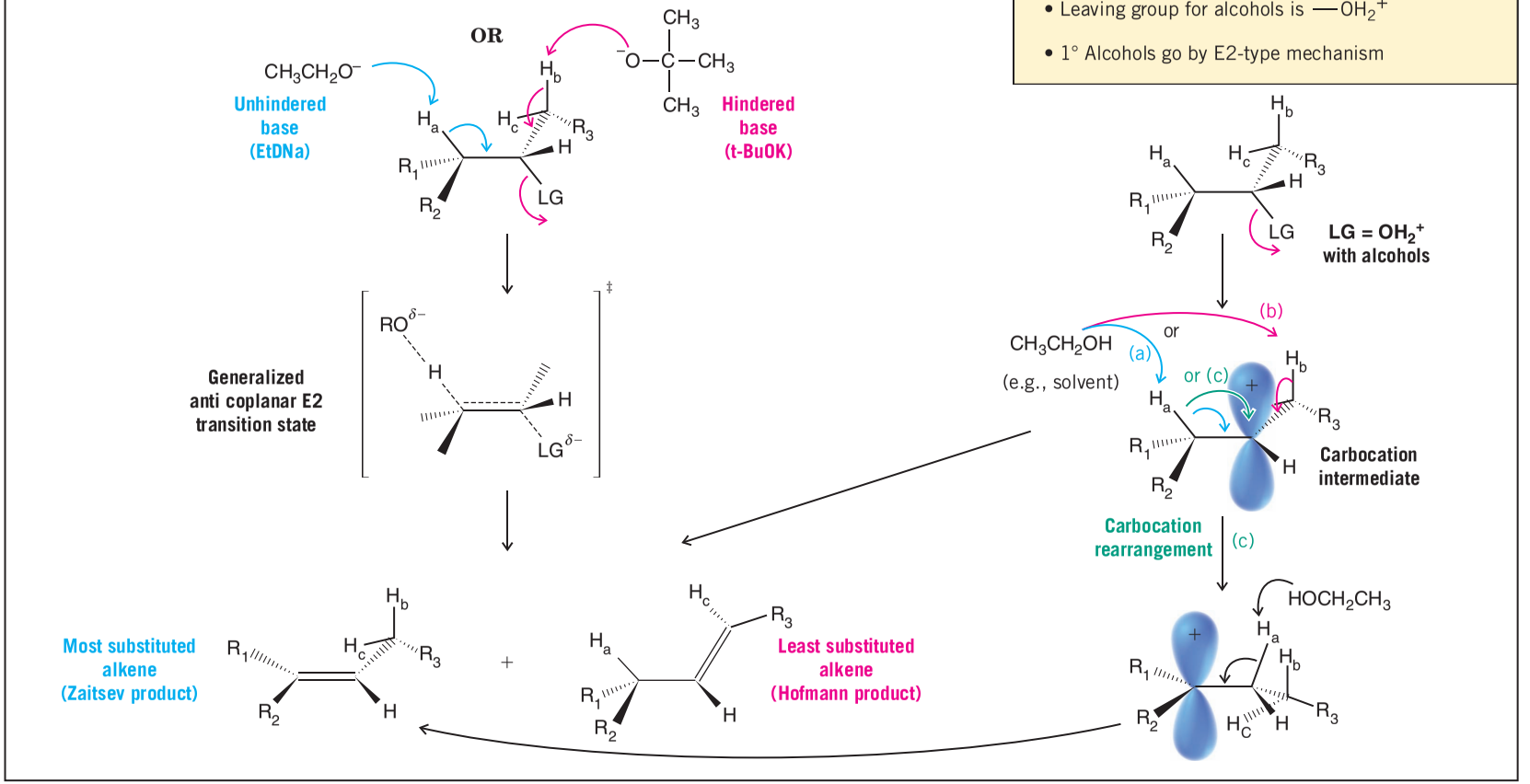
- Strong **unhindered base**, e.g., CH_3CH_2ONa(EtONa), HO^-
- Predominant formation of **most substituted alkene** (Zaitsev product)
- Anti coplanar transition state
- Bimolecular in rate-determining step

E2 via bulky base

- Strong **hindered base**, e.g. $(CH_3)_3COK$ (t-BuOK)
- Predominant formation of **least substituted alkene** (Hofmann product)
- Anti coplanar transition state
- Bimolecular in rate-determining step

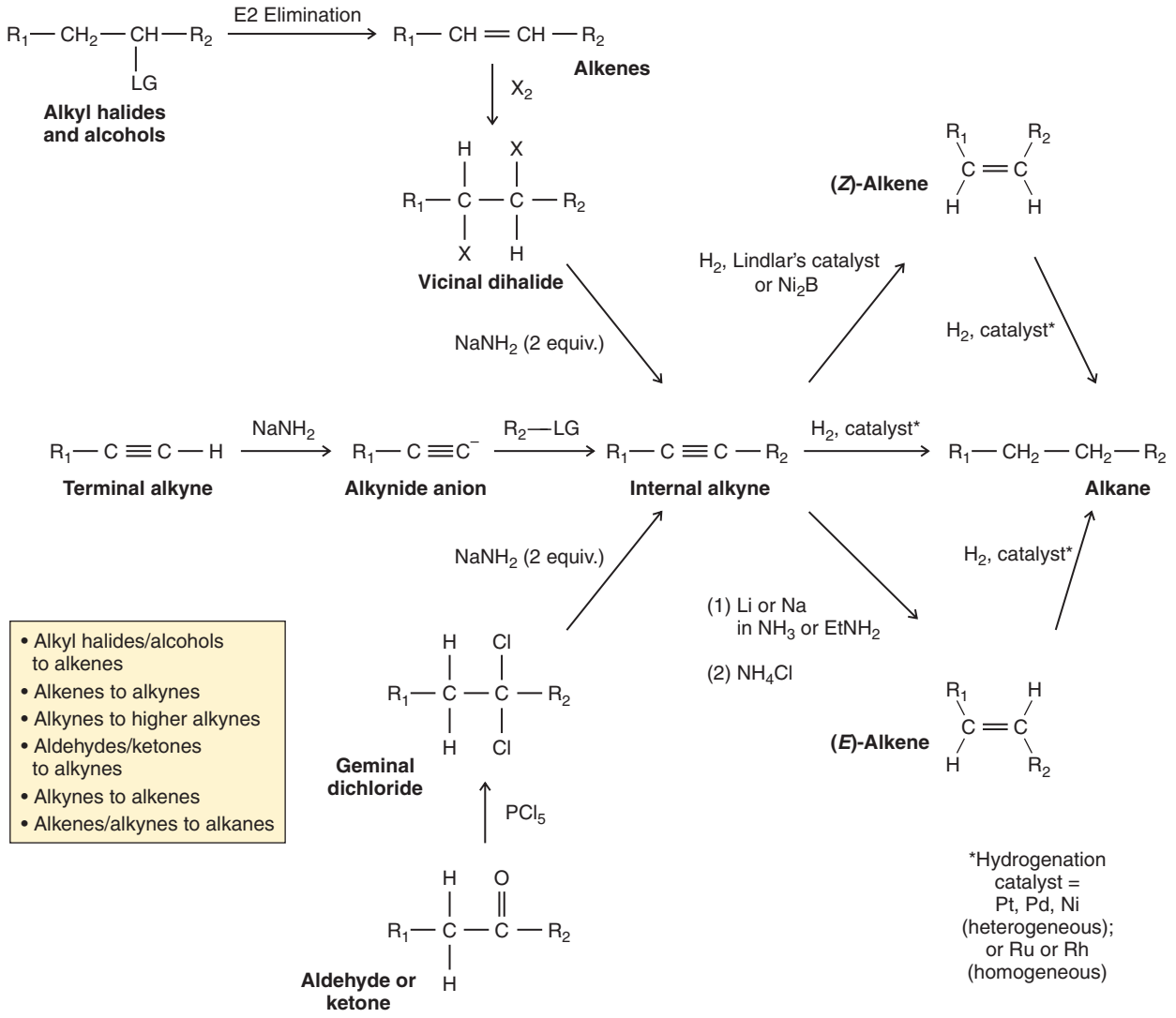
E1 (including Alcohol Dehydration)

- Absence of strong base (solvent is often the base)
- Alcohols require **strong acid catalyst**
- Carbocation formation is unimolecular rate-determining step
- Carbocation **may rearrange**
- Predominant formation of most substituted alkene (Zaitsev product)
- Leaving group for alcohols is $—OH_2^+$
- 1° Alcohols go by E2-type mechanism

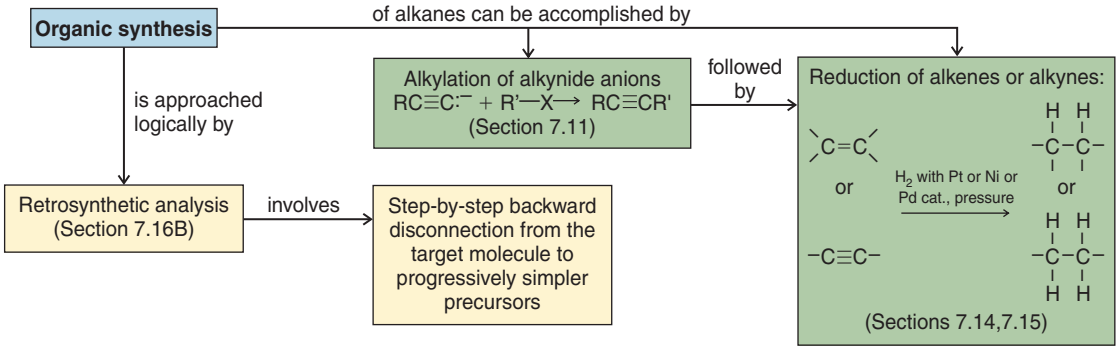


Summary and Review Tools

Synthetic Connections of Alkynes, Alkenes, Alkyl Halides, and Alcohols



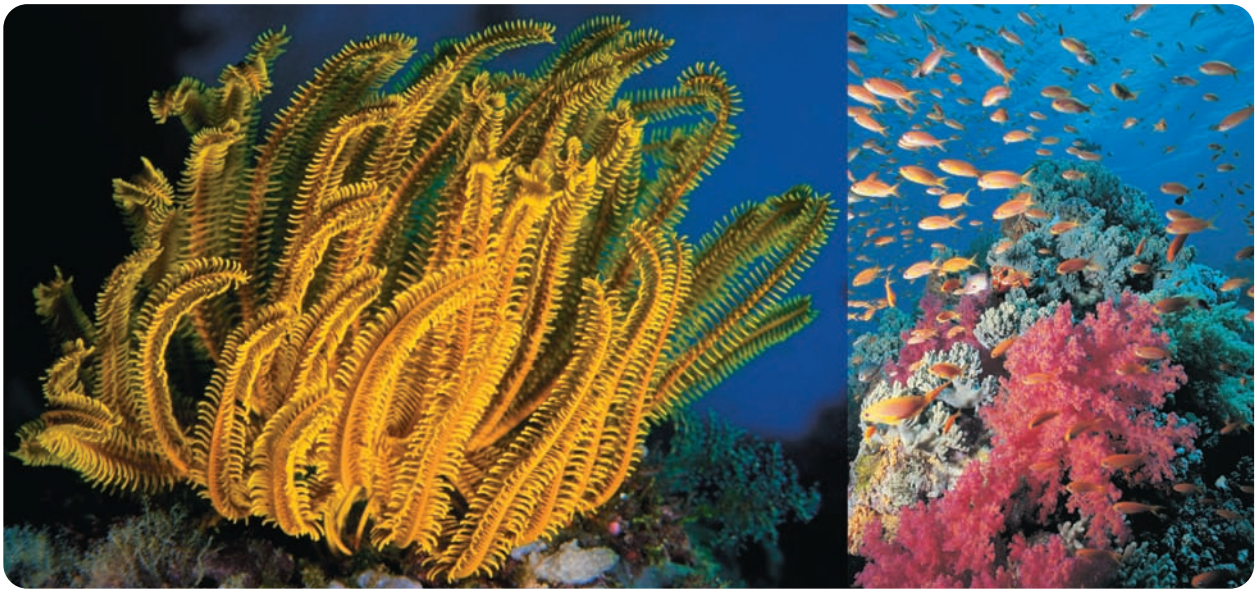
CONCEPT MAP



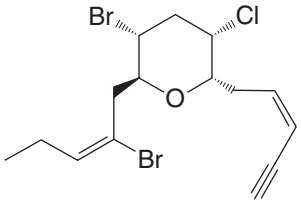
8

Alkenes and Alkynes II

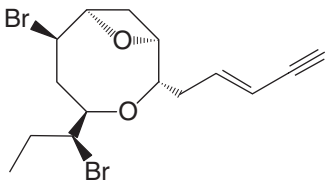
Addition Reactions



In recent chapters we have discussed mechanisms that involve electron pairs in bond-forming and bond-breaking steps of substitution and elimination reactions. Nucleophiles and bases served as electron pair donors in these reactions. In this chapter we discuss reactions of **alkenes** and **alkynes** in which a double or triple bond acts as the electron pair donor for bond formation. These reactions are called **addition reactions**.



Dactylyne

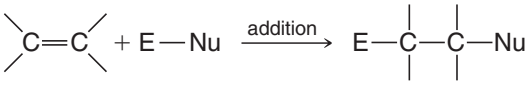


(3*E*)-Laureatin

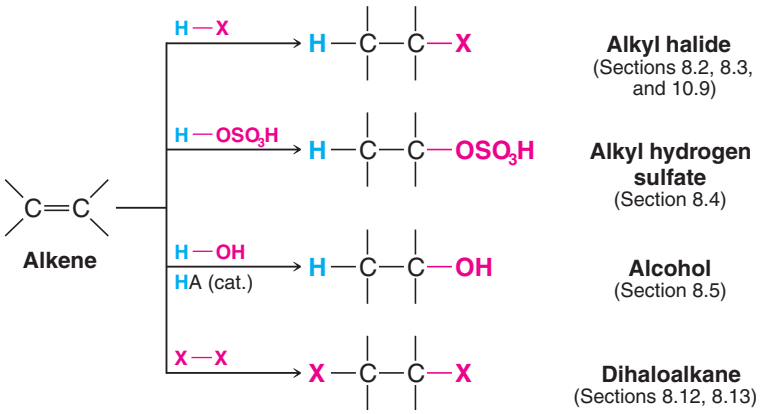
Alkenes and alkynes are very common in nature, both on land and in the sea. Examples from the sea include dactylyne and (3*E*)-laureatin, whose formulas are shown here. These compounds include halogens in their structures, as is the case for many other natural marine compounds. Certain marine organisms may produce compounds like these for the purpose of self-defense, since a number of them have cytotoxic properties. Interestingly, the halogens in these marine compounds are incorporated by biological reactions similar to those we shall study in this chapter (Section 8.12). Not only, therefore, do compounds like dactylyne and (3*E*)-laureatin have intriguing structures and properties, and arise in the beautiful environment of the sea, but they also have fascinating chemistry behind them.

8.1 Addition Reactions of Alkenes

We have already studied one addition reaction of alkenes—hydrogenation—in which a hydrogen atom is added at each end of a double (or triple) bond. In this chapter we shall study other alkene addition reactions that do not involve the same mechanism as hydrogenation. We can depict this type of reaction generally, using E for an electrophilic portion of a reagent and Nu for a nucleophilic portion, as follows.



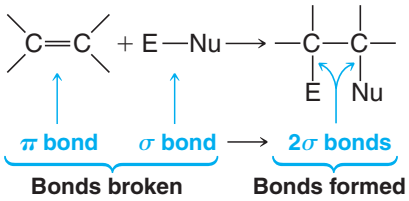
Some specific reactions of this type that we shall study in this chapter include addition of hydrogen halides, sulfuric acid, water (in the presence of an acid catalyst), and halogens. Later we shall also study some specialized reagents that undergo addition reactions with alkenes.



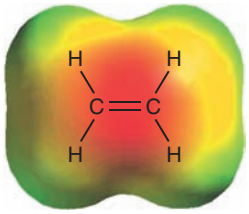
8.1A How to Understand Additions to Alkenes

Two characteristics of the double bond help us understand why these addition reactions occur:

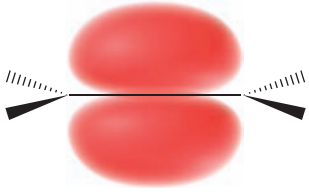
1. An addition reaction results in the conversion of one π bond and one σ bond (Sections 1.12 and 1.13) into two σ bonds. The result of this change is usually energetically favorable. The energy released in making two σ bonds exceeds that needed to break one σ bond and one π bond (because π bonds are weaker), and, therefore, addition reactions are usually exothermic:



2. The electrons of the π bond are exposed. Because the π bond results from overlapping p orbitals, the π electrons lie above and below the plane of the double bond:



An electrostatic potential map for ethene shows the higher density of negative charge in the region of the π bond.



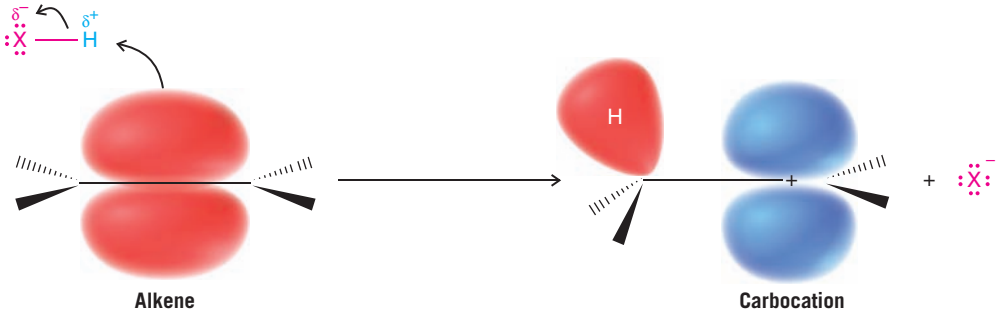
The electron pair of the π bond is distributed throughout both lobes of the π molecular orbital.

Electrophilic Addition

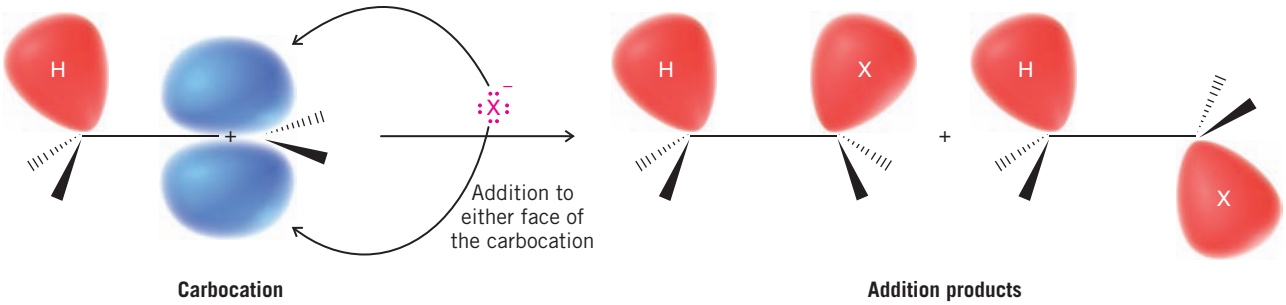
- Electrons in the π bond of alkenes react with electrophiles.
- **Electrophiles** are electron-seeking reagents. They have the property of being **electrophilic**.

Electrophiles include proton donors such as Brønsted-Lowry acids, neutral reagents such as bromine (because it can be polarized so that one end is positive), and Lewis acids such as BH_3, BF_3, and $AlCl_3$. Metal ions that contain vacant orbitals—the silver ion (Ag^+), the mercuric ion (Hg^{2+}), and the platinum ion (Pt^{2+}), for example—also act as electrophiles.

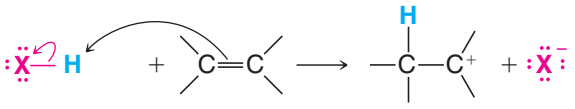
Hydrogen halides, for example, react with alkenes by accepting a pair of electrons from the π bond to form a σ bond between the hydrogen and one of the carbon atoms, with loss of the halide ion. This leaves a vacant p orbital and a + charge on the other carbon. The overall result is the formation of a carbocation and a halide ion from the alkene and HX:



Being highly reactive, the carbocation may then combine with the halide ion by accepting one of its electron pairs:



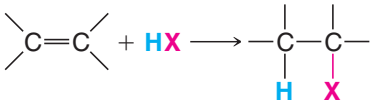
Electrophiles Are Lewis Acids Electrophiles are molecules or ions that can accept an electron pair. Nucleophiles are molecules or ions that can furnish an electron pair (i.e., Lewis bases). Any reaction of an electrophile also involves a nucleophile. In the protonation of an alkene the electrophile is the proton donated by an acid; the nucleophile is the alkene:



In the next step, the reaction of the carbocation with a halide ion, the carbocation is the electrophile and the halide ion is the nucleophile:

8.2 *Electrophilic Addition of Hydrogen Halides to Alkenes: Mechanism and Markovnikov's Rule*

Hydrogen halides (HI, HBr, HCl, and HF) add to the double bond of alkenes:

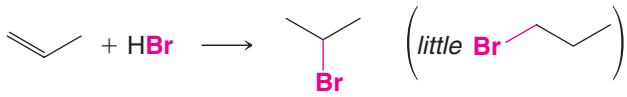


These additions are sometimes carried out by dissolving the hydrogen halide in a solvent, such as acetic acid or CH_2Cl_2, or by bubbling the gaseous hydrogen halide directly into the alkene and using the alkene itself as the solvent. HF is prepared as polyhydrogen fluoride in pyridine.

- The order of reactivity of the hydrogen halides in alkene addition is HI > HBr > HCl > HF.

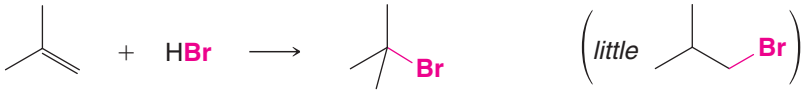
Unless the alkene is highly substituted, HCl reacts so slowly that the reaction is not one that is useful as a preparative method. HBr adds readily, but as we shall learn in Section 10.9, unless precautions are taken, the reaction may follow an alternate course.

The addition of HX to an unsymmetrical alkene could conceivably occur in two ways. In practice, however, one product usually predominates. The addition of HBr to propene, for example, could conceivably lead to either 1-bromopropane or 2-bromopropane. The main product, however, is 2-bromopropane:



2-Bromopropane **1-Bromopropane**

When 2-methylpropene reacts with HBr, the main product is 2-bromo-2-methylpropane, not 1-bromo-2-methylpropane:

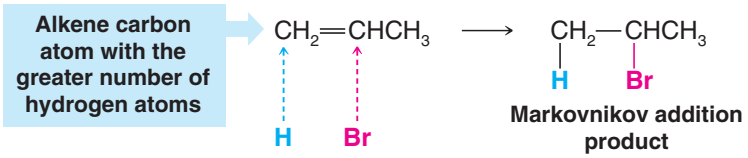


2-Methylpropene **2-Bromo-2-methylpropane** **1-Bromo-2-methylpropane**

Consideration of many examples like this led the Russian chemist Vladimir Markovnikov in 1870 to formulate what is now known as Markovnikov's rule.

- One way to state **Markovnikov's rule** is to say that ***in the addition of*** HX ***to an alkene, the hydrogen atom adds to the carbon atom of the double bond that already has the greater number of hydrogen atoms.****

The addition of HBr to propene is an illustration:



Markovnikov addition product

Reactions that illustrate Markovnikov's rule are said to be *Markovnikov additions*.

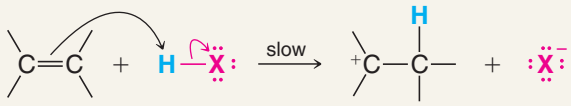
*In his original publication, Markovnikov described the rule in terms of the point of attachment of the halogen atom, stating that "if an unsymmetrical alkene combines with a hydrogen halide, the halide ion adds to the carbon atom with the fewer hydrogen atoms."

A mechanism for addition of a hydrogen halide to an alkene involves the following two steps:

A MECHANISM FOR THE REACTION

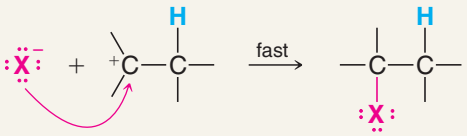
Addition of a Hydrogen Halide to an Alkene

Step 1



The π electrons of the alkene form a bond with a proton from HX to form a carbocation and a halide ion.

Step 2



The halide ion reacts with the carbocation by donating an electron pair; the result is an alkyl halide.

The important step—because it is the **rate-determining step**—is step 1. In step 1 the alkene donates a pair of electrons to the proton of the hydrogen halide and forms a carbocation. This step (Fig. 8.1) is highly endergonic and has a high free energy of activation. Consequently, it takes place slowly. In step 2 the highly reactive carbocation stabilizes itself by combining with a halide ion. This exergonic step has a very low free energy of activation and takes place very rapidly.

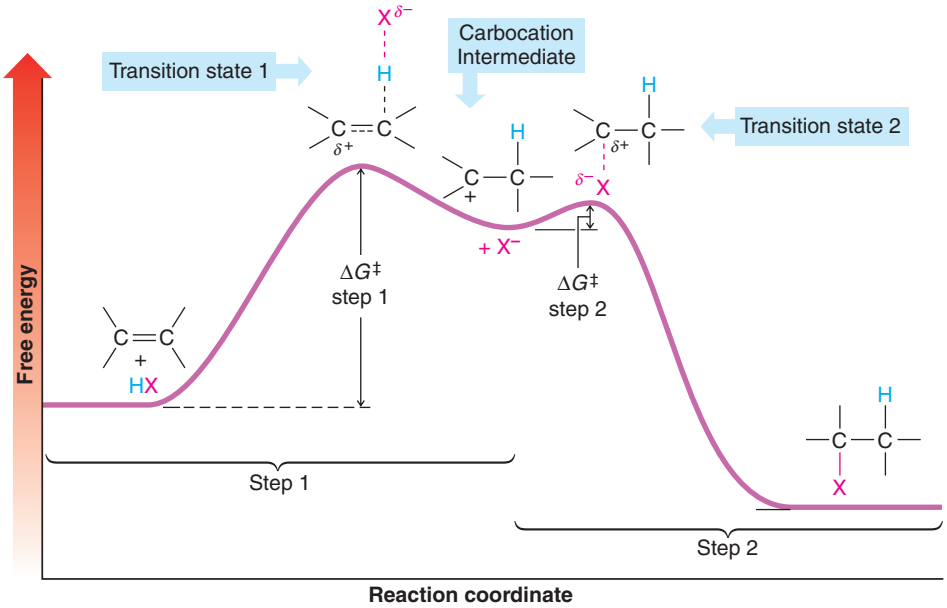
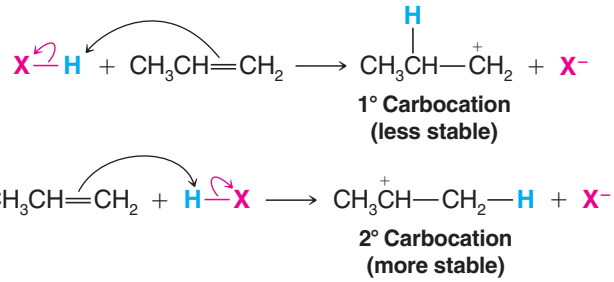


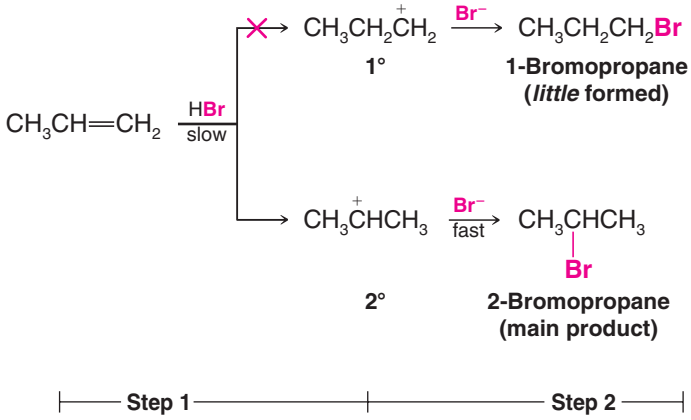
Figure 8.1 Free-energy diagram for the addition of HX to an alkene. The free energy of activation for step 1 is much larger than that for step 2.

8.2A Theoretical Explanation of Markovnikov's Rule

If the alkene that undergoes addition of a hydrogen halide is an unsymmetrical alkene such as propene, then step 1 could conceivably lead to two different carbocations:



These two carbocations are not of equal stability, however. The secondary carbocation is *more stable*, and it is the greater stability of the secondary carbocation that accounts for the correct prediction of the overall addition by Markovnikov's rule. In the addition of HBr to propene, for example, the reaction takes the following course:



The chief product of the reaction is 2-bromopropane because the more stable secondary carbocation is formed preferentially in the first step.

- The more stable carbocation predominates because it is formed faster.

We can understand why this is true if we examine the free-energy diagrams in Fig. 8.2.

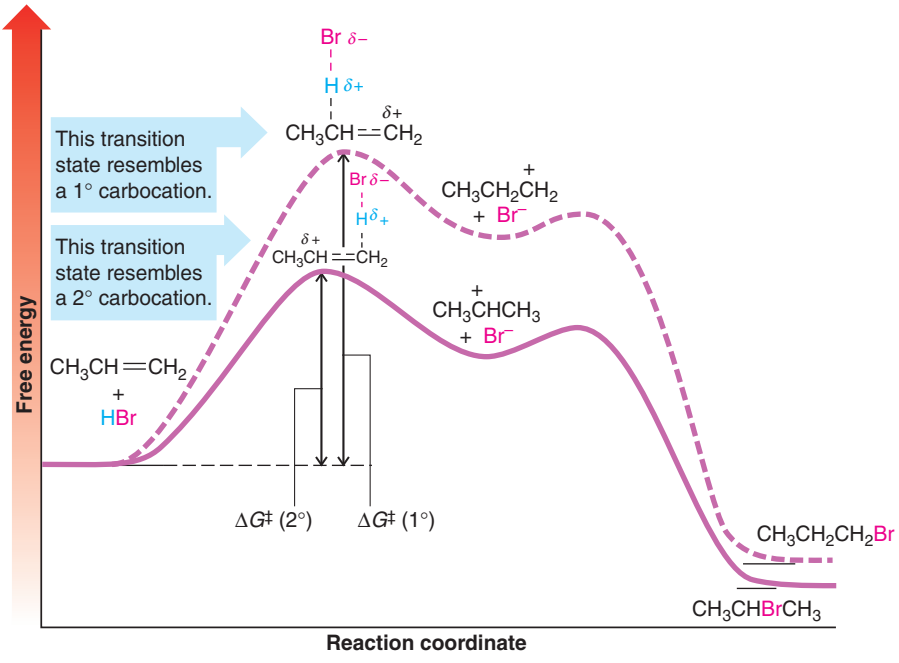


Figure 8.2 Free-energy diagrams for the addition of HBr to propene. $\delta G^{\ddagger}(2°)$ is less than $\delta G^{\ddagger}(1°)$.

- The reaction leading to the secondary carbocation (and ultimately to 2-bromopropane) has the lower free energy of activation. This is reasonable because its transition state resembles the more stable carbocation.
- The reaction leading to the primary carbocation (and ultimately to 1-bromopropane) has a higher free energy of activation because its transition state resembles a less stable primary carbocation. This second reaction is much slower and does not compete appreciably with the first reaction.

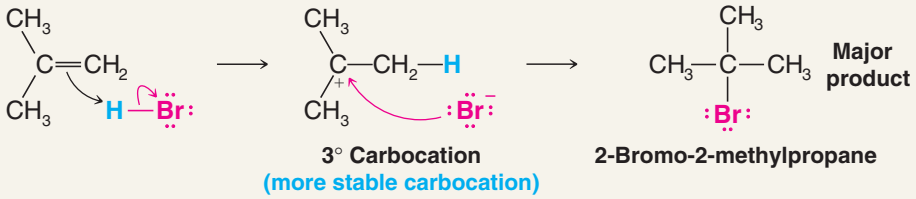
The reaction of HBr with 2-methylpropene produces only 2-bromo-2-methylpropane and for the same reason. Here, in the first step (i.e., the attachment of the proton) the choice is even more pronounced—between a tertiary carbocation and a primary carbocation. Thus, 1-bromo-2-methylpropane is *not* obtained as a product of the reaction because its formation would require the formation of a primary carbocation. Such a reaction would have a much higher free energy of activation than that leading to a tertiary carbocation.

Because carbocations are formed in the addition of HX to an alkene, rearrangements invariably occur when the carbocation initially formed can rearrange to a more stable one (see Section 7.8 and Review Problem 8.3).

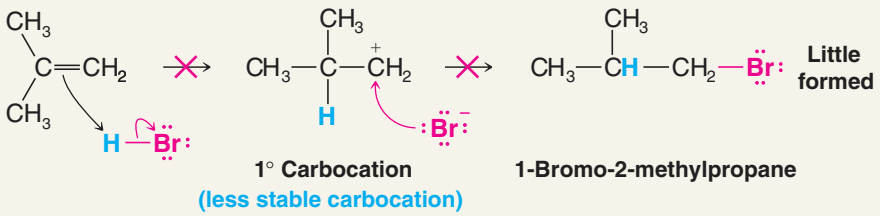
A MECHANISM FOR THE REACTION

Addition of HBr to 2-Methylpropene

This reaction takes place:



This reaction *does not* occur to any appreciable extent:



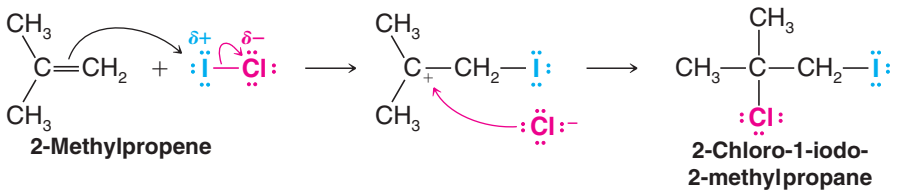
8.2B Modern Statement of Markovnikov's Rule

With this understanding of the mechanism for the ionic addition of hydrogen halides to alkenes, we can now give the following **modern statement of Markovnikov's rule**.

- In the ionic addition of an unsymmetrical reagent to a double bond, the positive portion of the adding reagent attaches itself to a carbon atom of the double bond so as to yield the more stable carbocation as an intermediate.

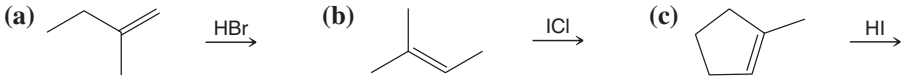
Because addition of the electrophile occurs first (before the addition of the nucleophilic portion of the adding reagent), it determines the overall orientation of the addition.

Notice that this formulation of Markovnikov's rule allows us to predict the outcome of the addition of a reagent such as ICl. Because of the greater electronegativity of chlorine, the positive portion of this molecule is iodine. The addition of ICl to 2-methylpropene takes place in the following way and produces 2-chloro-1-iodo-2-methylpropane:

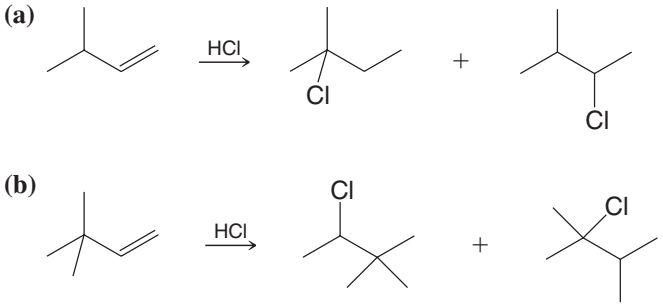


Review Problem 8.1 Give the structure and name of the product that would be obtained from the ionic addition of IBr to propene.

Review Problem 8.2 Outline mechanisms for the following addition reactions:



Review Problem 8.3 Provide mechanistic explanations for the following observations:



8.2C Regioselective Reactions

Chemists describe reactions like the Markovnikov additions of hydrogen halides to alkenes as being **regioselective**. *Regio* comes from the Latin word *regionem* meaning direction.

- When a reaction that can potentially yield two or more constitutional isomers actually produces only one (or a predominance of one), the reaction is said to be **regioselective**.

The addition of HX to an unsymmetrical alkene such as propene could conceivably yield two constitutional isomers, for example. As we have seen, however, the reaction yields only one, and therefore it is regioselective.

8.2D An Exception to Markovnikov's Rule

In Section 10.9 we shall study an exception to Markovnikov's rule. This exception concerns the addition of HBr to alkenes ***when the addition is carried out in the presence of peroxides*** (i.e., compounds with the general formula ROOR).

- When alkenes are treated with HBr in the presence of peroxides, an **anti-Markovnikov addition** occurs in the sense that the hydrogen atom becomes attached to the carbon atom with the fewer hydrogen atoms.

With propene, for example, the addition takes place as follows:

$$CH_3CH{=}CH_2 + HBr \xrightarrow{ROOR} CH_3CH_2CH_2Br$$

In Section 10.9 we shall find that this addition occurs by *a radical mechanism*, and not by the ionic mechanism given at the beginning of Section 8.2.

- This anti-Markovnikov addition occurs ***only when*** HBr ***is used in the presence of peroxides*** and does not occur significantly with HF, HCl, and HI even when peroxides are present.

8.3 Stereochemistry of the Ionic Addition to an Alkene

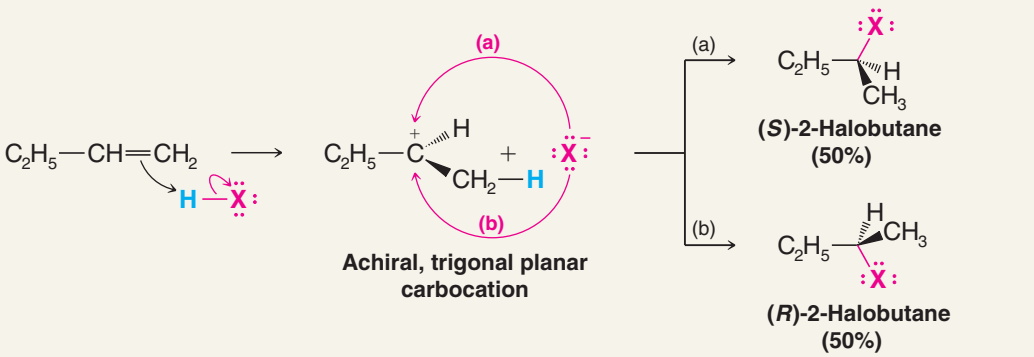
Consider the following addition of HX to 1-butene and notice that the reaction leads to the formation of a product, 2-halobutane, which contains a chirality center:

$$CH_3CH_2CH{=}CH_2 + HX \longrightarrow CH_3CH_2\overset{*}{C}HCH_3 \quad (X \text{ on } C)$$

The product, therefore, can exist as a pair of enantiomers. The question now arises as to how these enantiomers are formed. Is one enantiomer formed in greater amount than the other? The answer is *no*; the carbocation that is formed in the first step of the addition (see the following scheme) is trigonal planar and is ***achiral*** (a model will show that it has a plane of symmetry). When the halide ion reacts with this achiral carbocation in the second step, ***reaction is equally likely at either face.*** The reactions leading to the two enantiomers occur at the same rate, and the enantiomers, therefore, are produced in equal amounts ***as a racemic form***.

THE STEREOCHEMISTRY OF THE REACTION

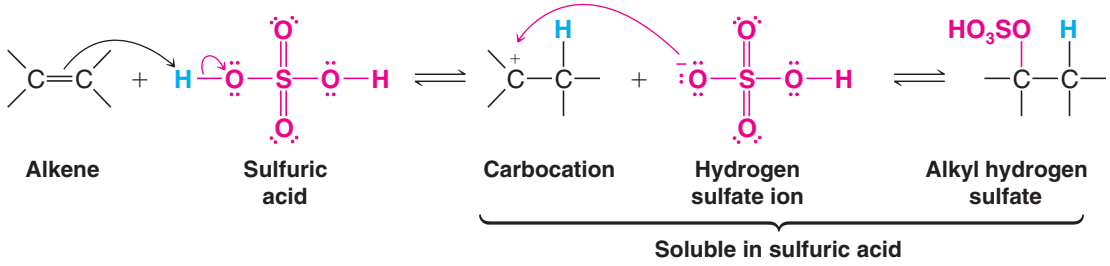
Ionic Addition to an Alkene



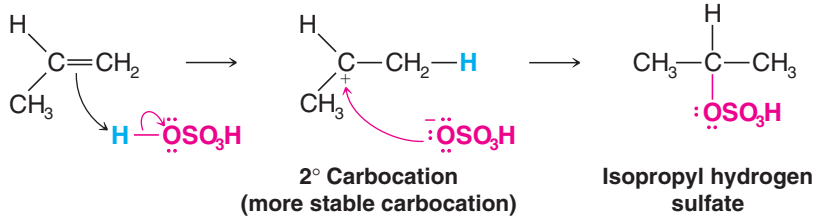
8.4 Addition of Sulfuric Acid to Alkenes

- When alkenes are treated with **cold** concentrated sulfuric acid, *they dissolve* because they react by electrophilic addition to form alkyl hydrogen sulfates.

The mechanism is similar to that for the addition of HX. In the first step of this reaction the alkene donates a pair of electrons to a proton from sulfuric acid to form a carbocation; in the second step the carbocation reacts with a hydrogen sulfate ion to form an alkyl hydrogen sulfate:

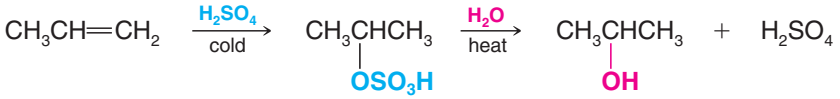


The addition of sulfuric acid is also regioselective, and it follows Markovnikov's rule. Propene, for example, reacts to yield isopropyl hydrogen sulfate rather than propyl hydrogen sulfate:



8.4A Alcohols from Alkyl Hydrogen Sulfates

Alkyl hydrogen sulfates can be easily hydrolyzed to alcohols by **heating** them with water. The overall result of the addition of sulfuric acid to an alkene followed by hydrolysis is the Markovnikov addition of H— and —OH:

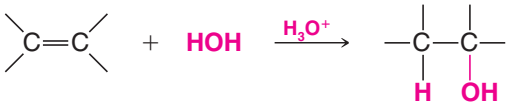


Review Problem 8.4

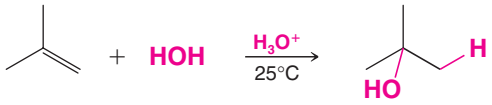
In one industrial synthesis of ethanol, ethene is first dissolved in 95% sulfuric acid. In a second step water is added and the mixture is heated. Outline the reactions involved.

8.5 Addition of Water to Alkenes: Acid-Catalyzed Hydration

The acid-catalyzed addition of water to the double bond of an alkene (**hydration** of an alkene) is a method for the preparation of low-molecular-weight alcohols. This reaction has its greatest utility in large-scale industrial processes. The acids most commonly used to catalyze the hydration of alkenes are dilute aqueous solutions of sulfuric acid and phosphoric acid. These reactions, too, are usually regioselective, and the addition of water to the double bond follows Markovnikov's rule. In general, the reaction takes the form that follows:

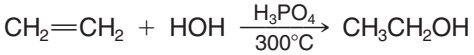


An example is the hydration of 2-methylpropene:



2-Methylpropene (isobutylene) **2-Methyl-2-propanol (*tert*-butyl alcohol)**

Because the reactions follow Markovnikov's rule, acid-catalyzed hydrations of alkenes do not yield primary alcohols except in the special case of the hydration of ethene:



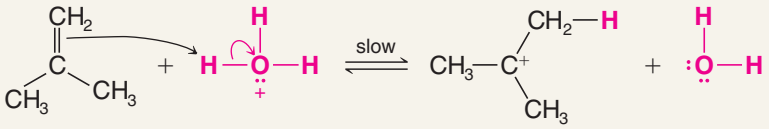
8.5A Mechanism

The mechanism for the hydration of an alkene is simply the reverse of the mechanism for the dehydration of an alcohol. We can illustrate this by giving the mechanism for the **hydration** of 2-methylpropene and by comparing it with the mechanism for the **dehydration** of 2-methyl-2-propanol given in Section 7.7A.

A MECHANISM FOR THE REACTION

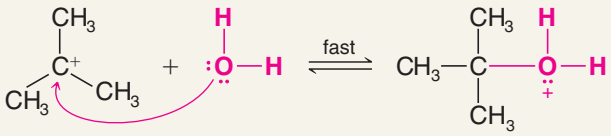
Acid-Catalyzed Hydration of an Alkene

Step 1



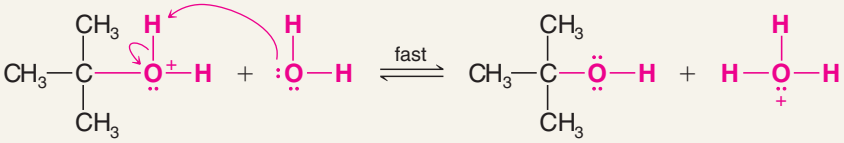
The alkene donates an electron pair to a proton to form the more stable 3° carbocation.

Step 2



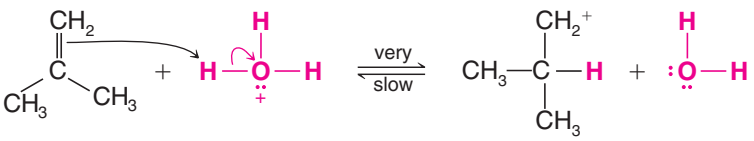
The carbocation reacts with a molecule of water to form a protonated alcohol.

Step 3



A transfer of a proton to a molecule of water leads to the product.

The rate-determining step in the *hydration* mechanism is step 1: the formation of the carbocation. It is this step, too, that accounts for the Markovnikov addition of water to the double bond. The reaction produces 2-methyl-2-propanol because step 1 leads to the formation of the more stable tertiary (3°) cation rather than the much less stable primary (1°) cation:

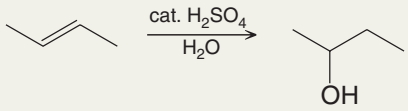


For all practical purposes this reaction does not take place because it produces a 1° carbocation.

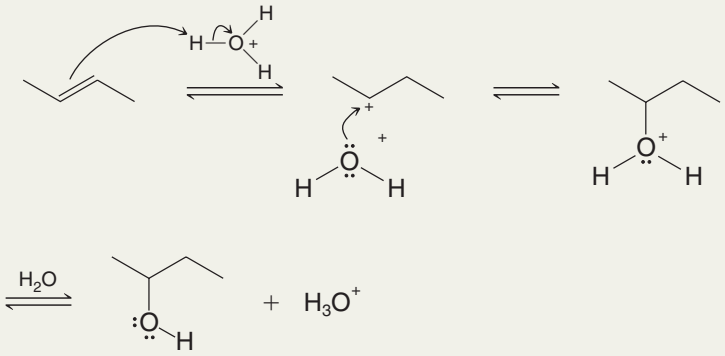
The reactions whereby *alkenes are hydrated or alcohols are dehydrated* are reactions in which the ultimate product is governed by the position of an equilibrium. Therefore, in the *dehydration of an alcohol* it is best to use a concentrated acid so that the concentration of water is low. (The water can be removed as it is formed, and it helps to use a high temperature.) In the *hydration of an alkene* it is best to use dilute acid so that the concentration of water is high. (It also usually helps to use a lower temperature.)

Solved Problem 8.1

Write a mechanism that explains the following reaction.

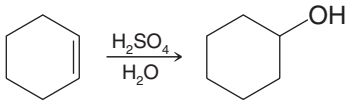


STRATEGY AND ANSWER We know that a hydronium ion, formed from sulfuric acid and water, can donate a proton to an alkene to form a carbocation. The carbocation can then accept an electon pair from a molecule of water to form a protonated alcohol. The protonated alcohol can donate a proton to water to become an alcohol.



Review Problem 8.5

(a) Write a mechanism for the following reaction.



(b) What general conditions would you use to ensure a good yield of the product?

(c) What general conditions would you use to carry out the reverse reaction, i.e., the dehydration of cyclohexanol to produce cyclohexene?

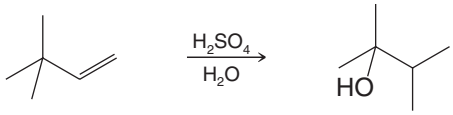
(d) What product would you expect to obtain from the acid-catalyzed hydration of 1-methylcyclohexene? Explain your answer.

8.5B Rearrangements

- One complication associated with alkene hydrations is the occurrence of **rearrangements**.

Because the reaction involves the formation of a carbocation in the first step, the carbocation formed initially invariably rearranges to a more stable one (or possibly to an isoener-

getic one) if such a rearrangement is possible. An illustration is the formation of 2,3-dimethyl-2-butanol as the major product when 3,3-dimethyl-1-butene is hydrated:



3,3-Dimethyl-1-butene **2,3-Dimethyl-2-butanol (major product)**

Review Problem 8.6

Outline all steps in a mechanism showing how 2,3-dimethyl-2-butanol is formed in the acid-catalyzed hydration of 3,3-dimethyl-1-butene.

Review Problem 8.7

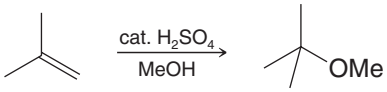
The following order of reactivity is observed when the following alkenes are subjected to acid-catalyzed hydration:

$$(CH_3)_2C{=}CH_2 > CH_3CH{=}CH_2 > CH_2{=}CH_2$$

Explain this order of reactivity.

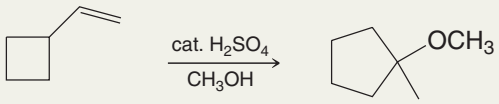
Review Problem 8.8

Write a mechanism for the following reaction.

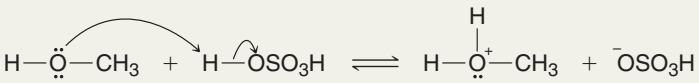


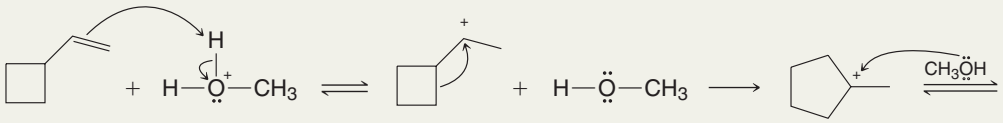
Solved Problem 8.2

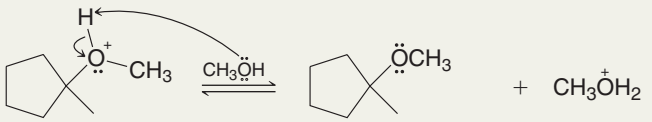
Write a mechanism that will explain the course of the following reaction



STRATEGY AND ANSWER As we have learned, in a strongly acidic medium such as methanol containing catalytic sulfuric acid, an alkene can accept a proton to become a carbocation. In the reaction above, the 2° carbocation formed initially can rearrange as shown below to become a 3° carbocation, which can then react with the solvent (methanol) to form an ether.





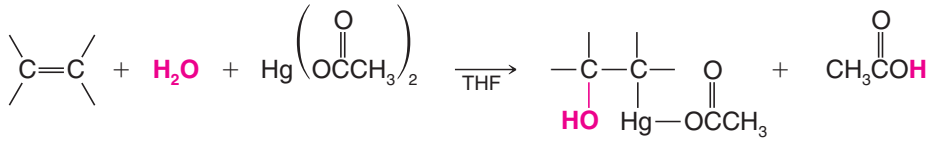


8.6 *Alcohols from Alkenes through Oxymercuration–Demercuration: Markovnikov Addition*

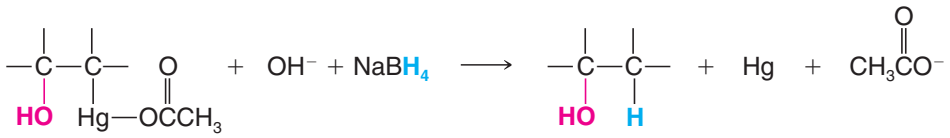
A useful laboratory procedure for synthesizing alcohols from alkenes that avoids rearrangement is a two-step method called **oxymercuration–demercuration**.

- Alkenes react with mercuric acetate in a mixture of tetrahydrofuran (THF) and water to produce (hydroxyalkyl)mercury compounds. These (hydroxyalkyl)mercury compounds can be reduced to alcohols with sodium borohydride.

Step 1: Oxymercuration



Step 2: Demercuration



- In the first step, **oxymercuration**, water and mercuric acetate add to the double bond.
- In the second step, **demercuration**, sodium borohydride reduces the acetoxymercury group and replaces it with hydrogen. (The acetate group is often abbreviated —OAc.)

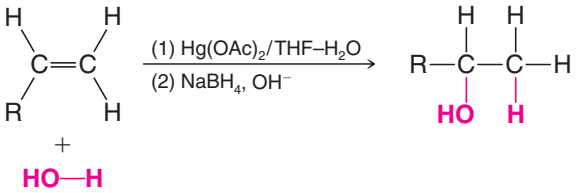
Mercury compounds are extremely hazardous. Before you carry out a reaction involving mercury or its compounds, you should familiarize yourself with current procedures for its use and containment. There are no satisfactory methods for disposal of mercury.

Both steps can be carried out in the same vessel, and both reactions take place very rapidly at room temperature or below. The first step—oxymercuration—usually goes to completion within a period of 20 s to 10 min. The second step—demercuration—normally requires less than an hour. The overall reaction gives alcohols in very high yields, usually greater than 90%.

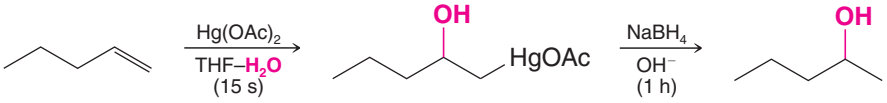
8.6A Regioselectivity of Oxymercuration–Demercuration

Oxymercuration–demercuration is also highly regioselective.

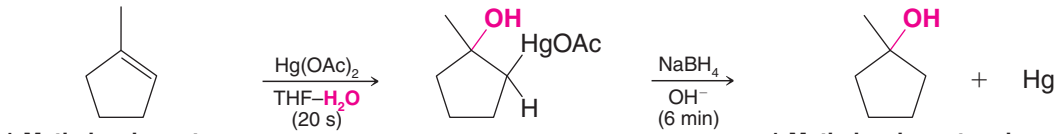
- In oxymercuration–demercuration, the net orientation of the addition of the elements of water, H— and —OH, ***is in accordance with Markovnikov's rule***. The H— becomes attached to the carbon atom of the double bond with the greater number of hydrogen atoms.



The following are specific examples:



1-Pentene **2-Pentanol (93%)**



1-Methylcyclopentene **1-Methylcyclopentanol**

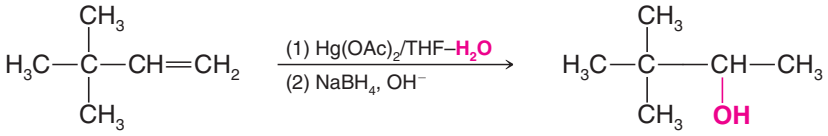
8.6B Rearrangements Seldom Occur in Oxymercuration–Demercuration

Helpful Hint

Oxymercuration–demercuration is not prone to hydride or alkanide rearrangements.

- Rearrangements of the carbon skeleton seldom occur in oxymercuration–demercuration.

The oxymercuration–demercuration of 3,3-dimethyl-1-butene is a striking example illustrating this feature. It is in direct contrast to the hydration of 3,3-dimethyl-1-butene we studied previously (Section 8.5B).



3,3-Dimethyl-1-butene **3,3-Dimethyl-2-butanol (94%)**

Analysis of the mixture of products by gas chromatography failed to reveal the presence of any 2,3-dimethyl-2-butanol. The acid-catalyzed hydration of 3,3-dimethyl-1-butene, by contrast, gives 2,3-dimethyl-2-butanol as the major product.

8.6C Mechanism of Oxymercuration

A mechanism that accounts for the orientation of addition in the oxymercuration stage, and one that also explains the general lack of accompanying rearrangements, is shown below.

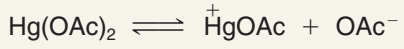
- Central to this mechanism is an electrophilic attack by the mercury species, $\overset{+}{H}gOAc$, at the less substituted carbon of the double bond (i.e., at the carbon atom that bears the greater number of hydrogen atoms), and the formation of a bridged intermediate.

We illustrate the mechanism using 3,3-dimethyl-1-butene as the example:

A MECHANISM FOR THE REACTION

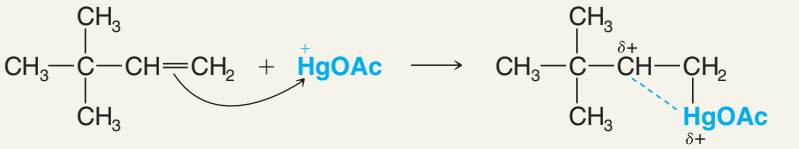
Oxymercuration

Step 1



Mercuric acetate dissociates to form a $\overset{+}{H}gOAc$ cation and an acetate anion.

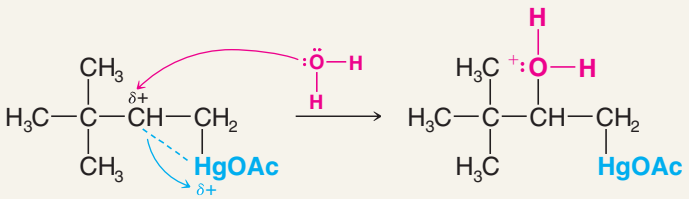
Step 2



3,3-Dimethyl-1-butene **Mercury-bridged carbocation**

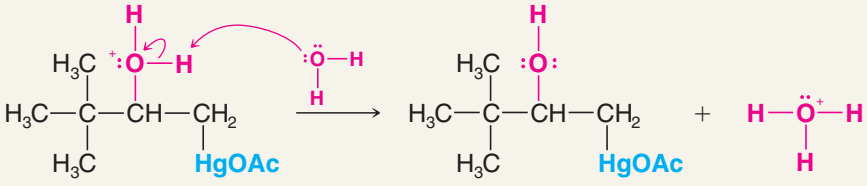
The alkene donates a pair of electrons to the electrophilic $HgOAc^+$ cation to form a mercury-bridged carbocation. In this carbocation, the positive charge is shared between the 2° (more substituted) carbon atom and the mercury atom. The charge on the carbon atom is large enough to account for the Markovnikov orientation of the addition, but not large enough for a rearrangement to occur.

Step 3



A water molecule attacks the carbon of the bridged mercurinium ion that is better able to bear the partial positive charge.

Step 4



(Hydroxyalkyl)mercury compound

An acid–base reaction transfers a proton to another water molecule (or to an acetate ion). This step produces the (hydroxyalkyl)mercury compound.

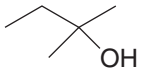
Calculations indicate that mercury-bridged carbocations (termed mercurinium ions) such as those formed in this reaction retain much of the positive charge on the mercury moiety. Only a small portion of the positive charge resides on the more substituted carbon atom. The charge is large enough to account for the observed Markovnikov addition, but it is too small to allow the usual rapid carbon skeleton rearrangements that take place with more fully developed carbocations.

Although attack by water on the bridged mercurinium ion leads to anti addition of the hydroxyl and mercury groups, the reaction that replaces mercury with hydrogen is not stereocontrolled (it likely involves radicals; see Chapter 10). This step scrambles the overall stereochemistry.

- The net result of oxymercuration–demercuration is a mixture of syn and anti addition of —H and —OH to the alkene.
- As already noted, oxymercuration–demercuration takes place with Markovnikov regiochemistry.

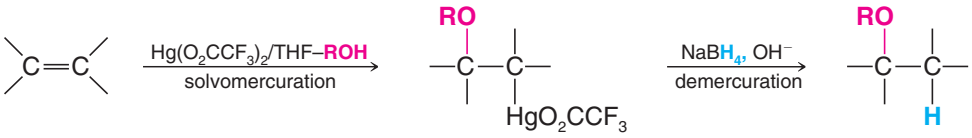
Review Problem 8.9

Write the structure of the appropriate alkene and specify the reagents needed for synthesis of the following alcohols by oxymercuration–demercuration:

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

When an alkene is treated with mercuric trifluoroacetate, $Hg(O_2CCF_3)_2$, in THF containing an alcohol, ROH, the product is an (alkoxyalkyl)mercury compound. Treating this product with $NaBH_4/OH^-$ results in the formation of an ether.

- When a solvent molecule acts as the nucleophile in the oxymercuration step the overall process is called *solvomercuration–demercuration*:



Alkene **(Alkoxyalkyl)mercuric trifluoroacetate** **Ether**

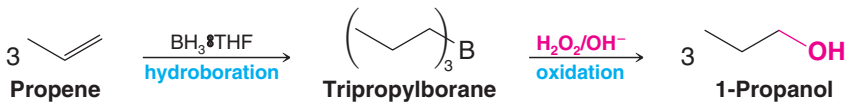
(a) Outline a likely mechanism for the solvomercuration step of the ether synthesis just shown. **(b)** Show how you would use solvomercuration–demercuration to prepare *tert*-butyl methyl ether. **(c)** Why would one use $Hg(O_2CCF_3)_2$ instead of $Hg(OAc)_2$?

Review Problem 8.10

8.7 Alcohols from Alkenes through Hydroboration–Oxidation: Anti-Markovnikov Syn Hydration

- **Anti-Markovnikov** hydration of a double bond can be achieved through the use of diborane (B_2H_6) or a solution of borane in tetrahydrofuran (BH_3:THF).

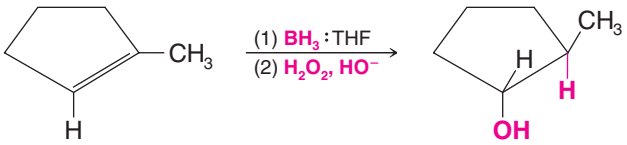
The addition of water is indirect in this process, and two reactions are involved. The first is the addition of a boron atom and hydrogen atom to the double bond, called **hydroboration**; the second is **oxidation** and hydrolysis of the alkylborane intermediate to an alcohol and boric acid. The anti-Markovnikov regiochemistry of the addition is illustrated by the hydroboration–oxidation of propene:



Propene — Tripropylborane — 1-Propanol

- Hydroboration–oxidation takes place with **syn** stereochemistry, as well as anti-Markovnikov regiochemistry.

This can be seen in the following example with 1-methylcyclopentene:



In the following sections we shall consider details of the mechanism that lead to the anti-Markovnikov regiochemistry and syn stereochemistry of hydroboration–oxidation.

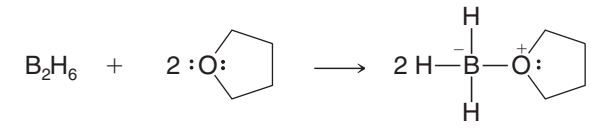
8.8 Hydroboration: Synthesis of Alkylboranes

Hydroboration of an alkene is the starting point for a number of useful synthetic procedures, including the anti-Markovnikov syn hydration procedure we have just mentioned. Hydroboration was discovered by Herbert C. Brown (Purdue University), and it can be represented in its simplest terms as follows:

Brown's discovery of hydroboration led to his being named a co-winner of the 1979 Nobel Prize in Chemistry.

Alkene — Boron hydride — Alkylborane

Hydroboration can be accomplished with diborane (B_2H_6), which is a gaseous dimer of borane (BH_3), or more conveniently with a reagent prepared by dissolving diborane in THF. When diborane is introduced to THF, it reacts to form a Lewis acid–base complex of borane (the Lewis acid) and THF. The complex is represented as BH_3:THF.

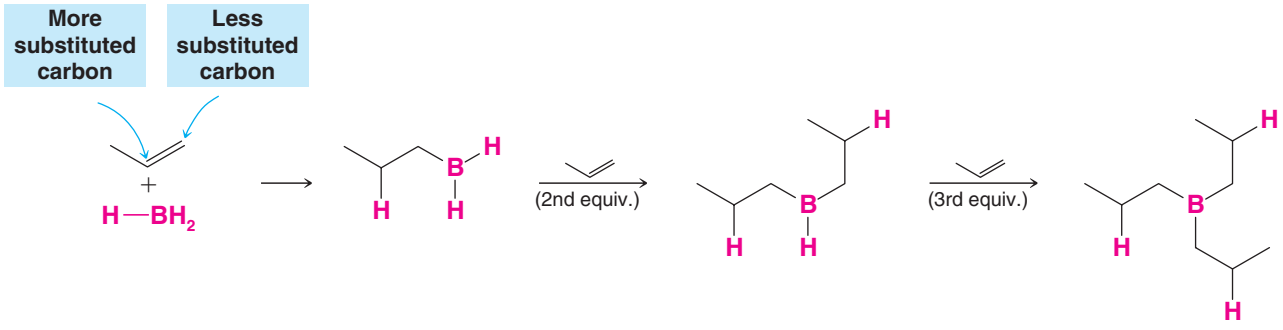


Diborane — THF (tetrahydrofuran) — BH_3:THF

Solutions containing the BH_3:THF complex can be obtained commercially. Hydroboration reactions are usually carried out in ethers: either in diethyl ether, $(CH_3CH_2)_2O$, or in some higher molecular weight ether such as "diglyme" [$(CH_3OCH_2CH_2)_2O$, *di*ethylene *gly*col di*me*thyl ether]. Great care must be used in handling diborane and alkylboranes because they ignite spontaneously in air (with a green flame). The solution of BH_3:THF must be used in an inert atmosphere (e.g., argon or nitrogen) and with care.

8.8A Mechanism of Hydroboration

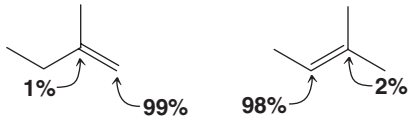
When a terminal alkene such as propene is treated with a solution containing BH_3:THF, the boron hydride adds successively to the double bonds of three molecules of the alkene to form a trialkylborane:



Tripropylborane

- In each addition step ***the boron atom becomes attached to the less substituted carbon atom of the double bond***, and a hydrogen atom is transferred from the boron atom to the other carbon atom of the double bond.
- Hydroboration is **regioselective** and it is **anti-Markovnikov** (the hydrogen atom becomes attached to the carbon atom with fewer hydrogen atoms).

Other examples that illustrate the tendency for the boron atom to become attached to the less substituted carbon atom are shown here. The percentages designate where the boron atom becomes attached.



These percentages, indicating where boron becomes attached in reactions using these starting materials, illustrate the tendency for boron to bond at the less substituted carbon of the double bond.

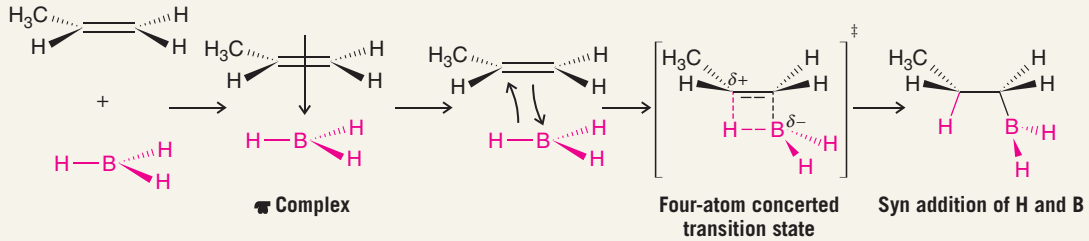
This observed attachment of boron to the less substituted carbon atom of the double bond seems to result in part from **steric factors**—the bulky boron-containing group can approach the less substituted carbon atom more easily.

In the mechanism proposed for hydroboration, addition of BH_3 to the double bond begins with a donation of π electrons from the double bond to the vacant p orbital of BH_3 (see the mechanism on the following page). In the next step this complex becomes the addition product by passing through a four-atom transition state in which the boron atom is partially bonded to the less substituted carbon atom of the double bond and one hydrogen atom is partially bonded to the other carbon atom. As this transition state is approached, electrons shift in the direction of the boron atom and away from the more substituted carbon atom of the double bond. This makes the more substituted carbon atom develop a partial positive charge, *and because it bears an electron-releasing alkyl group, it is better able to accommodate this positive charge*. Thus, electronic factors also favor addition of boron at the least substituted carbon.

- Overall, both *electronic* and *steric factors* account for the anti-Markovnikov orientation of the addition.

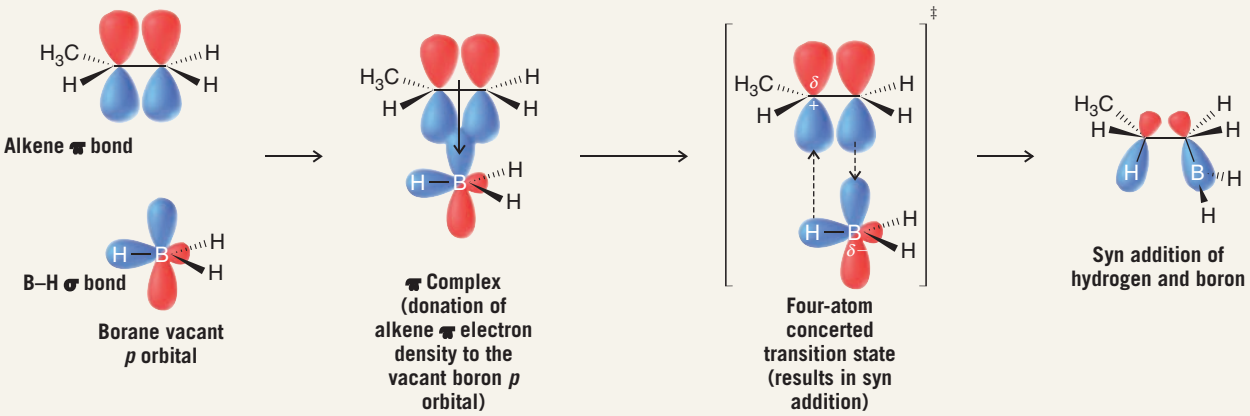
A MECHANISM FOR THE REACTION

Hydroboration



Addition takes place through the initial formation of a π complex, which changes into a cyclic four-atom transition state with the boron adding to the less hindered carbon atom. The dashed bonds in the transition state represent bonds that are partially formed or partially broken. The transition state results in syn addition of the hydrogen and boron group, leading to an alkylborane. The other B–H bonds of the alkylborane can undergo similar additions, leading finally to a trialkylborane.

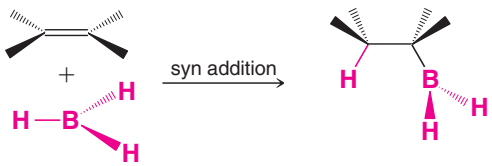
An orbital view of hydroboration



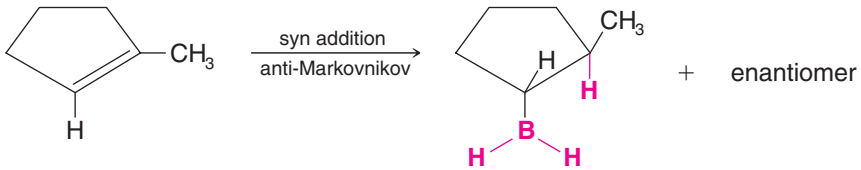
8.8B Stereochemistry of Hydroboration

- The transition state for hydroboration requires that the boron atom and the hydrogen atom add to the same face of the double bond:

Stereochemistry of Hydroboration



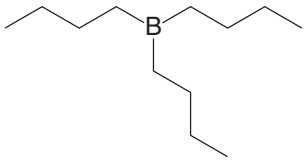
We can see the results of a syn addition in our example involving the hydroboration of 1-methylcyclopentene. Formation of the enantiomer, which is equally likely, results when the boron hydride adds to the top face of the 1-methylcyclopentene ring:



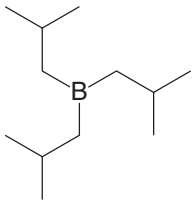
Review Problem 8.11

Specify the alkene needed for synthesis of each of the following alkylboranes by hydroboration:

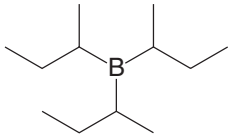
(a)



(b)



(c)



(d) Show the stereochemistry involved in the hydroboration of 1-methylcyclohexene.

Review Problem 8.12

Treating a hindered alkene such as 2-methyl-2-butene with BH_3:THF leads to the formation of a dialkylborane instead of a trialkylborane. When 2 mol of 2-methyl-2-butene is added to 1 mol of BH_3, the product formed is bis(3-methyl-2-butyl)borane, nicknamed "disiamylborane." Write its structure. Bis(3-methyl-2-butyl)borane is a useful reagent in certain syntheses that require a sterically hindered borane. (The name "disiamyl" comes from "*di*-secondary-*i*so-*amyl*," a completely unsystematic and unacceptable name. The name "amyl" is an old common name for a five-carbon alkyl group.)

8.9 Oxidation and Hydrolysis of Alkylboranes

The alkylboranes produced in the hydroboration step are usually not isolated. They are oxidized and hydrolyzed to alcohols in the same reaction vessel by the addition of hydrogen peroxide in an aqueous base:

$$R_3B \xrightarrow[\text{(oxdidation and hydrolysis)}]{H_2O_2,\ \text{aq. NaOH},\ 25^\circ C} 3R\text{—}\mathbf{OH} + B(\mathbf{ONa})_3$$

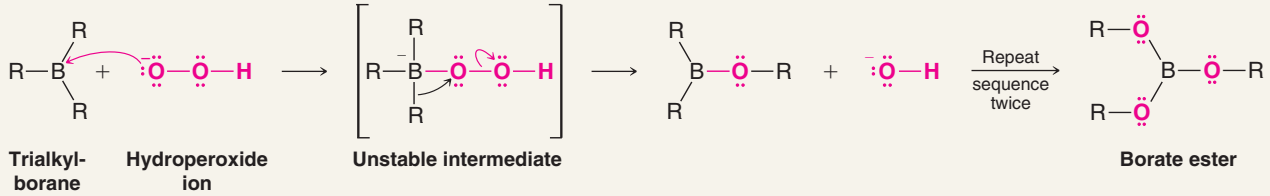
- **The oxidation and hydrolysis steps take place with retention of configuration** at the carbon initially bearing boron and ultimately bearing the hydroxyl group.

We shall see how this occurs by considering the mechanisms of oxidation and hydrolysis.

Alkylborane oxidation begins with addition of a hydroperoxide anion (HOO^-) to the trivalent boron atom. An unstable intermediate is formed that has a formal negative charge on the boron. Migration of an alkyl group with a pair of electrons from the boron to the adjacent oxygen leads to neutralization of the charge on boron and displacement of a hydroxide anion. The alkyl migration takes place with retention of configuration at the migrating carbon. Repetition of the hydroperoxide anion addition and migration steps occurs twice more until all of the alkyl groups have become attached to oxygen atoms, resulting in a trialkyl borate ester, $B(OR)_3$. The borate ester then undergoes basic hydrolysis to produce three molecules of the alcohol and an inorganic borate anion.

A MECHANISM FOR THE REACTION

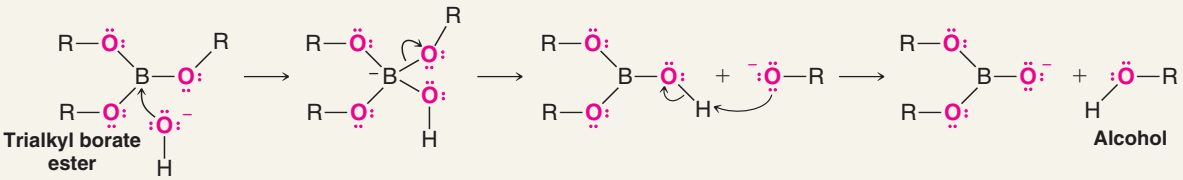
Oxidation of Trialkylboranes



The boron atom accepts an electron pair from the hydroperoxide ion to form an unstable intermediate.

An alkyl group migrates from boron to the adjacent oxygen atom as a hydroxide ion departs. The configuration at the migrating carbon remains unchanged.

Hydrolysis of the Borate Ester



Hydroxide anion attacks the boron atom of the borate ester.

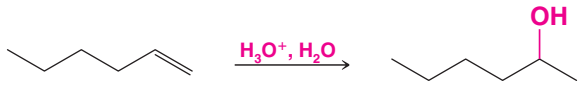
An alkoxide anion departs from the borate anion, reducing the formal change on boron to zero.

Proton transfer completes the formation of one alcohol molecule. The sequence repeats until all three alkoxy groups are released as alcohols and inorganic borate remains.

8.9A Regiochemistry and Stereochemistry of Alkylborane Oxidation and Hydrolysis

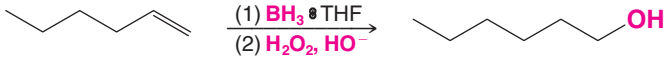
- Hydroboration–oxidation reactions are **regioselective**; the net result of hydroboration–oxidation is **anti-Markovnikov** addition of water to an alkene.
- As a consequence, hydroboration–oxidation gives us a method for the preparation of alcohols that cannot normally be obtained through the acid-catalyzed hydration of alkenes or by oxymercuration–demercuration.

For example, the acid-catalyzed hydration (or oxymercuration–demercuration) of 1-hexene yields 2-hexanol, the Markovnikov addition product.

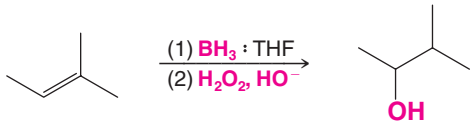


1-Hexene 2-Hexanol

In contrast, hydroboration–oxidation of 1-hexene yields 1-hexanol, the anti-Markovnikov product.



1-Hexene 1-Hexanol (90%)



2-Methyl-2-butene 3-Methyl-2-butanol

- Hydroboration–oxidation reactions are **stereospecific**; the net addition of —H and —OH is **syn**, and if chirality centers are formed, their configuration depends on the stereochemistry of the starting alkene.

Because the oxidation step in the hydroboration–oxidation synthesis of alcohols takes place with retention of configuration, **the hydroxyl group replaces the boron atom where it stands in the alkylboron compound**. The net result of the two steps (hydroboration and oxidation) is the syn addition of —H and —OH. We can review the anti-Markovnikov and syn aspects of hydroboration–oxidation by considering the hydration of 1-methylcyclopentene, as shown in Fig. 8.3.

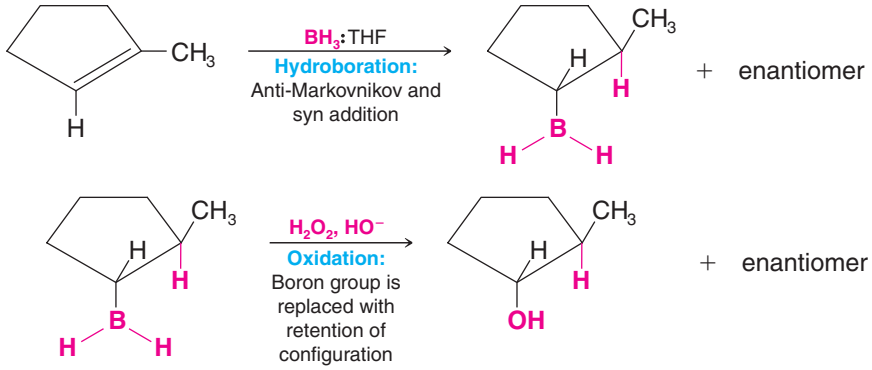
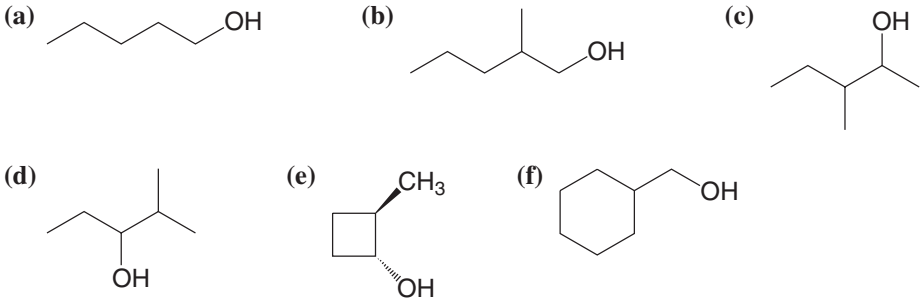


Figure 8.3 The hydroboration–oxidation of 1-methylcyclopentene. The first reaction is a syn addition of borane. In this illustration we have shown the boron and hydrogen entering from the bottom side of 1-methylcyclopentene. The reaction also takes place from the top side at an equal rate to produce the enantiomer. In the second reaction the boron atom is replaced by a hydroxyl group with retention of configuration. The product is *trans*-2-methylcyclopentanol, and the overall result is the syn addition of —H and —OH.

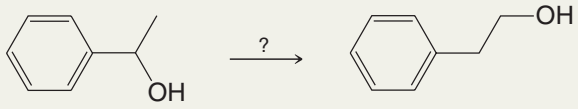
Review Problem 8.13

Specify the appropriate alkene and reagents for synthesis of each of the following alcohols by hydroboration–oxidation.



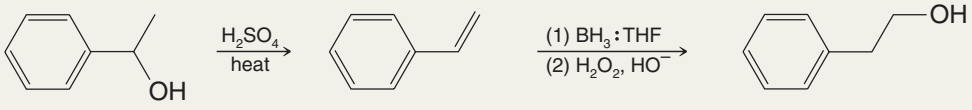
Solved Problem 8.3

Outline a method for carrying out the following conversion.



1-Phenylethanol **2-Phenylethanol**

STRATEGY AND ANSWER Working backward we realize we could synthesize 2-phenylethanol by hydroboration–oxidation of phenylethene (styrene), and that we could make phenylethene by dehydrating 1-phenylethanol.



Phenylethene

8.10 Summary of Alkene Hydration Methods

The three methods we have studied for alcohol synthesis by addition reactions to alkenes have different regiochemical and stereochemical characteristics.

1. Acid-catalyzed hydration of alkenes takes place with Markovnikov regiochemistry but may lead to a mixture of constitutional isomers if the carbocation intermediate in the reaction undergoes rearrangement to a more stable carbocation.
2. Oxymercuration–demercuration occurs with Markovnikov regiochemistry and results in hydration of alkenes without complication from carbocation rearrangement. It is often the preferred choice over acid-catalyzed hydration for Markovnikov addition. The overall stereochemistry of addition in acid-catalyzed hydration and oxymercuration–demercuration is not controlled—they both result in a mixture of cis and trans addition products.
3. Hydroboration–oxidation results in anti-Markovnikov and syn hydration of an alkene.

The complementary regiochemical and stereochemical aspects of these methods provide useful alternatives when we desire to synthesize a specific alcohol by hydration of an alkene. We summarize them here in Table 8.1.

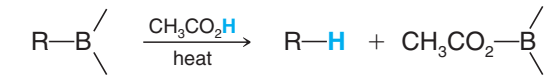
TABLE 8.1 Summary of Methods for Converting an Alkene to an Alcohol

Reaction	Regiochemistry	Stereochemistry[a]	Occurrence of Rearrangements
Acid-catalyzed hydration	Markovnikov addition	Not controlled	Frequent
Oxymercuration–demercuration	Markovnikov addition	Not controlled	Seldom
Hydroboration–oxidation	Anti-Markovnikov addition	Stereospecific: syn addition of H— and —OH	Seldom

[a]All of these methods produce racemic mixtures in the absence of a chiral influence.

8.11 Protonolysis of Alkylboranes

Heating an alkylborane with acetic acid causes cleavage of the carbon–boron bond and replacement with hydrogen:



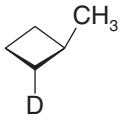
Alkylborane **Alkane**

- Protonolysis of an alkylborane takes place with retention of configuration; hydrogen replaces boron **where it stands** in the alkylborane.
- The overall stereochemistry of hydroboration–protonolysis, therefore, is **syn** (like that of the oxidation of alkylboranes).

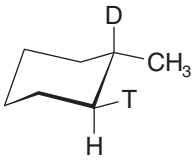
Hydroboration followed by protonolysis of the resulting alkylborane can be used as an alternative method for hydrogenation of alkenes, although catalytic hydrogenation (Section 7.13) is the more common procedure. Reaction of alkylboranes with deuterated or tritiated acetic acid also provides a very useful way to introduce these isotopes into a compound in a specific way.

Review Problem 8.14

Starting with any needed alkene (or cycloalkene) and assuming you have deuterioacetic acid (CH_3CO_2D) available, outline syntheses of the following deuterium-labeled compounds.

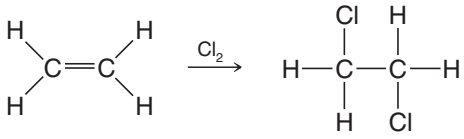
(a) $(CH_3)_2CHCH_2CH_2D$ **(b)** $(CH_3)_2CHCHDCH_3$ **(c)**  (+ enantiomer)

(d) Assuming you also have available BD_3:THF and CH_3CO_2T, can you suggest a synthesis of the following?

 (+ enantiomer)

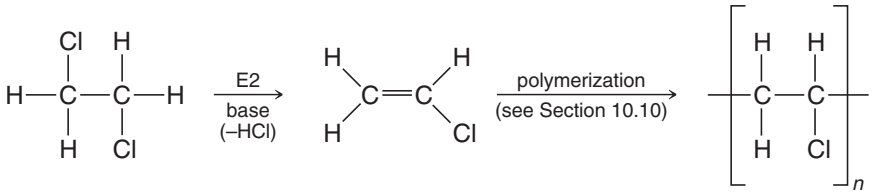
8.12 *Electrophilic Addition of Bromine and Chlorine to Alkenes*

Alkenes react rapidly with bromine and chlorine in nonnucleophilic solvents to form **vicinal dihalides**. An example is the addition of chlorine to ethene.



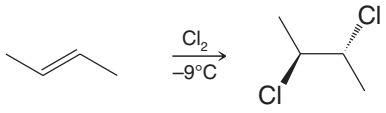
Ethene **1,2-Dichloroethane**

This addition is a useful industrial process because 1,2-dichloroethane can be used as a solvent and can be used to make vinyl chloride, the starting material for poly(vinyl chloride).

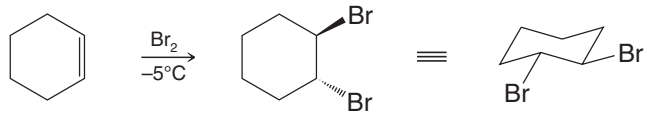


1,2-Dichloroethane **Vinyl chloride** **Poly(vinyl chloride)**

Other examples of the addition of halogens to a double bond are the following:



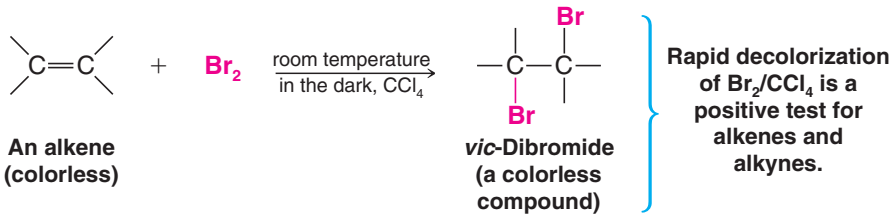
***trans*-2-Butene** ***meso*-1,2-Dichlorobutane**



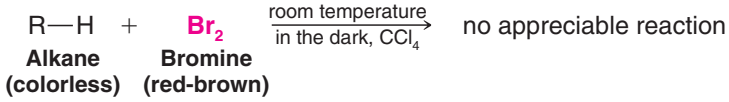
Cyclohexene ***trans*-1,2-Dibromocyclohexane (racemic)**

These two examples show an aspect of these additions that we shall address later when we examine a mechanism for the reaction: **The addition of halogens is an anti addition to the double bond**.

When bromine is used for this reaction, it can serve as a test for the presence of carbon–carbon multiple bonds. If we add bromine to an alkene (or alkyne, see Section 8.18), the red-brown color of the bromine disappears almost instantly as long as the alkene (or alkyne) is present in excess:

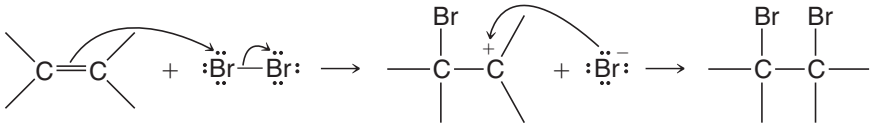


This behavior contrasts markedly with that of **alkanes**. Alkanes do not react appreciably with bromine or chlorine at room temperature and in the absence of light. When alkanes *do* react under those conditions, however, it is by substitution rather than addition and by a mechanism involving radicals that we shall discuss in Chapter 10:



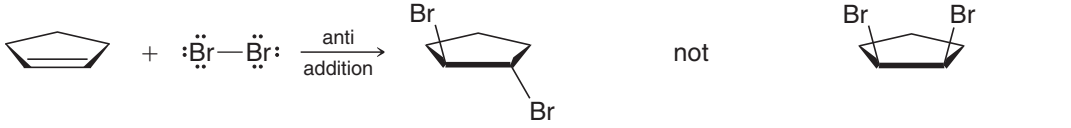
8.12A Mechanism of Halogen Addition

A possible mechanism for the addition of a bromine or chlorine to an alkene is one that involves the formation of a carbocation.



Although this mechanism is similar to ones we have studied earlier, such as the addition of H—X to an alkene, it does not explain an important fact. As we have just seen (in Section 8.12) the addition of bromine or chlorine to an alkene is an **anti addition**.

The addition of bromine to cyclopentene, for example, produces *trans*-1,2-dibromocyclopentane, not *cis*-1,2-dibromocyclopentane.



***trans*-1,2-Dibromocyclopentane**
(as a racemic mixture)

***cis*-1,2-Dibromocyclohexane**
(a meso compound)

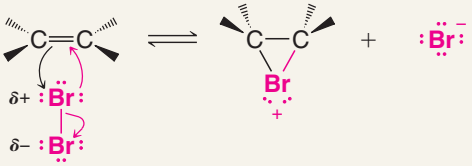
A mechanism that explains anti addition is one in which a bromine molecule transfers a bromine atom to the alkene to form a cyclic **bromonium ion** and a bromide ion, as shown in step 1 of "A Mechanism for the Reaction" that follows. The cyclic bromonium ion causes net anti addition, as follows.

In step 2, a bromide ion attacks the back side of either carbon 1 or carbon 2 of the bromonium ion (an S_N2 process) to open the ring and produce the *trans*-1,2-dibromide. Attack occurs from the side **opposite the bromine of the bromonium ion** because attack from this direction is unhindered. Attack at the other carbon of the cyclic bromonium ion produces the enantiomer.

A MECHANISM FOR THE REACTION

Addition of Bromine to an Alkene

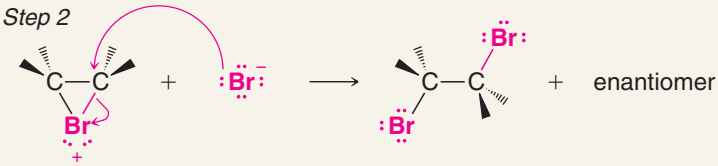
Step 1



Bromonium ion **Bromide ion**

As a bromine molecule approaches an alkene, the electron density of the alkene π bond repels electron density in the closer bromine, polarizing the bromine molecule and making the closer bromine atom electrophilic. The alkene donates a pair of electrons to the closer bromine, causing displacement of the distant bromine atom. As this occurs, the newly bonded bromine atom, due to its size and polarizability, donates an electron pair to the carbon that would otherwise be a carbocation, thereby stabilizing the positive charge by delocalization. The result is a bridged bromonium ion intermediate.

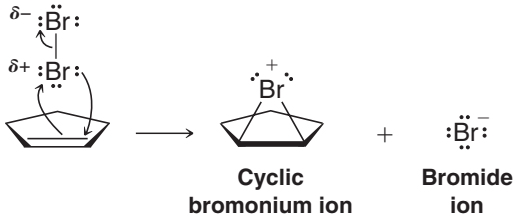
Step 2

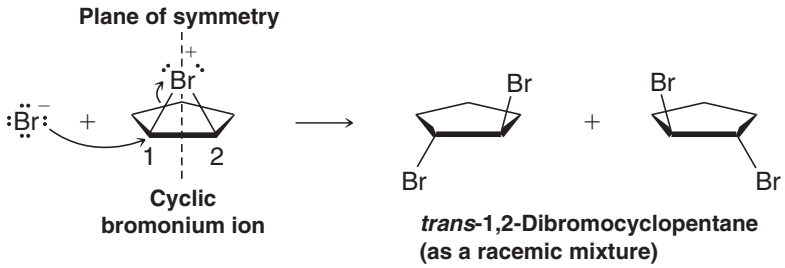


Bromonium ion **Bromide ion** ***vic*-Dibromide**

A bromide anion attacks at the back side of one carbon (or the other) of the bromonium ion in an S_N2 reaction, causing the ring to open and resulting in the formation of a *vic*-dibromide.

This process is shown for the addition of bromine to cyclopentene below.

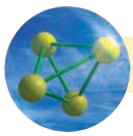




Attack at either carbon of the cyclopentene bromonium ion is equally likely because the cyclic bromonium ion is symmetric. It has a vertical plane of symmetry passing through the bromine atom and halfway between carbons 1 and 2. The *trans*-dibromide, therefore, is formed as a racemic mixture.

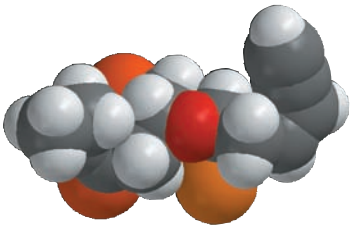
The mechanisms for addition of Cl_2 and I_2 to alkenes are similar to that for Br_2, involving formation and ring opening of their respective **halonium ions**.

As with bridged mercurinium ions, the bromonium ion does not necessarily have symmetrical charge distribution at its two carbon atoms. If one carbon of the bromonium ion



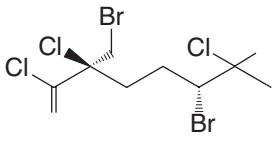
THE CHEMISTRY OF . . .

The Sea: A Treasury of Biologically Active Natural Products

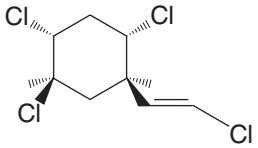


Dactylyne, a halogenated marine natural product.

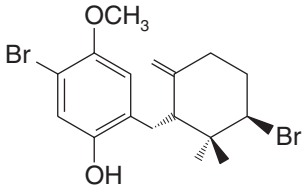
The world's oceans are a vast storehouse of dissolved halide ions. The concentration of halides in the ocean is approximately 0.5 *M* in chloride, 1 m*M* in bromide, and 1 μM in iodide ions. Perhaps it is not surprising, then, that marine organisms have incorporated halogen atoms into the structures of many of their metabolites. Among these are such intriguing polyhalogenated compounds as halomon, dactylyne, tetrachloromertensene, (3*E*)-laureatin, and (3*R*)- and (3*S*)-cyclocymopol. Just the sheer number of halogen atoms in these metabolites is cause for wonder. For the organisms that make them, some of these molecules are part of defense mechanisms that serve to promote the species' survival by deterring predators or inhibiting the growth of competing organisms. For humans, the vast resource of marine natural products shows ever-greater potential as a source of new therapeutic agents. Halomon, for example, is in preclinical evaluation as a cytotoxic agent against certain tumor cell types, dactylyne is an inhibitor of pentobarbital metabolism, and the cyclocymopol enantiomers show agonistic or antagonistic effects on the human progesterone receptor, depending on which enantiomer is used.



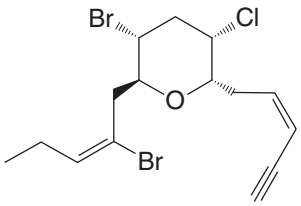
Halomon



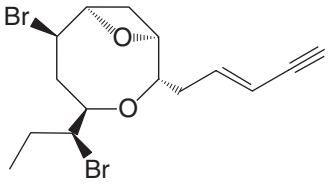
Tetrachloromertensene



Cyclocymopol monomethyl ether



Dactylyne



(3*E*)-Laureatin

The biosynthesis of certain halogenated marine natural products is intriguing. Some of their halogens appear to have been introduced as *electrophiles* rather than as Lewis bases or nucleophiles, which is their character when they are solutes in seawater. But how do marine organisms transform nucleophilic halide anions into *electrophilic* species for incorporation into their metabolites? It happens that many marine organisms have enzymes called haloperoxidases that convert nucleophilic iodide, bromide, or chloride anions into electrophilic species that react like I^+, Br^+, or Cl^+. In the biosynthetic schemes proposed for some halogenated natural products, positive halogen intermediates are attacked by electrons from the π bond of an alkene or alkyne in what is called an addition reaction.

The final Learning Group Problem for this chapter asks you to propose a scheme for biosynthesis of the marine natural product kumepaloxane by electrophilic halogen addition. Kumepaloxane is a fish antifeedant synthesized by the Guam bubble snail *Haminoea cymbalum*, presumably as a defense mechanism for the snail. In later chapters we shall see other examples of truly remarkable marine natural products, such as brevetoxin B, associated with deadly "red tides," and eleutherobin, a promising anticancer agent.

is more highly substituted than the other, and therefore able to stabilize positive charge better, it may bear a greater fraction of positive charge than the other carbon (i.e., the positively charged bromine draws electron density from the two carbon atoms of the ring,

but not equally if they are of different substitution). Consequently, the more positively charged carbon may be attacked by the reaction nucleophile more often than the other carbon. However, in reactions with symmetrical reagents (e.g., Br_2, Cl_2, and I_2) there is no observed difference. (We shall discuss this point further in Section 8.14, where we will study a reaction where we can discern regioselectivity of attack on a halonium ion by the nucleophile.)

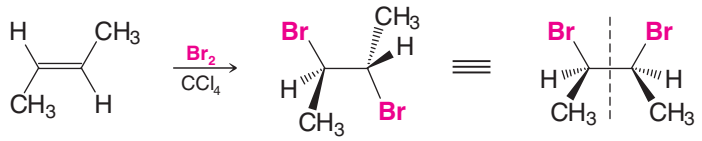
8.13 Stereospecific Reactions

The anti addition of a halogen to an alkene provides us with an example of what is called a **stereospecific reaction**.

- A reaction is stereospecific when a particular stereoisomeric form of the starting material reacts by a mechanism that gives a specific stereoisomeric form of the product.

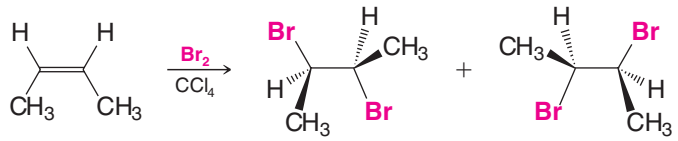
Consider the reactions of *cis*- and *trans*-2-butene with bromine shown below. When *trans*-2-butene adds bromine, the product is the meso compound, (2*R*,3*S*)-2,3-dibromobutane. When *cis*-2-butene adds bromine, the product is a *racemic mixture* of (2*R*,3*R*)-2,3-dibromobutane and (2*S*,3*S*)-2,3-dibromobutane:

Reaction 1



***trans*-2-Butene** **(2*R*,3*S*)-2,3-Dibromobutane (a meso compound)**

Reaction 2



***cis*-2-Butene** **(2*R*,3*R*)** **(2*S*,3*S*)**

(a pair of enantiomers)

The reactants *cis*-2-butene and *trans*-2-butene are stereoisomers; they are *diastereomers*. The product of reaction 1, (2*R*,3*S*)-2,3-dibromobutane, is a meso compound, and it is a stereoisomer of both of the products of reaction 2 (the enantiomeric 2,3-dibromobutanes). Thus, by definition, both reactions are stereospecific. One stereoisomeric form of the reactant (e.g., *trans*-2-butene) gives one product (the meso compound), whereas the other stereoisomeric form of the reactant (*cis*-2-butene) gives a stereoisomerically different product (the enantiomers).

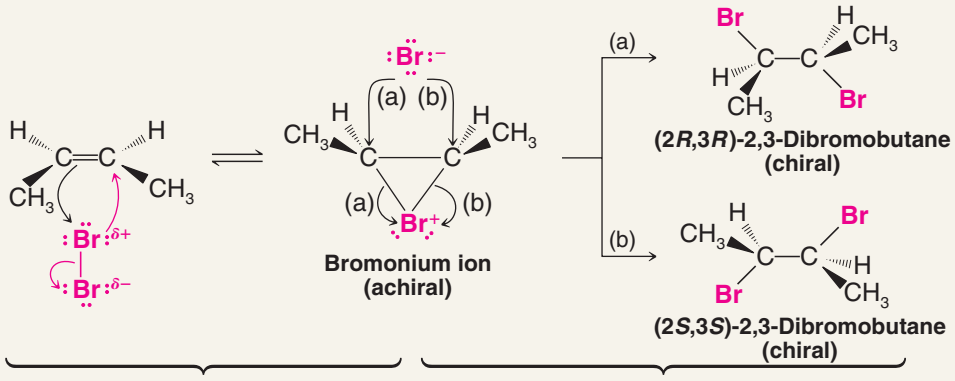
We can better understand the results of these two reactions if we examine their mechanisms. The first mechanism in the following box shows how *cis*-2-butene adds bromine to yield intermediate bromonium ions that are achiral. (The bromonium ion has a plane of symmetry.) These bromonium ions can then react with bromide ions by either path (a) or path (b). Reaction by path (a) yields one 2,3-dibromobutane enantiomer; reaction by path (b) yields the other enantiomer. The reaction occurs at the same rate by either path; therefore, the two enantiomers are produced in equal amounts (as a racemic form).

The second mechanism in the box shows how *trans*-2-butene reacts at the bottom face to yield an intermediate bromonium ion that is chiral. (Reaction at the other face would produce the enantiomeric bromonium ion.) Reaction of this chiral bromonium ion (or its enantiomer) with a bromide ion either by path (a) or by path (b) yields the same achiral product, *meso*-2,3-dibromobutane.

THE STEREOCHEMISTRY OF THE REACTION

Addition of Bromine to *cis*- and *trans*-2-Butene

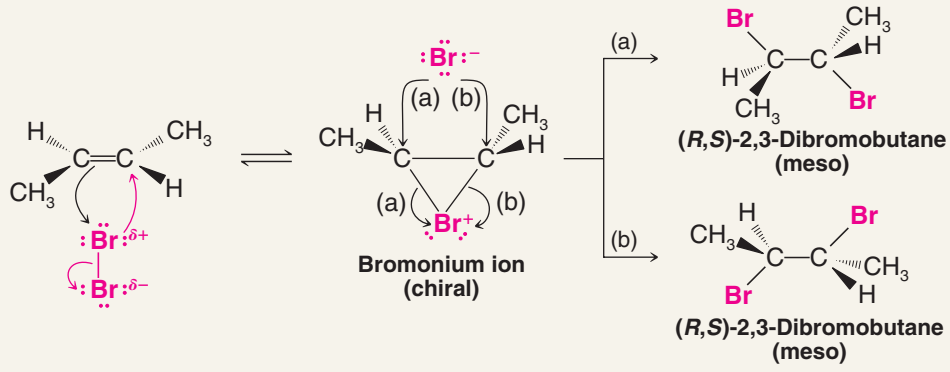
cis-2-Butene reacts with bromine to yield the enantiomeric 2,3-dibromobutanes by the following mechanism:



***cis*-2-Butene reacts with bromine to yield an achiral bromonium ion and a bromide ion. [Reaction at the other face of the alkene (top) would yield the same bromonium ion.]**

The bromonium ion reacts with the bromide ions at equal rates by paths (a) and (b) to yield the two enantiomers in equal amounts (i.e., as the racemic form).

trans-2-Butene reacts with bromine to yield *meso*-2,3-dibromobutane.



***trans*-2-Butene reacts with bromine to yield chiral bromonium ions and bromide ions. [Reaction at the other face (top) would yield the enantiomer of the bromonium ion as shown here.]**

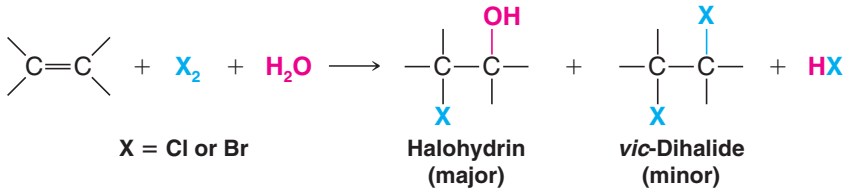
When the bromonium ions react by either path (a) or path (b), they yield the *same* achiral meso compound. (Reaction of the enantiomer of the intermediate bromonium ion would produce the same result.)

8.14 Halohydrin Formation

- When the halogenation of an alkene is carried out in aqueous solution, rather than in a non-nucleophilic solvent, the major product is a **halohydrin** (also called a halo alcohol) instead of a *vic*-dihalide.

Molecules of water react with the halonium ion intermediate as the predominant nucleophile because they are in high concentration (as the solvent). The result is formation of a halo-

hydrin as the major product. If the halogen is bromine, it is called a **bromohydrin**, and if chlorine, a **chlorohydrin**.

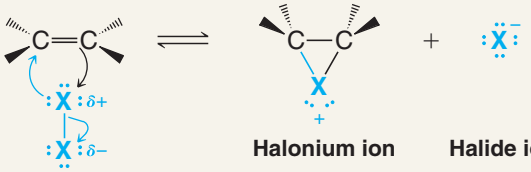


Halohydrin formation can be described by the following mechanism.

A MECHANISM FOR THE REACTION

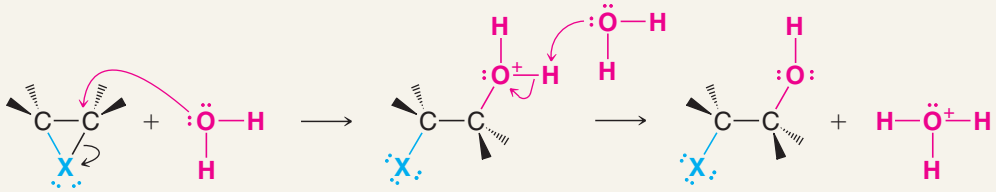
Halohydrin Formation from an Alkene

Step 1



This step is the same as for halogen addition to an alkene (see Section 8.12A).

Steps 2 and 3



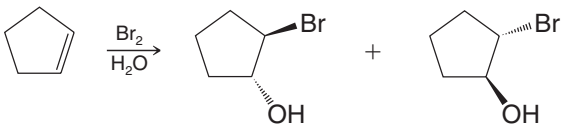
Here, however, a water molecule acts as the nucleophile and attacks a carbon of the ring, causing the formation of a protonated halohydrin.

The protonated halohydrin loses a proton (it is transferred to a molecule of water). This step produces the halohydrin and hydronium ion.

The first step is the same as that for halogen addition. In the second step, however, the two mechanisms differ. In halohydrin formation, water acts as the nucleophile and attacks one carbon atom of the halonium ion. The three-membered ring opens, and a protonated halohydrin is produced. Loss of a proton then leads to the formation of the halohydrin itself.

Review Problem 8.15

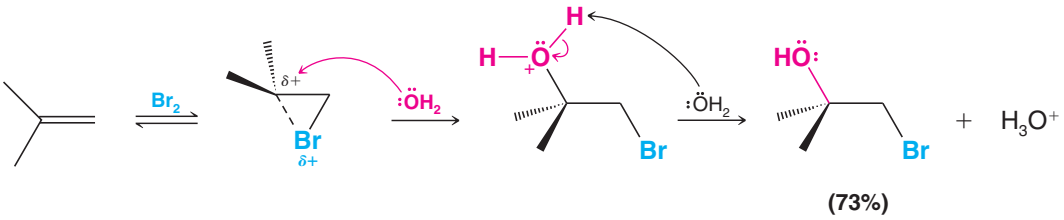
Write a mechanism to explain the following reaction.



(as a racemic mixture)

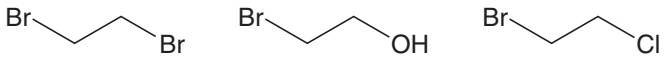
- If the alkene is unsymmetrical, the halogen ends up on the carbon atom with the greater number of hydrogen atoms.

Bonding in the intermediate bromonium ion is *unsymmetrical*. The more highly substituted carbon atom bears the greater positive charge because it resembles the more stable carbocation. Consequently, water attacks this carbon atom preferentially. The greater positive charge on the tertiary carbon permits a pathway with a lower free energy of activation even though attack at the primary carbon atom is less hindered:



Review Problem 8.16

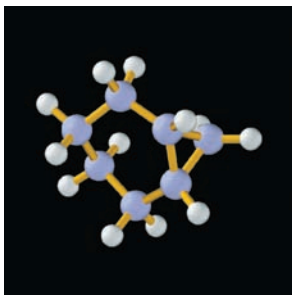
When ethene gas is passed into an aqueous solution containing bromine and sodium chloride, the products of the reaction are the following:



Write mechanisms showing how each product is formed.

8.15 Divalent Carbon Compounds: Carbenes

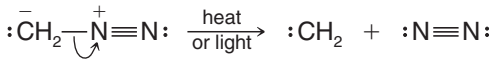
There is a group of compounds in which carbon forms only *two bonds*. These neutral divalent carbon compounds are called **carbenes**. Most carbenes are highly unstable compounds that are capable of only fleeting existence. Soon after carbenes are formed, they usually react with another molecule. The reactions of carbenes are especially interesting because, in many instances, the reactions show a remarkable degree of stereospecificity. The reactions of carbenes are also of great synthetic use in the preparation of compounds that have three-membered rings, for example, bicyclo[4.1.0]heptane, shown at right.



Bicyclo[4.1.0]heptane.

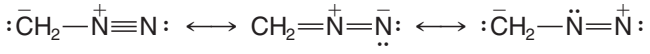
8.15A Structure and Reactions of Methylene

The simplest carbene is the compound called **methylene** ($:CH_2$). Methylene can be prepared by the decomposition of diazomethane (CH_2N_2), a very poisonous yellow gas. This decomposition can be accomplished by heating diazomethane (thermolysis) or by irradiating it with light of a wavelength that it can absorb (photolysis):



Diazomethane **Methylene** **Nitrogen**

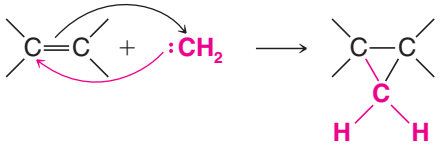
The structure of diazomethane is actually a resonance hybrid of three structures:



I **II** **III**

We have chosen resonance structure **I** to illustrate the decomposition of diazomethane because with **I** it is readily apparent that heterolytic cleavage of the carbon–nitrogen bond results in the formation of methylene and molecular nitrogen.

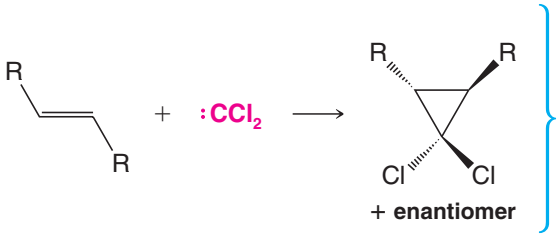
Methylene reacts with alkenes by adding to the double bond to form cyclopropanes:



Alkene **Methylene** **Cyclopropane**

8.15B Reactions of Other Carbenes: Dihalocarbenes

Dihalocarbenes are also frequently employed in the synthesis of cyclopropane derivatives from alkenes. Most reactions of dihalocarbenes are stereospecific:



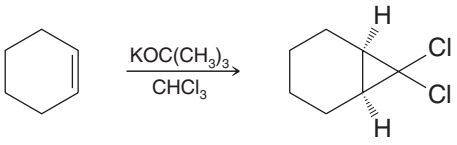
The addition of $:CX_2$ is stereospecific. If the R groups of the alkene are trans, they will be trans in the product. (If the R groups were initially cis, they would be cis in the product.)

Dichlorocarbene can be synthesized by the ***α elimination*** of the elements of hydrogen chloride from chloroform. [The hydrogen of chloroform is mildly acidic ($pK_a \approx 24$) due to the inductive effect of the chlorine atoms.] This reaction resembles the β-elimination reactions by which alkenes are synthesized from alkyl halides (Section 6.15):

Dichlorocarbene

Compounds *with a β hydrogen* react by β elimination preferentially. Compounds with no β hydrogen but with an α hydrogen (such as chloroform) react by α elimination.

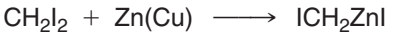
A variety of cyclopropane derivatives have been prepared by generating dichlorocarbene in the presence of alkenes. Cyclohexene, for example, reacts with dichlorocarbene generated by treating chloroform with potassium *tert*-butoxide to give a bicyclic product:



7,7-Dichlorobicyclo[4.1.0]heptane (59%)

8.15C Carbenoids: The Simmons–Smith Cyclopropane Synthesis

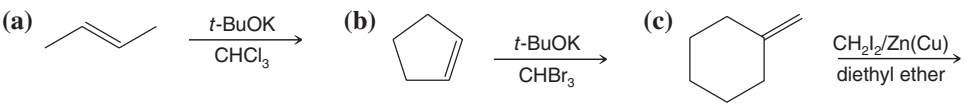
A useful cyclopropane synthesis was developed by H. E. Simmons and R. D. Smith of the DuPont Company. In this synthesis diiodomethane and a zinc–copper couple are stirred together with an alkene. The diiodomethane and zinc react to produce a carbene-like species called a **carbenoid**:



A carbenoid

The carbenoid then brings about the stereospecific addition of a CH_2 group directly to the double bond.

Review Problem 8.17 What products would you expect from each of the following reactions?



Review Problem 8.18 Starting with cyclohexene and using any other needed reagents, outline a synthesis of 7,7-dibromobicyclo[4.1.0]heptane.

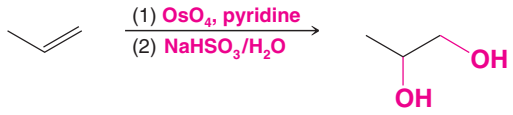
Review Problem 8.19 Treating cyclohexene with 1,1-diiodoethane and a zinc–copper couple leads to two isomeric products. What are their structures?

8.16 Oxidation of Alkenes: Syn 1,2-Dihydroxylation

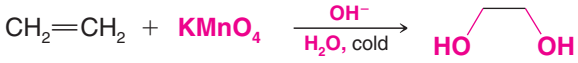
Alkenes undergo a number of reactions in which the carbon–carbon double bond is oxidized.

- **1,2-Dihydroxylation** is an important oxidative addition reaction of alkenes.

Osmium tetroxide is widely used to synthesize **1,2-diols** (the products of 1,2-dihydroxylation, sometimes also called **glycols**). Potassium permanganate can also be used, although because it is a stronger oxidizing agent it is prone to cleave the diol through further oxidation (Section 8.17).



Propene — **1,2-Propanediol (propylene glycol)**

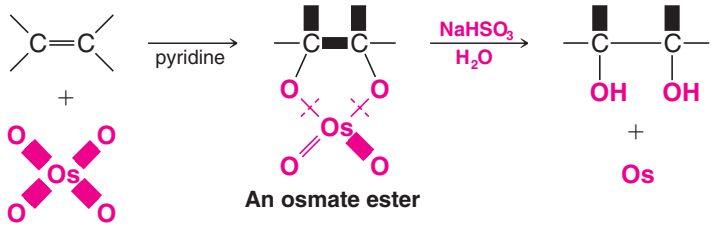


Ethene — **1,2-Ethanediol (ethylene glycol)**

8.16A Mechanism for Syn Dihydroxylation of Alkenes

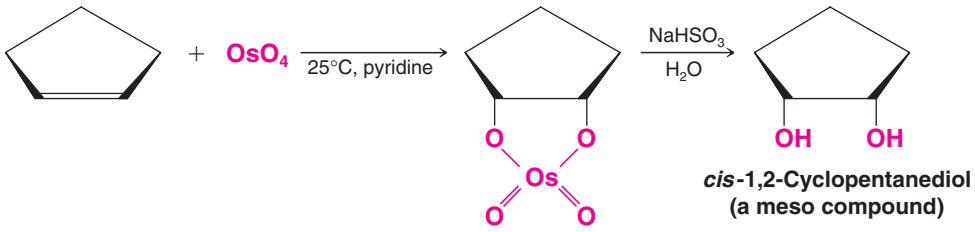
- The mechanism for the formation of a 1,2-diol by osmium tetroxide involves a cyclic intermediate that results in **syn addition** of the oxygen atoms (see below).

After formation of the cyclic intermediate with osmium, cleavage at the oxygen–metal bonds takes place without altering the stereochemistry of the two new C—O bonds.



An osmate ester

The syn stereochemistry of this dihydroxylation can readily be observed by the reaction of cyclopentene with osmium tetroxide. The product is *cis*-1,2-cyclopentanediol.



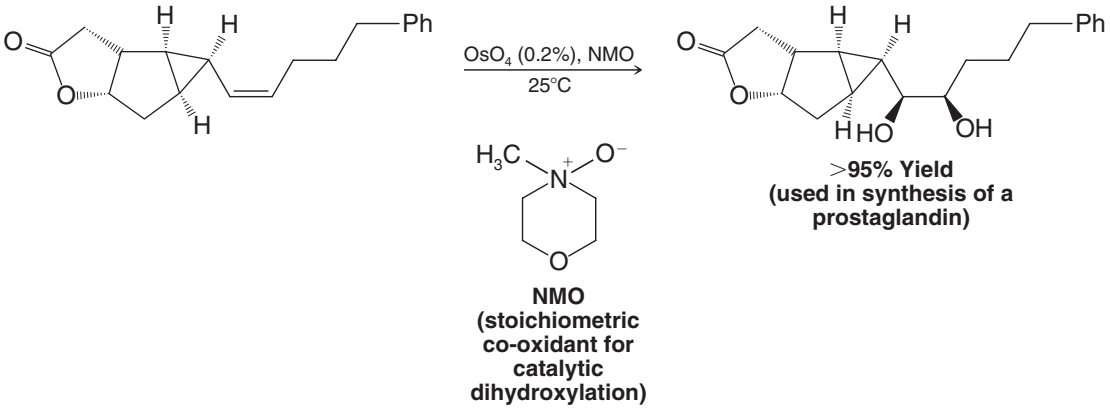
***cis*-1,2-Cyclopentanediol (a meso compound)**

Osmium tetroxide is highly toxic, volatile, and very expensive. For these reasons, methods have been developed that permit OsO_4 to be used *catalytically* in conjunction with a co-oxidant.* A very small molar percentage of OsO_4 is placed in the reaction mixture to do the dihydroxylation step, while a stoichiometric amount of co-oxidant reoxidizes the OsO_4 as it

*See Nelson, D. W., et al., *J. Am. Chem. Soc.* **1997**, *119*, 1840–1858; and Corey, E. J., et al., *J. Am. Chem. Soc.* **1996**, *118*, 319–329.

is used in each cycle, allowing oxidation of the alkene to continue until all has been converted to the diol. *N*-Methylmorpholine *N*-oxide (NMO) is one of the most commonly used co-oxidants with catalytic OsO_4. The method was discovered at Upjohn Corporation in the context of reactions for synthesis of a prostaglandin* (Section 23.5):

Catalytic OsO_4 1,2-Dihydroxylation

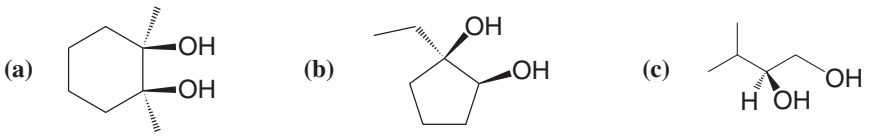


>95% Yield (used in synthesis of a prostaglandin)

NMO (stoichiometric co-oxidant for catalytic dihydroxylation)

Review Problem 8.20

Specify the alkene and reagents needed to synthesize each of the following diols.

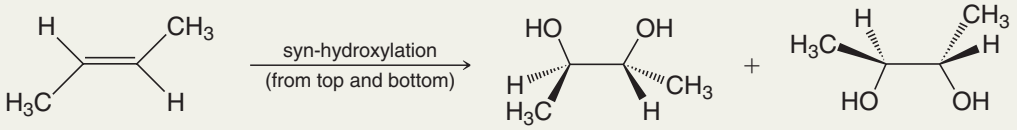


(racemic) **(racemic)**

Solved Problem 8.4

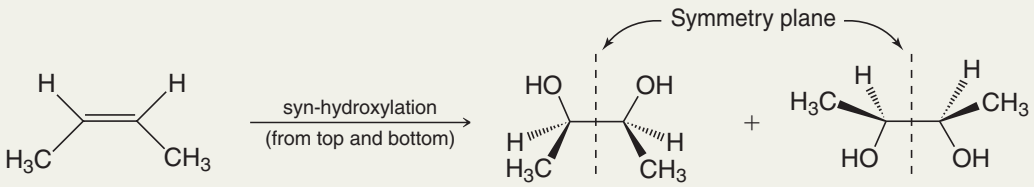
Explain the following facts: Treating (*Z*)-2-butene with OsO_4 in pyridine and then $NaHSO_3$ in water gives a diol that is optically inactive and cannot be resolved. Treating (*E*)-2-butene with the same reagents gives a diol that is optically inactive but can be resolved into enantiomers.

STRATEGY AND ANSWER Recall that the reaction in either instance results in syn hydroxylation of the double bond of each compound. Syn hydroxylation of (*E*)-2-butene gives a pair of enantiomers, while syn hydroxylation of (*Z*)-2-butene gives a single product that is a meso compound.



(*E*)-2-Butene

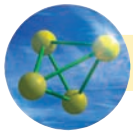
Enantiomers (separable and when separated, optically active)



(*Z*)-2-Butene

Identical (a meso compound)

*Van Rheenan, V., Kelley, R. C., and Cha, D. Y., *Tetrahedron Lett*. **1976**, *25*, 1973.

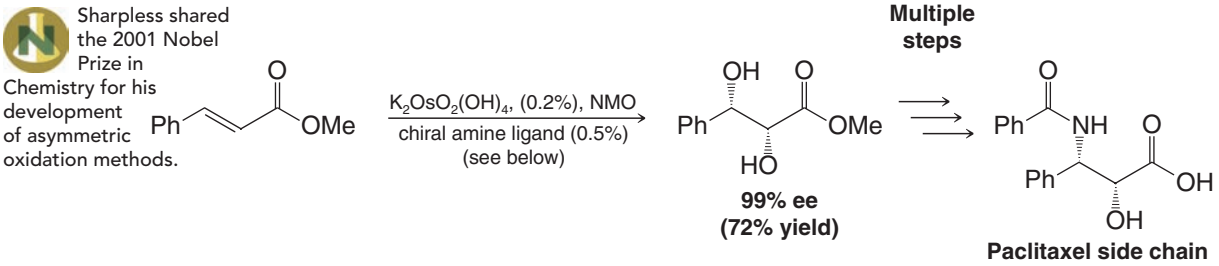


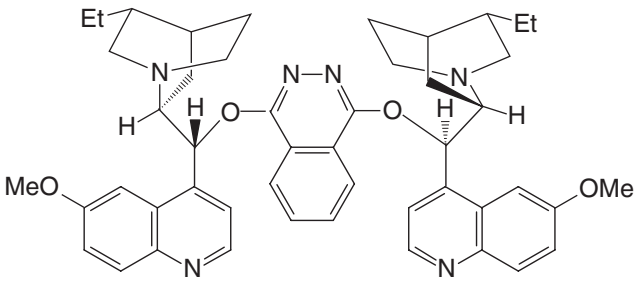
THE CHEMISTRY OF . . .

Catalytic Asymmetric Dihydroxylation

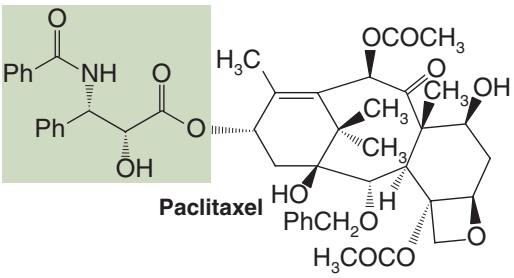
Methods for catalytic *asymmetric* syn dihydroxylation have been developed that significantly extend the synthetic utility of dihydroxylation. K. B. Sharpless (The Scripps Research Institute) and co-workers discovered that addition of a chiral amine to the oxidizing mixture leads to enantioselective catalytic syn dihydroxylation. Asymmetric dihydroxylation has become an important and widely used tool in the synthesis of complex organic molecules. In recognition of this and other advances in asymmetric oxidation procedures developed by his group (Section 11.13), Sharpless was awarded half of the 2001 Nobel Prize in Chemistry. (The other half of the 2001 prize was awarded to W. Knowles and R. Noyori for their development of catalytic asymmetric reduction reactions; see Section 7.14A.) The following reaction, involved in an enantioselective synthesis of the side chain of the anticancer drug paclitaxel (Taxol), serves to illustrate Sharpless's catalytic asymmetric dihydroxylation. The example utilizes a catalytic amount of $K_2OsO_2(OH)_4$, an OsO_4 equivalent, a chiral amine ligand to induce enantioselectivity, and NMO as the stoichiometric co-oxidant. The product is obtained in 99% enantiomeric excess (ee):

Asymmetric Catalytic OsO_4 1,2-Dihydroxylation*





A chiral amine ligand used in catalytic asymmetric dihydroxylation



Adapted with permission from Sharpless et al., *The Journal of Organic Chemistry, Vol. 59*, p. 5104, 1994. Copyright 1994 American Chemical Society.

8.17 Oxidative Cleavage of Alkenes

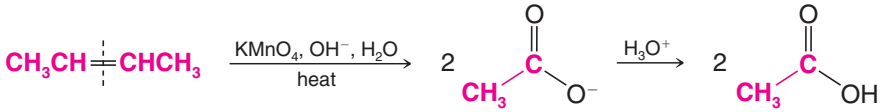
Alkenes can be **oxidatively cleaved** using potassium permanganate or ozone (as well as by other reagents). Potassium permanganate ($KMnO_4$) is used when strong oxidation is needed. Ozone (O_3) is used when mild oxidation is desired. [Alkynes and aromatic rings are also oxidized by $KMnO_4$ and O_3 (Sections 8.20 and 15.13D).]

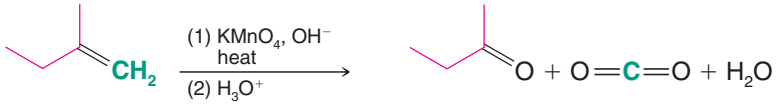
8.17A Cleavage with Hot Basic Potassium Permanganate

- Treatment with hot basic potassium permanganate oxidatively cleaves the double bond of an alkene.

Cleavage is believed to occur via a cyclic intermediate similar to the one formed with osmium tetroxide (Section 8.16A) and intermediate formation of a 1,2-diol. Alkenes with monosubstituted carbon atoms are oxidatively cleaved to salts of carboxylic acids.

Disubstituted alkene carbons are oxidatively cleaved to ketones. Unsubstituted alkene carbons are oxidized to carbon dioxide. The following examples illustrate the results of potassium permanganate cleavage of alkenes with different substitution patterns. In the case where the product is a carboxylate salt, an acidification step is required to obtain the carboxylic acid.



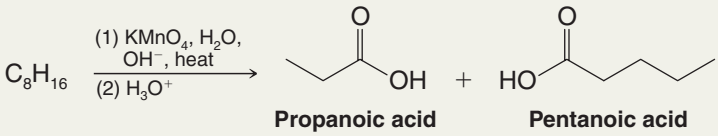


One of the uses of potassium permanganate, other than for desired oxidative cleavage, is as a chemical test for the presence of unsaturation in an unknown compound. Solutions of potassium permanganate are purple. If an alkene is present (or an alkyne, Section 8.20), the purple color is discharged and a brown precipitate of manganese dioxide (MnO_2) forms as the oxidation takes place.

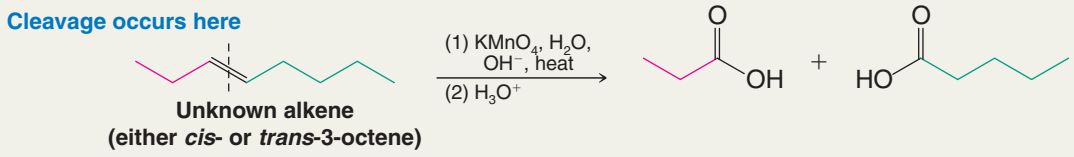
The oxidative cleavage of alkenes has also been used to establish the location of the double bond in an alkene chain or ring. The reasoning process requires us to think backward much as we do with retrosynthetic analysis. Here we are required to work backward from the products to the reactant that might have led to those products. We can see how this might be done with the following example.

Solved Problem 8.5

An unknown alkene with the formula C_8H_{16} was found, on oxidation with hot basic permanganate, to yield a three-carbon carboxylic acid (propanoic acid) and a five-carbon carboxylic acid (pentanoic acid). What was the structure of this alkene?



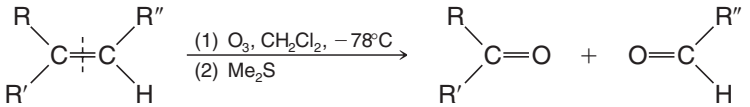
STRATEGY AND ANSWER The carbonyl groups in the products are the key to seeing where the oxidative cleavage occurred. Therefore, oxidative cleavage must have occurred as follows, and the unknown alkene must have been *cis*- or *trans*-3-octene, which is consistent with the molecular formula given.



8.17B Cleavage with Ozone

- The most useful method for cleaving alkenes is to use ozone (O_3).

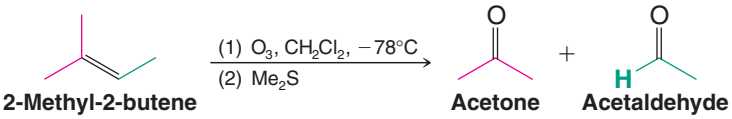
Ozonolysis consists of bubbling ozone into a very cold (−78°C) solution of the alkene in CH_2Cl_2, followed by treatment of the solution with dimethyl sulfide (or zinc and acetic acid). The overall result is as follows:

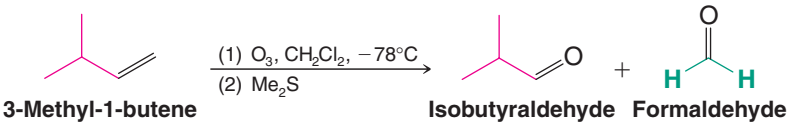


The reaction is useful as a synthetic tool, as well as a method for determining the location of a double bond in an alkene by reasoning backward from the structures of the products.

- The overall process (above) results in alkene cleavage at the double bond, with each carbon of the double bond becoming doubly bonded to an oxygen atom.

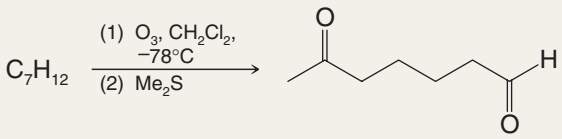
The following examples illustrate the results for each type of alkene carbon.



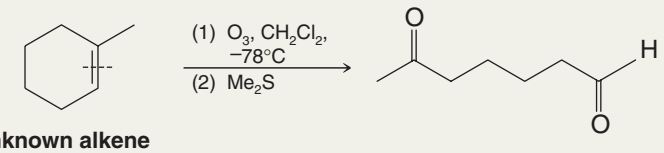


Solved Problem 8.6

Give the structure of an unknown alkene with the formula C_7H_{12} that undergoes ozonolysis to yield, after acidification, *only the following product*:



STRATEGY AND ANSWER Since there is only a single product containing the same number of carbon atoms as the reactant, the only reasonable explanation is that the reactant has a double bond contained in a ring. Ozonolysis of the double bond opens the ring:

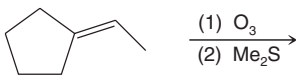


Unknown alkene (1-methylcyclohexene)

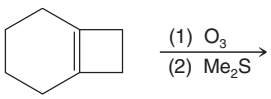
Review Problem 8.21

Predict the products of the following ozonolysis reactions.

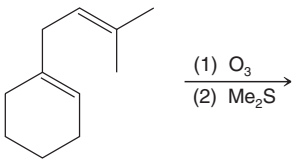
(a)



(b)



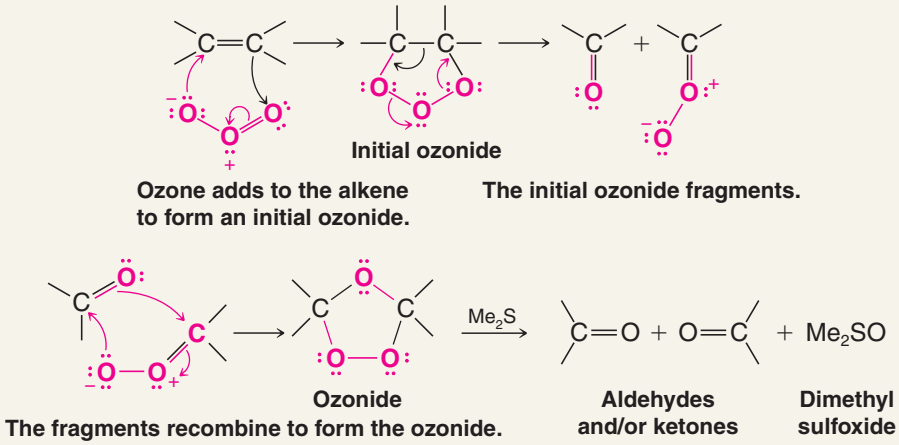
(c)



The mechanism of ozone addition to alkenes begins with formation of unstable compounds called *initial ozonides* (sometimes called molozonides). The process occurs vigorously and leads to spontaneous (and sometimes noisy) rearrangement to compounds known as **ozonides.** The rearrangement is believed to occur with dissociation of the initial ozonide into reactive fragments that recombine to yield the ozonide. Ozonides are very unstable compounds, and low-molecular-weight ozonides often explode violently.

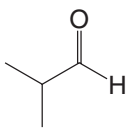
A MECHANISM FOR THE REACTION

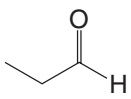
Ozonolysis of an Alkene

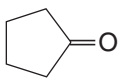
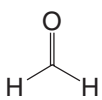


Review Problem 8.22

Write the structures of the alkenes that would yield the following carbonyl compounds when treated with ozone and then with dimethyl sulfide.

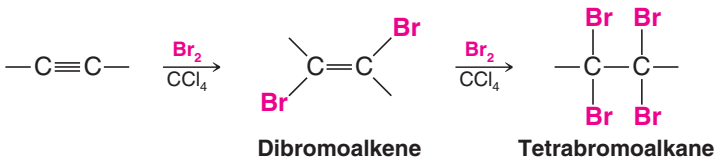
(a)  and 

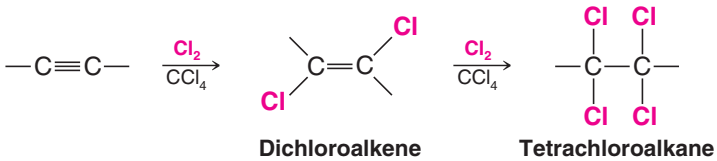
(b)  (2 mol is produced from 1 mol of alkene)

(c)  and 

8.18 *Electrophilic Addition of Bromine and Chlorine to Alkynes*

- Alkynes show the same kind of addition reactions with chlorine and bromine that alkenes do.
- With alkynes **the addition may occur once or twice**, depending on the number of molar equivalents of halogen we employ:

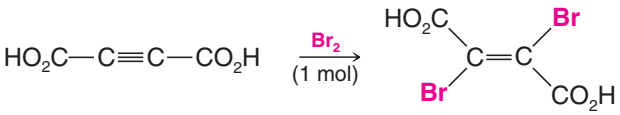




It is usually possible to prepare a dihaloalkene by simply adding one molar equivalent of the halogen:

- Addition of one molar equivalent of chlorine or bromine to an alkyne generally results in anti addition and yields a *trans*-dihaloalkene.

Addition of bromine to acetylenedicarboxylic acid, for example, gives the trans isomer in 70% yield:



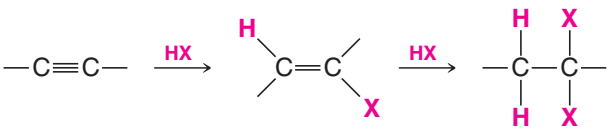
Acetylenedicarboxylic acid **(70%)**

Alkenes are more reactive than alkynes toward addition of electrophilic reagents (i.e., Br_2, Cl_2, or HCl). Yet when alkynes are treated with one molar equivalent of these same electrophilic reagents, it is easy to stop the addition at the "alkene stage." This appears to be a paradox and yet it is not. Explain.

Review Problem 8.23

8.19 Addition of Hydrogen Halides to Alkynes

- Alkynes react with one molar equivalent of hydrogen chloride or hydrogen bromide to form haloalkenes, and with two molar equivalents to form geminal dihalides.
- Both additions are regioselective and follow Markovnikov's rule:

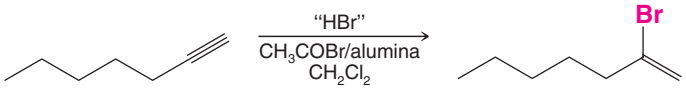


Haloalkene ***gem*-Dihalide**

The hydrogen atom of the hydrogen halide becomes attached to the carbon atom that has the greater number of hydrogen atoms. 1-Hexyne, for example, reacts slowly with one molar equivalent of hydrogen bromide to yield 2-bromo-1-hexene and with two molar equivalents to yield 2,2-dibromohexane:

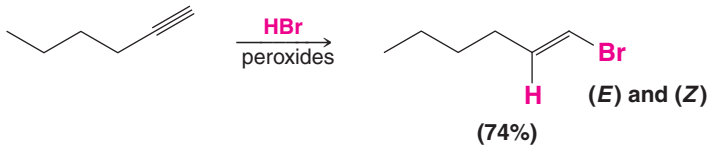
2-Bromo-1-hexene **2,2-Dibromohexane**

The addition of HBr to an alkyne can be facilitated by using acetyl bromide (CH_3COBr) and alumina instead of aqueous HBr. Acetyl bromide acts as an HBr precursor by reacting with the alumina to generate HBr. For example, 1-heptyne can be converted to 2-bromo-1-heptene in good yield using this method:



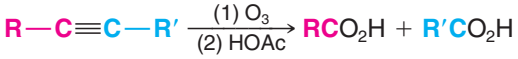
(82%)

Anti-Markovnikov addition of hydrogen bromide to alkynes occurs when peroxides are present in the reaction mixture. These reactions take place through a free-radical mechanism (Section 10.9):

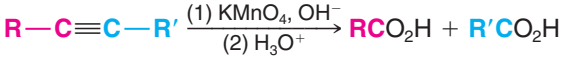


8.20 Oxidative Cleavage of Alkynes

Treating alkynes with ozone followed by acetic acid, or with basic potassium permanganate followed by acid, leads to cleavage at the carbon–carbon triple bond. The products are carboxylic acids:

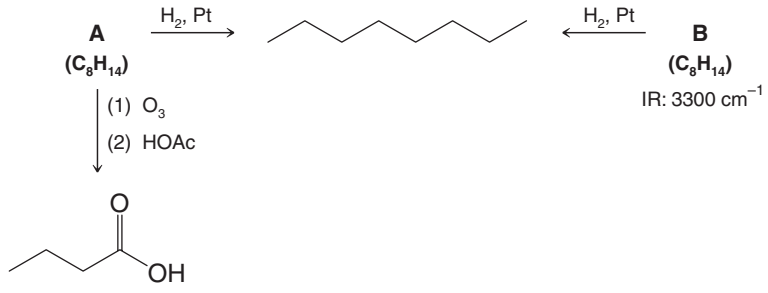


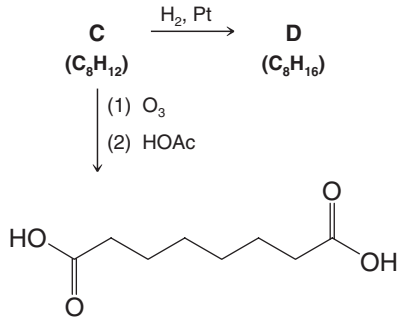
or



Review Problem 8.24

A, **B**, and **C** are alkynes. Elucidate their structures and that of **D** using the following reaction roadmap.





8.21 How to Plan a Synthesis: Some Approaches and Examples

In planning a synthesis we often have to consider four interrelated aspects:

1. construction of the carbon skeleton,
2. functional group interconversions,
3. control of regiochemistry, and
4. control of stereochemistry.

You have had some experience with certain aspects of synthetic strategies in earlier sections.

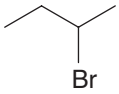
- In Section 7.16B you learned about *retrosynthetic analysis* and how this kind of thinking could be applied to the construction of carbon skeletons of alkanes and cycloalkanes.
- In Section 6.14 you learned the meaning of a *functional group interconversion* and how nucleophilic substitution reactions could be used for this purpose.

In other sections, perhaps without realizing it, you have begun adding to your basic store of methods for construction of carbon skeletons and for making functional group interconversions. This is the time to begin keeping a card file for all the reactions that you have learned, noting especially their applications to synthesis. This file will become your **Tool Kit for Organic Synthesis.** Now is also the time to look at some new examples and to see how we integrate all four aspects of synthesis into our planning.

8.21A Retrosynthetic Analysis

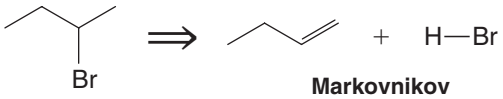
Consider a problem in which we are asked to outline a synthesis of 2-bromobutane from compounds of two carbon atoms or fewer. This synthesis, as we shall see, involves construction of the carbon skeleton, functional group interconversion, and control of regiochemistry.

How to Synthesize 2-Bromobutane

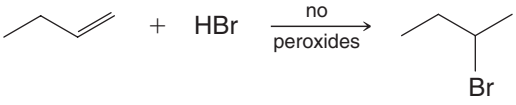


We begin by thinking backward. The final target, 2-bromobutane, can be made in one step from 1-butene by addition of hydrogen bromide. The regiochemistry of this functional group interconversion must be Markovnikov addition:

Retrosynthetic Analysis



Synthesis



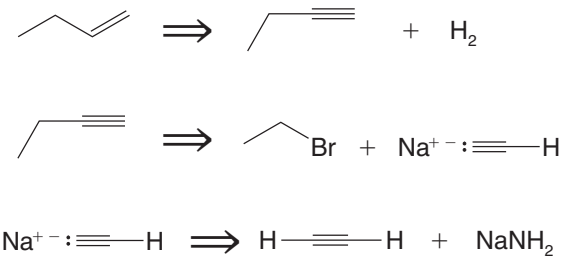
Remember: The open arrow is a symbol used to show a retrosynthetic process that relates the target molecule to its precursors:

Target molecule $\Longrightarrow$ precursors

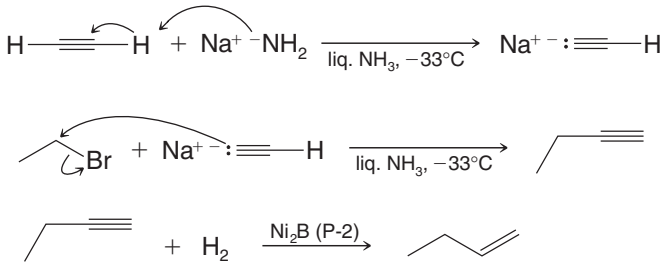
Continuing to work backward one hypothetical reaction at a time, we realize that a synthetic precursor of 1-butene is 1-butyne. Addition of 1 mol of hydrogen to 1-butyne would lead to 1-butene. With 1-butyne as our new target, and bearing in mind that we are told that we have to construct the carbon skeleton from compounds with two carbons or fewer, we realize that 1-butyne can be formed in one step from ethyl bromide and acetylene by an alkynide anion alkylation.

- The **key to retrosynthetic analysis** is to think of how to synthesize each target molecule in one reaction from an immediate precursor, considering first the ultimate target molecule and working backward.

Retrosynthetic Analysis



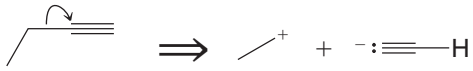
Synthesis



8.21B Disconnections, Synthons, and Synthetic Equivalents

- One approach to retrosynthetic analysis is to consider a retrosynthetic step as a "disconnection" of one of the bonds (Section 7.16).*

For example, an important step in the synthesis that we have just given is the one in which a new carbon–carbon bond is formed. Retrosynthetically, it can be shown in the following way:



The hypothetical fragments of this disconnection are an ethyl cation and an ethynide anion.

- In general, we call the fragments of a hypothetical retrosynthetic disconnection **synthons**.

Seeing the synthons above may help us to reason that we could, in theory, synthesize a molecule of 1-butyne by combining an ethyl cation with an ethynide anion. We know, however, that bottles of carbocations and carbanions are not to be found on our laboratory shelves and that even as a reaction intermediate, it is not reasonable to consider an ethyl carbocation. What we need are the **synthetic equivalents** of these synthons. The synthetic equivalent of an ethynide ion is sodium ethynide, because sodium ethynide contains an ethynide ion (and a sodium cation). The synthetic equivalent of an ethyl cation is ethyl bromide. To understand how this is true, we reason as follows: If ethyl bromide were to react by an S_N1 reaction, it would produce an ethyl cation and a bromide ion. However, we know that, being a primary halide, ethyl bromide is unlikely to react by an S_N1 reaction. Ethyl bromide, however, will react readily with a strong nucleophile such as sodium ethynide by an S_N2 reaction, and when it reacts, the product that is obtained is the same as the product that would have been obtained from the reaction of an ethyl cation with sodium ethynide. Thus, ethyl bromide, in this reaction, functions as the synthetic equivalent of an ethyl cation.

*For an excellent detailed treatment of this approach you may want to read the following: Warren, S., *Organic Synthesis, The Disconnection Approach*, Wiley: New York, 1982, and Warren, S., *Workbook for Organic Synthesis, The Disconnection Approach*, Wiley: New York, 1982.

2-Bromobutane could also be synthesized from compounds of two carbons or fewer by a route in which (*E*)- or (*Z*)-2-butene is an intermediate. You may wish to work out the details of that synthesis for yourself.

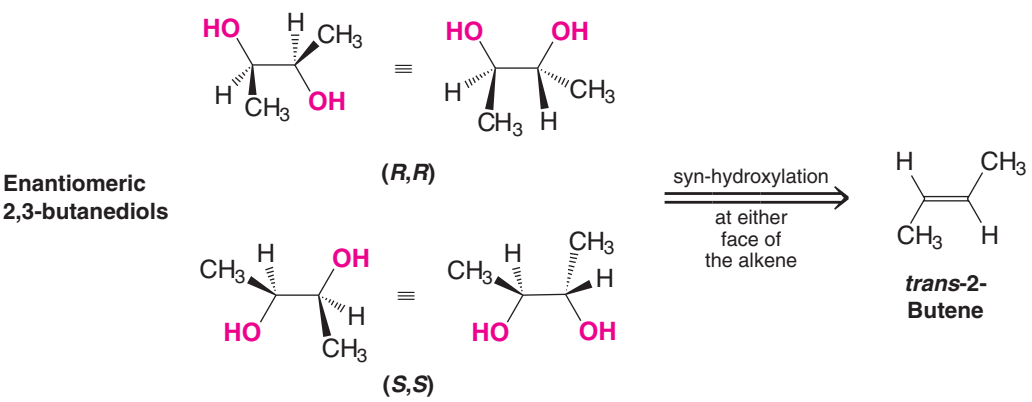
8.21C Stereochemical Considerations

Consider another example, a synthesis that requires stereochemical control: the synthesis of the enantiomeric 2,3-butanediols, (2*R*,3*R*)-2,3-butanediol and (2*S*,3*S*)-2,3-butanediol, from compounds of two carbon atoms or fewer, and in a way that does not produce the meso stereoisomer.

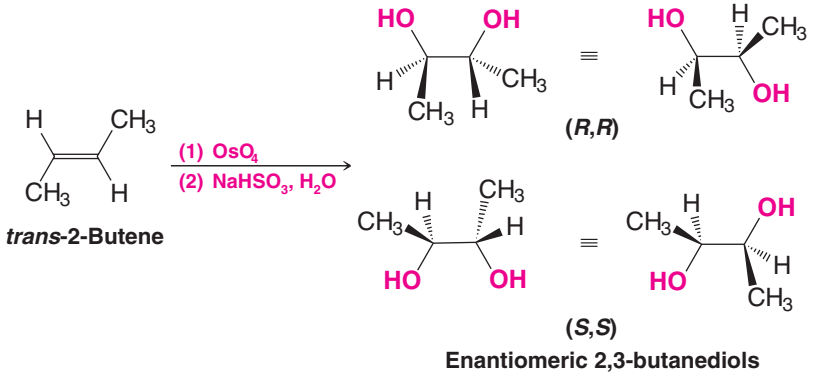
How to Synthesize the Enantiomeric 2,3-Butanediols (and Not the Meso Stereoisomer)

Here we see that a possible final step to the enantiomers is syn hydroxylation of *trans*-2-butene. This reaction is stereospecific and produces the desired enantiomeric 2,3-butanediols as a racemic form. Here we have made the key choice **not** to use *cis*-2-butene. Had we chosen *cis*-2-butene, our product would have been the meso 2,3-butanediol stereoisomer.

Retrosynthetic Analysis

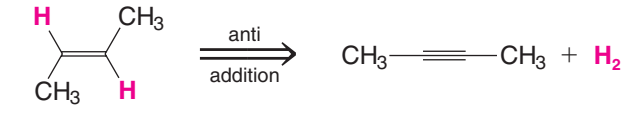


Synthesis

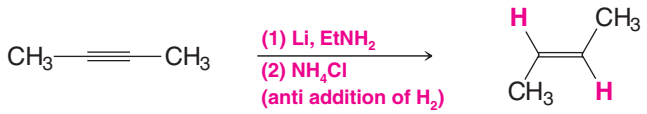


Synthesis of *trans*-2-butene can be accomplished by treating 2-butyne with lithium in liquid ammonia. The anti addition of hydrogen by this reaction gives us the trans product we need.

Retrosynthetic Analysis



Synthesis

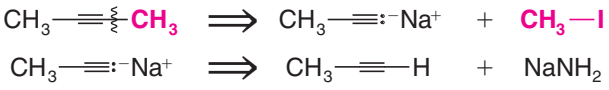


2-Butyne ***trans*-2-Butene**

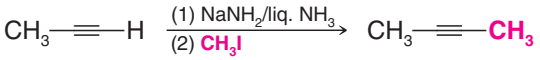
- The reaction above is an example of a **stereoselective reaction**. A stereoselective reaction is one in which the reactant is not necessarily chiral (as in the case of an alkyne) but in which the reaction produces predominantly or exclusively one stereoisomeric form of the product (or a certain subset of stereoisomers from among all those that are possible).
- Note the difference between stereoselective and stereospecific. A stereospecific reaction is one that produces predominantly or exclusively one stereoisomer of the product when a specific stereoisomeric form of the reactant is used. (All stereospecific reactions are stereoselective, but the reverse is not necessarily true.)

We can synthesize 2-butyne from propyne by first converting it to sodium propynide and then alkylating sodium propynide with methyl iodide:

Retrosynthetic Analysis

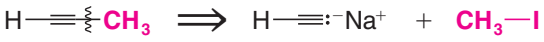


Synthesis

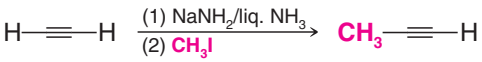


Finally, we can synthesize propyne from ethyne:

Retrosynthetic Analysis



Synthesis

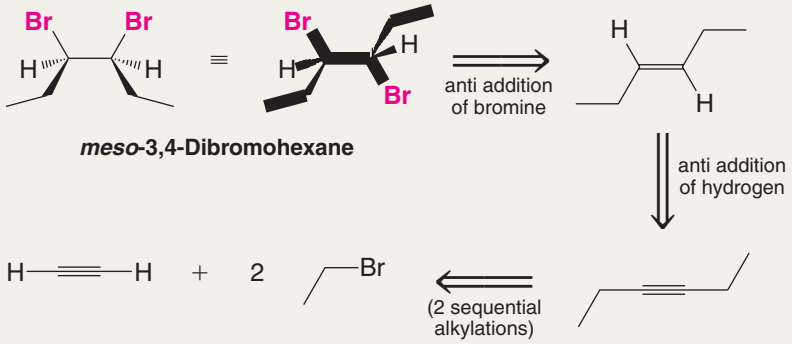


Solved Problem 8.7

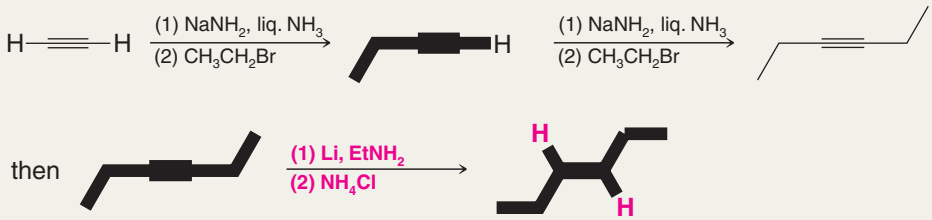
ILLUSTRATING A STEREOSPECIFIC MULTISTEP SYNTHESIS Starting with compounds of two carbon atoms or fewer, outline a stereospecific synthesis of *meso*-3,4-dibromohexane.

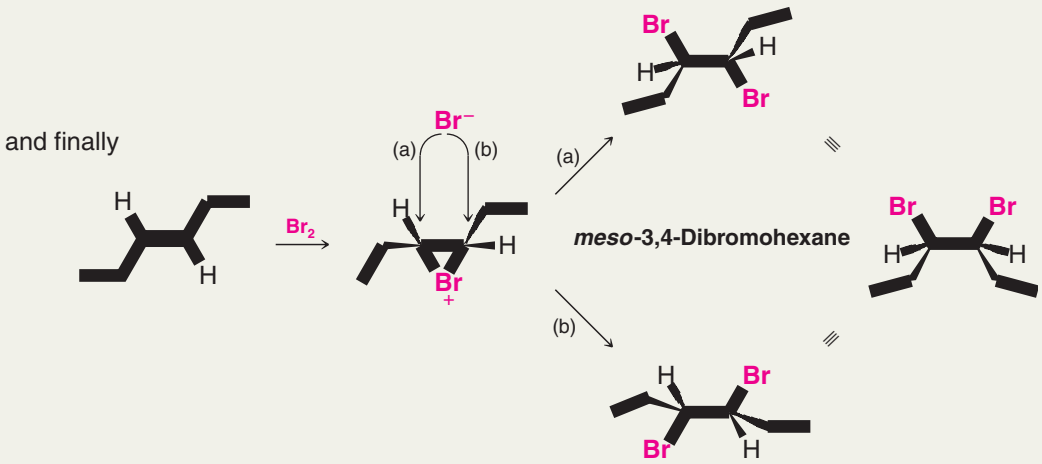
STRATEGY AND ANSWER We begin by working backward from the target molecule. Since the target molecule is a meso compound, it is convenient to start by drawing a formula that illustrates its internal plane of symmetry, as shown below. But since we also know that a vicinal dibromide can be formed by anti addition of bromine to an alkene, we redraw the target molecule formula in a conformation that shows the bromine atoms anti to each other, as they would be after addition to an alkene. Then, retaining the relative spatial relationship of the alkyl groups, we draw the alkene precursor to the 1,2-dibromide, and find that this compound is (*E*)-3-hexene. Knowing that an (*E*) alkene can be formed by anti addition of hydrogen to an alkyne using lithium in ethylamine or ammonia (Section 7.15B), we see that 3-hexyne is a suitable synthetic precursor to (*E*)-3-hexene. Lastly, because we know it is possible to alkylate terminal alkynes, we recognize that 3-hexyne could be synthesized from acetylene by two successive alkylations with an ethyl halide. The following is a retrosynthetic analysis.

Retrosynthetic Analysis



The synthesis could be written as follows:





How would you modify the procedure given in Solved Problem 8.7 so as to synthesize a racemic form of (3*R*,4*R*)- and (3*S*,4*S*)-3,4-dibromohexane?

Review Problem 8.25

Key Terms and Concepts

The key terms and concepts that are highlighted in **bold, blue text** within the chapter are defined in the glossary (at the back of the book) and have hyperlinked definitions in the accompanying ***WileyPLUS*** course (www.wileyplus.com).

Problems

Note to Instructors: Many of the homework problems are available for assignment via *WileyPLUS*, an online teaching and learning solution.

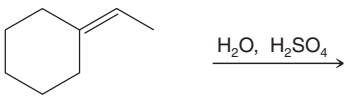
ALKENES AND ALKYNES REACTION TOOLKIT

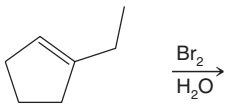
8.26 Write structural formulas for the products that form when 1-butene reacts with each of the following reagents:

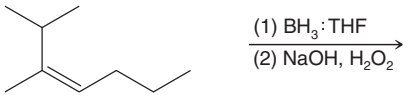
(a) HI
(b) H_2, Pt
(c) Dilute H_2SO_4, warm
(d) Cold concentrated H_2SO_4
(e) Cold concentrated H_2SO_4, then H_2O and heat
(f) HBr
(g) Br_2 in CCl_4
(h) Br_2 in H_2O
(i) HCl
(j) O_3, then Me_2S
(k) OsO_4, then $NaHSO_3/H_2O$
(l) $KMnO_4$, OH^-, heat, then H_3O^+
(m) $Hg(OAc)_2$ in THF and H_2O, then $NaBH_4$, OH^-
(n) BH_3:THF, then H_2O_2, OH^-

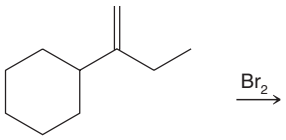
8.27 Repeat Exercise 8.26 using 1-methylcyclopentene instead of 1-butene.

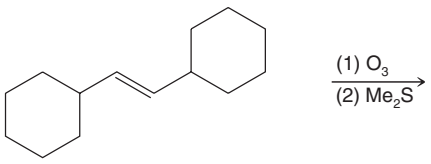
8.28 Write structures for the major organic products from the following reactions. Show stereoisomers where applicable.

(a) 

(b) 

(c) 

(d) 

(e) 

8.29 Give the structure of the products that you would expect from the reaction of 1-butyne with:

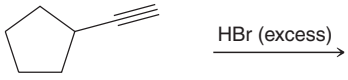
(a) One molar equivalent of Br_2
(b) One molar equivalent of HBr
(c) Two molar equivalents of HBr
(d) H_2 (in excess)/Pt
(e) H_2, Ni_2B (P-2)
(f) $NaNH_2$ in liquid NH_3, then CH_3I
(g) $NaNH_2$ in liquid NH_3, then $(CH_3)_3CBr$

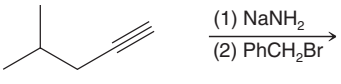
8.30 Give the structure of the products you would expect from the reaction (if any) of 2-butyne with:

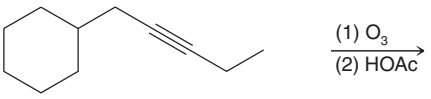
(a) One molar equivalent of HBr
(b) Two molar equivalents of HBr
(c) One molar equivalent of Br_2
(d) Two molar equivalents of Br_2
(e) H_2, Ni_2B (P-2)
(f) One molar equivalent of HCl
(g) Li/liquid NH_3
(h) H_2 (in excess), Pt
(i) Two molar equivalents of H_2, Pt
(j) Hot $KMnO_4$, OH^-, then H_3O^+
(k) O_3, then HOAc
(l) $NaNH_2$, liquid NH_3

8.31 Write structures for the major organic products from the following reactions. Show stereoisomers where applicable.

(a) 

(b) 

(c) 

(d) 

8.32 Show how 1-butyne could be synthesized from each of the following:

(a) 1-Butene

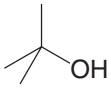
(b) 1-Chlorobutane

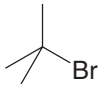
(c) 1-Chloro-1-butene

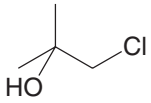
(d) 1,1-Dichlorobutane

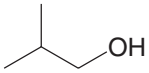
(e) Ethyne and ethyl bromide

8.33 Starting with 2-methylpropene (isobutylene) and using any other needed reagents, outline a synthesis of each of the following:

(a) 

(b) 

(c) 

(d) 

MECHANISMS

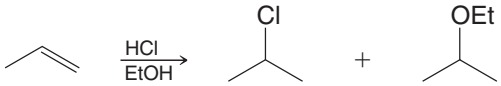
8.34 Write a three-dimensional formula for the product formed when 1-methylcyclohexene is treated with each of the following reagents. In each case, designate the location of deuterium or tritium atoms.

(a) (1) BH_3:THF, (2) CH_3CO_2T

(b) (1) BD_3:THF, (2) CH_3CO_2D

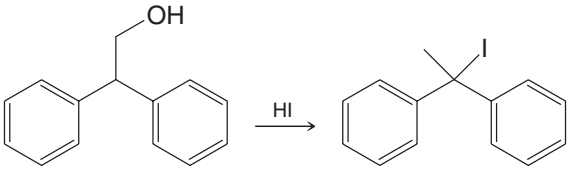
(c) (1) BD_3:THF, (2) NaOH, H_2O_2, H_2O

8.35 Write a mechanism that accounts for the formation of ethyl isopropyl ether in the following reaction.



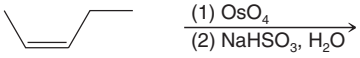
8.36 When, in separate reactions, 2-methylpropene, propene, and ethene are allowed to react with HI under the same conditions (i.e., identical concentration and temperature), 2-methylpropene is found to react fastest and ethene slowest. Provide an explanation for these relative rates.

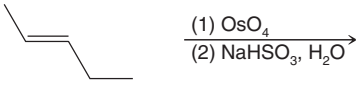
8.37 Propose a mechanism that accounts for the following reaction.



8.38 When 3,3-dimethyl-2-butanol is treated with concentrated HI, a rearrangement takes place. Which alkyl iodide would you expect from the reaction? (Show the mechanism by which it is formed.)

8.39 Write stereochemical formulas for all of the products that you would expect from each of the following reactions. (You may find models helpful.)

(a) 

(b) 

(c) 

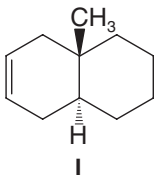
(d) 

8.40 Give (*R*, *S*) designations for each different compound given as an answer to Problem 8.39.

8.41 The double bond of tetrachloroethene is undetectable in the bromine/carbon tetrachloride test for unsaturation. Give a plausible explanation for this behavior.

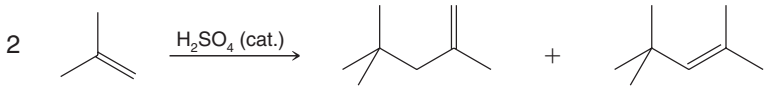
8.42 The reaction of bromine with cyclohexene involves anti addition, which generates, initially, the diaxial conformation of the addition product that then undergoes a ring flip to the diequatorial conformation of *trans*-1,2-dibromocyclohexane.

However, when the unsaturated bicyclic compound **I** is the alkene, instead of cyclohexene, the addition product is exclusively in a stable diaxial conformation. Account for this. (You may find it helpful to build handheld molecular models.)



I

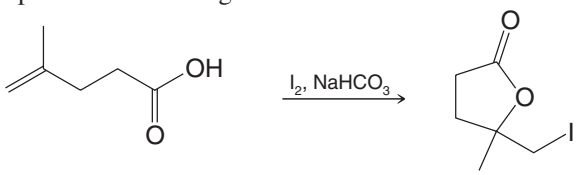
8.43 Propose a mechanism that explains formation of the products from the following reaction, including the distribution of the products as major and minor.



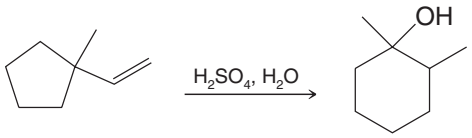
Minor **Major**

8.44 Internal alkynes can be isomerized to terminal alkynes on treatment with $NaNH_2$. The process is much less successful when NaOH is used. Why is there this difference?

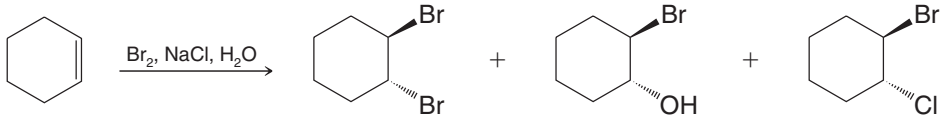
8.45 Write a mechanism that explains the following reaction.



8.46 Write a mechanism for the following reaction.



8.47 Write a mechanism that explains formation of the products shown in the following reaction.



STRUCTURE ELUCIDATION

8.48 Myrcene, a fragrant compound found in bayberry wax, has the formula $C_{10}H_{16}$ and is known not to contain any triple bonds.

(a) What is the index of hydrogen deficiency of myrcene? When treated with excess hydrogen and a platinum catalyst, myrcene is converted to a compound **(A)** with the formula $C_{10}H_{22}$.

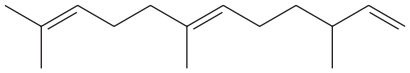
(b) How many rings does myrcene contain?

(c) How many double bonds? Compound **A** can be identified as 2,6-dimethyloctane. Ozonolysis of myrcene followed by treatment with dimethyl sulfide yields 2 mol of formaldehyde (HCHO), 1 mol of acetone (CH_3COCH_3), and a third compound **(B)** with the formula $C_5H_6O_3$.

(d) What is the structure of compound **B**?

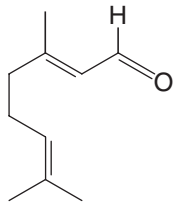
(e) What is the structure of myrcene?

8.49 Farnesene (below) is a compound found in the waxy coating of apples. (**a**) Give the structure and IUPAC name of the product formed when farnesene is allowed to react with excess hydrogen in the presence of a platinum catalyst. (**b**) How many stereoisomers of the product are possible?



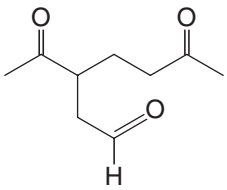
Farnesene

8.50 Write structural formulas for the products that would be formed when geranial, a component of lemongrass oil, is treated with ozone and then with dimethyl sulfide (Me_2S).

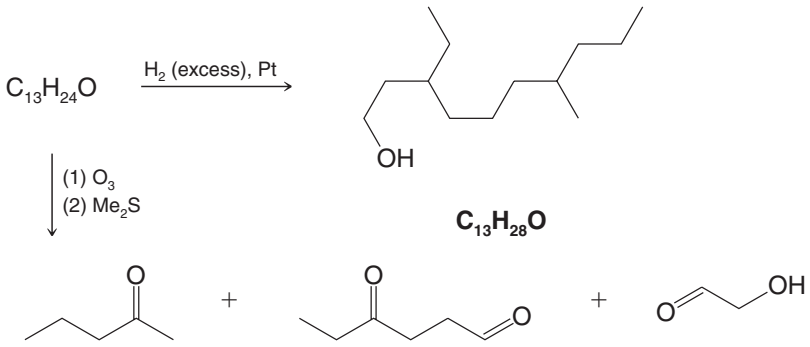


Geranial

8.51 Limonene is a compound found in orange oil and lemon oil. When limonene is treated with excess hydrogen and a platinum catalyst, the product of the reaction is 1-isopropyl-4-methylcyclohexane. When limonene is treated with ozone and then with dimethyl sulfide (Me_2S), the products of the reaction are formaldehyde ($HCHO$) and the following compound. Write a structural formula for limonene.

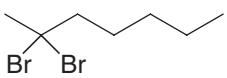


8.52 Pheromones (Section 4.7) are substances secreted by animals that produce a specific behavioral response in other members of the same species. Pheromones are effective at very low concentrations and include sex attractants, warning substances, and "aggregation" compounds. The sex attractant pheromone of the codling moth has the molecular formula $C_{13}H_{24}O$. Using information you can glean from the following reaction diagram, deduce the structure of the codling moth sex pheromone. The double bonds are known (on the basis of other evidence) to be (2*Z*,6*E*).

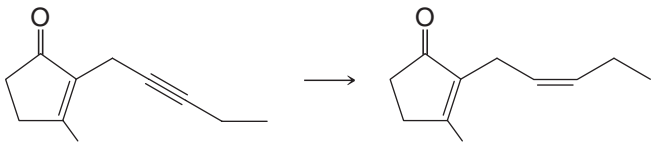


GENERAL PROBLEMS

8.53 Synthesize the following compound starting with ethyne and 1-bromopentane as your only organic reagents (except for solvents) and using any needed inorganic compounds.



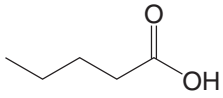
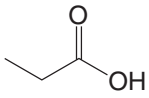
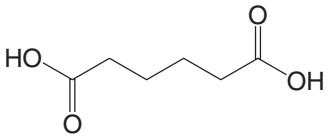
8.54 Shown below is the final step in a synthesis of an important perfume constituent, *cis*-jasmone. Which reagents would you choose to carry out this last step?



***cis*-Jasmone**

8.55 Predict features of their IR spectra that you could use to distinguish between the members of the following pairs of compounds. You may find the IR chart in the endpapers of the book and Table 2.1 useful.

(a) Pentane and 1-pentyne
(b) Pentane and 1-pentene
(c) 1-Pentene and 1-pentyne
(d) Pentane and 1-bromopentane
(e) 2-Pentyne and 1-pentyne
(f) 1-Pentene and 1-pentanol
(g) Pentane and 1-pentanol
(h) 1-Bromo-2-pentene and 1-bromopentane
(i) 1-Pentanol and 2-penten-1-ol

8.56 Deduce the structures of compounds **A**, **B**, and **C**, which all have the formula C_6H_{10}. As you read the information that follows, draw reaction flowcharts (roadmaps) like those in Problems 8.24 and 8.52. This approach will help you solve the problem. All three compounds rapidly decolorize bromine in CCl_4; all three are soluble in cold concentrated sulfuric acid. Compound **A** has an absorption in its IR spectrum at about 3300 cm^{-1}, but compounds **B** and **C** do not. Compounds **A** and **B** both yield hexane when they are treated with excess hydrogen in the presence of a platinum catalyst. Under these conditions **C** absorbs only one molar equivalent of hydrogen and gives a product with the formula C_6H_{12}. When **A** is oxidized with hot basic potassium permanganate and the resulting solution acidified, the only organic product that can be isolated is  . Similar oxidation of **B** gives only  , and similar treatment of **C** gives only  .

8.57 Ricinoleic acid, a compound that can be isolated from castor oil, has the structure $CH_3(CH_2)_5CHOHCH_2CH{=}CH(CH_2)_7CO_2H$.

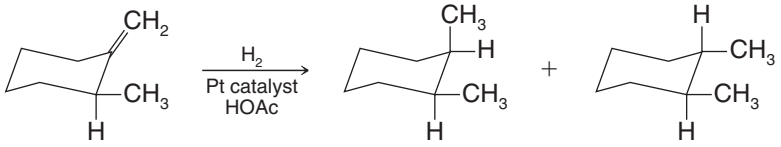
(a) How many stereoisomers of this structure are possible? **(b)** Write these structures.

8.58 There are two dicarboxylic acids with the general formula $HO_2CCH{=}CHCO_2H$. One dicarboxylic acid is called maleic acid; the other is called fumaric acid. When treated with OsO_4, followed by $NaHSO_3/H_2O$, maleic acid yields *meso*-tartaric acid and fumaric acid yields (±)-tartaric acid. Show how this information allows one to write stereochemical formulas for maleic acid and fumaric acid.

8.59 Use your answers to the preceding problem to predict the stereochemical outcome of the addition of bromine to maleic acid and to fumaric acid. **(a)** Which dicarboxylic acid would add bromine to yield a meso compound? **(b)** Which would yield a racemic form?

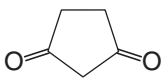
8.60 Alkyl halides add to alkenes in the presence of $AlCl_3$; yields are the highest when tertiary halides are used. Predict the outcome of the reaction of *tert*-pentyl chloride (1-chloro-2,2-dimethylpropane) with propene and specify the mechanistic steps.

8.61 Explain the stereochemical results observed in this catalytic hydrogenation. (You may find it helpful to build hand-held molecular models.)



I (70%) **II (30%)**

8.62 Make a reaction flowchart (roadmap diagram), as in previous problems, to organize the information provided to solve this problem. An optically active compound **A** (assume that it is dextrorotatory) has the molecular formula $C_7H_{11}Br$. **A** reacts with hydrogen bromide, in the absence of peroxides, to yield isomeric products, **B** and **C**, with the molecular formula $C_7H_{12}Br_2$. Compound **B** is optically active; **C** is not. Treating **B** with 1 mol of potassium *tert*-butoxide yields (+)-**A**. Treating **C** with 1 mol of potassium *tert*-butoxide yields (±)-**A**. Treating **A** with potassium *tert*-butoxide yields **D** (C_7H_{10}). Subjecting 1 mol of **D** to ozonolysis followed by treatment with dimethyl sulfide (Me_2S) yields 2 mol of formaldehyde and 1 mol of 1,3-cyclopentanedione.



1,3-Cyclopentanedione

Propose stereochemical formulas for **A**, **B**, **C**, and **D** and outline the reactions involved in these transformations.

8.63 A naturally occurring antibiotic called mycomycin has the structure shown here. Mycomycin is optically active. Explain this by writing structures for the enantiomeric forms of mycomycin.

$$HC{\equiv}C{-}C{\equiv}C{-}CH{=}C{=}CH{-}(CH{=}CH)_2CH_2CO_2H$$

Mycomycin

8.64 An optically active compound **D** has the molecular formula C_6H_{10} and shows a peak at about 3300 cm^{-1} in its IR spectrum. On catalytic hydrogenation **D** yields **E** (C_6H_{14}). Compound **E** is optically inactive and cannot be resolved. Propose structures for **D** and **E**.

8.65 **(a)** Based on the following information, draw three-dimensional formulas for **A**, **B**, and **C**.

Reaction of cyclopentene with bromine in water gives **A**.

Reaction of **A** with aqueous NaOH (1 equivalent, cold) gives **B**, C_5H_8O (no 3590–3650-cm^{-1} infrared absorption). (See the squalene cyclization discussion in "The Chemistry of... Cholesterol Biosynthesis" in *WileyPLUS* for a hint.)

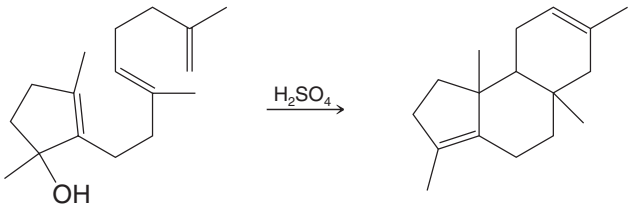
Heating of **B** in methanol containing a catalytic amount of strong acid gives **C**, $C_6H_{12}O_2$, which does show 3590–3650-cm^{-1} infrared absorption.

(b) Specify the (*R*) or (*S*) configuration of the chirality centers in your predicted structures for **C**. Would **C** be formed as a single stereoisomer or as a racemate?

(c) How could you experimentally confirm your predictions about the stereochemistry of **C**?

Challenge Problems

8.66 Propose a mechanism that explains the following transformation. (Note its similarity to the cyclization of squalene oxide to lanosterol, as shown in "The Chemistry of . . . Cholesterol Biosynthesis." in *WileyPLUS*)



8.67 Triethylamine, $(C_2H_5)_3N$, like all amines, has a nitrogen atom with an unshared pair of electrons. Dichlorocarbene also has an unshared pair of electrons. Both can be represented as shown below. Draw the structures of compounds **D**, **E**, and **F**.

$$(C_2H_5)_3N{:} + {:}CCl_2 \rightarrow \mathbf{D} \quad \text{(an unstable adduct)}$$

$$\mathbf{D} \longrightarrow \mathbf{E} + C_2H_4 \quad \text{(by an intramolecular E2 reaction)}$$

$$\mathbf{E} \xrightarrow{H_2O} \mathbf{F} \text{ (Water effects a replacement that is the reverse of that used to make } \textit{gem}\text{-dichlorides.)}$$

8.68 In Chapter 3 we first mentioned the importance of the interaction of a HOMO (highest occupied molecular orbital) of one molecule with the LUMO (lowest unoccupied molecular orbital) of another when two molecules react with each other (see "The Chemistry of . . ." box, Section 3.3A). These ideas carry forth into our understanding of addition reactions between alkenes and electrophiles. Open the molecular models at the book's website for ethene and BH_3 and view the HOMO and LUMO for each reactant. Which reactant is likely to have its HOMO involved in the hydroboration of ethene? Which molecule's LUMO will be involved? As you view the models, can you envision favorable overlap of these orbitals as the reaction occurs?

8.69 Hydroboration reactions are frequently done using BH_3:THF as a complex in solution. BH_3 in pure form is a gas, and in the absence of other Lewis bases it exists as the dimer diborane, B_2H_6. Open the molecular model at the book's website for the BH_3:THF complex and display its LUMO. Does the LUMO have lobes suitably disposed to allow the BH_3 portion of the BH_3:THF complex to interact with other Lewis bases, e.g., an alkene π bond in the

course of a hydroboration reaction? Such an interaction is required at the beginning of a hydroboration reaction with BH_3:THF because the reaction begins with a complex between BH_3 and the alkene π bond, which then changes to the four-atom transition state of the addition as the reaction proceeds.

8.70 Open the molecular model at the book's website for diborane (B_2H_6) and examine its HOMO and LUMO. Is the LUMO of B_2H_6 readily accessible to the HOMO of an alkene or other Lewis base? How does the orientation of the diborane LUMO compare with that of its HOMO?

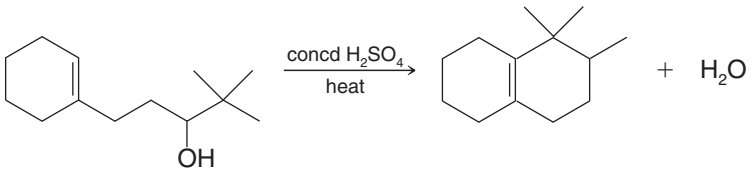
Learning Group Problems

1. **(a)** Synthesize (3*S*,4*R*)-3,4-dibromo-1-cyclohexylpentane (and its enantiomer, since a racemic mixture will be formed) from ethyne, 1-chloro-2-cyclohexylethane, bromomethane, and any other reagents necessary. (Use ethyne, 1-chloro-2-cyclohexylethane, and bromomethane as the sole sources of carbon atoms.) Start the problem by showing a retrosynthetic analysis. In the process, decide which atoms of the target molecule will come from which atoms of the starting reagents. Also, bear in mind how the stereospecificity of the reactions you employ can be used to achieve the required stereochemical form of the final product.

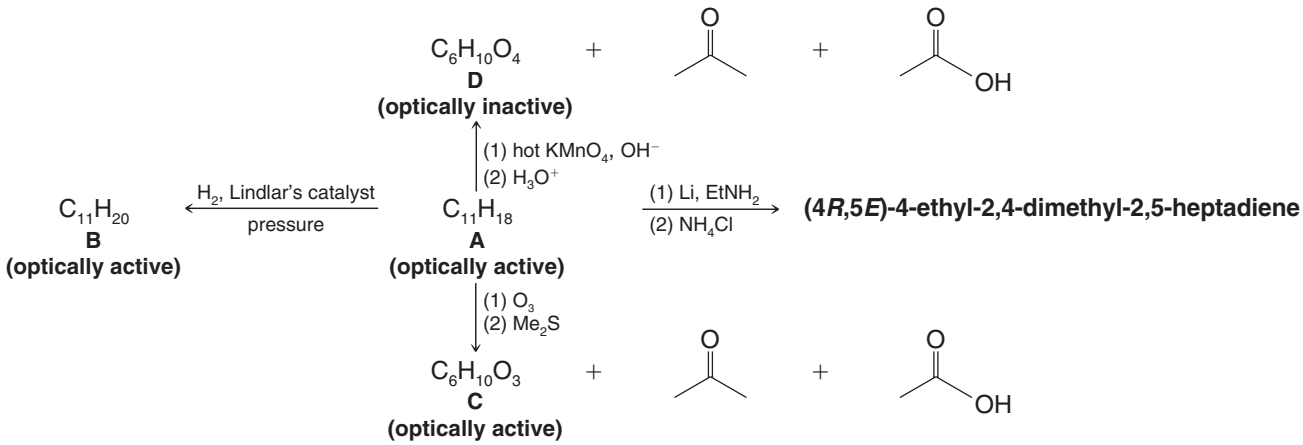
(b) Explain why a racemic mixture of products results from this synthesis.

(c) How could the synthesis be modified to produce a racemic mixture of the (3*R*,4*R*) and (3*S*,4*S*) isomers instead?

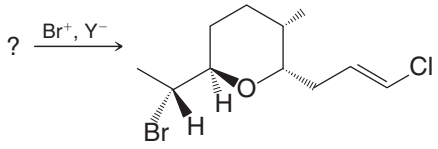
2. Write a reasonable and detailed mechanism for the following transformation:



3. Deduce the structures of compounds **A–D**. Draw structures that show stereochemistry where appropriate:

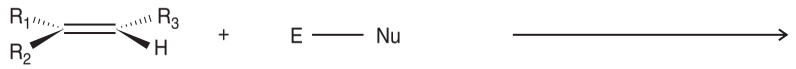


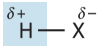
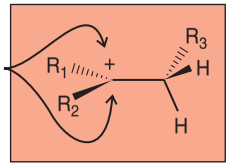
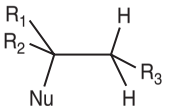
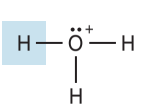
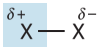
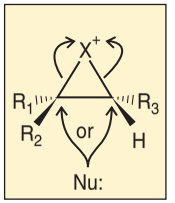
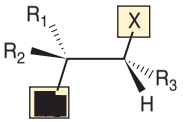
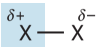
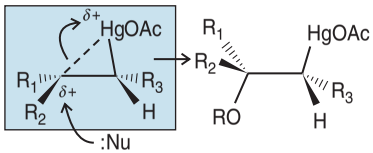
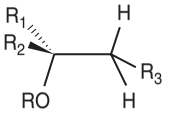
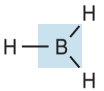
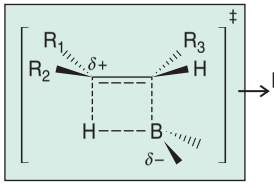
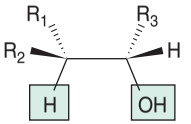
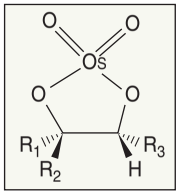
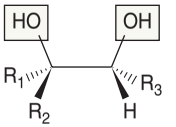
4. The Guam bubble snail *(Haminoea cymbalum)* contains kumepaloxane (shown below), a chemical signal agent discharged when this mollusk is disturbed by predatory carnivorous fish. The biosynthesis of bromoethers like kumepaloxane is thought to occur via the enzymatic intermediacy of a "Br^+" agent. Draw the structure of a possible biosynthetic precursor (*hint*: an alkene alcohol) to kumepaloxane and write a plausible and detailed mechanism by which it could be converted to kumepaloxane using Br^+ and some generic proton acceptor Y^-.



Kumepaloxane

Mechanism Review: Summary of Alkene Addition Reactions



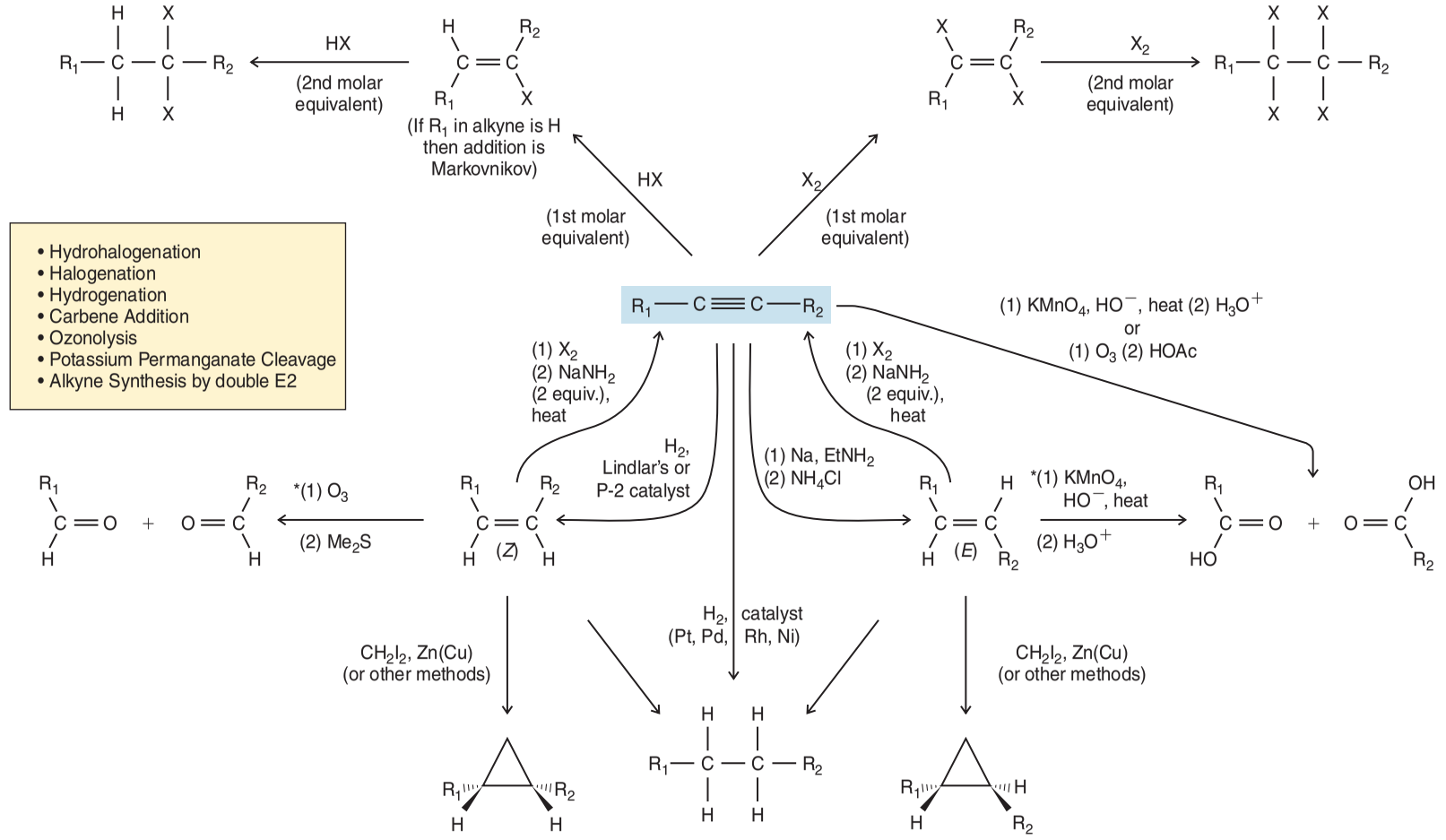
	Reaction Conditions	Electrophile	Nucleophile	Key Intermediates or Transition State	Regiochemistry	Stereochemistry of Addition	Product*
Hydrohalogenation	H — X				Markovnikov	Not controlled	 Nu = X or OH
Hydration (acid cat.)	Cat. HA, H_2O				Markovnikov	Not controlled	
Halogenation	X_2 (non nucleophilic solvent)				Not applicable	Anti	 Nu = X or OR
Halohydrin Formation	X_2, ROH; R = H or C (nucleophilic solvent)				Markovnikov	Anti	
Oxymercuration–Demercuration	(1) $Hg(OAc)_2$, HOR: THF (R = H or C) (2) $NaBH_4$, OH^-				Markovnikov	Not controlled	
Hydroboration–Oxidation	(1) BH_3:THF (2) H_2O_2, HO^-				Net anti-Markovnikov	Syn	
1,2-Dihydroxylation	(1) OsO_4 (2) aq $NaHSO_3$					Syn	

*The generic alkene chosen has a substitution pattern that allows both regiochemistry and stereochemistry of the products to be discerned.

*The products are formed as a mixture of enantiomers in each case.

Summary and Review Tools

Synthetic Connections of Alkynes and Alkenes: II

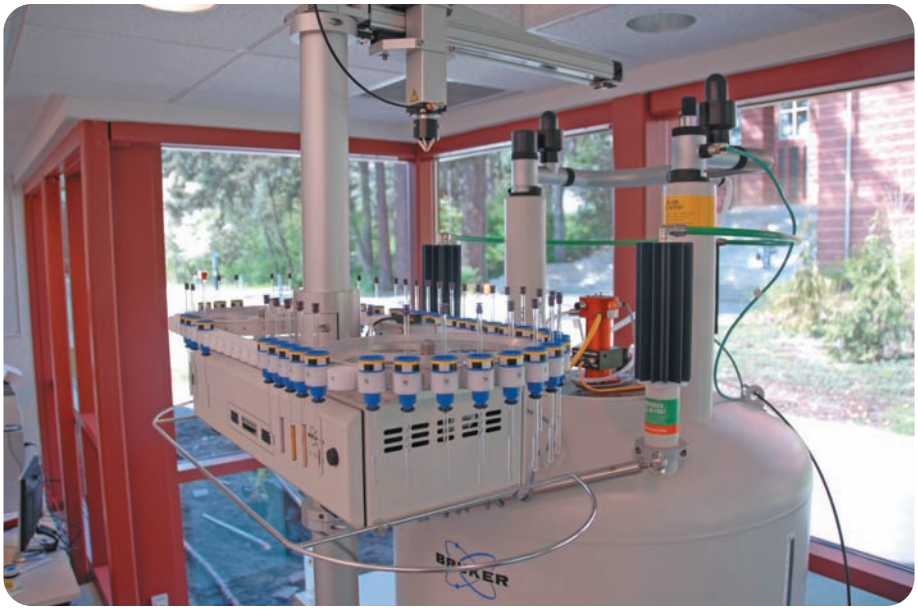


*If R_1 is H, then alkene ozonolysis generates formaldehyde and $KMnO_4$ generates CO_2.
If the alkene is disubstituted at one end, a ketone results from cleavage by either ozonolysis or $KMnO_4$.

9

Nuclear Magnetic Resonance and Mass Spectrometry

Tools for Structure Determination



Have you known someone who needed an MRI (magnetic resonance imaging) scan for a medical condition, or have you needed one yourself? Have you ever observed someone in an airport security line having their belongings wiped down with a pad which was then placed in some kind of analytical instrument? Have you wondered how scientists determine the structures of compounds found in nature, or have you known a fellow student in a laboratory class who extracted bark, leaves, or fruit to isolate and identify some natural compounds? Or have you wondered how forensic evidence is analyzed in criminal cases, or how pesticides are identified in food samples?

If you have wondered about any of these things, then some of your curiosity will be satisfied by learning about spectroscopic methods such as nuclear magnetic resonance (NMR) spectrometry, which involves the same physical principles as MRI imaging, and MS (mass spectrometry), which is used in some airport screening processes as well as many forensic applications. NMR and MS are workhorse techniques for the study of both biological and nonbiological molecular structure.

9.1 Introduction

- **Spectroscopy** is the study of the interaction of energy with matter.

When energy is applied to matter, it can be absorbed, emitted, cause a chemical change, or be transmitted. In this chapter we shall see how detailed information about molecular structure can be obtained by interpreting results from the interaction of energy with molecules. In our study of nuclear magnetic resonance (NMR) spectroscopy we shall focus our attention on energy absorption by molecules that have been placed in a strong magnetic field. When we study mass spectrometry (MS), we shall learn how molecular structure can be probed by bombarding molecules with a beam of high-energy electrons. These two techniques (NMR and MS) are a powerful combination for elucidating the structures of organic molecules. Together with infrared (IR) spectroscopy (Section 2.15), these methods comprise the typical array of spectroscopic tools used by organic chemists. Later, we shall briefly discuss how gas chromatography (GC) is linked with mass spectrometry in GC/MS instruments to obtain mass spectrometric data from individual components of a mixture.

We begin our study with a discussion of nuclear magnetic resonance spectroscopy.

9.2 Nuclear Magnetic Resonance (NMR) Spectroscopy

The 1952 Nobel Prize in Physics was awarded to Felix Bloch (Stanford) and Edward M. Purcell (Harvard) for their discoveries relating to nuclear magnetic resonance.

The nuclei of certain elements, including ^{1}H nuclei (protons) and ^{13}C (carbon-13) nuclei, behave as though they were magnets spinning about an axis. When a compound containing protons or carbon-13 nuclei is placed in a very strong magnetic field and simultaneously irradiated with electromagnetic energy of the appropriate frequency, nuclei of the compound absorb energy through a process called magnetic resonance. The absorption of energy is quantized.

- A graph that shows the characteristic energy absorption frequencies and intensities for a sample in a magnetic field is called a **nuclear magnetic resonance (NMR) spectrum**.

As a typical example, the proton (^{1}H) NMR spectrum of 1-bromoethane is shown in Fig. 9.1.

We can use NMR spectra to provide valuable information about the structure of any molecule we might be studying. In the following sections we shall explain how four features of a molecule's proton NMR spectrum can help us arrive at its structure.

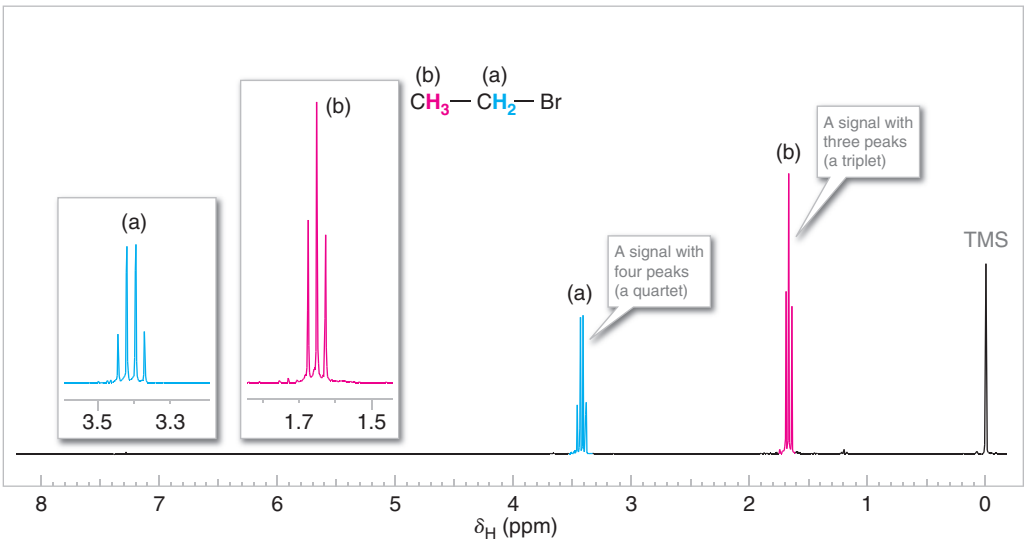


Figure 9.1 The 300-MHz ^{1}H NMR spectrum of 1-bromoethane (ethyl bromide). Zoomed-in expansions of the signals are shown in the offset plots.

1. **The number of signals in the spectrum** tells us **how many different sets of protons there are in the molecule**. In the spectrum for 1-bromoethane (Fig. 9.1) there are *two signals arising from two different sets of protons*. One signal (consisting of four peaks) is shown in blue and labeled (a). The other signal (consisting of three peaks) is in red and is labeled (b). These signals are shown twice in the spectrum, at a smaller scale on the baseline spectrum, and expanded and moved to the left above the base spectrum. [Don't worry now about the signal at the far right of the spectrum (labeled TMS); it comes from a compound (tetramethylsilane) that was added to the 1-bromoethane so as to calibrate the positions of the other signals.]
2. **The position of the signals in the spectrum along the *x*-axis** tells us about the magnetic environment of each set of protons arising largely from the electron density in their environment. We'll learn more about this in Section 9.2A.
3. **The area under the signal** tells us about **how many protons there are in the set being measured**. We'll learn how this is done in Section 9.2B.
4. **The multiplicity (or splitting pattern) of each signal** tells us about about **the number of protons on atoms adjacent to the one whose signal is being measured**. In 1-bromoethane, signal (a) is split into a *quartet* of peaks by the three protons of set (b), and signal (b) is split into a *triplet* of peaks by the two protons of set (a). We'll explain splitting patterns in Section 9.2C.

9.2A Chemical Shift

- The position of a signal along the *x*-axis of an NMR spectrum is called its **chemical shift**.
- **The chemical shift of each signal gives information about the structural environment of the nuclei producing that signal**.
- Counting the number of signals in a ^{1}H NMR spectrum indicates, at a first approximation, the number of distinct proton environments in a molecule.

Tables and charts have been developed that allow us to correlate chemical shifts of NMR signals with likely structural environments for the nuclei producing the signals. Table 9.1 and Fig. 9.2, for example, are useful for this purpose. ^{1}H NMR chemical shifts generally fall in the range of 13–0 ppm (δ).

TABLE 9.1 Approximate Proton Chemical Shifts

Type of Proton	Chemical Shift (δ, ppm)	Type of Proton	Chemical Shift (δ, ppm)
1° Alkyl, RCH_3	0.8–1.2	Alkyl bromide, RCH_2Br	3.4–3.6
2° Alkyl, RCH_2R	1.2–1.5	Alkyl chloride, RCH_2Cl	3.6–3.8
3° Alkyl, R_3CH	1.4–1.8	Vinylic, $R_2C{=}CH_2$	4.6–5.0
Allylic, $R_2C{=}C(R){-}CH_3$	1.6–1.9	Vinylic, $R_2C{=}CHR$	5.2–5.7
Ketone, $RC(=O)CH_3$	2.1–2.6	Aromatic, ArH	6.0–8.5
Benzylic, $ArCH_3$	2.2–2.5	Aldehyde, $RC(=O)H$	9.5–10.5
Acetylenic, $RC{\equiv}CH$	2.5–3.1	Alcohol hydroxyl, ROH	0.5–6.0[a]
Alkyl iodide, RCH_2I	3.1–3.3	Amino, $R{-}NH_2$	1.0–5.0[a]
Ether, $ROCH_2R$	3.3–3.9	Phenolic, ArOH	4.5–7.7[a]
Alcohol, $HOCH_2R$	3.3–4.0	Carboxylic, $RC(=O)OH$	10–13[a]

[a]The chemical shifts of these protons vary in different solvents and with temperature and concentration.

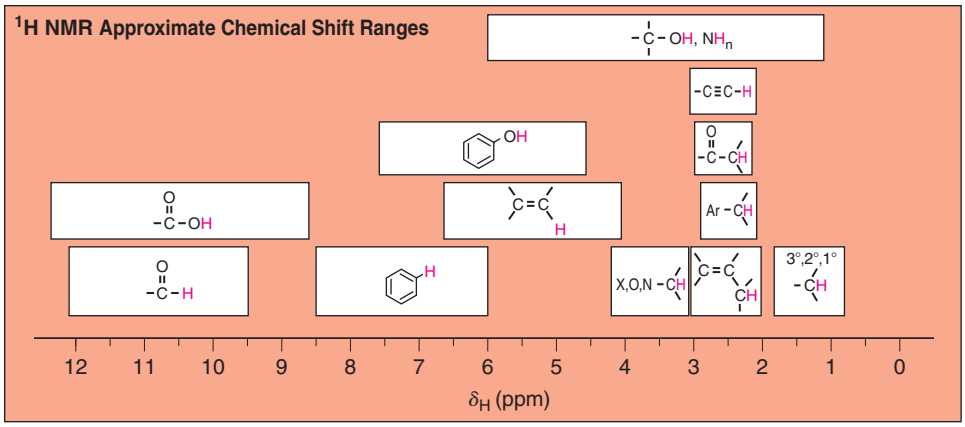


Figure 9.2 Approximate proton chemical shifts.

The chemical shift of a signal in an NMR spectrum depends on the local magnetic environment of the nucleus producing the signal. The local magnetic environment of a nucleus is influenced by electron density and other factors we shall discuss shortly. The physical meaning of chemical shift values relates to the actual frequency of the NMR signals produced by the nuclei. The *practical* importance of chemical shift information is that it gives important clues about molecular structure. Each NMR signal indicates the presence of nuclei in a different magnetic environment.

Chemical shifts are measured along the spectrum axis using a delta (δ) scale, in units of parts per million (ppm). When comparing one signal with another:

- A signal that occurs further to the left in the spectrum than another (i.e., at a higher δ or ppm value) is said to occur **downfield**.
- A signal to the right is said to occur **upfield**.

The terms upfield and downfield relate to the strength of the magnetic field (higher versus lower, respectively) that is required to bring the nuclei into resonance.

Solved Problem 9.1

Consider the spectrum of ethyl bromide (Fig. 9.1). What is the chemical shift of the signal that is furthest downfield?

STRATEGY AND ANSWER A downfield signal is one that appears at higher ppm or δ values. The quartet is the furthest downfield signal in the NMR spectrum of ethyl bromide. For a signal with multiple peaks, such as a quartet, the chemical shift is reported as the midpoint of the peaks in the signal. Estimating as well as possible from the zoomed-in offset expansion in Fig. 9.1, the chemical shift of the ethyl bromide quartet is 3.4 ppm.

The ^{1}H NMR spectrum of 1,4-dimethylbenzene (*p*-xylene), shown in Fig. 9.3, is a simple example that we can use to learn how to interpret chemical shifts. First, note that there is a signal at δ 0. The signal at δ 0 is *not* from 1,4-dimethylbenzene, but from tetramethylsilane (TMS), a compound that is sometimes added to samples as an internal standard to calibrate the chemical shift scale. If the signal from TMS appears at zero ppm, the chemical shift axis is calibrated correctly.

Next we observe that there are only two other signals in the ^{1}H NMR spectrum of 1,4-dimethylbenzene, at approximately δ 7.0 and δ 2.3. The existence of just two signals implies that there are only two distinct proton environments in 1,4-dimethylbenzene, a fact we can easily verify for ourselves by examining its structure.

We say, then, that there are "two types" of hydrogen atoms in 1,4-dimethylbenzene, and these are the hydrogen atoms of the methyl groups and the hydrogen atoms of the benzene ring. The two methyl groups produce only one signal because they are equivalent by virtue of the plane of symmetry between them. Furthermore, the three hydrogen atoms of each

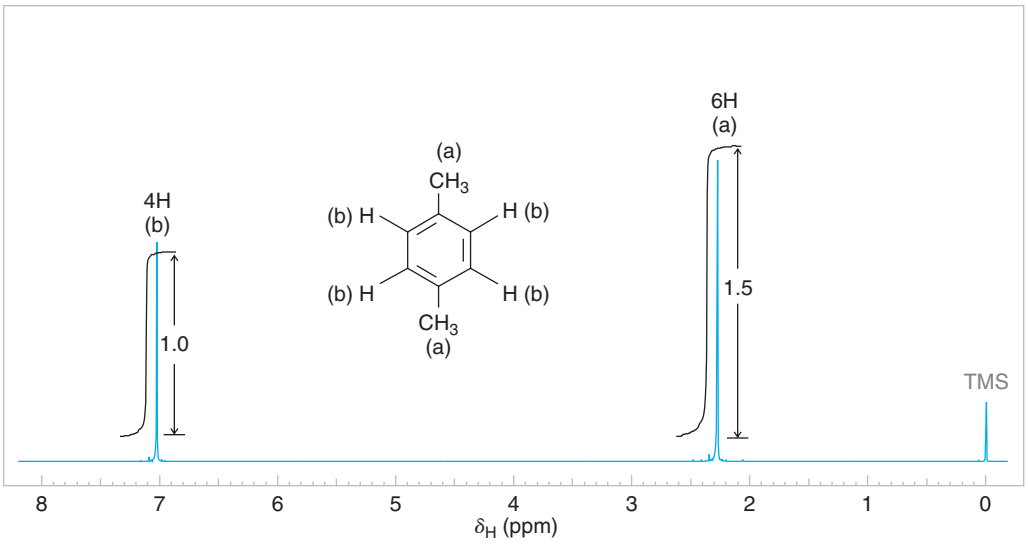


Figure 9.3 The 300-MHz ^{1}H NMR spectrum of 1,4-dimethylbenzene.

methyl group are equivalent due to free rotation about the bond between the methyl carbon and the ring. The benzene ring hydrogen atoms also produce only one signal because they are equivalent to each other by symmetry.

Referring to Table 9.1 or Fig. 9.2, we can see that ^{1}H NMR signals for hydrogen atoms bonded to a benzene ring typically occur between δ 6 and 8.5, and that signals for hydrogen atoms on an sp^3 carbon bonded to a benzene ring (benzylic hydrogens) typically occur between δ 2 and 3. Thus, chemical shifts for the signals from 1,4-dimethylbenzene occur where we would expect them to according to NMR spectral correlation charts.

In the case of this example, the structure of the compound under consideration was known from the outset. Had we not known its structure in advance, however, we would have used chemical shift correlation tables to infer likely structural environments for the hydrogen atoms. We would also have considered the relative area of the signals and signal multiplicity, factors we shall discuss in the following sections.

Solved Problem 9.2

Based on the information in Table 9.1, in what ppm range would you expect to find the protons of (**a**) acetone (CH_3COCH_3) and (**b**) ethanol?

STRATEGY AND ANSWER We use a chemical shift correlation table, such as Table 9.1, to find the closest match between the compound of interest and the partial structures shown in the table.

(a) Acetone is a ketone bearing hydrogen atoms on the carbons adjacent to its carbonyl group. Ketones are listed in Table 9.1 as a representative substructure whose protons have a chemical shift range of 2.1–2.6 ppm. Thus, we expect the proton NMR signal from acetone to appear in the 2.1–2.6 ppm range. There will be one signal for all of the hydrogen atoms in acetone because, due to free rotation, they can occupy equivalent magnetic environments at any given instant. (In actuality, the signal from acetone appears at 2.1 ppm, at the upfield end of the range. Structural attributes of more complicated ketones extend the range downfield.)

(b) Ethanol is expected to exhibit three proton NMR signals, one for each of its three distinct hydrogen environments. Ethanol contains an alcohol hydroxyl proton, which Table 9.1 lists in the range of 0.5–6.0 ppm; two protons on the carbon bearing the hydroxyl group, which according to Table 9.1 we expect in the 3.3–4.0 ppm range; and a methyl group bonded to no functional groups, which, as a 1° alkyl group, should appear in the 0.8–1.2 ppm range.

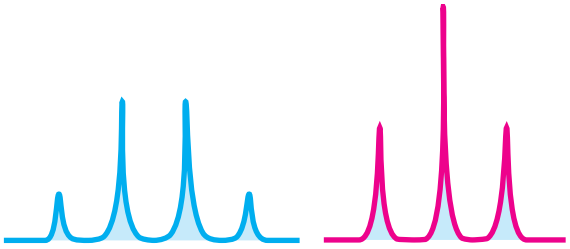
Review Problem 9.1

In what chemical shift ranges would you expect to find the proton NMR signals of ethyl acetate ($CH_3CO_2CH_2CH_3$)?

9.2B Integration of Signal Areas

- **The area under each signal in a ^{1}H NMR spectrum is proportional to the number of hydrogen atoms producing that signal.**

In the ^{1}H NMR spectrum of 1,4-dimethylbenzene (Fig. 9.3), you may have noticed curves that resemble steps over each signal. The height of each step (using any unit of measure) is proportional to the area of the NMR signal underneath it, and also to the number of hydrogen atoms giving rise to that signal. Taking the ratio of the step height associated with one signal to the step height associated with another provides the ratio of the areas for the signals, and therefore represents the number of hydrogen atoms producing one signal as compared to the other. Note that we are discussing the height of the integral steps, not the heights of the signals. It is signal area (**integration**), not signal height, that is important.



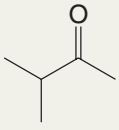
The area under each signal (shown with blue shading above) is what is measured (integrated) and taken as a ratio to compare the relative numbers of hydrogen atoms producing each signal in an NMR spectrum.

In Fig. 9.3 we have indicated the relative step heights as 1.0 and 1.5 (in dimensionless units). Had these values not been given, we would have measured the step heights with a ruler and taken their ratio. Since the actual number of hydrogen atoms giving rise to the signals is not likely to be 1 and 1.5 (we cannot have a fraction of an atom), we can surmise that the true number of hydrogens producing the signals is probably 2 and 3, or 4 and 6, etc. For 1,4-dimethylbenzene the actual values are, of course, 4 and 6.

Whether NMR data are provided as in Fig. 9.3 with an integral step over each signal, or simply with numbers that represent each signal's relative area, the process of interpreting the data is the same because the area of each signal is proportional to the number of hydrogen atoms producing that signal. (It is important to note that in ^{13}C NMR spectroscopy signal area is not relevant in routine analyses.)

Solved Problem 9.3

What integral values (as whole number ratios) would you expect for signals in the proton NMR spectrum of 3-methyl-2-butanone?



STRATEGY AND ANSWER There are three distinct proton environments in 3-methyl-2-butanone: the methyl at C1, the methine hydrogen at C3, and the two methyl groups bonded to C3, which are equivalent. The ratio of these signals, in the order just listed, would be 3 : 1 : 6.

9.2C Coupling (Signal Splitting)

Coupling, also referred to as **signal splitting** or signal multiplicity, is a third feature of ^{1}H NMR spectra that provides very useful information about the structure of a compound.

- Coupling is caused by the magnetic effect of nonequivalent hydrogen atoms that are within 2 or 3 bonds of the hydrogens producing the signal.

The effect of the nearby hydrogens is to split (or couple with) the energy levels of the hydrogens whose signal is being observed, and the result is a signal with multiple peaks. (Notice that we have been careful to differentiate use of the words signal and peak. A group of equivalent atoms produces one *signal* that may be split into multiple *peaks*.) We shall explain the physical origin of coupling further in Section 9.9; however, **the importance of coupling is that it is predictable, and it gives us specific information about the constitution of the molecule under study**.

The typical coupling we observe is from nonequivalent, **vicinal** hydrogens, that is, from hydrogens on adjacent carbons, separated by three bonds from the hydrogens producing the signal. Coupling can also occur between nonequivalent **geminal** hydrogens (hydrogens bonded to the same carbon) if the geminal hydrogens are in a chiral or conformationally restricted molecule. (We shall discuss cases of chiral and conformationally restricted molecules in Section 9.8.)

A simple rule exists for predicting the number of peaks expected from vicinal coupling in ^{1}H NMR:

Number of peaks from vicinal coupling in a ^{1}H NMR signal	$= n + 1$	Where n is the number of vicinal hydrogen atoms that are nonequivalent to those producing the signal

This rule is applicable in general to achiral molecules without conformational barriers.

The ^{1}H NMR spectrum of 1,4-dimethylbenzene (Fig. 9.3) is an example where $n = 0$ (in the above equation) regarding the hydrogen atoms producing the signals at δ 7.0 and at δ 2.3. There are no hydrogen atoms on the carbons adjacent to the methyl groups; hence $n = 0$ for the signal at δ 2.3, and the signal is a singlet (signals with only one peak are called **singlets**). And, since all of the hydrogen atoms on the ring are equivalent by symmetry and there are no adjacent nonequivalent hydrogen atoms, $n = 0$ for the hydrogens on the ring producing the signal at δ 7.0, and hence this signal is a singlet as well.

The ^{1}H NMR spectrum of 1,1,2-trichloroethane, shown in Fig. 9.4, provides an example where n is not equal to zero, and coupling is therefore evident. In the spectrum of 1,1,2-trichloroethane we see two signals: one with three peaks and one with two peaks. These signals are called, respectively, a **triplet** and a **doublet**. The signal for the $-CHCl_2$ hydrogen is a triplet because there are two hydrogen atoms on the adjacent carbon ($n = 2$). The signal for the $-CH_2Cl$ hydrogens is a doublet because there is one hydrogen on the adjacent carbon ($n = 1$). We shall consider why this is so in Section 9.9.

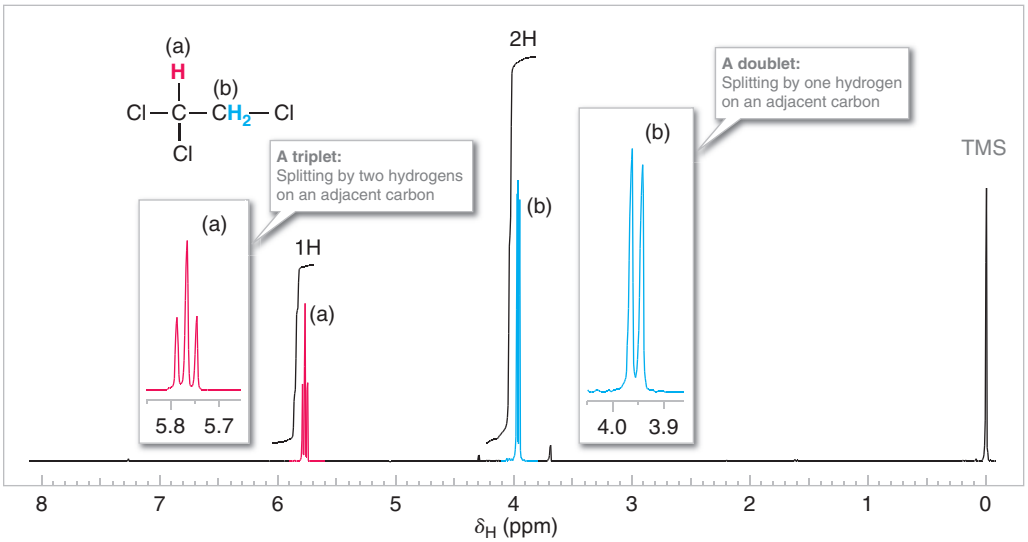


Figure 9.4 The 300-MHz ^{1}H NMR spectrum of 1,1,2-trichloroethane. Zoomed-in expansions of the signals are shown in the offset plots.

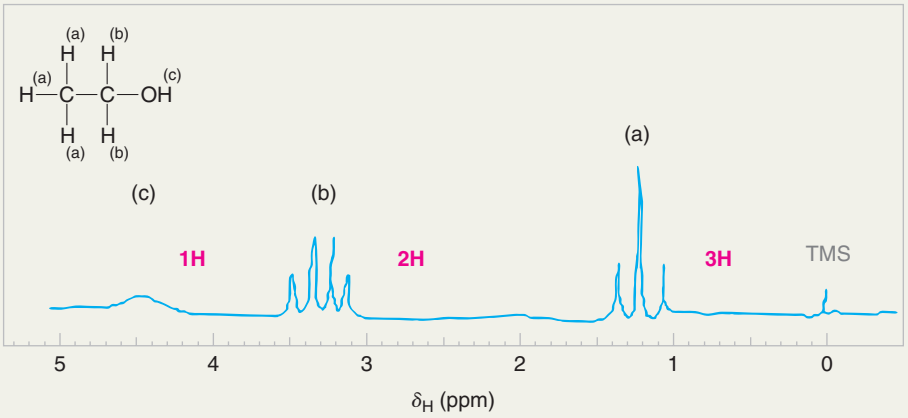
Solved Problem 9.4

Sketch a predicted proton NMR spectrum for ethanol, showing signals in the expected chemical shift ranges (based on Table 9.1) and with the appropriate number of peaks in each. (Note one important fact: Hydrogen atoms bonded to oxygen and nitrogen do not usually show coupling, but often exhibit a single broad peak instead. We shall explain why later in Section 9.10.)

STRATEGY AND ANSWER There are four things to pay attention to: (1) the number of signals, (2) the chemical shifts of the signals, (3) the coupling patterns (signal splitting) in the signals, and (4) the relative signal areas. We have already predicted the first two of these in Solved Problem 9.2, part b.

1. In ethanol there are protons in three distinct environments; thus, we expect three signals.
2. The predicted chemical shifts are 3.3–4.0 ppm for the two protons on the alcohol carbon, 0.8–1.2 ppm for the three methyl protons, and 0.5–6.0 ppm for the hydroxyl proton (showing it anywhere in this broad range is acceptable—we shall explain why the range is broad in Section 9.10).
3. Regarding coupling patterns, the alcohol hydrogen does not couple, as we stated earlier. The alcohol —CH_2— group has three vicinal protons (the methyl group); following the $n + 1$ rule these should appear as a quartet. The methyl group has two vicinal protons (the alcohol —CH_2— group), thus it should be a triplet.
4. The relative signal areas are 1 : 2 : 3, according to the number of protons producing each signal, which we indicate as 1H, 2H, and 3H in our sketch.

Lastly, it is helpful to use letters to assign the protons in a formula to signals associated with them in a spectrum, and we shall do that here.



To verify our sketch we can consult the actual NMR spectrum for ethanol shown in Fig. 9.28. Note that the —OH signal can appear in a wide range, as indicated in Table 9.1.

9.3 How to Interpret Proton NMR Spectra

Now that we have had an introduction to key aspects of ^{1}H NMR spectra (chemical shift, peak area, and signal splitting), we can start to apply ^{1}H NMR spectroscopy to elucidating the structure of unknown compounds. The following steps summarize the process:

1. Count the number of signals to determine how many distinct proton environments are in the molecule (neglecting, for the time being, the possibility of overlapping signals).
2. Use chemical shift tables or charts, such as Table 9.1 or Fig. 9.2 (or your own experience over time), to correlate chemical shifts with possible structural environments.
3. Determine the relative area of each signal, as compared with the area of other signals, as an indication of the relative number of protons producing the signal.

4. Interpret the splitting pattern for each signal to determine how many hydrogen atoms are present on carbon atoms adjacent to those producing the signal and sketch possible molecular fragments.
5. Join the fragments to make a molecule in a fashion that is consistent with the data.

As a beginning example, let's interpret the ^{1}H NMR spectrum in Fig. 9.5 for a compound with the molecular formula C_3H_7Br.

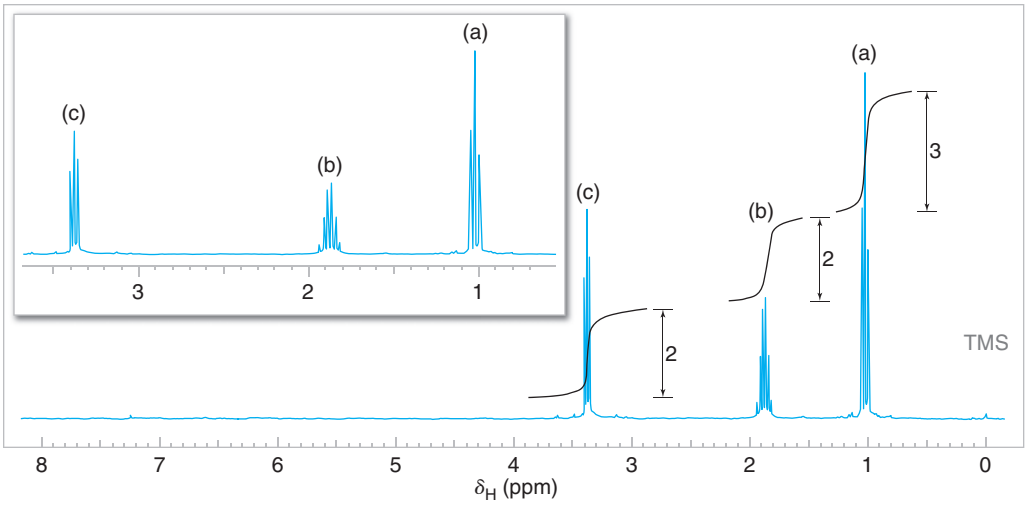
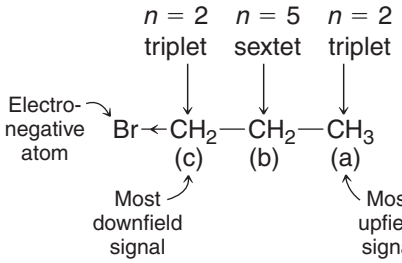


Figure 9.5 The 300-MHz ^{1}H NMR spectrum of a compound with the formula C_3H_7Br. Expansions of the signals are shown in the offset plots. (Adapted from the original [www.sigmaaldrich.com/spectra/fnmr/FNMR010277.PDF] with permission from Sigma-Aldrich © Sigma-Aldrich Co.)

1. First, we observe that there are three distinct signals, with chemical shifts of approximately δ 3.4, 1.8, and 1.1. One of these signals (δ 3.4) is noticeably downfield of the others, indicating hydrogen atoms that are likely to be near an electronegative group. This is not surprising given the presence of bromine in the formula. The presence of three distinct signals suggests that there are only three distinct proton environments in the molecule. For this example, this information alone makes it possible to reach a conclusion about the structure of the compound, since its molecular formula is as simple as C_3H_7Br. (Do you know what the compound is? Even if you do, you should still demonstrate that all of the information in the spectrum is consistent with the structure you propose.)
2. Next, we measure (or estimate) the step heights of the integral curves and reduce them to whole number ratios. Doing so, we find that the ratio is 2 : 2 : 3 (from the most downfield to the most upfield signal). Given a molecular formula that contains seven hydrogen atoms, we infer that these signals likely arise from two CH_2 groups and one CH_3 group, respectively. One of the CH_2 groups must bear the bromine. (Although you almost certainly know the structure of the compound at this point, let's continue with the analysis.) At this point we can begin to sketch molecular fragments, if we wish.
3. Next we evaluate the multiplicity of the signals. The signal at δ 3.4 is a triplet, indicating that there are two hydrogen atoms on the adjacent carbon. Since this signal is downfield and has an integral value that suggests two hydrogens, we conclude that this signal is from the CH_2Br group, and that it is next to a CH_2 group. The signal at δ 1.8 is a sextet, indicating five hydrogen atoms on adjacent carbons. The presence of five neighboring hydrogen atoms ($n = 5$, producing six peaks) is consistent with a CH_2 group on one side and a CH_3 group on the other. Lastly, the signal at δ 1.1 is a triplet, indicating two adjacent hydrogen atoms. Joining these molecular pieces together on paper or in our mind gives us $BrCH_2CH_2CH_3$ for the structural formula.

1-Bromopropane.



We have been careful in the above analysis to evaluate each aspect of the data (chemical shift, integration, and signal splitting). As you gain more skill at interpreting NMR data, you may find that just a portion of the data is sufficient to determine a compound's identity. At other times, however, you will find that more data are necessary than solely a ^{1}H NMR spectrum. Combined analysis of ^{13}C NMR, IR, and other information may be needed, for example. In the above case, knowing the molecular formula, conceiving of the possible isomers, and comparing these with the number of signals (i.e., distinct hydrogen environments) would have been enough by itself to come to the conclusion that the compound is 1-bromopropane. Nevertheless, when working a problem one should still check the final conclusion by verifying the consistency of all data with the proposed structure.

Solved Problem 9.5

What compound with molecular formula $C_3H_6Cl_2$ is consistent with the ^{1}H NMR spectrum shown in Fig. 9.6? Interpret the data by assigning each aspect of the spectrum to the structure you propose.

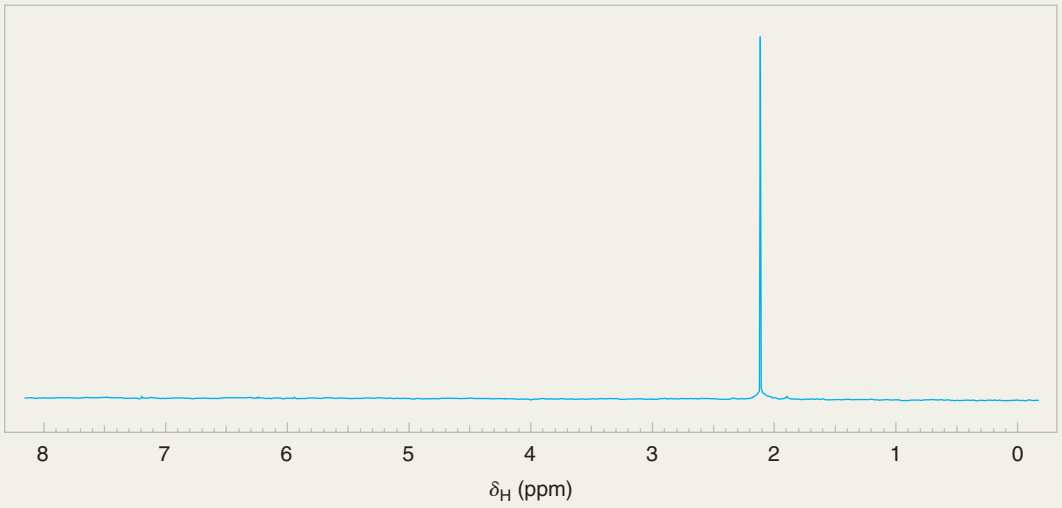


Figure 9.6 The 300-MHz ^{1}H NMR spectrum of the compound in Solved Problem 9.5 with molecular formula $C_3H_6Cl_2$. (Adapted from the original [www.sigmaaldrich.com/spectra/fnmr/FNMR004611.PDF] with permission from Sigma-Aldrich © Sigma-Aldrich Co.)

STRATEGY AND ANSWER The spectrum shown in Fig. 9.6 shows only one signal (therefore its integral is irrelevant and not shown). This must mean that the six hydrogen atoms in the formula $C_3H_6Cl_2$ all exist in the same magnetic environment. The presence of two equivalent methyl groups is a likely scenario for six equivalent hydrogen atoms. The only way to have two identical methyl groups with the formula $C_3H_6Cl_2$ is for both chlorine atoms to be bonded at C2 resulting in the structure shown to the right.

Review Problem 9.2

What compound with molecular formula $C_3H_6Cl_2$ is consistent with the ^{1}H NMR spectrum shown in Fig. 9.7? Interpret the data by assigning each aspect of the spectrum to the structure you propose. (In other words, explain how the chemical shifts, signal areas, and splitting patterns support your conclusion.)

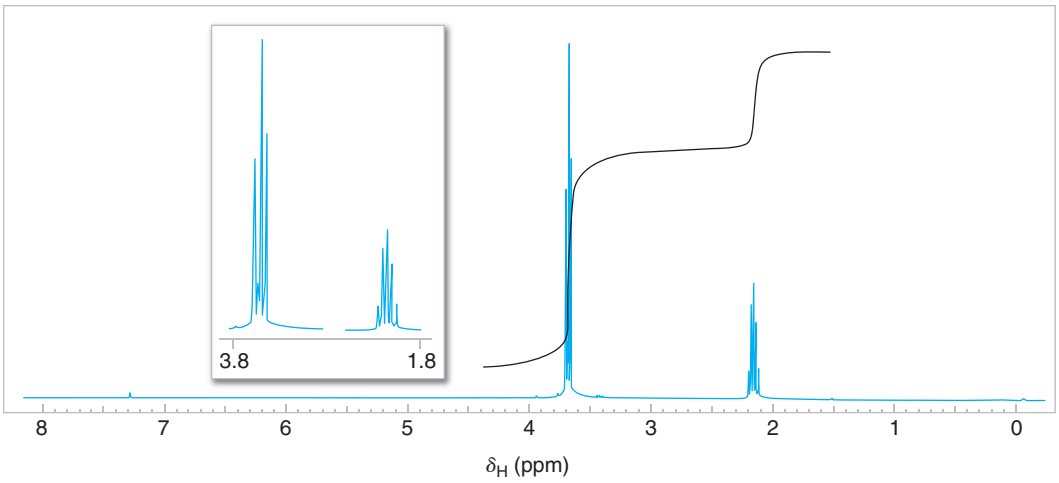


Figure 9.7 The 300-MHz ^{1}H NMR spectrum of the compound in Review Problem 9.2 with formula $C_3H_6Cl_2$. Expansions of the signals are shown in the offset plots. (Adapted from the original [www.sigmaaldrich.com/spectra/fnmr/FNMR010277.PDF] with permission from Sigma-Aldrich © Sigma-Aldrich Co.)

Now that we have had an introduction to interpreting NMR spectra, let us briefly explain the physical origin of NMR signals and how NMR spectrometers work, before returning to important information about factors that influence chemical shift and signal splitting.

9.4 Nuclear Spin: The Origin of the Signal

We are already familiar with the concepts of electron spin and electron spin quantum states from our discussions of bonding and molecular structure in Chapter 1. The nuclei of certain isotopes also possess the quality of spin, and therefore these nuclei have spin quantum numbers, designated I. The nucleus of ordinary hydrogen, ^{1}H, has a spin quantum number of $\frac{1}{2}$, and it can assume either of two spin states: $+\frac{1}{2}$ or $-\frac{1}{2}$. These correspond to the magnetic moments (m) allowed for $I = \frac{1}{2}$, which are $m = +\frac{1}{2}$ or $m = -\frac{1}{2}$. Other nuclei with spin quantum numbers $I = \frac{1}{2}$ are ^{13}C, ^{19}F, and ^{31}P. Some nuclei, such as ^{12}C, ^{16}O, and ^{32}S, have no spin ($I = 0$), and these nuclei do not give an NMR spectrum. Other nuclei have spin quantum numbers greater than $\frac{1}{2}$. In our treatment here, however, we are concerned primarily with the spectra that arise from ^{1}H and from ^{13}C, both of which have $I = \frac{1}{2}$.

Since the proton is electrically charged, the spinning charge generates a tiny magnetic moment—one that coincides with the axis of spin (Fig. 9.8). This tiny magnetic moment gives the spinning proton properties analogous to those of a tiny bar magnet.

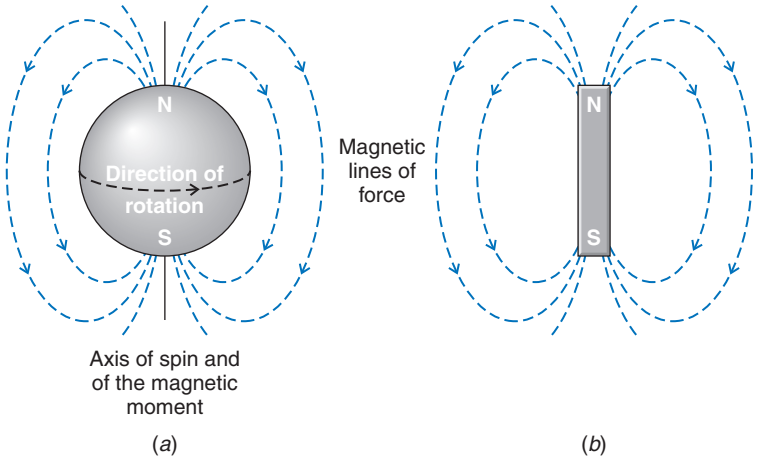


Figure 9.8 *(a)* The magnetic field associated with a spinning proton. *(b)* The spinning proton resembles a tiny bar magnet.

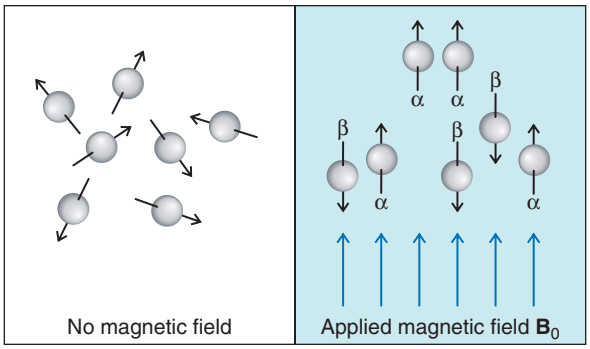


Figure 9.9 *(a)* In the absence of a magnetic field the magnetic moments of protons (represented by arrows) are randomly oriented. *(b)* When an external magnetic field (B_0) is applied, the protons orient themselves. Some are aligned with the applied field (α spin state) and some against it (β spin state). The difference in the number of protons aligned with and against the applied field is very small, but is observable with an NMR spectrometer.

In the absence of a magnetic field (Fig. 9.9*a*), the magnetic moments of the protons of a given sample are randomly oriented. When a compound containing hydrogen (and thus protons) is placed in an applied external magnetic field, however, the magnetic moment of the protons may assume one of two possible orientations with respect to the external magnetic field (other orientations are disallowed on the basis of quantum mechanics). The magnetic moment of the proton may be aligned "with" the external field or "against" it (Fig. 9.9*b*). These alignments correspond to the two spin states mentioned earlier.

- The two alignments of the proton's magnetic moment in an external field are not of equal energy. When the proton's magnetic moment is aligned with the magnetic field, its energy is lower than when it is aligned against the magnetic field. The lower energy state is slightly more populated in the ground state.
- Energy is required to "flip" the proton's magnetic moment from its lower energy state (with the field) to its higher energy state (against the field). In an NMR spectrometer this energy is supplied by electromagnetic radiation in the RF (radio frequency) region. When this energy absorption occurs, the nuclei are said to be *in resonance* with the electromagnetic radiation.

The energy required to excite the proton is proportional to the strength of the magnetic field (Fig. 9.10). One can show by relatively simple calculations that, in a magnetic field of approximately 7.04 tesla, for example, electromagnetic radiation of 300×10^6 cycles per second (300 MHz) supplies the correct amount of energy for protons.* The proton NMR spectra shown in this chapter are 300-MHz spectra.

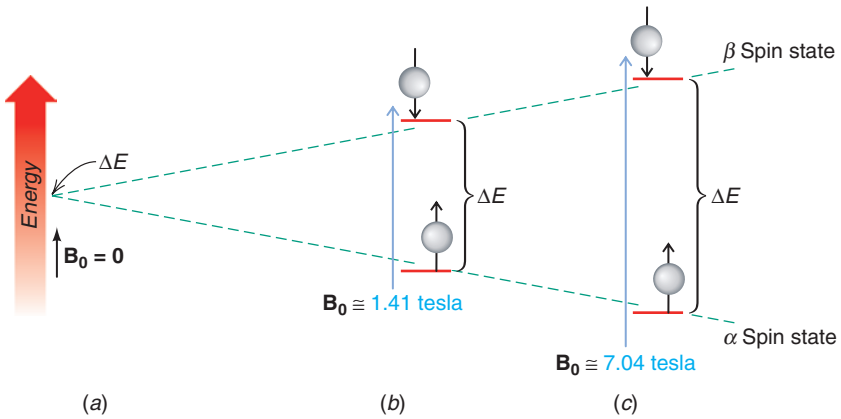


Figure 9.10 The energy difference between the two spin states of a proton depends on the strength of the applied external magnetic field, B_0. *(a)* If there is no applied field ($B_0 = 0$), there is no energy difference between the two states. *(b)* If $B_0 \cong 1.41$ tesla, the energy difference corresponds to that of electromagnetic radiation of 60×10^6 Hz (60 MHz). *(c)* In a magnetic field of approximately 7.04 tesla, the energy difference corresponds to electromagnetic radiation of 300×10^6 Hz (300 MHz). Instruments are available that operate at these and even higher frequencies (as high as 800 MHz to 1 GHz).

*The relationship between the frequency of the radiation (ν) and the strength of the magnetic field (B_0) is

$$\nu = \frac{\gamma B_0}{2\pi}$$

where γ is the magnetogyric (or gyromagnetic) ratio. For a proton, $\gamma = 26.753$ rad s^{-1} tesla^{-1}.

Let us now consider how the signal from nuclei that are in resonance is detected by NMR spectrometers, and how it is converted to an NMR spectrum.

9.5 Detecting the Signal: Fourier Transform NMR Spectrometers

Most NMR spectrometers use superconducting magnets that have very high magnetic field strengths. Superconducting magnets operate in a bath of liquid helium at 4.3 degrees above absolute zero, and they have magnetic field strengths more than 100,000 times as strong as Earth's magnetic field.

The stronger the magnet is in a spectrometer, the more sensitive the instrument. Figure 9.11 shows a diagram of a **Fourier transform NMR** spectrometer.

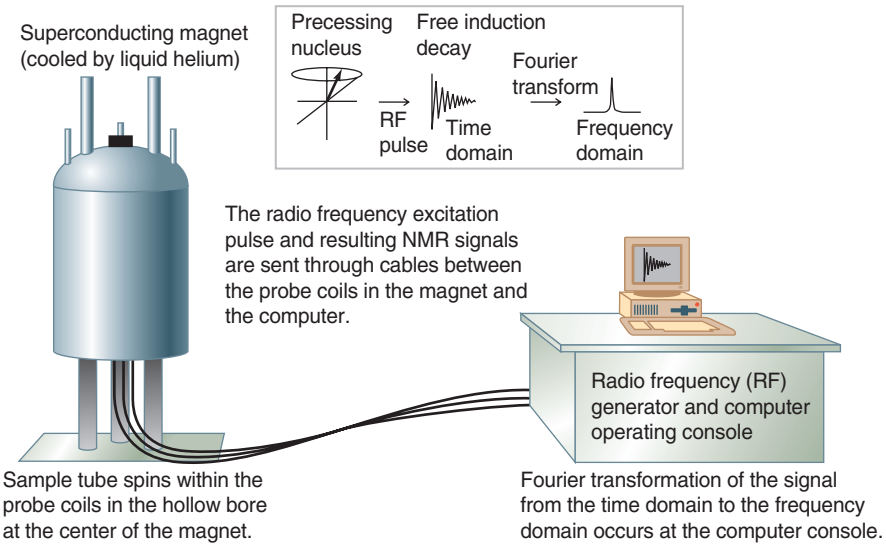
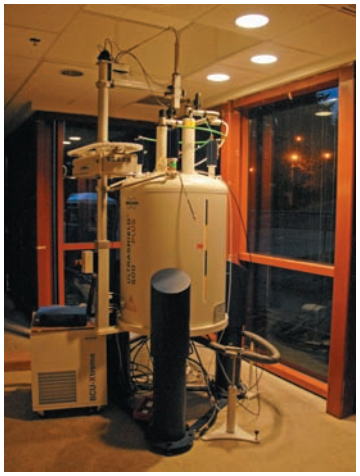


Figure 9.11 Diagram of a Fourier transform NMR spectrometer.



The superconducting magnet of an FTNMR spectrometer.

As we discussed in the previous section, certain nuclei in the presence of a magnetic field behave as though they were tiny bar magnets that align themselves with or against the applied magnetic field. The nuclei spin (precess) about the spectrometer's magnetic field axis (the "applied" magnetic field), much the same way that a spinning top gyrates around the axis of gravity. The precessional frequency of each nucleus is directly related to its chemical shift. We can illustrate a nuclear magnetic moment precessing about the axis of an applied magnetic field ($\mathbf{B_0}$) using a vector representation, as shown in Fig. 9.12*a*.

Applying a pulse of radio frequency energy that matches the precessional frequency of the nuclear magnetic moment causes the magnetic vector of the nucleus to tip away from the applied magnetic field axis (the *z*-axis) toward the *x*–*y* plane (Fig. 9.12*b*). The nuclear magnetic vector still precesses about the *z*-axis, but it lies in the *x*–*y* plane. From the perspective of a tiny coil of wire (called a receiver coil) situated next to the *x*–*y* plane, rotation of this vector around the *z*-axis but in the *x*–*y* plane presents an oscillating magnetic field to the receiver coil. And just as with large-scale electrical generators, this oscillating magnetic field induces an oscillating electric current in the coil (Fig. 9.12*c*). This current is the signal detected by the NMR spectrometer. Let us briefly explain the properties of this signal further.

Tipping the nuclear magnetic vector away from the axis of the applied magnetic field requires absorption of radio frequency energy by the nucleus. This energy comes from a radio frequency pulse generated by the NMR spectrometer. In a matter of seconds or less, however, the nucleus releases the energy it absorbed back to the sample environment, returning the nucleus to its ground state energy as it moves back toward the *z*-axis. As it does so, the vector component of magnetization in the *x*–*y* axis diminishes, and the observed electrical signal decays (Fig. 9.12*d*). The oscillating electrical signal produced by the excited

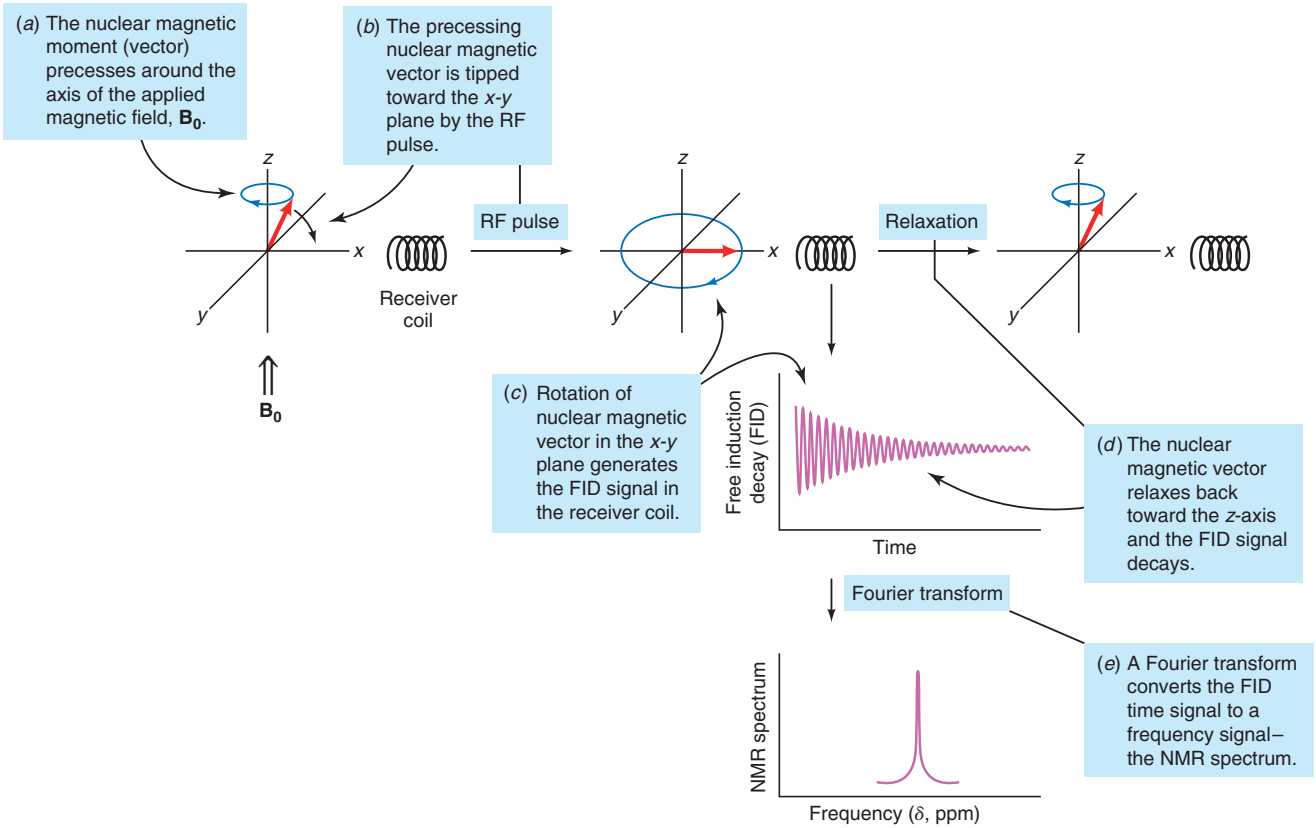


Figure 9.12 Origin of the signal in FTNMR spectroscopy.

nucleus is therefore not a signal of steady amplitude, but one which dies away exponentially. This signal is called a free induction decay (FID). The NMR computer applies a mathematical operation called a Fourier transform to convert the signal from a time versus amplitude signal (the FID) to a frequency versus amplitude signal (the NMR spectrum that we interpret) (Fig. 9.12*e*).

There is much more that could be said about the origin of NMR signals and how NMR spectrometers work. The interested student is referred to advanced texts on spectroscopy for further information. However, let us conclude with a few final points.

As we mentioned, the chemical shift of an NMR signal is directly related to its precessional frequency. Since most compounds have nuclei in a variety of environments, they have nuclei that precess at a variety of frequencies, and therefore exhibit signals at a variety of chemical shifts. The FID signal detected by the NMR spectrometer is an aggregate of all of these frequencies. A powerful aspect of the Fourier transform (FT), as a mathematical process, is that it extracts these combined frequencies from the FID and converts them to discrete signals that we can interpret in an NMR spectrum.

Another great advantage to Fourier transform spectrometers is that the FT process allows computerized signal averaging of many data scans, which cancels out random electronic noise and enhances the actual NMR signals. This is especially important for samples that produce weak signals. Furthermore, acquisition of the data from each scan is very fast. The radio-frequency pulse used to excite the sample is typically on the order of only 10^{-5} s, and pulses can be repeated within a few seconds or less. Thus, many data scans can be acquired over just a short time, so as to maximize signal averaging and enhance the clarity of the data.

With this introduction to the origin of NMR signals and how spectrometers work, we return to consider further aspects of shielding and deshielding, chemical shift, and signal splitting.

9.6 Shielding and Deshielding of Protons

- All protons do not absorb energy at the same frequency in a given external magnetic field.

For example, the aromatic protons of 1,4-dimethylbenzene absorb at higher frequency (δ 7.05) than the various alkyl protons of 1,4-dimethylbenzene and 1,1,2-trichloroethane (Figs. 9.3 and 9.4).

- Lower chemical shift values correspond with lower frequency.
- Higher chemical shift values correspond with higher frequency.

The general position of a signal in an NMR spectrum—that is, the frequency of radiation required to bring about absorption of energy at a given magnetic field strength—can be related to electron densities and electron circulations in the compounds. Under the influence of an external magnetic field the electrons move in certain preferred paths. Because they do, and because electrons are charged particles, they generate tiny magnetic fields.

We can see how this happens if we consider the electrons around the proton in a σ bond of a C—H group. In doing so, we shall oversimplify the situation by assuming that σ electrons move in generally circular paths. The magnetic field generated by these σ electrons is shown in Fig. 9.13.

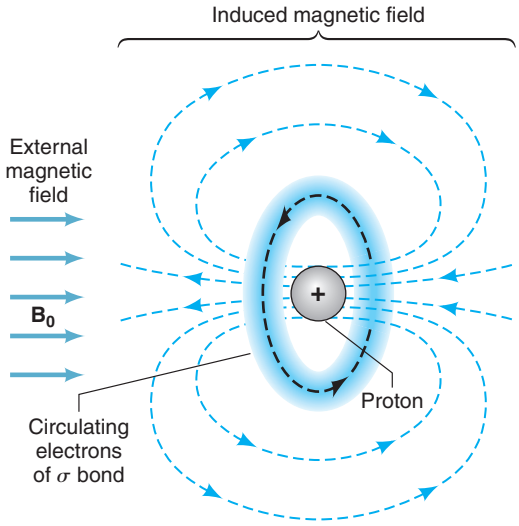


Figure 9.13 Circulations of the electrons of a C—H bond under the influence of an external magnetic field. The electron circulations generate a small magnetic field (an induced field) that shields the proton from the external field.

The small magnetic field generated by the electrons is called an **induced field**. ***At the proton, the induced magnetic field opposes the external magnetic field***. This means that the actual magnetic field sensed by the proton is slightly less than the external field. The electrons are said *to shield* the proton.

A proton strongly shielded by electrons does not, of course, absorb at the same frequency as a proton that is less shielded by electrons.

- A shielded proton will absorb *at lower frequency (upfield)* (Fig. 9.14).

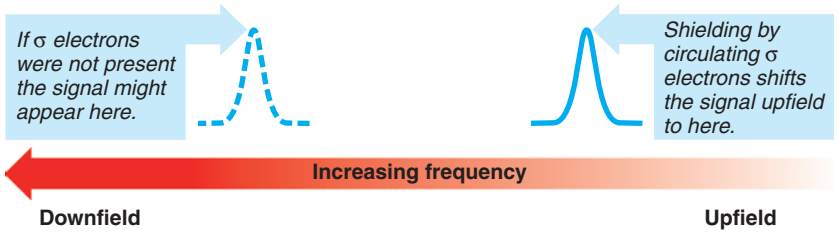


Figure 9.14 Shielding by σ electrons causes ^{1}H NMR absorptions to be shifted to lower frequency.

Deshielding by Electronegative Groups The extent to which a proton is shielded by the circulation of σ electrons depends on the relative electron density around the proton. This electron density depends largely on the presence or absence of electronegative groups. Electronegative groups withdraw electron density from the C—H bond, particularly if they are attached to the same carbon. We have seen an example of this effect in the spectrum of 1,1,2-trichloroethane (Fig. 9.4). The proton of C1 absorbs at higher frequency (δ 5.77) than the protons of C2 (δ 3.95). Carbon 1 bears two highly electronegative chlorine atoms, whereas C2 bears only one. The protons of C2, consequently, are more effectively shielded because the σ-electron density around them is greater, and they absorb at lower frequency.

Shielding and Deshielding by Circulation of π Electrons The circulations of delocalized π electrons generate magnetic fields that can either **shield** or **deshield** nearby protons. Whether shielding or deshielding occurs depends on the location of the proton in the *induced* field. The aromatic protons of benzene derivatives (Section 14.7B) are *deshielded* because their locations are such that the induced magnetic field reinforces the applied magnetic field.

Because of this deshielding effect, the absorption of energy by aromatic protons occurs downfield at higher frequency. The protons of benzene itself absorb at δ 7.27. The aromatic protons of 1,4-dimethylbenzene (Fig. 9.3) absorb at δ 7.05.

Magnetic fields created by circulating π electrons *shield* the protons of ethyne (and other terminal alkynes), causing them to absorb at lower frequency than we might otherwise expect. If we were to consider *only* the relative electronegativities of carbon in its three hybridization states (Section 3.8A), we might expect the following order of protons attached to each type of carbon:

(higher frequency) $sp < sp^2 < sp^3$ (lower frequency)

In fact, protons of terminal alkynes absorb between δ 2.0 and δ 3.0, and the order is

(higher frequency) $sp^2 < sp < sp^3$ (lower frequency)

This upfield shift (lower frequency) of the absorption of protons of terminal alkynes is a result of shielding produced by the circulating π electrons of the triple bond. The origin of this shielding is illustrated in Fig. 9.15.

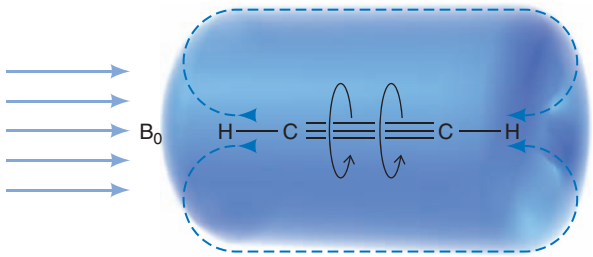


Figure 9.15 The shielding of protons of ethyne by π-electron circulations. Shielding causes protons attached to the *sp* carbons to absorb further upfield (at lower frequency) than vinylic protons.

9.7 The Chemical Shift

We have now seen that shielding and deshielding effects cause the absorptions of protons to have different chemical shifts along the *x*-axis of NMR spectra.

As we have also mentioned, chemical shifts are most often measured with reference to the absorption of the protons of TMS (tetramethylsilane). A small amount of TMS is usually added to the sample, and its signal establishes zero on the delta (δ) scale.

$Si(CH_3)_4$

Tetramethylsilane (TMS)

- The signal from TMS defines zero ppm on the chemical shift (δ) scale.

Tetramethylsilane was chosen as a reference compound for several reasons. It has 12 equivalent hydrogen atoms, and, therefore, a very small amount of TMS gives a relatively large signal. Because the hydrogen atoms are all equivalent, they give a *single signal*. Since silicon is

less electronegative than carbon, the protons of TMS are in regions of high electron density. They are, as a result, highly shielded, and the signal from TMS occurs upfield in a region of the spectrum where few other hydrogen atoms absorb. Thus, their signal seldom interferes with the signals from other hydrogen atoms. Tetramethylsilane, like an alkane, is relatively inert. It is also volatile, having a boiling point of 27°C. After the spectrum has been determined, the TMS can be removed from the sample easily by evaporation.

9.7A PPM and the δ Scale

The chemical shift of a proton, when expressed in **hertz (Hz)**, is proportional to the strength of the external magnetic field. Since spectrometers with different magnetic field strengths are commonly used, it is desirable to express chemical shifts in a form that is independent of the strength of the external field. This can be done easily by dividing the chemical shift by the frequency of the spectrometer, with both numerator and denominator of the fraction expressed in frequency units (hertz). Since chemical shifts are always very small (typically <5000 Hz) compared with the total field strength (commonly the equivalent of 60, 300, or 600 *million* hertz), it is convenient to express these fractions in units of *parts per million* (ppm). This is the origin of the delta scale for the expression of chemical shifts relative to TMS:

$$\delta = \frac{(\text{observed shift from TMS in hertz}) \times 10^6}{(\text{operating frequency of the instrument in hertz})}$$

For example, the chemical shift for benzene protons is 2181 Hz when the instrument is operating at 300 MHz. Therefore,

$$\delta = \frac{2181 \text{ Hz} \times 10^6}{300 \times 10^6 \text{ Hz}} = 7.27$$

The chemical shift of benzene protons in a 60-MHz instrument is 436 Hz:

$$\delta = \frac{436 \text{ Hz} \times 10^6}{60 \times 10^6 \text{ Hz}} = 7.27$$

Thus, the chemical shift expressed in ppm is the same whether measured with an instrument operating at 300 or 60 MHz (or any other field strength).

Figure 9.2 (Section 9.2A) gives the *approximate* values of proton chemical shifts for some common hydrogen-containing groups.

9.8 Chemical Shift Equivalent and Nonequivalent Protons

Two or more protons that are in identical environments have the same chemical shift and, therefore, give only one ^{1}H NMR signal. How do we know when protons are in the same environment? For most compounds, protons that are in the same environment are also equivalent in chemical reactions. That is, **chemically equivalent** protons are **chemical shift equivalent** in ^{1}H NMR spectra.

9.8A Homotopic and Heterotopic Atoms

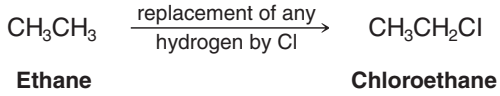
How do we decide whether two or more protons in a molecule are in identical environments?

- One way to decide is to replace each hydrogen in turn by some other atom or group (which may be real or imaginary) and then use the result of the replacement to make our decision.

If replacing the hydrogens by a different atom gives the same compound, the hydrogens are said to be **homotopic**.

- Homotopic hydrogens have identical environments and will have the same chemical shift. They are said to be **chemical shift equivalent**.

Consider the hydrogens of ethane as an example. Replacing any one of the six hydrogens of ethane by a different atom, say, by chlorine, gives the same compound: chloroethane.

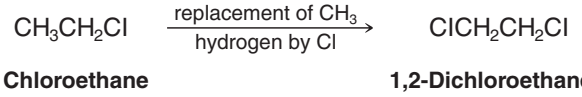


The six hydrogens of ethane are *homotopic* and are, therefore, *chemical shift equivalent*. **Ethane, consequently, gives only one signal in its ^{1}H NMR spectrum**. [Remember, the barrier to rotation of the carbon–carbon bond of ethane is so low (Section 4.8), the various conformations of chloroethane interconvert rapidly.]

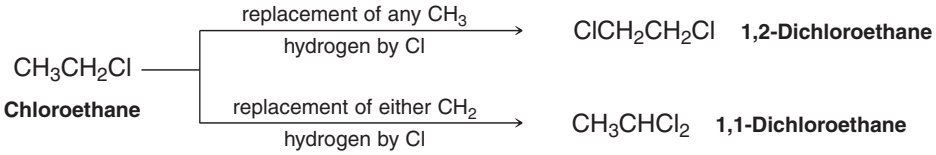
If replacing hydrogens by a different atom gives **different compounds**, the hydrogens are said to be **heterotopic**.

- **Heterotopic atoms have different chemical shifts and are not chemical shift equivalent**.

Consider the set of methyl hydrogens of chloroethane next. Replacing any one of the three hydrogens of the CH_3 group of chloroethane with chlorine yields the same compound, 1,2-dichloroethane. The three protons of the CH_3 group are **homotopic** with respect to each other, and the CH_3 group gives only one ^{1}H NMR signal.

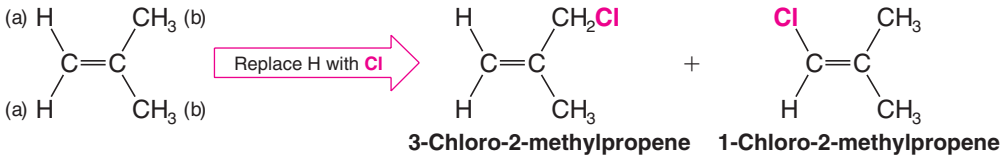


However, if we compare the set of hydrogens of the CH_2 group of chloroethane with those of its CH_3 set we find that the hydrogens of the CH_3 and CH_2 groups are **heterotopic** with respect to each other. Replacing either of the two hydrogens of the CH_2 set by chlorine yields 1,1-dichloroethane, whereas replacing any one of the set of three CH_3 hydrogens yields a different compound, 1,2-dichloroethane.



Chloroethane, therefore, has two sets of hydrogens that are heterotopic with respect to each other, the CH_3 hydrogens and the CH_2 hydrogens. The hydrogens of these two sets are not chemical shift equivalent, and chloroethane gives two ^{1}H NMR signals.

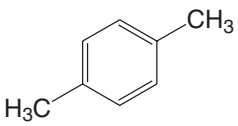
Consider 2-methylpropene as a further example:

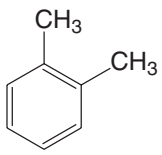


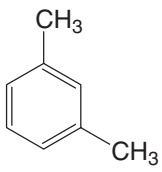
The six methyl hydrogens (b) are one set of homotopic hydrogens; replacing any one of them with chlorine, for example, leads to the same compound, 3-chloro-2-methylpropene. The two vinyl hydrogens (a) are another set of homotopic hydrogens; replacing either of these leads to 1-chloro-2-methylpropene. 2-Methylpropene, therefore, gives two ^{1}H NMR signals.

Review Problem 9.3

Using the method of Section 9.8A, determine the number of expected signals for the following compounds.

(a) 

(b) 

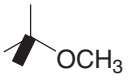
(c) 

Review Problem 9.4

How many signals would each compound give in its ^{1}H NMR spectrum?

(a) CH_3OCH_3

(b) 

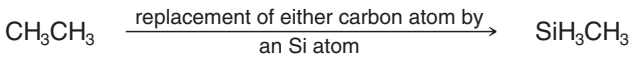
(c) 

(d) 2,3-Dimethyl-2-butene

(e) (*Z*)-2-Butene

(f) (*E*)-2-Butene

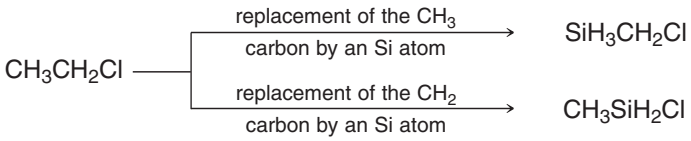
Application to ^{13}C NMR Spectroscopy As a preview of what is to come later in this chapter when we study ^{13}C NMR spectroscopy, let us look briefly at the carbon atoms of ethane to see whether we can use a similar method to decide whether they are homotopic or heterotopic, and whether ethane would give one or two ^{13}C signals. Here we can make our imaginary replacements using a silicon atom.



Ethane

Only one product is possible; therefore, the carbons of ethane are **homotopic**, and **ethane would give only one signal in its ^{13}C spectrum**.

On the other hand, if we consider chloroethane, replacement of a carbon atom by a silicon atom gives two possibilities:

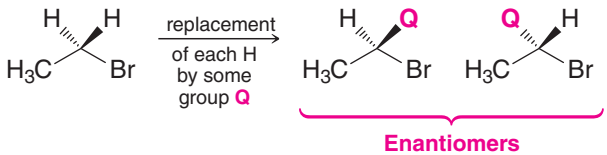


We do not get the same compounds from each replacement. We can conclude, therefore, that the two carbon atoms of chloroethane are **heterotopic**. They are not chemical shift equivalent, and each carbon atom of chloroethane would give a ^{13}C signal at a different chemical shift. **Chloroethane gives two ^{13}C NMR signals**.

9.8B Enantiotopic and Diastereotopic Hydrogen Atoms

If replacement of each of two hydrogen atoms by the same group yields compounds that are enantiomers, the two hydrogen atoms are said to be **enantiotopic**.

- Enantiotopic hydrogen atoms have the same chemical shift and give only one ^{1}H NMR signal:*



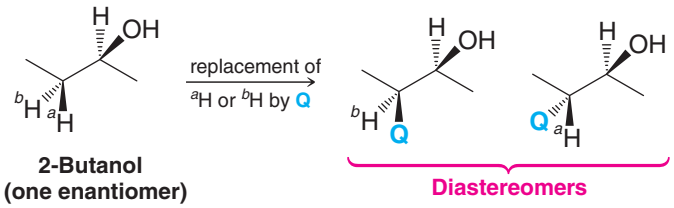
*Enantiotopic hydrogen atoms may not have the same chemical shift if the compound is dissolved in a chiral solvent. However, most ^{1}H NMR spectra are determined using achiral solvents, and in this situation enantiotopic protons have the same chemical shift.

The two hydrogen atoms of the $—CH_2Br$ group of bromoethane are enantiotopic. Bromoethane, then, gives two signals in its ^1H NMR spectrum. The three equivalent protons of the $—CH_3$ group give one signal; the two enantiotopic protons of the $—CH_2Br$ group give the other signal. [The ^1H NMR spectrum of bromoethane, as we shall see, actually consists of seven peaks (three in one signal, four in the other). This is a result of signal splitting, which is explained in Section 9.9.]

If replacement of each of two hydrogen atoms by a group, Q, gives compounds that are diastereomers, the two hydrogens are said to be **diastereotopic**.

- Except for accidental coincidence, diastereotopic protons do not have the same chemical shift and give rise to different ^1H NMR signals.

The two methylene hydrogens labeled ^aH and ^bH at C3 in 2-butanol are **diastereotopic**. We can illustrate this by imagining replacement of ^aH or ^bH with some imaginary group Q. The result is a pair of diastereomers. As diastereomers, they have different physical properties, including chemical shifts, especially for those protons near the chirality center.



The diastereotopic nature of ^aH and ^bH at C3 in 2-butanol can also be appreciated by viewing Newman projections. In the conformations shown below (Fig. 9.16), as is the case for every possible conformation of 2-butanol, ^aH and ^bH experience different environments because of the asymmetry from the chirality center at C2. That is, the "molecular landscape" of 2-butanol appears different to each of these diastereotopic hydrogens. ^aH and ^bH experience different magnetic environments, and are therefore not chemical shift equivalent. This is true in general: **diastereotopic hydrogens are not chemical shift equivalent**.

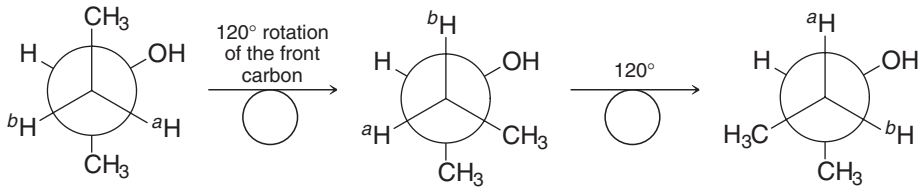
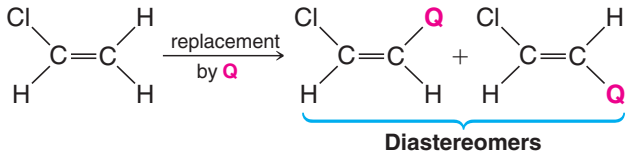


Figure 9.16 ^aH and ^bH (on C3, the front carbon in the Newman projection) experience different environments in these three conformations, *as well as in every other possible conformation of 2-butanol*, because of the chirality center at C2 (the back carbon in the Newman projection). In other words, the molecular landscape as viewed from one diastereotopic hydrogen will always appear different from that viewed by the other. Hence, ^aH and ^bH experience different magnetic environments and therefore should have different chemical shifts (though the difference may be small). They are not chemical shift equivalent.

Alkene hydrogens can also be diastereotopic. The two protons of the $=CH_2$ group of chloroethene are diastereotopic:



Chloroethene, then, should give signals from three nonequivalent protons: one for the proton of the ClCH= group, and one for each of the diastereotopic protons of the $=CH_2$ group.

Review Problem 9.5

(a) Show that replacing each of the two methylene protons by **Q** in the other enantiomer of 2-butanol also leads to a pair of diastereomers.

(b) How many chemically different kinds of protons are there in 2-butanol?

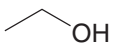
(c) How many ^{1}H NMR signals would you expect to find in the spectrum of 2-butanol?

Review Problem 9.6

How many ^{1}H NMR signals would you expect from each of the following compounds?

(a)

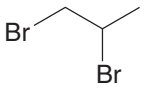
(b)



(c)

(d)

(e)



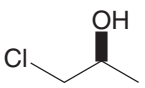
(f)

(g)

(h)

(i)

(j)

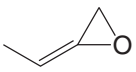


(k)

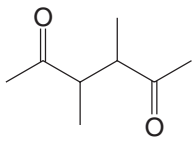
(l)

(m)

(n)



(o)



(p)

9.9 Signal Splitting: Spin–Spin Coupling

Signal splitting arises from a phenomenon known as spin–spin coupling. Spin–spin coupling effects are transferred primarily through bonding electrons and lead to **spin–spin splitting**.

- **Vicinal coupling** is coupling between hydrogen atoms on adjacent carbons (vicinal hydrogens), where separation between the hydrogens is by three σ bonds.

The most common occurrence of coupling is vicinal coupling. Hydrogens bonded to the same carbon (geminal hydrogens) can also couple, but only if they are diastereotopic. Long-range coupling can be observed over more than three bond lengths in very rigid molecules such as bicyclic compounds, and in systems where π bonds are involved. We shall limit our discussion to vicinal coupling, however.

9.9A Vicinal Coupling

- Vicinal coupling between heterotopic protons generally follows the $n + 1$ rule (Section 9.2C). Exceptions to the $n + 1$ rule can occur when diastereotopic hydrogens or conformationally restricted systems are involved.

We have already seen an example of vicinal coupling and how the $n + 1$ rule applies in our discussion of the spectrum of 1,1,2-trichloroethane (Fig. 9.4). To review, the signal from the two equivalent protons of the $-CH_2Cl$ group of 1,1,2-trichloroethane is split into a doublet by the proton of the $CHCl_2-$ group. The signal from the proton of the $CHCl_2-$ group is split into a triplet by the two protons of the $-CH_2Cl$ group.

Before we explain the origin of signal splitting, however, let us also consider two examples where signal splitting would *not* be observed. Part of understanding signal splitting is recognizing when you would not observe it. Consider ethane and methoxyacetonitrile. All of the hydrogen atoms in ethane are equivalent, and therefore they have the same chemical shift and do not split each other. The ^{1}H NMR spectrum of ethane consists of one signal that is a

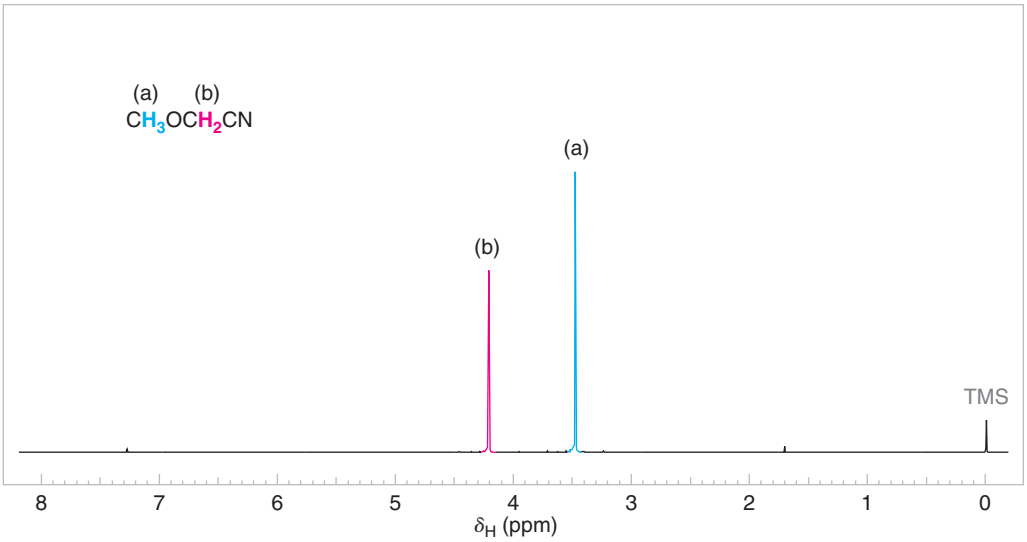


Figure 9.17 The 300-MHz ^{1}H NMR spectrum of methoxyacetonitrile. The signal of the enantiotopic protons (b) is not split.

singlet. The spectrum of methoxyacetonitrile is shown in Fig. 9.17. While there are two signals in the spectrum of methoxyacetonitrile, no coupling is observed and therefore both signals are singlets because (1) the hydrogens labeled (a) and (b) are more than three single bonds apart, and (2) the hydrogens labeled (a) are homotopic and those labeled (b) are enantiotopic.

- **Signal splitting is not observed for protons that are homotopic (chemical shift equivalent) or enantiotopic**.

Let us now explain how signal splitting arises from coupled sets of protons that are not homotopic.

9.9B Splitting Tree Diagrams and the Origin of Signal Splitting

Signal splitting is caused by the magnetic effect of protons that are nearby and nonequivalent to those protons producing a given signal. Nearby protons have magnetic moments that can either add to or subtract from the magnetic field around the proton being observed. This effect splits the energy levels of the protons whose signal is being observed into a signal with multiple peaks.

We can illustrate the origin of signal splitting using **splitting tree diagrams** and by showing the possible combinations of magnetic moment alignments for the adjacent protons. In Figures 9.18, 9.19, and 9.20 we apply this sort of analysis to splitting that would cause the patterns of a doublet, triplet, and quartet.

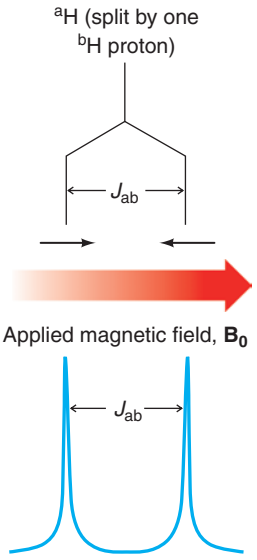
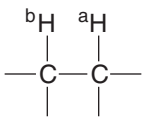


Figure 9.18 Splitting tree diagram for a doublet. The signal from the observed hydrogen (^{a}H) is split into two peaks of 1 : 1 intensity by the additive and subtractive effects of the magnetic field from one adjacent hydrogen (^{b}H) on $\mathbf{B_0}$ (the applied field). J_{ab}, the spacing between the peaks (measured in hertz), is called the coupling constant.



Splitting Analysis for a Doublet Figure 9.18 shows a splitting tree diagram for a doublet. The signal from the observed hydrogen (^{a}H) is split into two peaks of **1 : 1 intensity** by the additive and subtractive effects of the magnetic field from a single adjacent hydrogen (^{b}H) on the applied magnetic field, $\mathbf{B_0}$. The two possible magnetic orientations for the adjacent hydrogen (^{b}H) that align either against or with the applied magnetic field are shown underneath the splitting tree using arrows. J_{ab}, the spacing between the peaks (measured in hertz), is called the coupling constant. (We shall have more to say about coupling constants later.)

Splitting Analysis for a Triplet Figure 9.19 shows a splitting tree diagram for a triplet. The signal from the observed hydrogen (^{a}H) is split into three peaks of **1 : 2 : 1 intensity** by the magnetic effects of two adjacent equivalent hydrogens (^{b}H). The upper level in the diagram represents splitting from one of the adjacent ^{b}H hydrogens, leading initially to two

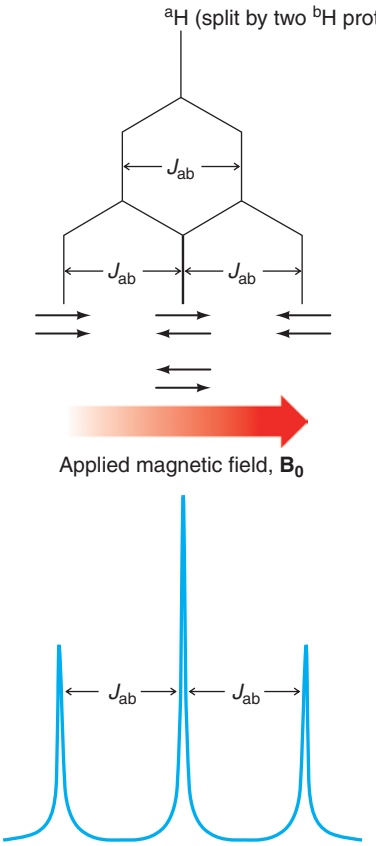
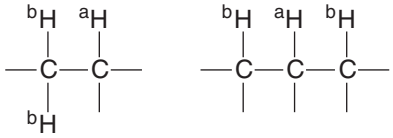


Figure 9.19 Splitting tree diagram for a triplet. The signal from the observed hydrogen (^{a}H) is split into three peaks of 1 : 2 : 1 intensity by two adjacent equivalent hydrogens (^{b}H). The upper level of splitting in the diagram represents splitting from one of the adjacent ^{b}H hydrogens, producing a doublet shown as two legs. The second ^{b}H hydrogen splits each of these legs again, as shown at the next level. The center legs at this level overlap however, because J_{ab} is the same* for the coupling of both ^{b}H hydrogens with ^{a}H. This analysis accounts for the observed 1 : 2 : 1 ratio of intensities in a spectrum (simulated in blue). In any splitting tree diagram, the lowermost level most closely represents what we observe in the actual spectrum. The possible magnetic orientations of the two ^{b}H hydrogens are shown under the tree diagram with arrows indicating that both of the adjacent hydrogens may be aligned with the applied field, or one may be aligned with and the other against (in two equal energy combinations, hence twice the intensity), or both may be aligned against the applied field.



*In this example, J_{ab} is the same for both ^{b}H hydrogens because we assume them to be homotopic or enantiotopic (chemical shift equivalent). If they were diastereotopic or otherwise chemical shift nonequivalent, each may have had a different coupling constant with ^{a}H, and the splitting pattern would not have been a pure triplet (or not even a triplet at all). For example, if the two coupling constants had been significantly different, the pattern would have been a doublet of doublets instead of a triplet. Diastereotopic geminal hydrogens that couple with a vicinal hydrogen typically produce a doublet of doublets, because geminal coupling constants are often larger than vicinal coupling constants.

legs that appear like the diagram for a doublet. Each of these legs is split by the second ^{b}H hydrogen, as shown at the next level. The center legs at this level overlap, however, because J_{ab} is the same for coupling of both of the ^{b}H hydrogens with ^{a}H. This overlap of the two center legs reflects the observed 1 : 2 : 1 ratio of intensities in a spectrum, as shown in the simulated triplet in Fig. 9.19. (Note that in any splitting tree diagram, the lowermost level schematically represents the peaks we observe in the actual spectrum.)

The possible magnetic orientations of the two ^{b}H hydrogens that cause the triplet are shown under the splitting diagram with arrows. The arrows indicate that both of the adjacent hydrogens may be aligned with the applied field, or one may be aligned with and the other against (in two equal energy combinations, causing a doubling of intensity), or both may be aligned against the applied field. Diagraming the possible combinations for the nuclear magnetic moments is another way (in addition to the splitting tree diagram) to show the origin of the 1 : 2 : 1 peak intensities that we observe in a triplet.

Splitting Analysis for a Quartet Figure 9.20 shows the splitting tree diagram for a quartet. The signal from the observed hydrogen (^{a}H) is split into three peaks of **1 : 3 : 3 : 1 intensity** by the magnetic effects of three equivalent hydrogens (^{b}H). The same method of analysis used for the triplet pattern applies here, wherein each successively lower level in the tree diagram represents splitting by another one of the coupled hydrogens. Again, because in this case J_{ab} is the same for the splitting of ^{a}H by all three of the adjacent ^{b}H hydrogens, the internal legs of the diagram overlap, and the intensities are additive each time this occurs. The result is a pattern of 1 : 3 : 3 : 1 intensities, as we would observe for a quartet in an actual spectrum.

The possible magnetic orientations shown under the tree diagram for the three ^{b}H hydrogens indicate that all three of the adjacent hydrogens may be aligned with the applied field, or two may be aligned with the field and one against (in three equal energy combinations), or two against and one with the field (again, in three equal energy combinations), or all

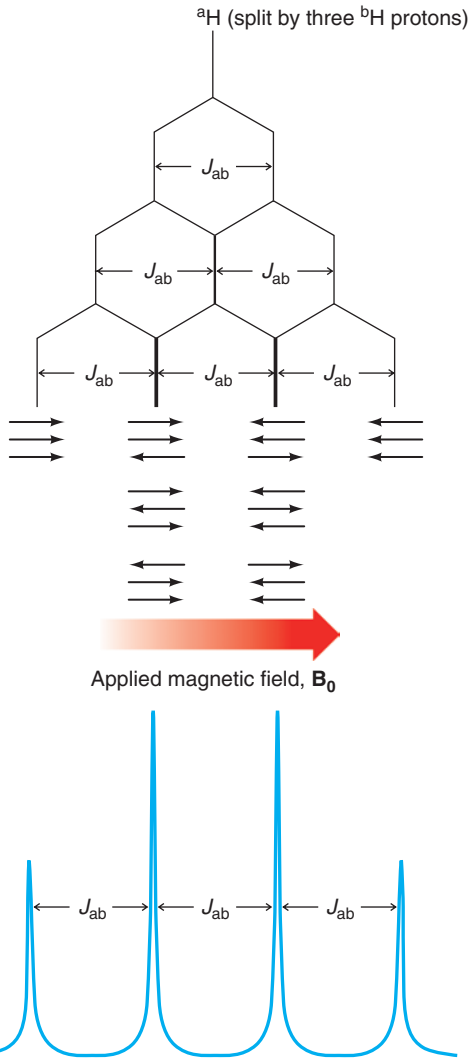
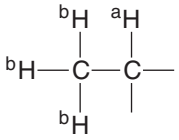


Figure 9.20 Splitting tree diagram for a quartet. The signal from the observed hydrogen (^{a}H) is split into four peaks of 1 : 3 : 3 : 1 intensity by three equivalent hydrogens (^{b}H). The same method of analysis we used for the triplet pattern applies here, wherein each successively lower level in the tree diagram represents splitting by another one of the coupled hydrogens. Again, because in this case J_{ab} is the same for splitting of the ^{a}H the signal by all three ^{b}H hydrogens, internal legs of the diagram overlap, and intensities amplify each time this occurs. The result is a pattern of 1 : 3 : 3 : 1 intensities, as we would observe for a quartet in an actual spectrum. The possible magnetic orientations shown under the tree diagram for the three ^{b}H hydrogens indicate that all three of the adjacent hydrogens may be aligned with the applied field, or two may be aligned with the field and one against (in three equal energy combinations), or two against and one with the field (in three equal energy combinations), or all three may be aligned against the applied field.



three may be aligned against the applied field. This analysis shows how a quartet results from three hydrogens that split the signal of another.

Let us conclude this section with two last examples. The spectrum of 1,1,2,3,3-pentachloropropane (Fig. 9.21) is similar to that of 1,1,2-trichloroethane in that it also consists of a 1:2:1 triplet and a 1:1 doublet. The two hydrogen atoms ^{b}H of 1,1,2,3,3-pentachloropropane are equivalent even though they are on separate carbon atoms.

Review Problem 9.7

The relative positions of the doublet and triplet of 1,1,2-trichloroethane (Fig. 9.4) and 1,1,2,3,3-pentachloropropane (Fig. 9.21) are reversed. Explain this.

Finally, returning to the spectrum of bromoethane that we used as the opening example in this chapter, the signal from two equivalent protons of the $—CH_2Br$ group (Fig. 9.1) appears as a 1:3:3:1 quartet because of the type of signal splitting shown in Fig. 9.20. The three equivalent protons of the $CH_3—$ group are split into a 1:2:1 triplet by the two protons of the $—CH_2Br$ group.

The kind of analysis that we have just given can be extended to compounds with even larger numbers of equivalent protons on adjacent atoms. These analyses also show that ***if there are n equivalent protons on adjacent atoms, these will split a signal into n + 1 peaks***.

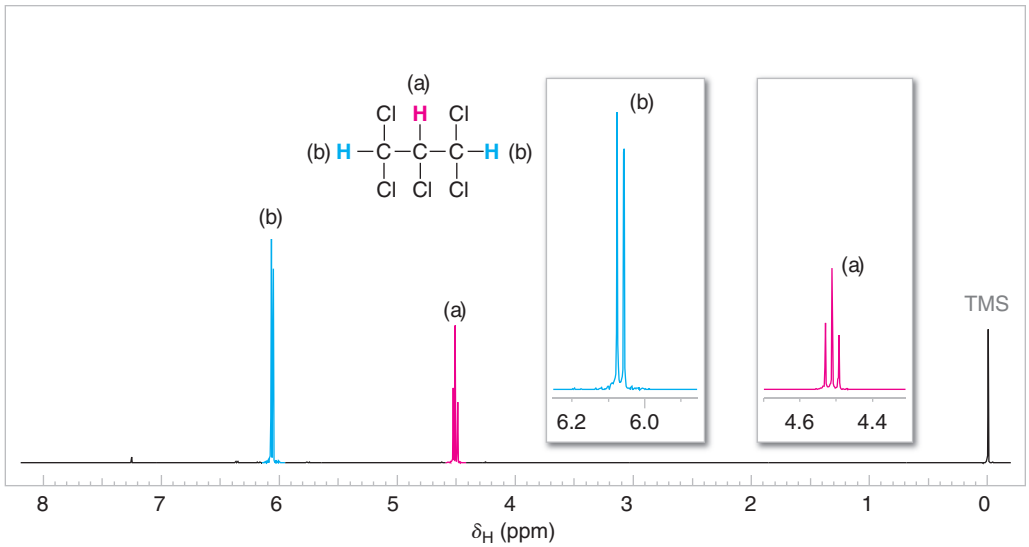
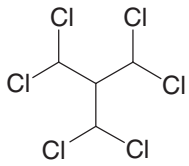


Figure 9.21 The 300-MHz ^{1}H NMR spectrum of 1,1,2,3,3-pentachloropropane. Expansions of the signals are shown in the offset plots.

(We may not always see all of these peaks in actual spectra, however, because some of them may be very small.)

Review Problem 9.8

Sketch the ^{1}H NMR spectrum you would expect for the following compound, showing the splitting patterns and relative position of each signal.



Review Problem 9.9

Propose a structure for each of the compounds whose spectra are shown in Fig. 9.22, and account for the splitting pattern of each signal.

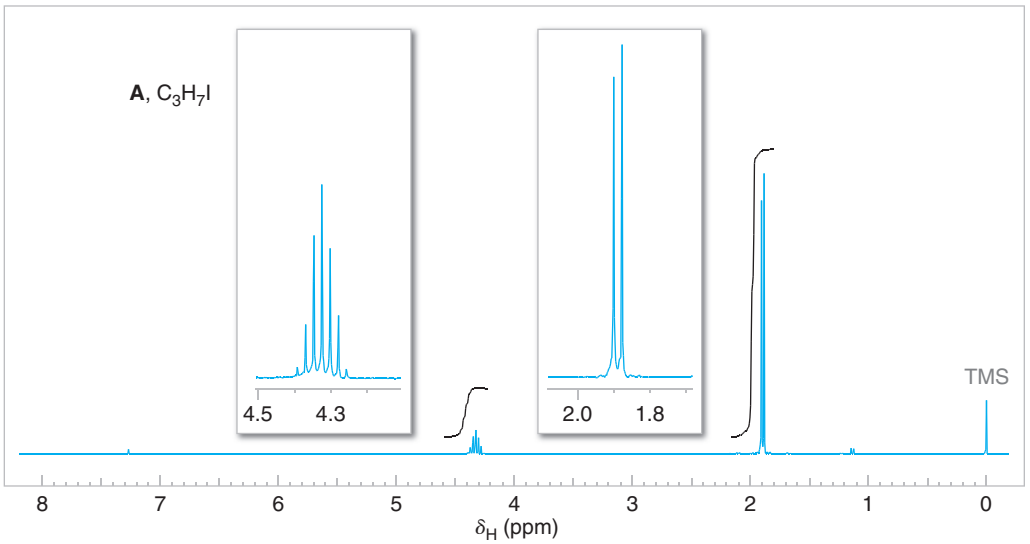


Figure 9.22 The 300-MHz ^{1}H NMR spectra for compounds **A**, **B**, and **C** in Review Problem 9.9. Expansions are shown in the offset plots.

(continues on the next page)

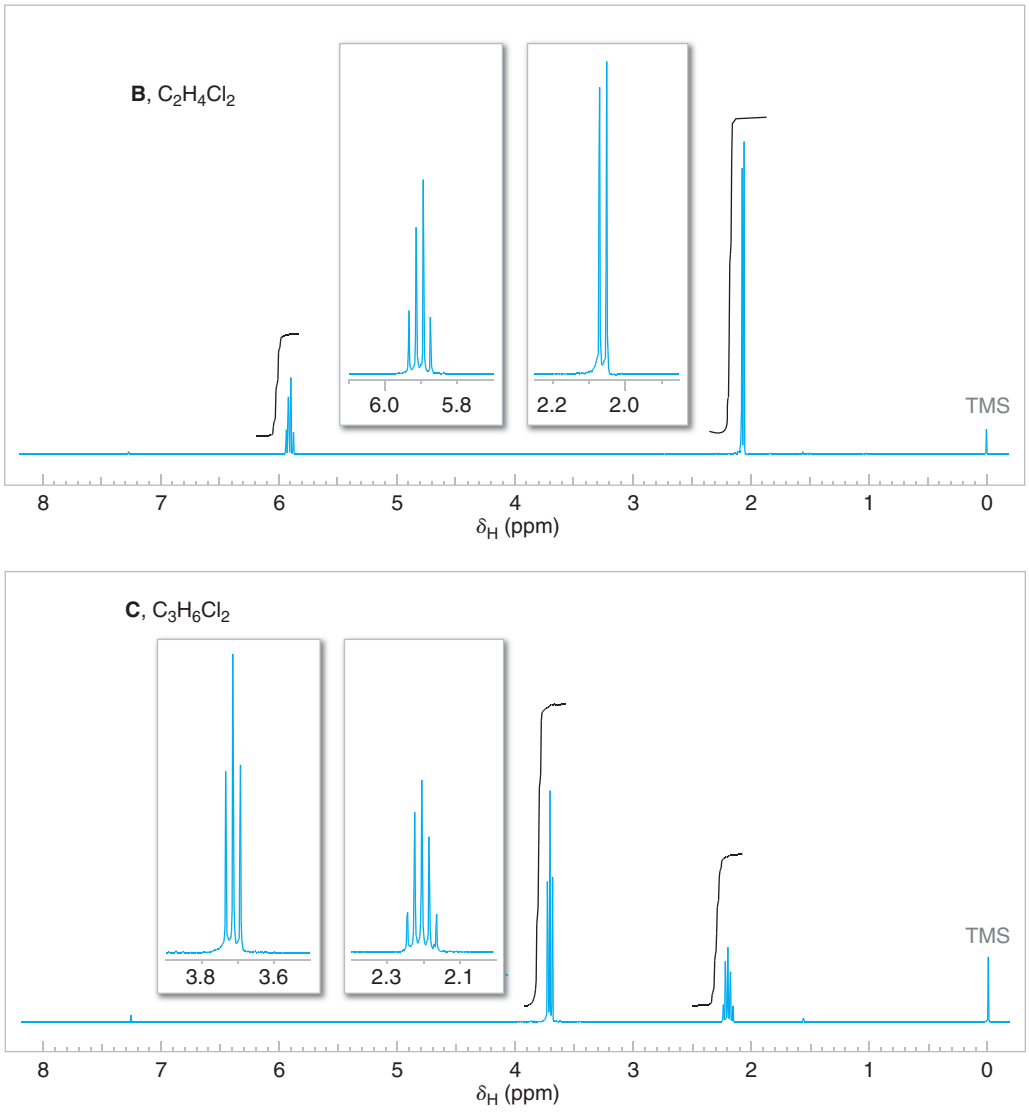


Figure 9.22 *(continued).*

9.9C Coupling Constants—Recognizing Splitting Patterns

Signals from coupled protons share a common coupling constant value. Coupling constants are determined by measuring the separation in **hertz** between each peak of a signal. A typical vicinal coupling constant is 6–8 hertz. We showed how coupling constants are measured in Figs. 9.18–9.20, where J_{ab} denotes the **coupling constant** between coupled hydrogens ^{a}H and ^{b}H. Coupling constants are also used when drawing splitting tree diagrams, as shown in Figs. 9.18–9.20.

If we were to measure the separation of peaks in both the quartet and the triplet in the NMR spectrum of bromoethane (Fig. 9.1), we would find that they have the same coupling constant. This phenomenon is called **the reciprocity of coupling constants**.

Helpful Hint

Reciprocity of coupling constants.

A simulation of the reciprocity of coupling constants for bromoethane is represented in Fig. 9.23. While it is easy to assign the splitting patterns in bromoethane without the analysis of coupling constants, i.e., using solely the $n + 1$ rule (as is also the case for the spectra shown in Fig. 9.22), the reciprocity of coupling constants can be very helpful when assigning sets of coupled protons in the spectra of more complicated molecules.

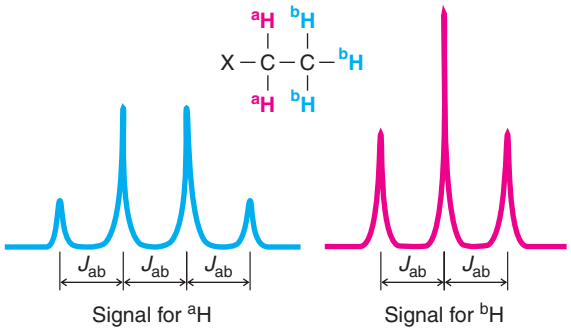


Figure 9.23 A theoretical splitting pattern for an ethyl group. For an actual example, see the spectrum of bromoethane (Fig. 9.1).

Other techniques in FTNMR spectroscopy also facilitate the analysis of coupling relationships. One such technique is ^{1}H–^{1}H **co**rrelation **s**pectroscop**y**, also known as ^{1}H–^{1}H COSY (Section 9.12A).

9.9D The Dependence of Coupling Constants on Dihedral Angle

The magnitude of a coupling constant can be indicative of the **dihedral angle** between coupled protons. This fact has been used to explore molecular geometry and perform conformational analysis by NMR spectroscopy. The dependence of the coupling constant on dihedral angles was explored by Martin Karplus (Harvard University), and has become well known as the **Karplus correlation**. A diagram showing the Karplus correlation is given in Fig. 9.24.

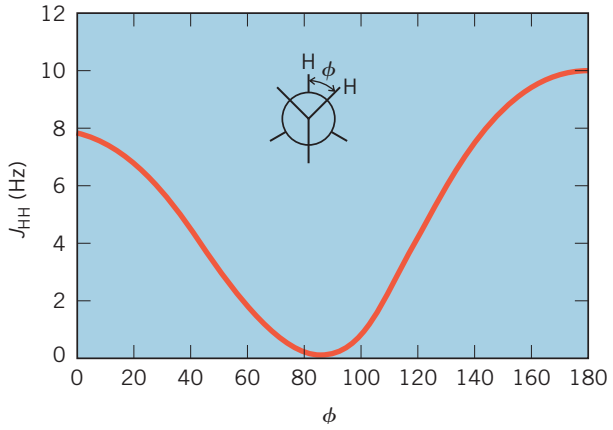
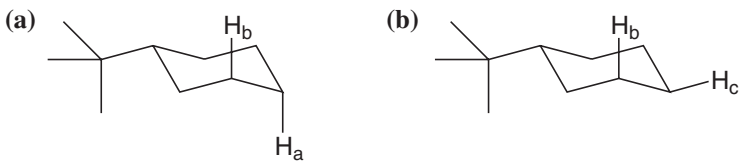


Figure 9.24 The Karplus correlation defines a relationship between dihedral angle (ϕ) and coupling constant for vicinal protons. (Reprinted with permission of John Wiley & Sons, Inc. from Silverstein, R., and Webster, F. X., *Spectrometric Identification of Organic Compounds*, Sixth Edition, p. 186. Copyright 1998.)

The influence of dihedral angles on coupling constants is often evident in the ^{1}H NMR spectra of substituted cyclohexanes. The coupling constant between vicinal axial protons ($J_{ax,ax}$) is typically 8–10 Hz, which is larger than the coupling constant between vicinal axial and equatorial protons ($J_{ax,eq}$), which is typically 2–3 Hz. Measuring coupling constants in the NMR spectrum of a substituted cyclohexane can therefore provide information about low energy conformations available to the compound.

Review Problem 9.10

What is the dihedral angle and expected coupling constant between the labeled protons in each of the following molecules?

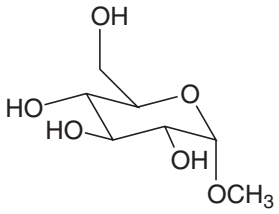


Review Problem 9.11

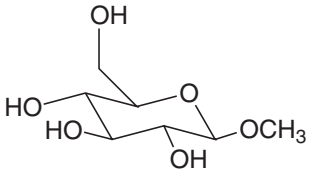
Draw the most stable chair conformation of 1-bromo-2-chlorocyclohexane, if the coupling constant between hydrogens on C1 and C2 was found to be 7.8 Hz ($J_{1,2}$ = 7.8 Hz).

Review Problem 9.12

Explain how you could distinguish between the following two compounds using NMR coupling constants. (These compounds are derived from glucose, by a reaction we shall study in Chapters 16 and 22.)



A

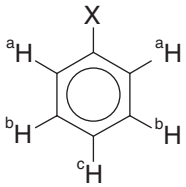


B

9.9E Complicating Features

Proton NMR spectra have other features, however, that are not at all helpful when we try to determine the structure of a compound. For example:

1. Signals may overlap. This happens when the chemical shifts of the signals are very nearly the same. In the 60-MHz spectrum of ethyl chloroacetate (Fig. 9.25, top) we see that the singlet of the $-CH_2Cl$ group falls directly on top of one of the outermost peaks of the ethyl quartet. Using NMR spectrometers with higher magnetic field strength (corresponding to ^1H resonance frequencies of 300, 500, or 600 MHz) often allows separation of signals that would overlap at lower magnetic field strengths (for an example, see Fig. 9.25, next page).
2. Spin–spin couplings between the protons of nonadjacent atoms may occur. This long-range coupling happens frequently in compounds when π-bonded atoms intervene between the atoms bearing the coupled protons, and in some cyclic molecules that are rigid.
3. The splitting patterns of aromatic groups can be difficult to analyze. A monosubstituted benzene ring (a phenyl group) has three different kinds of protons:



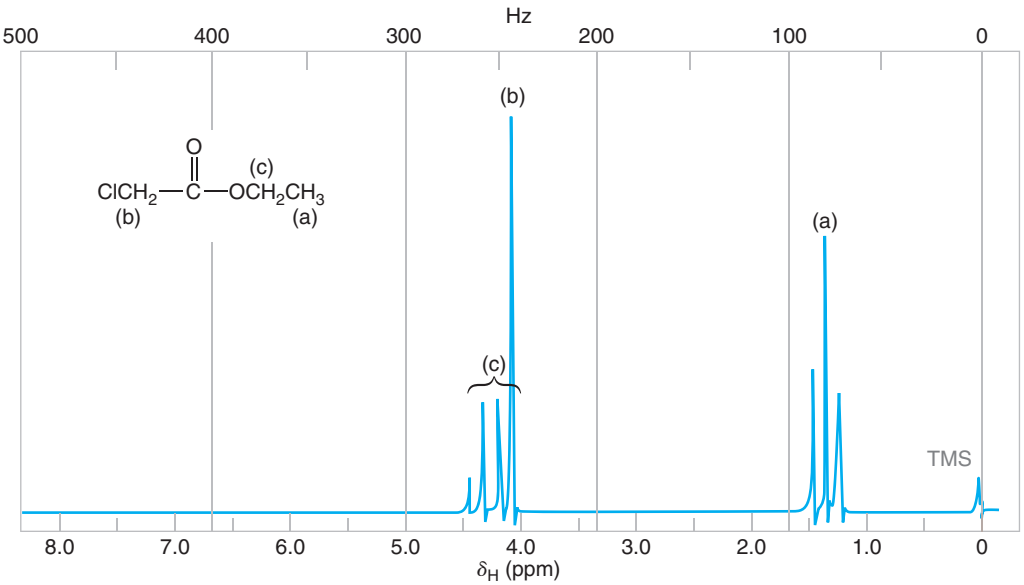
The chemical shifts of these protons may be so similar that the phenyl group gives a signal that resembles a singlet. Or the chemical shifts may be different and, because of long-range couplings, the phenyl group signal may appear as a very complicated multiplet.

9.9F Analysis of Complex Interactions

In all of the ^1H NMR spectra that we have considered so far, we have restricted our attention to signal splittings arising from interactions of only two sets of equivalent protons on adjacent atoms. What kinds of patterns should we expect from compounds in which more than two sets of equivalent protons are interacting? We cannot answer this question completely because of limitations of space, but we can give an example that illustrates the kind of analysis that is involved. Let us consider a 1-substituted propane:

$$\overset{(a)}{CH_3}-\overset{(b)}{CH_2}-\overset{(c)}{CH_2}-Z$$

Here, there are three sets of equivalent protons. We have no problem in deciding what kind of signal splitting to expect from the protons of the CH_3- group or the $-CH_2Z$ group.



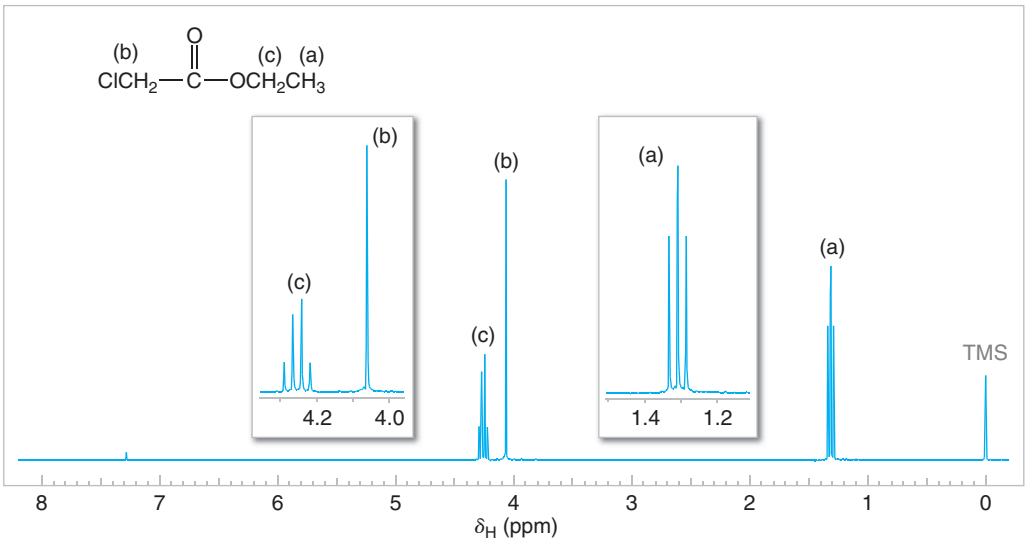


Figure 9.25 (*Top*) The 60-MHz ^{1}H NMR spectrum of ethyl chloroacetate. Note the overlapping signals at δ 4. (*Bottom*) The 300-MHz ^{1}H NMR spectrum of ethyl chloroacetate, showing resolution at higher magnetic field strength of the signals that overlapped at 60 MHz. Expansions of the signals are shown in the offset plots.

The methyl group is spin–spin coupled only to the two protons of the central —CH_2— group. Therefore, the methyl group should appear as a triplet. The protons of the —CH_2Z group are similarly coupled only to the two protons of the central —CH_2— group. Thus, the protons of the —CH_2Z group should also appear as a triplet.

But what about the protons of the central —CH_2— group (b)? They are spin–spin coupled with the three protons at (a) and with two protons at (c). The protons at (a) and (c), moreover, are not equivalent. If the coupling constants J_{ab} and J_{bc} have quite different values, then the protons at (b) could be split into a quartet by the three protons at (a) and each line of the quartet could be split into a triplet by the two protons at (c), resulting in 12 peaks (Fig. 9.26).

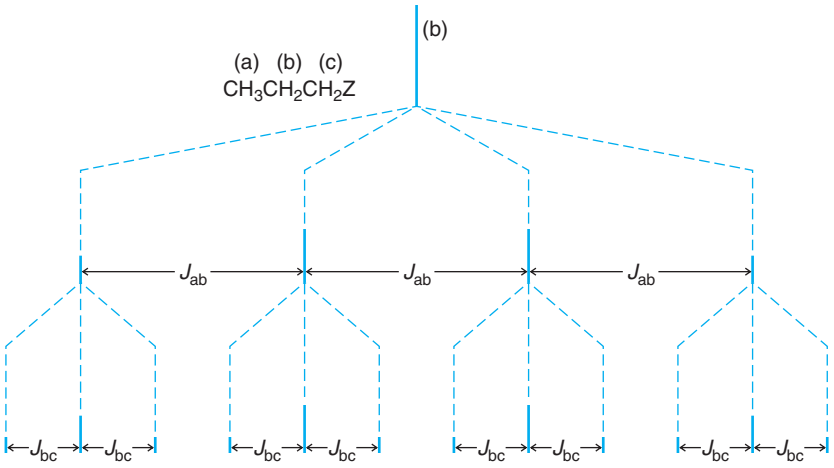


Figure 9.26 The splitting pattern that would occur for the (b) protons of $CH_3CH_2CH_2Z$ if J_{ab} were much larger than J_{bc}. Here $J_{ab} = 3J_{bc}$.

It is unlikely, however, that we would observe as many as 12 peaks in an actual spectrum because the coupling constants are such that peaks usually fall on top of peaks. The ^{1}H NMR spectrum of 1-nitropropane (Fig. 9.27) is typical of 1-substituted propane compounds, in that the central —CH_2— group "sees" five approximately equivalent adjacent protons. Hence, by the $n + 1$ rule, we see that the (b) protons are split into six major peaks.

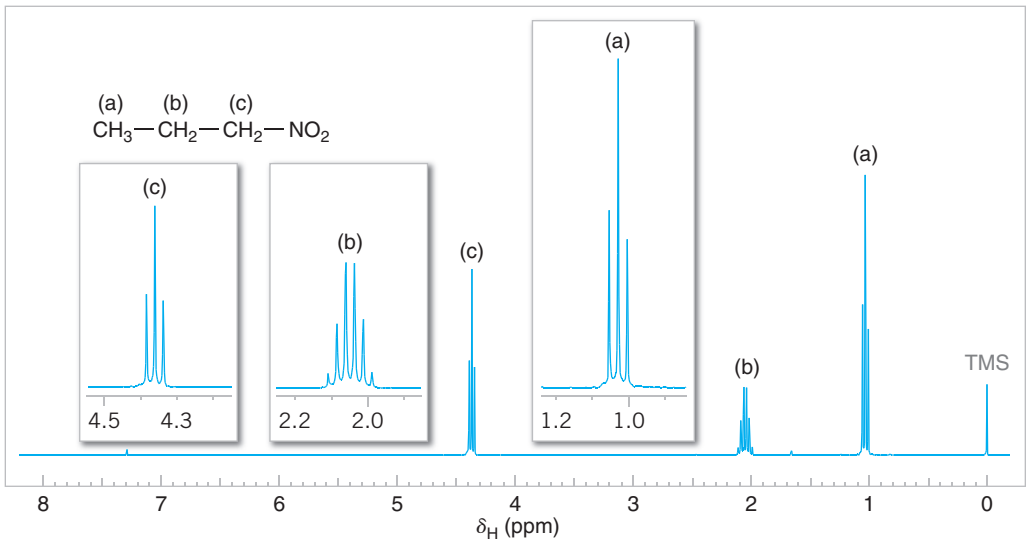


Figure 9.27 The 300-MHz ^{1}H NMR spectrum of 1-nitropropane. Expansions of the signals are shown in the offset plots.

Review Problem 9.13

Carry out an analysis like that shown in Fig. 9.26 and show how many peaks the signal from (b) would be split into if $J_{ab} = 2J_{bc}$ and if $J_{ab} = J_{bc}$. [*Hint*: In both cases peaks will fall on top of peaks so that the total number of peaks in the signal is fewer than 12.]

The presentation we have given here applies only to what are called *first-order spectra*. In first-order spectra, the distance in hertz ($\Delta\nu$) that separates the coupled signals is very much larger than the coupling constant, J. That is, $\Delta\nu >> J$. In *second-order spectra* (which we have not discussed), $\Delta\nu$ approaches J in magnitude and the situation becomes much more complex. The number of peaks increases and the intensities are not those that might be expected from first-order considerations.

9.10 Proton NMR Spectra and Rate Processes

J. D. Roberts (Emeritus Professor, California Institute of Technology), a pioneer in the application of NMR spectroscopy to problems of organic chemistry, has compared the NMR spectrometer to a camera with a relatively slow shutter speed. Just as a camera with a slow shutter speed blurs photographs of objects that are moving rapidly, the NMR spectrometer blurs its picture of molecular processes that are occurring rapidly.

What are some of the rapid processes that occur in organic molecules? Two processes that we shall mention are chemical exchange of hydrogen atoms bonded to heteroatoms (such as oxygen and nitrogen), and conformational changes.

Chemical Exchange Causes Spin Decoupling An example of a rapidly occurring process can be seen in ^{1}H NMR spectra of ethanol. The ^{1}H NMR spectrum of ordinary ethanol shows the hydroxyl proton as a singlet and the protons of the $-CH_2-$ group as a quartet (Fig. 9.28). In ordinary ethanol we observe *no signal splitting arising from coupling between the hydroxyl proton and the protons of the* $-CH_2-$ *group even though they are on adjacent atoms*.

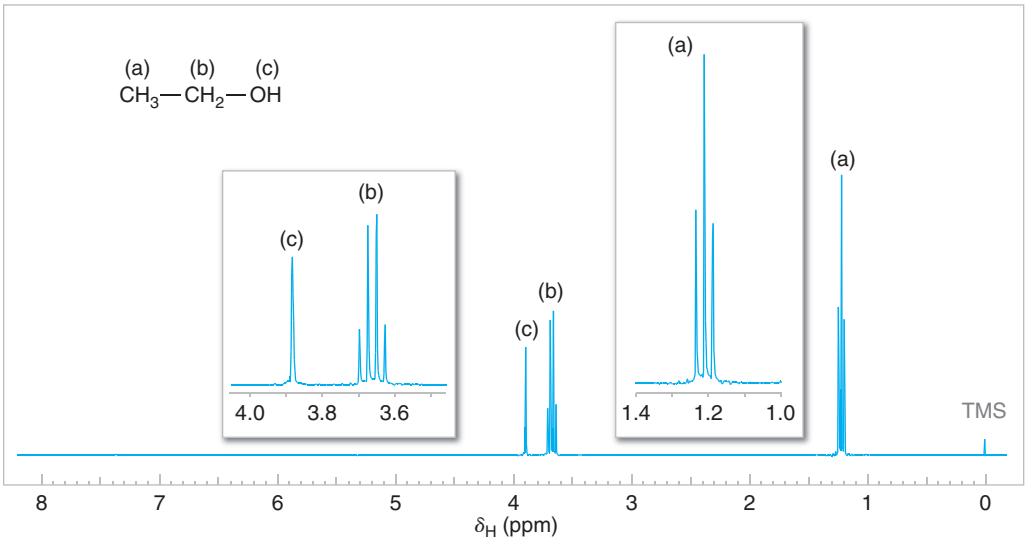


Figure 9.28 The 300-MHz ^{1}H NMR spectrum of ordinary ethanol. There is no signal splitting by the hydroxyl proton due to rapid chemical exchange. Expansions of the signals are shown in the offset plots.

If we were to examine a ^{1}H NMR spectrum of *very pure* ethanol, however, we would find that the signal from the hydroxyl proton was split into a triplet and that the signal from the protons of the $-CH_2-$ group was split into a multiplet of eight peaks. Clearly, in very pure ethanol the spin of the proton of the hydroxyl group is coupled with the spins of the protons of the $-CH_2-$ groups.

Whether coupling occurs between the hydroxyl protons and the methylene protons depends on the length of time the proton spends on a particular ethanol molecule.

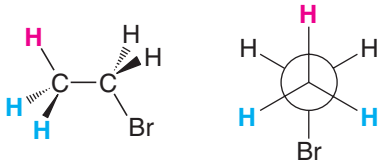
- Protons attached to electronegative atoms with lone pairs such as oxygen (or nitrogen) can undergo rapid **chemical exchange**. That is, they can be transferred rapidly from one molecule to another and are therefore called **exchangeable protons**.

The chemical exchange in very pure ethanol is slow and, as a consequence, we see the signal splitting of and by the hydroxyl proton in the spectrum. In ordinary ethanol, acidic and basic impurities catalyze the chemical exchange; the exchange occurs so rapidly that the hydroxyl proton gives an unsplit signal and that of the methylene protons is split only by coupling with the protons of the methyl group.

- Rapid exchange causes **spin decoupling**.
- Spin decoupling is found in the ^{1}H NMR spectra of alcohols, amines, and carboxylic acids. The signals of OH and NH protons are normally unsplit and broad.
- Protons that undergo rapid chemical exchange (i.e., those attached to oxygen or nitrogen) can be easily detected by placing the compound in D_2O. The protons are rapidly replaced by deuterons, and the proton signal disappears from the spectrum.

Conformational Changes At temperatures near room temperature, groups connected by carbon–carbon single bonds rotate very rapidly (unless rotation is prevented by some structural constraint, e.g., a rigid ring system). Because of this, when we determine spectra of compounds with single bonds that allow rotation, the spectra that we obtain often reflect the individual hydrogen atoms in their average environment—that is, in an environment that is an average of all the environments that the protons have as a result of conformational changes.

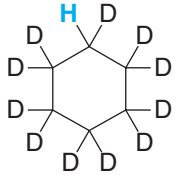
To see an example of this effect, let us consider the spectrum of bromoethane again. The most stable conformation is the one in which the groups are perfectly staggered. In this staggered conformation one hydrogen of the methyl group (in red in the following structure) is in a different environment from that of the other two methyl hydrogen atoms. If the NMR spectrometer were to detect this specific conformation of bromoethane, it would show the protons of the methyl group at *a different chemical shift*. We know, however, that in the spectrum of bromoethane (Fig. 9.1), the three protons of the methyl group give *a single signal* (a signal that is split into a triplet by spin–spin coupling with the two protons of the adjacent carbon).



The methyl protons of bromoethane give a single signal because at room temperature the groups connected by the carbon–carbon single bond rotate approximately 1 million times each second. The "shutter speed" of the NMR spectrometer is too slow to "photograph" this rapid rotation; instead, it photographs the methyl hydrogen atoms in their average environments, and in this sense, it gives us a blurred picture of the methyl group.

Rotations about single bonds slow down as the temperature of the compound is lowered. Sometimes, this slowing of rotations allows us to "see" the different conformations of a molecule when we determine the spectrum at a sufficiently low temperature.

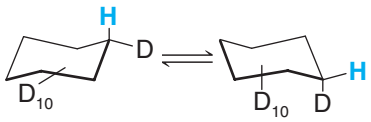
An example of this phenomenon, and one that also shows the usefulness of deuterium labeling, can be seen in the low-temperature ^{1}H NMR spectra of cyclohexane and of undecadeuteriocyclohexane. (These experiments originated with F. A. L. Anet, Emeritus Professor, University of California, Los Angeles, another pioneer in the applications of NMR spectroscopy to organic chemistry, especially to conformational analysis.)



Undecadeuteriocyclohexane

At room temperature, ordinary cyclohexane gives one signal because interconversion of chair forms occurs very rapidly. At low temperatures, however, ordinary cyclohexane gives a very complex ^{1}H NMR spectrum. At low temperatures interconversions are slow; the chemical shifts of the axial and equatorial protons are resolved, and complex spin–spin couplings occur.

At −100°C, however, undecadeuteriocyclohexane gives only two signals of equal intensity. These signals correspond to the axial and equatorial hydrogen atoms of the following two chair conformations. Interconversions between these conformations occur at this low temperature, but they happen slowly enough for the NMR spectrometer to detect the individual conformations. [The nucleus of a deuterium atom (a deuteron) has a much smaller magnetic moment than a proton, and signals from deuteron absorption do not occur in ^{1}H NMR spectra.]



Review Problem 9.14

How many signals would you expect to obtain in the ^{1}H NMR spectrum of undecadeuteriocyclohexane at room temperature?

9.11 Carbon-13 NMR Spectroscopy

9.11A Interpretation of ^{13}C NMR Spectra

We begin our study of **^{13}C NMR spectroscopy** with a brief examination of some special features of spectra arising from carbon-13 nuclei. Although ^{13}C accounts for only 1.1% of naturally occurring carbon, the fact that ^{13}C can produce an NMR signal has profound importance for the analysis of organic compounds. In some important ways ^{13}C spectra are usually less complex and easier to interpret than ^{1}H NMR spectra. The major isotope of carbon, on the other hand, carbon-12 (^{12}C), with a natural abundance of about 99%, has no net magnetic spin and therefore cannot produce NMR signals.

9.11B One Peak for Each Magnetically Distinct Carbon Atom

The interpretation of ^{13}C NMR spectra is greatly simplified by the following facts:

- Each distinct carbon produces a single peak in a ^{13}C NMR spectrum.
- Splitting of signals into multiple peaks is not observed in routine ^{13}C NMR spectra.

Recall that in ^{1}H NMR spectra, hydrogen nuclei that are near each other (within a few bonds) couple with each other and cause the signal for each hydrogen to be split into a multiplet of peaks. Coupling is not observed for adjacent carbons because only one carbon atom of every 100 carbon atoms is a ^{13}C nucleus (1.1% natural abundance). Therefore, the probability of there being two ^{13}C atoms adjacent to each other in a molecule is only about 1 in 10,000 (1.1% × 1.1%), essentially eliminating the possibility of two neighboring carbon atoms splitting each other's signal into a multiplet of peaks. The low natural abundance of ^{13}C nuclei and its inherently low sensitivity also have another effect: Carbon-13 NMR spectra can be obtained only on pulse FTNMR spectrometers, where signal averaging is possible.

Whereas carbon–carbon signal splitting does not occur in ^{13}C NMR spectra, hydrogen atoms attached to carbon can split ^{13}C NMR signals into multiple peaks. However, it is useful to simplify the appearance of ^{13}C NMR spectra by initially eliminating signal splitting for ^{1}H–^{13}C coupling. This can be done by choosing instrumental parameters that decouple the proton–carbon interactions, and such a spectrum is said to be **broadband (BB) proton decoupled**.

- In a broadband proton-decoupled ^{13}C NMR spectrum, each carbon atom in a distinct environment gives a signal consisting of only one peak.

Most ^{13}C NMR spectra are obtained in the simplified broadband decoupled mode first and then in modes that provide information from the ^{1}H–^{13}C couplings (Sections 9.11D and 9.11E).

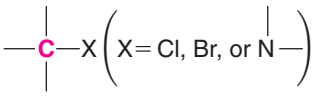
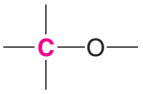
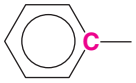
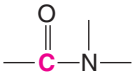
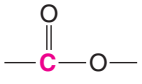
9.11C ^{13}C Chemical Shifts

As we found with ^{1}H spectra, the chemical shift of a given nucleus depends on the relative electron density around that atom.

- Decreased electron density around an atom **deshields** the atom from the magnetic field and causes its signal to occur further **downfield** (higher ppm, to the left) in the NMR spectrum.
- Relatively higher electron density around an atom **shields** the atom from the magnetic field and causes the signal to occur **upfield** (lower ppm, to the right) in the NMR spectrum.

For example, carbon atoms that are attached only to other carbon and hydrogen atoms are relatively shielded from the magnetic field by the density of electrons around them, and, as a consequence, carbon atoms of this type produce peaks that are upfield in ^{13}C NMR spectra. On the other hand, carbon atoms bearing electronegative groups are deshielded from the magnetic field by the electron-withdrawing effects of these groups and, therefore, produce peaks that are downfield in the NMR spectrum. Electronegative groups such as halogens, hydroxyl groups, and other electron-withdrawing functional groups deshield the carbons to which they are attached, causing their ^{13}C NMR peaks to occur further downfield than those of unsubstituted carbon atoms. Reference tables of approximate chemical shift ranges for carbons bearing different substituents are available. Figure 9.29 and Table 9.2 are examples. [The reference standard assigned as zero ppm in ^{13}C NMR spectra is also tetramethylsilane (TMS), $Si(CH_3)_4$.]

TABLE 9.2 Approximate Carbon-13 Chemical Shifts

Type of Carbon Atom	Chemical Shift (δ, ppm)
1° Alkyl, RCH_3	0–40
2° Alkyl, RCH_2R	10–50
3° Alkyl, $RCHR_2$	15–50
Alkyl halide or amine, 	10–65
Alcohol or ether, 	50–90
Alkyne, 	60–90
Alkene, 	100–170
Aryl, 	100–170
Nitrile, 	120–130
Amide, 	150–180
Carboxylic acid or ester, 	160–185
Aldehyde or ketone, 	182–215

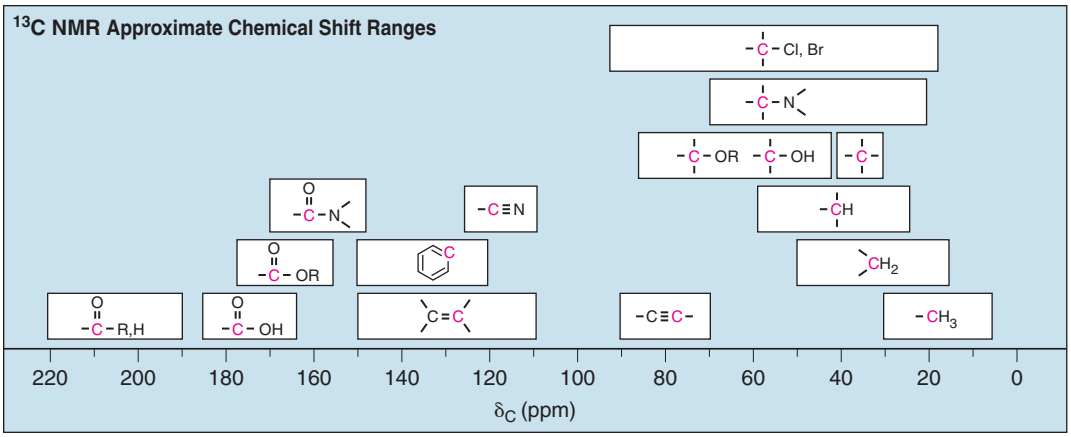
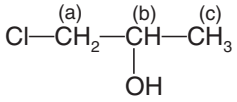


Figure 9.29 Approximate ^{13}C chemical shifts.

As a first example of the interpretation of ^{13}C NMR spectra, let us consider the ^{13}C spectrum of 1-chloro-2-propanol (Fig. 9.30*a*):



1-Chloro-2-propanol

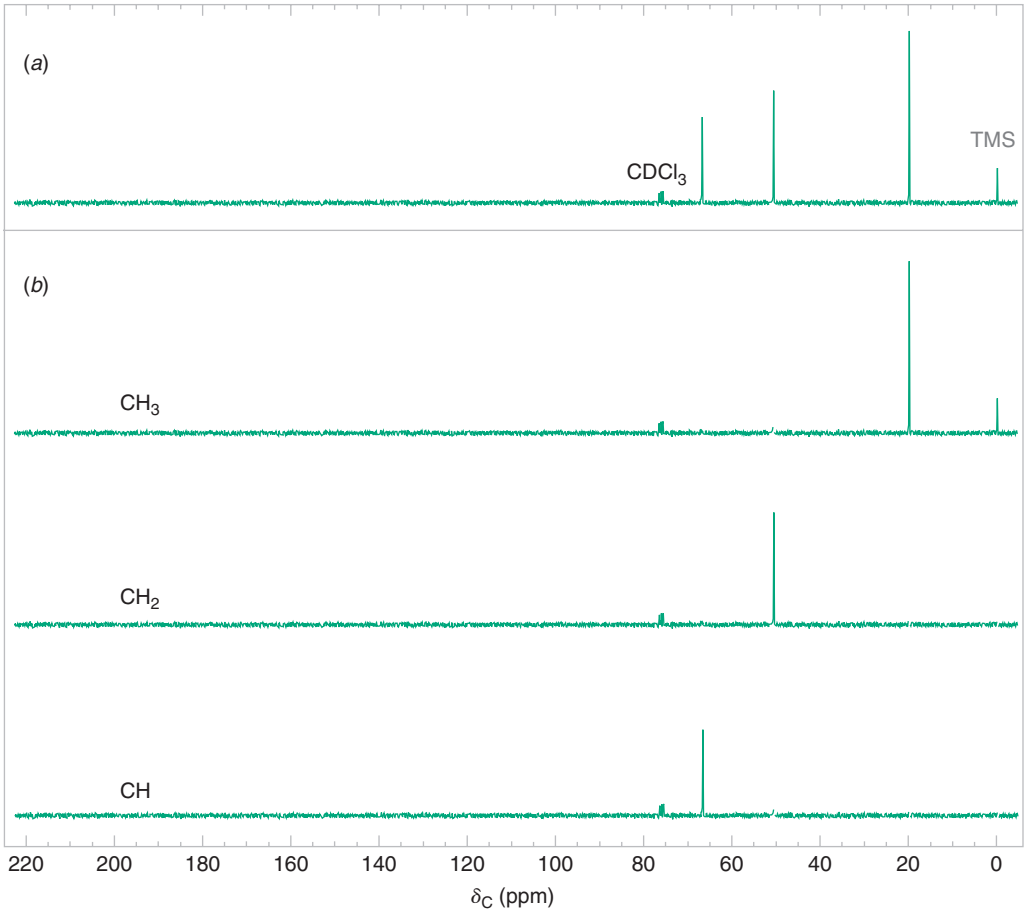


Figure 9.30 *(a)* The broadband proton-decoupled ^{13}C NMR spectrum of 1-chloro-2-propanol. *(b)* These three spectra show the DEPT ^{13}C NMR data from 1-chloro-2-propanol (see Section 9.11E). (This will be the only full display of a DEPT spectrum in the text. Other ^{13}C NMR figures will show the full broadband proton-decoupled spectrum but with information from the DEPT ^{13}C NMR spectra indicated near each peak as C, CH, CH_2, or CH_3.)

1-Chloro-2-propanol contains three carbon atoms in distinct environments, and therefore produces three peaks in its broadband decoupled ^{13}C NMR spectrum: approximately at δ 20, δ 51, and δ 67. Figure 9.30 also shows a close grouping of three peaks at δ 77. These peaks come from the deuteriochloroform ($CDCl_3$) used as a solvent for the sample. Many ^{13}C NMR spectra contain these peaks. Although not of concern to us here, the signal for the single carbon of deuteriochloroform is split into three peaks by an effect of the attached deuterium.

- The $CDCl_3$ solvent peaks at δ 77 should be disregarded when interpreting ^{13}C spectra.

As we can see, the chemical shifts of the three peaks from 1-chloro-2-propanol are well separated from one another. This separation results from differences in shielding by circulating electrons in the local environment of each carbon. Remember: The lower the electron density in the vicinity of a given carbon, the less that carbon will be shielded, and the more downfield will be the signal for that carbon. The oxygen of the hydroxyl group is the most electronegative atom; it withdraws electrons most effectively. Therefore, the carbon bearing the —OH group is the most *deshielded* carbon, and so this carbon gives the signal that is the furthest downfield, at δ 67. Chlorine is less electronegative than oxygen, causing the peak for the carbon to which it is attached to occur more upfield, at δ 51. The methyl group carbon has no electronegative groups directly attached to it, so it occurs the furthest upfield, at δ 20. Using tables of typical chemical shift values (such as Fig. 9.29 and Table 9.2), one can usually assign ^{13}C NMR signals to each carbon in a molecule, on the basis of the groups attached to each carbon.

9.11D Off-Resonance Decoupled Spectra

At times, more information than a predicted chemical shift is needed to assign an NMR peak to a specific carbon atom of a molecule. Fortunately, NMR spectrometers can differentiate among carbon atoms on the basis of the number of hydrogen atoms that are attached to each carbon. Several methods to accomplish this are available. One method not widely used anymore is called **off-resonance decoupling**. In an off-resonance decoupled ^{13}C NMR spectrum, each carbon signal is split into a multiplet of peaks, depending on how many hydrogens are attached to that carbon. An $n + 1$ rule applies, where n is the number of hydrogens on the carbon in question. Thus, a carbon with no hydrogens produces a singlet ($n = 0$), a carbon with one hydrogen produces a doublet (two peaks), a carbon with two hydrogens produces a triplet (three peaks), and a methyl group carbon produces a quartet (four peaks). Interpretation of off-resonance decoupled ^{13}C spectra, however, is often complicated by overlapping peaks from the multiplets.

9.11E DEPT ^{13}C Spectra

DEPT ^{13}C NMR spectra are very simple to interpret.

- **DEPT ^{13}C NMR spectra** indicate how many hydrogen atoms are bonded to each carbon, while also providing the chemical shift information contained in a broadband proton-decoupled ^{13}C NMR spectrum. The carbon signals in a DEPT spectrum are classified as CH_3, CH_2, CH, or C accordingly.

A DEPT (**d**istortionless **e**nhancement by **p**olarization **t**ransfer) spectrum is actually produced using data from several ^{13}C spectra of the same sample (Fig. 9.30*b*), with the net spectrum result providing the information about the hydrogen substitution at each carbon (Fig. 9.30*a*). In this text we show the ^{13}C peaks labeled according to the information gained from the DEPT spectra for the compound under consideration, rather than reproducing the entire family of spectra that lead to the final result.

As a further example of interpreting ^{13}C NMR spectra, let us look at the spectrum of methyl methacrylate (Fig. 9.31). (This compound is the monomeric starting material for the commercial polymers Lucite and Plexiglas, see Chapter 10.) The five carbons of methyl methacrylate represent carbon types from several chemical shift regions of ^{13}C spectra.

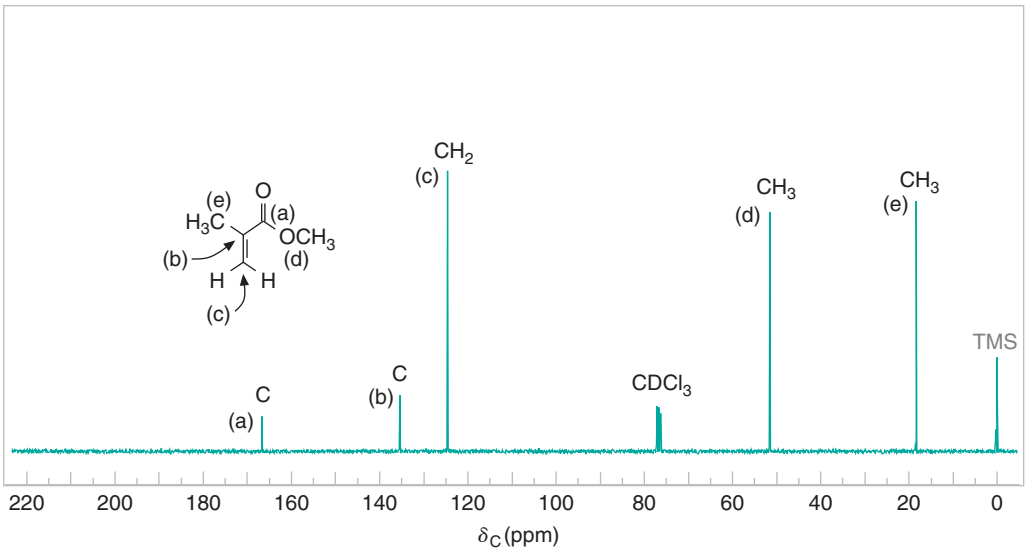


Figure 9.31 The broadband proton-decoupled ^{13}C NMR spectrum of methyl methacrylate. Information from the DEPT ^{13}C NMR spectra is given above the peaks.

Furthermore, because there is no symmetry in the structure of methyl methacrylate, all of its carbon atoms are chemically unique and so produce five distinct carbon NMR signals. Making use of our table of approximate ^{13}C chemical shifts (Fig. 9.29 and Table 9.2), we can readily deduce that the peak at δ 167.3 is due to the ester carbonyl carbon, the peak at δ 51.5 is for the methyl carbon attached to the ester oxygen, the peak at δ 18.3 is for the methyl attached to C2, and the peaks at δ 136.9 and δ 124.7 are for the alkene carbons. Additionally, employing the information from the DEPT ^{13}C spectra, we can unambiguously assign signals to the alkene carbons. The DEPT spectra tell us definitively that the peak at δ 124.7 has two attached hydrogens, and so it is due to C3, the terminal alkene carbon of methyl methacrylate. The alkene carbon with no attached hydrogens is then, of course, C2.

Review Problem 9.15

Compounds **A, B**, and **C** are isomers with the formula $C_5H_{11}Br$. Their broadband proton-decoupled ^{13}C NMR spectra are given in Fig. 9.32. Information from the DEPT ^{13}C NMR spectra is given near each peak. Give structures for **A, B**, and **C**.

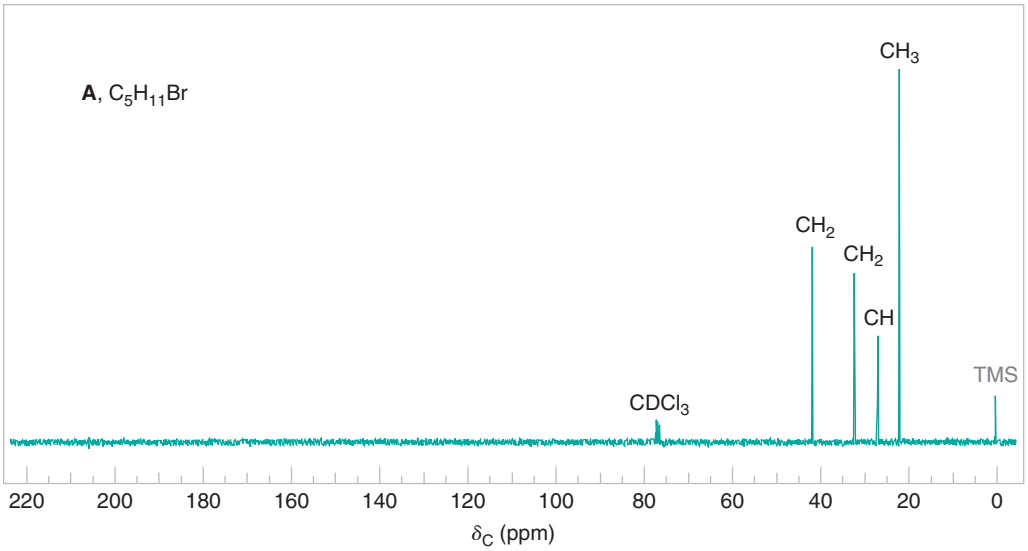


Figure 9.32 The broadband proton-decoupled ^{13}C NMR spectra of compounds **A, B**, and **C**, Review Problem 9.15. Information from the DEPT ^{13}C NMR spectra is given above the peaks.

(continues on the next page)

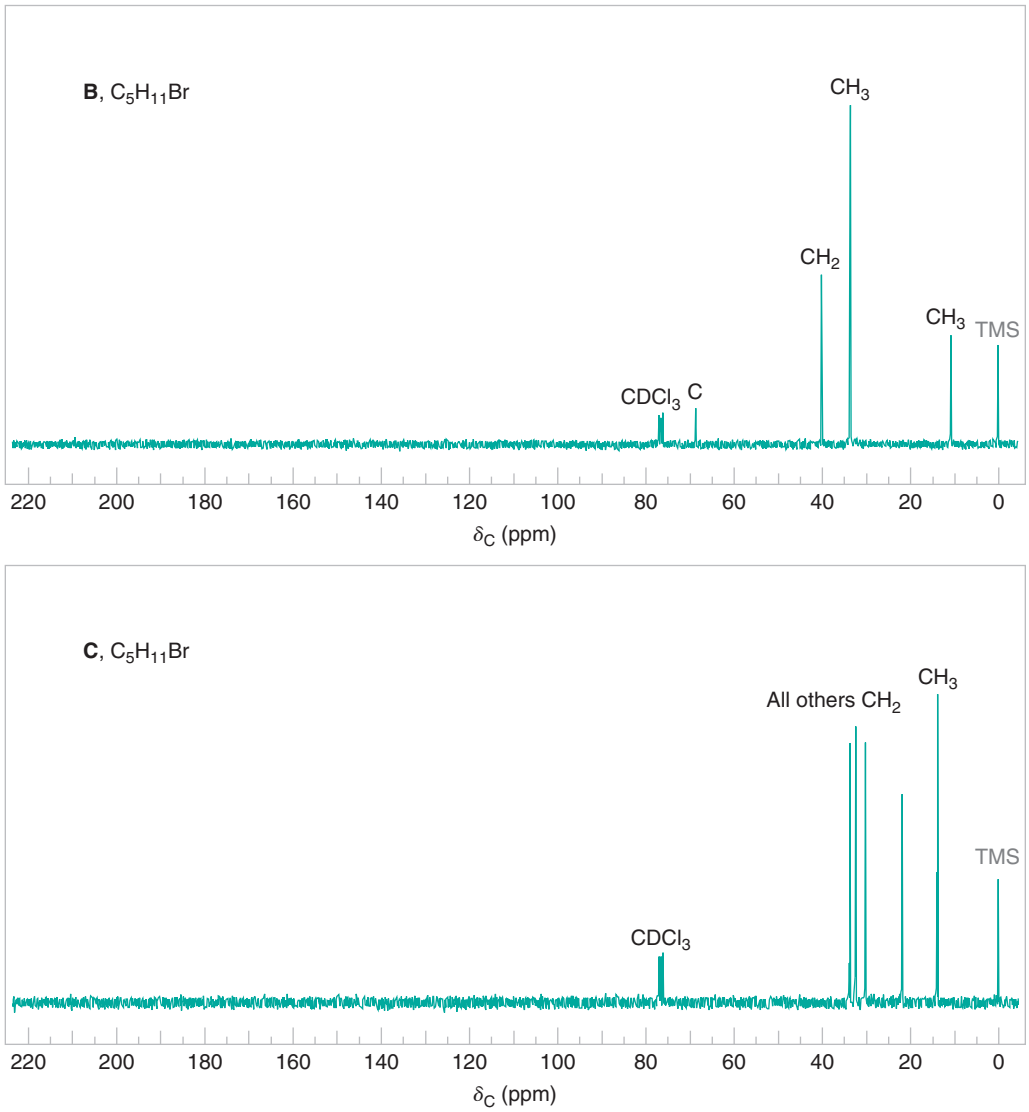


Figure 9.32 *(continued).*

9.12 *Two-Dimensional (2D) NMR Techniques*

Many NMR techniques are now available that greatly simplify the interpretation of NMR spectra. Chemists can now readily glean information about spin–spin coupling and the exact *connectivity* of atoms in molecules through techniques called **multidimensional NMR spectroscopy**. These techniques require an NMR spectrometer of the pulse (Fourier transform) type. The most common multidimensional techniques utilize **two-dimensional NMR (2D NMR)** and go by acronyms such as COSY, HETCOR, and a variety of others. [Even three-dimensional techniques (and beyond) are possible, although computational requirements can limit their feasibility.] The two-dimensional sense of 2D NMR spectra does not refer to the way they appear on paper but instead reflects the fact that the data are accumulated using two radio frequency pulses with a varying time delay between them. Sophisticated application of other instrumental parameters is involved as well. Discussion of these parameters and the physics behind multidimensional NMR is beyond the scope of this text. The result, however, is an NMR spectrum with the usual one-dimensional spectrum along the horizontal and vertical axes and a set of correlation peaks that appear in the *x*–*y* field of the graph.

When 2D NMR is applied to ^{1}H NMR it is called **^{1}H–^{1}H correlation spectroscopy** (or **COSY** for short). COSY spectra are exceptionally useful for deducing proton–proton coupling relationships. Two-dimensional NMR spectra can also be obtained that indicate coupling between hydrogens and the *carbons* to which they are attached. In this case it is called **heteronuclear correlation spectroscopy** (**HETCOR**, or **C–H HETCOR**). When ambiguities are present in the one-dimensional ^{1}H and ^{13}C NMR spectra, a HETCOR spectrum can be very useful for assigning precisely which hydrogens and carbons are producing their respective peaks.

9.12A COSY Cross-Peak Correlations

Figure 9.33 shows the COSY spectrum for 1-chloro-2-propanol. In a COSY spectrum the ordinary one-dimensional ^{1}H spectrum is shown along both the horizontal and the vertical axes. Meanwhile, the *x*–*y* field of a COSY spectrum is similar to a topographic map and can be thought of as looking down on the contour lines of a map of a mountain range. Along the diagonal of the COSY spectrum is a view that corresponds to looking down on the ordinary one-dimensional spectrum of 1-chloro-2-propanol as though each peak were a mountain. The one-dimensional counterpart of a given peak on the diagonal lies directly below that peak on each axis. The peaks on the diagonal provide no new information relative to that obtained from the one-dimensional spectrum along each axis.

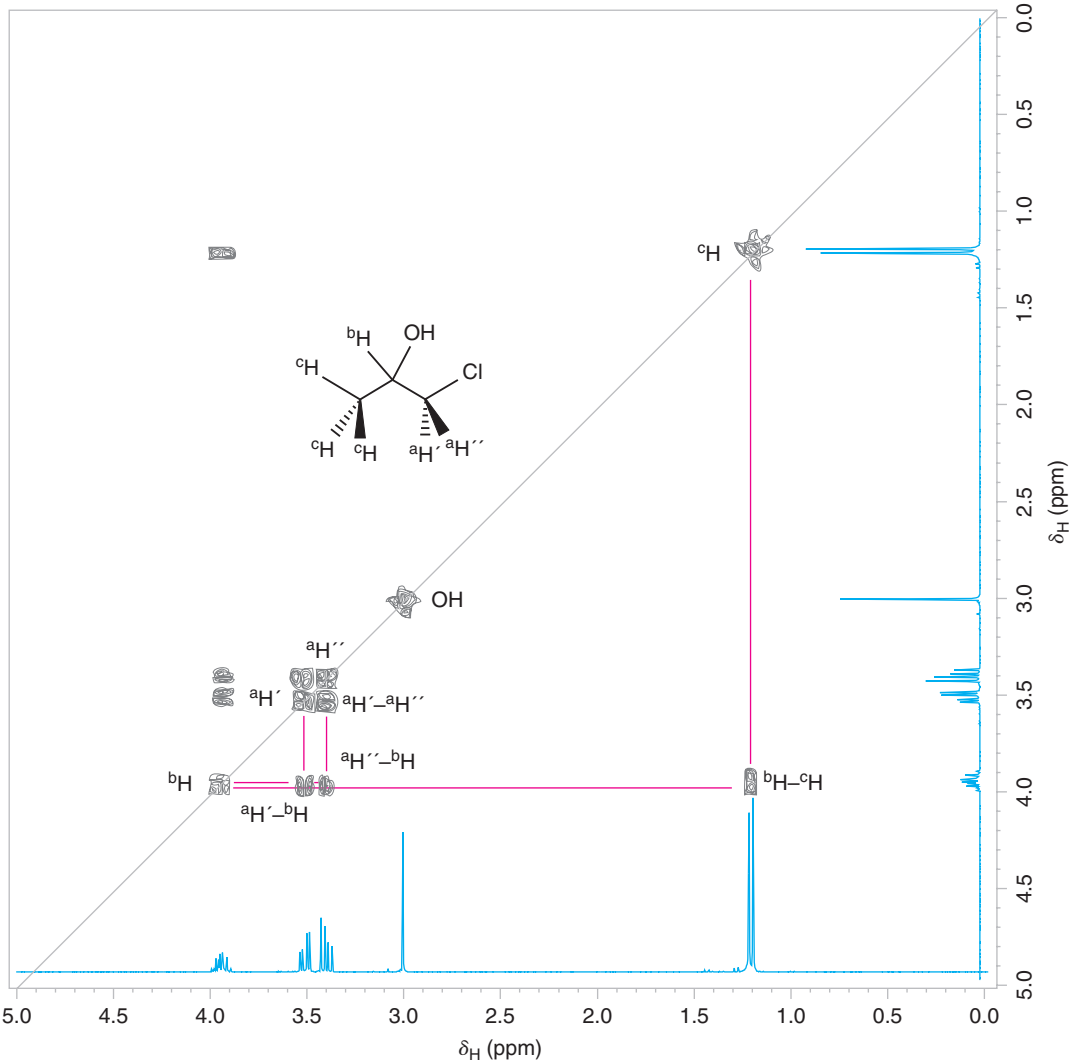


Figure 9.33 COSY spectrum of 1-chloro-2-propanol.

The important and new information from the COSY spectrum, however, comes from the correlation peaks ("mountains") that appear off the diagonal (called "cross peaks"). If one starts at a given cross peak and imagines two perpendicular lines (i.e., parallel to each spectrum axis) leading back to the diagonal, the peaks intersected on the diagonal by these lines are coupled to each other. Hence, the peaks on the one-dimensional spectrum directly below the coupled diagonal peaks are coupled to each other. The cross peaks above the diagonal are mirror reflections of those below the diagonal; thus the information is redundant and only cross peaks on one side of the diagonal need be interpreted. The *x*–*y* field cross-peak correlations are the result of instrumental parameters used to obtain the COSY spectrum.

Let's trace the coupling relationships in 1-chloro-2-propanol made evident in its COSY spectrum (Fig. 9.33). (Even though coupling relationships from the ordinary one-dimensional spectrum for 1-chloro-2-propanol are fairly readily interpreted, this compound makes a good beginning example for interpretation of COSY spectra.) First, one chooses a starting point in the COSY spectrum from which to begin tracing the coupling relationships. A peak whose assignment is relatively apparent in the one-dimensional spectrum is a good point of reference. For this compound, the doublet from the methyl group at 1.2 ppm is quite obvious and readily assigned. If we find the peak on the diagonal that corresponds to the methyl doublet (labeled ^{c}H in Fig. 9.33 and directly above the one-dimensional methyl doublet on both axes), an imaginary line can be drawn parallel to the vertical axis that intersects a correlation peak (labeled ^{b}H–^{c}H) in the *x*–*y* field off the diagonal. From here a perpendicular imaginary line can be drawn back to its intersection with the diagonal peaks. At its intersection we see that this diagonal peak is directly above the one-dimensional spectrum peak at δ 3.9. Thus, the methyl hydrogens at δ 1.2 are coupled to the hydrogen whose signal appears at δ 3.9. It is now clear that the peaks at δ 3.9 are due to the hydrogen on the alcohol carbon in 1-chloro-2-propanol (^{b}H on C2).

Returning to the peak on the diagonal above δ 3.9, we can trace a line back parallel to the horizontal axis that intersects a pair of cross peaks between δ 3.4 and δ 3.5. Moving back up to the diagonal from each of these cross peaks (^{a}H′–^{b}H and ^{a}H″–^{b}H) indicates that the hydrogen whose signal appears at δ 3.9 is coupled to the hydrogens whose signals appear at δ 3.4 and δ 3.5. The hydrogens at δ 3.4 and δ 3.5 are therefore the two hydrogens on the carbon that bears the chlorine (^{a}H′ and ^{a}H″). One can even see that ^{a}H′ and ^{a}H″ couple with each other by the cross peak they have in common between them right next to their diagonal peaks. (^{a}H′ and ^{a}H″ are diastereotopic. See Section 9.8B.) Thus, from the COSY spectrum we can quickly see which hydrogens are coupled to each other. Furthermore, from the reference starting point, we can "walk around" a molecule, tracing the neighboring coupling relationships along the molecule's carbon skeleton as we go through the COSY spectrum.

9.12B HETCOR Cross-Peak Correlations

In a HETCOR spectrum a ^{13}C spectrum is presented along one axis and a ^{1}H spectrum is shown along the other. Cross peaks relating the two types of spectra to each other are found in the *x*–*y* field. Specifically, the cross peaks in a HETCOR spectrum indicate which hydrogens are attached to which carbons in a molecule, or vice versa. These cross-peak correlations are the result of instrumental parameters used to obtain the HETCOR spectrum. There is no diagonal spectrum in the *x*–*y* field like that found in the COSY spectrum. If imaginary lines are drawn from a given cross peak in the *x*–*y* field to each respective axis, the cross peak indicates that the hydrogen giving rise to the ^{1}H NMR signal on one axis is coupled (and attached) to the carbon that gives rise to the corresponding ^{13}C NMR signal on the other axis. Therefore, it is readily apparent which hydrogens are attached to which carbons.

Let us take a look at the HETCOR spectrum for 1-chloro-2-propanol (Fig. 9.34). Having interpreted the COSY spectrum already, we know precisely which hydrogens of 1-chloro-2-propanol produce each signal in the ^{1}H spectrum. If an imaginary line is taken from the methyl doublet of the proton spectrum at 1.2 ppm (vertical axis) out to the correlation peak in the *x*–*y* field and then dropped down to the ^{13}C spectrum axis (horizontal axis), it is apparent that the ^{13}C peak at 20 ppm is produced by the methyl carbon of 1-chloro-2-propanol (C3). Having assigned the ^{1}H NMR peak at 3.9 ppm to the hydrogen on the alcohol carbon of the molecule (C2), tracing out to the correlation peak and down to the ^{13}C spectrum indicates that the ^{13}C

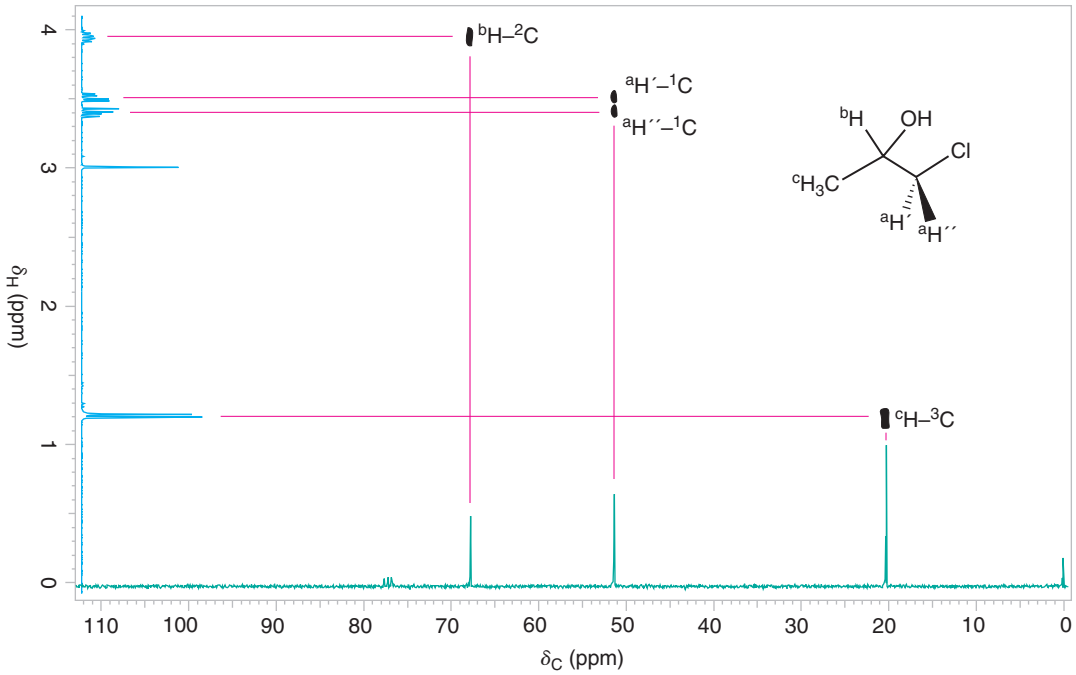
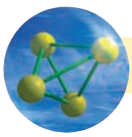


Figure 9.34 ^{1}H–^{13}C HETCOR NMR spectrum of 1-chloro-2-propanol. The ^{1}H NMR spectrum is shown in blue and the ^{13}C NMR spectrum is shown in green. Correlations of the ^{1}H–^{13}C cross peaks with the one-dimensional spectra are indicated by red lines.

NMR signal at 67 ppm arises from the alcohol carbon (C2). Finally, from the ^{1}H NMR peaks at 3.4–3.5 ppm for the two hydrogens on the carbon bearing the chlorine, our interpretation leads us out to the cross peak and down to the ^{13}C peak at 51 ppm (C1).

Thus, by a combination of COSY and HETCOR spectra, all ^{13}C and ^{1}H peaks can be unambiguously assigned to their respective carbon and hydrogen atoms in 1-chloro-2-propanol. (In this simple example using 1-chloro-2-propanol, we could have arrived at complete assignment of these spectra without COSY and HETCOR data. For many compounds, however, the assignments are quite difficult to make without the aid of these 2D NMR techniques.)

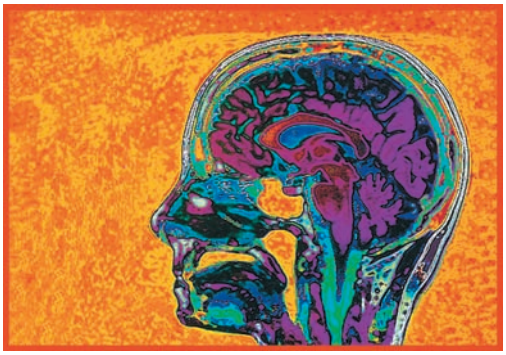


THE CHEMISTRY OF . . .

Magnetic Resonance Imaging in Medicine

An important application of ^{1}H NMR spectroscopy in medicine today is a technique called **magnetic resonance imaging**, or **MRI**. One great advantage of MRI is that, unlike X-rays, it does not use dangerous ionizing radiation, and it does not require the injection of potentially harmful chemicals in order to produce contrasts in the image. In MRI, a portion of the patient's body is placed in a powerful magnetic field and irradiated with RF energy.

A typical MRI image is shown at the right. The instruments used in producing images like this one use the pulse method (Section 9.5) to excite the protons in the tissue under observation and use a Fourier transformation to translate the information into an image. The brightness of various regions of the image is related to two things.



An image obtained by magnetic resonance imaging.

(continues on the next page)

The first factor is the number of protons in the tissue at that particular place. The second factor arises from what are called the **relaxation times** of the protons. When protons are excited to a higher energy state by the pulse of RF energy, they absorb energy. They must lose this energy to return to the lower energy spin state before they can be excited again by a second pulse. The process by which the nuclei lose this energy is called **relaxation**, and the time it takes to occur is the relaxation time.

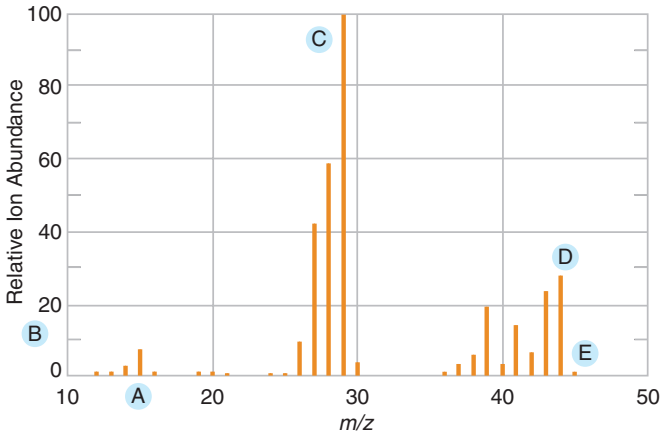
There are two basic modes of relaxation available to protons. In one, called *spin–lattice relaxation*, the extra energy is transferred to neighboring molecules in the surroundings (or lattice). The time required for this to happen is called T_1 and is characteristic of the time required for the spin system to return to thermal equilibrium with its surroundings. In solids, T_1 can be hours long. For protons in pure liquid water, T_1 is only a few seconds. In the other type of relaxation, called *spin–spin relaxation*, the extra energy is dissipated by being transferred to nuclei of nearby atoms. The time required for this is called T_2. In liquids the magnitude of T_2 is approximately equal to T_1. In solids, however, the T_1 is very much longer.

Various techniques based on the time between pulses of RF radiation have been developed to utilize the differences in relaxation times in order to produce contrasts between different regions in soft tissues. The soft tissue contrast is inherently higher than that produced with X-ray techniques. Magnetic resonance imaging is being used to great effect in locating tumors, lesions, and edemas. Improvements in this technique are occurring rapidly, and the method is not restricted to observation of proton signals.

One important area of medical research is based on the observation of signals from ^{31}P. Compounds that contain phosphorus as phosphate esters (Section 11.10) such as adenosine triphosphate (ATP) and adenosine diphosphate (ADP), are involved in most metabolic processes. By using techniques based on NMR, researchers now have a noninvasive way to follow cellular metabolism.

9.13 An Introduction to Mass Spectrometry

Mass spectrometry (MS) involves formation of ions in a mass spectrometer followed by separation and detection of the ions according to mass and charge. A mass spectrum is a graph that on the *x*-axis represents the formula weights of the detected ions, and on the *y*-axis represents the abundance of each detected ion. The *x*-axis is labeled *m*/*z*, where m = mass and z = charge. In examples we shall consider, z equals +1, and hence the *x*-axis effectively represents the formula weight of each detected ion. The *y*-axis expresses relative ion abundance, usually as a percentage of the tallest peak or directly as the number of detected ions. The tallest peak is called the **base peak**. As a typical example, the mass spectrum of propane is shown in Fig. 9.35.



A The *x*-axis, in units of *m*/*z*, represents the formula weight of the detected ions. ***m/z*** is the mass (*m*) to charge (*z*) ratio. Because z is typically +1, *m*/*z* represents the formula weight of each ion.

B The *y*-axis represents the relative abundance of each detected ion.

C The most abundant ion (tallest peak) is called the **base peak**. The base peak is usually an easily formed fragment of the original compound. In this case it is an ethyl fragment ($C_2H_5^+$, *m*/*z* 29).

D One of the higher value *m*/*z* peaks may or may not represent the **molecular ion** (the ion with the formula weight of the original compound). When present, the molecular ion (*m*/*z* 44 in the case of propane) is usually not the base peak, because ions from the original molecule tend to fragment, resulting in the other *m*/*z* peaks in the spectrum.

E Small peaks having *m*/*z* values 1 or 2 higher than the formula weight of the compound are due to ^{13}C and other isotopes (Section 9.17).

Figure 9.35 A mass spectrum of propane. (NIST Mass Spec Data Center, S. E. Stein, director, "Mass Spectra" in **NIST Chemistry WebBook, NIST Standard Reference Database Number 69**, Eds. P. J. Linstrom and W. G. Mallard, June 2005, National Institute of Standards and Technology, Gaithersburg, MD, 20899 (http://webbook.nist.gov).)

9.14 Formation of Ions: Electron Impact Ionization

The ions in mass spectrometry may be formed in a variety of ways. One method for converting molecules to ions (**ionization**) in a mass spectrometer is to place a sample under high vacuum and bombard it with a beam of high-energy electrons (~70 eV, or ~6.7×10^3 kJ mol^{-1}). This method is called **electron impact (EI)** ionization mass spectrometry. The impact of the electron beam dislodges a valence electron from the gas-phase molecules, leaving them with a +1 charge and an unshared electron. This species is called the **molecular ion ($M^{+\cdot}$).** We can represent this process as follows:

Note the $^{+}_{\bullet}$, representing an unshared electron and the net +1 charge.

$$\underset{\text{Molecule}}{M} + \underset{\text{High-energy electron}}{e^-} \longrightarrow \underset{\text{Molecular ion}}{M^{+\cdot}} + 2\,e^-$$

The molecular ion is a **radical cation** because it contains both an unshared electron and a positive charge. Using propane as an example, we can write the following equation to represent formation of its molecular ion by electron impact ionization:

A radical cation

$$CH_3CH_2CH_3 + e^- \rightarrow [CH_3CH_2CH_3]^{+\cdot} + 2e^-$$

9.15 Depicting the Molecular Ion

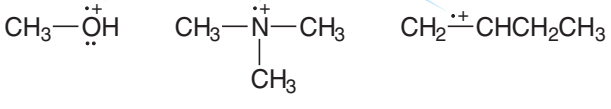
Notice that we have written the above formula for the propane radical cation in brackets. This is because we do not know precisely from where the electron was lost in propane. We only know that one valence electron in propane was dislodged by the electron impact process. However, depicting the molecular ion with a localized charge and odd electron is sometimes useful (as we shall discuss in Section 9.16 when considering fragmentation reactions). One possible formula representing the molecular ion from propane with a localized charge and an odd electron is the following:

$$CH_3CH_2^{+}\!\!\cdot CH_3$$

In many cases, the choice of just where to localize the odd electron and charge is arbitrary, however. This is especially true if there are only carbon–carbon and carbon–hydrogen single bonds, as in propane. When possible, though, we write the structure showing the molecular ion that would result from the removal of one of the most loosely held valence electrons of the original molecule. Just which valence electrons are most loosely held can usually be estimated from ionization potentials (Table 9.3). [The ionization potential of a molecule is the amount of energy (in electron volts) required to remove a valence electron from the molecule.]

As we might expect, ionization potentials indicate that the nonbonding electrons of nitrogen, oxygen, and halogens and the π electrons of alkenes and aromatic molecules are held more loosely than the electrons of carbon–carbon and carbon–hydrogen σ bonds. Therefore, the convention of localizing the odd electron and charge is especially applicable when the molecule contains oxygen, nitrogen, or a π bond. The following are examples of these cases.

Radical cations from ionization of nonbonding or π electrons.



Methanol **Trimethylamine** **1-Butene**

TABLE 9.3
Ionization Potentials of Selected Molecules

Compound	Ionization Potential (eV)
$CH_3(CH_2)_3NH_2$	8.7
C_6H_6 (benzene)	9.2
C_2H_4	10.5
CH_3OH	10.8
C_2H_6	11.5
CH_4	12.7

9.16 Fragmentation

Molecular ions formed by EI mass spectrometry are highly energetic species, and in the case of complex molecules, a great many things can happen to them. A molecular ion can break apart in a variety of ways, the fragments that are produced can undergo further **fragmentation**, and so on. We cannot go into all of the processes that are possible, but we can examine a few of the more important ones.

As we begin, let us keep three important principles in mind:

1. The reactions that take place in a mass spectrometer are unimolecular, that is, they do not involve collisions between molecules or ions. This is true because the pressure is kept so low (10^{-6} torr) that reactions involving bimolecular collisions do not occur.
2. We use single-barbed arrows to depict mechanisms involving single electron movements (see Section 3.1A).
3. The relative ion abundances, as indicated by peak intensities, are very important. We shall see that the appearance of certain prominent peaks in the spectrum gives us key information about the structures of the fragments produced and about their original locations in the molecule.

9.16A Fragmentation by Cleavage at a Single Bond

One important type of fragmentation is the simple cleavage of a single bond. With a radical cation this cleavage can take place in at least two ways; each way produces a *cation* and a *radical*. Only the cations are detected in a positive ion mass spectrometer. (The radicals, because they are not charged, are not detected.) With the molecular ion obtained from propane by loss of one carbon–carbon σ bonding electron, for example, two possible modes of cleavage are

$$[CH_3CH_2CH_3]^{+\cdot} \longrightarrow CH_3CH_2^+ + \cdot CH_3$$
$$[CH_3CH_2CH_3]^{+\cdot} \longrightarrow CH_3CH_2\cdot + {}^+CH_3$$

These two modes of cleavage do not take place at equal rates, however. Although the relative abundance of cations produced by such a cleavage is influenced by the stability of both the carbocation and the radical, the *carbocation's stability is more important*.* In the spectrum of propane shown earlier (Fig. 9.35), the peak at *m/z* 29 ($CH_3CH_2^+$) is the most intense peak; the peak at *m/z* 15 (CH_3^+) has a relative abundance of only 5.6%. This reflects the greater stability of $CH_3CH_2^+$ as compared to CH_3^+.

When drawing mechanism arrows to show cleavage reactions it is convenient to choose a localized representation of the radical cation, as we have done above for propane. (When showing only an equation for the cleavage and not a mechanism, however, we would use the convention of brackets around the formula with the odd electron and charge shown outside.) Fragmentation equations for propane would be written in the following way (note the use of single-barbed arrows):

$$CH_3CH_2CH_3 \xrightarrow[-e^-]{} CH_3CH_2^{+\cdot}CH_3 \longrightarrow CH_3CH_2^+ + \cdot CH_3 \quad (m/z\ 29)$$
$$\text{or}$$
$$CH_3CH_2^{+\cdot}CH_3 \longrightarrow CH_3CH_2\cdot + {}^+CH_3 \quad (m/z\ 15)$$

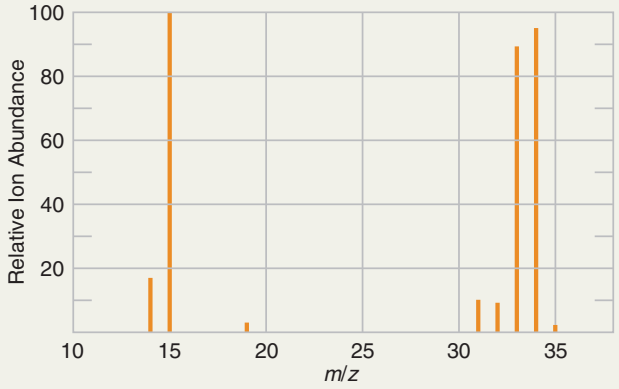
Helpful Hint

Recall that we use single-barbed arrows to show the movement of single electrons, as in the case of these homolytic bond cleavages and other processes involving radicals (see Section 3.1A).

*This can be demonstrated through thermochemical calculations that we cannot go into here. The interested student is referred to McLafferty, F. W., *Interpretation of Mass Spectra*, 2nd ed.; Benjamin: Reading, MA, 1973; pp. 41, 210–211.

Solved Problem 9.6

The mass spectrum of CH_3F is given in Fig. 9.36. **(a)** Draw a likely structure for the molecular ion (*m/z* 34). **(b)** Assign structural formulas to the two other high abundance peaks (*m/z* 33 and *m/z* 15) in the spectrum. **(c)** Propose an explanation for the low abundance of the peak at *m/z* 19.

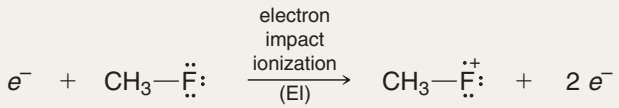


m/z	Relative Ion Abundance
14	17.2
15	100.0
19	2.0
31	10.4
32	9.4
33	89.5
34	95.4
35	1.1

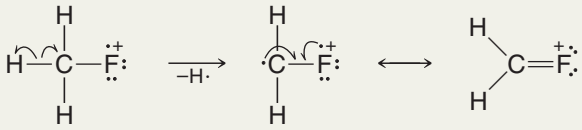
Figure 9.36 Mass spectrum for Solved Problem 9.6.

STRATEGY AND ANSWER

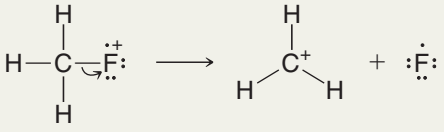
(a) Nonbonding electrons have lower ionization energies than bonding electrons, so we can expect that the molecular ion for CH_3F was formed by loss of an electron from the fluorine atom.



(b) The ion with *m/z* 33 differs from the molecular ion by one atomic mass unit, thus a hydrogen atom must have been lost. Cleavage with loss of a hydrogen atom could occur as follows, leaving both the carbon and fluorine with full valence electron shells, but as a cationic species overall.



The ion with *m/z* 15 must be a methyl carbocation formed by loss of a fluorine atom, as shown below. The fleeting existence of a methyl carbocation is possible in electron impact ionization (EI) mass spectrometry (MS) because electrons with high kinetic energy bombard the species undergoing analysis, allowing higher energy pathways to be followed than occur with reactions that take place in solution.



(c) The *m/z* 19 peak in this spectrum would have to be a fluorine cation. The presence of only 6 valence electrons in an F^+ ion and the strong electronegativity of fluorine would create a very high energy barrier to formation of F^+ and hence, cause it to be formed in very low abundance relative to other ionization and cleavage pathways for CH_3F^+.

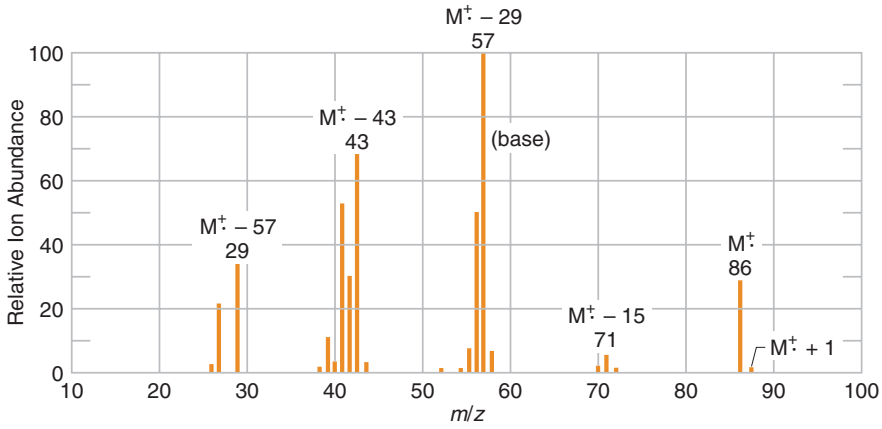
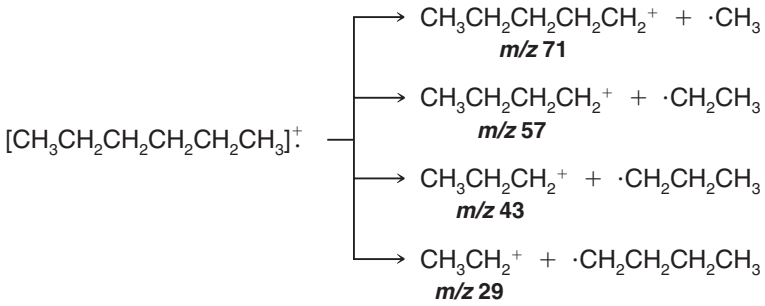


Figure 9.37 Mass spectrum of hexane.

9.16B Fragmentation of Longer Chain and Branched Alkanes

The mass spectrum of hexane shown in Fig. 9.37 illustrates the kind of fragmentation a longer chain alkane can undergo. Here we see a reasonably abundant molecular ion at *m/z* 86 accompanied by a small $M^{+\cdot} + 1$ peak. There is also a smaller peak at *m/z* 71 ($M^{+\cdot} - 15$) corresponding to the loss of $\cdot CH_3$, and the base peak is at *m/z* 57 ($M^{+\cdot} - 29$) corresponding to the loss of $\cdot CH_2CH_3$. The other prominent peaks are at *m/z* 43 ($M^{+\cdot} - 43$) and *m/z* 29 ($M^{+\cdot} - 57$), corresponding to the loss of $\cdot CH_2CH_2CH_3$ and $\cdot CH_2CH_2CH_2CH_3$, respectively. The important fragmentations are just the ones we would expect:



Chain branching increases the likelihood of cleavage at a branch point because a more stable carbocation can result. When we compare the mass spectrum of 2-methylbutane (Fig. 9.38) with the spectrum of hexane, we see a much more intense peak at $M^{+\cdot} - 15$.

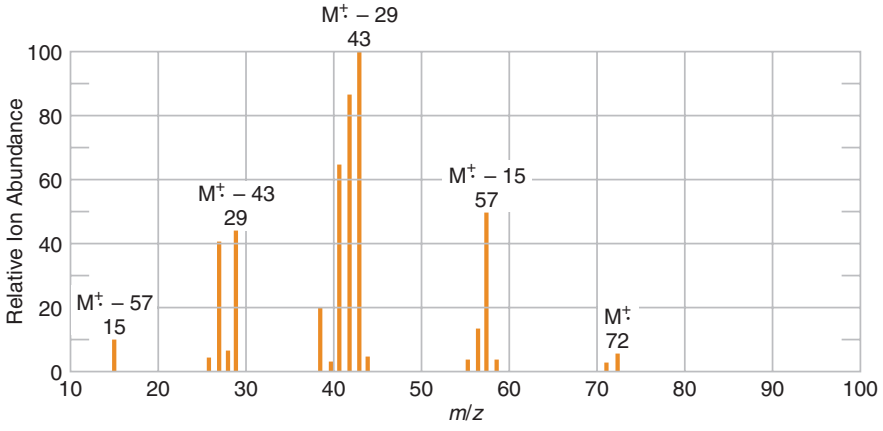
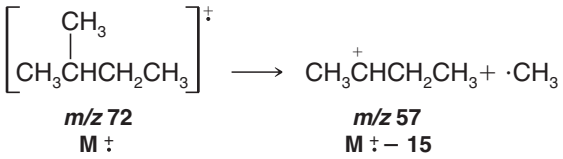


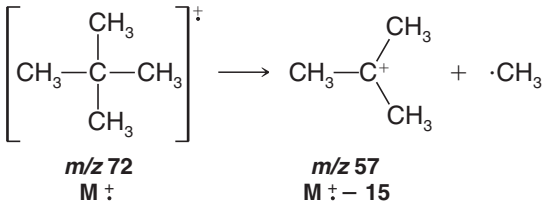
Figure 9.38 Mass spectrum of 2-methylbutane.

Loss of a methyl radical from the molecular ion of 2-methylbutane can give a secondary carbocation:



whereas with hexane loss of a methyl radical can yield only a primary carbocation.

With neopentane (Fig. 9.39), this effect is even more dramatic. Loss of a methyl radical by the molecular ion produces a *tertiary* carbocation, and this reaction takes place so readily that virtually none of the molecular ions survive long enough to be detected:



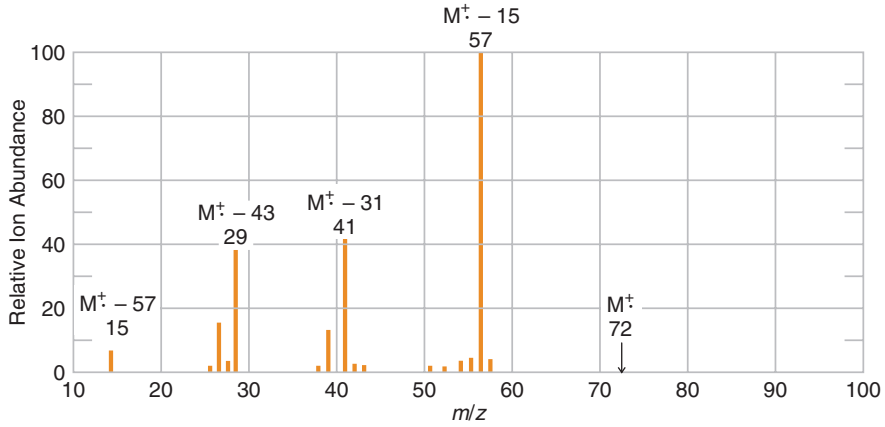


Figure 9.39 Mass spectrum of neopentane.

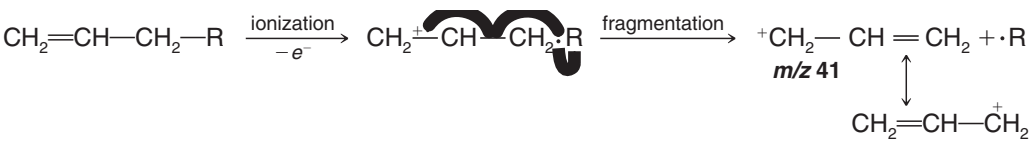
Review Problem 9.16

In contrast to 2-methylbutane and neopentane, the mass spectrum of 3-methylpentane (not given) has a peak of very low relative abundance at $M^{+\cdot} - 15$. It has a peak of very high relative abundance at $M^{+\cdot} - 29$, however. Explain.

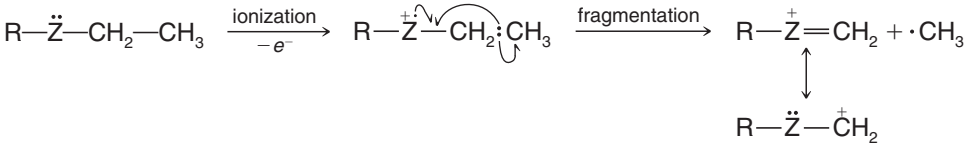
9.16C Fragmentation to Form Resonance-Stabilized Cations

Carbocations stabilized by resonance are usually prominent in mass spectra. Several ways that resonance-stabilized carbocations can be produced are outlined in the following list. These examples begin by illustrating the likely sites for initial ionization (π and nonbonding electrons), as well.

1. Alkenes ionize and frequently undergo fragmentations that yield resonance-stabilized allylic cations:

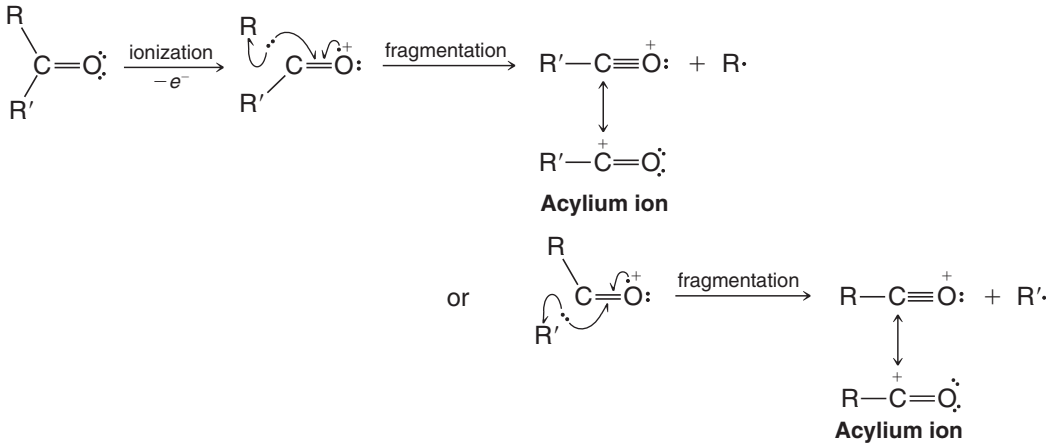


2. Carbon–carbon bonds next to an atom with an unshared electron pair usually break readily because the resulting carbocation is resonance stabilized:

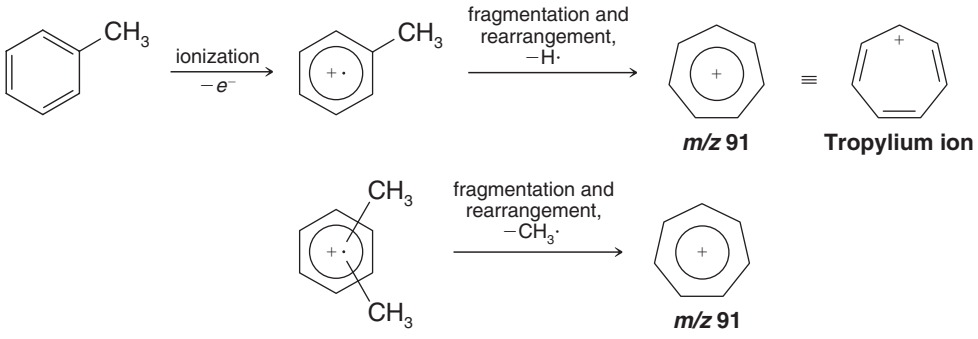


where Z = N, O, or S; R may also be H.

3. Carbon–carbon bonds next to the carbonyl group of an aldehyde or ketone break readily because resonance-stabilized ions called **acylium ions** are produced:



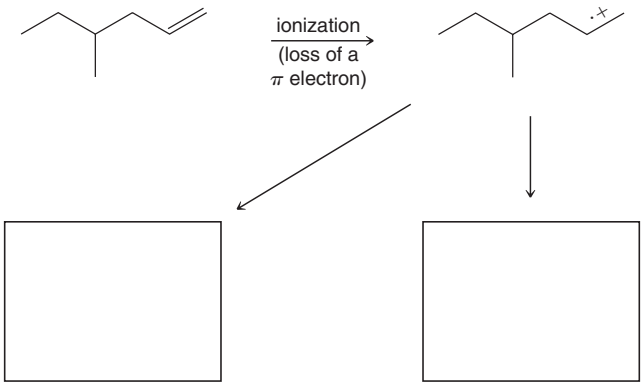
4. Alkyl-substituted benzenes ionize by loss of a π electron and undergo loss of a hydrogen atom or methyl group to yield the relatively stable tropylium ion (see Section 14.7C). This fragmentation gives a prominent peak (sometimes the base peak) at *m/z* 91:



5. Monosubstituted benzenes with other than alkyl groups also ionize by loss of a π electron and then lose their substituent to yield a phenyl cation with *m/z* 77:

Review Problem 9.17

Propose structures and fragmentation mechanisms corresponding to ions with *m/z* 57 and 41 in the mass spectrum of 4-methyl-1-hexene.



***m/z* 57** ***m/z* 41**

Solved Problem 9.7

Explain the following observations that can be made about the mass spectra of alcohols:

(a) The molecular ion peak of a primary or secondary alcohol is very small; with a tertiary alcohol it is usually undetectable.

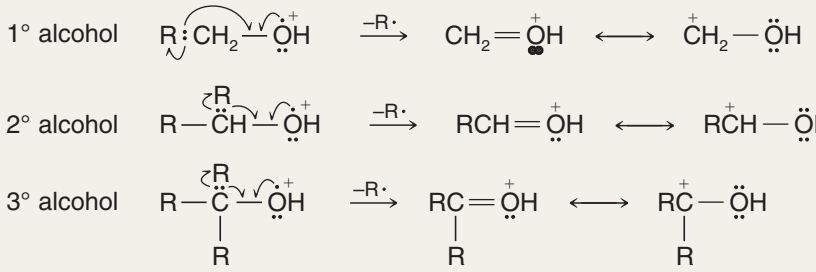
(b) Primary alcohols show a prominent peak at *m/z* 31.

(c) Secondary alcohols usually give prominent peaks at *m/z* 45, 59, 73, and so on.

(d) Tertiary alcohols have prominent peaks at *m/z* 59, 73, 87, and so on.

STRATEGY AND ANSWER

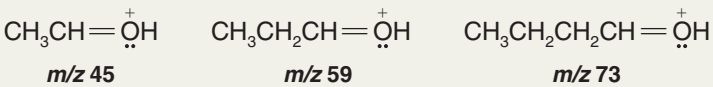
(a) Alcohols undergo rapid cleavage of a carbon–carbon bond next to oxygen because this leads to a resonance-stabilized cation.



The cation obtained from a tertiary alcohol is the most stable (because of the electron-releasing R groups).

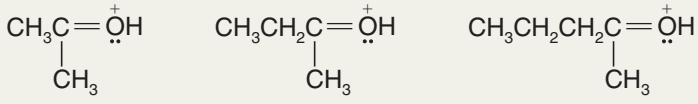
(b) Primary alcohols give a peak at *m/z* 31 due to $CH_2{=}\overset{+}{O}H$.

(c) Secondary alcohols give peaks at *m/z* 45, 59, 73, and so forth, because ions like the following are produced.



***m/z* 45** ***m/z* 59** ***m/z* 73**

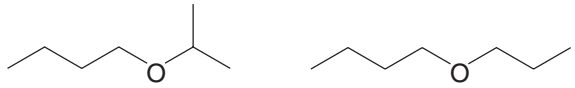
(d) Tertiary alcohols give peaks at *m/z* 59, 73, 87, and so forth, because ions like the following are produced.



***m/z* 59** ***m/z* 73** ***m/z* 87**

Review Problem 9.18

Match the mass spectra in Figs. 9.40 and 9.41 to the corresponding compounds shown below. Explain your answer.



Butyl isopropyl ether **Butyl propyl ether**

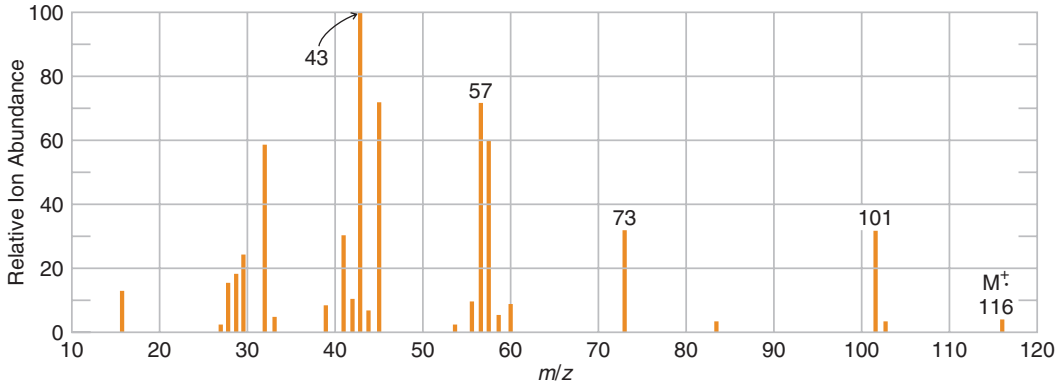


Figure 9.40 Mass spectrum for Review Problem 9.18.

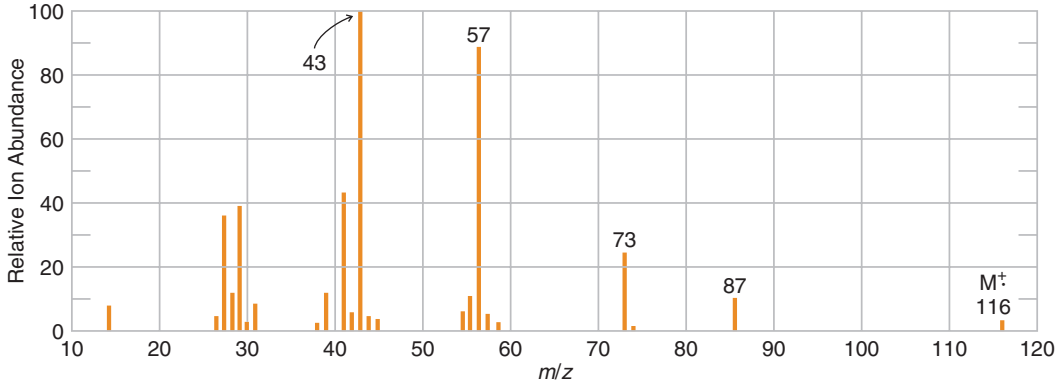
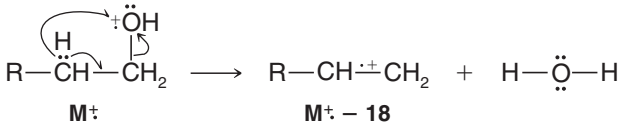


Figure 9.41 Mass spectrum for Review Problem 9.18.

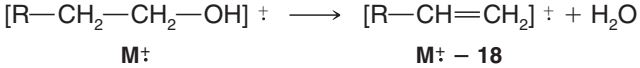
9.16D Fragmentation by Cleavage of Two Bonds

Many peaks in mass spectra can be explained by fragmentation reactions that involve the breaking of two covalent bonds. When a radical cation undergoes this type of fragmentation, the products are *a new radical cation* and *a neutral molecule*. Some important examples, starting from the initial radical cation, are the following:

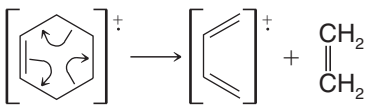
1. Alcohols frequently show a prominent peak at $M^{+\cdot} - 18$. This corresponds to the loss of a molecule of water:



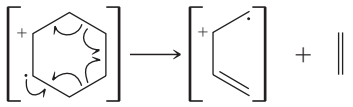
which can also be written as



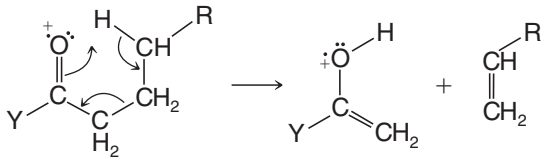
2. Cycloalkenes can undergo a retro-Diels–Alder reaction (Section 13.11) that produces an alkene and an alkadienyl radical cation:



which can also be written as



3. Carbonyl compounds with a hydrogen on their γ carbon undergo a fragmentation called the *McLafferty rearrangement*.



where Y = R, H, OR, OH, and so on.

In addition to these reactions, we frequently find peaks in mass spectra that result from the elimination of other small stable neutral molecules, for example, H_2, NH_3, CO, HCN, H_2S, alcohols, and alkenes.

9.17 How to Determine Molecular Formulas and Molecular Weights Using Mass Spectrometry

9.17A Isotopic Peaks and the Molecular Ion

Most of the common elements found in organic compounds have naturally occurring *heavier* isotopes. Table 9.4 lists some elements and their isotopes, with the natural abundance of each isotope given as the number of isotopic atoms per 100 atoms of the most abundant

TABLE 9.4 Principal Stable Isotopes of Common Elements[a]

Element	Most Common Isotope		Natural Abundance of Other Isotopes (Based on 100 Atoms of Most Common Isotope)			
Carbon	^{12}C	100	^{13}C	1.11		
Hydrogen	^{1}H	100	^{2}H	0.016		
Nitrogen	^{14}N	100	^{15}N	0.38		
Oxygen	^{16}O	100	^{17}O	0.04	^{18}O	0.20
Fluorine	^{19}F	100				
Silicon	^{28}Si	100	^{29}Si	5.10	^{30}Si	3.35
Phosphorus	^{31}P	100				
Sulfur	^{32}S	100	^{33}S	0.78	^{34}S	4.40
Chlorine	^{35}Cl	100	^{37}Cl	32.5		
Bromine	^{79}Br	100	^{81}Br	98.0		
Iodine	^{127}I	100				

[a]Reprinted with permission of John Wiley & Sons, Inc. from Silverstein, R. and Webster, F. X., *Spectrometric Identification of Organic Compounds, Sixth Edition*, p. 7. Copyright 1998.

isotope. For three of the elements—carbon, hydrogen, and nitrogen—the principal heavier isotope is one mass unit greater than the most common isotope.

- The presence of isotopes of carbon, hydrogen, and nitrogen in a compound gives rise to a small $M^{+\cdot} + 1$ peak.

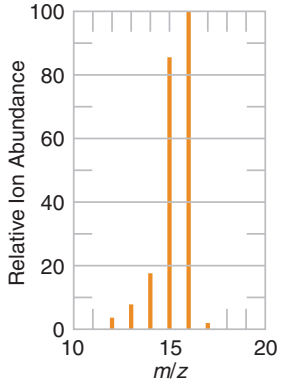
For four of the elements—oxygen, sulfur, chlorine, and bromine—the principal heavier isotope is two mass units greater than the most common isotope.

- The presence of oxygen, sulfur, chlorine, or bromine in a compound gives rise to an $M^{+\cdot} + 2$ peak.

$M^{+\cdot} + 1$ Elements: C, H, N

$M^{+\cdot} + 2$ Elements: O, S, Br, Cl

- The $M^{+\cdot} + 1$ peak can be used to determine the number of carbons in a molecule.
- The $M^{+\cdot} + 2$ peak can indicate whether bromine or chlorine is present.
- The isotopic peaks, in general, give us one method for determining molecular formulas.



m/z	Relative Ion Abundance
12	2.6
13	8.6
14	17.1
15	85.6
16	100.0
17	1.15

Figure 9.42 Mass spectrum for methane.

To understand how we can determine the number of carbons, let us begin by noticing that the isotope abundances in Table 9.4 are based on 100 atoms of the normal isotope. Now let us suppose, as an example, that we have 100 molecules of methane (CH_4). On the average there will be 1.11 molecules that contain a ^{13}C atom and 4×0.016 molecules that contain a ^{2}H atom. Altogether, then, these heavier isotopes should contribute an $M^{+\cdot} + 1$ peak whose intensity is about 1.17% of the intensity of the peak for the molecular ion:

$$1.11 + 4(0.016) \cong 1.17\%$$

This correlates well with the observed intensity of the $M^{+\cdot} + 1$ peak in the actual spectrum of methane given in Fig. 9.42.

9.17B How to Determine the Molecular Formula

For molecules with a modest number of atoms we can determine molecular formulas in the following way. If the $M^{+\cdot}$ peak is not the base peak, the first thing we do with the mass spectrum of an unknown compound is to recalculate the intensities of the $M^{+\cdot} + 1$ and $M^{+\cdot} + 2$ peaks to express them as percentages of the intensity of the $M^{+\cdot}$ peak.

Consider, for example, the mass spectrum of an unknown compound given in Fig. 9.43. The $M^{+\cdot}$ peak at *m/z* 72 is not the base peak. Therefore, we need to recalculate the intensities of the peaks in our spectrum at *m/z* 72, 73, and 74 as percentages of the peak at *m/z* 72. We do this by dividing each intensity by the intensity of the $M^{+\cdot}$ peak, which is 73%, and multiplying by 100. These results are shown here and in the second column of Fig. 9.43.

m/z	Intensity (% of $M^{+\cdot}$)
72	$73.0/73 \times 100 = 100$
73	$3.3/73 \times 100 = 4.5$
74	$0.2/73 \times 100 = 0.3$

Helpful Hint

How to determine a molecular formula using MS.

Then we use the following guides to determine the molecular formula:

1. **Is $M^{+\cdot}$ odd or even? According to the nitrogen rule, if it is even, then the compound must contain an even number of nitrogen atoms (zero is an even number).** For our unknown, $M^{+\cdot}$ is even. The compound must have an even number of nitrogen atoms.

m/z	Intensity (as percent of base peak)	*m/z*	Intensity (as percent of $M^{+\cdot}$)
27	59.0	72	$M^{+\cdot}$ 100.0
28	15.0	73	$M^{+\cdot}$ + 1 4.5
29	54.0	74	$M^{+\cdot}$ + 2 0.3
39	23.0		
41	60.0		Recalculated to base on $M^{+\cdot}$
42	12.0		
43	79.0		
44	100.0 (base)		
72	73.0 $M^{+\cdot}$		
73	3.3		
74	0.2		

Figure 9.43 Mass spectrum of an unknown compound.

2. **The relative abundance of the $M^{+\cdot}$ + 1 peak indicates the number of carbon atoms. Number of C atoms ■ relative abundance of $(M^{+\cdot} + 1)/1.1$.** For our unknown (Fig. 9.43),

$$\text{Number of C atoms} = \frac{4.5}{1.1} \cong 4$$

(This formula works because ^{13}C is the most important contributor to the $M^{+\cdot}$ + 1 peak and the approximate natural abundance of ^{13}C is 1.1%.)

3. **The relative abundance of the $M^{+\cdot}$ + 2 peak indicates the presence (or absence) of S (4.4%), Cl (33%), or Br (98%)** (see Table 9.4). For our unknown, $M^{+\cdot} + 2 = 0.3\%$; thus, we can assume that S, Cl, and Br are absent.

4. **The molecular formula can now be established by determining the number of hydrogen atoms and adding the appropriate number of oxygen atoms, if necessary**.

For our unknown the $M^{+\cdot}$ peak at *m/z* 72 gives us the molecular weight. It also tells us (since it is even) that nitrogen is absent because a compound with four carbons (as established above) and two nitrogens (to get an even molecular weight) would have a molecular weight (76) greater than that of our compound.

For a molecule composed of C and H only,

$$H = 72 - (4 \times 12) = 24$$

but C_4H_{24} is impossible.

For a molecule composed of C, H, and one O,

$$H = 72 - (4 \times 12) - 16 = 8$$

and thus our unknown has the molecular formula C_4H_8O.

Review Problem 9.19

Determine the molecular formula for a compound that gives the following mass spectral data:

m/z	Intensity (as % of base peak)
86 $M^{+\cdot}$	10.00
87	0.56
88	0.04

Solved Problem 9.8

(a) What approximate intensities would you expect for the $M^{+\cdot}$ and $M^{+\cdot} + 2$ peaks of CH_3Cl?

(b) For the $M^{+\cdot}$ and $M^{+\cdot} + 2$ peaks of CH_3Br?

(c) An organic compound gives an $M^{+\cdot}$ peak at *m/z* 122 and a peak of nearly equal intensity at *m/z* 124. What is a likely molecular formula for the compound?

STRATEGY AND ANSWER

(a) The $M^{+\cdot} + 2$ peak due to $CH_3—{}^{37}Cl$ (at *m/z* 52) should be almost one-third (32.5%) as large as the $M^{+\cdot}$ peak at *m/z* 50 because of the relative natural abundances of ^{35}Cl and ^{37}Cl.

(b) The peaks due to $CH_3—{}^{79}Br$ and $CH_3—{}^{81}Br$ (at *m/z* 94 and *m/z* 96, respectively) should be of nearly equal intensity due to the relative natural abundances of ^{79}Br and ^{81}Br.

(c) That the $M^{+\cdot}$ and $M^{+\cdot} + 2$ peaks are of nearly equal intensity tells us that the compound contains bromine. C_3H_7Br is therefore a likely molecular formula.

C_3	= 36	C_3	= 36
H_7	= 7	H_7	= 7
^{79}Br	= 79	^{81}Br	= 81
m/z	= 122	*m/z*	= 124

Review Problem 9.20

Use the mass spectral data below to calculate the $M^{+\cdot} + 1$ and $M^{+\cdot} + 2$ ratios with respect to the molecular ion ($M^{+\cdot}$). Then determine the molecular formula for the compound by consulting Table 9.5.

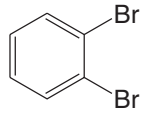
m/z	Intensity (as % of base peak)	*m/z*	Intensity (as % of base peak)
14	8.0	43	10.7
15	38.6	44	100.0 (base)
18	16.3	73	86.1 $M^{+\cdot}$
28	39.7	74	3.2 $M^{+\cdot} + 1$
29	23.4	75	0.2 $M^{+\cdot} + 2$
42	46.6		

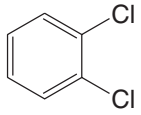
TABLE 9.5 Relative Intensities of $M^{+\cdot} + 1$ and $M^{+\cdot} + 2$ Peaks for Various Combinations of C, H, N, and O for Masses 72 and 73

		Percentage of $M^{+\cdot}$ Intensity				Percentage of $M^{+\cdot}$ Intensity	
$M^{+\cdot}$	Formula	$M^{+\cdot} + 1$	$M^{+\cdot} + 2$	$M^{+\cdot}$	Formula	$M^{+\cdot} + 1$	$M^{+\cdot} + 2$
72	CH_2N_3O	2.30	0.22	73	CHN_2O_2	1.94	0.41
	CH_4N_4	2.67	0.03		CH_3N_3O	2.31	0.22
	$C_2H_2NO_2$	2.65	0.42		CH_5N_4	2.69	0.03
	$C_2H_4N_2O$	3.03	0.23		C_2HO_3	2.30	0.62
	$C_2H_6N_3$	3.40	0.04		$C_2H_3NO_2$	2.67	0.42
	$C_3H_4O_2$	3.38	0.44		$C_2H_5N_2O$	3.04	0.23
	C_3H_6NO	3.76	0.25		$C_2H_7N_3$	3.42	0.04
	$C_3H_8N_2$	4.13	0.07		$C_3H_5O_2$	3.40	0.44
	C_4H_8O	4.49	0.28		C_3H_7NO	3.77	0.25
	$C_4H_{10}N$	4.86	0.09		$C_3H_9N_2$	4.15	0.07
	C_5H_{12}	5.60	0.13		C_4H_9O	4.51	0.28
					$C_4H_{11}N$	4.88	0.10
					C_6H	6.50	0.18

Review Problem 9.21

What are the expected ratios of the $M^{+\cdot}$, $M^{+\cdot} + 2$, and $M^{+\cdot} + 4$ peaks for the following compounds?

(a) 

(b) 

Review Problem 9.22

(a) Determine the molecular formula of the compound whose mass spectrum is given in the following tabulation:

m/z	Intensity (as % of base peak)	*m/z*	Intensity (as % of base peak)
27	34	65	8
39	11	78	24 $M^{+\cdot}$
41	22	79	0.8 $M^{+\cdot} + 1$
43	100 (base)	80	8 $M^{+\cdot} + 2$
63	26		

(b) The ^1H NMR spectrum of this compound consists only of a large doublet and a small septet. What is the structure of the compound?

As the number of atoms in a molecule increases, molecular weight calculations like this become more and more complex and time-consuming. Fortunately, however, these calculations can be done readily with computers, and tables are now available that give relative values for the $M^{+\cdot} + 1$ and $M^{+\cdot} + 2$ peaks for all combinations of common elements with molecular formulas up to mass 500. Part of the data obtained from one of these tables is given in Table 9.5. Use Table 9.5 to check the results of our example (Fig. 9.43).

9.17C High-Resolution Mass Spectrometry

All of the spectra that we have described so far have been determined on what are called "low-resolution" mass spectrometers. These spectrometers, as we noted earlier, measure *m/z* values to the nearest whole-number mass unit. Many laboratories are equipped with this type of mass spectrometer.

Some laboratories, however, are equipped with the more expensive "high-resolution" mass spectrometers. These spectrometers can measure *m/z* values to three or four decimal places and thus provide an extremely accurate method for determining molecular weights. And because molecular weights can be measured so accurately, these spectrometers also allow us to determine molecular formulas.

The determination of a molecular formula by an accurate measurement of a molecular weight is possible because the actual masses of atomic particles (nuclides) are not integers (see Table 9.6). Consider, as examples, the three molecules O_2, N_2H_4, and CH_3OH.

TABLE 9.6 Exact Masses of Nuclides

Isotope	Mass	Isotope	Mass
^1H	1.00783	^{19}F	18.9984
^2H	2.01410	^{32}S	31.9721
^{12}C	12.00000 (std)	^{33}S	32.9715
^{13}C	13.00336	^{34}S	33.9679
^{14}N	14.0031	^{35}Cl	34.9689
^{15}N	15.0001	^{37}Cl	36.9659
^{16}O	15.9949	^{79}Br	78.9183
^{17}O	16.9991	^{81}Br	80.9163
^{18}O	17.9992	^{127}I	126.9045

The actual atomic masses of the molecules are all different (though nominally they all have atomic mass of 32):

$$O_2 = 2(15.9949) = 31.9898$$
$$N_2H_4 = 2(14.0031) + 4(1.00783) = 32.0375$$
$$CH_4O = 12.00000 + 4(1.00783) + 15.9949 = 32.0262$$

High-resolution mass spectrometers are available that are capable of measuring mass with an accuracy of 1 part in 40,000 or better. Thus, such a spectrometer can easily distinguish among these three molecules and, in effect, tell us the molecular formula.

The ability of high-resolution instruments to measure exact masses has been put to great use in the analysis of biomolecules such as proteins and nucleic acids. For example, one method that has been used to determine the amino acid sequence in oligopeptides is to measure the exact mass of fragments derived from an original oligopeptide, where the mixture of fragments includes oligopeptides differing in length by one amino acid residue. The exact mass difference between each fragment uniquely indicates the amino acid residue that occupies that position in the intact oligopeptide (see Section 24.5E). Another application of exact mass determinations is the identification of peptides in mixtures by comparison of mass spectral data with a database of exact masses for known peptides. This technique has become increasingly important in the field of proteomics (Section 24.14).

9.18 Mass Spectrometer Instrument Designs

There are two principal components of mass spectrometers: the ionization chamber, where ionization of the sample occurs, and the mass analyzer, where ion sorting and detection occur. Mass spectrometer instruments vary in design with regard to both of these components. Thus far we have mentioned only one ionization technique, electron impact (EI). In Section 9.18A we discuss EI ionization in more detail, as well as discuss two other important ionization methods: electrospray ionization (ESI) and matrix-assisted laser desorption ionization (MALDI).

A variety of mass analyzer designs are in use as well, including magnetic focusing, quadrupole, ion trap, and time-of-flight (TOF). In Section 9.18B we explain the classical method for ion sorting (magnetic focusing), and briefly mention the other methods. The student is referred to textbooks of spectroscopy and instrumental analysis for further information.

9.18A Ionization Techniques: Electron Impact, Electrospray, and MALDI

Helpful Hint

A classic and highly useful reference on MS, NMR, and IR methods is Silverstein, R. M.; and Webster, F. X. *Spectrometric Identification of Organic Compounds*, 6th ed.; Wiley: New York, 1998.

Electron Impact Ionization Electron impact ionization can be described as a "brute-force" method because it involves striking an organic molecule with 70 eV electrons, a technique akin to firing a howitzer at a house made of matchsticks. It is no wonder that significant fragmentation takes place. Figure 9.44 shows a schematic diagram of a mass spectrometer that employs electron impact ionization. Ionization occurs in the ionizing chamber as gas-phase analyte molecules are struck by the electron beam. Positive ions formed from the analyte are accelerated and focused into the mass analyzer by passage through slits in negatively charged plates.

Electron impact ionization requires molecules of the analyte to be sufficiently volatile that they can be transferred to the gas phase in the high vacuum conditions of the ionizing chamber. This requirement for volatility essentially limits EI mass spectrometry to molecules that have formula weights of less than 1000 daltons (atomic mass units) and to molecules that are not very polar. While EI mass spectrometry is suitable for most of the types of organic molecules we shall study, it is not generally suitable for biomolecules that have high molecular weights, high polarity, or both. Fortunately, very effective methods have been developed for ionization of biomolecules and other molecules not suited to EI mass spectrometry. Among these techniques are electrospray ionization (ESI), ion spray, matrix-assisted laser desorption ionization (MALDI), and fast atom bombardment (FAB).

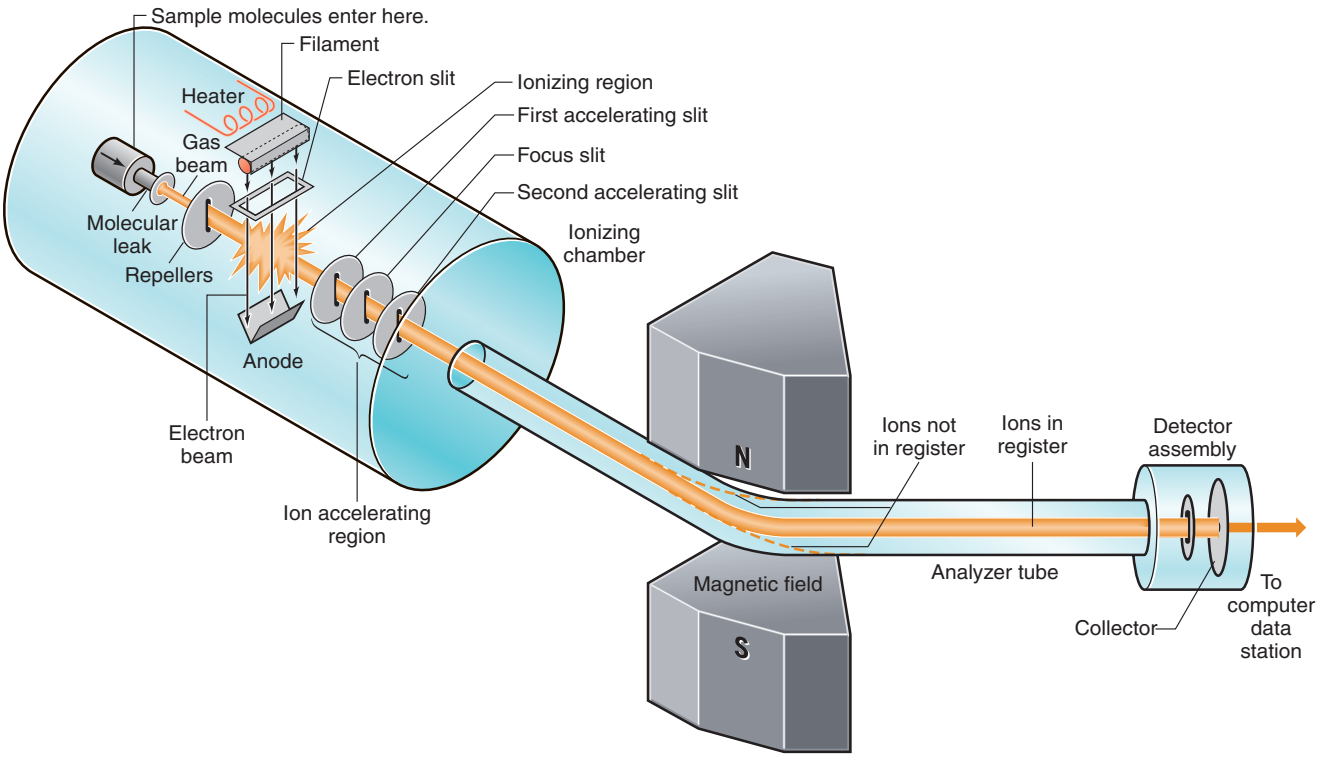


Figure 9.44 Mass spectrometer. Schematic diagram of CEG model 21-103. The magnetic field that brings ions of varying mass-to-charge ratios (m/z) into register is perpendicular to the page. (Reprinted with permission of John Wiley & Sons, Inc. from Holum, J. R., *Organic Chemistry: A Brief Course*, Copyright 1975.)

Electrospray Ionization—A Technique Especially Useful for Biomolecules

Electrospray ionization works especially well for mass spectrometry of proteins, carbohydrates, and nucleic acids. ESI mass spectrometry has been used to study protein molecular weights and sequence, enzyme–substrate complexes, antibody–antigen binding, drug–receptor interactions, and DNA oligonucleotide sequence, as well as simply for small molecules that cannot be ionized by electron impact.

In **electrospray ionization (ESI)** a solution of the analyte is sprayed into the vacuum chamber of the mass spectrometer from the tip of a high-voltage needle. The extreme electrical potential imparts charge to the mixture, which on evaporation of the solvent in the mass spectrometer affords charged species of the analyte. The analyte may actually acquire multiple charges through ESI (i.e., z can have a range of values in the m/z ratio), and hence a family of m/z peaks typically results for each analyte. This distribution can be converted by the mass spectrometer software to the formula weight of the original analyte. Another advantage of ESI MS is that a high-performance liquid chromatograph (HPLC) can be used to introduce the sample to the mass spectrometer. Linking chromatographic separation techniques with molecular spectroscopy, as in tandem HPLC and ESI MS analysis, affords a powerful analytical combination. We shall see another example below when we consider GC/MS (gas chromatography with mass spectrometry). We shall also have more to say about ESI MS when we study proteins in Chapter 24.

MALDI—A Technique Useful for Both Biomolecules and Synthetic Polymers

Matrix-assisted laser desorption–ionization (MALDI) works very well for synthetic polymers, such as polybutadiene and polystyrene, as well as for other classes of molecules that do not ionize well by electrospray ionization. MALDI is also useful for biomolecules, and hence can complement ESI methods.

In MALDI mass spectrometry the analyte is mixed with low-molecular-weight organic molecules that are known for their ability to absorb and transfer energy from the laser in the mass

spectrometer. After evaporation of the solvent, this mixture is called the sample matrix. The matrix is placed in the mass spectrometer under high vacuum and pulsed with laser radiation. Molecules of the matrix absorb radiation from the laser and transfer energy to the analyte. Many of the analyte molecules acquire a +1 charge through this process and are transferred to the vapor phase, after which the ions are drawn into the mass analyzer for separation and detection.

9.18B Mass Analysis: Ion Sorting and Detection

Once ions of the sample have been formed by one of the methods above, they are separated and detected by the mass analyzer component of the spectrometer. Several common ways exist to accomplish mass analysis. We shall first describe the classic method of magnetic focusing, and then briefly mention several other important approaches.

Magnetic Focusing Classic mass spectrometers accelerate ions formed in the ionization chamber into a curved tube (see Fig. 9.44). This curved tube passes through a variable magnetic field that exerts an influence on the moving ions. Depending on the magnetic field strength at a given moment, ions with a particular *m*/*z* will follow a curved path that exactly matches the curvature of the tube. These ions are said to be "in register." Because they are in register, these ions pass through another slit and impinge on an ion collector where the intensity of the ion beam is measured electronically. The intensity of the beam is simply a measure of the relative abundance of the ions with a particular *m*/*z*. Some mass spectrometers are so sensitive that they can detect the arrival of a *single ion*.

The actual sorting of ions takes place in the magnetic field, and this sorting takes place because laws of physics govern the paths followed by charged particles when they move through magnetic fields. Generally speaking, a magnetic field such as this will cause ions moving through it to move in a path that represents part of a circle. The radius of curvature of this circular path is related to the *m*/*z* of the ions, to the strength of the magnetic field ($\mathbf{B_0}$, in tesla), and to the accelerating voltage. If we keep the accelerating voltage constant and progressively increase the magnetic field, ions whose *m*/*z* values are progressively larger will travel in a circular path that exactly matches that of the curved tube. Hence, by steadily increasing $\mathbf{B_0}$, ions with progressively increasing *m*/*z* will be brought into register and so will be detected at the ion collector. Since, as we said earlier, the charge on nearly all of the ions is unity, this means that *ions of progressively increasing mass arrive at the collector and are detected.*

Quadrupole, Ion Trap, and Time-of-Flight (TOF) Mass Analyzers A variety of other methods are used for **ion sorting** in mass spectrometers, including quadrupole mass filtering, ion trapping, and time-of-flight mass analyzers. In a quadrupole mass analyzer, ions are filtered by varying the electrical signal in four parallel charged rods. At any given instant, only ions of certain mass-to-charge ratio are able to travel through the quadrupole region to the detector. Other ions collide with the rods and are neutralized. By varying the electrical state of the four rods in pairs, a range of masses can be scanned. Ion trap mass analyzers involve a ring electrode charged with a varying radio frequency voltage. Ions enter the cavity enclosed by the ring, and those of appropriate mass take up a stable orbit. As the voltage state of the ring varies, so does the mass for which a stable orbit is possible. Varying the ring voltage allows a range of masses to be scanned by progressively trapping and releasing them to the detector. In time-of-flight mass analyzers, ions are accelerated into a tube that is free of electrical fields. The ions drift toward the detector, and the time it takes to traverse the tube is correlated with their respective masses.

9.19 GC/MS Analysis

Gas chromatography is often coupled with mass spectrometry in a technique called **GC/MS analysis**. The gas chromatograph separates components of a mixture, while the mass spectrometer then gives structural information about each one (Fig. 9.45). GC/MS can also provide quantitative data when standards of known concentration are used with the unknown.

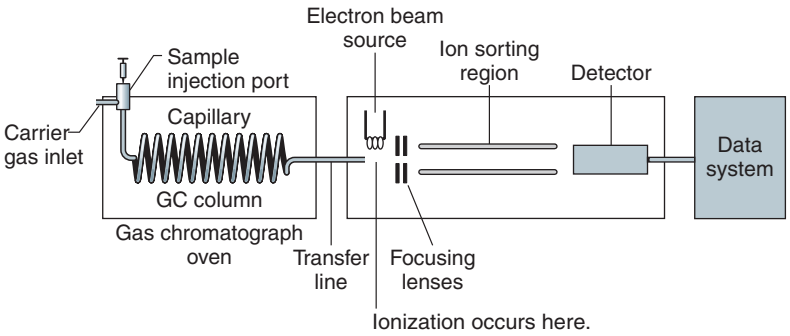


Figure 9.45 Schematic of a typical capillary gas chromatograph/mass spectrometer (GC/MS).

In GC analysis, a minute amount of a mixture to be analyzed, typically 0.001 mL (1.0 μL) or less of a dilute solution containing the sample, is injected by syringe into a heated port of the gas chromatograph. The sample is vaporized in the injector port and swept by a flow of inert gas into a capillary column. The capillary column is a thin tube usually 10–30 meters long and 0.1–0.5 mm in diameter. It is contained in a chamber (the "oven") whose temperature can be varied according to the volatility of the samples being analyzed. The inside of the capillary column is typically coated with a "stationary phase" of low polarity (essentially a high-boiling and very viscous liquid that is often a nonpolar silicon-based polymer). As molecules of the mixture are swept by the inert gas through the column, they travel at different rates according to their boiling points and the degree of affinity for the stationary phase. Materials with higher boiling points or stronger affinity for the stationary phase take longer to pass through the column. Low-boiling and nonpolar materials pass through very quickly. The length of time each component takes to travel through the column is called the retention time. Retention times typically range from 1 to about 30 minutes, depending on the sample and the specific column used.

As each component of the mixture exits the GC column it travels into a mass spectrometer. Here, molecules of the sample are bombarded by electrons; ions and fragments of the molecule are formed, and a mass spectrum results similar to those we have studied earlier in this chapter. The important thing, however, is that mass spectra are obtained for *each* component of the original mixture that is separated. This ability of GC/MS to separate mixtures and give information about the structure of each component makes it a virtually indispensable tool in analytical, forensic, and organic synthesis laboratories.

9.20 Mass Spectrometry of Biomolecules

Advances in mass spectrometry have made it a tool of exceptional power for analysis of large biomolecules. Electrospray ionization, MALDI, and other "soft ionization" techniques for nonvolatile compounds and macromolecules make possible analyses of proteins, nucleic acids, and other biologically relevant compounds with molecular weights up to and in excess of 100,000 daltons. Electrospray ionization with quadrupole mass analysis is now routine for biomolecule analysis as is analysis using MALDI–TOF instruments. Extremely high resolution can be achieved using Fourier transform–ion cyclotron resonance (FT ICR, or FTMS). We shall discuss ESI and MALDI applications of mass spectrometry to protein sequencing and analysis in Sections 24.5E, 24.13B, and 24.14.

Key Terms and Concepts

The key terms and concepts that are highlighted in **bold, blue text** within the chapter are defined in the glossary (at the back of the book) and have hyperlinked definitions in the accompanying ***WileyPLUS*** course (www.wileyplus.com).

Problems

Note to Instructors: Many of the homework problems are available for assignment via *WileyPLUS*, an online teaching and learning solution.

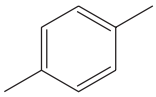
NMR SPECTROSCOPY

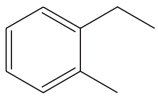
The following are some abbreviations used to report spectroscopic data:
^{1}H NMR: s = singlet, d = doublet, t = triplet, q = quartet, bs = broad singlet, m = multiplet
IR absorptions: s = strong, m = moderate, br = broad

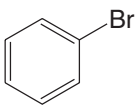
9.23 How many ^{1}H NMR signals (not peaks) would you predict for each of the following compounds? (Consider all protons that would be chemical shift nonequivalent.)

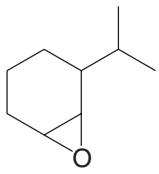
(a) 

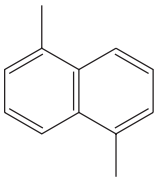
(b) 

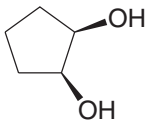
(c) 

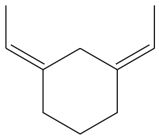
(d) 

(e) 

(f) 

(g) 

(h) 

(i) 

9.24 How many ^{13}C NMR signals would you predict for the compounds shown in Problem 9.23?

9.25 Propose a structure for an alcohol with molecular formula $C_5H_{12}O$ that has the ^{1}H NMR spectrum given in Fig. 9.46. Assign the chemical shifts and splitting patterns to specific aspects of the structure you propose.

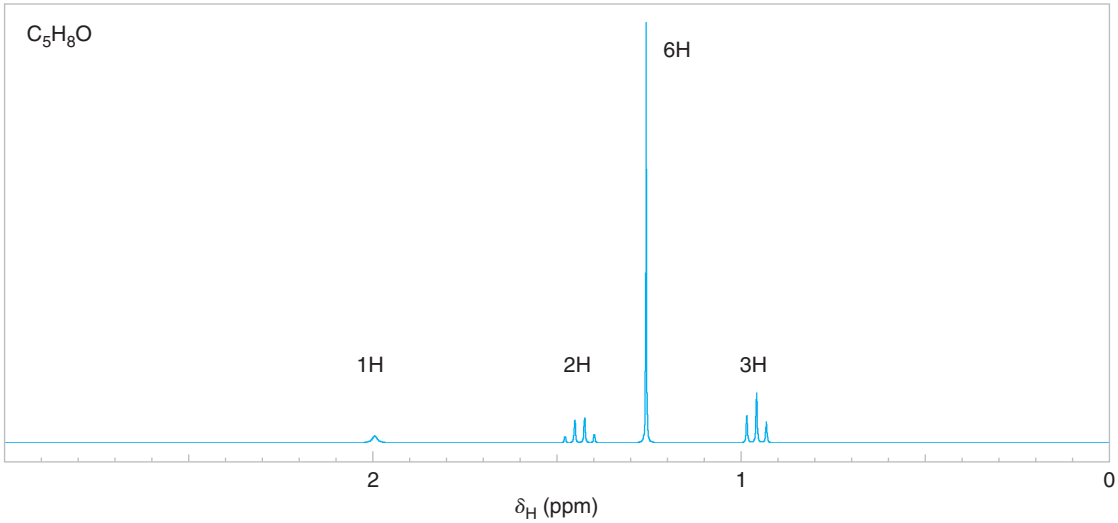


Figure 9.46 The ^{1}H NMR spectrum (simulated) of alcohol C_5H_8O, Problem 9.25.

9.26 Propose structures for the compounds **G** and **H** whose ^{1}H NMR spectra are shown in Figs. 9.47 and 9.48.

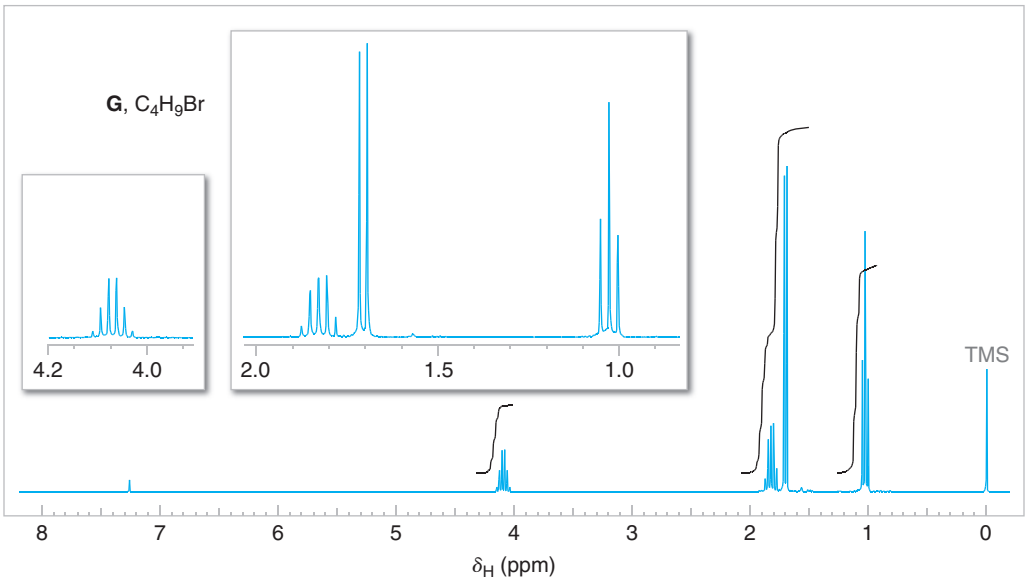


Figure 9.47 The 300-MHz ^{1}H NMR spectrum of compound **G**, Problem 9.26. Expansions of the signals are shown in the offset plots.

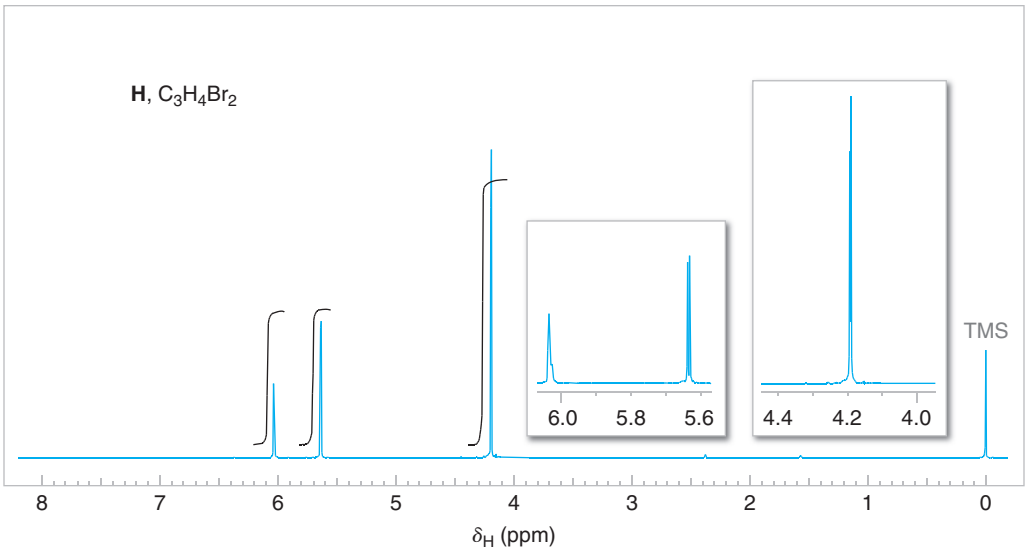


Figure 9.48 The 300-MHz ^{1}H NMR spectrum of compound **H**, Problem 9.26. Expansions of the signals are shown in the offset plots.

9.27 Assume that in a certain ^{1}H NMR spectrum you find two peaks of roughly equal intensity. You are not certain whether these two peaks are *singlets* arising from uncoupled protons at different chemical shifts or are two peaks of a *doublet* that arises from protons coupling with a single adjacent proton. What simple experiment would you perform to distinguish between these two possibilities?

9.28 Propose structures for compounds **O** and **P** that are consistent with the following information.

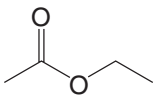
$$\underset{\textbf{O}}{C_6H_8} \xrightarrow[pt]{H_2\text{(2 Equiv.)}} \underset{\textbf{P}}{C_6H_{12}}$$

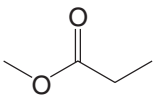
^{13}C NMR for Compound **O**	δ (ppm)	DEPT
	26.0	CH_2
	124.5	CH

9.29 Compound **Q** has the molecular formula C_7H_8. The broad-band proton decoupled ^{13}C spectrum of **Q** has signals at δ 50 (CH), 85 (CH_2), and 144 (CH). On catalytic hydrogenation **Q** is converted to **R** (C_7H_{12}). Propose structures for **Q** and **R**.

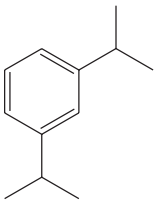
9.30 Explain in detail how you would distinguish between the following sets of compounds using the indicated method of spectroscopy.

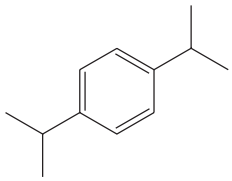
(a) ^1H NMR



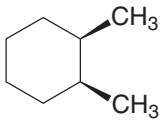


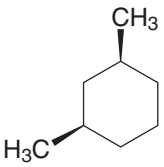
(b) ^{13}C and ^1H NMR





(c) ^{13}C NMR





9.31 Compound **S** (C_8H_{16}) reacts with one mole of bromine to form a compound with molecular formula $C_8H_{16}Br_2$. The broadband proton-decoupled ^{13}C spectrum of **S** is given in Fig. 9.49. Propose a structure for **S**.

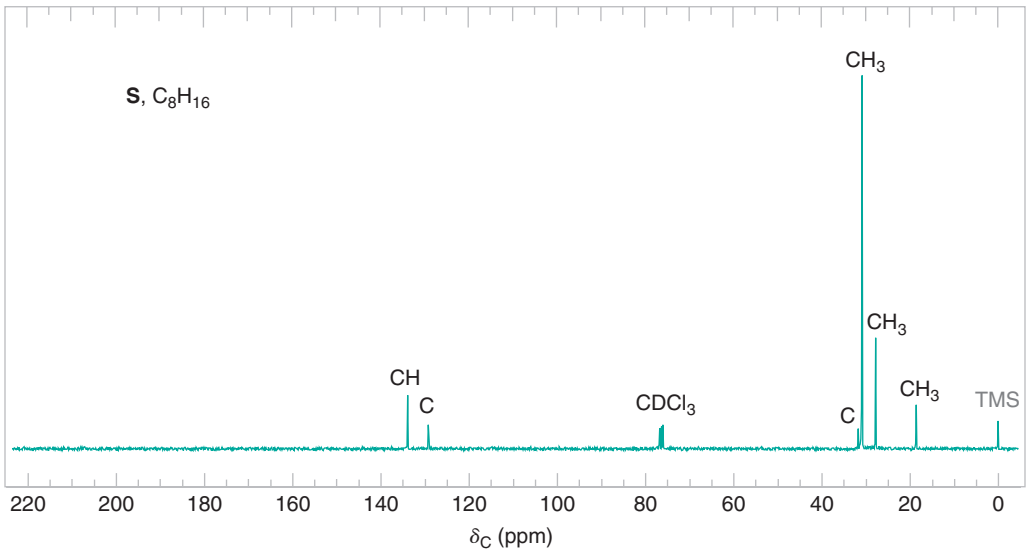
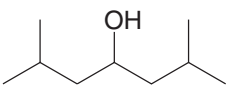


Figure 9.49 The broadband proton-decoupled ^{13}C NMR spectrum of compound ***S***, Problem 9.31. Information from the DEPT ^{13}C NMR spectra is given above each peak.

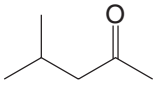
MASS SPECTROMETRY

9.32 A compound with molecular formula C_4H_8O has a strong IR absorption at 1730 cm^{-1}. Its mass spectrum is tabulated in Fig. 9.43, and includes key peaks at *m/z* 44 (the base peak) and *m/z* 29. Propose a structure for the compound and write fragmentation equations showing how peaks having these *m/z* values arise.

9.33 In the mass spectrum of 2,6-dimethyl-4-heptanol there are prominent peaks at *m/z* 87, 111, and 126. Propose reasonable structures for these fragment ions.



9.34 In the mass spectrum of 4-methyl-2-pentanone a McLafferty rearrangement and two other major fragmentation pathways occur. Propose reasonable structures for these fragment ions and specify the *m/z* value for each.



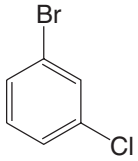
9.35 What are the masses and structures of the ions produced in the following cleavage pathways?

(a) α-cleavage of 2-methyl-3-hexanone (two pathways)

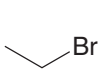
(b) dehydration of cyclopentanol

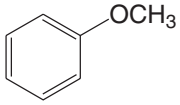
(c) McLafferty rearrangement of 4-methyl-2-octanone (two pathways)

9.36 Predict the masses and relative intensities of the peaks in the molecular ion region for the following compound.



9.37 Ethyl bromide and methoxybenzene (shown below) have the same nominal molecular weights, displaying a significant peak at m/z 108. Regarding their molecular ions, what other features would allow the two compounds to be distinguished on the basis of their mass spectra?





9.38 The homologous series of primary amines, $CH_3(CH_2)_nNH_2$, from CH_3NH_2 to $CH_3(CH_2)_{13}NH_2$ all have their base (largest) peak at m/z 30. What ion does this peak represent, and how is it formed?

INTEGRATED STRUCTURE ELUCIDATION

9.39 Propose a structure that is consistent with each set of **^{1}H NMR** data. **IR** data is provided for some compounds.

(a) $C_4H_{10}O$

δ (ppm)	Splitting	Integration
1.28	s	9H
1.35	s	1H

(b) C_3H_7Br

δ (ppm)	Splitting	Integration
1.71	d	6H
4.32	Septet	1H

(c) C_4H_8O

δ (ppm)	Splitting	Integration	IR
1.05	t	3H	1720 cm^{-1} (strong)
2.13	s	3H	
2.47	q	2H	

(d) C_7H_8O

δ (ppm)	Splitting	Integration	IR
2.43	s	1H	3200–3550 cm^{-1} (broad)
4.58	s	2H	
7.28	m	5H	

(e) C_4H_9Cl

δ (ppm)	Splitting	Integration
1.04	d	6H
1.95	m	1H
3.35	d	2H

(f) $C_{15}H_{14}O$

δ (ppm)	Splitting	Integration	IR
2.20	s	3H	1720 cm^{-1} (strong)
5.08	s	1H	
7.25	m	10H	

(g)	$C_4H_7BrO_2$	**δ (ppm)**	**Splitting**	**Integration**	**IR**
		1.08	t	3H	2500–3500 cm^{-1} (broad)
		2.07	m	2H	1715 cm^{-1} (strong)
		4.23	t	1H	
		10.97	s	1H	
(h)	C_8H_{10}	**δ (ppm)**	**Splitting**	**Integration**	
		1.25	t	3H	
		2.68	q	2H	
		7.23	m	5H	
(i)	$C_4H_8O_3$	**δ (ppm)**	**Splitting**	**Integration**	**IR**
		1.27	t	3H	2500–3550 cm^{-1} (broad)
		3.66	q	2H	1715 cm^{-1} (strong)
		4.13	s	2H	
		10.95	s	1H	
(j)	$C_3H_7NO_2$	**δ (ppm)**	**Splitting**	**Integration**	
		1.55	d	6H	
		4.67	Septet	1H	
(k)	$C_4H_{10}O_2$	**δ (ppm)**	**Splitting**	**Integration**	
		3.25	s	6H	
		3.45	s	4H	
(l)	$C_5H_{10}O$	**δ (ppm)**	**Splitting**	**Integration**	**IR**
		1.10	d	6H	1720 cm^{-1} (strong)
		2.10	s	3H	
		2.50	Septet	1H	
(m)	C_8H_9Br	**δ (ppm)**	**Splitting**	**Integration**	
		2.0	d	3H	
		5.15	q	1H	
		7.35	m	5H	

9.40 Propose structures for compounds **E** and **F**. Compound **E** (C_8H_6) reacts with 2 molar equivalents of bromine to form **F** ($C_8H_6Br_4$). **E** has the IR spectrum shown in Fig. 9.50. What are the structures of **E** and **F**?

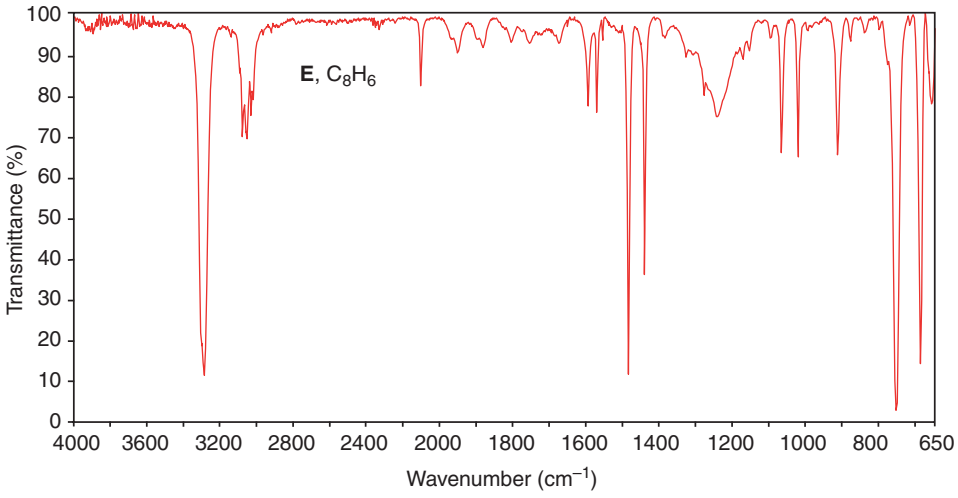


Figure 9.50 The IR spectrum of compound **E**, Problem 9.40. (Spectrum courtesy of Sadtler Research Laboratories, Inc., Philadelphia. © BioRad Laboratories, Inc., Information Division, Sadtler Software & Databases. All rights reserved. Permission for the publication herein of Sadtler Spectra has been granted by BioRad Laboratories, Inc., Informatics Division.)

9.41 Regarding compound **J**, $C_2H_xCl_y$, use the ^1H NMR and IR data below to propose a stereochemical formula that is consistent with the data.

^1H NMR	δ (ppm)	Splitting	Integration
	6.3	s	—

IR
3125 cm^{-1}
1625 cm^{-1}
1280 cm^{-1}
820 cm^{-1}
695 cm^{-1}

9.42 When dissolved in $CDCl_3$, a compound (**K**) with the molecular formula $C_4H_8O_2$ gives a ^1H NMR spectrum that consists of a doublet at δ 1.35, a singlet at δ 2.15, a broad singlet at δ 3.75 (1H), and a quartet at δ 4.25 (1H). When dissolved in D_2O, the compound gives a similar ^1H NMR spectrum, with the exception that the signal at δ 3.75 has disappeared. The IR spectrum of the compound shows a strong absorption peak near 1720 cm^{-1}.

(a) Propose a structure for compound **K**.

(b) Explain why the NMR signal at δ 3.75 disappears when D_2O is used as the solvent.

9.43 Compound **T** (C_5H_8O) has a strong IR absorption band at 1745 cm^{-1}. The broad-band proton decoupled ^{13}C spectrum of **T** shows three signals: at δ 220 (C), 23 (CH_2), and 38 (CH_2). Propose a structure for **T**.

9.44 Deduce the structure of the compound that gives the following ^1H, ^{13}C, and IR spectra (Figs. 9.51–9.53). Assign all aspects of the ^1H, and ^{13}C spectra to the structure you propose. Use letters to correlate protons with signals in the ^1H NMR spectrum, and numbers to correlate carbons with signals in the ^{13}C spectrum. The mass spectrum of this compound shows the molecular ion at *m/z* 96.

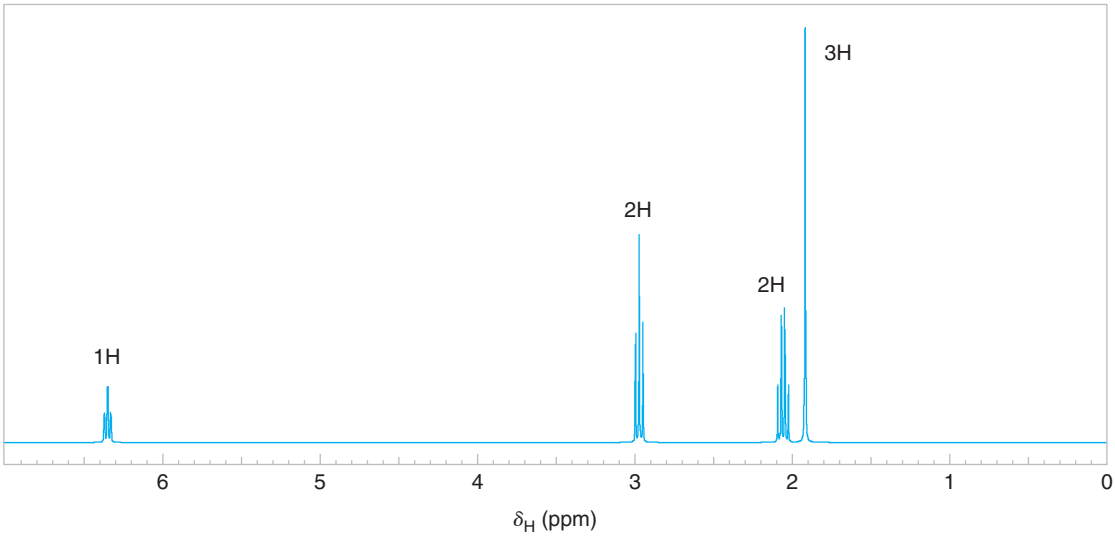


Figure 9.51 The ^1H NMR spectrum (simulated) for Problem 9.44.

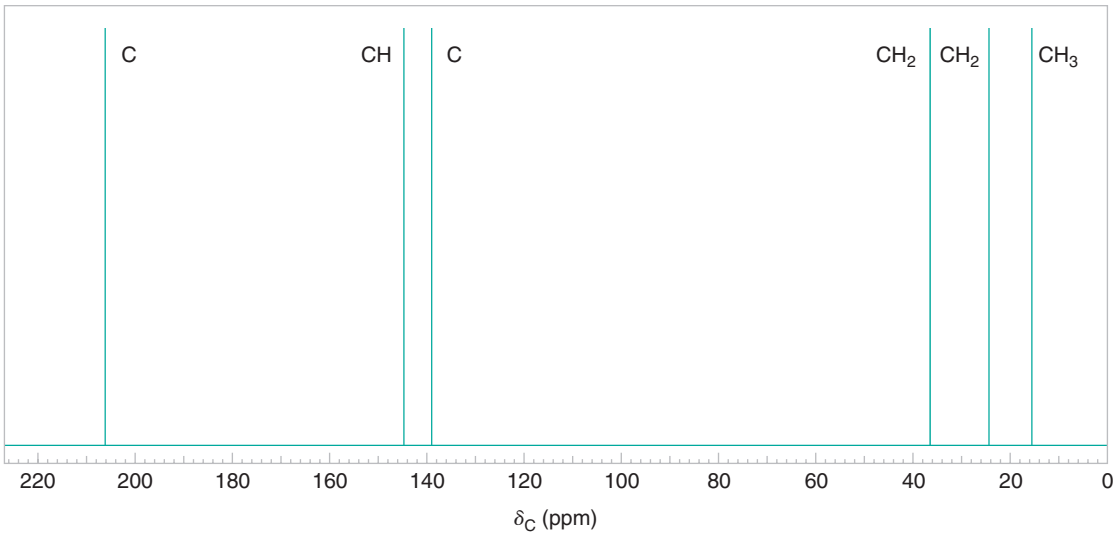


Figure 9.52 A simulated broadband proton-decoupled ^{13}C NMR spectrum for Problem 9.44. Information from the DEPT ^{13}C spectra is given above each peak.

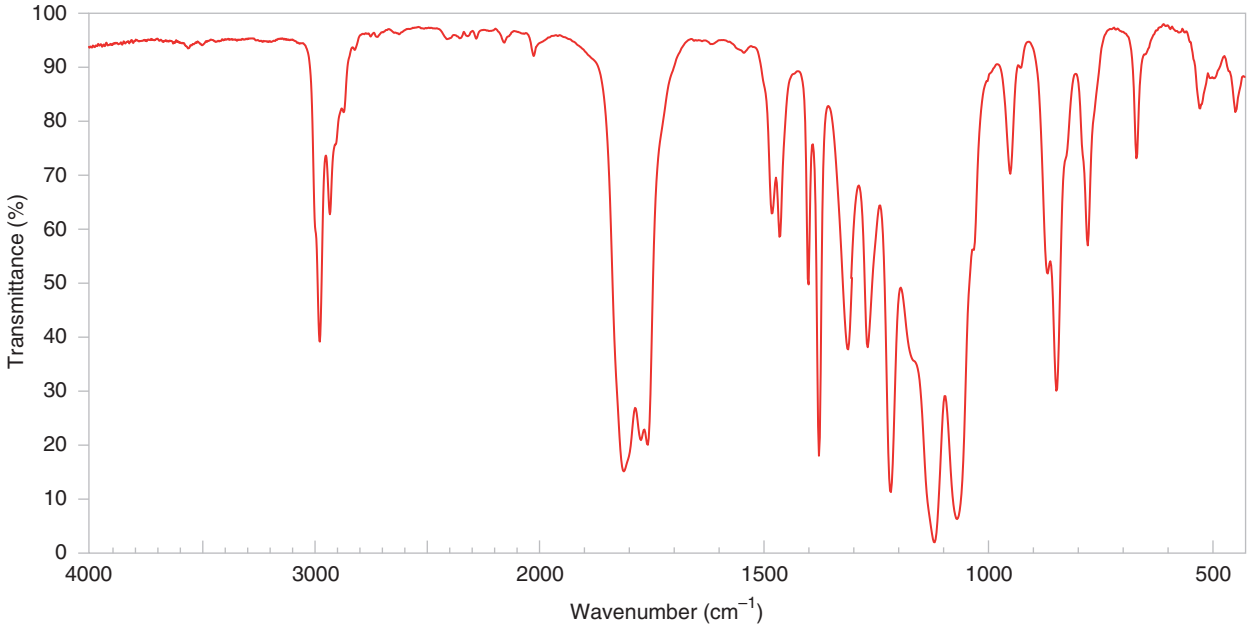


Figure 9.53 The IR spectrum for Problem 9.44. Spectra adapted from Sigma-Aldrich Co.

9.45 Deduce the structure of the compound that gives the following ^{1}H, ^{13}C, and IR spectra (Figs. 9.54–9.56). Assign all aspects of the ^{1}H and ^{13}C spectra to the structure you propose. Use letters to correlate protons with the signals in the ^{1}H NMR spectrum, and numbers to correlate carbons with the signals in the ^{13}C spectrum. The mass spectrum of this compound shows the molecular ion at *m*/*z* 148.

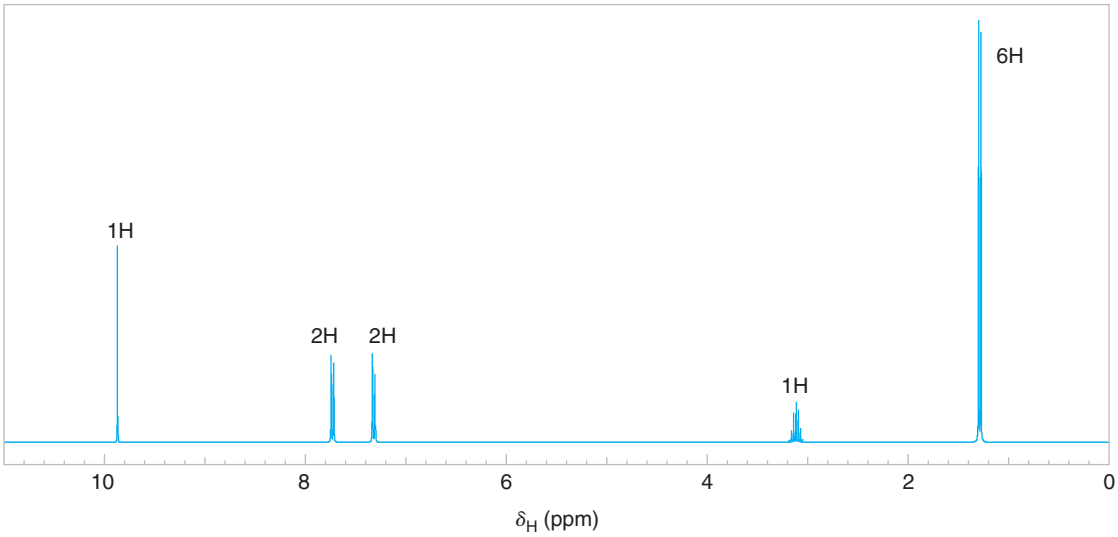


Figure 9.54 The 300-MHz ^{1}H NMR spectrum (simulated) for Problem 9.45.

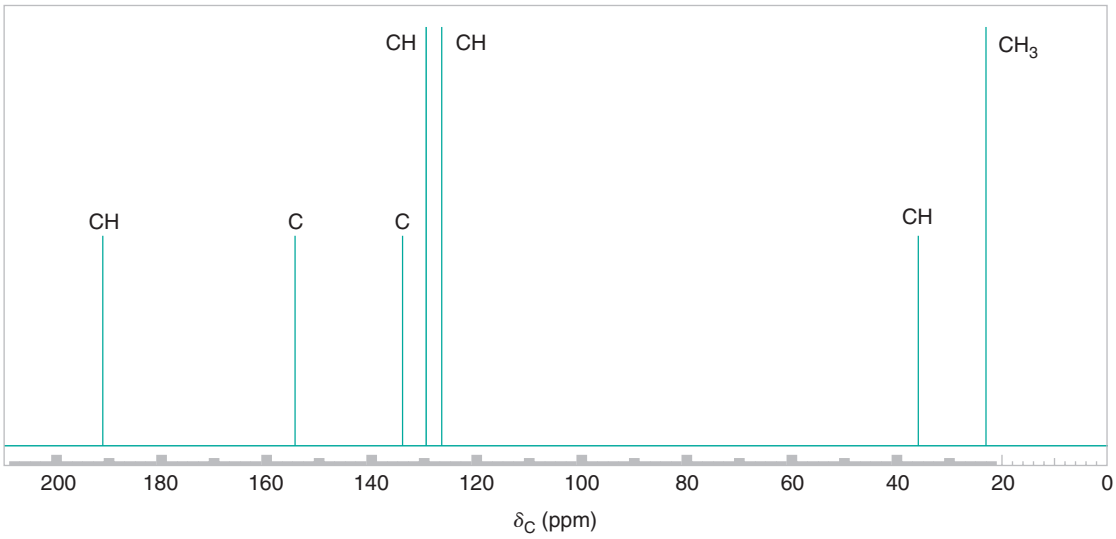


Figure 9.55 A simulated broadband proton-decoupled ^{13}C NMR spectrum for Problem 9.45. Information from the DEPT ^{13}C spectra is given above each peak.

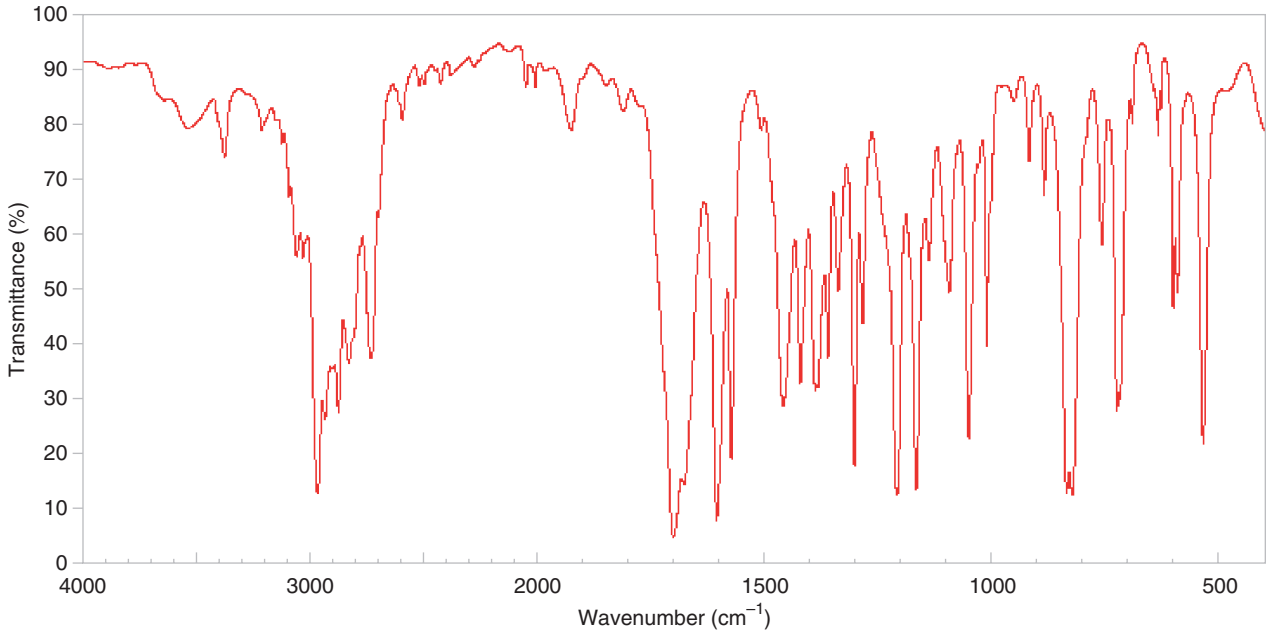


Figure 9.56 The IR spectrum for Problem 9.45. SDBSWeb : *http://riodb01.ibase.aist.go.jp/sdbs/* (National Institute of Advanced Industrial Science and Technology, September 24, 2009).

9.46 Deduce the structure of the compound that gives the following ^{1}H, ^{13}C, and IR spectra (Figs. 9.57–9.59). Assign all aspects of the ^{1}H and ^{13}C spectra to the structure you propose. Use letters to correlate protons with signals in the ^{1}H NMR spectrum, and numbers to correlate carbons with signals in the ^{13}C spectrum. The mass spectrum of this compound shows the molecular ion at *m/z* 204.

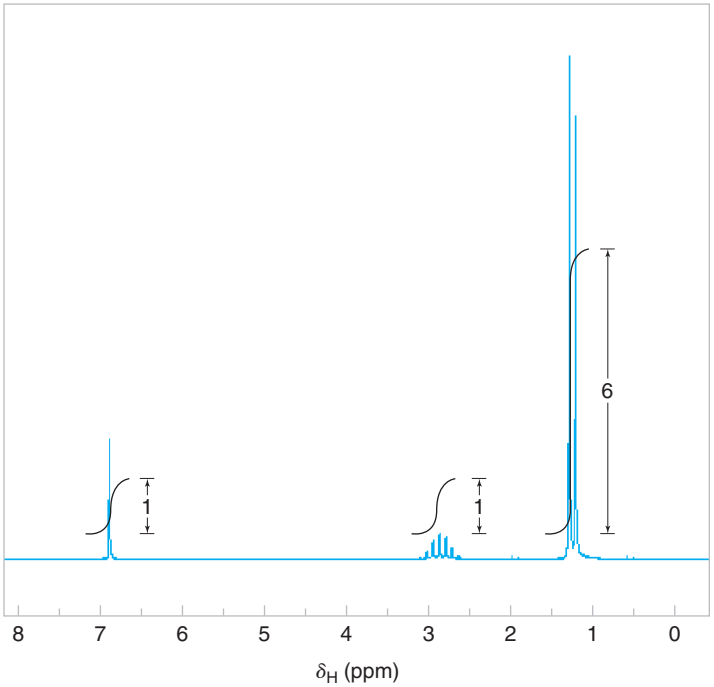


Figure 9.57 The 300-MHz ^{1}H NMR spectrum (simulated) for Problem 9.46.

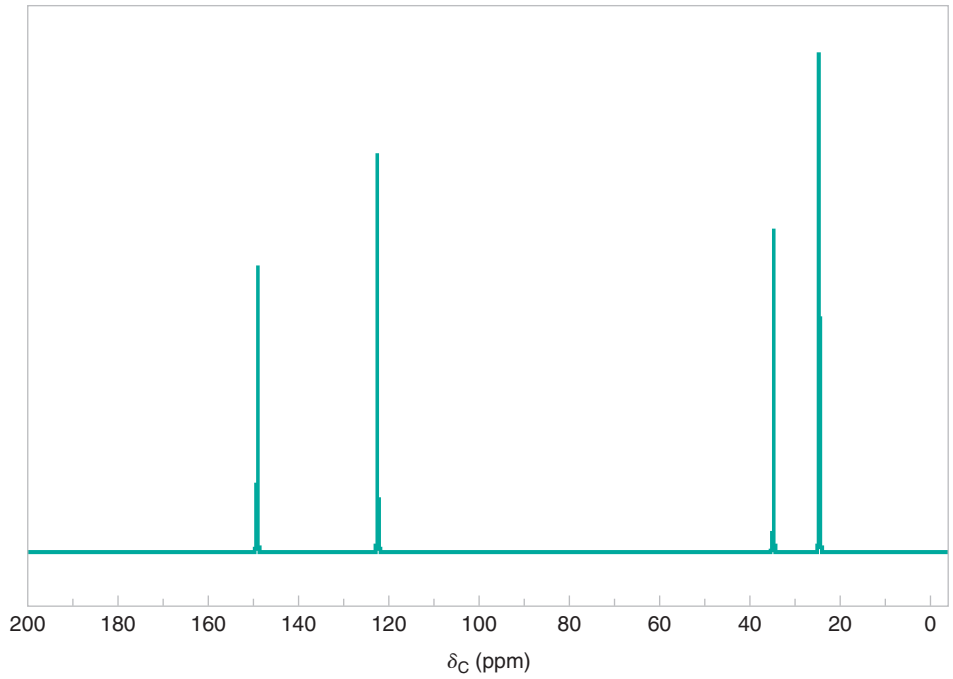


Figure 9.58 A simulated broadband proton-decoupled ^{13}C NMR spectrum for Problem 9.46.

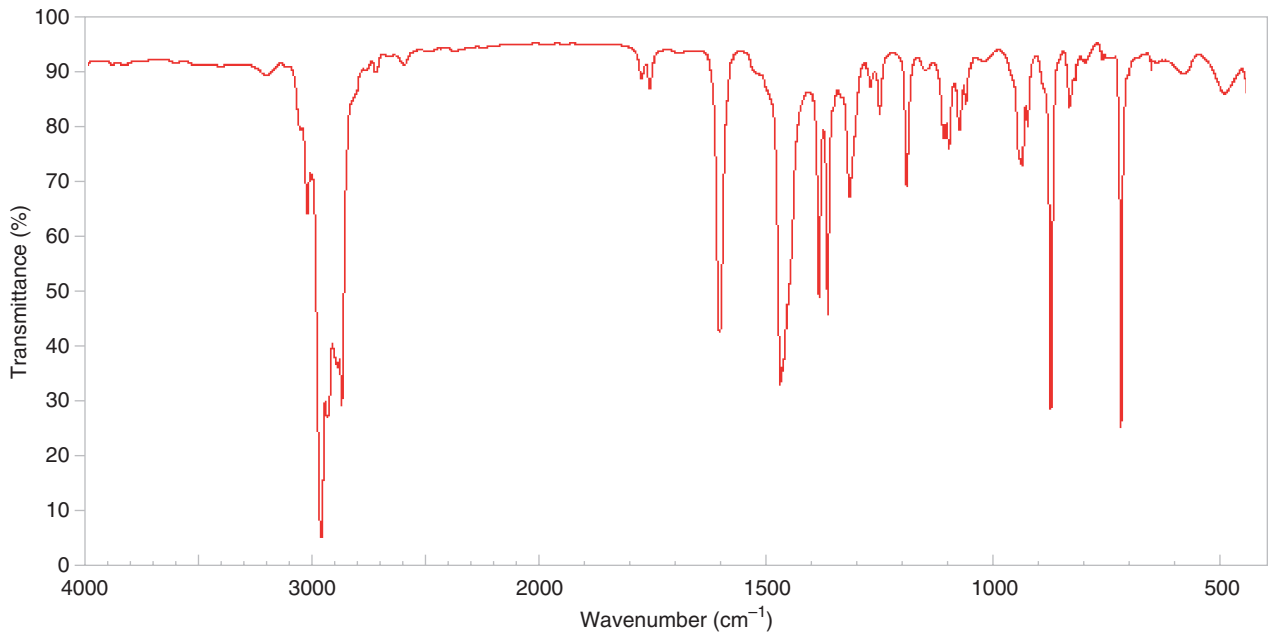


Figure 9.59 The IR spectrum for Problem 9.46. SDBSWeb: *http://riodb01.ibase.aist.go.jp/sdbs/* (National Institute of Advanced Industrial Science and Technology, September 24, 2009).

9.47 Deduce the structure of the compound ($C_5H_{10}O_3$) that gives the following ^1H, ^{13}C, and IR spectra (Figs. 9.60–9.62), Assign all aspects of the ^1H and ^{13}C spectra to the structure you propose. Use letters to correlate protons with signals in the ^1H NMR spectrum, and numbers to correlate carbons with signals in the ^{13}C spectrum.

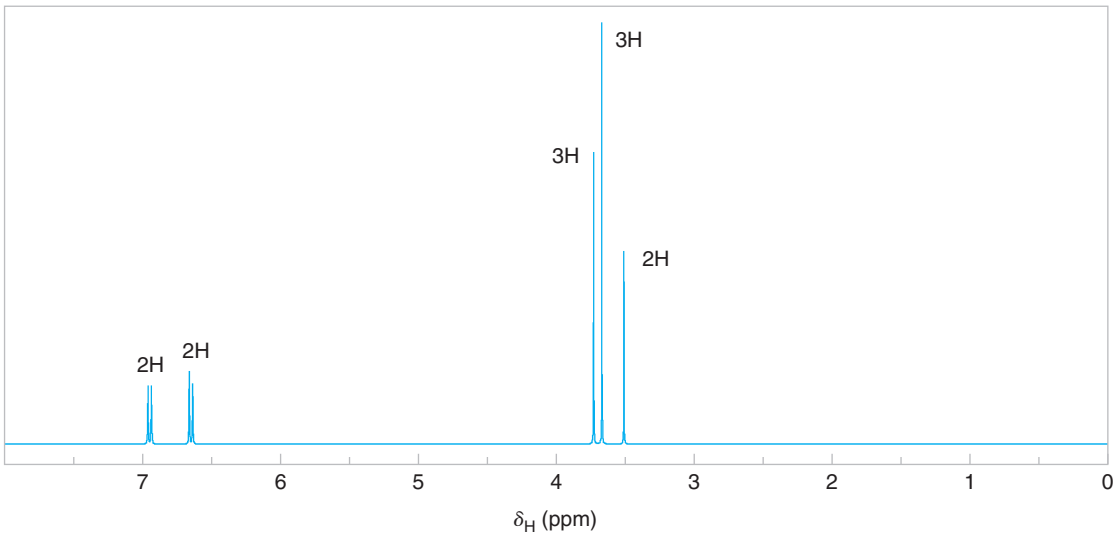


Figure 9.60 The 300-MHz ^1H NMR spectrum (simulated) for Problem 9.47.

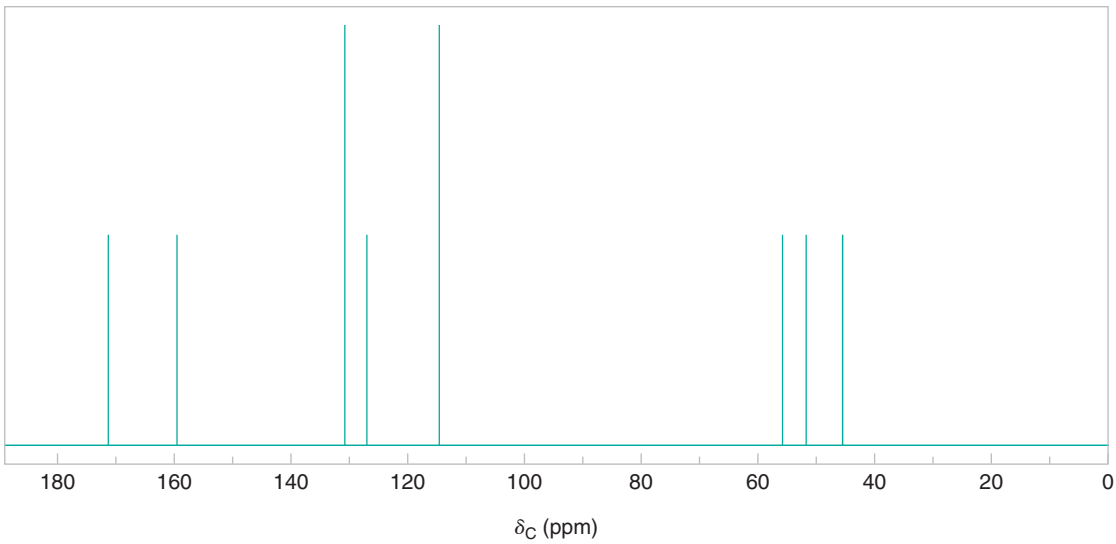


Figure 9.61 A simulated broadband proton-decoupled ^{13}C NMR spectrum for Problem 9.47.

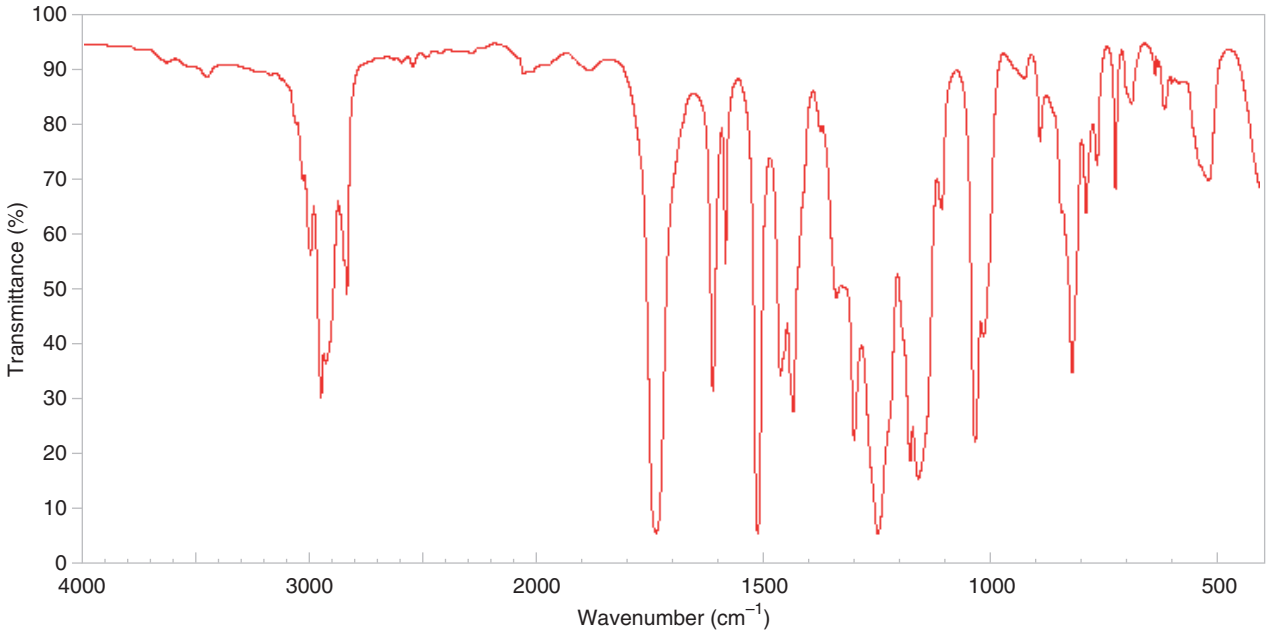


Figure 9.62 The IR spectrum for Problem 9.47. SDBSWeb: *http://riodb01.ibase.aist.go.jp/sdbs/* (National Institute of Advanced Industrial Science and Technology, September 24, 2009).

Challenge Problems

9.48 The ^{1}H NMR examination of a solution of 1,3-dimethylcyclopentadiene in concentrated sulfuric acid shows three peaks with relative areas of 6:4:1. What is the explanation for the appearance of the spectrum?

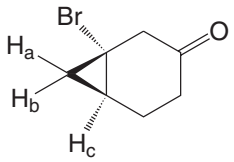
9.49 Acetic acid has a mass spectrum showing a molecular ion peak at *m/z* 60. Other unbranched monocarboxylic acids with four or more carbon atoms also have a peak, frequently prominent, at *m/z* 60. Show how this can occur.

9.50 The ^{1}H NMR peak for the hydroxyl proton of alcohols can be found anywhere from δ 0.5 to δ 5.4. Explain this variability.

9.51 The ^{1}H NMR study of DMF (*N,N*-dimethylformamide) results in different spectra according to the temperature of the sample. At room temperature, two signals are observed for the protons of the two methyl groups. On the other hand, at elevated temperatures (>130°C) a singlet is observed that integrates for six hydrogens. Explain these differences.

9.52 The mass spectra of many benzene derivatives show a peak at *m/z* 51. What could account for this fragment?

9.53 Consider the following information.



$J_{ab} = 5.3$ Hz
$J_{ac} = 8.2$ Hz
$J_{bc} = 10.7$ Hz

(a) How many total ^{1}H NMR signals would you expect for the above molecule?

(b) H_a appears as a doublet of doublets (dd) at 1.32 ppm in the ^{1}H NMR spectrum. Draw a labeled splitting tree diagram for H_a using the coupling constant values given above.

Learning Group Problems

1. Given the following information, elucidate the structures of compounds **A** and **B**. Both compounds are soluble in dilute aqueous HCl, and both have the same molecular formula. The mass spectrum of **A** has $M^{+\cdot}$ 149 (intensity 37.1% of base peak) and $M^{+\cdot} + 1$ 150 (intensity 4.2% of base peak). Other spectroscopic data for **A** and **B** are given below. Justify the structures you propose by assigning specific aspects of the data to the structures. Make sketches of the NMR spectra.

(a) The IR spectrum for compound **A** shows two bands in the 3300–3500-cm^{-1} region. The broadband proton-decoupled ^{13}C NMR spectrum displayed the following signals (information from the DEPT ^{13}C spectra is given in parentheses with the ^{13}C chemical shifts):

^{13}C NMR: δ 140 (C), 127 (C), 125 (CH), 118 (CH), 24 (CH_2), 13 (CH_3)

(b) The IR spectrum for compound **B** shows no bands in the 3300–3500-cm^{-1} region. The broadband proton-decoupled ^{13}C NMR spectrum displayed the following signals (information from the DEPT ^{13}C spectra is given in parentheses with the ^{13}C chemical shifts):

^{13}C NMR: δ 147 (C), 129 (CH), 115 (CH), 111 (CH), 44 (CH_2), 13 (CH_3)

2. Two compounds with the molecular formula $C_5H_{10}O$ have the following ^1H and ^{13}C NMR data. Both compounds have a strong IR absorption band in the 1710–1740-cm^{-1} region. Elucidate the structure of these two compounds and interpret the spectra. Make a sketch of each NMR spectrum.

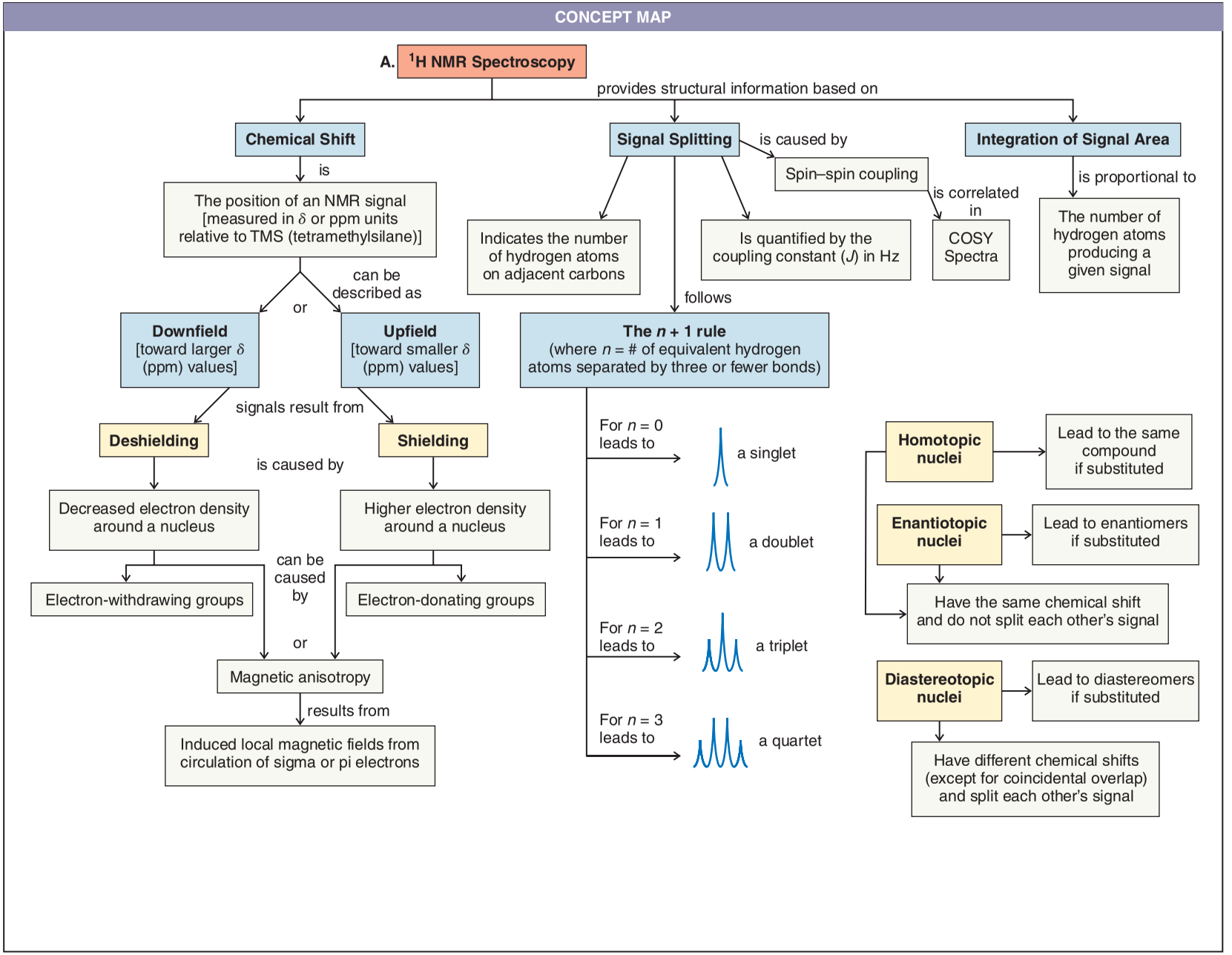
(a) ^1H NMR: δ 2.55 (septet, 1H), 2.10 (singlet, 3H), 1.05 (doublet, 6H)

^{13}C NMR: δ 212.6, 41.5, 27.2, 17.8

(b) ^1H NMR: δ 2.38 (triplet, 2H), 2.10 (singlet, 3H), 1.57 (sextet, 2H), 0.88 (triplet, 3H)

^{13}C NMR: δ 209.0, 45.5, 29.5, 17.0, 13.2

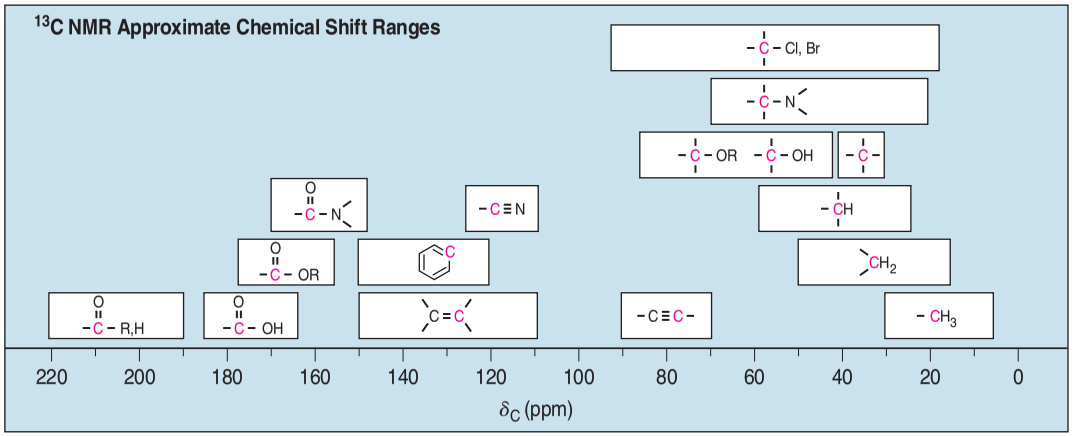
CONCEPT MAP

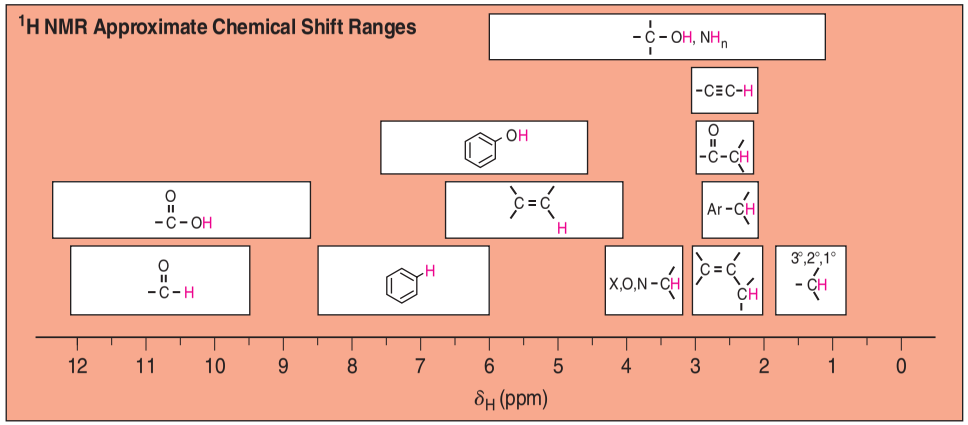


CONCEPT MAP

B. ^{13}C NMR Spectroscopy

- **Broadband Decoupled Spectra** → exhibit → One signal for each magnetically distinct carbon atom
- **DEPT Spectra** → indicate the → Number of hydrogen atoms bonded to a given carbon and its carbon chemical shift
- **HETCOR Spectra** → indicate → Correlation of ^{1}H NMR signals with ^{13}C NMR signals (i.e., which hydrogen atoms are bonded to which carbon atoms)
- Absence of signal splitting and peak integration information in routine ^{13}C NMR spectra





10

Radical Reactions

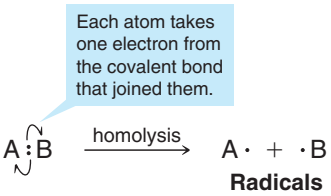
Unpaired electrons lead to many burning questions about radical types of reactivity. In fact, species with unpaired electrons are called radicals, and they are involved in the chemistry of burning, aging, disease, as well as in reactions related to destruction of the ozone layer and the synthesis of products that enhance our everyday lives. For example, polyethylene, which can have a molecular weight from the thousands to the millions, and practical uses ranging from plastic films and wraps to water bottles, bulletproof vests, and hip and knee replacements, is made by a reaction involving radicals. Oxygen that we breathe and nitric oxide that serves as a chemical signaling agent for some fundamental biological processes are both molecules with unpaired electrons. Highly colored natural compounds like those found in blueberries and carrots react with radicals and may protect us from undesirable biological radical reactions. Large portions of the economy hinge on radicals, as well, from reactions used to make polymers like polyethylene, to the target action of pharmaceuticals like Cialis, Levitra, and Viagra, which act on a nitric oxide biological signaling pathway.

Reactions with radicals also play a role in organic synthesis. In this chapter we study the properties and reactivity of species with unpaired electrons, and we shall find that they are radically important to chemistry and life.

10.1 Introduction: How Radicals Form and How They React

So far almost all of the reactions whose mechanisms we have studied have been **ionic reactions.** Ionic reactions are those in which covalent bonds break **heterolytically** and in which ions are involved as reactants, intermediates, or products.

Another broad category of reactions has mechanisms that involve **homolysis** of covalent bonds with the production of intermediates possessing unpaired electrons called **radicals** (or **free radicals**):



Helpful Hint

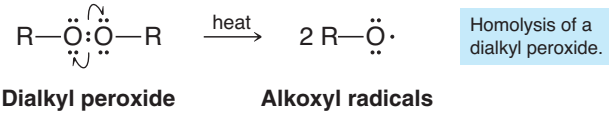
A single-barbed curved arrow shows movement of one electron.

This simple example illustrates the way we use **single-barbed** curved arrows to show the movement of **a single electron** (not of an electron pair as we have done earlier). In this instance, each group, A and B, comes away with one of the electrons of the covalent bond that joined them.

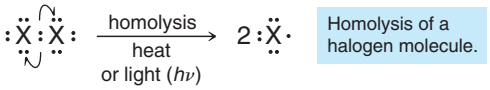
10.1A Production of Radicals

- Energy in the form of heat or light must be supplied to cause homolysis of covalent bonds (Section 10.2).

For example, compounds with an oxygen–oxygen single bond, called **peroxides**, undergo homolysis readily when heated, because the oxygen–oxygen bond is weak. The products are two radicals, called alkoxyl radicals:



Halogen molecules (X_2) also contain a relatively weak bond. As we shall soon see, halogens undergo homolysis readily when heated or when irradiated with light of a wavelength that can be absorbed by the halogen molecule:



The products of this homolysis are halogen atoms, and because halogen atoms contain an unpaired electron, they are radicals.

10.1B Reactions of Radicals

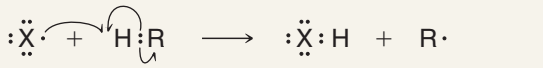
- Almost all small radicals are short-lived, highly reactive species.

When radicals collide with other molecules, they tend to react in a way that leads to pairing of their unpaired electron. One way they can do this is by abstracting an atom from another molecule. For example, a halogen atom may abstract a hydrogen atom from an alkane. This **hydrogen abstraction** gives the halogen atom an electron (from the hydrogen atom) to pair with its unpaired electron. Notice, however, that the other product of this abstraction *is another radical intermediate*, in this case, an alkyl radical, R·, which goes on to react further, as we shall see in this chapter.

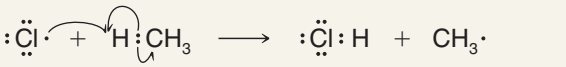
A MECHANISM FOR THE REACTION

Hydrogen Atom Abstraction

General Reaction



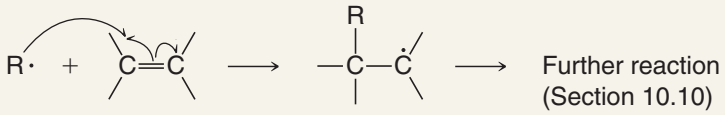
Specific Example



This behavior is characteristic of **radical reactions**. Consider another example, one that shows another way in which radicals can react: They can combine with a compound containing a multiple bond to produce a new radical, which goes on to react further. (We shall study reactions of this type in Section 10.10.)

A MECHANISM FOR THE REACTION

Radical Addition to a π Bond



10.2 *Homolytic Bond Dissociation Energies (DH°)*

When atoms combine to form molecules, energy is released as covalent bonds form. The molecules of the products have lower enthalpy than the separate atoms. When hydrogen atoms combine to form hydrogen molecules, for example, the reaction is *exothermic*; it evolves 436 kJ of heat for every mole of hydrogen that is produced. Similarly, when chlorine atoms combine to form chlorine molecules, the reaction evolves 243 kJ mol^{-1} of chlorine produced:

$$H\cdot + H\cdot \longrightarrow H{-}H \qquad \Delta H^\circ = -436 \text{ kJ mol}^{-1}$$
$$Cl\cdot + Cl\cdot \longrightarrow Cl{-}Cl \qquad \Delta H^\circ = -243 \text{ kJ mol}^{-1}$$

Bond formation is an exothermic process.

Reactions in which only bond breaking occurs are always endothermic. The energy required to break the covalent bonds of hydrogen or chlorine homolytically is exactly equal

to that evolved when the separate atoms combine to form molecules. In the bond cleavage reaction, however, $\Delta H°$ is positive:

$$H{-}H \longrightarrow H\cdot + H\cdot \qquad \Delta H° = +436 \text{ kJ mol}^{-1}$$
$$Cl{-}Cl \longrightarrow Cl\cdot + Cl\cdot \qquad \Delta H° = +243 \text{ kJ mol}^{-1}$$

Bond breaking is an endothermic process.

- Energy must be supplied to break covalent bonds.
- The energies required to break covalent bonds homolytically are called **homolytic bond dissociation energies**, and they are usually abbreviated by the symbol ***DH°***.

The homolytic bond dissociation energies of hydrogen and chlorine, for example, can be written in the following way:

H—H	Cl—Cl
(***DH°*** = **436 kJ mol^{-1}**)	(***DH°*** = **243 kJ mol^{-1}**)

The homolytic bond dissociation energies of a variety of covalent bonds have been determined experimentally or calculated from related data. Some of these *DH°* values are listed in Table 10.1.

TABLE 10.1 Single-Bond Homolytic Dissociation Energies (*DH°*) at 25°C[a]

$$A{:}B \longrightarrow A\cdot + B\cdot$$

Bond Broken (shown in red)	kJ mol^{-1}	Bond Broken (shown in red)	kJ mol^{-1}	Bond Broken (shown in red)	kJ mol^{-1}
H—H	436	CH_3CH_2—OCH_3	352	$CH_2{=}CHCH_2$—H	369
D—D	443	$CH_3CH_2CH_2$—H	423	$CH_2{=}CH$—H	465
F—F	159	$CH_3CH_2CH_2$—F	444	C_6H_5—H	474
Cl—Cl	243	$CH_3CH_2CH_2$—Cl	354	HC≡C—H	547
Br—Br	193	$CH_3CH_2CH_2$—Br	294	CH_3—CH_3	378
I—I	151	$CH_3CH_2CH_2$—I	239	CH_3CH_2—CH_3	371
H—F	570	$CH_3CH_2CH_2$—OH	395	$CH_3CH_2CH_2$—CH_3	374
H—Cl	432	$CH_3CH_2CH_2$—OCH_3	355	CH_3CH_2—CH_2CH_3	343
H—Br	366	$(CH_3)_2CH$—H	413	$(CH_3)_2CH$—CH_3	371
H—I	298	$(CH_3)_2CH$—F	439	$(CH_3)_3C$—CH_3	363
CH_3—H	440	$(CH_3)_2CH$—Cl	355	HO—H	499
CH_3—F	461	$(CH_3)_2CH$—Br	298	HOO—H	356
CH_3—Cl	352	$(CH_3)_2CH$—I	222	HO—OH	214
CH_3—Br	293	$(CH_3)_2CH$—OH	402	$(CH_3)_3CO$—$OC(CH_3)_3$	157
CH_3—I	240	$(CH_3)_2CH$—OCH_3	359	C_6H_5CO—OCC_6H_5	139
CH_3—OH	387	$(CH_3)_2CHCH_2$—H	422	CH_3CH_2O—OCH_3	184
CH_3—OCH_3	348	$(CH_3)_3C$—H	400	CH_3CH_2O—H	431
CH_3CH_2—H	421	$(CH_3)_3C$—Cl	349	CH_3C—H	364
CH_3CH_2—F	444	$(CH_3)_3C$—Br	292		
CH_3CH_2—Cl	353	$(CH_3)_3C$—I	227		
CH_3CH_2—Br	295	$(CH_3)_3C$—OH	400		
CH_3CH_2—I	233	$(CH_3)_3C$—OCH_3	348		
CH_3CH_2—OH	393	$C_6H_5CH_2$—H	375		

[a]Data compiled from the *National Institute of Standards (NIST) Standard Reference Database Number 69*, July 2001 Release, accessed via *NIST Chemistry WebBook* (http://webbook.nist.gov/chemistry/). Copyright 2000. *From CRC Handbook of Chemistry and Physics, Updated 3rd Electronic Edition*; Lide, David R., ed. Reproduced by permission of Routledge/Taylor & Francis Group, LLC. *DH°* values were obtained directly or calculated from heat of formation (H_f) data using the equation $DH°[A{-}B] = H_f[A\cdot] + H_f[B\cdot] - H_f[A{-}B]$.

10.2A How to Use Homolytic Bond Dissociation Energies to Calculate Heats of Reaction

Bond dissociation energies have, as we shall see, a variety of uses. They can be used, for example, to calculate the enthalpy change ($\Delta H°$) for a reaction. To make such a calcula-

tion (see following reaction), we must remember that **for bond breaking $\Delta H°$ is positive and for bond formation $\Delta H°$ is negative**.

$$\Delta H° = -(\text{net } DH°_{\text{products}}) + (\text{net } DH°_{\text{reactants}})$$

Negative sign because energy is released in bond formation

or $$\Delta H° = -\Sigma\, DH°_{\text{products}} + \Sigma\, DH°_{\text{reactants}}$$ (Σ is the mathematical symbol for summation)

Let us consider, for example, the reaction of hydrogen and chlorine to produce 2 mol of hydrogen chloride. From Table 10.1 we get the following values of $DH°$:

H—H	+	Cl—Cl	⟶	2 H—Cl
($DH°$ = 436 kJ mol^{-1})		**($DH°$ = 243 kJ mol^{-1})**		**($DH°$ = 432 kJ mol^{-1}) × 2**
+679 kJ is required to **cleave** 1 mol of H_2 bonds and 1 mol of Cl_2 bonds.				−864 kJ is evolved in **formation** of the bonds in 2 mol of HCl.

Overall, the reaction of 1 mol of H_2 and 1 mol of Cl_2 to form 2 mol of HCl is exothermic:

Two moles of product formed

$$\Delta H° = -2\,(432 \text{ kJ mol}^{-1}) + (436 \text{ kJ mol}^{-1} + 243 \text{ kJ mol}^{-1})$$

Bond forming (exothermic; negative sign) — **Bond breaking (endothermic; positive sign)**

$$= -864 \text{ kJ mol}^{-1} + 679 \text{ kJ mol}^{-1}$$
$$= -185 \text{ kJ mol}^{-1}$$

Overall $\Delta H°$ for 2 mol HCl produced from H_2 + Cl_2

For the purpose of our calculation, we have assumed a particular pathway, which amounts to

$$\text{H—H} \longrightarrow 2\ \text{H}\cdot$$
and $$\text{Cl—Cl} \longrightarrow 2\ \text{Cl}\cdot$$
then $$2\ \text{H}\cdot + 2\ \text{Cl}\cdot \longrightarrow 2\ \text{H—Cl}$$

This is not the way the reaction actually occurs. Nevertheless, the heat of reaction, $\Delta H°$, is a thermodynamic quantity that is dependent *only* on the initial and final states of the reacting molecules. Here, $\Delta H°$ is independent of the path followed (Hess's law), and, for this reason, our calculation is valid.

Review Problem 10.1

Calculate the heat of reaction, $\Delta H°$, for the following reactions:

(a) $H_2 + F_2 \longrightarrow 2\ HF$

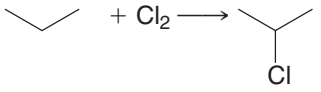
(b) $CH_4 + F_2 \longrightarrow CH_3F + HF$

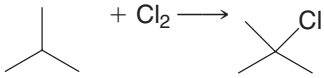
(c) $CH_4 + Cl_2 \longrightarrow CH_3Cl + HCl$

(d) $CH_4 + Br_2 \longrightarrow CH_3Br + HBr$

(e) $CH_4 + I_2 \longrightarrow CH_3I + HI$

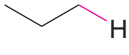
(f) $CH_3CH_3 + Cl_2 \longrightarrow CH_3CH_2Cl + HCl$

(g)  + HCl

(h)  + HCl

10.2B How to Use Homolytic Bond Dissociation Energies to Determine the Relative Stabilities of Radicals

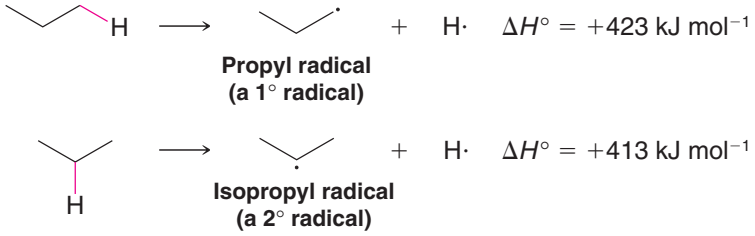
Homolytic bond dissociation energies also provide us with a convenient way to estimate the relative stabilities of radicals. If we examine the data given in Table 10.1, we find the following values of $DH°$ for the primary and secondary C—H bonds of propane:



($DH°$ = 423 kJ mol^{-1})

($DH°$ = 413 kJ mol^{-1})

This means that for the reaction in which the designated C—H bonds are broken homolytically, the values of $\Delta H°$ are those given here.



These reactions resemble each other in two respects: They both begin with the same alkane (propane), and they both produce an alkyl radical and a hydrogen atom. They differ, however, in the amount of energy required and in the type of carbon radical produced. These two differences are related to each other.

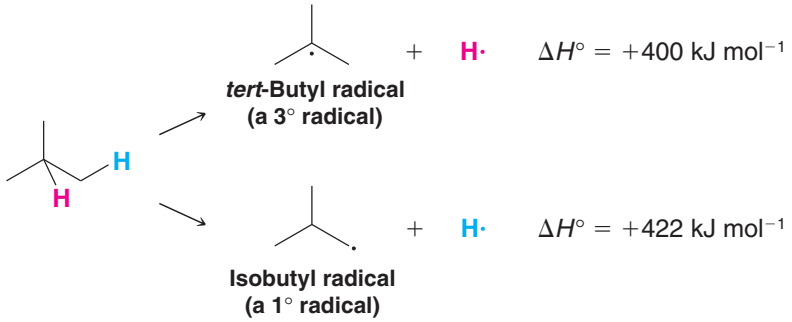
- Alkyl radicals are classified as being 1°, 2°, or 3° based on the carbon atom that has the unpaired electron, the same way that we classify carbocations based on the carbon atom with the positive charge.

More energy must be supplied to produce a primary alkyl radical (the propyl radical) from propane than is required to produce a secondary carbon radical (the isopropyl radical) from the same compound. This must mean that the primary radical has absorbed more energy and thus has greater *potential energy*. Because the relative stability of a chemical species is inversely related to its potential energy, the secondary radical must be the *more stable* radical (Fig. 10.1*a*). In fact, the secondary isopropyl radical is more stable than the primary propyl radical by 10 kJ mol^{-1}.

We can use the data in Table 10.1 to make a similar comparison of the *tert*-butyl radical (a 3° radical) and the isobutyl radical (a 1° radical) relative to isobutane:

Helpful Hint

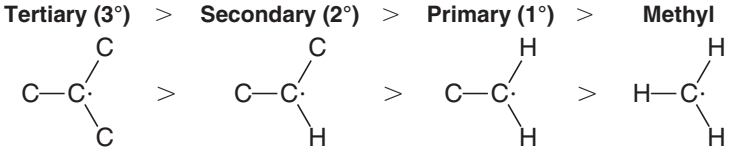
Knowing the relative stability of radicals is important for predicting reactions.



Here we find (Fig. 10.1*b*) that the difference in stability of the two radicals is even larger. The tertiary radical is more stable than the primary radical by 22 kJ mol^{-1}.

The kind of pattern that we find in these examples is found with alkyl radicals generally.

- Overall, the relative stabilities of radicals are 3° > 2° > 1° > methyl.



- The order of stability of alkyl radicals is the same as for carbocations (Section 6.11B).

Although alkyl radicals are uncharged, the carbon that bears the odd electron is *electron deficient*. Therefore, alkyl groups attached to this carbon provide a stabilizing effect through hyperconjugation, and the more alkyl groups bonded to it, the more stable the radical is. Thus, the reasons for the relative stabilities of radicals and carbocations are similar.

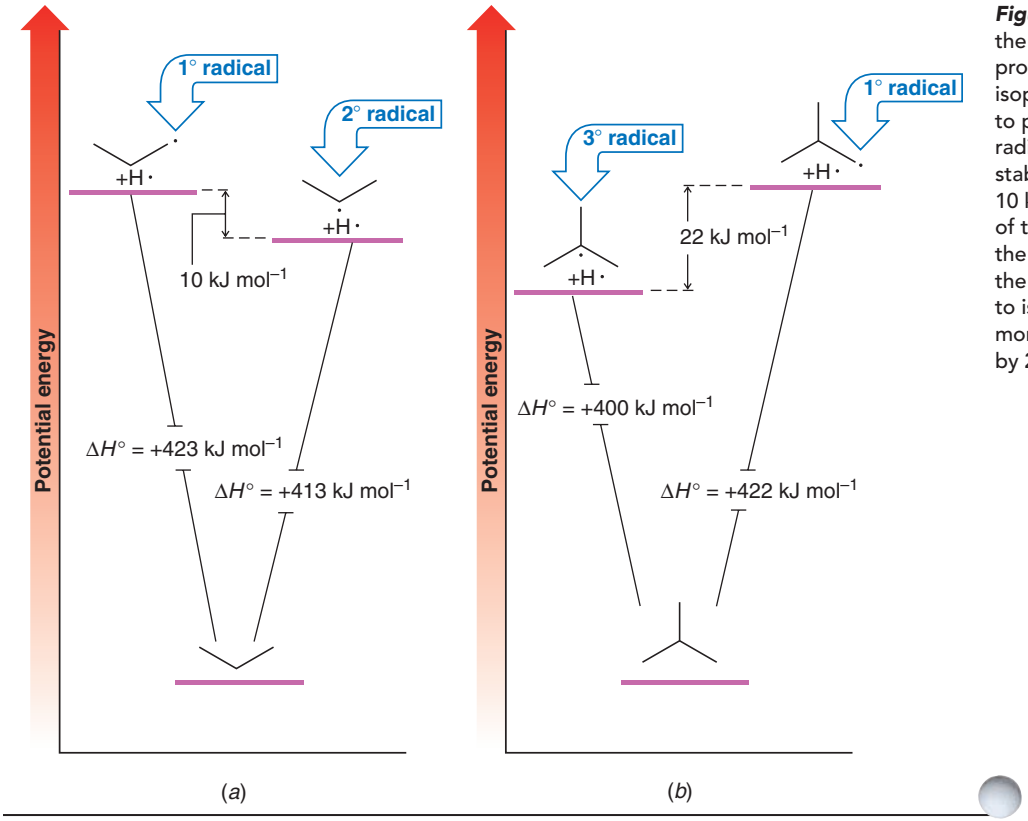
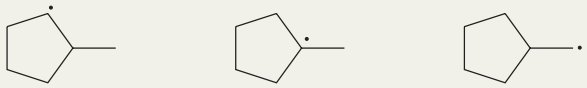


Figure 10.1 *(a)* Comparison of the potential energies of the propyl radical (+H·) and the isopropyl radical (+H·) relative to propane. The isopropyl radical (a 2° radical) is more stable than the 1° radical by 10 kJ mol^{-1}. *(b)* Comparison of the potential energies of the *tert*-butyl radical (+H·) and the isobutyl radical (+H·) relative to isobutane. The 3° radical is more stable than the 1° radical by 22 kJ mol^{-1}.

Solved Problem 10.1

Classify each of the following radicals as being 1°, 2°, or 3°, and rank them in order of decreasing stability.

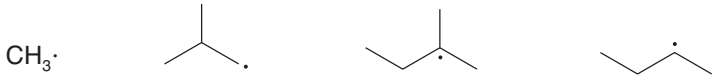


A **B** **C**

STRATEGY AND ANSWER We examine the carbon bearing the unpaired electron in each radical to classify the radical as to its type. **B** is a tertiary radical (the carbon bearing the unpaired electron is tertiary) and is, therefore, most stable. **C** is a primary radical and is least stable. **A**, being a secondary radical, falls in between. The order of stability is **B** > **A** > **C**.

Review Problem 10.2

List the following radicals in order of decreasing stability:



10.3 Reactions of Alkanes with Halogens

- Alkanes react with molecular halogens to produce alkyl halides by a substitution reaction called **radical halogenation**.

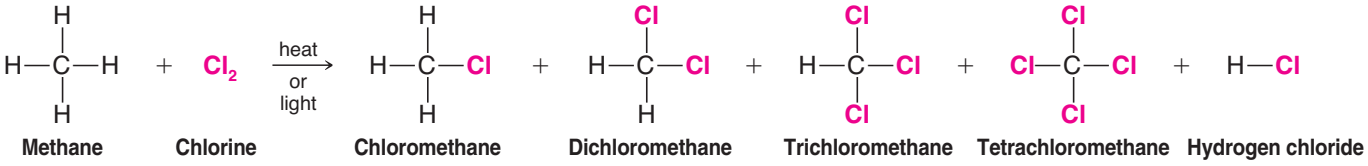
A general reaction showing formation of a monohaloalkane by radical halogenation is shown below. It is called radical halogenation because, as we shall see, the mechanism involves species with unpaired electrons called radicals. This reaction is not a nucleophilic substitution reaction.

$$R{-}H + X_2 \longrightarrow R{-}X + HX$$

In these reactions a halogen atom replaces one or more of the hydrogen atoms of the alkane and the corresponding hydrogen halide is formed as a by-product. Only fluorine, chlorine, and bromine react this way with alkanes. Iodine is essentially unreactive, for a reason that we shall explain later.

10.3A Multiple Halogen Substitution

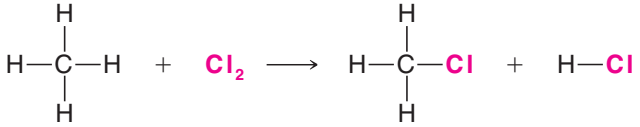
One complicating factor of alkane halogenations is that multiple substitutions almost always occur. The following example illustrates this phenomenon. If we mix an equimolar ratio of methane and chlorine (both substances are gases at room temperature) and then either heat the mixture or irradiate it with light of the appropriate wavelength, a reaction begins to occur vigorously and ultimately produces the following mixture of products.



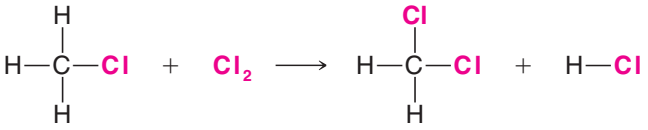
Methane **Chlorine** **Chloromethane** **Dichloromethane** **Trichloromethane** **Tetrachloromethane** **Hydrogen chloride**

(The sum of the number of moles of each chlorinated methane produced equals the number of moles of methane that reacted.)

To understand the formation of this mixture, we need to consider how the concentration of reactants and products changes as the reaction proceeds. At the outset, the only compounds that are present in the mixture are chlorine and methane, and the only reaction that can take place is one that produces chloromethane and hydrogen chloride:



As the reaction progresses, however, the concentration of chloromethane in the mixture increases, and a second substitution reaction begins to occur. Chloromethane reacts with chlorine to produce dichloromethane:



The dichloromethane produced can then react to form trichloromethane, and trichloromethane, as it accumulates in the mixture, can react with chlorine to produce tetrachloromethane. Each time a substitution of —Cl for —H takes place, a molecule of H—Cl is produced.

Solved Problem 10.2

If the goal of a synthesis is to prepare chloromethane (CH_3Cl), its formation can be maximized and the formation of CH_2Cl_2, $CHCl_3$, and CCl_4 minimized by using a large excess of methane in the reaction mixture. Explain why this is possible.

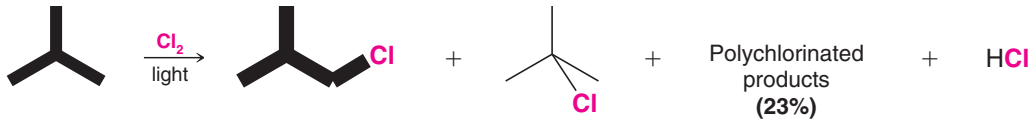
ANSWER The use of a large excess of methane maximizes the probability that chlorine will attack methane molecules because the concentration of methane in the mixture will always be relatively large. It also minimizes the probability that chlorine will attack molecules of CH_3Cl, CH_2Cl_2, and $CHCl_3$, because their concentrations will always be relatively small. After the reaction is over, the unreacted excess methane can be recovered and recycled.

10.3B Lack of Chlorine Selectivity

Chlorination of most higher alkanes gives a mixture of isomeric monochloro products as well as more highly halogenated compounds.

- Chlorine is relatively ***unselective;*** it does not discriminate greatly among the different types of hydrogen atoms (primary, secondary, and tertiary) in an alkane.

An example is the light-promoted chlorination of isobutane:



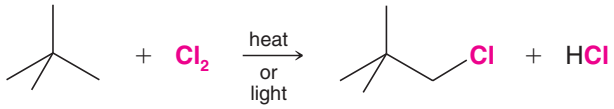
Isobutane — **Isobutyl chloride (48%)** — ***tert*-Butyl chloride (29%)**

- Because alkane chlorinations usually yield a complex mixture of products, they are not useful as synthetic methods when the goal is preparation of a specific alkyl chloride.

Helpful Hint
Chlorination is unselective.

- An exception is the halogenation of an alkane (or cycloalkane) whose hydrogen atoms *are all equivalent*. [Equivalent hydrogen atoms are defined as those which on replacement by some other group (e.g., chlorine) yield the same compound.]

Neopentane, for example, can form only one monohalogenation product, and the use of a large excess of neopentane minimizes polychlorination:



Neopentane (excess) — **Neopentyl chloride**

- Bromine is generally less reactive toward alkanes than chlorine, and bromine is ***more selective*** in the site of attack when it does react.

We shall examine the selectivity of bromination further in Section 10.6A.

10.4 Chlorination of Methane: Mechanism of Reaction

The reaction of methane with chlorine (in the gas phase) provides a good example for studying the mechanism of radical halogenation.

$$CH_4 + Cl_2 \longrightarrow CH_3Cl + HCl \quad (+ CH_2Cl_2,\ CHCl_3,\ \text{and}\ CCl_4)$$

Several experimental observations help in understanding the mechanism of this reaction:

1. **The reaction is promoted by heat or light**. At room temperature methane and chlorine do not react at a perceptible rate as long as the mixture is kept away from light. Methane and chlorine do react, however, at room temperature if the gaseous reaction mixture is irradiated with UV light at a wavelength absorbed by Cl_2, and they react in the dark if the gaseous mixture is heated to temperatures greater than 100°C.
2. **The light-promoted reaction is highly efficient**. A relatively small number of light photons permits the formation of relatively large amounts of chlorinated product.

A mechanism that is consistent with these observations has several steps, shown below. The first step involves the dissociation of a chlorine molecule, by heat or light, into two chlorine atoms. The second step involves hydrogen abstraction by a chlorine atom.

A MECHANISM FOR THE REACTION

Radical Chlorination of Methane

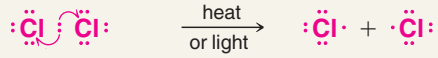
REACTION

$$CH_4 + Cl_2 \xrightarrow[\text{or light}]{\text{heat}} CH_3Cl + HCl$$

MECHANISM

Chain Initiation

Step 1: ***Halogen dissociation***

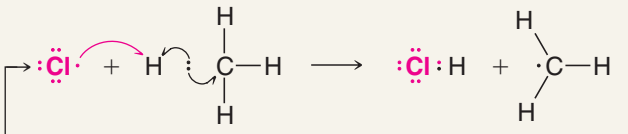


Under the influence of heat or light a molecule of chlorine dissociates; each atom takes one of the bonding electrons.

This step produces two highly reactive chlorine atoms.

Chain Propagation

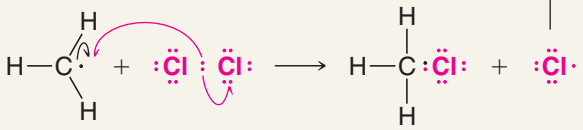
Step 2: ***Hydrogen abstraction***



A chlorine atom abstracts a hydrogen atom from a methane molecule.

This step produces a molecule of hydrogen chloride and a methyl radical.

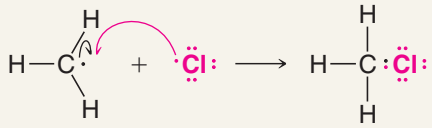
Step 3: ***Halogen abstraction***



A methyl radical abstracts a chlorine atom from a chlorine molecule.

This step produces a molecule of methyl chloride and a chlorine atom. The chlorine atom can now cause a repetition of step 2.

Chain Termination



Coupling of any two radicals depletes the supply of reactive intermediates and terminates the chain. Several pairings are possible for radical coupling termination steps (see text).

Helpful Hint

Remember: These conventions are used in illustrating reaction mechanisms in this text.

1. Curved arrows ↷ or ↷ always show the direction of movement of electrons.
2. Single-barbed arrows ↷ show the attack (or movement) of an unpaired electron.
3. Double-barbed arrows ↷ show the attack (or movement) of an electron pair.

In step 3 the highly reactive methyl radical reacts with a chlorine molecule by abstracting a chlorine atom. This results in the formation of a molecule of chloromethane (one of the ultimate products of the reaction) and a *chlorine atom*. The latter product is particularly significant, for the chlorine atom formed in step 3 can attack another methane molecule and cause

a repetition of step 2. Then, step 3 is repeated, and so forth, for hundreds or thousands of times. (With each repetition of step 3 a molecule of chloromethane is produced.) This type of sequential, stepwise mechanism, in which each step generates the reactive intermediate that causes the next cycle of the reaction to occur, is called a **chain reaction**.

Step 1 is called the **chain-initiating step**. In the chain-initiating step ***radicals are created.*** Steps 2 and 3 are called **chain-propagating steps**. In chain-propagating steps ***one radical generates another***.

Chain Initiation: *creation of radicals*

Step 1 $Cl_2 \xrightarrow[\text{or light}]{\text{heat}} 2\ Cl\cdot$

Chain Propagation: *reaction and regeneration of radicals*

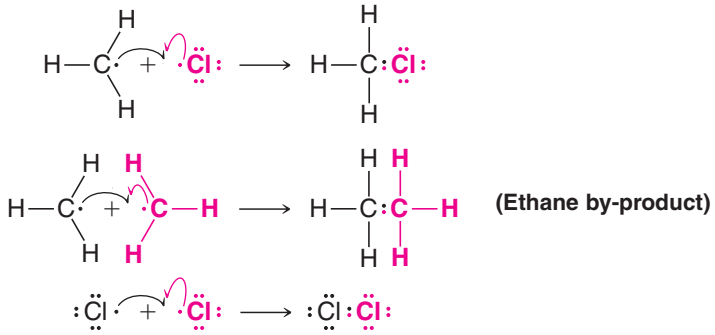
Step 2 $CH_4 + Cl\cdot \longrightarrow CH_3\cdot + H{-}Cl$

Step 3 $CH_3\cdot + Cl_2 \longrightarrow CH_3Cl + Cl\cdot$

The chain nature of the reaction accounts for the observation that the light-promoted reaction is highly efficient. The presence of a relatively few atoms of chlorine at any given moment is all that is needed to cause the formation of many thousands of molecules of chloromethane.

What causes the chain reaction to terminate? Why does one photon of light not promote the chlorination of all of the methane molecules present? We know that this does not happen because we find that, at low temperatures, continuous irradiation is required or the reaction slows and stops. The answer to these questions is the existence of ***chain-terminating steps***: steps that happen infrequently but occur often enough to *use up one or both of the reactive intermediates*. The continuous replacement of intermediates used up by chain-terminating steps requires continuous irradiation. Plausible chain-terminating steps are as follows.

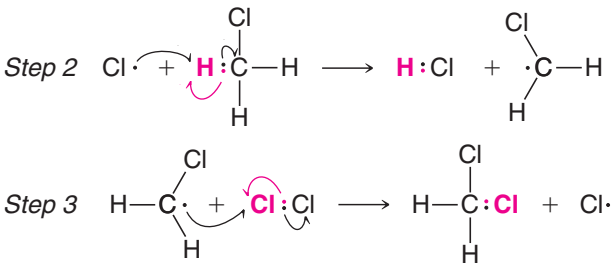
Chain Termination: *consumption of radicals (e.g., by coupling)*



(Ethane by-product)

Our radical mechanism also explains how the reaction of methane with chlorine produces the more highly halogenated products, CH_2Cl_2, $CHCl_3$, and CCl_4 (as well as additional HCl). As the reaction progresses, chloromethane (CH_3Cl) accumulates in the mixture and its hydrogen atoms, too, are susceptible to abstraction by chlorine. Thus chloromethyl radicals are produced that lead to dichloromethane (CH_2Cl_2).

Side Reactions: *multihalogenated by-product formation*



(Dichloromethane)

Then step 2 is repeated, then step 3 is repeated, and so on. Each repetition of step 2 yields a molecule of HCl, and each repetition of step 3 yields a molecule of CH_2Cl_2.

Solved Problem 10.3

When methane is chlorinated, among the products found are traces of chloroethane. How is it formed? Of what significance is its formation?

STRATEGY AND ANSWER A small amount of ethane is formed by the combination of two methyl radicals:

$$2\ CH_3\cdot \longrightarrow CH_3 : CH_3$$

The ethane byproduct formed by coupling then reacts with chlorine in a radical halogenation reaction (see Section 10.6) to form chloroethane.

The significance of this observation is that it is evidence for the proposal that the combination of two methyl radicals is one of the chain-terminating steps in the chlorination of methane.

Review Problem 10.3 Suggest a method for separating and isolating the CH_3Cl, CH_2Cl_2, $CHCl_3$, and CCl_4 that may be formed as a mixture when methane is chlorinated. (You may want to consult a handbook.) What analytical method could be used to separate this mixture and give structural information about each component?

Review Problem 10.4 How would the molecular ion peaks in the respective mass spectra of CH_3Cl, CH_2Cl_2, $CHCl_3$, and CCl_4 differ on the basis of the number of chlorines (remember that chlorine has isotopes ^{35}Cl and ^{37}Cl found in a 3 : 1 ratio)?

Review Problem 10.5 If the goal is to synthesize CCl_4 in maximum yield, this can be accomplished by using a large excess of chlorine. Explain.

10.5 Chlorination of Methane: Energy Changes

We saw in Section 10.2A that we can calculate the overall heat of reaction from bond dissociation energies. We can also calculate the heat of reaction for each individual step of a mechanism:

Chain Initiation

Step 1 $Cl{-}Cl \longrightarrow 2\ Cl\cdot$ $\quad \Delta H° = +243\ kJ\ mol^{-1}$

(***DH°* = 243**)

Chain Propagation

Step 2 $CH_3{-}H + Cl\cdot \longrightarrow CH_3\cdot + H{-}Cl$ $\quad \Delta H° = +8\ kJ\ mol^{-1}$

(***DH°* = 440**) (***DH°* = 432**)

Step 3 $CH_3\cdot + Cl{-}Cl \longrightarrow CH_3{-}Cl + Cl\cdot$ $\quad \Delta H° = -109\ kJ\ mol^{-1}$

(***DH°* = 243**) (***DH°* = 352**)

Chain Termination

$CH_3\cdot + Cl\cdot \longrightarrow CH_3{-}Cl$ $\quad \Delta H° = -352\ kJ\ mol^{-1}$

(***DH°* = 352**)

$CH_3\cdot + \cdot CH_3 \longrightarrow CH_3{-}CH_3$ $\quad \Delta H° = -378\ kJ\ mol^{-1}$

(***DH°* = 378**)

$Cl\cdot + Cl\cdot \longrightarrow Cl{-}Cl$ $\quad \Delta H° = -243\ kJ\ mol^{-1}$

(***DH°* = 243**)

In the chain-initiating step only one bond is broken—the bond between two chlorine atoms—and no bonds are formed. The heat of reaction for this step is simply the bond dissociation energy for a chlorine molecule, and it is highly endothermic.

In the chain-terminating steps bonds are formed, but no bonds are broken. As a result, all of the chain-terminating steps are highly exothermic.

Each of the chain-propagating steps, on the other hand, requires the breaking of one bond and the formation of another. The value of $\Delta H°$ for each of these steps is the difference between the bond dissociation energy of the bond that is broken and the bond dissociation energy for the bond that is formed. The first chain-propagating step is slightly endothermic ($\Delta H° = +8$ kJ mol^{-1}), but the second is exothermic by a large amount ($\Delta H° = -109$ kJ mol^{-1}).

Assuming the same mechanism applies, calculate $\Delta H°$ for the chain-initiating, chain-propagating, and chain-terminating steps involved in the fluorination of methane.

Review Problem 10.6

The addition of the chain-propagating steps, cancelling species that appear on both sides of the arrows, yields the overall equation for the chlorination of methane:

$$\begin{array}{lll} \cancel{Cl\cdot} + CH_3{-}H \longrightarrow \cancel{CH_3\cdot} + H{-}Cl & \Delta H° = +8 \text{ kJ mol}^{-1} \\ \cancel{CH_3\cdot} + Cl{-}Cl \longrightarrow CH_3{-}Cl + \cancel{Cl\cdot} & \Delta H° = -109 \text{ kJ mol}^{-1} \\ \hline CH_3{-}H + Cl{-}Cl \longrightarrow CH_3{-}Cl + H{-}Cl & \Delta H° = -101 \text{ kJ mol}^{-1} \end{array}$$

Helpful Hint

Calculating overall $\Delta H°$ for a chain reaction.

and the addition of the values of $\Delta H°$ for the individual chain-propagating steps yields the overall value of $\Delta H°$ for the reaction.

Show how you can use the chain-propagating steps (see Review Problem 10.6) to calculate the overall value of $\Delta H°$ for the fluorination of methane.

Review Problem 10.7

10.5A The Overall Free-Energy Change

For many reactions the entropy change is so small that the term $T\,\Delta S°$ in the expression

$$\Delta G° = \Delta H° - T\,\Delta S°$$

is almost zero, and $\Delta G°$ is approximately equal to $\Delta H°$. This happens when the reaction is one in which the relative order or disorder of reactants and products is about the same. Recall (Section 3.10) that entropy measures the relative disorder or randomness of a system. For a chemical system the relative disorder of the molecules can be related to the number of *degrees of freedom* available to the molecules and their constituent atoms. Degrees of freedom are associated with ways in which *movement or changes in relative position can occur*. Molecules have three sorts of degrees of freedom: translational degrees of freedom associated with movements of the whole molecule through space, rotational degrees of freedom associated with the tumbling motions of the molecule, and vibrational degrees of freedom associated with the stretching and bending motion of atoms about the bonds that connect them (Fig. 10.2). If the atoms of the products of a reaction have more degrees of freedom available than they did as reactants, the entropy change ($\Delta S°$) for the reaction will be positive. If, on the other hand, the atoms of the products are more constrained (have fewer degrees of freedom) than the reactants, a negative $\Delta S°$ results.

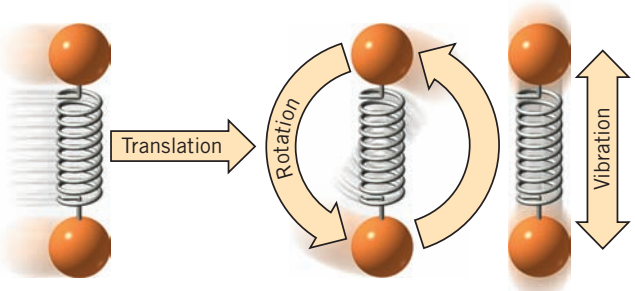


Figure 10.2 Translational, rotational, and vibrational degrees of freedom for a simple diatomic molecule.

Consider the reaction of methane with chlorine:

$$CH_4 + Cl_2 \longrightarrow CH_3Cl + HCl$$

Here, 2 mol of the products are formed from the same number of moles of the reactants. Thus the number of translational degrees of freedom available to products and reactants is the same. Furthermore, CH_3Cl is a tetrahedral molecule like CH_4, and HCl is a diatomic molecule like Cl_2. This means that vibrational and rotational degrees of freedom available to products and reactants should also be approximately the same. The actual entropy change for this reaction is quite small, $\Delta S^\circ = +2.8\ \text{J K}^{-1}\ \text{mol}^{-1}$. Therefore, at room temperature (298 K) the $T\,\Delta S^\circ$ term is 0.8 kJ mol^{-1}, and thus the enthalpy change for the reaction and the free-energy change are almost equal: $\Delta H^\circ = -101\ \text{kJ mol}^{-1}$ and $\Delta G^\circ = -102\ \text{kJ mol}^{-1}$.

In situations like this one it is often convenient to make predictions about whether a reaction will proceed to completion on the basis of ΔH° rather than ΔG° since ΔH° values are readily obtained from bond dissociation energies.

10.5B Activation Energies

For many reactions that we shall study in which entropy changes are small, it is also often convenient to base our estimates of reaction rates simply on **energies of activation, E_{act}**, rather than on free energies of activation, $\Delta G^\ddagger$. Without going into detail, suffice it to say that these two quantities are closely related and that **both measure the difference in energy between the reactants and the transition state**.

- A low energy of activation means a reaction will take place rapidly; a high energy of activation means that a reaction will take place slowly.

Having seen earlier in this section how to calculate ΔH° for each step in the chlorination of methane, let us consider the energy of activation for each step. These values are as follows:

Chain Initiation

Step 1 $Cl_2 \longrightarrow 2\ Cl\cdot$ $\qquad E_{act} = +243\ \text{kJ mol}^{-1}$

Chain Propagation

Step 2 $Cl\cdot + CH_4 \longrightarrow HCl + CH_3\cdot$ $\qquad E_{act} = +16\ \text{kJ mol}^{-1}$

Step 3 $CH_3\cdot + Cl_2 \longrightarrow CH_3Cl + Cl\cdot$ $\qquad E_{act} = \sim 8\ \text{kJ mol}^{-1}$

How does one know what the energy of activation for a reaction will be? Could we, for example, have predicted from bond dissociation energies that the energy of activation for the reaction $Cl\cdot + CH_4 \longrightarrow HCl + CH_3\cdot$ would be precisely 16 kJ mol^{-1}? The answer is *no*. The energy of activation must be determined from other experimental data. It cannot be directly measured—it is calculated. Certain principles have been established, however, that enable one to arrive at estimates of energies of activation:

1. **Any reaction in which *bonds are broken* will have an energy of activation greater than zero. This will be true even if a stronger bond is formed and the reaction is exothermic. The reason: Bond formation and bond breaking do not occur simultaneously in the transition state. Bond formation lags behind, and its energy is not all available for bond breaking.**
2. **Activation energies of *endothermic reactions that involve both bond formation and bond rupture will be greater than the heat of reaction*, ΔH°.** Two examples illustrate this principle, namely, the first chain-propagating step in the chlorination of methane and the corresponding step in the bromination of methane:

$$Cl\cdot + CH_3{-}H \longrightarrow H{-}Cl + CH_3\cdot \qquad \Delta H^\circ = +8\ \text{kJ mol}^{-1}$$
$$(DH^\circ = 440) \qquad (DH^\circ = 432) \qquad E_{act} = +16\ \text{kJ mol}^{-1}$$

$$Br\cdot + CH_3{-}H \longrightarrow H{-}Br + CH_3\cdot \qquad \Delta H^\circ = +74\ \text{kJ mol}^{-1}$$
$$(DH^\circ = 440) \qquad (DH^\circ = 366) \qquad E_{act} = +78\ \text{kJ mol}^{-1}$$

In both of these reactions the energy released in bond formation is less than that required for bond rupture; both reactions are, therefore, endothermic. We can easily see why the energy of activation for each reaction is greater than the heat of reaction by looking at the potential energy diagrams in Fig. 10.3. In each case the path from reactants to products is from a lower energy plateau to a higher one. In each case the intervening energy hill is higher still, and since the energy of activation is the vertical (energy) distance between the plateau of reactants and the top of this hill, the energy of activation exceeds the heat of reaction.

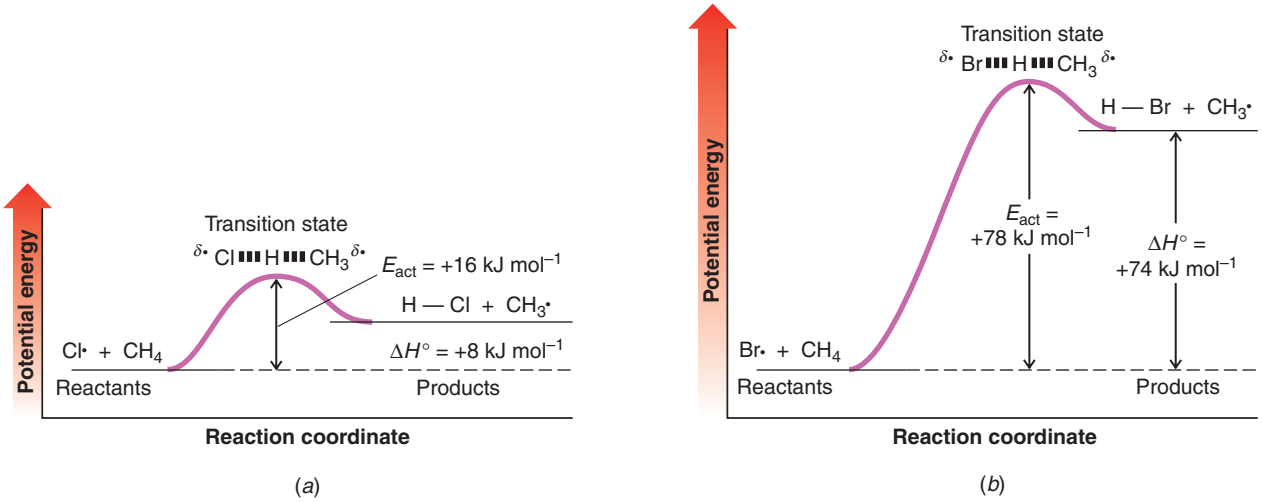


Figure 10.3 Potential energy diagrams for *(a)* the reaction of a chlorine atom with methane and *(b)* the reaction of a bromine atom with methane.

3. **The energy of activation of a gas-phase reaction where bonds are broken homolytically but no bonds are formed is equal to $\Delta H°$.*** An example of this type of reaction is the chain-initiating step in the chlorination of methane—the dissociation of chlorine molecules into chlorine atoms:

$$\underset{(DH° = 243)}{Cl—Cl} \longrightarrow 2Cl\cdot \qquad \Delta H° = +243 \text{ kJ mol}^{-1} \qquad E_{act} = +243 \text{ kJ mol}^{-1}$$

The potential energy diagram for this reaction is shown in Fig. 10.4.

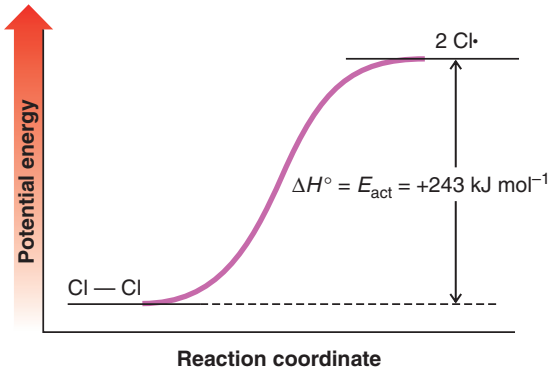


Figure 10.4 Potential energy diagram for the dissociation of a chlorine molecule into chlorine atoms.

4. **The energy of activation for a gas-phase reaction in which small radicals combine to form molecules is usually zero**. In reactions of this type the problem of nonsimultaneous bond formation and bond rupture does not exist; only one process occurs: that of bond formation. All of the chain-terminating steps in the chlorination

*This rule applies only to radical reactions taking place in the gas phase. It does not apply to reactions taking place in solution, especially where ions are involved, because solvation energies are also important.

of methane fall into this category. An example is the combination of two methyl radicals to form a molecule of ethane:

$$2\ CH_3\cdot \longrightarrow \underset{(DH^\circ = 378)}{CH_3{-}CH_3} \qquad \Delta H^\circ = -378\ \text{kJ mol}^{-1},\quad E_{act} = 0$$

Figure 10.5 illustrates the potential energy changes that occur in this reaction.

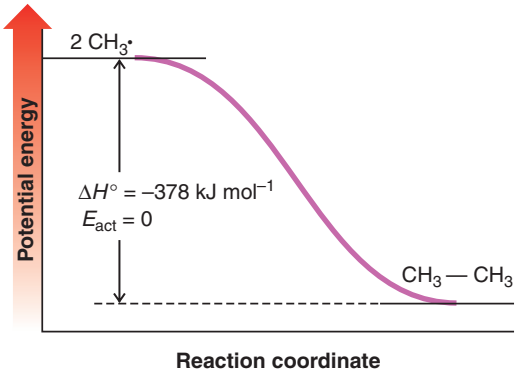


Figure 10.5 Potential energy diagram for the combination of two methyl radicals to form a molecule of ethane.

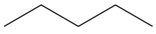
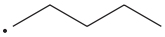
Review Problem 10.8

When pentane is heated to a very high temperature, radical reactions take place that produce (among other products) methane, ethane, propane, and butane. This type of change is called **thermal cracking**. Among the reactions that take place are the following:

(1) 

(2) 

(3) $CH_3\cdot + CH_3\cdot \longrightarrow CH_3CH_3$

(4) $CH_3\cdot +$  $\longrightarrow CH_4 +$ 

(5) $CH_3\cdot + CH_3CH_2\cdot \longrightarrow$ 

(6) $CH_3CH_2\cdot + CH_3CH_2\cdot \longrightarrow$ 

(a) For which of these reactions would you expect E_{act} to equal zero?

(b) To be greater than zero?

(c) To equal ΔH°?

Review Problem 10.9

(a) Consider the chain-propagating steps shown here for the fluorination of methane and the accompanying data. Sketch a potential energy diagram for each step. Label energy differences quantitatively, and sketch the transition state structures.

$$CH_4 + F\cdot \longrightarrow CH_3\cdot + HF \qquad E_{act} = +5.0\ \text{kJ mol}^{-1},\quad \Delta H^\circ = -130\ \text{kJ mol}^{-1}$$

$$CH_3\cdot + F_2 \longrightarrow CH_3{-}F + F\cdot \qquad E_{act} = +1.0\ \text{kJ mol}^{-1},\quad \Delta H^\circ = -302\ \text{kJ mol}^{-1}$$

(b) Consider the chain-initiating and chain-terminating steps shown here for the fluorination of methane. Sketch and label potential energy diagrams for these reactions, in the same way as specified in part (a).

$$F_2 \longrightarrow 2F\cdot \qquad E_{act} = +159\ \text{kJ mol}^{-1}$$

$$CH_3\cdot + F\cdot \longrightarrow CH_3{-}F \qquad \Delta H^\circ = -461\ \text{kJ mol}^{-1}$$

(c) Sketch a potential energy diagram for the following reaction. Note that it is the reverse of a reaction in part (a).

$$CH_3\cdot + H{-}F \longrightarrow CH_4 + F\cdot$$

10.5C Reaction of Methane with Other Halogens

The *reactivity* of one substance toward another is measured by the *rate* at which the two substances react. A reagent that reacts very rapidly with a particular substance is said to be highly reactive toward that substance. One that reacts slowly or not at all under the same experimental conditions (e.g., concentration, pressure, and temperature) is said to have a low relative reactivity or to be unreactive. The reactions of the halogens (fluorine, chlorine, bromine, and iodine) with methane show a wide spread of relative reactivities. Fluorine is most reactive—so reactive, in fact, that without special precautions mixtures of fluorine and methane explode. Chlorine is the next most reactive. However, the chlorination of methane is easily controlled by the judicious control of heat, light, and concentration. Bromine is much less reactive toward methane than chlorine, and iodine is so unreactive that for all practical purposes we can say that no reaction takes place.

If the mechanisms for fluorination, bromination, and iodination of methane are the same as for its chlorination, we can explain the wide variation in reactivity of the halogens by a careful examination of $\Delta H°$ and E_{act} for each step.

FLUORINATION

	$\Delta H°$ (kJ mol^{-1})	E_{act} (kJ mol^{-1})
Chain Initiation		
$F_2 \longrightarrow 2\ F\cdot$	+159	+159
Chain Propagation		
$F\cdot + CH_4 \longrightarrow HF + CH_3\cdot$	−130	+5.0
$CH_3\cdot + F_2 \longrightarrow CH_3F + F\cdot$	−302	Small
Overall $\Delta H°$ =	−432	

The chain-initiating step in **fluorination** is highly endothermic and thus has a high energy of activation.

If we did not know otherwise, we might carelessly conclude from the energy of activation of the chain-initiating step alone that fluorine would be quite unreactive toward methane. (If we then proceeded to try the reaction, as a result of this careless assessment, the results would be literally disastrous.) We know, however, that the chain-initiating step occurs only infrequently relative to the chain-propagating steps. One initiating step is able to produce thousands of fluorination reactions. As a result, the high activation energy for this step is not an impediment to the reaction.

Chain-propagating steps, by contrast, cannot afford to have high energies of activation. If they do, the highly reactive intermediates are consumed by chain-terminating steps before the chains progress very far. Both of the chain-propagating steps in fluorination have very small energies of activation. This allows a relatively large fraction of energetically favorable collisions even at room temperature. Moreover, the overall heat of reaction, $\Delta H°$, is very large. This means that as the reaction occurs, a large quantity of heat is evolved. This heat may accumulate in the mixture faster than it dissipates to the surroundings, causing the temperature to rise and with it a rapid increase in the frequency of additional chain-initiating steps that would generate additional chains. These two factors, the low energy of activation for the chain-propagating steps and the large overall heat of reaction, account for the high reactivity of fluorine toward methane. (Fluorination reactions can be controlled. This is usually accomplished by diluting both the hydrocarbon and the fluorine with an inert gas such as helium before bringing them together. The reaction is also carried out in a reactor packed with copper shot. The copper, by absorbing the heat produced, moderates the reaction.)

CHLORINATION

	$\Delta H°$ (kJ mol^{-1})	E_{act} (kJ mol^{-1})
Chain Initiation		
$Cl_2 \longrightarrow 2\ Cl\cdot$	+243	+243
	$\Delta H°$ (kJ mol^{-1})	E_{act} (kJ mol^{-1})
Chain Propagation		
$Cl\cdot + CH_4 \longrightarrow HCl + CH_3\cdot$	+8	+16
$CH_3\cdot + Cl_2 \longrightarrow CH_3Cl + Cl\cdot$	−109	Small
Overall $\Delta H°$ =	−101	

The higher energy of activation of the first chain-propagating step (the hydrogen abstraction step) in the chlorination of methane (+16 kJ mol^{-1}), compared to the lower energy of activation (+5.0 kJ mol^{-1}) in the fluorination, partly explains the lower reactivity of chlorine. The greater energy required to break the chlorine–chlorine bond in the initiating step (243 kJ mol^{-1} for Cl_2 versus 159 kJ mol^{-1} for F_2) has some effect, too. However, the much greater overall heat of reaction in fluorination probably plays the greatest role in accounting for the much greater reactivity of fluorine.

BROMINATION

	$\Delta H°$ (kJ mol^{-1})	E_{act} (kJ mol^{-1})
Chain Initiation		
$Br_2 \longrightarrow 2\ Br\cdot$	+193	+193
Chain Propagation		
$Br\cdot + CH_4 \longrightarrow HBr + CH_3\cdot$	+74	+78
$CH_3\cdot + Br_2 \longrightarrow CH_3Br + Br\cdot$	−100	Small
Overall $\Delta H°$ =	−26	

In contrast to chlorination, the hydrogen atom abstraction step in **bromination** has a very high energy of activation (E_{act} = 78 kJ mol^{-1}). This means that only a very tiny fraction of all of the collisions between bromine atoms and methane molecules will be energetically effective even at a temperature of 300°C. Bromine, as a result, is much less reactive toward methane than chlorine, even though the net reaction is slightly exothermic.

IODINATION

	$\Delta H°$ (kJ mol^{-1})	E_{act} (kJ mol^{-1})
Chain Initiation		
$I_2 \longrightarrow 2\ I\cdot$	+151	+151
Chain Propagation		
$I\cdot + CH_4 \longrightarrow HI + CH_3\cdot$	+142	+140
$CH_3\cdot + I_2 \longrightarrow CH_3I + I\cdot$	−89	Small
Overall $\Delta H°$ =	+53	

The thermodynamic quantities for **iodination** of methane make it clear that the chain-initiating step is not responsible for the observed order of reactivities: $F_2 > Cl_2 > Br_2 > I_2$. The iodine–iodine bond is even weaker than the fluorine–fluorine bond. On this basis alone, one would predict iodine to be the most reactive of the halogens. This clearly is not the case. Once again, it is the hydrogen atom–abstraction step that correlates with the experimentally determined order of reactivities. The energy of activation of this step in the iodine reaction (140 kJ mol^{-1}) is so large that only two collisions out of every 10^{12} have sufficient energy to produce reactions at 300°C. As a result, iodination is not a feasible reaction experimentally.

Before we leave this topic, one further point needs to be made. We have given explanations of the relative reactivities of the halogens toward methane that have been based on energy considerations alone. This has been possible *only because the reactions are quite similar and thus have similar entropy changes*. Had the reactions been of different types, this kind of analysis would not have been proper and might have given incorrect explanations.

10.6 Halogenation of Higher Alkanes

Higher alkanes react with halogens by the same kind of chain mechanism as those that we have just seen. Ethane, for example, reacts with chlorine to produce chloroethane (ethyl chloride). The mechanism is as follows:

A MECHANISM FOR THE REACTION

Radical Halogenation of Ethane

Chain Initiation

Step 1

$$Cl_2 \xrightarrow[\text{or heat}]{\text{light}} 2\ Cl\cdot$$

Chain Propagation

Step 2

$$CH_3CH_2{:}H + \cdot Cl \longrightarrow CH_3CH_2\cdot + H{:}Cl$$

Step 3

$$CH_3CH_2\cdot + Cl{:}Cl \longrightarrow CH_3CH_2{:}Cl + Cl\cdot$$

Chain propagation continues with steps 2, 3, 2, 3, and so on.

Chain Termination

$$CH_3CH_2\cdot + \cdot Cl \longrightarrow CH_3CH_2{:}Cl$$

$$CH_3CH_2\cdot + \cdot CH_2CH_3 \longrightarrow CH_3CH_2{:}CH_2CH_3$$

$$Cl\cdot + \cdot Cl \longrightarrow Cl{:}Cl$$

Review Problem 10.10

(a) Consider the hydrogen abstraction step in the chlorination of ethane.

$$CH_3{-}CH_3 + Cl\cdot \longrightarrow CH_3{-}CH_2\cdot + HCl \quad E_{act} = 4.2\ kJ\ mol^{-1}$$

Calculate $\Delta H°$ for this step using data from Table 10.1, and draw a fully labeled potential energy diagram, similar to that shown in Fig. 10.3*a*.

(b) When an equimolar mixture of methane and ethane is chlorinated, the reaction yields chloroethane and chloromethane in a ratio of 400 : 1.

$$CH_3{-}CH_3 + CH_4 \xrightarrow[h\nu]{Cl_2} CH_3{-}CH_2Cl + CH_3Cl + 2\ HCl$$

400 : 1

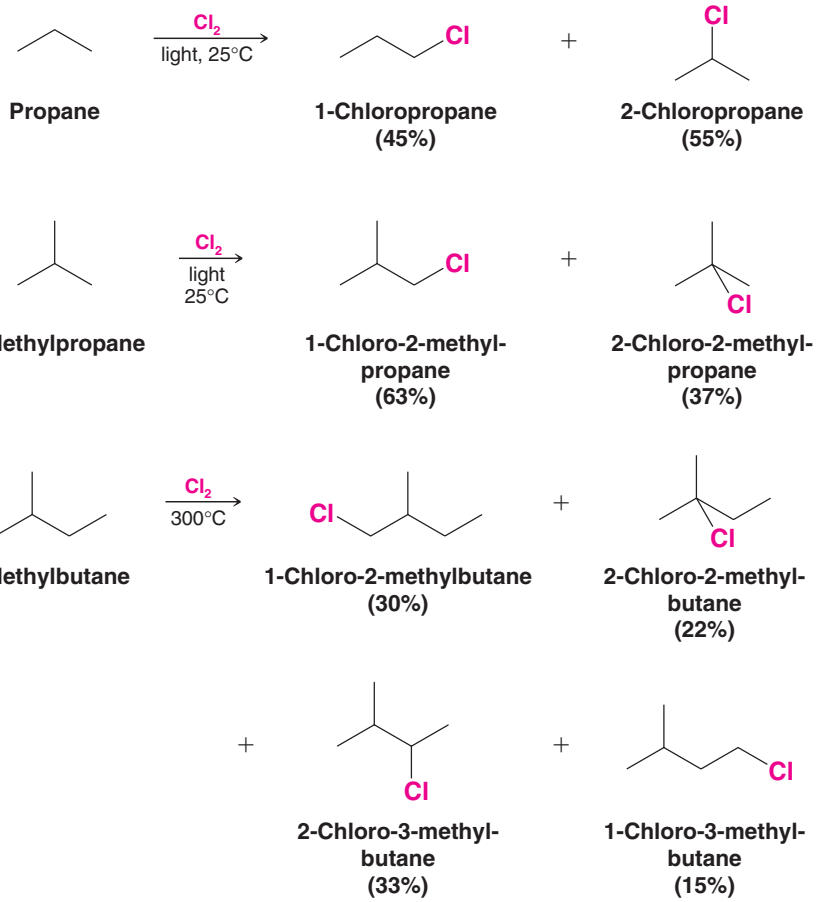
Explain the observed ratio of products.

Review Problem 10.11

When ethane is chlorinated, 1,1-dichloroethane and 1,2-dichloroethane, as well as more highly chlorinated ethanes, are formed in the mixture (see Section 10.3A). Write chain reaction mechanisms accounting for the formation of 1,1-dichloroethane and 1,2-dichloroethane.

Chlorination of most alkanes whose molecules contain more than two carbon atoms gives a mixture of isomeric monochloro products (as well as more highly chlorinated compounds).

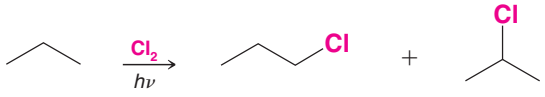
Several examples follow. The percentages given are based on the total amount of monochloro products formed in each reaction.



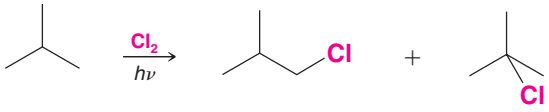
The ratios of products that we obtain from chlorination reactions of higher alkanes are not identical with what we would expect if all the hydrogen atoms of the alkane were equally reactive. We find that there is a correlation between reactivity of different hydrogen atoms and the type of hydrogen atom (1°, 2°, or 3°) being replaced. The tertiary hydrogen atoms of an alkane are most reactive, secondary hydrogen atoms are next most reactive, and primary hydrogen atoms are the least reactive (see Review Problem 10.12).

Review Problem 10.12

(a) What percentages of 1-chloropropane and 2-chloropropane would you expect to obtain from the chlorination of propane if 1° and 2° hydrogen atoms were equally reactive?



(b) What percentages of 1-chloro-2-methylpropane and 2-chloro-2-methylpropane would you expect from the chlorination of 2-methylpropane if the 1° and 3° hydrogen atoms were equally reactive?



(c) Compare these calculated answers with the results actually obtained (above in Section 10.6) and justify the assertion that the order of reactivity of the hydrogen atoms is $3° > 2° > 1°$.

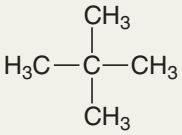
We can account for the relative reactivities of the primary, secondary, and tertiary hydrogen atoms in a chlorination reaction on the basis of the homolytic bond dissociation energies we saw earlier (Table 10.1). Of the three types, breaking a tertiary C—H bond requires the least energy, and breaking a primary C—H bond requires the most. Since the step in which the C—H bond is broken (i.e., the hydrogen atom–abstraction step) determines the location or orientation of the chlorination, we would expect the E_{act} for abstracting a tertiary hydrogen atom to be least and the E_{act} for abstracting a primary hydrogen atom to be greatest. Thus tertiary hydrogen atoms should be most reactive, secondary hydrogen atoms should be the next most reactive, and primary hydrogen atoms should be the least reactive.

The differences in the rates with which primary, secondary, and tertiary hydrogen atoms are replaced by chlorine are not large, however. Chlorine, as a result, does not discriminate among the different types of hydrogen atoms in a way that makes chlorination of higher alkanes a generally useful laboratory synthesis. (Alkane chlorinations do find use in some industrial processes, especially in those instances where mixtures of alkyl chlorides can be used.)

Solved Problem 10.4

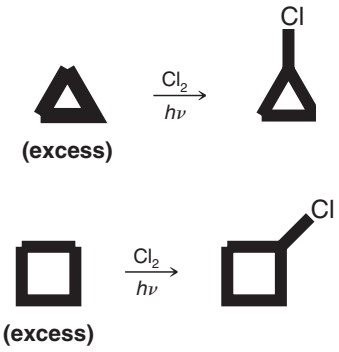
An alkane with the formula C_5H_{12} undergoes chlorination to give only one product with the formula $C_5H_{11}Cl$. What is the structure of this alkane?

STRATEGY AND ANSWER The hydrogen atoms of the alkane must all be equivalent, so that replacing any one of them leads to the same product. The only five-carbon alkane for which this is true is neopentane.



Review Problem 10.13

Chlorination reactions of certain alkanes can be used for laboratory preparations. Examples are the preparation of chlorocyclopropane from cyclopropane and chlorocyclobutane from cyclobutane.



What structural feature of these molecules makes this possible?

Review Problem 10.14

Each of the following alkanes reacts with chlorine to give a single monochloro substitution product. On the basis of this information, deduce the structure of each alkane.

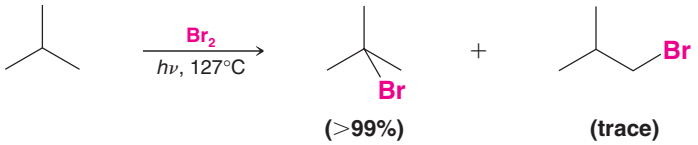
(a) C_5H_{10} **(b)** C_8H_{18}

10.6A Selectivity of Bromine

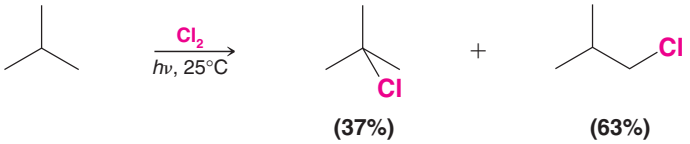
- Bromine is less reactive than chlorine toward alkanes in general but bromine is more *selective* in the site of attack.

Helpful Hint
Bromination is selective.

Bromine shows a much greater ability to discriminate among the different types of hydrogen atoms. The reaction of 2-methylpropane and bromine, for example, gives almost exclusive replacement of the tertiary hydrogen atom:



A very different result is obtained when 2-methylpropane reacts with chlorine:



Fluorine, being much more reactive than chlorine, *is even less selective than chlorine*. Because the energy of activation for the abstraction of any type of hydrogen by a fluorine atom is low, there is very little difference in the rate at which a 1°, 2°, or 3° hydrogen reacts with fluorine. Reactions of alkanes with fluorine give (almost) the distribution of products that we would expect if all of the hydrogens of the alkane were equally reactive.

Solved Problem 10.5

Explain why temperature is an important variable to consider when using isomer distribution to evaluate the reactivities of the hydrogens of an alkane toward radical chlorination.

STRATEGY AND ANSWER At lower temperatures, isomer distribution accurately reflects the inherent reactivities of the hydrogens of the alkanes. As the temperature is raised, more chlorine atoms have sufficient energy to surmount the larger energy of activation that accompanies hydrogen abstraction at the less substituted carbons. If the temperature is high enough, hydrogens are replaced by chlorine on a purely statistical basis.

10.7 The Geometry of Alkyl Radicals

Experimental evidence indicates that the geometric structure of most alkyl radicals is trigonal planar at the carbon having the unpaired electron. This structure can be accommodated by an sp^2-hybridized central carbon. In an alkyl radical, the *p* orbital contains the unpaired electron (Fig. 10.6).

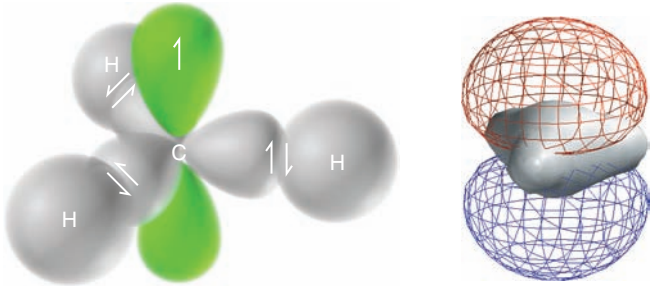


Figure 10.6 *(a)* Drawing of a methyl radical showing the sp^2-hybridized carbon atom at the center, the unpaired electron in the half-filled *p* orbital, and the three pairs of electrons involved in covalent bonding. The unpaired electron could be shown in either lobe. *(b)* Calculated structure for the methyl radical showing the highest occupied molecular orbital, where the unpaired electron resides, in red and blue. The region of bonding electron density around the carbons and hydrogens is in gray.

10.8 *Reactions That Generate Tetrahedral Chirality Centers*

- When achiral molecules react to produce a compound with a single tetrahedral chirality center, the product will be a racemic form.

This will always be true in the absence of any chiral influence on the reaction such as an enzyme or the use of a chiral reagent or solvent.

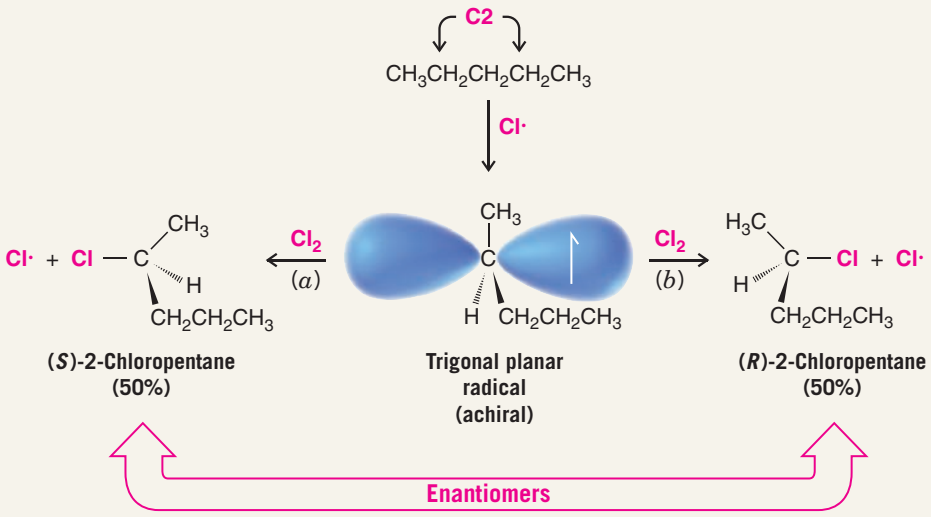
Let us examine a reaction that illustrates this principle, the radical chlorination of pentane:

Pentane (achiral) | **1-Chloropentane (achiral)** | **(±)-2-Chloropentane (a racemic form)** | **3-Chloropentane (achiral)**

The reaction will lead to the products shown here, as well as more highly chlorinated products. (We can use an excess of pentane to minimize multiple chlorinations.) Neither 1-chloropentane nor 3-chloropentane contains a chirality center, but 2-chloropentane does, and it is *obtained as a racemic form*. If we examine the mechanism we shall see why.

A MECHANISM FOR THE REACTION

The Stereochemistry of Chlorination at C2 of Pentane



Abstraction of a hydrogen atom from C2 produces a trigonal planar radical that is achiral. This radical then reacts with chlorine at either face [by path (a) or path (b)]. Because the radical is achiral, the probability of reaction by either path is the same; therefore, the two enantiomers are produced in equal amounts, and a racemic form of 2-chloropentane results.

10.8A Generation of a Second Chirality Center in a Radical Halogenation

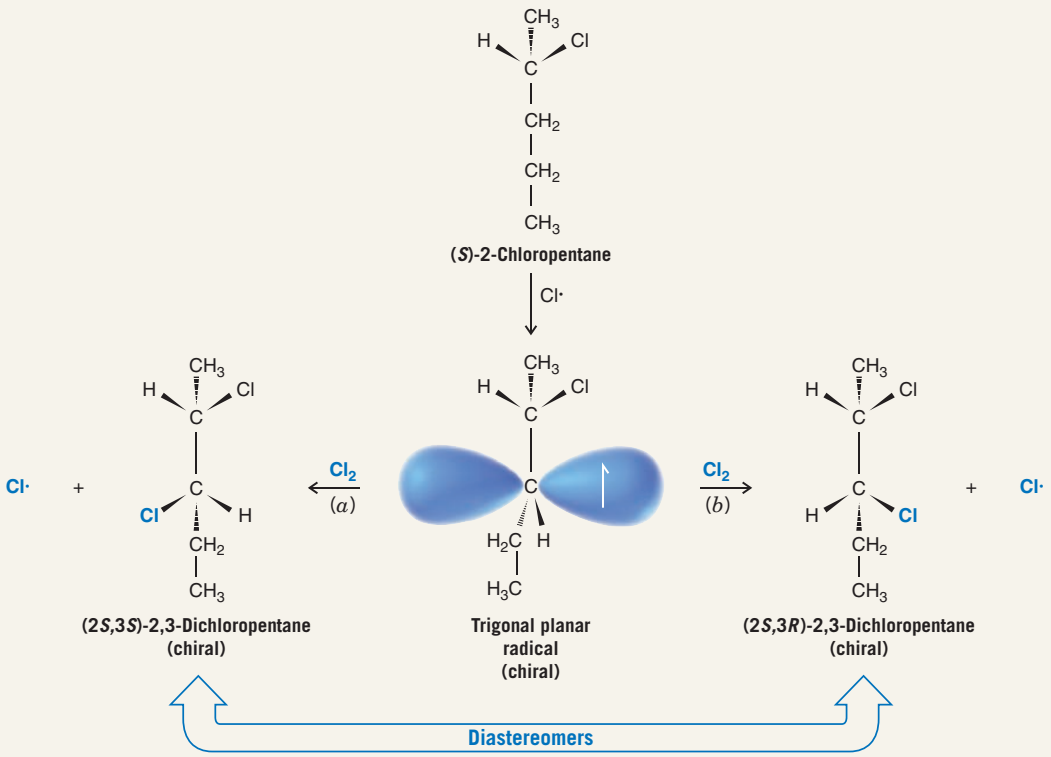
Let us now examine what happens when a chiral molecule (containing one chirality center) reacts so as to yield a product with a second chirality center. As an example consider what happens when (*S*)-2-chloropentane undergoes chlorination at C3 (other products are formed, of course, by chlorination at other carbon atoms). The results of chlorination at C3 are shown in the box below.

The products of the reactions are (2*S*,3*S*)-2,3-dichloropentane and (2*S*,3*R*)-2,3-dichloropentane. These two compounds are **diastereomers**. (They are stereoisomers but they are not mirror images of each other.) The two diastereomers are *not* produced in equal amounts. Because the intermediate radical itself is chiral, reactions at the two faces are not equally likely. The radical reacts with chlorine to a greater extent at one face than the other (although we cannot easily predict which). That is, the presence of a chirality center in the radical (at C2) influences the reaction that introduces the new chirality center (at C3).

Both of the 2,3-dichloropentane diastereomers are chiral and, therefore, each exhibits optical activity. Moreover, because the two compounds are *diastereomers*, they have different physical properties (e.g., different melting points and boiling points) and are separable by conventional means (by gas chromatography or by careful fractional distillation).

A MECHANISM FOR THE REACTION

The Stereochemistry of Chlorination at C3 of (*S*)-2-Chloropentane



Abstraction of a hydrogen atom from C3 of (S)-2-chloropentane produces a radical that is chiral (it contains a chirality center at C2). This chiral radical can then react with chlorine at one face [path (a)] to produce (2S, 3S)-2,3-dichloropentane and the other face [path (b)] to yield (2S, 3R) -2,3-dichloropentane. These two compounds are diastereomers, and they are not produced in equal amounts. Each product is chiral, and each alone would be optically active.

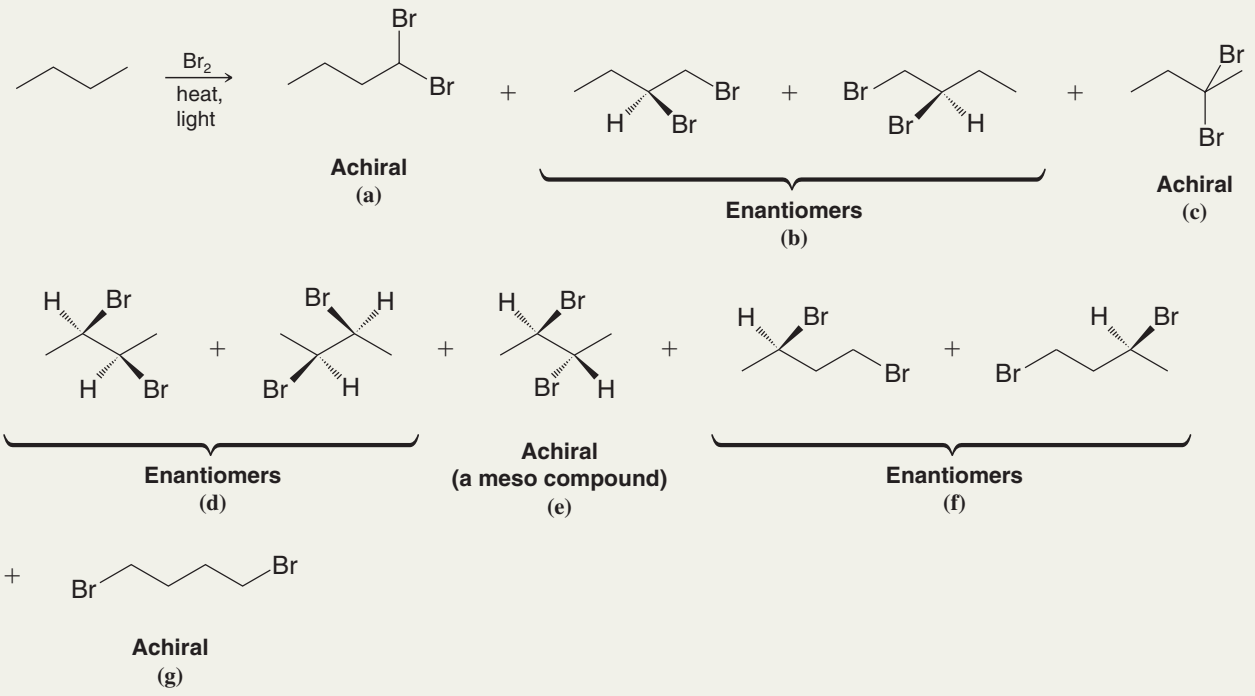
Review Problem 10.15

Consider the chlorination of (*S*)-2-chloropentane at C4. **(a)** Write structural formulas for the products, showing three dimensions at all chirality centers. Give each its proper (*R,S*) designation. **(b)** What is the stereoisomeric relationship between these products? **(c)** Are both products chiral? **(d)** Are both optically active? **(e)** Could the products be separated by conventional means? **(f)** What other dichloropentanes would be obtained by chlorination of (*S*)-2-chloropentane? **(g)** Which of these are optically active?

Solved Problem 10.6

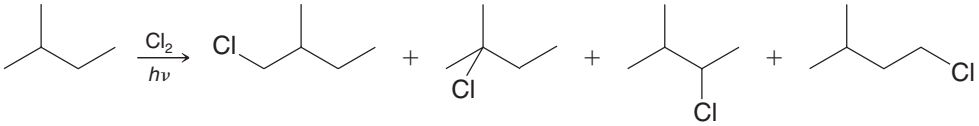
Consider the bromination of butane using sufficient bromine to cause dibromination. After the reaction is over, you separate all the dibromobutane isomers by gas chromatography or by fractional distillation. How many fractions would you obtain, and what compounds would the individual fractions contain? Which if any of the fractions would be optically active?

STRATEGY AND ANSWER The construction of handheld models will help in solving this problem. First, decide how many constitutional isomers are possible by replacing two hydrogens of butane with two bromine atoms. There are six: 1,1-dibromobutane, 1,2-dibromobutane, 2,2-dibromobutane, 2,3-dibromobutane, 1,3-dibromobutane, and 1,4-dibromobutane. Then recall that constitutional isomers have different physical properties (i.e., boiling points, and retention times in a gas chromatograph), so there should be at least six fractions. In actuality there are seven. See fractions (**a**)–(**g**) below. We soon see why there are seven fractions if we examine each constitutional isomer looking for chirality centers and stereoisomers. Isomers (**a**), (**c**), and (**g**) have no chirality centers and are, therefore, achiral and are optically inactive. 1,2-Dibromobutane in fraction (**b**) and 1,4-dibromobutane in fraction (**f**) each have one chirality center and, because there is no chiral influence on the reaction, they will be formed as a 50 : 50 mixture of enantiomers (a racemate). A racemate cannot be separated by distillation or conventional gas chromatography; therefore, fractions (**b**) and (**f**) will not be optically active. 2,3-Dibromobutane has two chirality centers and will be formed as a racemate [fraction (**d**)] and as a meso compound, fraction (**e**). Both fractions will be optically inactive. The meso compound is a diastereomer of the enantiomers in fraction (**d**) (and has different physical properties from them); therefore, it is separated from them by distillation or gas chromatography.



Review Problem 10.16

Consider the monochlorination of 2-methylbutane.



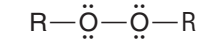
(a) Assuming that the product mixture was subjected to fractional distillation, which fractions, if any, would show optical activity? **(b)** Could any of these fractions be resolved, theoretically, into enantiomers? **(c)** Could each fraction from the distillation be identified on the basis of ^{1}H NMR spectroscopy? What specific characteristics in a ^{1}H NMR spectrum of each fraction would indicate the identity of the component(s) in that fraction?

10.9 *Radical Addition to Alkenes: The Anti-Markovnikov Addition of Hydrogen Bromide*

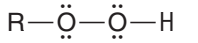
Before 1933, the orientation of the addition of hydrogen bromide to alkenes was the subject of much confusion. At times addition occurred in accordance with Markovnikov's rule; at other times it occurred in just the opposite manner. Many instances were reported where, under what seemed to be the same experimental conditions, Markovnikov additions were obtained in one laboratory and anti-Markovnikov additions in another. At times even the same chemist would obtain different results using the same conditions but on different occasions.

The mystery was solved in 1933 by the research of M. S. Kharasch and F. R. Mayo (of the University of Chicago). The explanatory factor turned out to be organic peroxides present in the alkenes—peroxides that were formed by the action of atmospheric oxygen on the alkenes (Section 10.11D).

- When alkenes containing peroxides or hydroperoxides react with hydrogen bromide, anti-Markovnikov addition of HBr occurs.

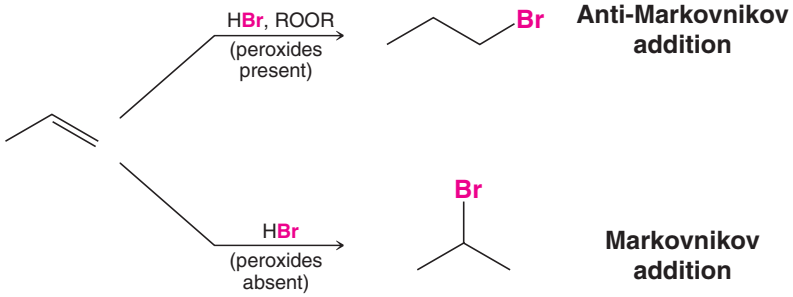


An organic peroxide



An organic hydroperoxide

For example, in the *presence* of peroxides propene yields 1-bromopropane. In the *absence* of peroxides, or in the presence of compounds that "trap" radicals, normal Markovnikov addition occurs.



- Hydrogen bromide is the only hydrogen halide that gives anti-Markovnikov addition when peroxides are present.

Hydrogen fluoride, hydrogen chloride, and hydrogen iodide *do not* give anti-Markovnikov addition even when peroxides are present.

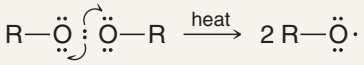
The mechanism for **anti-Markovnikov addition of hydrogen bromide** is a **radical chain reaction** initiated by peroxides.

A MECHANISM FOR THE REACTION

Anti-Markovnikov Addition

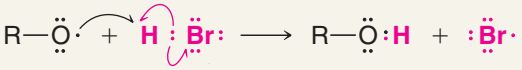
Chain Initiation

Step 1



Heat brings about homolytic cleavage of the weak oxygen–oxygen bond.

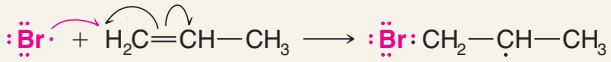
Step 2



The alkoxyl radical abstracts a hydrogen atom from HBr, producing a bromine radical.

Chain Propagation

Step 3



2° Radical

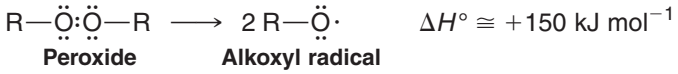
A bromine radical adds to the double bond to produce the more stable 2° alkyl radical.

Step 4

1-Bromopropane

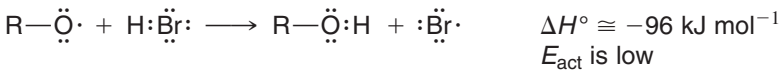
The alkyl radical abstracts a hydrogen atom from HBr. This leads to the product and regenerates a bromine radical. Then repetitions of steps 3 and 4 lead to a chain reaction.

Step 1 is the simple homolytic cleavage of the peroxide molecule to produce two alkoxyl radicals. The oxygen–oxygen bond of peroxides is weak, and such reactions are known to occur readily:



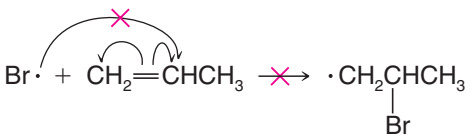
Peroxide **Alkoxyl radical**

Step 2 of the mechanism, abstraction of a hydrogen atom by the radical, is exothermic and has a low energy of activation:



E_{act} is low

Step 3 of the mechanism determines the final orientation of bromine in the product. It occurs as it does because a *more stable secondary radical* is produced and because *attack at the primary carbon atom is less hindered*. Had the bromine attacked propene at the secondary carbon atom, a less stable, primary radical would have been the result,



1° Radical (less stable)

and attack at the secondary carbon atom would have been more hindered.

Step 4 of the mechanism is simply the abstraction of a hydrogen atom from hydrogen bromide by the radical produced in step 3. This hydrogen atom abstraction produces a bromine atom (which, of course, is a radical due to its unpaired electron) that can bring about step 3 again; then step 4 occurs again—a chain reaction.

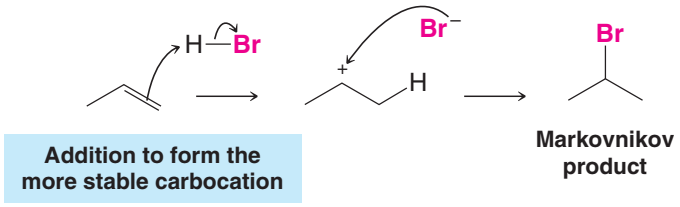
10.9A Summary of Markovnikov versus Anti-Markovnikov Addition of HBr to Alkenes

Helpful Hint

A tip for alkyl halide synthesis.

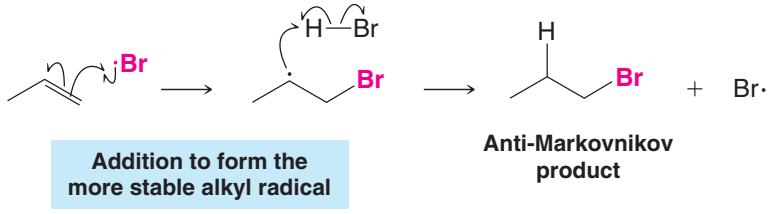
We can now see the contrast between the two ways that HBr can add to an alkene. In the *absence* of peroxides, the reagent that attacks the double bond first is a proton. Because a proton is small, steric effects are unimportant. It attaches itself to a carbon atom by an ionic mechanism so as to form the more stable carbocation. The result is Markovnikov addition. Polar, protic solvents favor this process.

Ionic Addition



In the *presence* of peroxides, the reagent that attacks the double bond first is the larger bromine atom. It attaches itself to the less hindered carbon atom by a radical mechanism, so as to form the more stable radical intermediate. The result is anti-Markovnikov addition. Nonpolar solvents are preferable for reactions involving radicals.

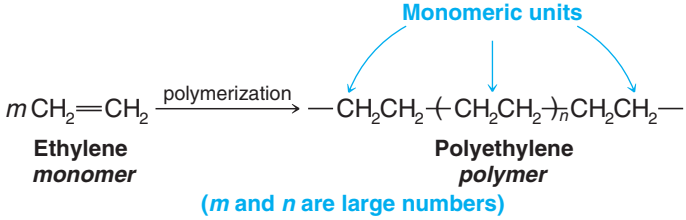
Radical Addition



10.10 Radical Polymerization of Alkenes: Chain-Growth Polymers

Polymers are substances that consist of very large molecules called **macromolecules** that are made up of many repeating subunits. The molecular subunits that are used to synthesize polymers are called **monomers**, and the reactions by which monomers are joined together are called **polymerizations**. Many polymerizations can be initiated by radicals.

Ethylene (ethene), for example, is the monomer that is used to synthesize the familiar polymer called *polyethylene*.



Because polymers such as polyethylene are made by addition reactions, they are often called **chain-growth polymers** or **addition polymers**. Let us now examine in some detail how polyethylene is made.

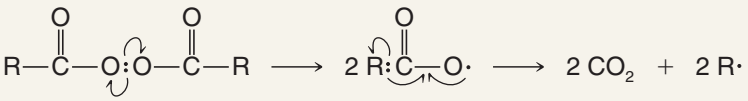
Ethylene polymerizes by a radical mechanism when it is heated at a pressure of 1000 atm with a small amount of an organic peroxide (called a diacyl peroxide).

A MECHANISM FOR THE REACTION

Radical Polymerization of Ethene

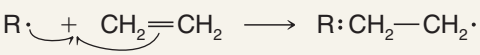
Chain Initiation

Step 1



Diacyl peroxide

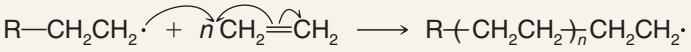
Step 2



The diacyl peroxide dissociates and releases carbon dioxide gas. Alkyl radicals are produced, which in turn initiate chains.

Chain Propagation

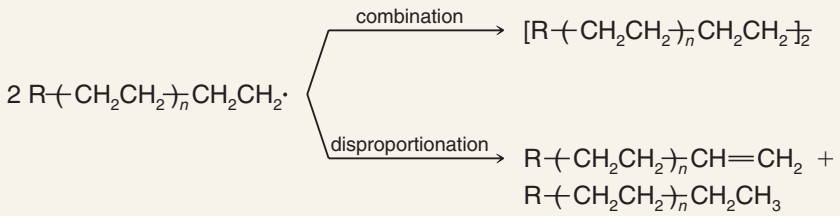
Step 3



Chains propagate by adding successive ethylene units, until their growth is stopped by combination or disproportionation.

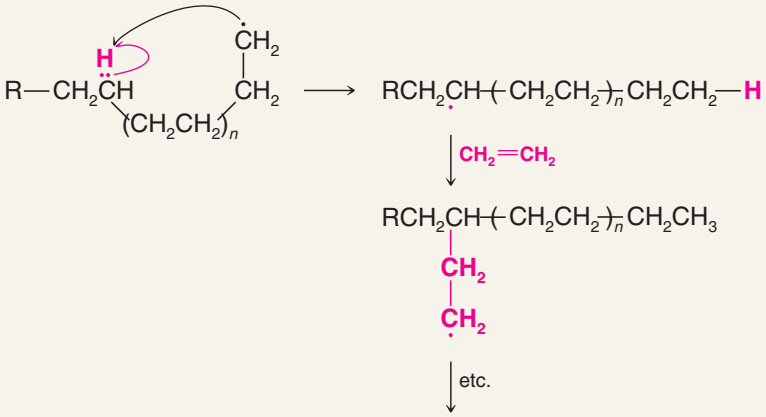
Chain Termination

Step 4



The radical at the end of the growing polymer chain can also abstract a hydrogen atom from itself by what is called "back biting." This leads to chain branching.

Chain Branching



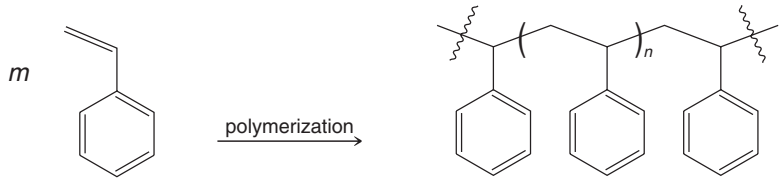
The polyethylene produced by radical polymerization is not generally useful unless it has a molecular weight of nearly 1,000,000. Very high molecular weight polyethylene can be obtained by using a low concentration of the initiator. This initiates the growth of only

a few chains and ensures that each chain will have a large excess of the monomer available. More initiator may be added as chains terminate during the polymerization, and, in this way, new chains are begun.

Polyethylene has been produced commercially since 1943. It is used in manufacturing flexible bottles, films, sheets, and insulation for electric wires. Polyethylene produced by radical polymerization has a softening point of about 110°C.

Polyethylene can be produced in a different way using (see Special Topic B) catalysts called **Ziegler–Natta catalysts** that are organometallic complexes of transition metals. In this process no radicals are produced, no back biting occurs, and, consequently, there is no chain branching. The polyethylene that is produced is of higher density, has a higher melting point, and has greater strength.

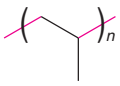
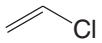
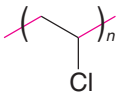
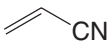
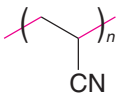
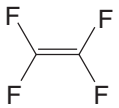
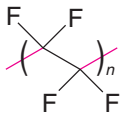
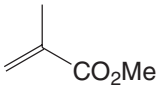
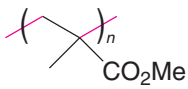
Another familiar polymer is *polystyrene*. The monomer used in making polystyrene is phenylethene, a compound commonly known as *styrene*.



Styrene **Polystyrene**

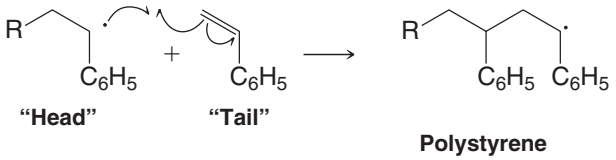
Table 10.2 lists several other common chain-growth polymers. Further information on each is provided in Special Topic B.

TABLE 10.2 Other Common Chain-Growth Polymers

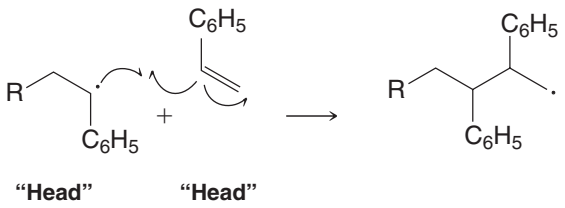
Monomer	Polymer	Names
		Polypropylene
		Poly(vinyl chloride), PVC
		Polyacrylonitrile, Orlon
		Poly(tetrafluoroethene), Teflon
		Poly(methyl methacrylate), Lucite, Plexiglas, Perspex

Review Problem 10.17

Can you suggest an explanation that accounts for the fact that the radical polymerization of styrene ($C_6H_5CH{-}CH_2$) to produce polystyrene occurs in a head-to-tail fashion,



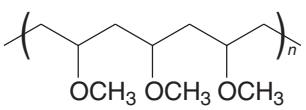
rather than the head-to-head manner shown here?



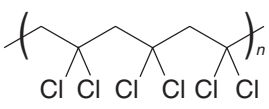
Review Problem 10.18

Outline a general method for the synthesis of each of the following polymers by radical polymerization. Show the monomers that you would use.

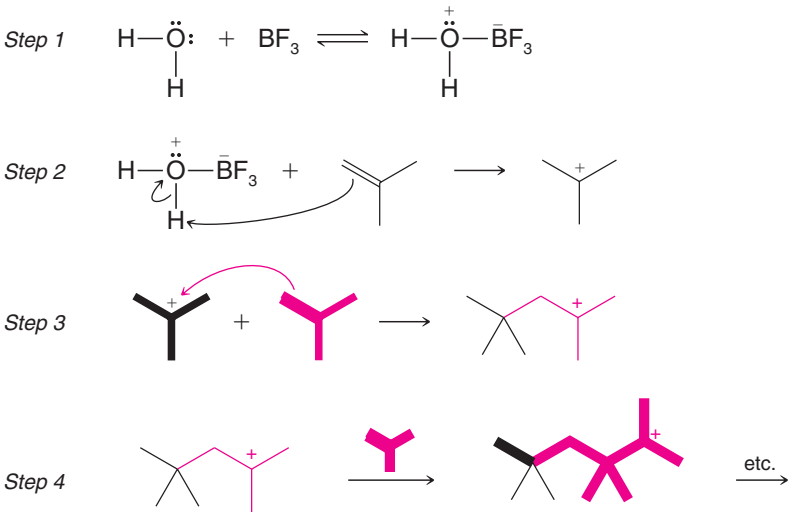
(a)



(b)



Alkenes also polymerize when they are treated with strong acids. The growing chains in acid-catalyzed polymerizations are *cations* rather than radicals. The following reactions illustrate the cationic polymerization of isobutylene:

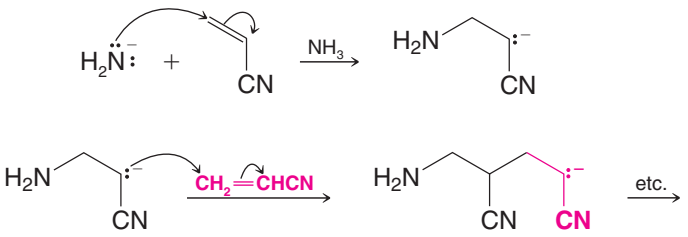


The catalysts used for cationic polymerizations are usually Lewis acids that contain a small amount of water. The polymerization of isobutylene illustrates how the catalyst (BF_3 and H_2O) functions to produce growing cationic chains.

Review Problems 10.19

Alkenes such as ethene, vinyl chloride, and acrylonitrile do not undergo cationic polymerization very readily. On the other hand, isobutylene undergoes cationic polymerization rapidly. Provide an explanation for this behavior.

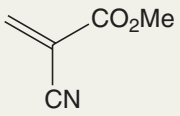
Alkenes containing electron-withdrawing groups polymerize in the presence of strong bases. Acrylonitrile, for example, polymerizes when it is treated with sodium amide ($NaNH_2$) in liquid ammonia. The growing chains in this polymerization are anions:



Anionic polymerization of acrylonitrile is less important in commercial production than the radical process illustrated in Special Topic B.

Solved Problem 10.7

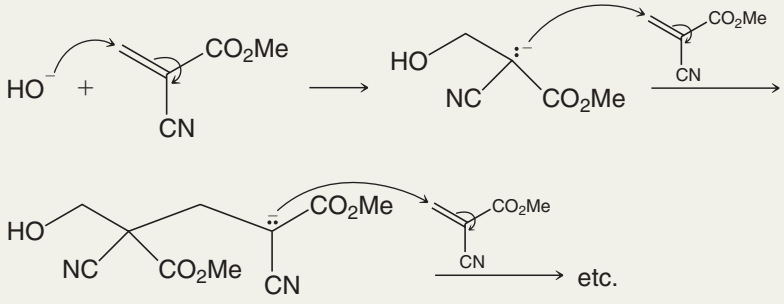
The remarkable adhesive called "superglue" is a result of anionic polymerization. Superglue is a solution containing methyl cyanoacrylate:



Methyl cyanoacrylate

Methyl cyanoacrylate can be polymerized by anions such as hydroxide ion, but it is even polymerized by traces of water found on the surfaces of the two objects being glued together. (These two objects, unfortunately, have often been two fingers of the person doing the gluing.) Show how methyl cyanoacrylate would undergo anionic polymerization.

STRATEGY AND ANSWER



10.11 *Other Important Radical Reactions*

Radical mechanisms are important in understanding many other organic reactions. We shall see other examples in later chapters, but let us examine a few important radicals and radical reactions here: oxygen and superoxide, the combustion of alkanes, DNA cleavage, autoxidation, antioxidants, and some reactions of chlorofluoromethanes that have threatened the protective layer of ozone in the stratosphere.

10.11A Molecular Oxygen and Superoxide

One of the most important radicals (and one that we encounter every moment of our lives) is molecular oxygen. Molecular oxygen in the ground state is a diradical with one unpaired electron on each oxygen. As a radical, oxygen can abstract hydrogen atoms just like other radicals we have seen. This is one way oxygen is involved in combustion reactions (Section 10.11C) and autoxidation (Section 10.11D). In biological systems, oxygen is an electron

acceptor. When molecular oxygen accepts one electron, it becomes a radical anion called superoxide ($O_2^{\cdot -}$). Superoxide is involved in both positive and negative physiological roles: The immune system uses superoxide in its defense against pathogens, yet superoxide is also suspected of being involved in degenerative disease processes associated with aging and oxidative damage to healthy cells. The enzyme superoxide dismutase regulates the level of superoxide by catalyzing conversion of superoxide to hydrogen peroxide and molecular oxygen. Hydrogen peroxide, however, is also harmful because it can produce hydroxyl (HO·) radicals. The enzyme catalase helps to prevent release of hydroxyl radicals by converting hydrogen peroxide to water and oxygen:

$$2\ O_2^{\cdot -} + 2\ H^+ \xrightarrow{\text{superoxide dismutase}} H_2O_2 + O_2$$

$$2\ H_2O_2 \xrightarrow{\text{catalase}} 2\ H_2O + O_2$$

10.11B Nitric Oxide

Nitric oxide, synthesized in the body from the amino acid arginine, serves as a chemical messenger in a variety of biological processes, including blood pressure regulation and the immune response. Its role in relaxation of smooth muscle in vascular tissues is shown in Fig. 10.7.

The 1998 Nobel Prize in Physiology or Medicine was awarded to R. F. Furchgott, L. J. Ignarro, and F. Murad for their discovery that NO is an important signaling molecule.

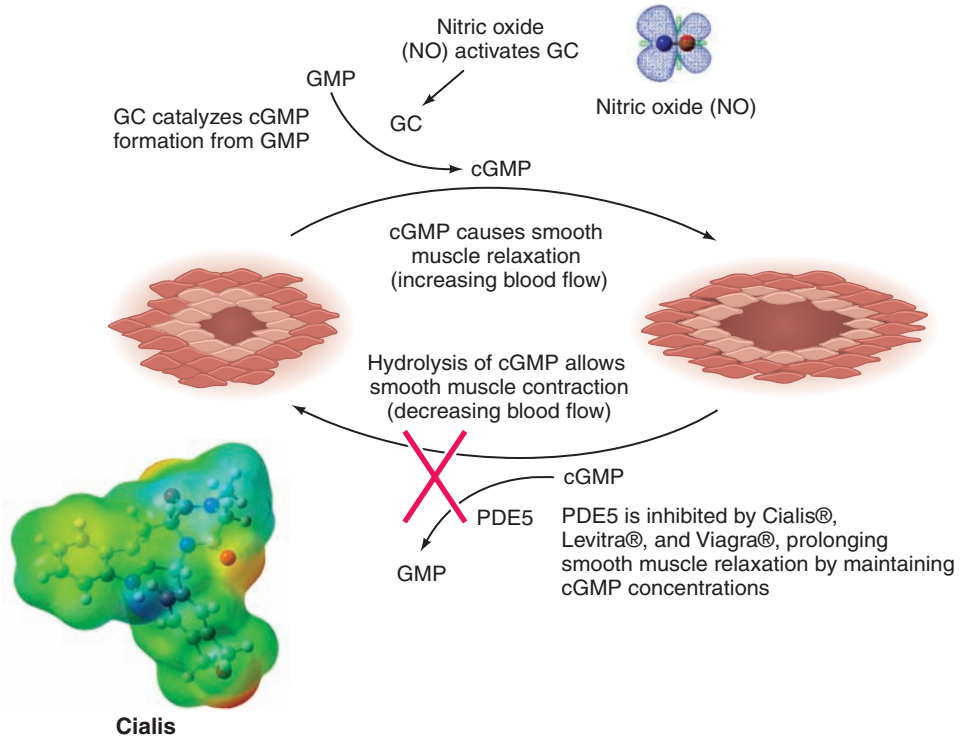


Figure 10.7 Nitric oxide (NO) activates guanylate cyclase (GC), leading to production of cyclic guanosine monophosphate (cGMP). cGMP signals processes that cause smooth muscle relaxation, ultimately resulting in increased blood flow to certain tissues. Phosphodiesterase V (PDE5) degrades cGMP, leading to smooth muscle contraction and a reduction of blood flow. Cialis, Levitra, and Viagra take their effect by inhibiting PDE5, thus maintaining concentrations of cGMP and sustaining smooth muscle relaxation and tissue engorgement. (Reprinted with permission from Christianson, *Accounts of Chemical Research*, *38*, p. 197, Figure 6b, 2005. Copyright 2005 by American Chemical Society.)

10.11C Combustion of Alkanes

When alkanes react with oxygen (e.g., in oil and gas furnaces and in internal combustion engines) a complex series of reactions takes place, ultimately converting the alkane to carbon dioxide and water. Although our understanding of the detailed mechanism of combustion is incomplete, we do know that the important reactions occur by radical chain mechanisms with chain-initiating and chain-propagating steps such as the following reactions:

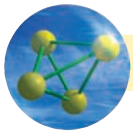
$$RH + O_2 \longrightarrow R\cdot + \cdot OOH \qquad \textbf{Initiating}$$

$$R\cdot + O_2 \longrightarrow R{-}OO\cdot$$

$$R{-}OO\cdot + R{-}H \longrightarrow R{-}OOH + R\cdot \qquad \textbf{Propagating}$$

One product of the second chain-propagating step is R—OOH, called an alkyl hydroperoxide. The oxygen–oxygen bond of an alkyl hydroperoxide is quite weak, and it can break and produce radicals that can initiate other chains:

$$RO—OH \longrightarrow RO\cdot + \cdot OH$$

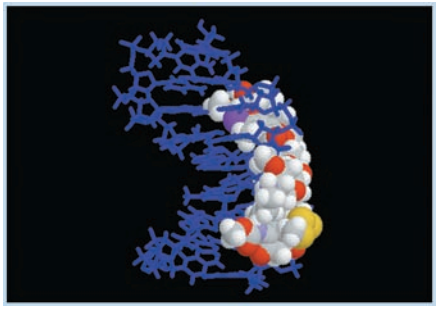


THE CHEMISTRY OF . . .

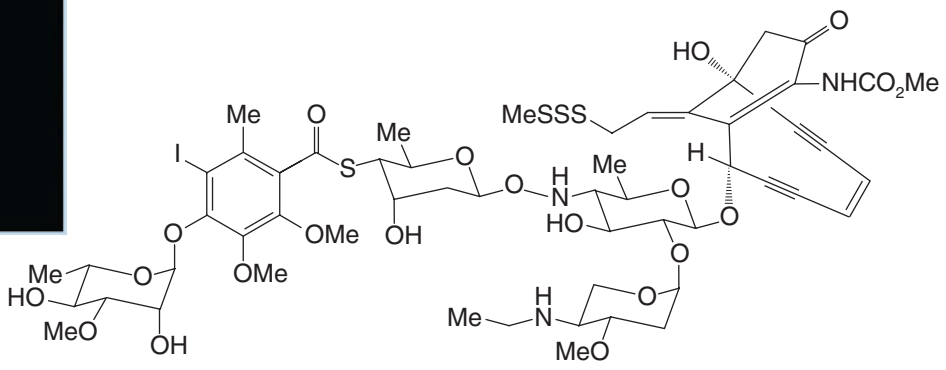
Calicheamicin γ_1^I: A Radical Device for Slicing the Backbone of DNA

The beautiful architecture of calicheamicin γ_1^I conceals a lethal reactivity. Calicheamicin γ_1^I binds to the minor groove of DNA where its unusual enediyne (pronounced ēn dī īn) moiety reacts to form a highly effective device for slicing the backbone of DNA. A model of calicheamicin bound to DNA is shown below, along with its structural formula. Calicheamicin γ_1^I and its analogs are of great clinical interest because they are extraordinarily deadly for cancer cells, having been shown to initiate apoptosis (programmed cell death). Indeed, research on calicheamicin has since led to development of the drug Mylotarg, now used to treat some cases of acute mylogenous leukemia. Mylotarg carries two calicheamicin "warheads" on an antibody that delivers it specifically to the cancerous cells. In nature, bacteria called *Micromonospora echinospora* synthesize calicheamicin γ_1^I as part of their normal metabolism, presumably as a chemical defense against other organisms. The laboratory synthesis of this complex molecule by the research group of K. C. Nicolaou (Scripps Research Institute, University of California, San Diego), on the other hand, represents a *tour de force* achievement in synthetic organic chemistry. Synthesis of calicheamicin and analogs, as well as investigations by many other researchers, has led to fascinating insights about its mechanism of action and biological properties.

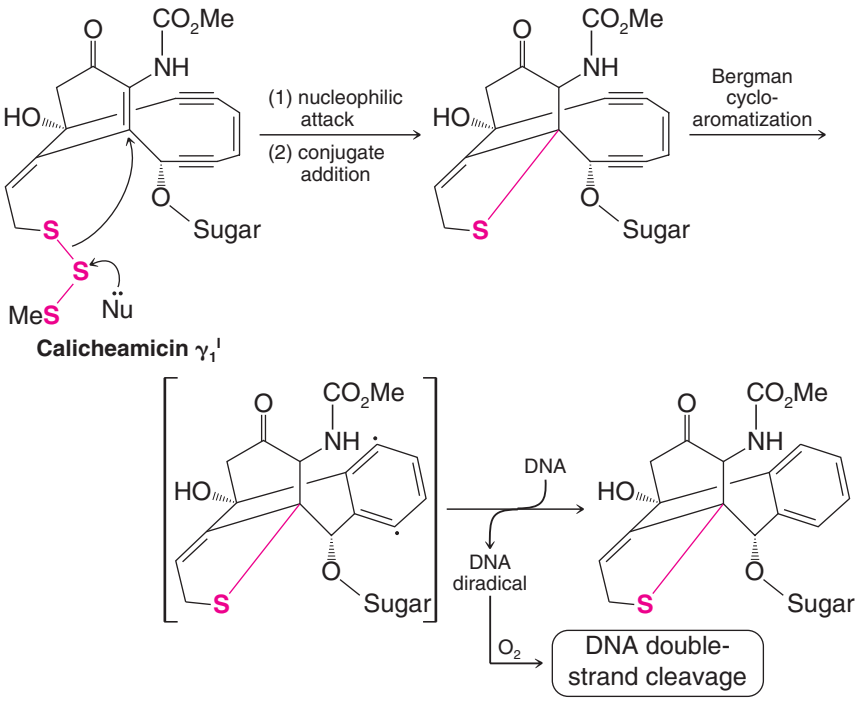
The DNA-slicing property of calicheamicin γ_1^I arises because it acts as a molecular machine for producing carbon radicals. A carbon radical is a highly reactive and unstable intermediate that has an unpaired electron. Once formed, a carbon radical can become a stable molecule again by removing a proton and one electron (i.e., a hydrogen atom) from another molecule. In this way, its unpaired electron becomes part of a bonding electron pair. (Other paths to achieve this are possible, too). The molecule that lost the hydrogen atom, however, becomes a new reactive radical intermediate. When the radical weaponry of each calicheamicin γ_1^I is activated, it removes a hydrogen atom from the backbone of DNA. This leaves the DNA molecule as an unstable radical intermediate which, in turn, results in double-strand cleavage of the DNA and cell death.



Calicheamicin bound to DNA. (PDB ID: 2PIK. Kumar, R. A.; Ikemoto, N., and Patel, D. J., Solution structure of the calicheamicin γ_1^I–DNA complex, *J. Mol. Biol.* **1997**, *265*, 187.) [Calicheamicin γ_1^I structure from Chemistry and Biology, 1994, 1(1). Nicolaou, K.C., Pitsinos, E.N., Theodorakis, A., Saimoto, H., and Wrasidio, W., *Chemistry and Biology of the Calicheamicins*, pp. 25-30. Copyright Elsevier 1994.



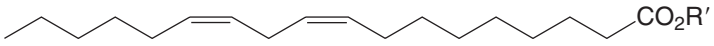
Calicheamicin γ_1^I



In Problem 10.29 and in "The Chemistry of . . . Calicheamicin γ_1^I Activation for Cleavage of DNA" box in Chapter 17, we shall revisit calicheamicin γ_1^I to consider the reactions that remodel its structure into a machine for producing radicals.

10.11D Autoxidation

Linoleic acid is an example of a *polyunsaturated fatty acid*, the kind of polyunsaturated acid that occurs as an ester in **polyunsaturated fats** (Section 7.13, "The Chemistry of . . . Hydrogenation in the Food Industry," and Chapter 23). By polyunsaturated, we mean that the compound contains two or more double bonds:



Linoleic acid (as an ester)

Polyunsaturated fats occur widely in the fats and oils that are components of our diets. They are also widespread in the tissues of the body where they perform numerous vital functions.

The hydrogen atoms of the —CH_2— group located between the two double bonds of linoleic ester (Lin—H) are especially susceptible to abstraction by radicals (we shall see why in Chapter 13). Abstraction of one of these hydrogen atoms produces a new radical (Lin·) that can react with oxygen in a chain reaction that belongs to a general type of reaction called **autoxidation** (Fig. 10.8). The result of autoxidation is the formation of a hydroperoxide. Autoxidation is a process that occurs in many substances; for example, autoxidation is responsible for the development of the rancidity that occurs when fats and oils spoil and for the spontaneous combustion of oily rags left open to the air. Autoxidation also occurs in the body, and here it may cause irreversible damage.

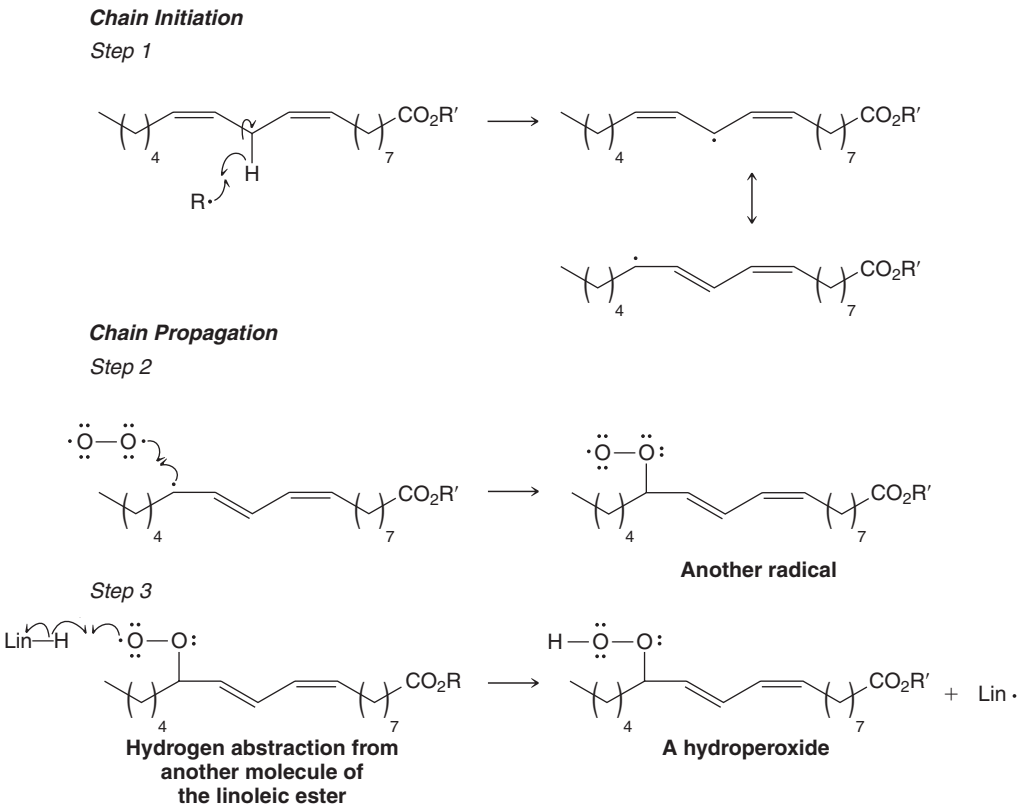
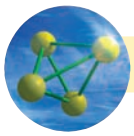


Figure 10.8 Autoxidation of a linoleic acid ester. In step 1 the reaction is initiated by the attack of a radical on one of the hydrogen atoms of the —CH_2— group between the two double bonds; this hydrogen abstraction produces a radical that is a resonance hybrid. In step 2 this radical reacts with oxygen in the first of two chain-propagating steps to produce an oxygen-containing radical, which in step 3 can abstract a hydrogen from another molecule of the linoleic ester (Lin—H). The result of this second chain-propagating step is the formation of a hydroperoxide and a radical (Lin·) that can bring about a repetition of step 2.



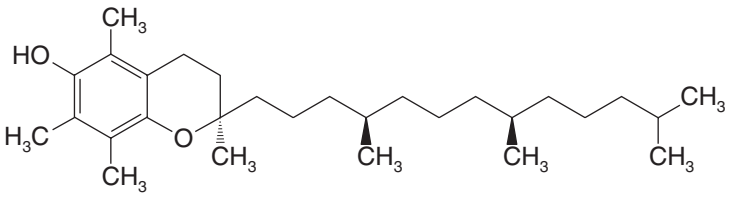
THE CHEMISTRY OF . . .

Antioxidants

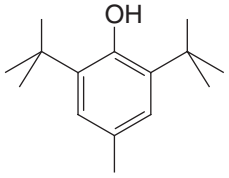
Autoxidation is inhibited when compounds called antioxidants are present that can rapidly "trap" peroxyl radicals by reacting with them to give stabilized radicals that do not continue the chain.

Vitamin E (α-tocopherol) is capable of acting as a radical trap, and one of the important roles that vitamin E plays in the body may be in inhibiting radical reactions that could cause cell damage. Vitamin C is also an antioxidant, although recent work indicates that supplements over 500 mg per day may have prooxidant effects. Compounds such as BHT are added to foods to prevent autoxidation. BHT is also known to trap radicals.

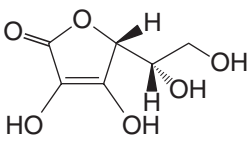
Vitamin E is found in vegetable oils.



Vitamin E (α-tocopherol)

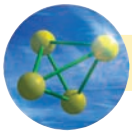


BHT (butylated hydroxytoluene)



Vitamin C

Vitamin C is found in citrus fruits.



THE CHEMISTRY OF . . .

Ozone Depletion and Chlorofluorocarbons (CFCs)

In the stratosphere at altitudes of about 25 km, very high-energy (very short wavelength) UV light converts diatomic oxygen (O_2) into ozone (O_3). The reactions that take place may be represented as follows:

Step 1 $O_2 + h\nu \longrightarrow O + O$

Step 2 $O + O_2 + M \longrightarrow O_3 + M + \text{heat}$

where M is some other particle that can absorb some of the energy released in the second step.

The ozone produced in step 2 can also interact with high-energy UV light in the following way:

Step 3 $O_3 + h\nu \longrightarrow O_2 + O + \text{heat}$

The oxygen atom formed in step 3 can cause a repetition of step 2, and so forth. The net result of these steps is to convert highly energetic UV light into heat. This is important because the existence of this cycle shields Earth from radiation that is destructive to living organisms. This shield makes life possible on Earth's surface. Even a relatively small increase in high-energy UV radiation at Earth's surface would cause a large increase in the incidence of skin cancers.

Production of chlorofluoromethanes (and of chlorofluoroethanes) called chlorofluorocarbons (CFCs) or **freons** began in 1930. These compounds have been used as refrigerants, solvents, and propellants in aerosol cans.

By 1974 world freon production was about 2 billion pounds annually. Most freon, even that used in refrigeration, eventually makes its way into the atmosphere where it diffuses unchanged into the stratosphere. In June 1974 F. S. Rowland and M. J. Molina published an article indicating, for the first time, that in the stratosphere freon is able to initiate radical chain reactions that can upset the natural ozone balance. The 1995 Nobel Prize in Chemistry was awarded to P. J. Crutzen, M. J. Molina, and F. S. Rowland for their combined work in this area. The reactions that take place are the following. (Freon-12 is used as an example.)

Typical freons are trichlorofluoromethane, $CFCl_3$ (called Freon-11), and dichlorodifluoromethane, CF_2Cl_2 (called Freon-12).

Chain Initiation

Step 1 $CF_2Cl_2 + h\nu \longrightarrow CF_2Cl\cdot + Cl\cdot$

Chain Propagation

Step 2 $Cl\cdot + O_3 \longrightarrow ClO\cdot + O_2$

Step 3 $ClO\cdot + O \longrightarrow O_2 + Cl\cdot$

In the chain-initiating step, UV light causes homolytic cleavage of one C—Cl bond of the freon. The chlorine atom thus produced is the real villain; it can set off a chain reaction that destroys thousands of molecules of ozone before it diffuses out of the stratosphere or reacts with some other substance.

In 1975 a study by the National Academy of Sciences supported the predictions of Rowland and Molina, and since January 1978 the use of freons in aerosol cans in the United States has been banned.

In 1985 a hole was discovered in the ozone layer above Antarctica. Studies done since then strongly suggest that chlorine atom destruction of the ozone is a factor in the formation of the hole. This ozone hole has continued to grow in size, and such a hole has also been discovered in the Arctic ozone layer. Should the ozone layer be depleted, more of the sun's damaging rays would penetrate to the surface of Earth.

Recognizing the global nature of the problem, the "Montreal Protocol" was initiated in 1987. This treaty required the signing nations to reduce their production and consumption of chlorofluorocarbons. Accordingly, the industrialized nations of the world ceased production of chlorofluorocarbons as of 1996, and over 120 nations have signed the Montreal Protocol. Increased worldwide understanding of stratospheric ozone depletion, in general, has accelerated the phasing out of chlorofluorocarbons.

Key Terms and Concepts

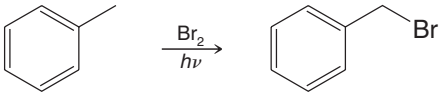
The key terms and concepts that are highlighted in **bold, blue text** within the chapter are defined in the glossary (at the back of the book) and have hyperlinked definitions in the accompanying ***WileyPLUS*** course (www.wileyplus.com).

Problems

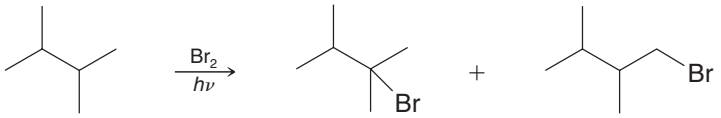
Note to Instructors: Many of the homework problems are available for assignment via ***WileyPLUS***, an online teaching and learning solution.

RADICAL MECHANISMS AND PROPERTIES

10.20 Write a mechanism for the following radical halogenation reaction.

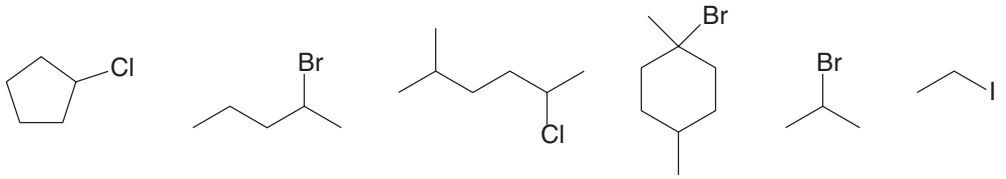


10.21 Explain the relative distribution of products below using reaction energy diagrams for the hydrogen abstraction step that leads to each product. (The rate-determining step in radical halogenation is the hydrogen abstraction step.) In energy diagrams for the two pathways, show the relative energies of the transition states and of the alkyl radical intermediate that results in each case.

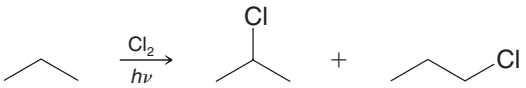


(92%) **(8%)**

10.22 Which of the following compounds can be prepared by radical halogenation with little complication by formation of isomeric by-products?

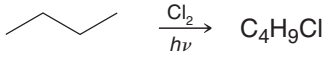


10.23 The radical reaction of propane with chlorine yields (in addition to more highly halogenated compounds) 1-chloropropane and 2-chloropropane.



Write chain-initiating and chain-propagating steps showing how each of the products above is formed.

10.24 In addition to more highly chlorinated products, chlorination of butane yields a mixture of compounds with the formula C_4H_9Cl.



(multiple isomers)

(a) Taking stereochemistry into account, how many different isomers with the formula C_4H_9Cl would you expect?

(b) If the mixture of C_4H_9Cl isomers were subjected to fractional distillation (or gas chromatography), how many fractions (or peaks) would you expect?

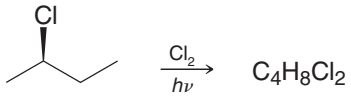
(c) Which fractions would be optically *inactive*?

(d) Which fractions could theoretically be resolved into enantiomers?

(e) Predict features in the ^1H and ^{13}C DEPT NMR spectra for each that would differentiate among the isomers separated by distillation or GC.

(f) How could fragmentation in their mass spectra be used to differentiate the isomers?

10.25 Chlorination of (*R*)-2-chlorobutane yields a mixture of dichloro isomers.



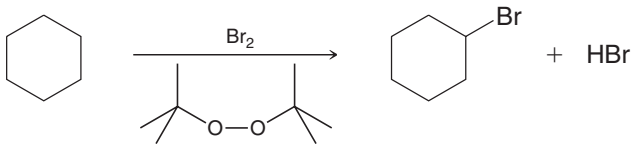
(multiple isomers)

(a) Taking into account stereochemistry, how many different isomers would you expect? Write their structures.

(b) How many fractions would be obtained upon fractional distillation?

(c) Which of these fractions would be optically active?

10.26 Peroxides are often used to initiate radical chain reactions such as in the following radical halogenation.



(Di-*tert*-butyl peroxide)

(a) Using bond dissociation energies in Table 10.1, explain why peroxides are especially effective as radical initiators.

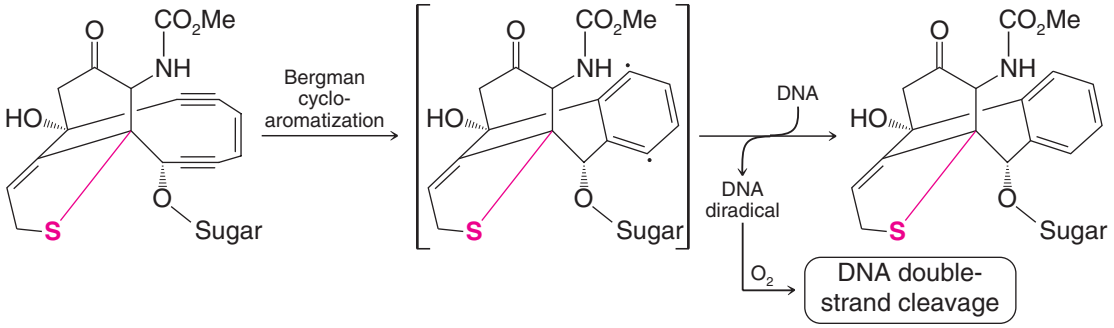
(b) Write a mechanism for the reaction above showing how it could be initiated by di-*tert*-butyl peroxide.

10.27 List in order of decreasing stability all of the radicals that can be obtained by abstraction of a hydrogen atom from 2-methylbutane.

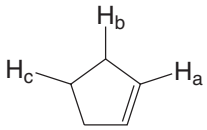
10.28 The relative stability of a series of primary, secondary, and tertiary alkyl radicals can be compared using R—CH_3 carbon–carbon bond dissociation energies instead of R—H bond dissociation energies (the method used in Section 10.2B). Bond dissociation energies ($DH°$) needed to make such a comparison for various R—CH_3 species can be calculated from values for the heat of formation (H_f) of radicals R·, CH_3·, and the molecule R—CH_3 using the following equation: $DH°[R—R'] = H_f[R·] + H_f[CH_3·] - H_f[R—CH_3]$. Using the data below, calculate the R—CH_3 bond dissociation energies for the examples given, and from your results compare the relative stabilities of the respective primary, secondary, and tertiary radicals in this series.

Chemical Species	H_f (Heat of Formation, kJ mol^{-1})
$CH_3CH_2CH_2CH_2—CH_3$	−146.8
$CH_3CH_2CH(CH_3)—CH_3$	−153.7
$(CH_3)_3C—CH_3$	−167.9
$CH_3CH_2CH_2CH_2·$	80.9
$CH_3CH_2CH(CH_3)·$	69
$(CH_3)_3C·$	48
$CH_3·$	147

10.29 Draw mechanism arrows to show electron movements in the Bergman cycloaromatization reaction that leads to the diradical believed responsible for the DNA-cleaving action of the antitumor agent calicheamicin (see "The Chemistry of . . . Calicheamicin" in Section 10.11C).



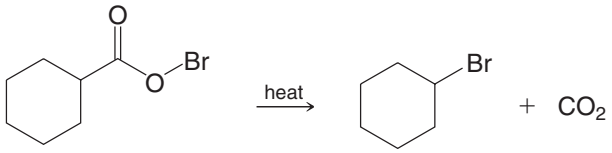
10.30 Find examples of C—H bond dissociation energies in Table 10.1 that are as closely related as possible to the bonds to H_a, H_b, and H_c in the molecule at right. Use these values to answer the questions below.



(a) What can you conclude about the relative ease of radical halogenation at H_a?

(b) Comparing H_b and H_c, which would more readily undergo substitution by radical halogenation?

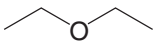
10.31 Write a radical chain mechanism for the following reaction (a reaction called the Hunsdiecker reaction).



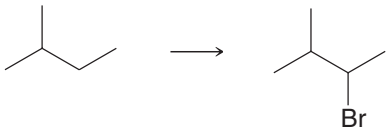
SYNTHESIS

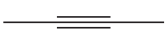
10.32 Starting with the compound or compounds indicated in each part and using any other needed reagents, outline syntheses of each of the following compounds. (You need not repeat steps carried out in earlier parts of this problem.)

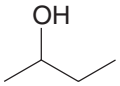
(a) CH_3CH_3 ⟶ 

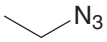
(b) CH_3CH_3 ⟶ 

(c) 

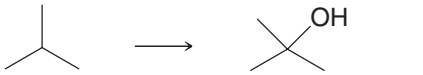
(d) 

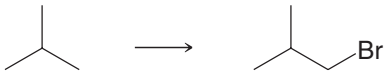
(e) CH_4 + $HC{\equiv}CH$ ⟶ 

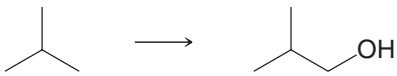
(f) CH_3CH_3 + $HC{\equiv}CH$ ⟶ 

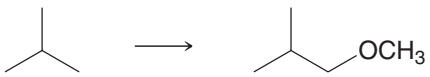
(g) CH_3CH_3 ⟶ 

10.33 Provide the reagents necessary for the following synthetic transformations. More than one step may be required.

(a) 

(b) 

(c) 

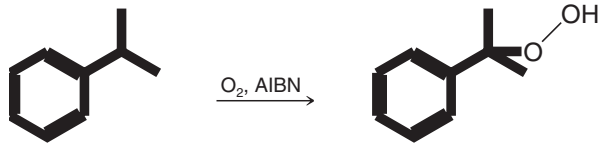
(d) 

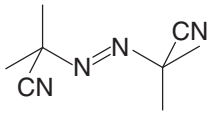
(e) 

(f) 

Challenge Problems

10.34 The following reaction is the first step in the industrial synthesis of acetone and phenol (C_6H_5OH). AIBN (2,2′-azobisisobutyronitrile) initiates radical reactions by breaking down to form two isobutyronitrile radicals and nitrogen gas. Using an isobutyronitrile radical to initiate the reaction, write a mechanism for the following process.

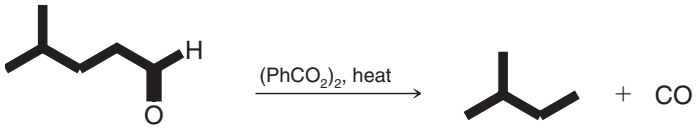




AIBN

10.35 In the radical chlorination of 2,2-dimethylhexane, chlorine substitution occurs much more rapidly at C5 than it does at a typical secondary carbon (e.g., C2 in butane). Consider the mechanism of radical polymerization and then suggest an explanation for the enhanced rate of substitution at C5 in 2,2-dimethylhexane.

10.36 Write a mechanism for the following reaction.

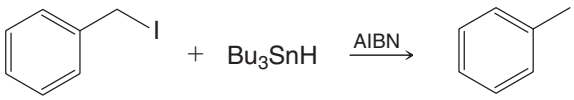


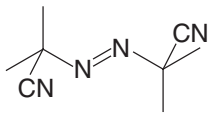
10.37 Hydrogen peroxide and ferrous sulfate react to produce hydroxyl radical (HO·), as reported in 1894 by English chemist H. J. H. Fenton. When *tert*-butyl alcohol is treated with HO· generated this way, it affords a crystalline reaction product **X**, mp 92°, which has these spectral properties:

MS: heaviest mass peak is at *m/z* 131
IR: 3620, 3350 (broad), 2980, 2940, 1385, 1370 cm^{-1}
^{1}H NMR: sharp singlets at δ 1.22, 1.58, and 2.95 (6:2:1 area ratio)
^{13}C NMR: δ 28 (CH_3), 35 (CH_2), 68 (C)

Draw the structure of **X** and write a mechanism for its formation.

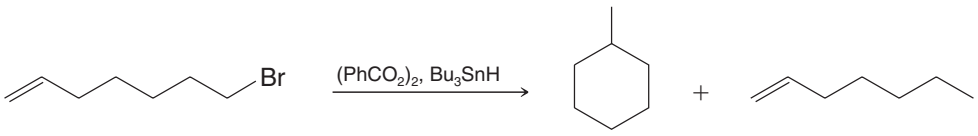
10.38 The halogen atom of an alkyl halide can be replaced by the hydrogen atom bonded to tin in tributyltin hydride (Bu_3SnH). The process, called dehalogenation, is a radical reaction, and it can be initiated by AIBN (2,2′-azobisisobutyronitrile). AIBN decomposes to form nitrogen gas and two isobutyronitrile radicals, which initiate the reaction. Write a mechanism for the reaction.





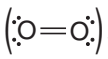
AIBN

10.39 Write a mechanism that accounts for the following reaction. Note that the hydrogen atom bonded to tin in tributyltin hydride is readily transferred in radical mechanisms.



(Major)

10.40 Molecular orbital calculations can be used to model the location of electron density from unpaired electrons in a radical. Open the molecular models on the book's website for the methyl, ethyl, and *tert*-butyl radicals. The gray wire mesh surfaces in these models represent volumes enclosing electron density from unpaired electrons. What do you notice about the distribution of unpaired electron density in the ethyl radical and *tert*-butyl radical, as compared to the methyl radical? What bearing does this have on the relative stabilities of the radicals in this series?

10.41 If one were to try to draw the simplest Lewis structure for molecular oxygen, the result might be the following (). However, it is known from the properties of molecular oxygen and experiments that O_2 contains two unpaired electrons, and therefore, the Lewis structure above is incorrect. To understand the structure of O_2, it is necessary to employ a molecular orbital representation. To do so, we will need to recall (1) the shapes of bonding and antibonding σ and π molecular orbitals, (2) that each orbital can contain a maximum of two electrons, (3) that molecular oxygen has 16 electrons in total, and (4) that the two unpaired electrons in oxygen occupy separate degenerate (equal-energy) orbitals. Now, open the molecular model on the book's website for oxygen and examine its molecular orbitals in sequence from the HOMO-7 orbital to the LUMO. [HOMO-7 means the seventh orbital in energy below the highest occupied molecular orbital (HOMO), HOMO-6 means the sixth below the HOMO, and so forth.] Orbitals HOMO-7 through HOMO-4 represent the $\sigma 1s$, $\sigma 1s^*$, $\sigma 2s$, and $\sigma 2s^*$ orbitals, respectively, each containing a pair of electrons.

(a) What type of orbital is represented by HOMO-3 and HOMO-2? [*Hint*: What types of orbitals are possible for second-row elements like oxygen, and which orbitals have already been used?]

(b) What type of orbital is HOMO-1? [*Hint*: The $\sigma 2s$ and $\sigma 2s^*$ orbitals are already filled, as are the HOMO-3 and HOMO-2 orbitals identified in part (b). What bonding orbital remains?]

(c) The orbitals designated HOMO and LUMO in O_2 have the same energy (they are degenerate), and each contains one of the unpaired electrons of the oxygen molecule. What type of orbitals are these?

Learning Group Problems

1. **(a)** Draw structures for all organic products that would result when an *excess* of *cis*-1,3-dimethylcyclohexane reacts with Br_2 in the presence of heat and light. Use three-dimensional formulas to show stereochemistry.

(b) Draw structures for all organic products that would result when an *excess* of *cis*-1,3-dimethylcyclohexane reacts with Cl_2 in the presence of heat and light. Use three-dimensional formulas to show stereochemistry.

(c) As an alternative, use *cis*-1,2-dimethylcyclohexane to answer parts (a) and (b) above.

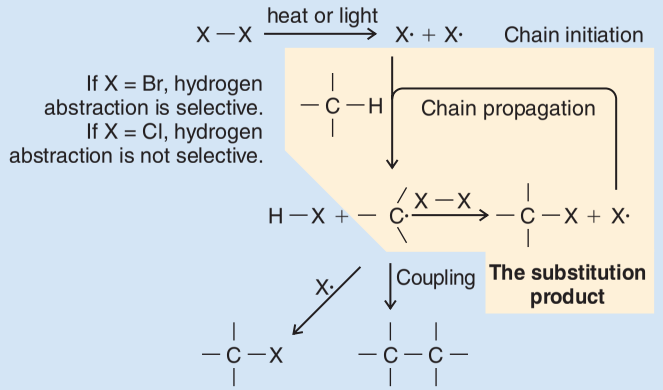
2. **(a)** Propose a synthesis of 2-methoxypropene starting with propane and methane as the sole source for carbon atoms. You may use any other reagents necessary. Devise a retrosynthetic analysis first.

(b) 2-Methoxypropene will form a polymer when treated with a radical initiator. Write the structure of this polymer and a mechanism for the polymerization reaction assuming a radical mechanism initiated by a diacyl peroxide.

CONCEPT MAP

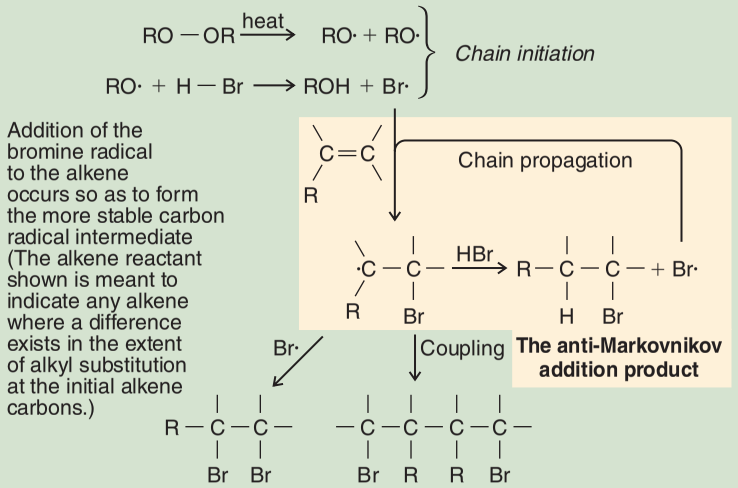
Mechanism Review of Radical Reactions

Radical Halogenation of Alkanes



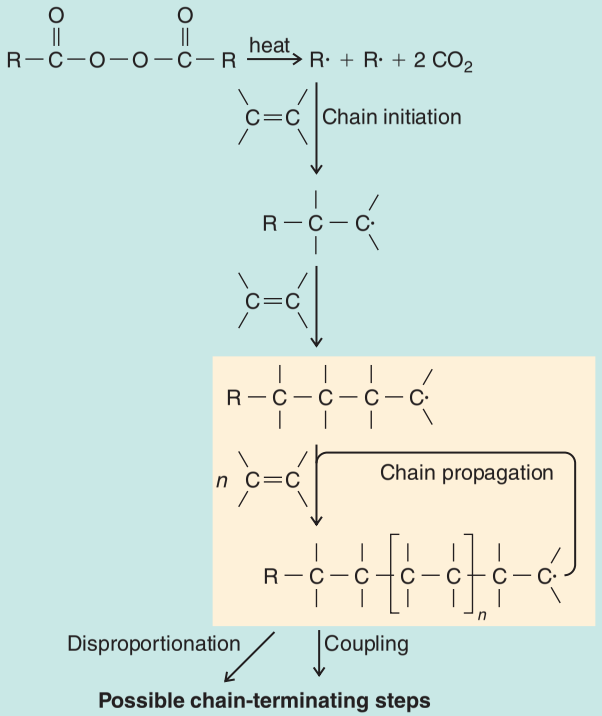
Some possible chain-terminating steps

Anti-Markovnikov Addition of HBr to Alkenes



Some possible chain-terminating steps

Radical Polymerization



Possible chain-terminating steps