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.
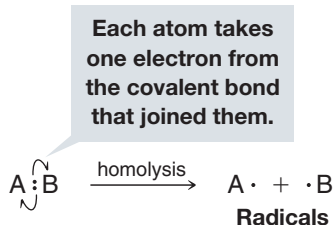
IN THIS CHAPTER WE WILL CONSIDER:

- the properties of radicals, their formation, and their reactivity
- significant radical-based reactions in nature

[WHY DO THESE TOPICS MATTER?] At the end of the chapter, we will show that there is a natural molecule that combines radical chemistry and molecular shape in a way that can cause cell death. Chemists have used this knowledge to fashion a few anticancer drugs.

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**):

> **Each atom takes one electron from the covalent bond that joined them.**
>
> $$A \colon B \xrightarrow{\text{homolysis}} A\cdot \; + \; \cdot B$$
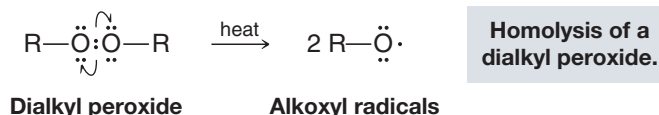> **Radicals**

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.
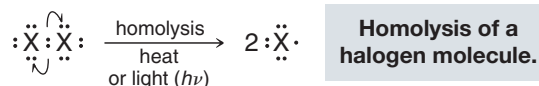
10.1A Production of Radicals

- 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:

$$R\!-\!\ddot{\text{O}}\colon\!\ddot{\text{O}}\!-\!R \xrightarrow{\text{heat}} 2\,R\!-\!\ddot{\text{O}}\cdot$$

Dialkyl peroxide   **Alkoxyl radicals**

Homolysis of a dialkyl peroxide.

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:

$$\colon\!\ddot{X}\colon\!\ddot{X}\colon \xrightarrow[\substack{\text{heat} \\ \text{or light } (h\nu)}]{\text{homolysis}} 2\colon\!\ddot{X}\cdot$$

Homolysis of a halogen molecule.

The products of this homolysis are halogen atoms, and because halogen atoms contain an unpaired electron, they are radicals.
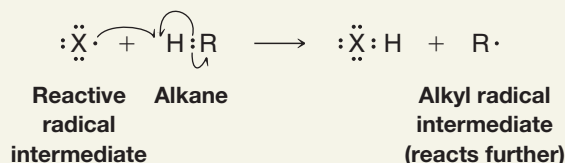
10.1B Reactions of Radicals

- 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. To abstract an atom means to remove an atom by homolytic bond cleavage as the atom forms a bond with another radical. 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, $R\cdot$, which goes on to react further, as we shall see in this chapter.
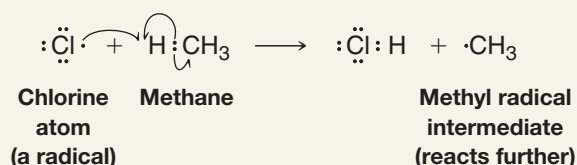
A MECHANISM FOR THE REACTION — **Hydrogen Atom Abstraction**
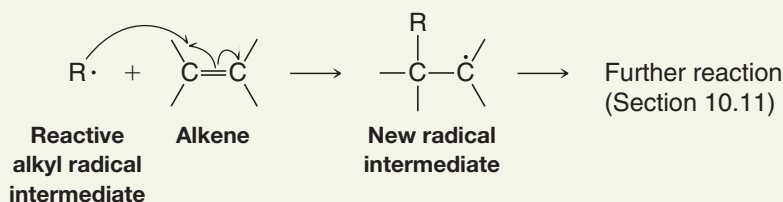
General Reaction

$$:\ddot{X}\cdot \ + \ H:R \ \longrightarrow \ :\ddot{X}:H \ + \ R\cdot$$

| Reactive radical intermediate | Alkane | | Alkyl radical intermediate (reacts further) |

Specific Example

$$:\ddot{Cl}\cdot \ + \ H:CH_3 \ \longrightarrow \ :\ddot{Cl}:H \ + \ \cdot CH_3$$

| Chlorine atom (a radical) | Methane | | Methyl radical intermediate (reacts further) |

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**

$$R\cdot \ + \ C{=}C \ \longrightarrow \ \overset{R}{\underset{|}{-C}}{-}\dot{C} \ \longrightarrow \ \text{Further reaction (Section 10.11)}$$

| Reactive alkyl radical intermediate | Alkene | New radical intermediate | |

THE CHEMISTRY OF... Acne Medications

It turns out that although certain peroxides are great at initiating radical reactions, peroxy radicals also have many valuable uses on their own. For example, benzoyl peroxide is an active ingredient typically found in many acne medications that breaks apart and forms radicals through the warmth of our skin and exposure to light. These radicals can then kill the bacteria that cause break-outs.

The same compound is also used as a whitening and bleaching agent. As we will see in Chapter 13, many colored compounds possess double bonds in conjugation; the benzoyl peroxide radicals can add to those bonds, break their conjugation, and remove their color to leave behind new white materials. If you have ever wiped your face after using an acne medication with a colored towel, you may already have seen these effects!

Benzoyl peroxide
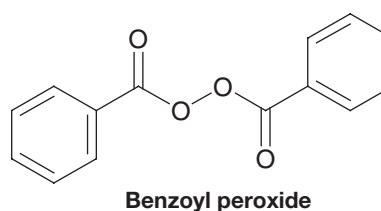
10.2 HOMOLYTIC BOND DISSOCIATION ENERGIES (*DH°*)

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· + H· $\longrightarrow$ H—H $\Delta H° = -436$ kJ mol^{-1}

Cl· + Cl· $\longrightarrow$ Cl—Cl $\Delta H° = -243$ kJ mol^{-1}
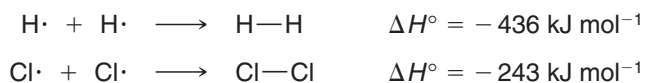
> **Bond formation is an exothermic process: $\Delta H°$ is negative.**

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· + H· $\Delta H° = +436$ kJ mol^{-1}

Cl—Cl $\longrightarrow$ Cl· + Cl· $\Delta H° = +243$ kJ mol^{-1}
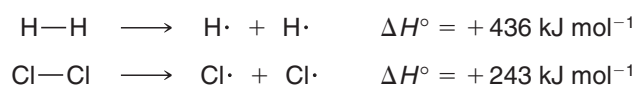
> **Bond breaking is an endothermic process: $\Delta H°$ is positive.**

- 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

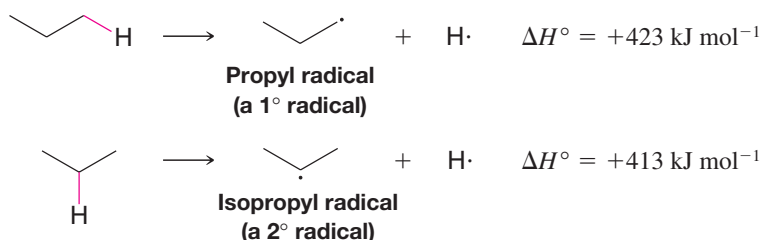(*DH°* = 436 kJ mol^{-1})   (*DH°* = 243 kJ mol^{-1})

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.

10.2A 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})
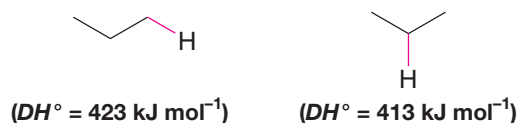
This means that for the reaction in which the designated C—H bonds are broken homolytically, the values of $\Delta H°$ are those given here.

Propyl radical
(a 1° radical)   + H· $\Delta H° = +423$ kJ mol^{-1}

Isopropyl radical
(a 2° radical)   + H· $\Delta H° = +413$ kJ mol^{-1}

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}.

**TABLE 10.1 SINGLE-BOND HOMOLYTIC DISSOCIATION ENERGIES (*DH°*) AT 25 °C^a**

A:B $\longrightarrow$ A· + B·					
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		
CH_3—OH	387	$(CH_3)_2CHCH_2$—H	422	$C_6H_5\overset{\displaystyle O}{\overset{\|}{C}}$—$\overset{\displaystyle O}{\overset{\|}{O}C}C_6H_5$	139
CH_3—OCH_3	348	$(CH_3)_3C$—H	400	CH_3CH_2O—OCH_3	184
CH_3CH_2—H	421	$(CH_3)_3C$—Cl	349	CH_3CH_2O—H	431
CH_3CH_2—F	444	$(CH_3)_3C$—Br	292		
CH_3CH_2—Cl	353	$(CH_3)_3C$—I	227	$CH_3\overset{\displaystyle O}{\overset{\|}{C}}$—H	364
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. Data from CRC Handbook of Chemistry and Physics, Updated 3rd Electronic Edition; Lide, David R., ed. DH° values were obtained directly or calculated from heat of formation (H$_f$) data using the equation DH° [A-B]= H$_f$ [A.] + H$_f$ [B.] - H$_f$ [A-B].

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:


tert-Butyl radical (a 3° radical) + H· $\Delta H° = +400 \text{ kJ mol}^{-1}$

Isobutyl radical (a 1° radical) + H· $\Delta H° = +422 \text{ kJ mol}^{-1}$
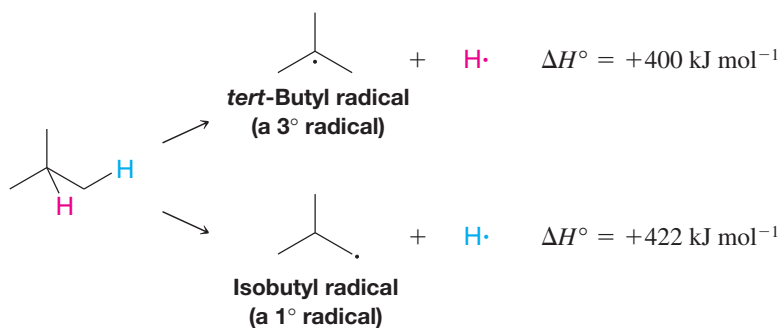
Here we find (Fig. 10.1*b*) that the difference in stability of the two radicals is even larger. The tertiary radical is more stable than the primary radical by 22 kJ mol^{-1}.
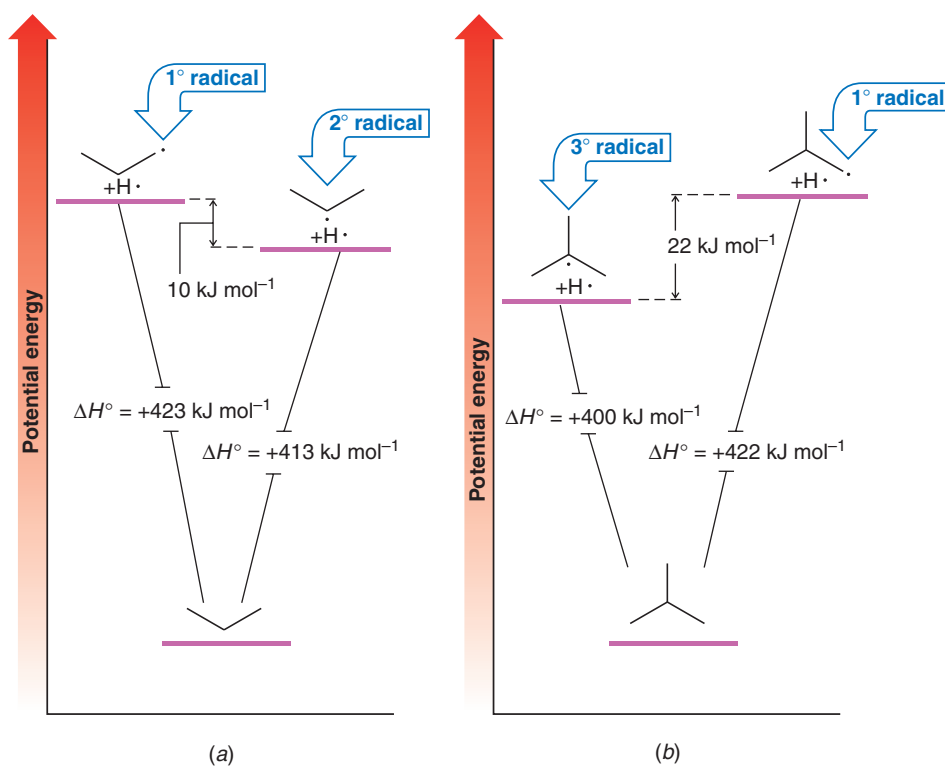
FIGURE 10.1 (*a*) Comparison of the potential energies of the propyl radical (+H·) and the isopropyl radical (+H·) relative to propane. The isopropyl radical (a 2° radical) is more stable than the 1° radical by 10 kJ mol^{-1}. (*b*) Comparison of the potential energies of the *tert*-butyl radical (+H·) and the isobutyl radical (+H·) relative to isobutane. The 3° radical is more stable than the 1° radical by 22 kJ mol^{-1}.

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.**

Tertiary (3°) > **Secondary (2°)** > **Primary (1°)** > **Methyl**
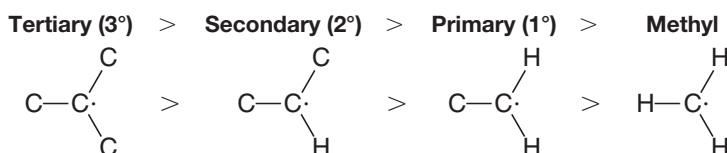
- **The order of stability of alkyl radicals is the same as for carbocations** (Section 6.11B).

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.

Helpful Hint

Knowing the relative stability of radicals is important for predicting reaction pathways.

Classify each of the following radicals as being 1°, 2°, or 3°, and rank them in order of decreasing stability.

A   **B**   **C**
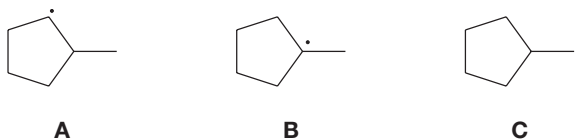
STRATEGY AND ANSWER: We examine the carbon bearing the unpaired electron in each radical to classify the radical as to its type. **B** is a tertiary radical (the carbon bearing the unpaired electron is tertiary) and is, therefore, most stable. **C** is a primary radical and is least stable. **A**, being a secondary radical, falls in between. The order of stability is **B** > **A** > **C**.

List the following radicals in order of decreasing stability:

·CH$_3$
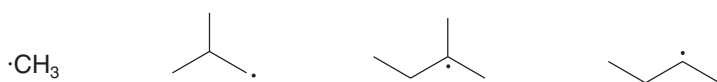
10.3 REACTIONS OF ALKANES WITH HALOGENS

- 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.
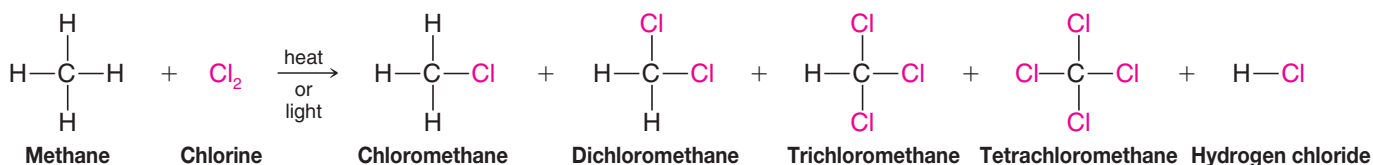
$$R-H + X_2 \longrightarrow R-X + HX$$

- 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 due to unfavorable reaction energetics.

10.3A Multiple Halogen Substitution

One complicating factor of alkane halogenations is that multiple substitutions almost always occur unless we use an excess of the alkane (see Solved Problem 10.2). 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** $\xrightarrow[\text{light}]{\text{heat or}}$ **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:
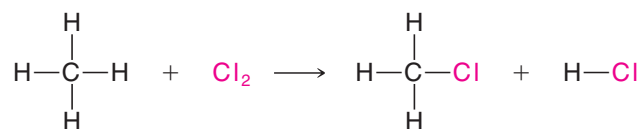
As the reaction progresses, however, the concentration of chloromethane in the mixture increases, and a second substitution reaction begins to occur. Chloromethane reacts with chlorine to produce dichloromethane:
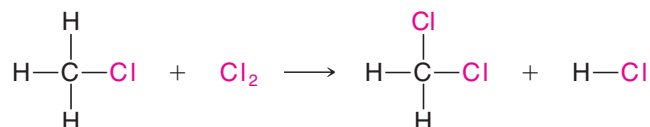
The dichloromethane produced can then react to form trichloromethane, and trichloromethane, as it accumulates in the mixture, can react with chlorine to produce tetrachloromethane. Each time a substitution of —Cl for —H takes place, a molecule of H—Cl is produced.

●●● 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 monochlorinated 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**   **tert-Butyl**
                          (48%)   **chloride (29%)**
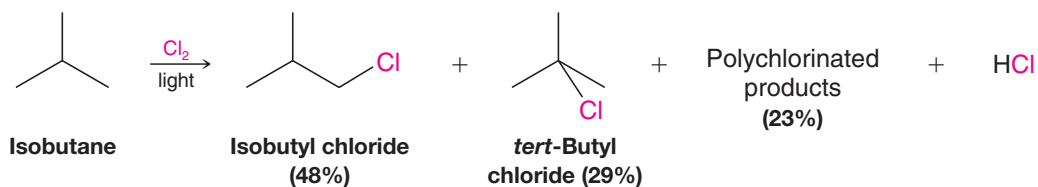
Helpful Hint

Chlorination is unselective.

- 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.
- An exception is the halogenation of an alkane (or cycloalkane) whose hydrogen atoms *are all equivalent* (i.e., homotopic). [Homotopic hydrogen atoms are defined as those that on replacement by some other group (e.g., chlorine) yield the same compound (Section 9.8).]

Neopentane, for example, can form only one monohalogenation product, and the use of a large excess of neopentane minimizes polychlorination:

Neopentane   **Neopentyl chloride**
(excess)
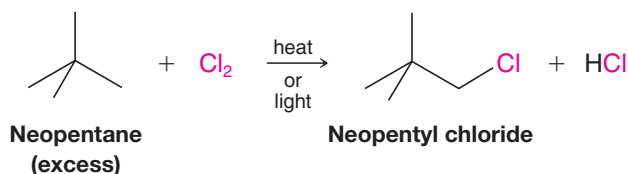
- Bromine is generally less reactive toward alkanes than chlorine, and bromine is *more selective* in the site of attack when it does react.

We shall examine the selectivity of bromination further in Section 10.5A.

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**.

$$CH_4 + Cl_2 \longrightarrow CH_3Cl + HCl \ (+ \ CH_2Cl_2, \ CHCl_3, \ and \ CCl_4)$$

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.

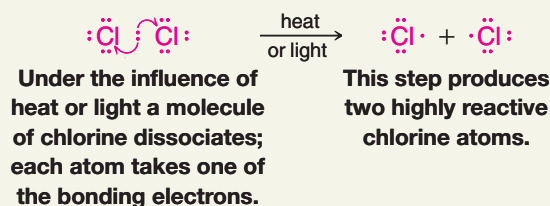## A MECHANISM FOR THE REACTION — Radical Chlorination of Methane

Reaction

$$CH_4 + Cl_2 \xrightarrow[\text{or light}]{\text{heat}} CH_3Cl + HCl$$
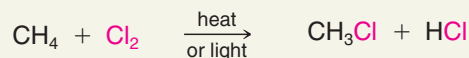
Mechanism

Chain Initiation

Step 1: Halogen dissociation

$$:\ddot{C}l \frown \ddot{C}l: \xrightarrow[\text{or light}]{\text{heat}} :\ddot{C}l\cdot \ + \ \cdot\ddot{C}l:$$

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.

(mechanism continues on the next page)

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.
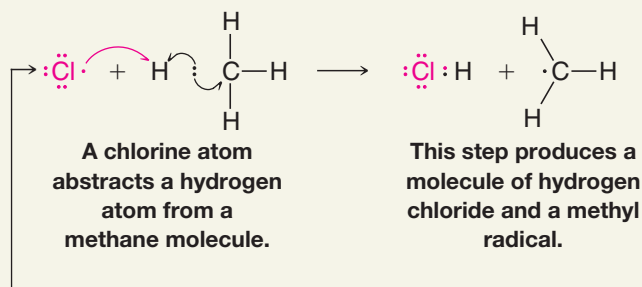
Step 3: Halogen abstraction

A methyl radical abstracts a chlorine atom from a chlorine molecule.

This step produces a molecule of chloromethane 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 the text).
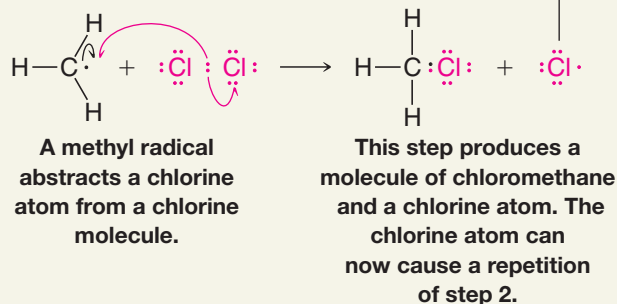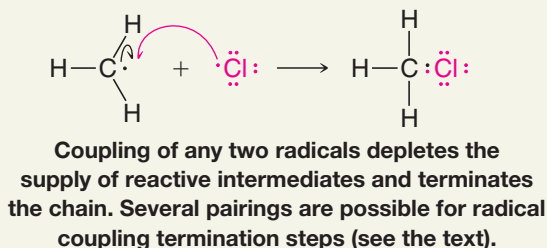
> **Helpful Hint**
>
> *Remember:* These conventions are used in illustrating reaction mechanisms in this text.
>
> 1. Curved arrows ⌢ or ⌢ always show the direction of movement of electrons.
> 2. Single-barbed arrows ⌢ show the attack (or movement) of an unpaired electron.
> 3. Double-barbed arrows ⌢ 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*

$$\text{Step 1} \qquad Cl_2 \xrightarrow[\text{or light}]{\text{heat}} 2\ Cl\cdot$$
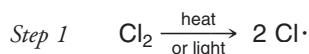
Chain Propagation: *reaction and regeneration of radicals*

$$\text{Step 2} \qquad CH_4 + Cl\cdot \longrightarrow \cdot CH_3 + H{-}Cl$$

$$\text{Step 3} \qquad \cdot CH_3 + Cl_2 \longrightarrow CH_3Cl + Cl\cdot$$
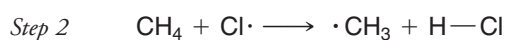
The chain nature of the reaction accounts for the observation that the light-promoted reaction is highly efficient. The presence of a relatively few atoms of chlorine at any given moment is all that is needed to cause the formation of many thousands of molecules of chloromethane.

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)
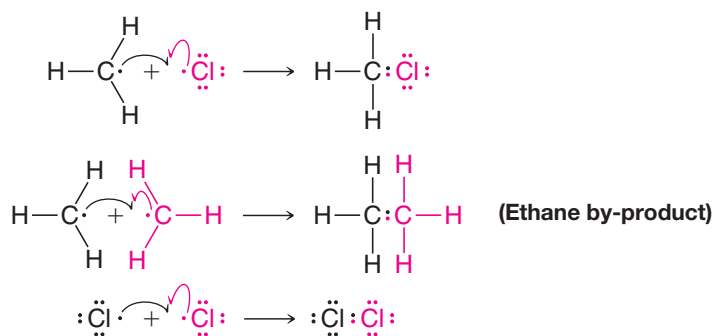
Our radical mechanism also explains how the reaction of methane with chlorine produces the more highly halogenated products, CH_2Cl_2, $CHCl_3$, and CCl_4 (as well as additional HCl). As the reaction progresses, chloromethane (CH_3Cl) accumulates in the mixture and its hydrogen atoms, too, are susceptible to abstraction by chlorine. Thus chloromethyl radicals are produced that lead to dichloromethane (CH_2Cl_2).

**Side Reactions:** *multihalogenated by-product formation*

(Dichloromethane)
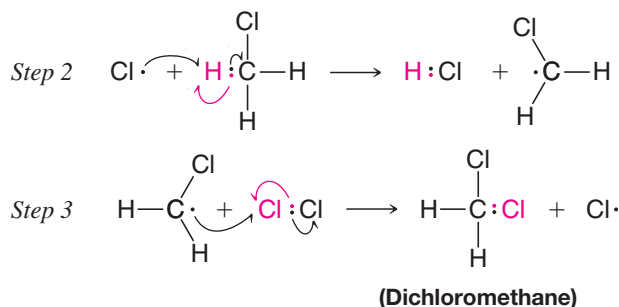
Then step 2 is repeated, then step 3 is repeated, and so on. Each repetition of step 2 yields a molecule of HCl, and each repetition of step 3 yields a molecule of CH_2Cl_2.

●●● **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:

$$2 \cdot CH_3 \longrightarrow CH_3 : CH_3$$
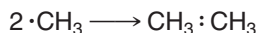
The ethane byproduct formed by coupling then reacts with chlorine in a radical halogenation reaction (see Section 10.5) to form chloroethane.

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.

•••

PRACTICE PROBLEM 10.2 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?

•••

PRACTICE PROBLEM 10.3 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.)

•••

PRACTICE PROBLEM 10.4 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 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:

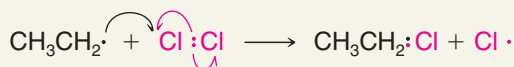## A MECHANISM FOR THE REACTION — **Radical Halogenation of Ethane**

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

$$CH_3CH_2{\cdot} + Cl{:}Cl \longrightarrow CH_3CH_2{:}Cl + Cl\cdot$$
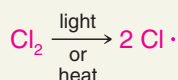
Chain propagation continues with steps 2, 3, 2, 3, and so on.

Chain Termination

$$CH_3CH_2{\cdot} + {\cdot}Cl \longrightarrow CH_3CH_2{:}Cl$$

$$CH_3CH_2{\cdot} + {\cdot}CH_2CH_3 \longrightarrow CH_3CH_2{:}CH_2CH_3$$

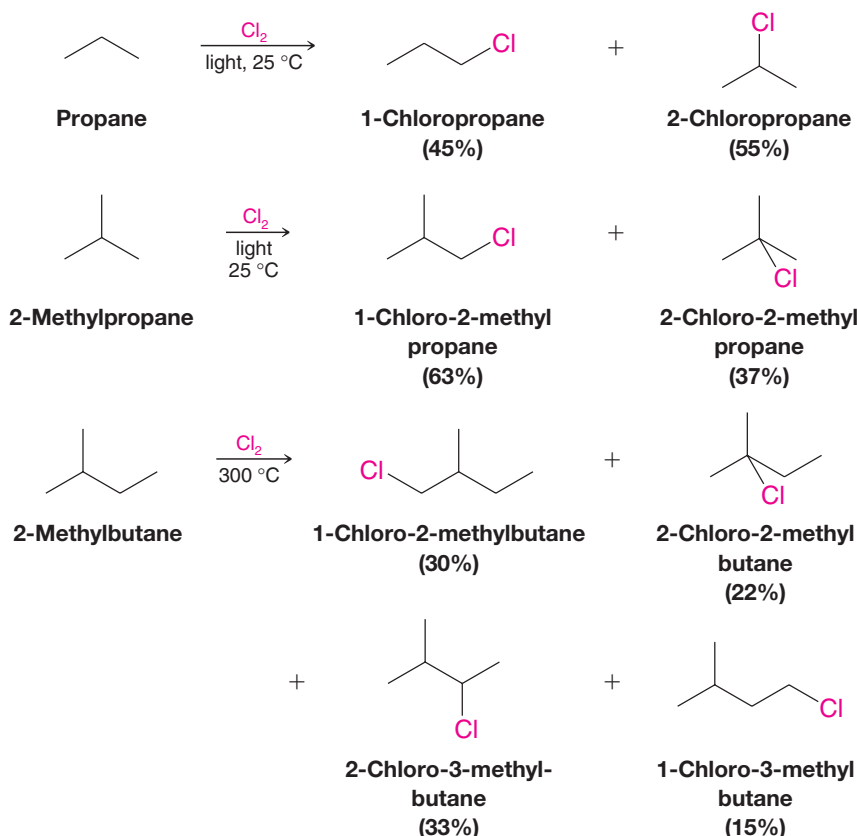$$Cl{\cdot} + {\cdot}Cl \longrightarrow Cl{:}Cl$$

•••
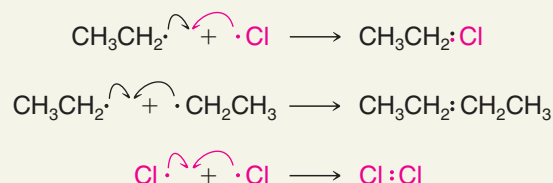
PRACTICE PROBLEM 10.5 When ethane is chlorinated, 1,1-dichloroethane and 1,2-dichloroethane, as well as more highly chlorinated ethanes, are formed in the mixture (see Section 10.3A). Write chain reaction mechanisms accounting for the formation of 1,1-dichloroethane and 1,2-dichloroethane.

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.

These examples show the nonselectivity of chlorination.

Propane → 1-Chloropropane (45%) + 2-Chloropropane (55%)

$\xrightarrow[\text{light, 25 °C}]{\text{Cl}_2}$

> **Helpful Hint**
>
> Chlorination is not selective.

2-Methylpropane → 1-Chloro-2-methyl propane (63%) + 2-Chloro-2-methyl propane (37%)

$\xrightarrow[\substack{\text{light}\\ \text{25 °C}}]{\text{Cl}_2}$

2-Methylbutane $\xrightarrow[\text{300 °C}]{\text{Cl}_2}$ 1-Chloro-2-methylbutane (30%) + 2-Chloro-2-methyl butane (22%)

+ 2-Chloro-3-methyl-butane (33%) + 1-Chloro-3-methyl butane (15%)

The ratios of products that we obtain from chlorination reactions of higher alkanes are not identical to 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 Practice Problem 10.6).
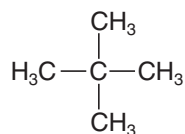
PRACTICE PROBLEM 10.6

(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?
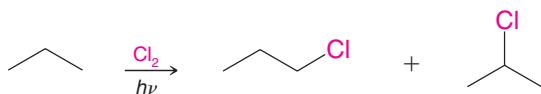
(b) What percentages of 1-chloro-2-methylpropane and 2-chloro-2-methylpropane would you expect from the chlorination of 2-methylpropane if the 1° and 3° hydrogen atoms were equally reactive?
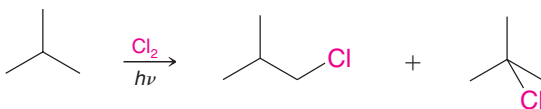
(c) Compare these calculated answers with the results actually obtained (above in Section 10.5) and justify the assertion that the order of reactivity of the hydrogen atoms is 3° > 2° > 1°.

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 does not discriminate among the different types of hydrogen atoms in a way that makes chlorination of higher alkanes a generally useful laboratory synthesis.

●●● 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 (homotopic), so that replacing any one of them leads to the same product. The only five-carbon alkane for which this is true is neopentane.

$$H_3C-\overset{\overset{\displaystyle CH_3}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{C}}-CH_3$$

●●●

PRACTICE PROBLEM 10.7 Chlorination reactions of certain alkanes can be used for laboratory preparations. Examples are the preparation of chlorocyclopropane from cyclopropane and chlorocyclobutane from cyclobutane.

(excess)

(excess)
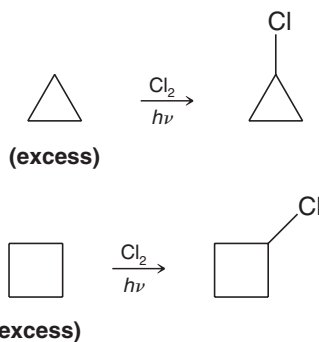
What structural feature of these molecules makes this possible?

●●●

PRACTICE PROBLEM 10.8 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}

10.5A Selectivity of Bromine

Bromine shows a much greater ability to discriminate among the different types of hydrogen atoms.

- Bromine is less reactive than chlorine toward alkanes in general but bromine is more *selective* in the site of attack.
- Bromination is selective for substitution where the most stable radical intermediate can be formed.

The reaction of 2-methylpropane and bromine, for example, gives almost exclusive replacement of the tertiary hydrogen atom:

$$\xrightarrow[h\nu,\ 127\ °C]{Br_2}$$

(>99%)   (trace)
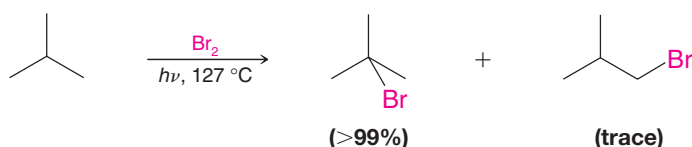
A very different result is obtained when 2-methylpropane reacts with chlorine:

$$\xrightarrow[h\nu,\ 25\ °C]{Cl_2}$$

(37%)   (63%)
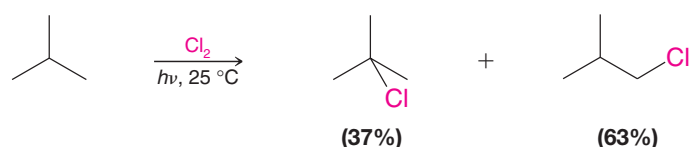
Fluorine, being much more reactive than chlorine, *is even less selective than chlorine.* Because the **energy of activation** for the abstraction of any type of hydrogen by a fluorine atom is low, there is very little difference in the rate at which a 1°, 2°, or 3° hydrogen reacts with fluorine. Reactions 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.

(a)

(b)

FIGURE 10.2 (*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.

10.6 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. 10.2).

10.7 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**.
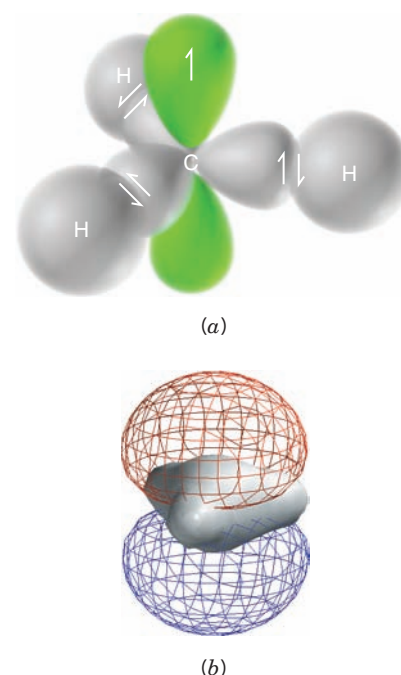
This will always be true in the absence of any chiral influence on the reaction such as an enzyme or the use of a chiral reagent or solvent.

Let us examine a reaction that illustrates this principle, the **radical** chlorination of pentane:

$$\xrightarrow[(achiral)]{Cl_2}$$

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
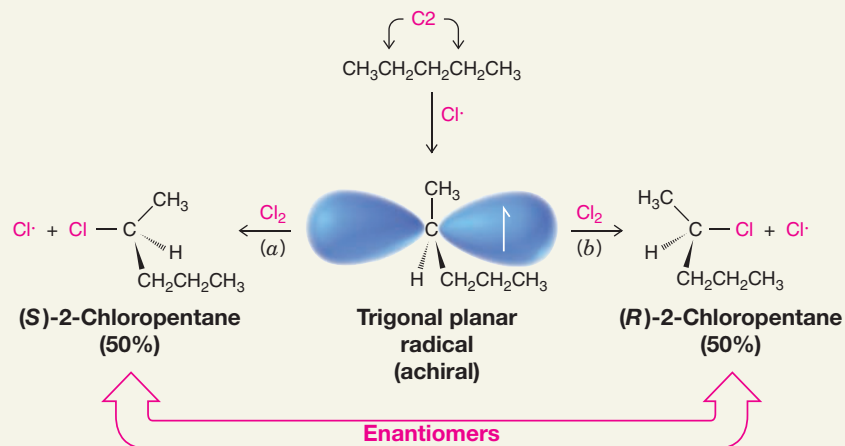
Abstraction of a hydrogen atom from C2 produces a trigonal planar radical that is achiral. This radical then reacts with chlorine at either face [by path (*a*) or path (*b*)]. Because the radical is achiral, the probability of reaction by either path is the same; therefore, the two enantiomers are produced in equal amounts, and a racemic form of 2-chloropentane results.

We can also say that the C2 hydrogens of pentane are **enantiotopic** because enantiomers are formed by reaction at each C2 hydrogen.

10.7A 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.) They each resulted by substitution of one of the **diastereotopic** hydrogens at C3. 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
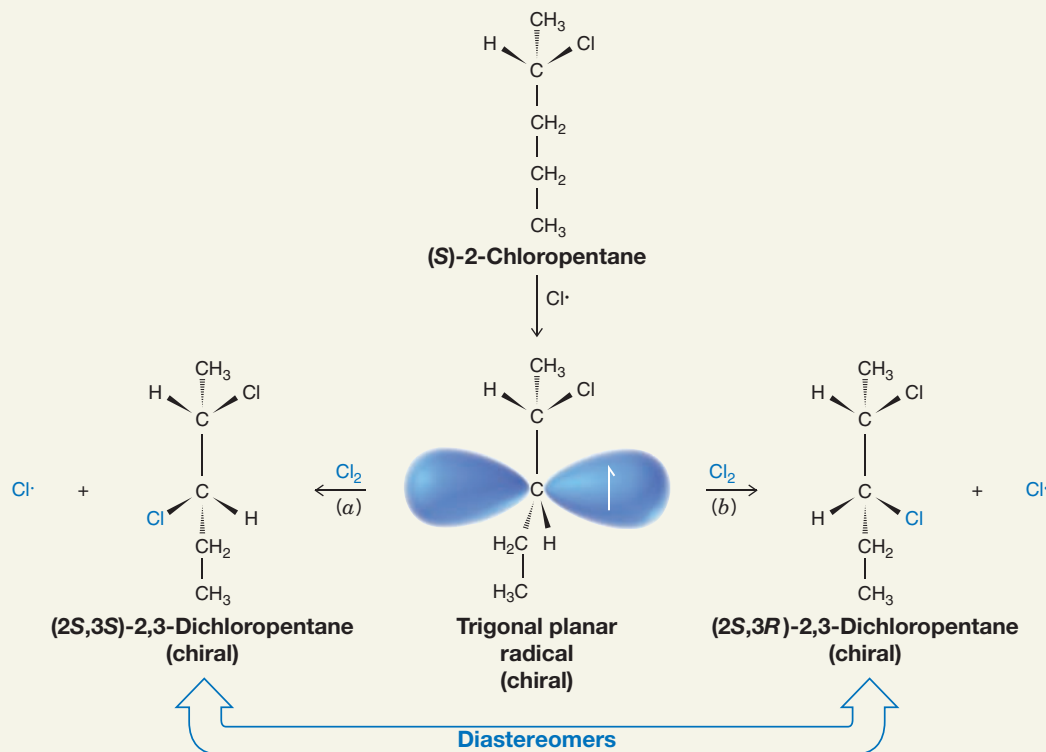
Abstraction of a hydrogen atom from C3 of (*S*)-2-chloropentane produces a radical that is chiral (it contains a chirality center at C2). This chiral radical can then react with chlorine at one face [path (*a*)] to produce (*2S, 3S*)-2,3-dichloropentane and the other face [path (*b*)] to yield (*2S, 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.

● ● ●

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?

PRACTICE PROBLEM 10.9

●●● **SOLVED PROBLEM 10.5**

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.

●●●
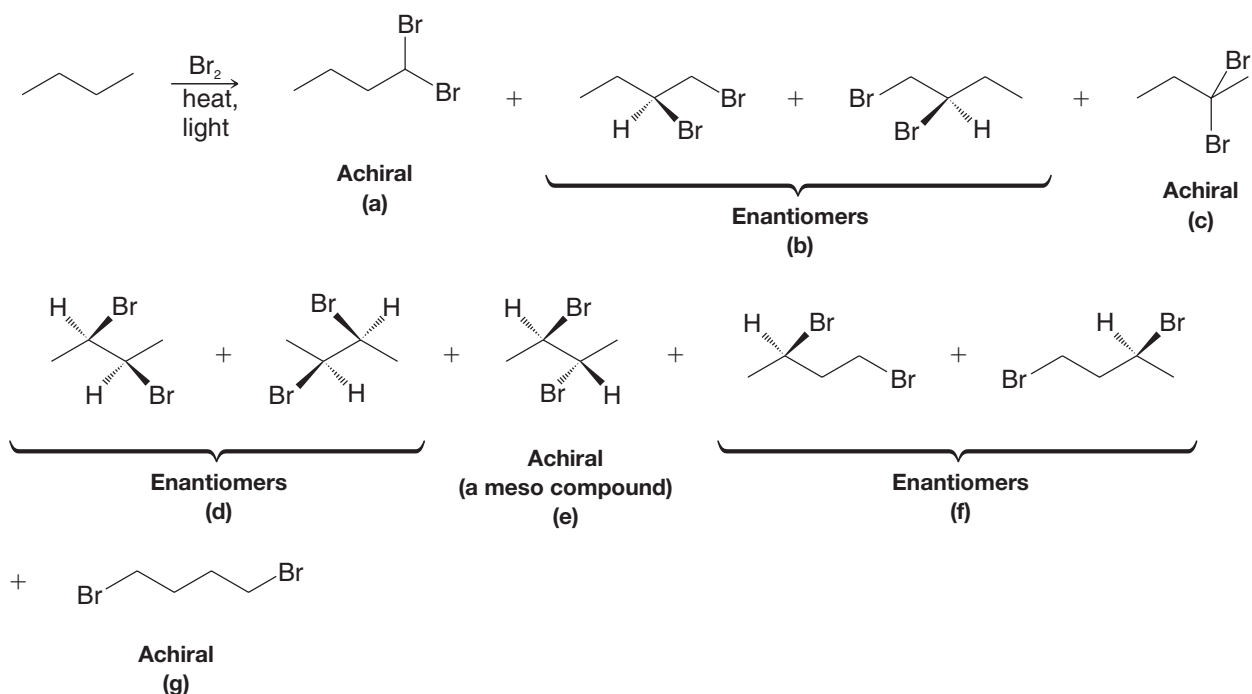
PRACTICE PROBLEM 10.10 Consider the monochlorination of 2-methylbutane.
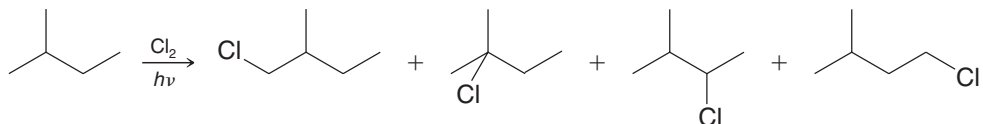
(a) Assuming that the product mixture was subjected to fractional distillation, which fractions, if any, would show optical activity? **(b)** Could any of these fractions be resolved, theoretically, into enantiomers? **(c)** Could the components of each fraction from the distillation be identified on 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?
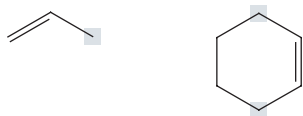
10.8 ALLYLIC SUBSTITUTION AND ALLYLIC RADICALS

- An atom or group that is bonded to an sp^3-hybridized carbon adjacent to an alkene double bond is called an **allylic group**. The group is said to be bonded at the **allylic position**.

The following are some examples.

| The hydrogen atoms bonded to the highlighted carbons below are allylic hydrogens.	The chlorine and bromine atoms below are bonded at allylic positions.
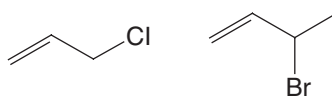
Allylic hydrogens are especially reactive in radical substitution reactions. We can synthesize allylic halides by substitution of allylic hydrogens. For example, when propene reacts with bromine or chlorine at high temperatures or under radical conditions where the concentration of the halogen is small, the result is **allylic substitution**.
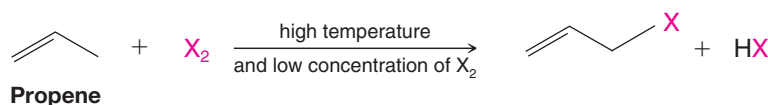
Propene

> At high temperature (or in the presence of a radical initiator) and low concentration of X_2 a substitution reaction occurs.

On the other hand, when propene reacts with bromine or chlorine at low temperatures, an addition reaction of the type we studied in Chapter 8 occurs.
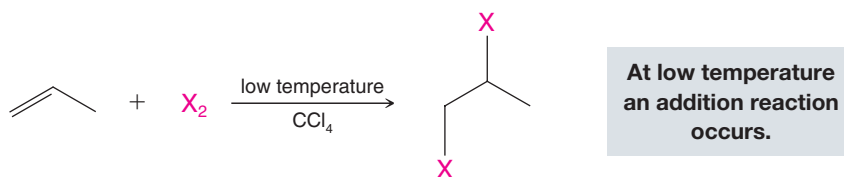
> At low temperature an addition reaction occurs.

To bias the reaction toward allylic substitution we need to use reaction conditions that favor formation of radicals and that provide a low but steady concentration of halogen.

10.8A Allylic Chlorination (High Temperature)

Propene undergoes allylic chlorination when propene and chlorine react in the gas phase at 400 °C.

Propene + Cl_2 →(400 °C, gas phase) **3-Chloropropene (allyl chloride)** + HCl
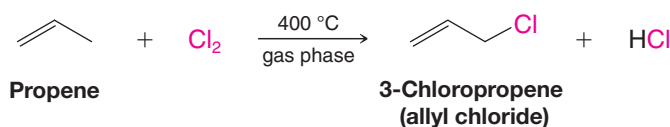
The mechanism for allylic substitution is the same as the chain mechanism for alkane **halogenations** that we saw earlier in the chapter. In the chain-initiating step, the chlorine molecule dissociates into chlorine atoms.

Chain-Initiating Step

$$:\ddot{\underset{..}{Cl}} \frown \frown \ddot{\underset{..}{Cl}}: \longrightarrow 2:\ddot{\underset{..}{Cl}}\cdot$$
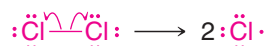
In the first chain-propagating step the chlorine atom abstracts one of the allylic hydrogen atoms. The radical that is produced in this step is called an **allylic radical**.

First Chain-Propagating Step

An allylic radical
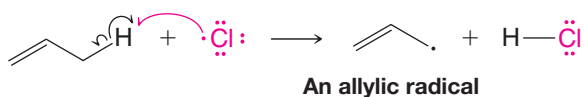
In the second chain-propagating step the allyl radical reacts with a molecule of chlorine.

Second Chain-Propagating Step

Allyl chloride

This step results in the formation of a molecule of allyl chloride (2-chloro-1-propene) and a chlorine atom. The chlorine atom then brings about a repetition of the first chain-propagating step. The chain reaction continues until the usual chain-terminating steps (see Section 10.4) consume the radicals.

10.8B Allylic Bromination with *N*-Bromosuccinimide (Low Concentration of Br$_2$)

Propene undergoes allylic bromination when it is treated with *N*-bromosuccinimide (NBS) in the presence of peroxides or light:

| *N*-Bromosuccinimide (NBS) | 3-Bromopropene (allyl bromide) | Succinimide |
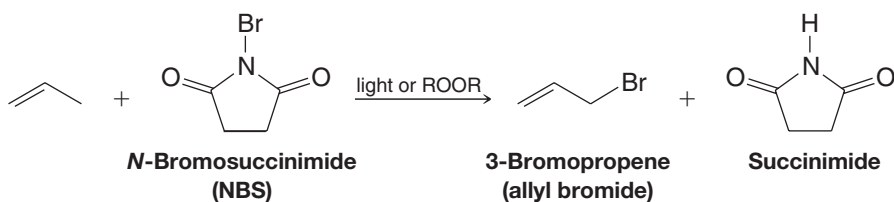
The reaction is initiated by the formation of a small amount of Br$\cdot$ (possibly formed by dissociation of the N—Br bond of the NBS). The main propagation steps for this reaction are the same as for allylic chlorination (Section 10.2A):
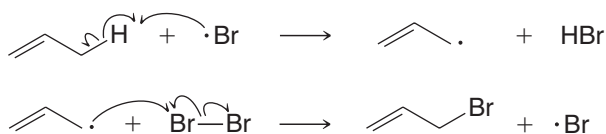

N-Bromosuccinimide is a solid that provides a constant but very low concentration of bromine in the reaction mixture. It does this by reacting very rapidly with the HBr formed in the substitution reaction. Each molecule of HBr is replaced by one molecule of Br$_2$.
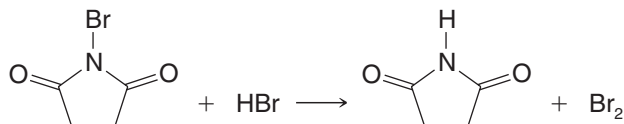
Under these conditions, that is, *in a nonpolar solvent and with a very low concentration of bromine*, very little bromine adds to the double bond; it reacts by substitution and replaces an allylic hydrogen atom instead.
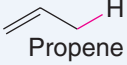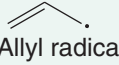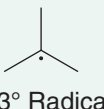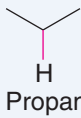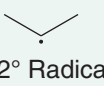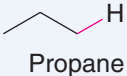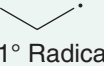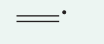
The following reaction with cyclohexene is another example of allylic bromination with NBS:

82–87%
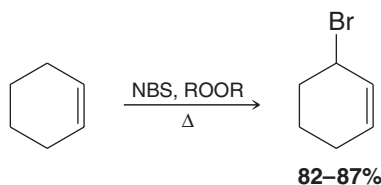
● In general, NBS is a good reagent to use for allylic bromination.

10.8C Allylic Radicals Are Stabilized by Electron Delocalization

Let us examine the bond dissociation energy of an allylic carbon–hydrogen bond and compare it with the bond dissociation energies of other carbon–hydrogen bonds.

See Table 10.1 for a list of additional bond dissociation energies.

We see that an allylic carbon–hydrogen bond of propene is broken with greater ease than even the tertiary carbon–hydrogen bond of isobutane and with far greater ease than a vinylic carbon–hydrogen bond:
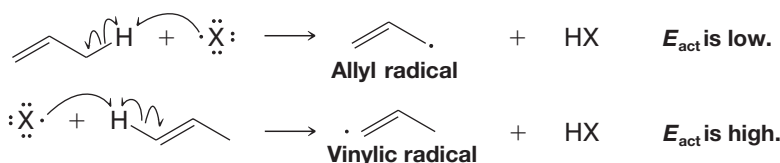
● The ease with which an allylic carbon–hydrogen bond is broken means that relative to primary, secondary, tertiary, and vinylic free radicals an allylic radical is the *most stable* (Fig. 10.3):

Relative stability: allylic or allyl > 3° > 2° > 1° > vinyl or vinylic

FIGURE 10.3 The relative stability of the allyl radical compared to 1°, 2°, 3°, and vinyl radicals. (The stabilities of the radicals are relative to the hydrocarbon from which each was formed, and the overall order of stability is allyl > 3° > 2° > 1° > vinyl.)
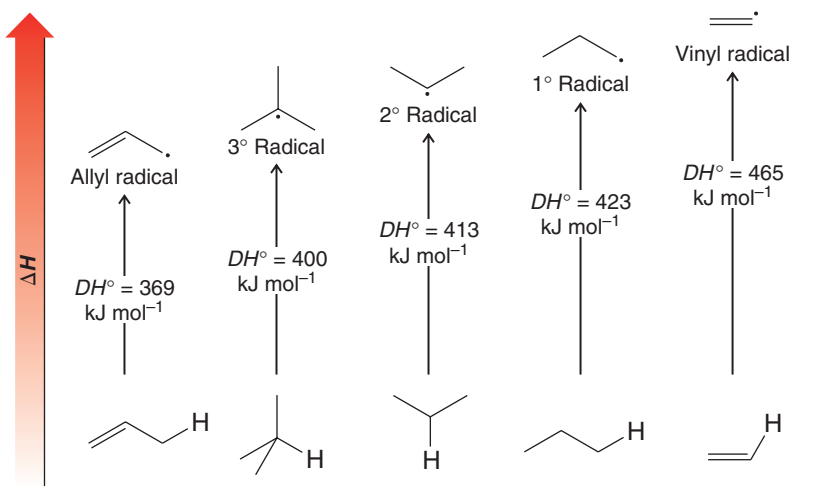
The reason that allylic radicals are more stable than alkyl radicals is due to electron delocalization. For example, we can draw the following contributing resonance structures and the corresponding resonance hybrid for the allylic radical from propene.

| **Contributing Resonance Structures** | **Resonance Hybrid** |

Resonance delocalization of allylic radicals means that bonding of the halogen can occur at either end of an allylic radical. With the allylic radical from propene the two possible substitutions are the same, but unsymmetrical allylic radicals lead to products that are constitutional isomers.

PRACTICE PROBLEM 10.11 **(a)** What monobromo allylic substitution products would result from reaction of each of the following compounds with NBS in the presence of peroxides and/or light? **(b)** In the case of isomeric products for any reaction, which would you predict to be the most stable based on the double bond in the product? **(c)** Draw the resonance hybrid(s) for the allylic radical that would be involved in each reaction.

(i)   **(ii)**   **(iii)**
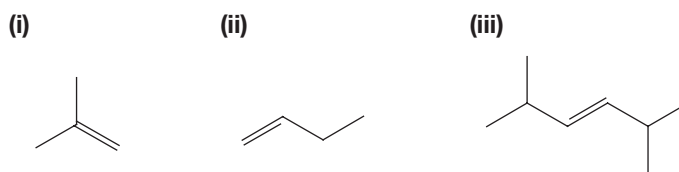
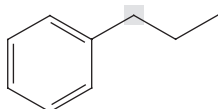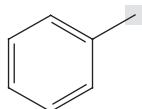## 10.9   BENZYLIC SUBSTITUTION AND BENZYLIC RADICALS

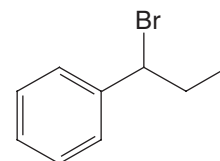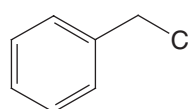- An atom or group bonded to an sp^3-hybridized carbon adjacent to a benzene ring is called a **benzylic group**. The group is said to be bonded at the **benzylic position**.

The following are some examples.

| **The hydrogen atoms bonded at the highlighted carbons are benzylic hydrogens.** | **The chlorine and bromine atoms are bonded at benzylic positions.** |

Benzylic hydrogens are even more reactive than allylic hydrogens in radical substitution reactions due to the additional delocalization that is possible for a benzylic radical intermediate (see Practice Problem 10.12).

When methylbenzene (toluene) reacts with *N*-bromosuccinimide (NBS) in the presence of light, for example, the major product is benzyl bromide. *N*-Bromosuccinimide furnishes a low concentration of Br_2, and the reaction is analogous to that for allylic bromination that we studied in Section 10.8B.

Methylbenzene
(Toluene) **NBS** **Benzyl bromide**
(α-bromotoluene)
(64%)
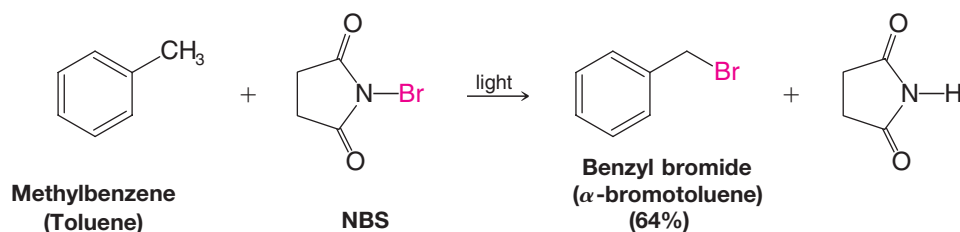
Benzylic chlorination of methylbenzene takes place in the gas phase at 400–600 °C or in the presence of UV light. When an excess of chlorine is used, multiple chlorinations of the side chain occur:

Benzyl
chloride **Dichloromethyl**
benzene **Trichloromethyl**
benzene
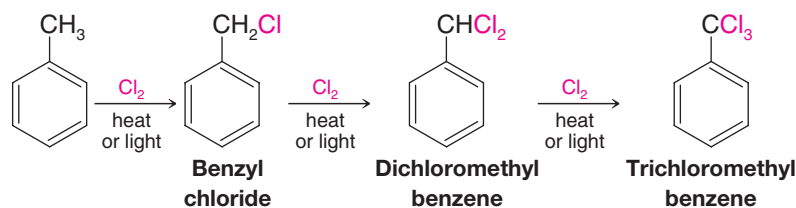
These halogenations take place through the same radical mechanism we saw for alkanes in Section 10.4. The halogens dissociate to produce halogen atoms and then the halogen atoms initiate chain reactions by abstracting hydrogens of the methyl group.

● ● ●

PRACTICE PROBLEM 10.12

Benzylic radicals, due to the adjacent benzene ring, have even greater possibility for delocalization than allylic radicals. Draw contributing resonance structures that show this delocalization for the benzylic radical derived from methylbenzene. (*Hint:* There are four contributing resonance structures for this benzylic radical.)

The greater stability of benzylic radicals accounts for the fact that when ethylbenzene is halogenated, the major product is the 1-halo-1-phenylethane. The benzylic radical is formed much faster than the 1° radical:

Benzylic radical
(more stable) **1-Halo-1-phenylethane**
(major product)

1° Radical
(less stable) **1-Halo-2-phenylethane**
(minor product)

●●●
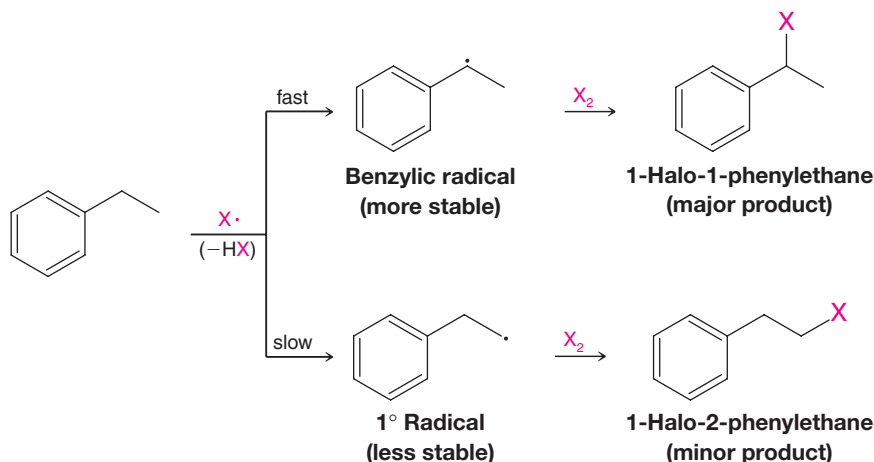
PRACTICE PROBLEM 10.13 When propylbenzene reacts with chlorine in the presence of UV radiation, the major product is 1-chloro-1-phenylpropane. Both 2-chloro-1-phenylpropane and 3-chloro-1-phenylpropane are minor products. Write the structure of the radical leading to each product and account for the fact that 1-chloro-1-phenylpropane is the major product.

Benzylic halogenation is useful for introducing a leaving group where none may have been present before. Consider the following solved problem regarding multistep synthesis, where introduction of a leaving group is a necessary step.

●●● SOLVED PROBLEM 10.6

ILLUSTRATING A MULTISTEP SYNTHESIS: Show how phenylacetylene ($C_6H_5C≡CH$) could be synthesized from ethylbenzene (phenylethane). Begin by writing a retrosynthetic analysis, and then write reactions needed for the synthesis.

ANSWER: Working backward, that is, using *retrosynthetic analysis*, we find that we can easily envision two syntheses of phenylacetylene. We can make phenylacetylene by dehydrohalogenation of 1,1-dibromo-1-phenylethane, which could have been prepared by allowing ethylbenzene (phenylethane) to react with 2 mol of NBS. Alternatively, we can prepare phenylacetylene from 1,2-dibromo-1-phenylethane, which could be prepared from styrene (phenylethene). Styrene can be made from 1-bromo-1-phenylethane, which can be made from ethylbenzene.
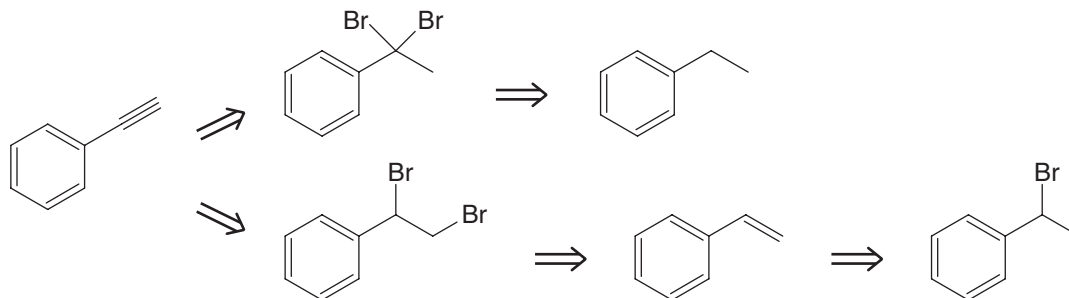
Following are the synthetic reactions we need for the two retrosynthetic analyses above:
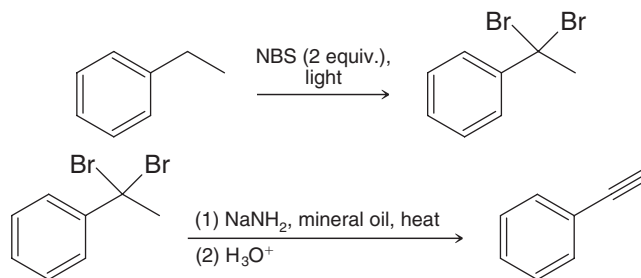
or

●●●
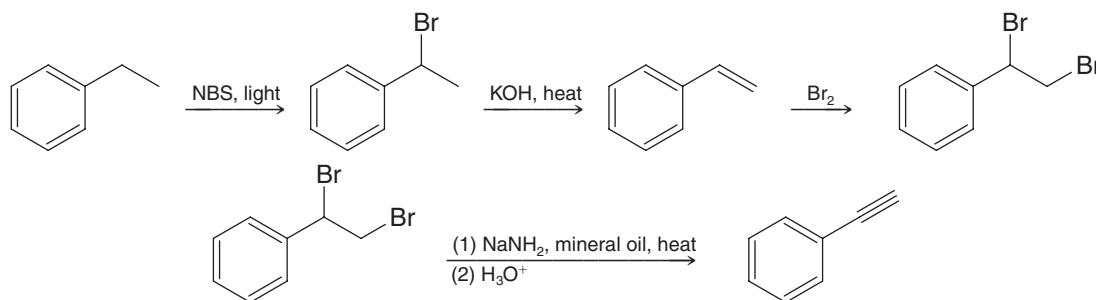
PRACTICE PROBLEM 10.14 Show how the following compounds could be synthesized from phenylacetylene ($C_6H_5C≡CH$): **(a)** 1-phenylpropyne, **(b)** 1-phenyl-1-butyne, **(c)** (*Z*)-1-phenylpropene, and **(d)** (*E*)-1-phenylpropene. Begin each synthesis by writing a retrosynthetic analysis.

10.10 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 10.12D).

$$R-\ddot{O}-\ddot{O}-R \qquad\qquad R-\ddot{O}-\ddot{O}-H$$

An organic peroxide   **An organic hydroperoxide**

- When alkenes containing peroxides or hydroperoxides react with hydrogen bromide, anti-Markovnikov addition of HBr occurs.

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.

HBr, ROOR
(peroxides present) → **Anti-Markovnikov addition**

HBr
(peroxides absent) → **Markovnikov addition**
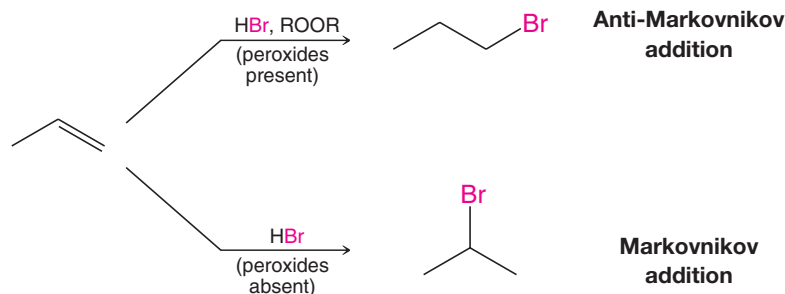
- Hydrogen bromide is the only hydrogen halide that gives anti-Markovnikov addition when peroxides are present.

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 of HBr

Chain Initiation

Step 1

$$R-\ddot{O}:\ddot{O}-R \xrightarrow{\text{heat}} 2\,R-\ddot{O}\cdot$$
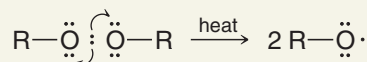
Heat brings about homolytic cleavage of the weak oxygen–oxygen bond.

Step 2

$$R-\ddot{O}\cdot \;+\; H:\ddot{B}r: \longrightarrow R-\ddot{O}:H \;+\; :\ddot{B}r\cdot$$
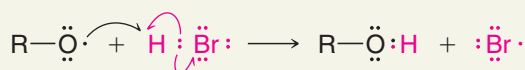
The alkoxyl radical abstracts a hydrogen atom from HBr, producing a bromine radical.

(mechanism continues on the next page)

Chain Propagation

Step 3

$$:\ddot{Br}\cdot + H_2C{=}CH{-}CH_3 \longrightarrow :\ddot{Br}:CH_2{-}\dot{C}H{-}CH_3$$

2° Radical

**A bromine radical adds to the double bond
to produce the more stable 2° alkyl radical.**

Step 4

$$:\ddot{Br}{-}CH_2{-}\dot{C}H{-}CH_3 + H{\cdot}\ddot{Br}: \longrightarrow :\ddot{Br}{-}CH_2{-}\underset{\underset{H}{|}}{C}H{-}CH_3 + \cdot\ddot{Br}:$$

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:
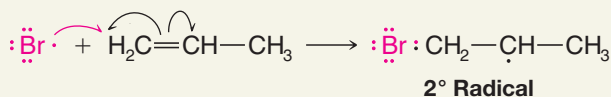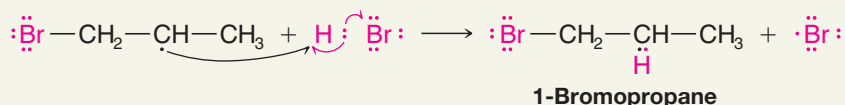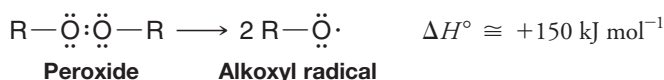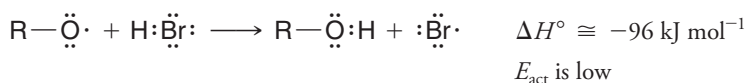
$$R{-}\ddot{O}:\ddot{O}{-}R \longrightarrow 2\,R{-}\ddot{O}\cdot \qquad \Delta H° \cong +150\ \text{kJ mol}^{-1}$$

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:

$$R{-}\ddot{O}\cdot + H:\ddot{Br}: \longrightarrow R{-}\ddot{O}:H + :\ddot{Br}\cdot \qquad \Delta H° \cong -96\ \text{kJ mol}^{-1}$$

$$E_{\text{act}}\ \text{is low}$$

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,

$$Br\cdot + CH_2{=}\dot{C}HCH_3 \xrightarrow{\times} \cdot CH_2\underset{\underset{Br}{|}}{C}HCH_3$$

**1° Radical
(less stable)**
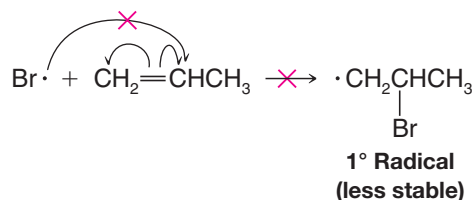
and attack at the secondary carbon atom would have been more hindered.

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.

10.10A Summary of Markovnikov versus Anti-Markovnikov Addition of HBr to Alkenes

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

Helpful Hint

How to achieve regioselective alkyl halide synthesis through alkene addition.

ionic mechanism so as to form the more stable carbocation. The result is Markovnikov addition. Polar, protic solvents favor this process.

Ionic Addition

Addition to form the more stable carbocation

Markovnikov product
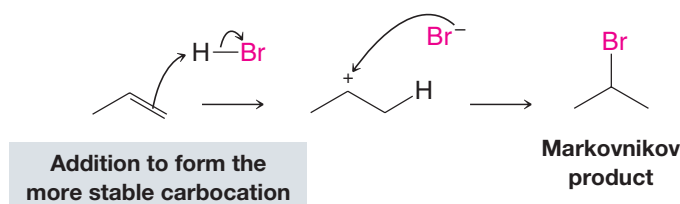
In the *presence* of peroxides, the reagent that attacks the double bond first is the larger bromine atom. It attaches itself to the less hindered carbon atom by a radical mechanism, so as to form the more stable radical intermediate. The result is anti-Markovnikov addition. Nonpolar solvents are preferable for reactions involving radicals.
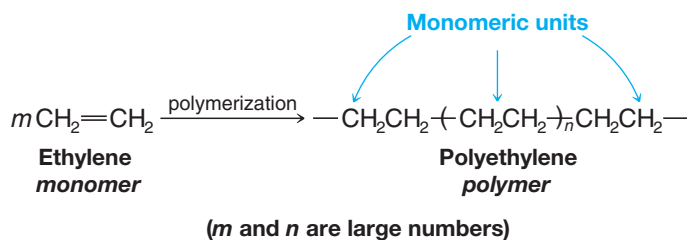
Radical Addition

Addition to form the more stable alkyl radical

Anti-Markovnikov product

$+$ Br·
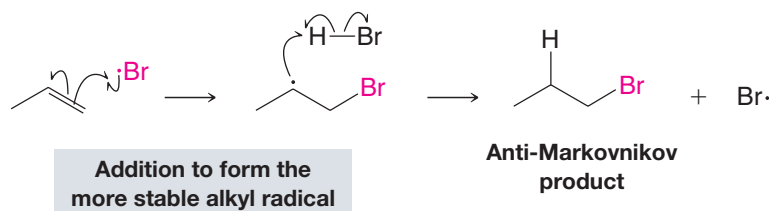
10.11 RADICAL POLYMERIZATION OF ALKENES: CHAIN-GROWTH POLYMERS

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*.

Monomeric units

$$m\,CH_2{=}CH_2 \xrightarrow{\text{polymerization}} {-}CH_2CH_2{+}CH_2CH_2{\overline{)}_n}CH_2CH_2{-}$$

Ethylene
monomer

Polyethylene
polymer

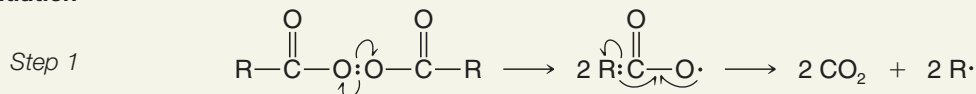**(*m* and *n* are large numbers)**

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.
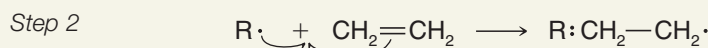
Ethene (ethylene) polymerizes by a radical mechanism when it is heated at a pressure of 1000 atm with a small amount of an organic peroxide (called a diacyl peroxide).

A MECHANISM FOR THE REACTION — Radical Polymerization of Ethene (Ethylene)

Chain Initiation

Step 1

Diacyl peroxide

$$R-C(=O)-O\!:\!O-C(=O)-R \longrightarrow 2\ R\!:\!C(=O)-O\cdot \longrightarrow 2\ CO_2 + 2\ R\cdot$$

Step 2

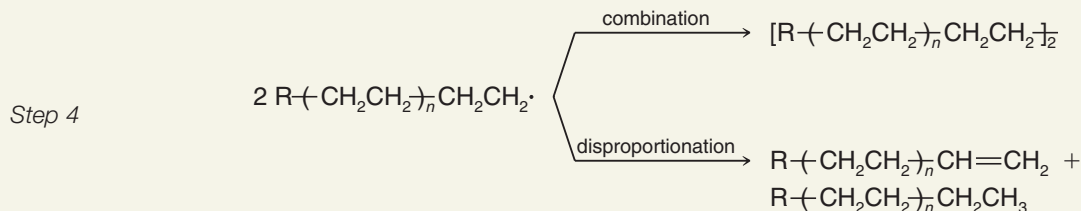$$R\cdot + CH_2\!=\!CH_2 \longrightarrow R\!:\!CH_2-CH_2\cdot$$

The diacyl peroxide dissociates and releases carbon dioxide gas. Alkyl radicals are produced, which in turn initiate chains.

Chain Propagation

Step 3

$$R-CH_2CH_2\cdot + n\ CH_2\!=\!CH_2 \longrightarrow R\text{-}(CH_2CH_2)_n\text{-}CH_2CH_2\cdot$$

Chains propagate by adding successive ethylene units, until their growth is stopped by combination or disproportionation.

Chain Termination

Step 4

$$2\ R\text{-}(CH_2CH_2)_n\text{-}CH_2CH_2\cdot$$

combination $\longrightarrow [R\text{-}(CH_2CH_2)_n\text{-}CH_2CH_2\text{-}]_2$

disproportionation $\longrightarrow R\text{-}(CH_2CH_2)_n\text{-}CH\!=\!CH_2\ +$
$R\text{-}(CH_2CH_2)_n\text{-}CH_2CH_3$

The radical at the end of the growing polymer chain can also abstract a hydrogen atom from itself by what is called "black biting." This leads to chain branching.

Chain Branching
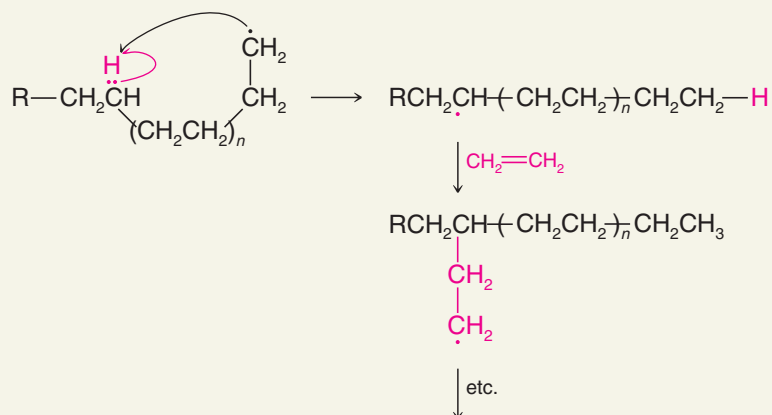
The polyethylene produced by radical polymerization is not generally useful unless it has a molecular weight of nearly 1,000,000. Very high molecular weight polyethylene can be obtained by using a low concentration of the initiator. This initiates the growth of only a few chains and ensures that each 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 in *WileyPLUS*) catalysts called **Ziegler–Natta catalysts** that are organometallic complexes

The 1963 Nobel Prize was awarded to Karl Ziegler and Guilio Natta for their research in polymers.

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*.
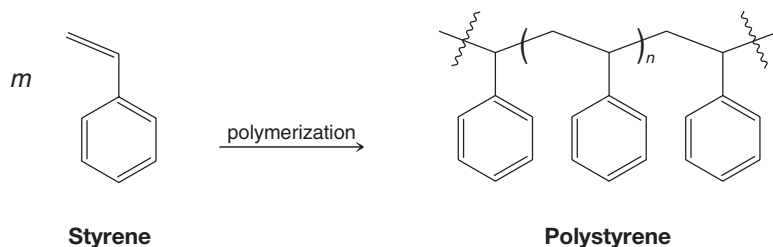

Styrene   **Polystyrene**

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

PRACTICE PROBLEM 10.15

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,

"Head"   **"Tail"**

Polystyrene
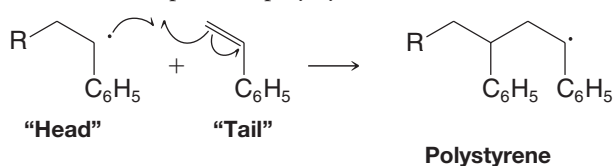
rather than the head-to-head manner shown here?

"Head"   **"Head"**
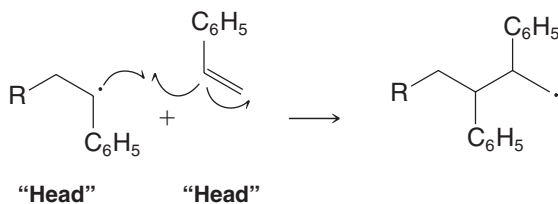
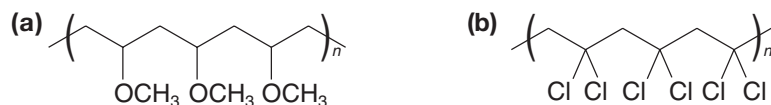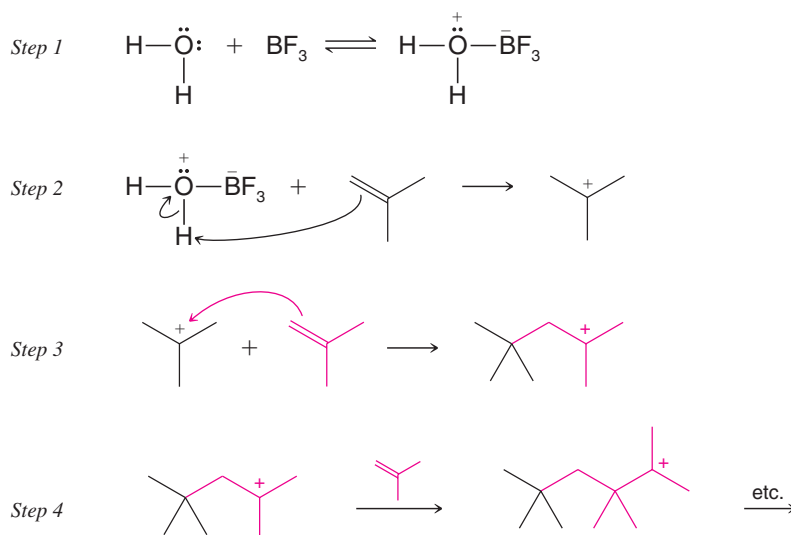**PRACTICE PROBLEM 10.16** Outline a general method for the synthesis of each of the following polymers by radical polymerization. Show the monomers that you would use.

(a)

OCH$_3$ OCH$_3$ OCH$_3$

(b)

Cl Cl Cl Cl Cl Cl

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:

Step 1

$$H—\overset{..}{O}: + BF_3 \rightleftharpoons H—\overset{+}{\overset{..}{O}}—\bar{B}F_3$$

$$\qquad\quad H \qquad\qquad\qquad\qquad H$$

Step 2

Step 3

Step 4

etc.

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$_2$O) functions to produce growing cationic chains.

PRACTICE PROBLEM 10.17 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:
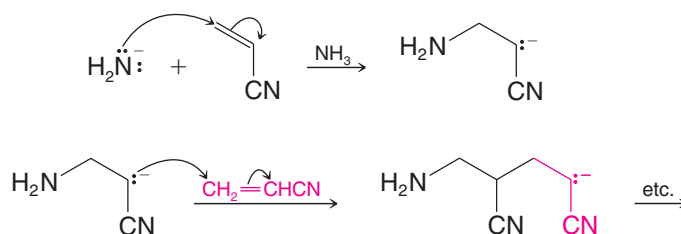

Anionic polymerization of acrylonitrile is less important in commercial production than the radical process illustrated in Special Topic B.

The remarkable adhesive called "superglue" is a result of anionic polymerization. Superglue is a solution containing 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.
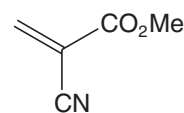
Methyl cyanoacrylate

STRATEGY AND ANSWER:
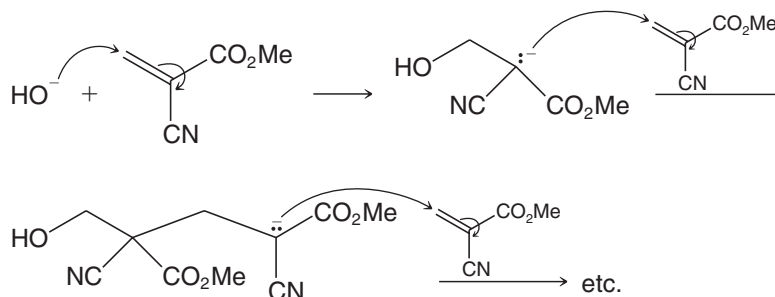

10.12 OTHER IMPORTANT RADICAL REACTIONS

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.

10.12A 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 autoxidation (Section 10.12C) and combustion reactions (Section 10.12D). 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 ($HO\cdot$) radicals. The enzyme catalase helps to prevent release of hydroxyl radicals by converting hydrogen peroxide to water and oxygen:
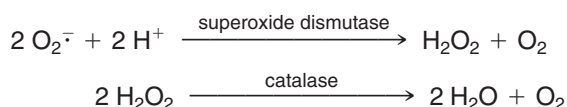
The 1998 Nobel Prize in Physiology or Medicine was awarded to R. F. Furchgott, L. J. Ignarro, and F. Murad for their discovery that NO is an important signaling molecule.

$$2\ O_2^{-\cdot} + 2\ H^+ \xrightarrow{\text{superoxide dismutase}} H_2O_2 + O_2$$

$$2\ H_2O_2 \xrightarrow{\text{catalase}} 2\ H_2O + O_2$$
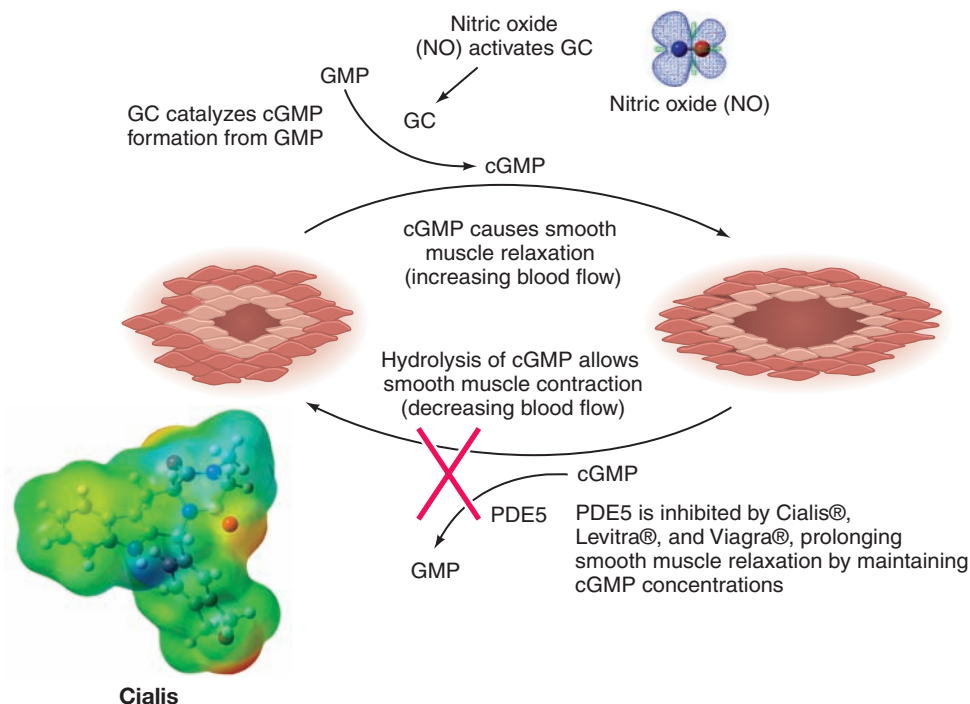
FIGURE 10.4 Nitric oxide (**NO**) activates guanylate cyclase (GC), leading to production of cyclic guanosine monophosphate (cGMP). cGMP signals processes that cause smooth muscle relaxation, ultimately resulting in increased blood flow to certain tissues. Phosphodiesterase V (PDE5) degrades cGMP, leading 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*, p197, Figure 6b 2005. Copyright 2005 American Chemical Society.)

10.12B 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. 10.4.

10.12C 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:
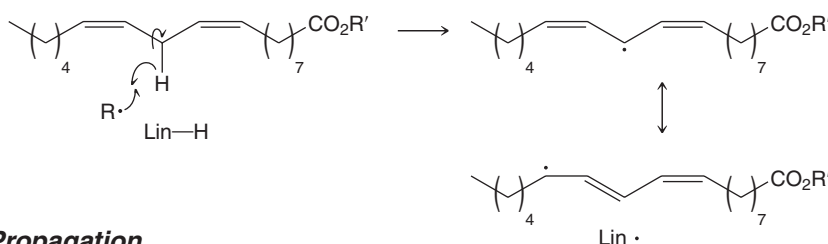

Linoleic acid
(as an ester)
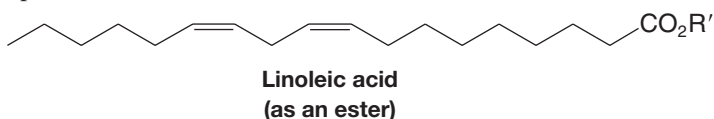
Polyunsaturated fats occur widely in the fats and oils that are components of our diets. They are also widespread in the tissues of the body where they perform numerous vital functions.

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. 10.5). 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.
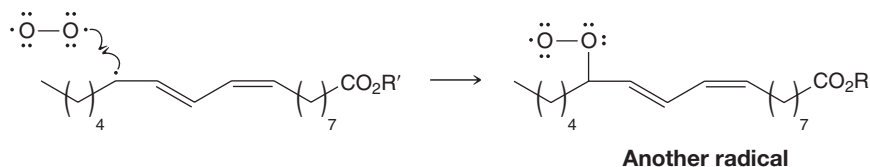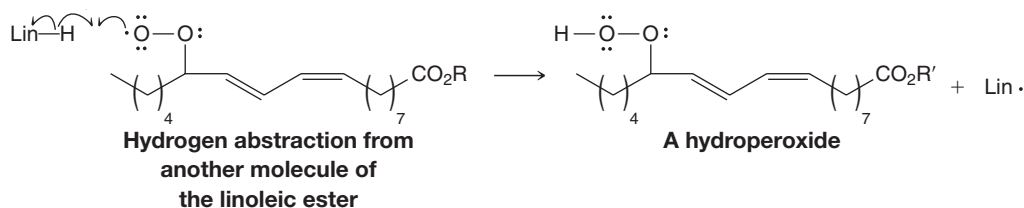
Chain Initiation
*Step 1*

Chain Propagation
Step 2

Another radical

Step 3

Hydrogen abstraction from another molecule of the linoleic ester

A hydroperoxide

FIGURE 10.5 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

If you want to stop the ability of radicals to generate more of themselves, especially in scenarios where they could be damaging like autoxidation, one needs to find a suitable trapping reagent. Such materials, known as antioxidants, succeed when they can lead to a new, and more stable, radical species that terminates the chain by no longer reacting, or by further consuming reactive radicals to generate additional nonradical species. Two such compounds are vitamin E (also known as α-tocopherol) and BHT (butylated hydroxytoluene), shown further below:
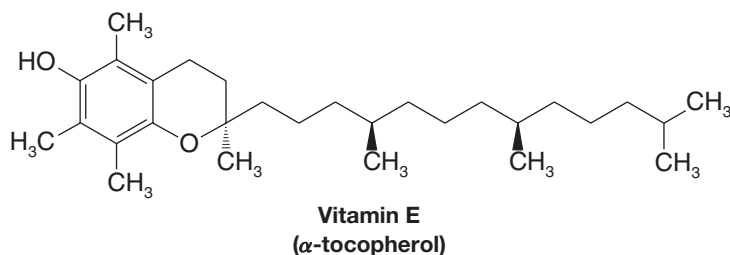
Vitamin E
(α-tocopherol)

Vitamin E is found in vegetable oils.

In both cases, reaction with a radical species initially leads to a phenoxy radical, shown below with BHT in its reaction with a peroxy radical (**ROO**·). This event is the key for antioxidant behavior, in that it turns a highly reactive radical species into a fully covalent molecule that is less reactive (here a hydroperoxide, **ROOH**), with the newly formed phenoxy radical stabilized by the neighboring aromatic ring and attendant steric bulk of the *tert*-butyl groups.

BHT
(Butylated hydroxytoluene)

ROO·

BHT radical

+ ROOH
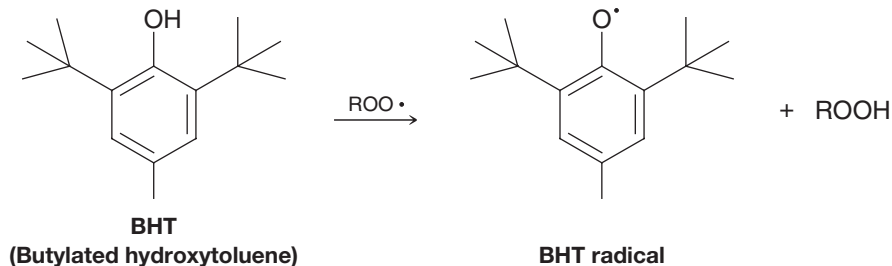
Worth noting is that vitamin E could be considered a natural antioxidant, since it is found in many foods and may work in our bodies to scavenge potentially damaging radical species, while BHT is a synthetic material that is added to many foods as a preservative.

10.12D 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:

$$RH + O_2 \longrightarrow R\cdot + \cdot OOH \qquad \textbf{Initiating}$$

$$R\cdot + O_2 \longrightarrow R{-}OO\cdot$$
$$R{-}OO\cdot + R{-}H \longrightarrow R{-}OOH + R\cdot \qquad \left.\right\} \textbf{Propagating}$$
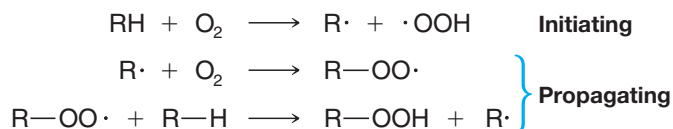
One product of the second chain-propagating step is R—OOH, called an alkyl hydroperoxide. The oxygen–oxygen bond of an alkyl hydroperoxide is quite weak, and it can break and produce radicals that can initiate other chains:

$$RO{-}OH \longrightarrow RO\cdot + \cdot OH$$
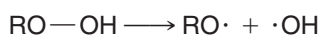
THE CHEMISTRY OF... Ozone Depletion and Chlorofluorocarbons (CFCs)

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:

$$\textit{Step 1} \quad O_2 + h\nu \longrightarrow O + O$$
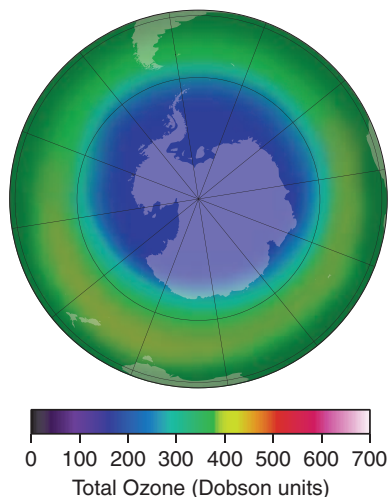$$\textit{Step 2} \quad O + O_2 + M \longrightarrow O_3 + M + heat$$
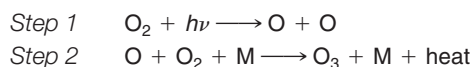
where M is some other particle that can absorb some of the energy released in the second step.

The ozone produced in step 2 can also interact with high-energy UV light in the following way:

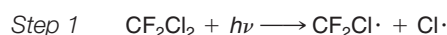$$\textit{Step 3} \quad O_3 + h\nu \longrightarrow O_2 + O + heat$$
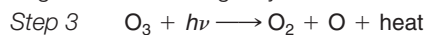
The oxygen atom formed in step 3 can cause a repetition of step 2, and so forth. The net result of these steps is to convert highly energetic UV light into heat. This is important because the existence of this cycle shields Earth from radiation that is destructive to living organisms. This shield makes 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.
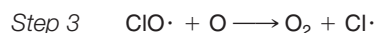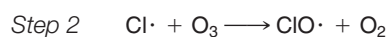
Production of chlorofluoromethanes (and of chlorofluoroethanes) called chlorofluorocarbons (CFCs) or **freons** began in 1930. These compounds have been used as refrigerants, solvents, and propellants in aerosol cans. Typical freons are trichlorofluoromethane, $CFCl_3$ (called Freon-11), and dichlorodifluoromethane, CF_2Cl_2 (called Freon-12).

Total Ozone (Dobson units)
0 100 200 300 400 500 600 700

Chain Initiation

$$\textit{Step 1} \quad CF_2Cl_2 + h\nu \longrightarrow CF_2Cl\cdot + Cl\cdot$$

Chain Propagation

$$\textit{Step 2} \quad Cl\cdot + O_3 \longrightarrow ClO\cdot + O_2$$

$$\textit{Step 3} \quad ClO\cdot + O \longrightarrow O_2 + Cl\cdot$$

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.

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.)

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.
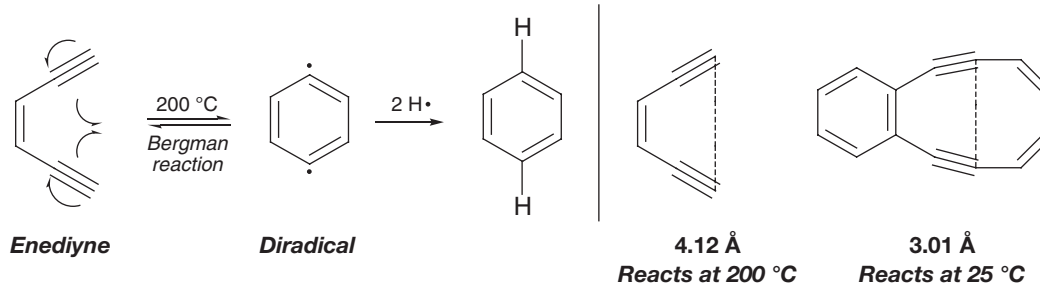
[**WHY** Do These Topics Matter?

### RADICALS FROM THE BERGMAN CYCLOAROMATIZATION REACTION

In 1972, chemists at the University of California at Berkeley under the direction of Robert Bergman discovered a new chemical reaction that could be used to synthesize a benzene ring from starting materials that contained two alkyne triple bonds connected by a cis double bond, an array of atoms also known as an enediyne. This process, known as a cycloaromatization since it makes a ring that is aromatic, involves radicals as shown below both in making new bonds as well as in adding the final hydrogen atoms needed to make a benzene ring system.

Equally interesting, it was discovered on further exploration that the temperature needed to make the reaction occur was directly correlated to the distance between the termini of the two alkynes. For most molecules, that distance is greater than 3.6 Å and temperatures in excess of 200 °C are required to initiate the event. However, if that length can be made shorter, for example by placing the alkynes within a constrained ring, then these processes can occur at lower temperatures. Typically, distances between 3.2 to 3.3 Å allow for the cycloaromatization at ambient temperature (i.e., 37 °C), while even shorter distances, such as 3.0 Å, allow the reaction to proceed at room temperature (i.e., 25 °C).

Globally, such studies highlight the ability of chemists to discover new reactivity and understand molecular processes at a very sophisticated level. In this case, however, it turns out that the process occurs in nature, a fact that chemists just did not know until the natural product calicheamicin γ_1^{I} was isolated from a bacterial strain!

Enediyne   *Diradical*   **4.12 Å**   **3.01 Å**
                                         Reacts at 200 °C **Reacts at 25 °C**

As you can see from its structure below, calicheamicin γ_1^{I} is highly complex. It has an enediyne motif, one that is stable at 37 °C (body temperature) since the distance between the ends of the two alkyne units in its natural form is calculated to be just longer than 3.3 Å. However, when this compound is brought into a cell's nucleus, the unique trisulfide portion of the molecule can be converted into a sulfide nucleophile. Once unveiled, this reactive group can then attack a neighboring group of atoms through a chemical reaction we will learn more about in Chapter 19. What is important to know for now, however, is that this event changes the conformation of the entire right-hand half of the molecule, bringing the ends of the two alkynes closer together, to a distance of ~3.2 Å. As a result, a Bergman cycloaromatization can now occur at 37 °C, immediately generating a diradical that can abstract hydrogen from DNA, creating new DNA radicals that lead to cell death.
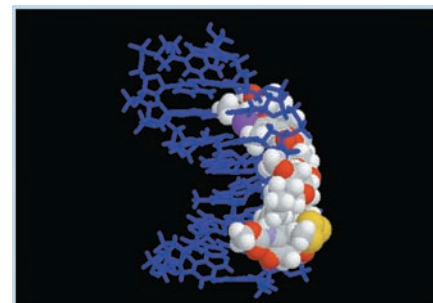
Calicheamicin bound to DNA. (PDB ID: 2PIK. Kumar, R. A.; Ikemoto, N., and Patel, D. J., Solution structure of the calicheamicin γ_1^{I}–DNA complex, J. Mol. Biol. 1997, 265, 187.) [Calicheamicin γ_1^{I} structure from Chemistry and Biology, 1994, 1(1). Nicolaou, K.C., Pitsinos, E.N., Theodorakis, A., Saimoto, H., and Wrasidio, W., Chemistry and Biology of the Calicheamicins, pp. 25-30. Copyright Elsevier 1994.

Calicheamicin γ_1^I

Diradical
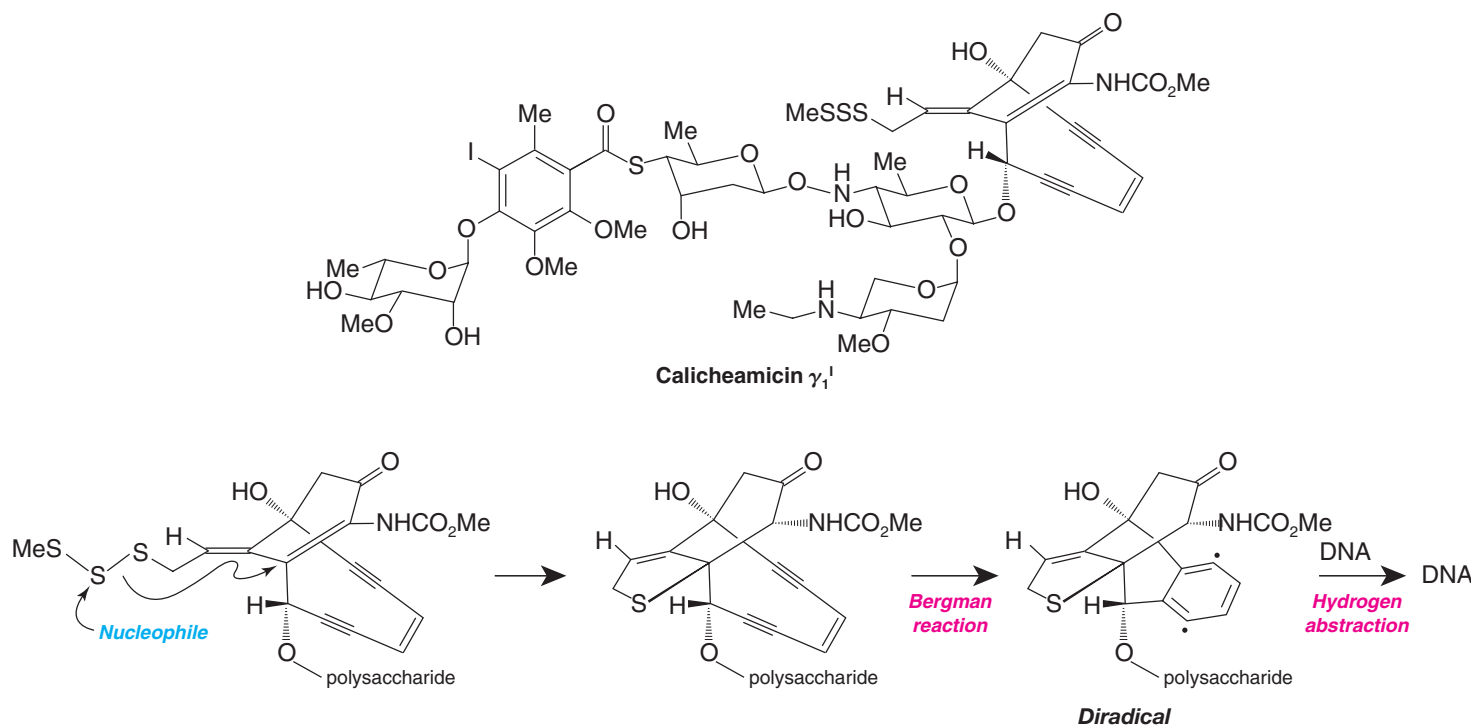
This chemistry shows that the Bergman reaction can occur naturally and that it functions in the formation of a molecule with a special triggering system that takes advantage of the differences in reactivity between different enediynes. Scientists in the pharmaceutical industry have since used this trigger system, as well as those of other related enediyne molecules from Nature, to create new drugs that have undergone clinical testing targeting a number of cancers such as acute forms of leukemia.

To learn more about these topics, see:

1. Bergman, R. G. "Reactive 1,4-Dehydroaromatics" in *Acc. Chem. Res.* **1973**, *6*, 25–31.

2. Nicolaou, K. C.; Smith, A. L.; Yue, E. W. "Chemistry and biology of natural and designed enediynes" in *Proc. Natl. Acad. Sci. USA* **1993**, *90*, 5881–5888 and references therein.

SUMMARY AND REVIEW TOOLS

The study aids for this chapter include key terms and concepts (which are hyperlinked to the Glossary from the bold, blue terms in the *WileyPLUS* version of the book at wileyplus.com) and a Mechanism Review regarding radical reactions.

PROBLEMS WILEY PLUS

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

RADICAL MECHANISMS AND PROPERTIES

10.18 Write a mechanism for the following radical halogenation reaction.
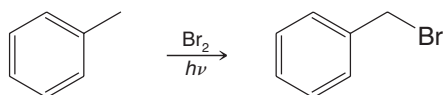
10.19 Explain the relative distribution of products below using reaction energy diagrams for the hydrogen abstraction step that leads to each product. (The rate-determining step in radical halogenation is the hydrogen abstraction step.) In energy diagrams for the two pathways, show the relative energies of the transition states and of the alkyl radical intermediate that results in each case.
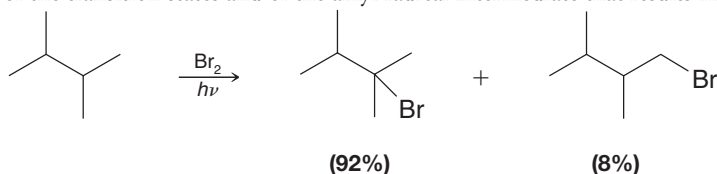
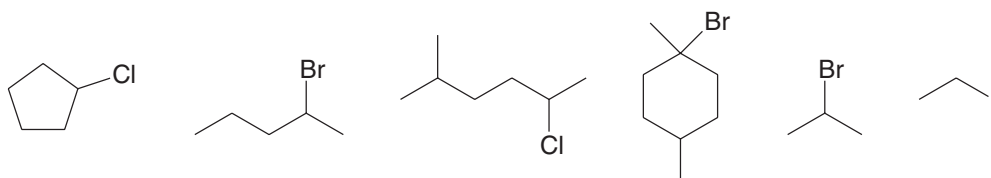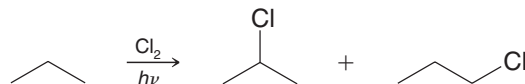**10.20** Which of the following compounds can be prepared by radical halogenation with little complication by formation of isomeric by-products?


10.21 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.

10.22 In addition to more highly chlorinated products, chlorination of butane yields a mixture of compounds with the formula C_4H_9Cl.
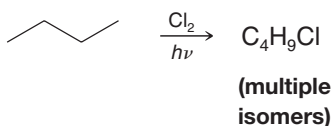

(a) Taking stereochemistry into account, how many different isomers with the formula C_4H_9Cl would you expect?

(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?

10.23 Chlorination of (R)-2-chlorobutane yields a mixture of dichloro isomers.
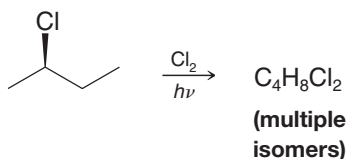
(a) Taking into account stereochemistry, how many different isomers would you expect? Write their structures.

(b) How many fractions would be obtained upon fractional distillation?

(c) Which of these fractions would be optically active?

10.24 Peroxides are often used to initiate radical chain reactions such as in the following radical halogenation.

(Di-*tert*-butyl peroxide)
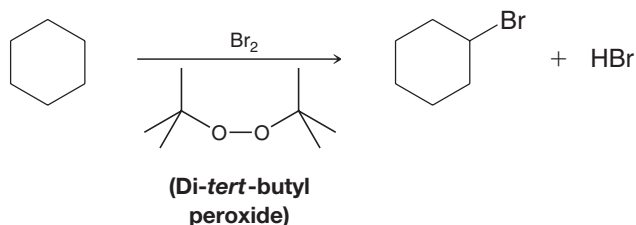
(a) Using bond dissociation energies in Table 10.1, explain why peroxides are especially effective as radical initiators.

(b) Write a mechanism for the reaction above showing how it could be initiated by di-*tert*-butyl peroxide.

10.25 List in order of decreasing stability all of the radicals that can be obtained by abstraction of a hydrogen atom from 2-methylbutane.

10.26 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 "Why Do These Topics Matter?" after Section 10.12).
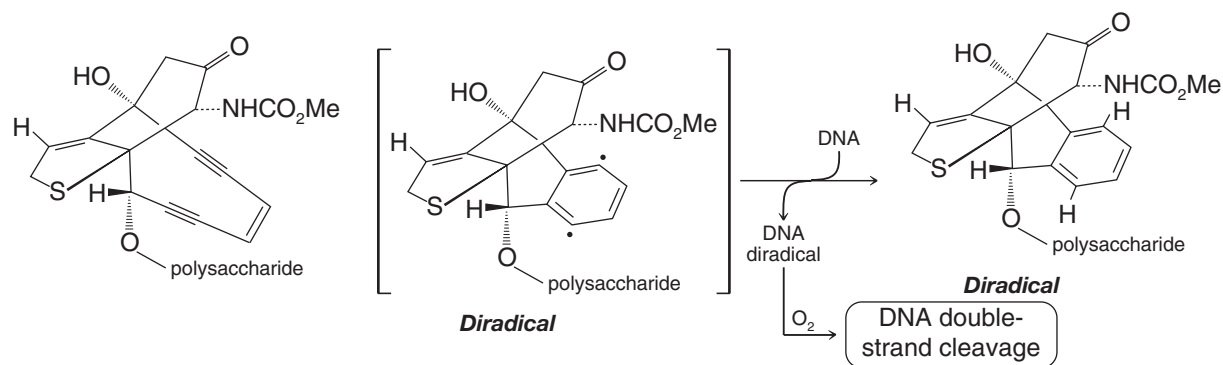
10.27 Find examples of C—H bond dissociation energies in Table 10.1 that are as closely related as possible to the bonds to H_a, H_b, and H_c in the molecule at right. Use these values to answer the questions below.

(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?

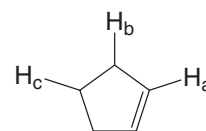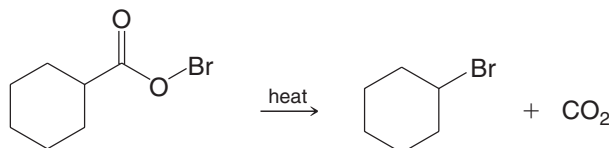**10.28** Write a radical chain mechanism for the following reaction (a reaction called the Hunsdiecker reaction).

SYNTHESIS

10.29 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) $CH_3CH_3 \longrightarrow$

(b) $CH_3CH_3 \longrightarrow$

(c)

(d)

(e) $CH_4 + HC\equiv CH \longrightarrow$

(f) $CH_3CH_3 + HC\equiv CH \longrightarrow$

(g) $CH_3CH_3 \longrightarrow$
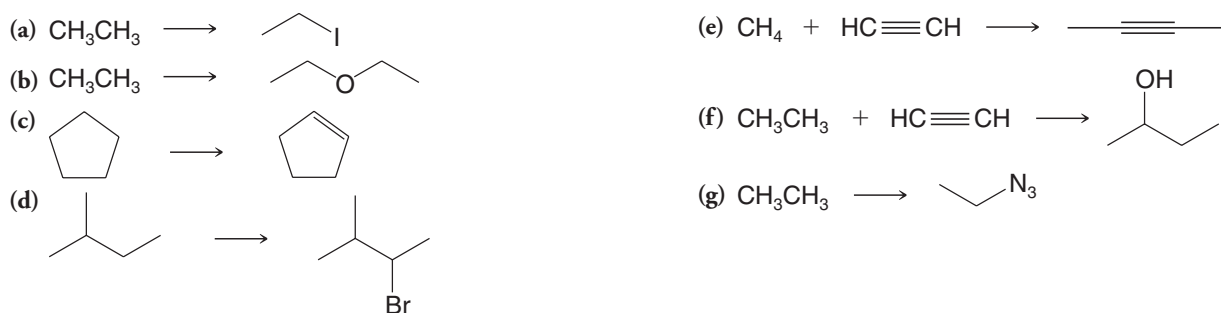
10.30 Provide the reagents necessary for the following synthetic transformations. More than one step may be required.

(a)

(b)

(c)

(d)

(e)

(f)
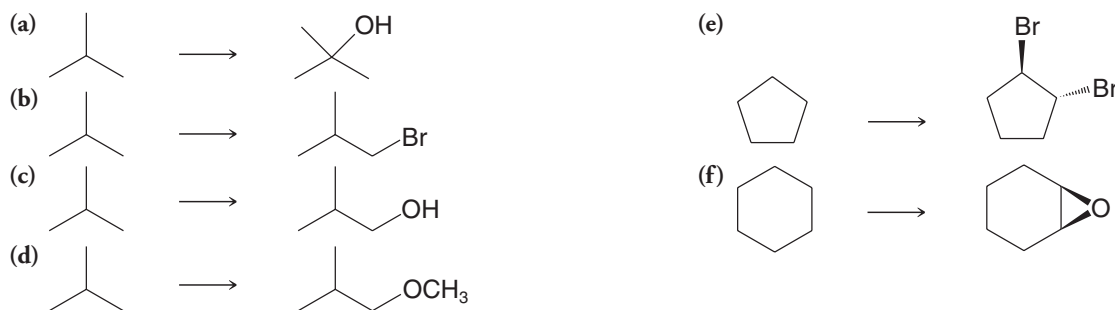
10.31 Synthesize each of the following compounds by routes that involve allylic bromination by NBS. Use starting materials having four carbons or fewer. Begin by writing a retrosynthetic analysis.

(a)

(b)

(c)
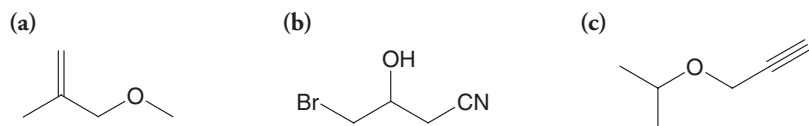
10.32 Synthesize each of the following compounds by routes that involve benzylic bromination by NBS and any other synthetic steps necessary. Begin by writing a retrosynthetic analysis.

(a)

(b)

(c)
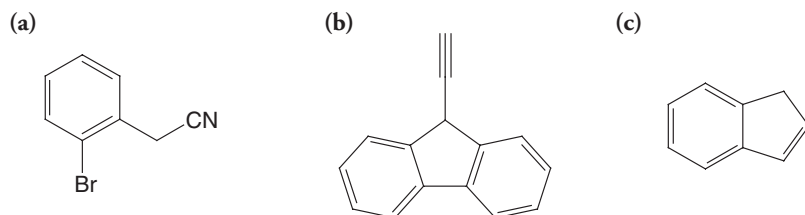
10.33 Synthesize each of the following compounds by routes that involve both allylic and benzylic bromination by NBS.

(a)

(b)

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 upon heating to form two isobutyronitrile radicals and nitrogen gas. Using an isobutyronitrile radical to initiate the reaction, write a mechanism for the following process.

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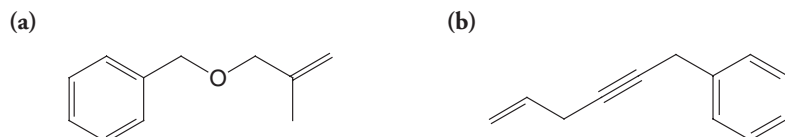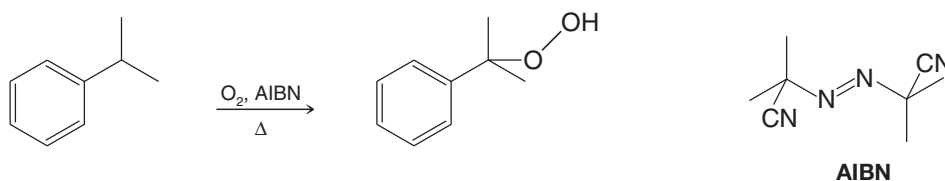 in butane). Consider the mechanism of radical polymerization and then suggest an explanation for the enhanced rate of substitution at C5 in 2,2-dimethylhexane.

10.36 Write a mechanism for the following reaction.
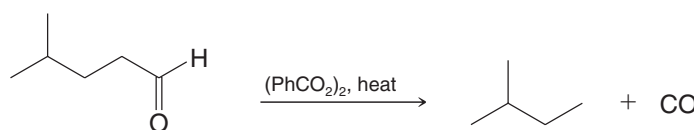
10.37 Hydrogen peroxide and ferrous sulfate react to produce hydroxyl radical (HO·), as reported in 1894 by English chemist H. J. H. Fenton. When *tert*-butyl alcohol is treated with HO· generated this way, it affords a crystalline reaction product **X**, mp 92 °C, which has these spectral properties:

   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.
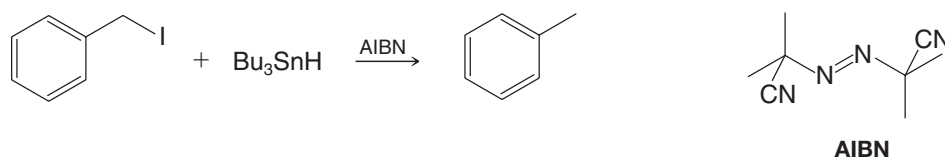
10.39 Write a mechanism that accounts for the following reaction. Note that the hydrogen atom bonded to tin in tributyltin hydride is readily transferred in radical mechanisms.

(Major)
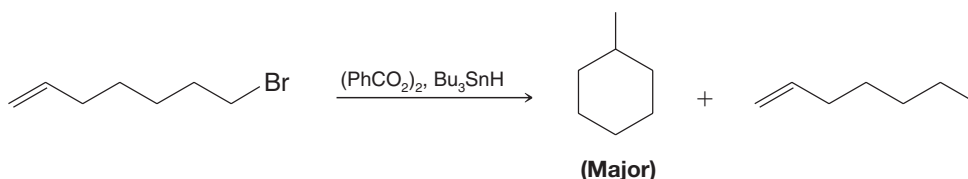
10.40 Molecular orbital calculations can be used to model the location of electron density from unpaired electrons in a radical. Open the molecular models on the book's website for the methyl, ethyl, and *tert*-butyl radicals. The gray wire mesh surfaces in these models represent volumes enclosing electron 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 $\left(\ddot{\text{O}}{=}\ddot{\text{O}} \right)$. 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 (a). 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.
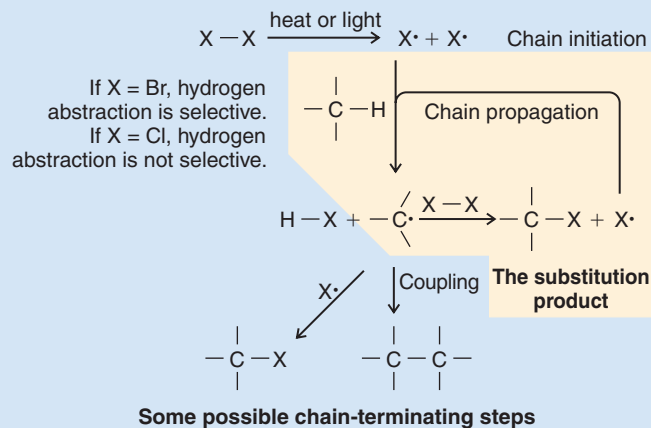
(b) 2-Methoxypropene will form a polymer when treated with a radical initiator. Write the structure of this polymer and a mechanism for the polymerization reaction assuming a radical mechanism initiated by a diacyl peroxide.
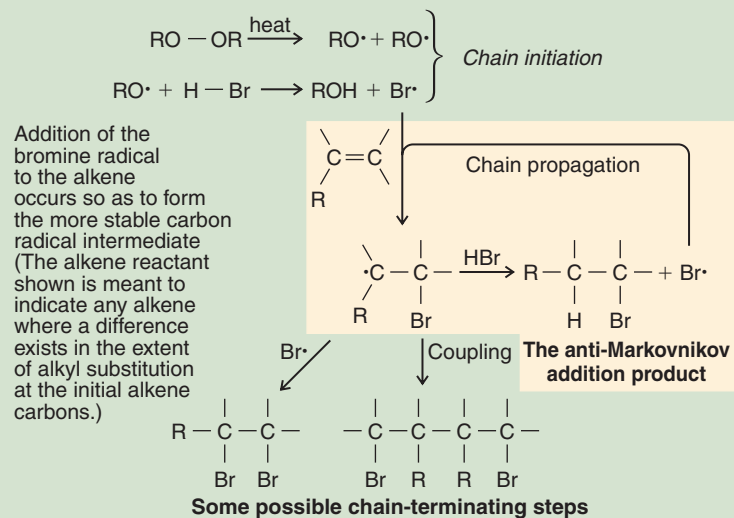
Mechanism Review of Radical Reactions

Radical Halogenation of Alkanes

$$X-X \xrightarrow{\text{heat or light}} X\cdot + X\cdot \qquad \text{Chain initiation}$$

If X = Br, hydrogen abstraction is selective.
If X = Cl, hydrogen abstraction is not selective.

Chain propagation

$$H-X + -\overset{|}{\underset{|}{C}}\cdot \xrightarrow{X-X} -\overset{|}{\underset{|}{C}}-X + X\cdot$$

Coupling   **The substitution product**

X·

$$-\overset{|}{\underset{|}{C}}-X \qquad -\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-$$

Some possible chain-terminating steps

Anti-Markovnikov Addition of HBr to Alkenes

$$RO-OR \xrightarrow{\text{heat}} RO\cdot + RO\cdot$$
$$RO\cdot + H-Br \longrightarrow ROH + Br\cdot$$
Chain initiation

Addition of the bromine radical to the alkene occurs so as to form the more stable carbon radical intermediate (The alkene reactant shown is meant to indicate any alkene where a difference exists in the extent of alkyl substitution at the initial alkene carbons.)

Chain propagation

$$\cdot\overset{|}{\underset{R}{C}}-\overset{|}{\underset{Br}{C}}- \xrightarrow{HBr} R-\overset{|}{\underset{H}{C}}-\overset{|}{\underset{Br}{C}}- + Br\cdot$$

Br·

Coupling   **The anti-Markovnikov addition product**

$$R-\overset{|}{\underset{Br}{C}}-\overset{|}{\underset{Br}{C}}- \qquad -\overset{|}{\underset{Br}{C}}-\overset{|}{\underset{R}{C}}-\overset{|}{\underset{R}{C}}-\overset{|}{\underset{Br}{C}}-$$

Some possible chain-terminating steps

Radical Polymerization

$$R-\overset{O}{\overset{\|}{C}}-O-O-\overset{O}{\overset{\|}{C}}-R \xrightarrow{\text{heat}} R\cdot + R\cdot + 2\,CO_2$$

C=C   Chain initiation

$$R-\overset{|}{\underset{|}{C}}-\overset{|}{C}\cdot$$

C=C

$$R-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-\overset{|}{C}\cdot$$

n C=C   Chain propagation

$$R-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-\left[\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}\right]_n\overset{|}{\underset{|}{C}}-\overset{|}{C}\cdot$$

Disproportionation   Coupling

Possible chain-terminating steps