10 Organohalides

Organic KNOWLEDGE TOOLS

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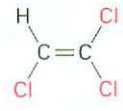
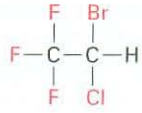
Online homework for this chapter may be assigned in Organic OWL.

Now that we've covered the chemistry of hydrocarbons, it's time to start looking at more complex substances that contain elements in addition to C and H. We'll begin by discussing the chemistry of **organohalides**, compounds that contain one or more halogen atoms.

Halogen-substituted organic compounds are widespread throughout nature, and approximately 5000 organohalides have been found in algae and various other marine organisms. Chloromethane, for example, is released in large amounts by oceanic kelp, as well as by forest fires and volcanoes. Halogen-containing compounds also have a vast array of industrial applications, including their use as solvents, inhaled anesthetics in medicine, refrigerants, and pesticides.



Trichloroethylene (a solvent)

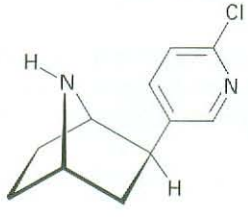


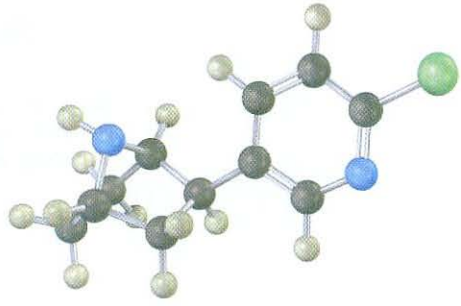
Halothane (an inhaled anesthetic)

Dichlorodifluoromethane (a refrigerant)

Bromomethane (a fumigant)

Still other halo-substituted compounds are providing important leads to new medicines. The compound epibatidine, for instance, has been isolated from the skin of Ecuadorian frogs and found to be more than 200 times as potent as morphine at blocking pain in animals.





Epibatidine (from the Ecuadorian frog *Epipedobates tricolor*)

Sean Duggan

A large variety of organohalides are known. The halogen might be bonded to an alkynyl group (C≡C–X), a vinylic group (C=C–X), an aromatic ring (Ar–X), or an alkyl group. We'll be concerned in this chapter, however, primarily with **alkyl halides**, compounds with a halogen atom bonded to a saturated, sp^3-hybridized carbon atom.

WHY THIS CHAPTER?

Alkyl halides are encountered less frequently than their oxygen-containing relatives alcohols and ethers, but some of the *kinds* of reactions they undergo—nucleophilic substitutions and eliminations—*are* encountered frequently. Thus, alkyl halide chemistry acts as a relatively simple model for many mechanistically similar but structurally more complex reactions found in biomolecules. We'll begin in this chapter with a look at how to name and prepare alkyl halides, and we'll see several of their reactions. Then in the following chapter, we'll make a detailed study of the substitution and elimination reactions of alkyl halides—two of the most important and well-studied reaction types in organic chemistry.

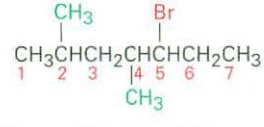
10.1 Naming Alkyl Halides

ThomsonNOW Click *Organic Interactive* to **practice assigning IUPAC names to organic halides.**

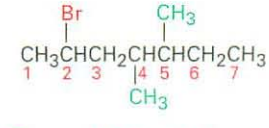
Although members of the class are commonly called *alkyl halides*, they are named systematically as *haloalkanes* (Section 3.4), treating the halogen as a substituent on a parent alkane chain. There are three steps:

Step 1 **Find the longest chain, and name it as the parent.** If a double or triple bond is present, the parent chain must contain it.

Step 2 **Number the carbons of the parent chain beginning at the end nearer the first substituent, whether alkyl or halo.** Assign each substituent a number according to its position on the chain.

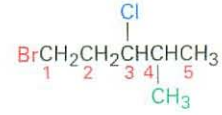


5-Bromo-2,4-dimethylheptane



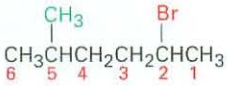
2-Bromo-4,5-dimethylheptane

If different halogens are present, number all and list them in alphabetical order when writing the name.



1-Bromo-3-chloro-4-methylpentane

Step 3 **If the parent chain can be properly numbered from either end by step 2, begin at the end nearer the substituent that has alphabetical precedence.**

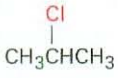


2-Bromo-5-methylhexane
(*NOT* 5-bromo-2-methylhexane)

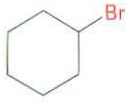
ThomsonNOW™ Click *Organic Interactive* to **use a web-based palette to draw structures for alkyl halides, based on their IUPAC names.**

In addition to their systematic names, many simple alkyl halides are also named by identifying first the alkyl group and then the halogen. For example, CH_3I can be called either iodomethane or methyl iodide. Such names are well entrenched in the chemical literature and in daily usage, but they won't be used in this book.

Iodomethane
(or methyl iodide)



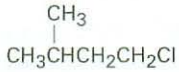
2-Chloropropane
(or isopropyl chloride)

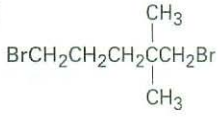


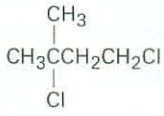
Bromocyclohexane
(or cyclohexyl bromide)

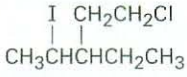
Problem 10.1 Give IUPAC names for the following alkyl halides:

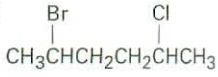
(a) $CH_3CH_2CH_2CH_2I$

(b) 

(c) 

(d) 

(e) 

(d) 

Problem 10.2 Draw structures corresponding to the following IUPAC names:

(a) 2-Chloro-3,3-dimethylhexane
(b) 3,3-Dichloro-2-methylhexane
(c) 3-Bromo-3-ethylpentane
(d) 1,1-Dibromo-4-isopropylcyclohexane
(e) 4-*sec*-Butyl-2-chlorononane
(f) 1,1-Dibromo-4-*tert*-butylcyclohexane

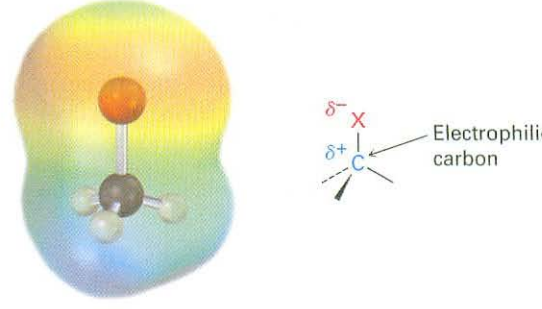
10.2 Structure of Alkyl Halides

Halogens increase in size going down the periodic table, so the lengths of the corresponding carbon–halogen bonds increase accordingly (Table 10.1). In addition, C–X bond strengths decrease going down the periodic table. As we've been doing consistently thus far, we'll continue to use the abbreviation X to represent any of the halogens F, Cl, Br, or I.

Table 10.1 A Comparison of the Halomethanes

Halomethane	Bond length (pm)	Bond strength (kJ/mol)	Bond strength (kcal/mol)	Dipole moment (*D*)
CH_3F	139	452	108	1.85
CH_3Cl	178	351	84	1.87
CH_3Br	193	293	70	1.81
CH_3I	214	234	56	1.62

In an earlier discussion of bond polarity in functional groups (Section 5.4), we noted that halogens are more electronegative than carbon. The C–X bond is therefore polar, with the carbon atom bearing a slight positive charge ($\delta+$) and the halogen a slight negative charge ($\delta-$). This polarity results in a substantial dipole moment for all the halomethanes (Table 10.1) and implies that the alkyl halide C–X carbon atom should behave as an electrophile in polar reactions. We'll see in the next chapter that much of the chemistry of alkyl halides is indeed dominated by their electrophilic behavior.



10.3 Preparing Alkyl Halides from Alkanes: Radical Halogenation

Structurally simple alkyl halides can sometimes be prepared by reaction of an alkane with Cl_2 or Br_2 through a radical chain-reaction pathway (Section 5.3). Although inert to most reagents, alkanes react readily with Cl_2 or Br_2 in the presence of light to give alkyl halide substitution products. The reaction occurs by the radical mechanism shown in Figure 10.1 for chlorination.

Recall from Section 5.3 that radical substitution reactions require three kinds of steps: *initiation*, *propagation*, and *termination*. Once an initiation step has started the process by producing radicals, the reaction continues in a self-sustaining cycle. The cycle requires two repeating propagation steps in which a radical, the halogen, and the alkane yield alkyl halide product plus more radical to carry on the chain. The chain is occasionally terminated by the combination of two radicals.

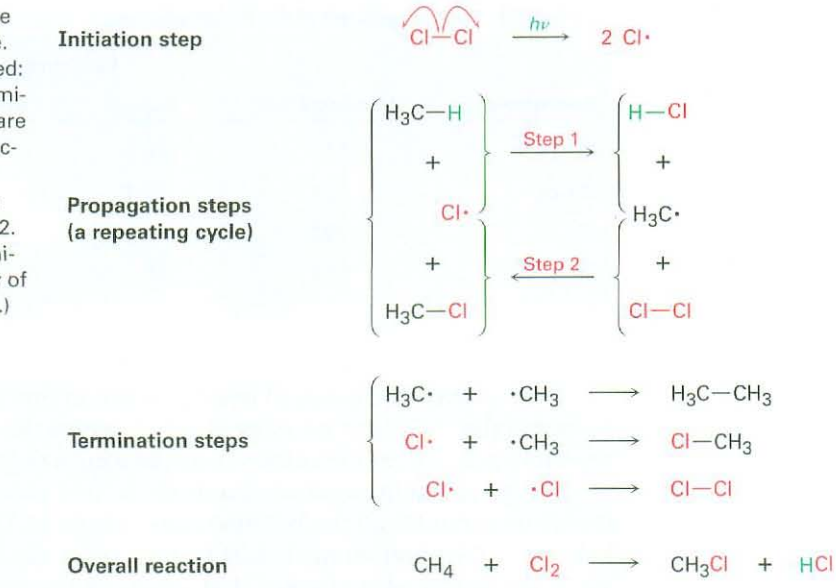
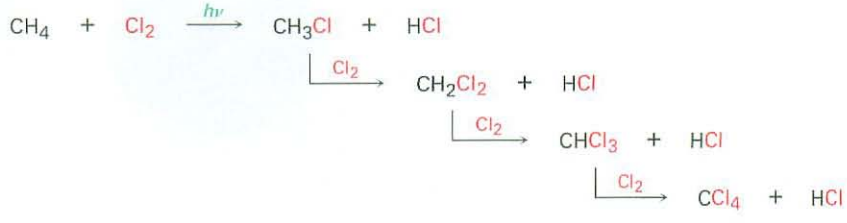
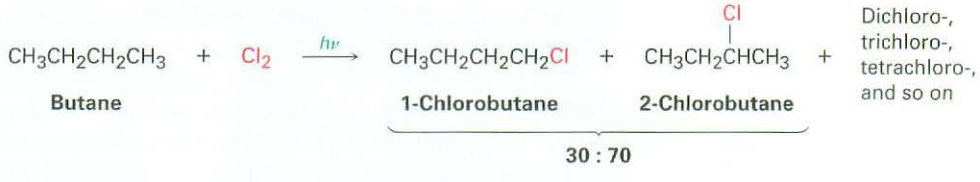


Figure 10.1 Mechanism of the radical chlorination of methane. Three kinds of steps are required: initiation, propagation, and termination. The propagation steps are a repeating cycle, with Cl· a reactant in step 1 and a product in step 2, and with $\cdot CH_3$ a product in step 1 and a reactant in step 2. (The symbol $h\nu$ shown in the initiation step is the standard way of indicating irradiation with light.)

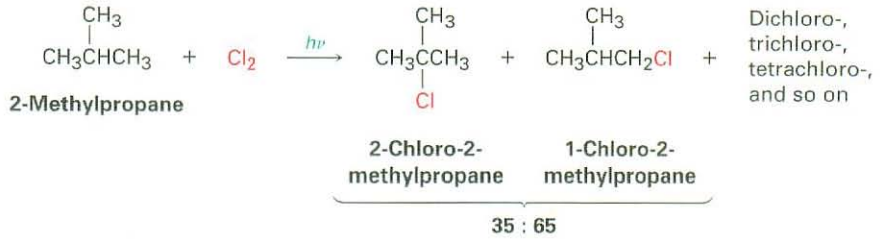
Although interesting from a mechanistic point of view, alkane halogenation is a poor synthetic method for preparing alkyl halides because mixtures of products invariably result. For example, chlorination of methane does not stop cleanly at the monochlorinated stage but continues to give a mixture of dichloro, trichloro, and even tetrachloro products.



The situation is even worse for chlorination of alkanes that have more than one sort of hydrogen. For example, chlorination of butane gives two monochlorinated products in addition to dichlorobutane, trichlorobutane, and so on. Thirty percent of the monochloro product is 1-chlorobutane, and seventy percent is 2-chlorobutane.

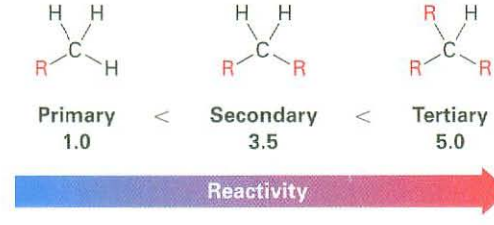


As another example, 2-methylpropane yields 2-chloro-2-methylpropane and 1-chloro-2-methylpropane in the ratio 35:65, along with more highly chlorinated products.

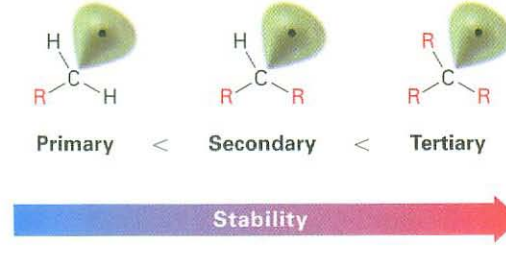


From these and similar reactions, it's possible to calculate a reactivity order toward chlorination for different sorts of hydrogen atoms in a molecule. Take the butane chlorination, for instance. Butane has six equivalent primary hydrogens ($-CH_3$) and four equivalent secondary hydrogens ($-CH_2-$). The fact that butane yields 30% of 1-chlorobutane product means that *each one* of the six primary hydrogens is responsible for 30% ÷ 6 = 5% of the product. Similarly, the fact that 70% of 2-chlorobutane is formed means that each of the four secondary hydrogens is responsible for 70% ÷ 4 = 17.5% of the product. Thus, reaction of a secondary hydrogen happens 17.5% ÷ 5% = 3.5 times as often as reaction of a primary hydrogen.

A similar calculation for the chlorination of 2-methylpropane indicates that each of the nine primary hydrogens accounts for 65% ÷ 9 = 7.2% of the product, while the single tertiary hydrogen (R_3CH) accounts for 35% of the product. Thus, a tertiary hydrogen is 35 ÷ 7.2 = 5 times as reactive as a primary hydrogen toward chlorination.



What are the reasons for the observed reactivity order of alkane hydrogens toward radical chlorination? A look at the bond dissociation energies given previously in Table 5.3 on page 156 hints at the answer. The data in Table 5.3 indicate that a tertiary C–H bond (390 kJ/mol; 93 kcal/mol) is weaker than a secondary C–H bond (401 kJ/mol; 96 kcal/mol), which is in turn weaker than a primary C–H bond (420 kJ/mol; 100 kcal/mol). Since less energy is needed to break a tertiary C–H bond than to break a primary or secondary C–H bond, the resultant tertiary radical is more stable than a primary or secondary radical.



An explanation of the relationship between reactivity and bond strength in radical chlorination reactions relies on the Hammond postulate, discussed in Section 6.10 to explain why more stable carbocations form faster than less stable ones in alkene electrophilic addition reactions. An energy diagram for the formation of an alkyl radical during alkane chlorination is shown in Figure 10.2. Although the hydrogen abstraction step is slightly exergonic, there is nevertheless a certain amount of developing radical character in the transition state. Since the increasing alkyl substitution that stabilizes the radical intermediate also stabilizes the transition state leading to that intermediate, the more stable radical forms faster than the less stable one.

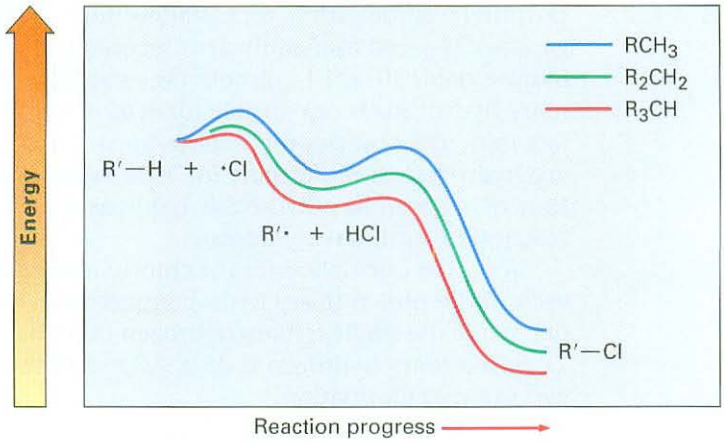
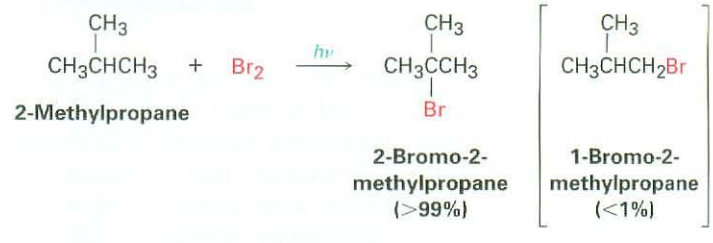
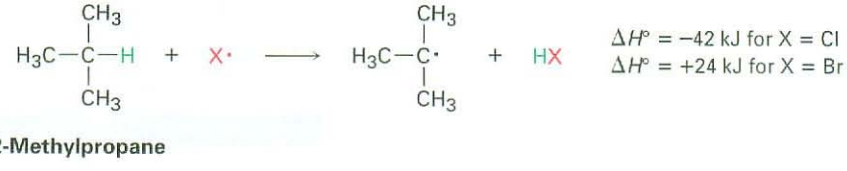


Figure 10.2 Energy diagram for alkane chlorination. The relative rates of formation of tertiary, secondary, and primary radicals are the same as their stability order.

In contrast with alkane chlorination, alkane bromination is usually much more selective. In its reaction with 2-methylpropane, for example, bromine abstracts the tertiary hydrogen with greater than 99% selectivity, as opposed to the 35 : 65 mixture observed in the corresponding chlorination.



The enhanced selectivity of alkane bromination over chlorination can be explained by turning once again to the Hammond postulate. In comparing the abstractions of an alkane hydrogen by Cl· and Br· radicals, reaction with Br· is less exergonic. As a result, the transition state for bromination resembles the alkyl radical more closely than does the transition state for chlorination, and the stability of that radical is therefore more important for bromination than for chlorination.

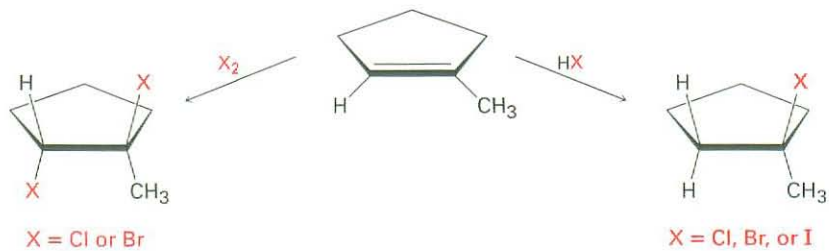


Problem 10.3 Draw and name all monochloro products you would expect to obtain from radical chlorination of 2-methylpentane. Which, if any, are chiral?

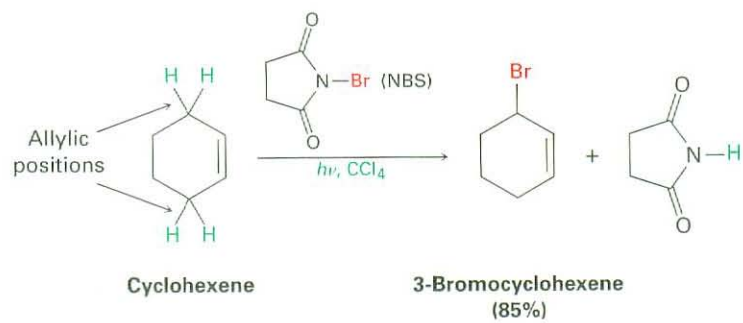
Problem 10.4 Taking the relative reactivities of 1°, 2°, and 3° hydrogen atoms into account, what product(s) would you expect to obtain from monochlorination of 2-methylbutane? What would the approximate percentage of each product be? (Don't forget to take into account the number of each sort of hydrogen.)

10.4 Preparing Alkyl Halides from Alkenes: Allylic Bromination

We've already seen several methods for preparing alkyl halides from alkenes, including the reactions of HX and X_2 with alkenes in electrophilic addition reactions (Sections 6.7 and 7.2). The hydrogen halides HCl, HBr, and HI react with alkenes by a polar mechanism to give the product of Markovnikov addition. Bromine and chlorine undergo anti addition through halonium ion intermediates to give 1,2-dihalogenated products.

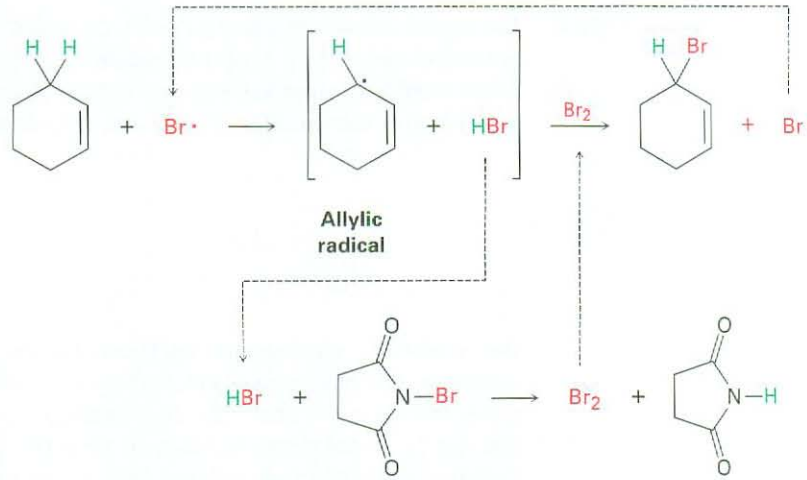


Another method for preparing alkyl halides from alkenes is by reaction with *N*-bromosuccinimide (abbreviated NBS) in the presence of light to give products resulting from substitution of hydrogen by bromine at the **allylic** position—the position *next to* the double bond. Cyclohexene, for example, gives 3-bromocyclohexene.



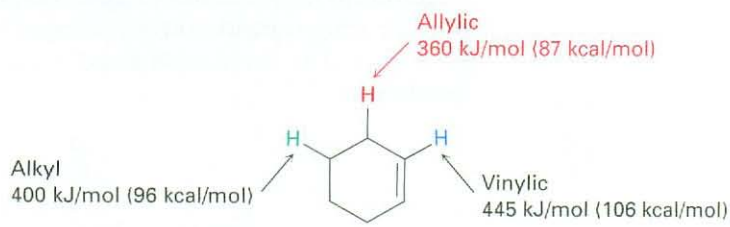
This allylic bromination with NBS is analogous to the alkane halogenation reaction discussed in the previous section and occurs by a radical chain reaction pathway. As in alkane halogenation, Br· radical abstracts an allylic hydrogen atom of the alkene, thereby forming an allylic radical plus HBr. This allylic radical then reacts with Br_2 to yield the product and a Br· radical, which cycles back

into the first step and carries on the chain. The Br_2 results from reaction of NBS with the HBr formed in the first step.

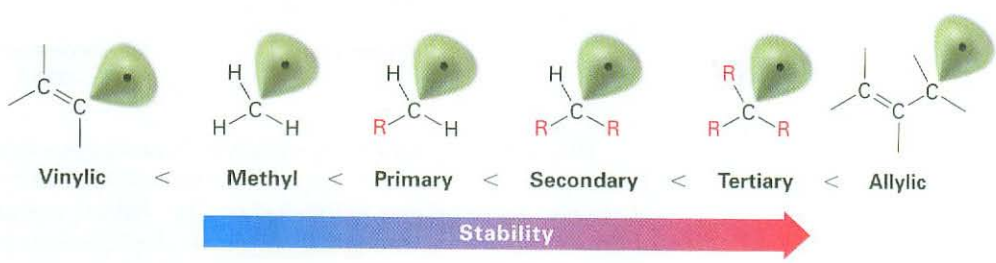


Why does bromination with NBS occur exclusively at an allylic position rather than elsewhere in the molecule? The answer, once again, is found by looking at bond dissociation energies to see the relative stabilities of various kinds of radicals.

There are three sorts of C–H bonds in cyclohexene, and Table 5.3 gives an estimate of their relative strengths. Although a typical secondary alkyl C–H bond has a strength of about 400 kJ/mol (96 kcal/mol) and a typical vinylic C–H bond has a strength of 445 kJ/mol (106 kcal/mol), an *allylic* C–H bond has a strength of only about 360 kJ/mol (87 kcal/mol). An allylic radical is therefore more stable than a typical alkyl radical with the same substitution by about 40 kJ/mol (9 kcal/mol).



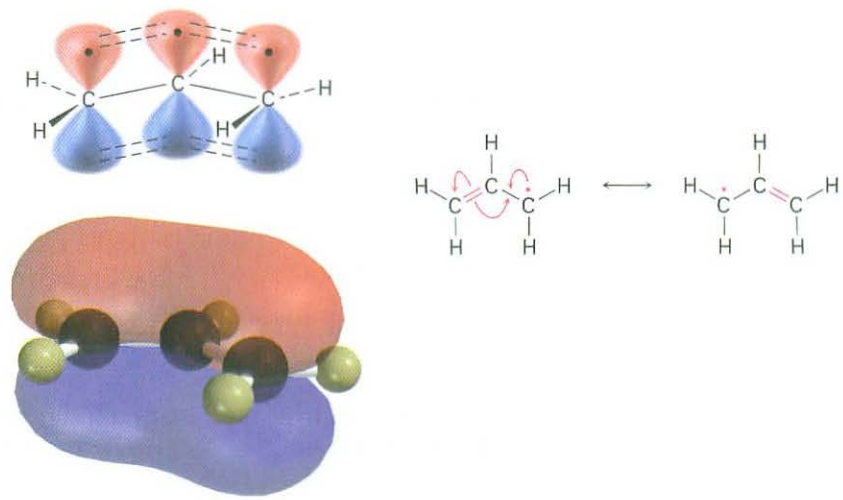
We can thus expand the stability ordering to include vinylic and allylic radicals.



10.5 Stability of the Allyl Radical: Resonance Revisited

To see why allylic radicals are so stable, look at the orbital picture in Figure 10.3. The radical carbon atom with an unpaired electron can adopt sp^2 hybridization, placing the unpaired electron in a *p* orbital and giving a structure that is electronically symmetrical. The *p* orbital on the central carbon can therefore overlap equally well with a *p* orbital on *either* of the two neighboring carbons.

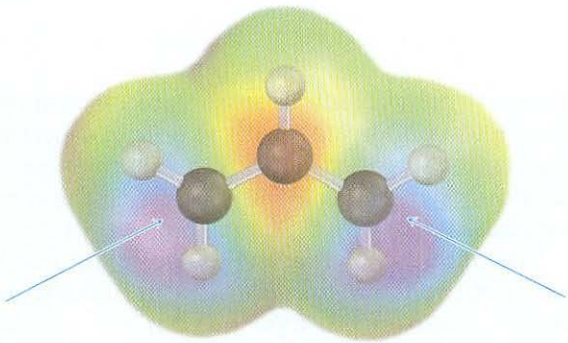
Because the allyl radical is electronically symmetrical, it can be drawn in either of two resonance forms—with the unpaired electron on the left and the double bond on the right or with the unpaired electron on the right and the double bond on the left. Neither structure is correct by itself; the true structure of the allyl radical is a resonance hybrid of the two. (You might want to review Sections 2.4–2.6 to brush up on resonance.) As noted in Section 2.5, the greater the number of resonance forms, the greater the stability of a compound because bonding electrons are attracted to more nuclei. An allyl radical, with two resonance forms, is therefore more stable than a typical alkyl radical, which has only a single structure.



Active Figure 10.3 An orbital view of the allyl radical. The *p* orbital on the central carbon can overlap equally well with a *p* orbital on either neighboring carbon, giving rise to two equivalent resonance structures. *Sign in at* **www.thomsonedu.com** *to see a simulation based on this figure and to take a short quiz.*

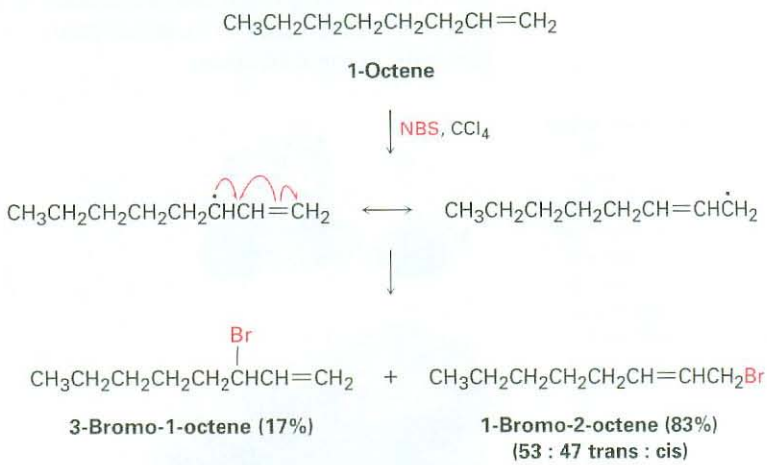
In molecular orbital terms, the stability of the allyl radical is due to the fact that the unpaired electron is **delocalized**, or spread out, over an extended π orbital network rather than localized at only one site, as shown by the computer-generated MO in Fig 10.3. This delocalization is particularly apparent in the so-called spin density surface in Figure 10.4, which shows the calculated location of the unpaired electron. The two terminal carbons share the unpaired electron equally.

In addition to its effect on stability, delocalization of the unpaired electron in the allyl radical has other chemical consequences. Because the unpaired electron is delocalized over both ends of the π orbital system, reaction with Br_2 can occur at either end. As a result, allylic bromination of an unsymmetrical alkene often leads to a mixture of products. For example, bromination of 1-octene gives a mixture of 3-bromo-1-octene and 1-bromo-2-octene. The two products are not formed in equal amounts, however, because the intermediate allylic radical is

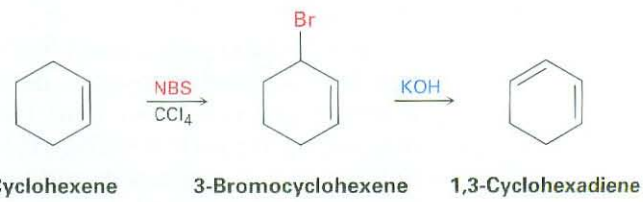


Active Figure 10.4 The spin density surface of the allyl radical locates the position of the unpaired electron (blue) and shows that it is equally shared between the two terminal carbons. *Sign in at* **www.thomsonedu.com** *to see a simulation based on this figure and to take a short quiz.*

not symmetrical and reaction at the two ends is not equally likely. Reaction at the less hindered, primary end is favored.



The products of allylic bromination reactions are useful for conversion into dienes by dehydrohalogenation with base. Cyclohexene can be converted into 1,3-cyclohexadiene, for example.



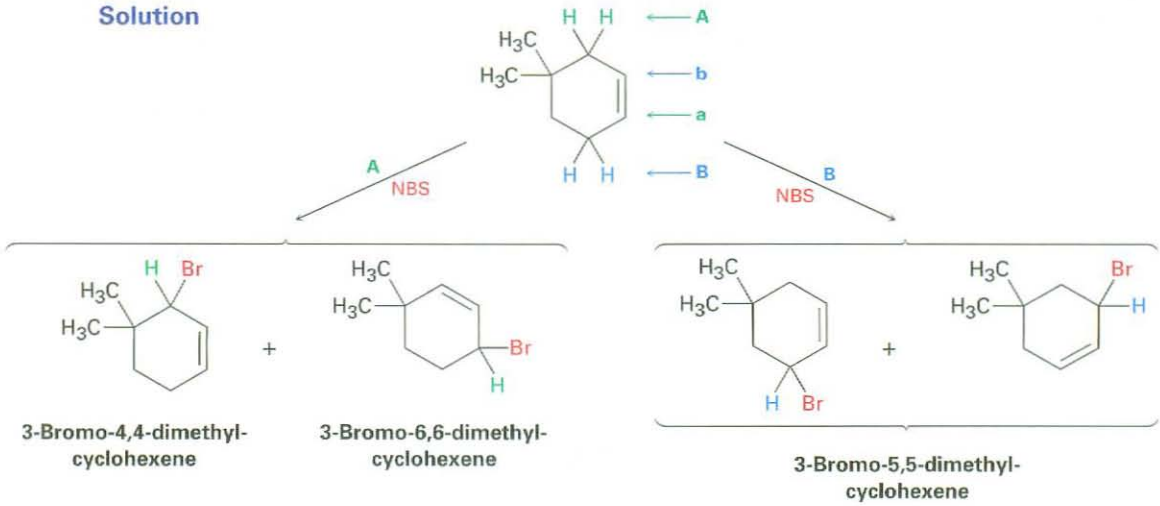
WORKED EXAMPLE 10.1 ***Predicting the Product of an Allylic Bromination Reaction***

What products would you expect from reaction of 4,4-dimethylcyclohexene with NBS?

Strategy Draw the alkene reactant, and identify the allylic positions. In this case, there are two different allylic positions; we'll label them **A** and **B**. Now abstract an allylic hydrogen

from each position to generate the two corresponding allylic radicals. Each of the two allylic radicals can add a Br atom at either end (**A** or **a**; **B** or **b**) to give a mixture of up to four products. Draw and name the products. In the present instance, the "two" products from reaction at position **B** are identical, so a total of only three products are formed in this reaction.

Solution



Problem 10.5 Draw three resonance forms for the cyclohexadienyl radical.

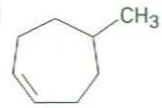
Cyclohexadienyl radical

Problem 10.6 The major product of the reaction of methylenecyclohexane with *N*-bromosuccinimide is 1-(bromomethyl)cyclohexene. Explain.

Major product

Problem 10.7 What products would you expect from reaction of the following alkenes with NBS? If more than one product is formed, show the structures of all.

(a)

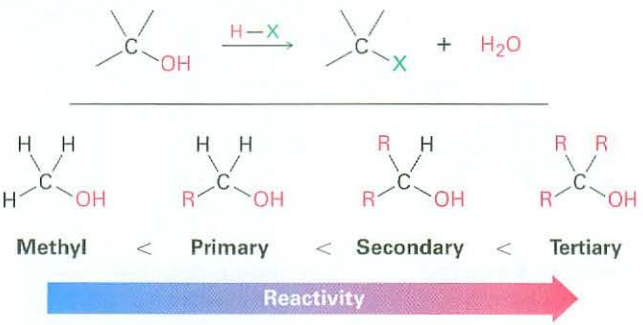


(b) $CH_3CHCH{=}CHCH_2CH_3$

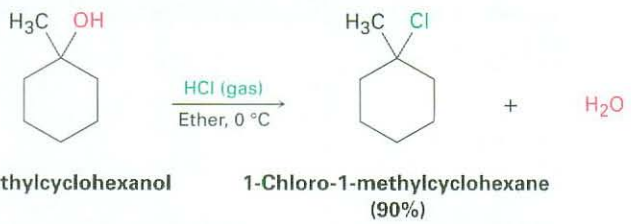
10.6 Preparing Alkyl Halides from Alcohols

ThomsonNOW Click *Organic Interactive* to **use a web-based palette to design a synthesis of alkyl halides, beginning with alcohols.**

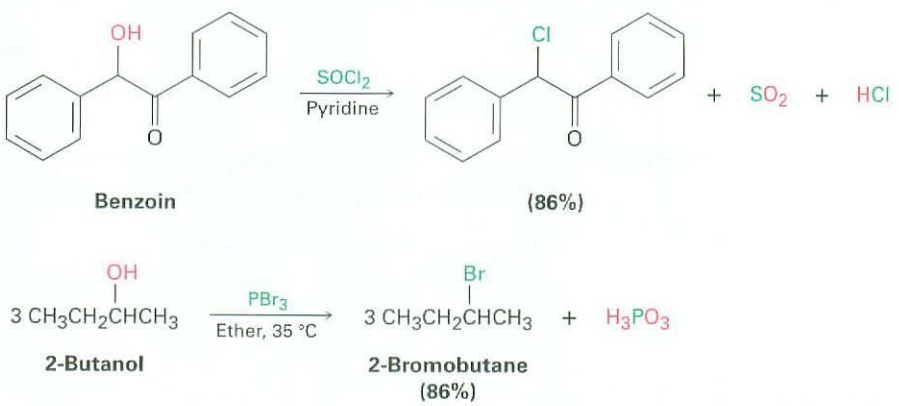
The most generally useful method for preparing alkyl halides is to make them from alcohols, which themselves can be obtained from carbonyl compounds, as we'll see in Sections 17.4 and 17.5. Because of the importance of the process, many different methods have been developed to transform alcohols into alkyl halides. The simplest method is to treat the alcohol with HCl, HBr, or HI. For reasons that will be discussed in Section 11.5, the reaction works best with tertiary alcohols, R_3COH. Primary and secondary alcohols react much more slowly and at higher temperatures.



The reaction of HX with a tertiary alcohol is so rapid that it's often carried out simply by bubbling the pure HCl or HBr gas into a cold ether solution of the alcohol. 1-Methylcyclohexanol, for example, is converted into 1-chloro-1-methylcyclohexane by treating with HCl.



Primary and secondary alcohols are best converted into alkyl halides by treatment with either thionyl chloride ($SOCl_2$) or phosphorus tribromide (PBr_3). These reactions, which normally take place readily under mild conditions, are less acidic and less likely to cause acid-catalyzed rearrangements than the HX method.



As the preceding examples indicate, the yields of these $SOCl_2$ and PBr_3 reactions are generally high, and other functional groups such as ethers, carbonyls, and aromatic rings don't usually interfere. We'll look at the mechanisms of these substitution reactions in the next chapter.

Problem 10.8 How would you prepare the following alkyl halides from the corresponding alcohols?

(a) CH_3CCH_3 (Cl, CH_3)

(b) $CH_3CHCH_2CHCH_3$ (Br, CH_3)

(c) $BrCH_2CH_2CH_2CH_2CHCH_3$ (CH_3)

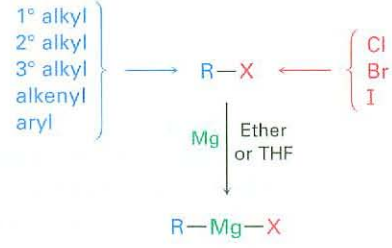
(d) $CH_3CH_2CHCH_2CCH_3$ (CH_3, Cl, CH_3)

10.7 Reactions of Alkyl Halides: Grignard Reagents

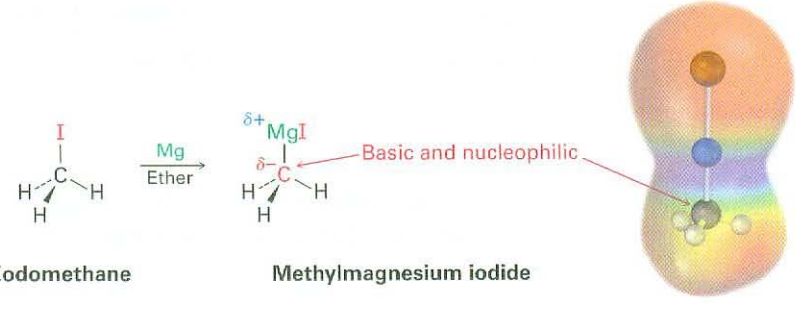
François Auguste Victor Grignard

François Auguste Victor Grignard (1871–1935) was born in Cherbourg, France, and received his Ph.D. at the University of Lyon in 1901. During his doctoral work under Philippe Barbier, Grignard discovered the preparation and usefulness of organomagnesium reagents. He became professor of chemistry at Nancy and at Lyon, and he won the Nobel Prize in chemistry in 1912. During World War I, he was drafted into the French army as a Corporal (a Nobel Prize–winning Corporal!), where he developed a method for detecting German war gases.

Alkyl halides, RX, react with magnesium metal in ether or tetrahydrofuran (THF) solvent to yield alkylmagnesium halides, RMgX. The products, called **Grignard reagents** after their discoverer, Victor Grignard, are examples of *organometallic* compounds because they contain a carbon–metal bond. In addition to alkyl halides, Grignard reagents can also be made from alkenyl (vinylic) and aryl (aromatic) halides. The halogen can be Cl, Br, or I, although chlorides are less reactive than bromides and iodides. Organofluorides rarely react with magnesium.



As you might expect from the discussion of electronegativity and bond polarity in Section 5.4, the carbon–magnesium bond is polarized, making the carbon atom of Grignard reagents both nucleophilic and basic. An electrostatic potential map of methylmagnesium iodide, for instance, indicates the electron-rich (red) character of the carbon bonded to magnesium.



In a formal sense, a Grignard reagent is the magnesium salt, $R_3C^- {}^+MgX$, of a carbon acid, R_3C-H. But because hydrocarbons are such weak acids, with pK_a's in the range of 44 to 60 (Section 8.7), carbon anions are very strong bases. Grignard reagents therefore react with such weak acids as H_2O, ROH, RCO_2H, and RNH_2 to abstract a proton and yield hydrocarbons. Thus, an organic halide can be reduced to a hydrocarbon by converting it to a Grignard reagent followed by protonation, $R-X \rightarrow R-MgX \rightarrow R-H$.

$$\underset{\text{1-Bromohexane}}{CH_3CH_2CH_2CH_2CH_2CH_2Br} \xrightarrow[\text{Ether}]{Mg} \underset{\text{1-Hexylmagnesium bromide}}{CH_3CH_2CH_2CH_2CH_2CH_2MgBr} \xrightarrow{H_2O} \underset{\text{Hexane (85\%)}}{CH_3CH_2CH_2CH_2CH_2CH_3}$$

We'll see many more uses of Grignard reagents as sources for carbon nucleophiles in later chapters.

Problem 10.9 How strong a base would you expect a Grignard reagent to be? Look at Table 8.1 on page 271, and then predict whether the following reactions will occur as written. (The pK_a of NH_3 is 35.)

(a) $CH_3MgBr + H-C\equiv C-H \rightarrow CH_4 + H-C\equiv C-MgBr$

(b) $CH_3MgBr + NH_3 \rightarrow CH_4 + H_2N-MgBr$

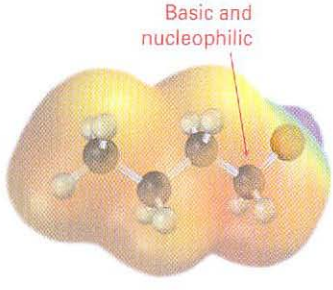
Problem 10.10 How might you replace a halogen substituent by a deuterium atom if you wanted to prepare a deuterated compound?

$$CH_3\underset{\displaystyle Br}{\underset{|}{C}}HCH_2CH_3 \xrightarrow{?} CH_3\underset{\displaystyle D}{\underset{|}{C}}HCH_2CH_3$$

10.8 Organometallic Coupling Reactions

Many other kinds of organometallic compounds can be prepared in a manner similar to that of Grignard reagents. For instance, alkyllithium reagents, RLi, can be prepared by the reaction of an alkyl halide with lithium metal. Alkyllithiums are both nucleophiles and strong bases, and their chemistry is similar in many respects to that of alkylmagnesium halides.

$$\underset{\text{1-Bromobutane}}{CH_3CH_2CH_2CH_2Br} \xrightarrow[\text{Pentane}]{2\,Li} \underset{\text{Butyllithium}}{CH_3CH_2CH_2CH_2Li} + LiBr$$



One particularly valuable reaction of alkyllithiums is in making lithium diorganocopper compounds, LiR_2Cu, by reaction with copper(I) iodide in

Henry Gilman

Henry Gilman (1893–1986) was born in Boston, Massachusetts, and received his Ph.D. in 1918 at Harvard. He then became professor of chemistry at Iowa State University (1919–1962), where he remained active until his death at age 93. An extremely prolific researcher, Gilman published more than 1000 scientific papers during his career. Remarkably, he lost much of his eyesight at age 53 but *still went on* to accomplish some of his finest work in later years.

diethyl ether as solvent. Called **Gilman reagents**, lithium diorganocopper compounds are useful because they undergo a *coupling* reaction with organochlorides, organobromides, and organoiodides (but not fluorides). One of the alkyl groups from the Gilman reagent replaces the halogen of the organohalide, forming a new carbon–carbon bond and yielding a hydrocarbon product. Lithium dimethylcopper, for example, reacts with 1-iododecane to give undecane in 90% yield.

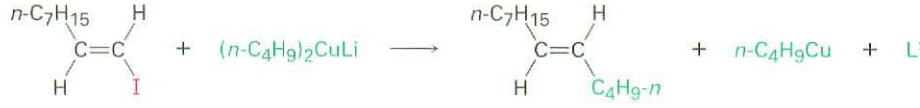
$$2\ CH_3Li + CuI \xrightarrow{\text{Ether}} (CH_3)_2Cu^-\ Li^+ + LiI$$

Methyllithium — **Lithium dimethylcopper (a Gilman reagent)**

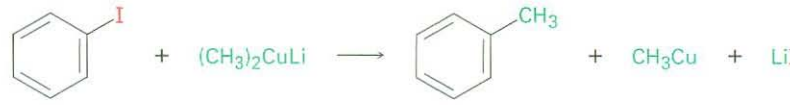
$$(CH_3)_2CuLi + CH_3(CH_2)_8CH_2I \xrightarrow[0\ ^\circ C]{\text{Ether}} CH_3(CH_2)_8CH_2CH_3 + LiI + CH_3Cu$$

Lithium dimethylcopper — **1-Iododecane** — **Undecane (90%)**

This organometallic coupling reaction is useful in organic synthesis because it forms carbon–carbon bonds, thereby making possible the preparation of larger molecules from smaller ones. As the following examples indicate, the coupling reaction can be carried out on aryl and vinylic halides as well as on alkyl halides.

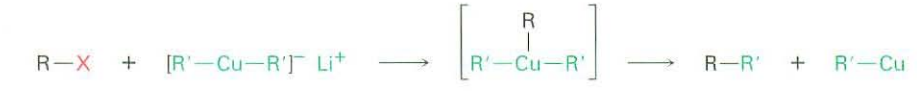


***trans*-1-Iodo-1-nonene** — ***trans*-5-Tridecene (71%)**



Iodobenzene — **Toluene (91%)**

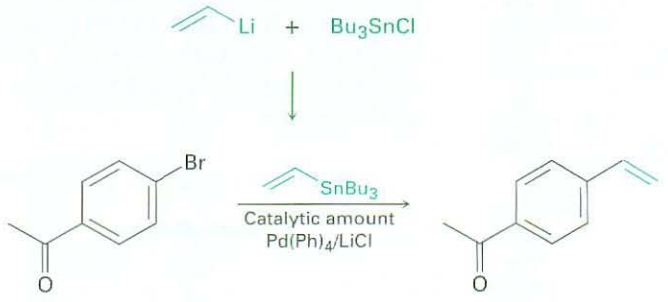
The mechanism of the reaction involves initial formation of a triorganocopper intermediate, followed by coupling and loss of RCu. The coupling is not a typical polar nucleophilic substitution reaction of the sort considered in the next chapter.



ThomsonNOW Click *Organic Interactive* to **learn more about the preparation of organometallics and their use in coupling reactions.**

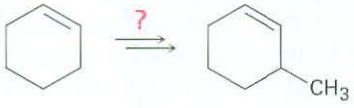
In addition to the coupling reaction of diorganocopper reagents with organohalides, related processes also occur with other organometallics, particularly organopalladium compounds. One of the more commonly used procedures is the palladium-catalyzed reaction of an aryl or vinyl substituted organotin reagent with an organohalide. The organotin is itself usually formed

by reaction of an organolithium such as vinyllithium with tributyltin chloride, Bu_3SnCl. For example:



para-Bromoacetophenone *para*-Vinylacetophenone

Problem 10.11 How would you carry out the following transformations using an organocopper coupling reaction? More than one step is required in each case.

(a) 

(b) $CH_3CH_2CH_2CH_2Br \xrightarrow{?} CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_3$

(c) $CH_3CH_2CH_2CH{=}CH_2 \xrightarrow{?} CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_3$

10.9 Oxidation and Reduction in Organic Chemistry

We've pointed out on several occasions that some of the reactions discussed in this and earlier chapters are either *oxidations* or *reductions*. As noted in Sections 7.7 and 7.8, an organic oxidation results in a loss of electron density by carbon, caused either by bond formation between carbon and a more electronegative atom (usually O, N, or a halogen) or by bond-breaking between carbon and a less electronegative atom (usually H). Conversely, an organic reduction results in a gain of electron density by carbon, caused either by bond formation between carbon and a less electronegative atom or by bond-breaking between carbon and a more electronegative atom.

Oxidation Decreases electron density on carbon by:
- forming one of these: C–O C–N C–X
- or breaking this: C–H

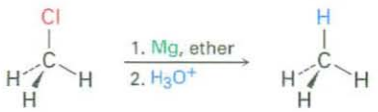
Reduction Increases electron density on carbon by:
- forming this: C–H
- or breaking one of these: C–O C–N C–X

Based on these definitions, the chlorination reaction of methane to yield chloromethane is an oxidation because a C–H bond is broken and a C–Cl bond

is formed. The conversion of an alkyl chloride to an alkane via a Grignard reagent followed by protonation is a reduction, however, because a C–Cl bond is broken and a C–H bond is formed.

Methane **Chloromethane**

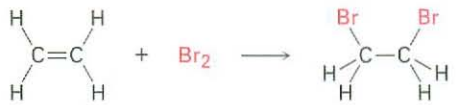
Oxidation: C–H bond broken and C–Cl bond formed



Chloromethane **Methane**

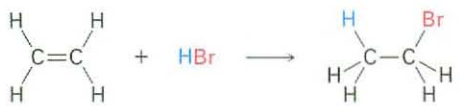
Reduction: C–Cl bond broken and C–H bond formed

As other examples, the reaction of an alkene with Br_2 to yield a 1,2-dibromide is an oxidation because two C–Br bonds are formed, but the reaction of an alkene with HBr to yield an alkyl bromide is neither an oxidation nor a reduction because both a C–H and a C–Br bond are formed.



Ethylene **1,2-Dibromoethane**

Oxidation: Two new bonds formed between carbon and a more electronegative element



Ethylene **Bromoethane**

Neither oxidation nor reduction: One new C–H bond and one new C–Br bond formed

A list of compounds of increasing oxidation level is shown in Figure 10.5. Alkanes are at the lowest oxidation level because they have the maximum possible number of C–H bonds per carbon, and CO_2 is at the highest level because it has the maximum possible number of C–O bonds per carbon. Any reaction that converts a compound from a lower level to a higher level is an oxidation, any reaction that converts a compound from a higher level to a lower level is a reduction, and any reaction that doesn't change the level is neither an oxidation nor a reduction.

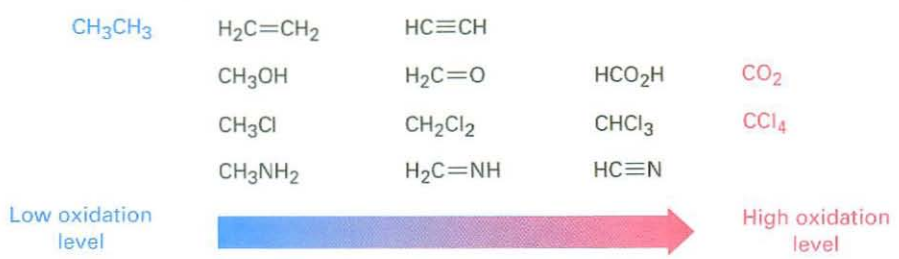
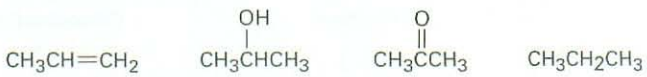


Figure 10.5 Oxidation levels of some common types of compounds.

Worked Example 10.2 shows how to compare the oxidation levels of different compounds with the same number of carbon atoms.

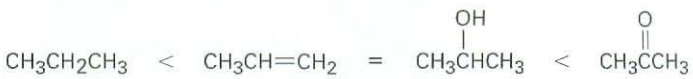
WORKED EXAMPLE 10.2 ***Comparing Oxidation Levels of Compounds***

Rank the following compounds in order of increasing oxidation level:



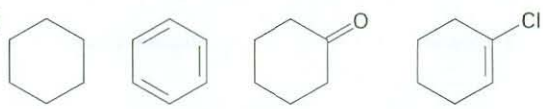
Strategy Compounds that have the same number of carbon atoms can be compared by adding the number of C–O, C–N, and C–X bonds in each and then subtracting the number of C–H bonds. The larger the resultant value, the higher the oxidation level.

Solution The first compound (propene) has six C–H bonds, giving an oxidation level of −6; the second (2-propanol) has one C–O bond and seven C–H bonds, giving an oxidation level of −6; the third (acetone) has two C–O bonds and six C–H bonds, giving an oxidation level of −4; and the fourth (propane) has eight C–H bonds, giving an oxidation level of −8. Thus, the order of increasing oxidation level is



Problem 10.12 Rank each of the following series of compounds in order of increasing *oxidation* level:

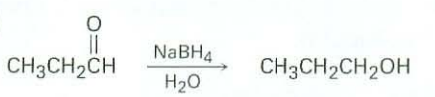
(a)



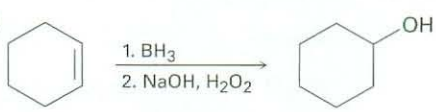
(b) CH_3CN $CH_3CH_2NH_2$ $H_2NCH_2CH_2NH_2$

Problem 10.13 Tell whether each of the following reactions is an oxidation, a reduction, or neither.

(a)



(b)



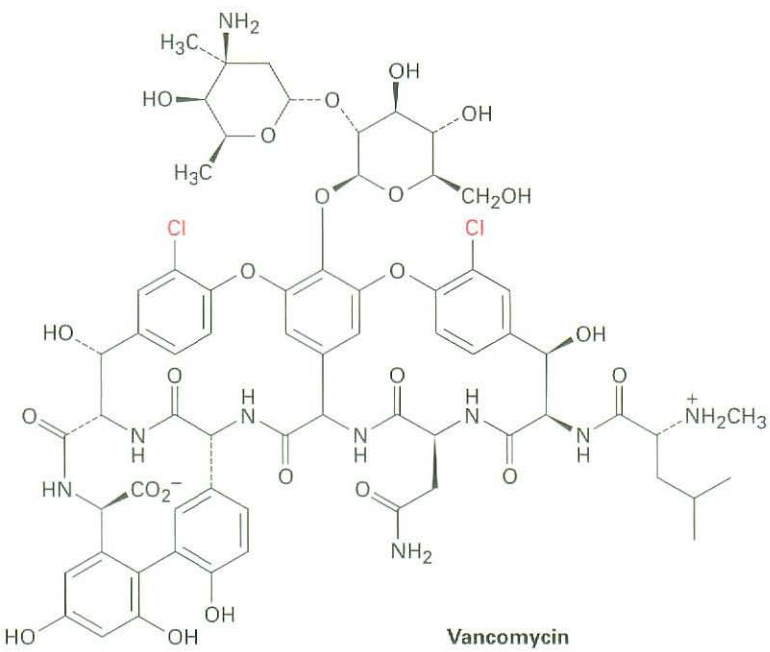
Focus On . . .

Naturally Occurring Organohalides

© Stuart Westmorland/Corbis

Marine corals secrete organohalogen compounds that act as a feeding deterrent to starfish.

As recently as 1970, only about 30 naturally occurring organohalogen compounds were known. It was simply assumed that chloroform, halogenated phenols, chlorinated aromatic compounds called PCBs, and other such substances found in the environment were industrial pollutants. Now, only a third of a century later, the situation is quite different. More than 5000 organohalogen compounds have been found to occur naturally, and tens of thousands more surely exist. From a simple compound like chloromethane to an extremely complex one like vancomycin, a remarkably diverse range of organohalogen compounds exists in plants, bacteria, and animals. Many even have valuable physiological activity. Vancomycin, for instance, is a powerful antibiotic produced by the bacterium *Amycolatopsis orientalis* and used clinically to treat methicillin-resistant *Staphylococcus aureus* (MRSA).



Vancomycin

Some naturally occurring organohalogen compounds are produced in massive quantities. Forest fires, volcanoes, and marine kelp release up to *5 million tons* of CH_3Cl per year, for example, while annual industrial emissions

(continued)

total about 26,000 tons. Termites are thought to release as much as 10^8 kg of chloroform per year. A detailed examination of the Okinawan acorn worm *Ptychodera flava* found that the 64 million worms living in a 1 km^2 study area excreted nearly 8000 pounds per year of bromophenols and bromoindoles, compounds previously thought to be nonnatural pollutants.

Why do organisms produce organohalogen compounds, many of which are undoubtedly toxic? The answer seems to be that many organisms use organohalogen compounds for self-defense, either as feeding deterrents, as irritants to predators, or as natural pesticides. Marine sponges, coral, and sea hares, for example, release foul-tasting organohalogen compounds that deter fish, starfish, and other predators from eating them. Even humans appear to produce halogenated compounds as part of their defense against infection. The human immune system contains a peroxidase enzyme capable of carrying out halogenation reactions on fungi and bacteria, thereby killing the pathogen. And most remarkable of all, even free chlorine—Cl_2—has been found to be present in humans.

Much remains to be learned—only a few hundred of the more than 500,000 known species of marine organisms have been examined—but it is clear that organohalogen compounds are an integral part of the world around us.

SUMMARY AND KEY WORDS

Alkyl halides contain a halogen bonded to a saturated, sp^3-hybridized carbon atom. The C–X bond is polar, and alkyl halides can therefore behave as electrophiles.

Simple alkyl halides can be prepared by radical halogenation of alkanes, but mixtures of products usually result. The reactivity order of alkanes toward halogenation is identical to the stability order of radicals: $R_3C\cdot > R_2CH\cdot > RCH_2\cdot$. Alkyl halides can also be prepared from alkenes by reaction with *N*-bromosuccinimide (NBS) to give the product of **allylic** bromination. The NBS bromination of alkenes takes place through an intermediate allylic radical, which is stabilized by resonance.

Alcohols react with HX to form alkyl halides, but the reaction works well only for tertiary alcohols, R_3COH. Primary and secondary alkyl halides are normally prepared from alcohols using either $SOCl_2$ or PBr_3. Alkyl halides react with magnesium in ether solution to form organomagnesium halides, called **Grignard reagents (RMgX)**. Because Grignard reagents are both nucleophilic and basic, they react with acids to yield hydrocarbons. The overall result of Grignard formation and protonation is the conversion of an alkyl halide into an alkane (RX $\rightarrow$ RMgX $\rightarrow$ RH).

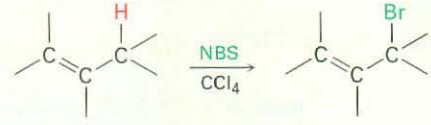
Alkyl halides also react with lithium metal to form organolithium reagents, RLi. In the presence of CuI, these form diorganocoppers, or **Gilman reagents (LiR_2Cu)**. Gilman reagents react with alkyl halides to yield coupled hydrocarbon products.

In organic chemistry, an *oxidation* is a reaction that causes a decrease in electron density on carbon, either by bond formation between carbon and a more electronegative atom (usually oxygen, nitrogen, or a halogen) or by bond-breaking

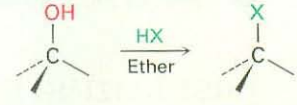
between carbon and a less electronegative atom (usually hydrogen). Conversely, a *reduction* causes an increase of electron density on carbon, either by bond-breaking between carbon and a more electronegative atom or by bond formation between carbon and a less electronegative atom. Thus, the halogenation of an alkane to yield an alkyl halide is an oxidation, while the conversion of an alkyl halide to an alkane by protonation of a Grignard reagent is a reduction.

SUMMARY OF REACTIONS

1. Preparation of alkyl halides
   (a) From alkenes by allylic bromination (Section 10.4)

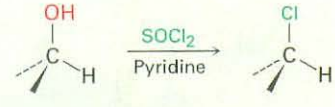


   (b) From alcohols (Section 10.6)
      (1) Reaction with HX

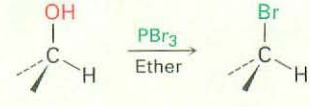


Reactivity order: 3° > 2° > 1°

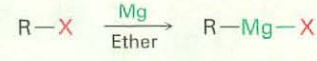
      (2) Reaction of 1° and 2° alcohols with $SOCl_2$



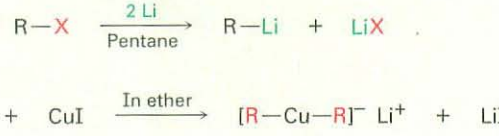
      (3) Reaction of 1° and 2° alcohols with PBr_3



2. Reactions of alkyl halides
   (a) Formation of Grignard (organomagnesium) reagents (Section 10.7)



   (b) Formation of Gilman (diorganocopper) reagents (Section 10.8)



(c) Organometallic coupling (Section 10.8)

$$R_2CuLi + R'-X \xrightarrow{\text{In ether}} R-R' + RCu + LiX$$

(d) Reduction of alkyl halides to alkanes (Section 10.7)

$$R-X \xrightarrow[\text{Ether}]{Mg} R-Mg-X \xrightarrow{H_3O^+} R-H + HOMgX$$

EXERCISES

Organic KNOWLEDGE TOOLS

ThomsonNOW Sign in at **www.thomsonedu.com** to assess your knowledge of this chapter's topics by taking a pre-test. The pre-test will link you to interactive organic chemistry resources based on your score in each concept area.

Online homework for this chapter may be assigned in Organic OWL.

■ indicates problems assignable in Organic OWL.

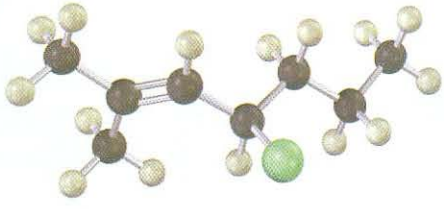
VISUALIZING CHEMISTRY

(Problems 10.1–10.13 appear within the chapter.)

10.14 ■ Give a IUPAC name for each of the following alkyl halides (yellow-green = Cl):

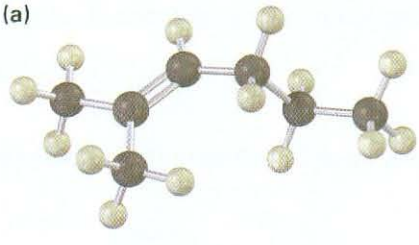
(a)

(b)

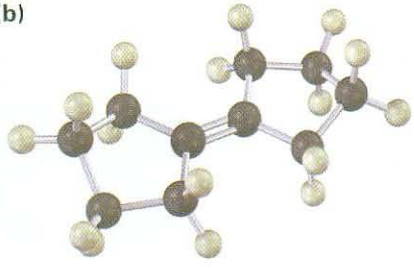


10.15 ■ Show the product(s) of reaction of the following alkenes with NBS:

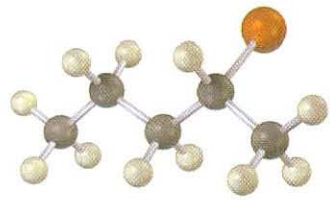
(a)



(b)



10.16 The following alkyl bromide can be prepared by reaction of the alcoho (*S*)-2-pentanol with PBr_3. Name the compound, assign (*R*) or (*S*) stereochemistry and tell whether the reaction of the alcohol occurs with retention of the same stereochemistry or with a change in stereochemistry (reddish brown = Br).



ADDITIONAL PROBLEMS

10.17 ■ Name the following alkyl halides:

(a) $CH_3CHCHCHCH_2CHCH_3$ (H, Br, Br, CH_3)

(b) $CH_3CH{=}CHCH_2CHCH_3$ (I)

(c) $CH_3CCH_2CHCHCH_3$ (Br, Cl, CH_3; CH_3)

(d) $CH_3CH_2CHCH_2CH_2CH_3$ (CH_2Br)

(e) $ClCH_2CH_2CH_2C{\equiv}CCH_2Br$

10.18 ■ Draw structures corresponding to the following IUPAC names:

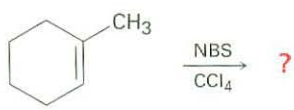
(a) 2,3-Dichloro-4-methylhexane
(b) 4-Bromo-4-ethyl-2-methylhexane
(c) 3-Iodo-2,2,4,4-tetramethylpentane
(d) *cis*-1-Bromo-2-ethylcyclopentane

10.19 ■ Draw and name the monochlorination products you might obtain by radical chlorination of 2-methylbutane. Which of the products are chiral? Are any of the products optically active?

10.20 A chemist requires a large amount of 1-bromo-2-pentene as starting material for a synthesis and decides to carry out an NBS allylic bromination reaction. What is wrong with the following synthesis plan? What side products would form in addition to the desired product?

$$CH_3CH_2CH{=}CHCH_3 \xrightarrow[CCl_4]{NBS} CH_3CH_2CH{=}CHCH_2Br$$

10.21 What product(s) would you expect from the reaction of 1-methylcyclohexene with NBS? Would you use this reaction as part of a synthesis?

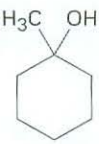


10.22 ■ How would you prepare the following compounds, starting with cyclopentene and any other reagents needed?

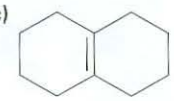
(a) Chlorocyclopentane
(b) Methylcyclopentane
(c) 3-Bromocyclopentene
(d) Cyclopentanol
(e) Cyclopentylcyclopentane
(f) 1,3-Cyclopentadiene

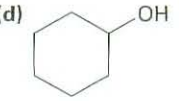
■ Assignable in OWL

10.23 ■ Predict the product(s) of the following reactions:

(a) 

(b) $CH_3CH_2CH_2CH_2OH \xrightarrow{SOCl_4}$?

(c) 

(d) 

(e) $CH_3CH_2CHBrCH_3 \xrightarrow[\text{Ether}]{Mg}$ A? $\xrightarrow{H_2O}$ B?

(f) $CH_3CH_2CH_2CH_2Br \xrightarrow[\text{Pentane}]{Li}$ A? $\xrightarrow{CuI}$ B?

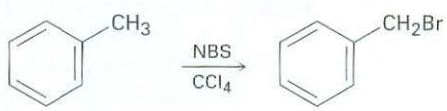
(g) $CH_3CH_2CH_2CH_2Br + (CH_3)_2CuLi \xrightarrow{\text{Ether}}$?

10.24 (*S*)-3-Methylhexane undergoes radical bromination to yield optically inactive 3-bromo-3-methylhexane as the major product. Is the product chiral? What conclusions can you draw about the radical intermediate?

10.25 Assume that you have carried out a radical chlorination reaction on (*R*)-2-chloropentane and have isolated (in low yield) 2,4-dichloropentane. How many stereoisomers of the product are formed and in what ratio? Are any of the isomers optically active? (See Problem 10.24.)

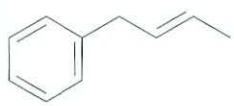
10.26 What product(s) would you expect from the reaction of 1,4-hexadiene with NBS? What is the structure of the most stable radical intermediate?

10.27 Alkylbenzenes such as toluene (methylbenzene) react with NBS to give products in which bromine substitution has occurred at the position next to the aromatic ring (the *benzylic* position). Explain, based on the bond dissociation energies in Table 5.3 on page 156.



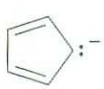
10.28 Draw resonance structures for the benzyl radical, $C_6H_5CH_2\cdot$, the intermediate produced in the NBS bromination reaction of toluene (Problem 10.27).

10.29 What product would you expect from the reaction of 1-phenyl-2-butene with NBS? Explain.



1-Phenyl-2-butene

10.30 ■ Draw resonance structures for the following species:

(a) $CH_3CH{=}CHCH{=}CHCH{=}\overset{+}{C}HCH_2$ (b)  (c) $CH_3C{\equiv}\overset{+}{N}{-}\ddot{\underset{\cdot\cdot}{O}}:^{-}$

10.31 ■ Rank the compounds in each of the following series in order of increasin oxidation level:

(a)

$CH_3CH{=}CHCH_3$ $CH_3CH_2CH{=}CH_2$ $CH_3CH_2CH_2\overset{\overset{O}{\|}}{C}H$ $CH_3CH_2CH_2\overset{\overset{O}{\|}}{C}OH$

(b)

$CH_3CH_2CH_2NH_2$ $CH_3CH_2CH_2Br$ $CH_3\overset{\overset{O}{\|}}{C}CH_2Cl$ $BrCH_2CH_2CH_2Cl$

10.32 Which of the following compounds have the same oxidation level, and which have different levels?

1 2 3 4 5

10.33 ■ Tell whether each of the following reactions is an oxidation, a reduction, or neither:

(a)

$$CH_3CH_2OH \xrightarrow{CrO_3} CH_3\overset{\overset{O}{\|}}{C}H$$

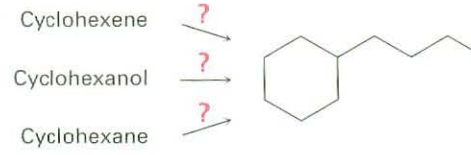
(b)

$$H_2C{=}CH\overset{\overset{O}{\|}}{C}CH_3 + NH_3 \longrightarrow H_2NCH_2CH_2\overset{\overset{O}{\|}}{C}CH_3$$

(c)

$$CH_3CH_2\overset{\overset{Br}{|}}{C}HCH_3 \xrightarrow[2.\ H_2O]{1.\ Mg} CH_3CH_2CH_2CH_3$$

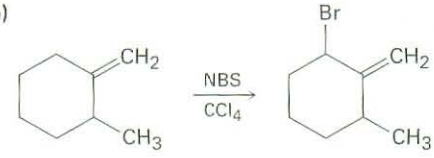
10.34 ■ How would you carry out the following syntheses?



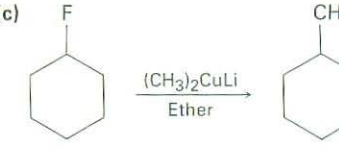
10.35 The syntheses shown here are unlikely to occur as written. What is wrong with each?

(a) $CH_3CH_2CH_2F \xrightarrow[2.\ H_3O^+]{1.\ Mg} CH_3CH_2CH_3$

(b)



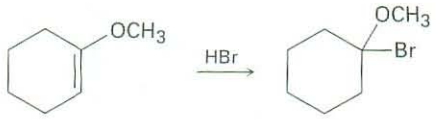
(c)



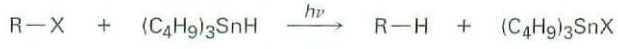
■ Assignable in OWL

10.36 Why do you suppose it's not possible to prepare a Grignard reagent from a bromo alcohol such as 4-bromo-1-pentanol? Give another example of a molecule that is unlikely to form a Grignard reagent.

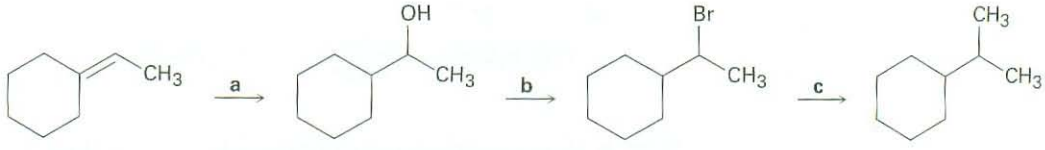
10.37 ■ Addition of HBr to a double bond with an ether (−OR) substituent occurs regiospecifically to give a product in which the −Br and −OR are bonded to the same carbon. Draw the two possible carbocation intermediates in this electrophilic addition reaction, and explain using resonance why the observed product is formed.



10.38 Alkyl halides can be reduced to alkanes by a radical reaction with tributyltin hydride, $(C_4H_9)_3SnH$, in the presence of light ($h\nu$). Propose a radical chain mechanism by which the reaction might occur. The initiation step is the light-induced homolytic cleavage of the Sn−H bond to yield a tributyltin radical.

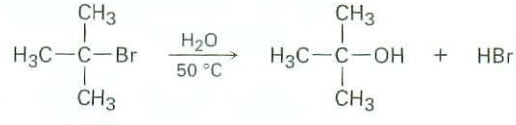


10.39 Identify the reagents a–c in the following scheme:



10.40 Tertiary alkyl halides, R_3CX, undergo spontaneous dissociation to yield a carbocation, R_3C^+, plus halide ion. Which do you think reacts faster, $(CH_3)_3CBr$ or $H_2C{=}CHC(CH_3)_2Br$? Explain.

10.41 In light of the fact that tertiary alkyl halides undergo spontaneous dissociation to yield a carbocation plus halide ion (Problem 10.40), propose a mechanism for the following reaction:



10.42 ■ Carboxylic acids (RCO_2H; $pK_a \approx 5$) are approximately 10^{11} times more acidic than alcohols (ROH; $pK_a \approx 16$). In other words, a carboxylate ion (RCO_2^-) is more stable than an alkoxide ion (RO^-). Explain, using resonance.