

MODULE

6

ORGANIC CHEMISTRY: REACTION MECHANISMS

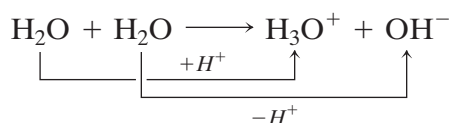
- O3.1 Acids and Bases
- O3.2 Carbanion Attack at a Carbonyl Group
- O3.3 The Mechanism of Reduction Reactions
- O3.4 Nucleophilic Attack by Water
- O3.5 Nucleophilic Attack by an Alcohol
- O3.6 Addition/Elimination Reactions of Carboxylic Acid Derivatives
- O3.7 Free Radical Reactions
- O3.8 Bimolecular Nucleophilic Substitution or S_N2 Reactions
- O3.9 Unimolecular Nucleophilic Substitution or S_N1 Reactions
- O3.10 Elimination Reactions
- O3.11 Substitution versus Elimination Reactions

O3.1 ACIDS AND BASES

As noted in Section 11.1, for more than 300 years, chemists have classified substances that behave like vinegar as **acids**, while those that have properties like the ash from a wood fire have been called **alkalies** or **bases**. Today, when chemists use the words “acid” or “base” they refer to a model developed independently by Brønsted, Lowry, and Bjerrum. Since the most explicit statement of this theory was contained in the writings of Brønsted, it is most commonly known as the “Brønsted acid–base” theory.

Brønsted Acid–Base Theory

Brønsted argued that all acid–base reactions involve the transfer of an H⁺ ion, or proton. Water reacts with itself, for example, by transferring an H⁺ ion from one molecule to another to form an H₃O⁺ ion and an OH⁻ ion.



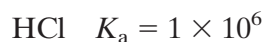
2 ORGANIC REACTION MECHANISMS

According to the theory, a **Brønsted acid** is a proton donor and a **Brønsted base** is a proton acceptor.

Acids are often divided into categories such as “strong” and “weak.” One measure of the strength of an acid is the **acid dissociation equilibrium constant, K_a** , for that acid.

$$K_a = \frac{[\text{H}_3\text{O}^+][\text{A}^-]}{[\text{HA}]}$$

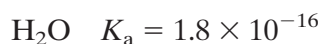
When K_a is relatively large, we have a strong acid.



When it is small, we have a weak acid.



When it is very small, we have a very weak acid.



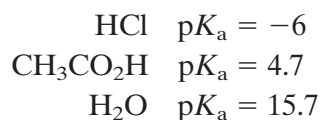
In 1909, S. P. L. Sørensen suggested that the enormous range of concentrations of the H_3O^+ and OH^- ions in aqueous solutions could be compressed into a more manageable set of data by taking advantage of logarithmic mathematics and calculating the pH or pOH of the solution.

$$\begin{aligned} \text{pH} &= -\log[\text{H}_3\text{O}^+] \\ \text{pOH} &= -\log[\text{OH}^-] \end{aligned}$$

The “p” in pH and pOH is an operator that indicates that the negative of the logarithm should be calculated for any quantity to which it is attached. Thus, $\text{p}K_a$ is the negative of the logarithm of the acid dissociation equilibrium constant.

$$\text{p}K_a = -\log K_a$$

The only disadvantage of using $\text{p}K_a$ as a measure of the relative strengths of acids is the fact that large numbers now describe weak acids, and small (negative) numbers describe strong acids.



An important feature of the Brønsted theory is the relationship it creates between acids and bases. Every Brønsted acid has a conjugate base, and vice versa.

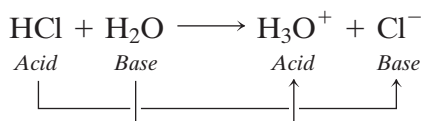


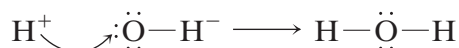
TABLE O3.1 Typical Brønsted Acids and Their Conjugate Bases

Compound	K_a	pK_a	Conjugate Base	K_b	pK_b
HI	3×10^9	-9.5	I^-	3×10^{-24}	23.5
HCl	1×10^6	-6	Cl^-	1×10^{-20}	20
H_2SO_4	1×10^3	-3	HSO_4^-	1×10^{-17}	17
H_3O^+	55	-1.7	H_2O	1.8×10^{-16}	15.7
HNO_3	28	-1.4	NO_3^-	3.6×10^{-16}	15.4
H_3PO_4	7.1×10^{-3}	2.1	$H_2PO_4^-$	1.4×10^{-12}	11.9
CH_3CO_2H	1.8×10^{-5}	4.7	$CH_3CO_2^-$	5.6×10^{-10}	9.3
H_2S	1.0×10^{-7}	7.0	HS^-	1×10^{-7}	7
H_2O	1.8×10^{-16}	15.7	OH^-	55	-1.7
CH_3OH	1×10^{-18}	18	CH_3O^-	1×10^4	-4
$HC\equiv CH$	1×10^{-25}	25	$HC\equiv C^-$	1×10^{11}	-11
NH_3	1×10^{-33}	33	NH_2^-	1×10^{19}	-19
H_2	1×10^{-35}	35	H^-	1×10^{21}	-21
$CH_2=CH_2$	1×10^{-44}	44	$CH_2=CH^-$	1×10^{30}	-30
CH_4	1×10^{-49}	49	CH_3^-	1×10^{35}	-35

Lewis Acid–Base Theory

In 1923, G. N. Lewis introduced a theory of acids and bases that is even more powerful than the Brønsted theory. As a result, it is important to differentiate between the terms “acid” and “base” as they have been used so far and the terms “Lewis acid” and “Lewis base.”

Lewis noted that the Brønsted theory was limited because it focused exclusively on the transfer of a proton (H^+). He noted that a more general definition of acid–base reactions could be obtained by looking at what happens when an H^+ ion combines with an OH^- ion to form water.



Lewis pointed out that the H^+ ion picks up (or accepts) a pair of electrons from the OH^- ion to form a new covalent bond. As a result, any substance that can act as an electron pair acceptor is a **Lewis acid**.

A Lewis acid is an electron pair acceptor, such as the H^+ ion.

The pair of electrons that went into the new covalent bond were donated by the OH^- ion. Lewis therefore argued that any substance that can act as an electron pair donor is a **Lewis base**.

A Lewis base is an electron pair donor, such as the OH^- ion.

The Lewis acid–base theory doesn’t affect the category of compounds we have called “bases” because any Brønsted base must have a pair of nonbonding electrons in order to accept a

proton. The Lewis theory, however, vastly expanded the family of compounds that can be called “acids.” Anything that has one or more empty valence-shell orbitals can act as an acid.

The theory explains why BF_3 reacts instantaneously with NH_3 . The nonbonding electrons on the nitrogen in ammonia are donated into an empty orbital on the boron to form a new covalent bond, as shown in Figure O3.1. It also explains why Cu^{2+} ions pick up ammonia to form the four-coordinate $\text{Cu}(\text{NH}_3)_4^{2+}$ ion.

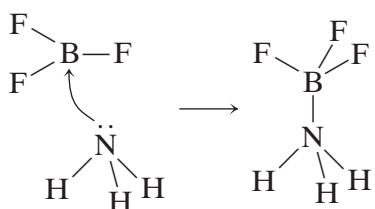
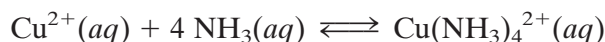
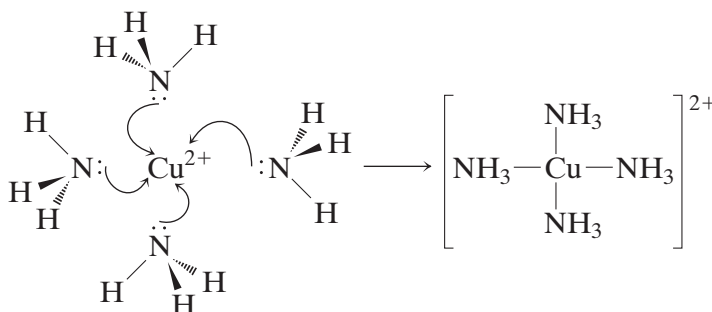


FIGURE O3.1 The reaction between BF_3 acting as a Lewis acid and NH_3 acting as a Lewis base to form an acid–base complex.

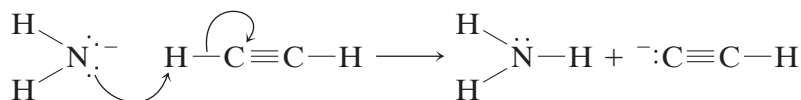


In this case, a pair of nonbonding electrons from each of the four NH_3 molecules is donated into an empty orbital on the Cu^{2+} ion to form a covalent $\text{Cu}-\text{N}$ bond.



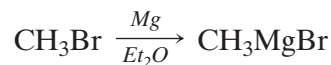
Curved Arrow Symbolism

The flow of electrons from a Lewis base to a Lewis acid is often indicated with a curved arrow. The arrow starts on a pair of nonbonding electrons on the Lewis base and points toward the Lewis acid with which it reacts. Because adding a pair of electrons to one point on a molecule often displaces electrons in the molecule, combinations of curved arrows are often used to describe even simple chemical reactions. Consider the following example, in which a pair of electrons on an NH_2^- ion are donated to the H^+ ion formed when the electrons in one of the $\text{C}-\text{H}$ bonds in acetylene are given to the carbon atom instead of being shared by the C and H atoms in the bond.

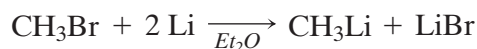


O3.2 CARBANION ATTACK AT A CARBONYL GROUP

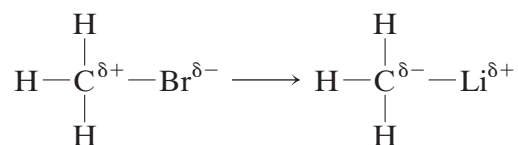
The discussion of acids and bases in the previous section helps us understand the chemistry of the Grignard reagents introduced in Section O2.10. Grignard reagents are made by reacting an alkyl bromide with magnesium metal in diethyl ether.



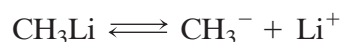
An analogous reagent, known as an alkyllithium, can be prepared by reacting the alkyl bromide with lithium metal in diethyl ether.



In the course of the reactions the carbon atom is reduced from the -2 to the -4 oxidation state. Whereas the starting material contains a carbon atom with a partial positive charge, the carbon atom in the products of these reactions carries a partial negative charge.



CH_3Li and CH_3MgBr can therefore be thought of as a source of the CH_3^- ion.



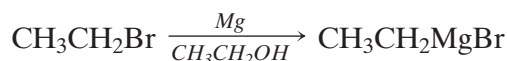
The CH_3^- ion is the conjugate base of methane, which is the weakest Brønsted acid in Table O3.1.



The CH_3^- ion is therefore the strongest Brønsted base in the table.

Exercise O3.1

A graduate student once tried to run the following reaction to prepare a Grignard reagent. Explain what he did wrong, state why the yield of the desired product was zero, and predict the product he obtained.



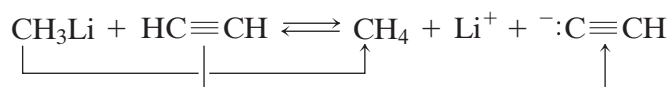
Solution

There is nothing wrong with the starting material ($\text{CH}_3\text{CH}_2\text{Br}$) or the product of the reaction ($\text{CH}_3\text{CH}_2\text{MgBr}$). Nor is there anything wrong with using magnesium metal to form a Grignard reagent. The only place where a mistake could have been made is in the choice of the solvent. The solvent that was used was ethanol ($\text{CH}_3\text{CH}_2\text{OH}$), whereas the usual solvent for a Grignard reagent is diethyl ether.

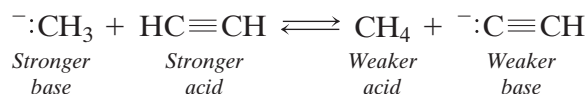
Ethanol is a *protic solvent* (see Section O2.4), which would react instantaneously with the carbanion in a Grignard reagent and thereby destroy the reagent to form ethane.



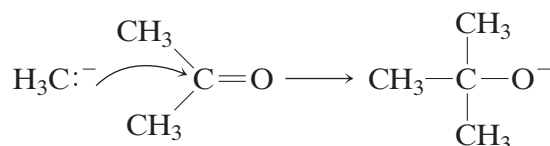
A subtle but important point must be made before we can extend our understanding of acid–base chemistry to the reaction between a Grignard or alkyllithium reagent and a carbonyl group. The data in Table O3.1 reflect the strengths of common acids and bases when they act as *Brønsted acids or bases*. The data predict that methyl lithium should react with acetylene to form methane and an acetylide ion, for example.



The reaction should occur because it converts the stronger of a pair of Brønsted acids and the stronger of a pair of Brønsted bases into a weaker acid and a weaker base.

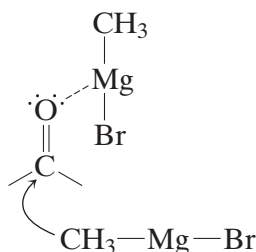


The reaction between a carbonyl and CH_3Li or CH_3MgBr , on the other hand, involves attack by a CH_3^- ion acting as a *Lewis base or nucleophile* at the positive end of the carbonyl group.



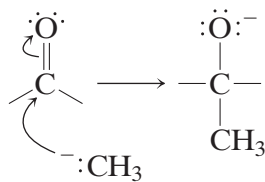
This raises an interesting question: *Is the stronger of a pair of Brønsted bases always the stronger of a pair of Lewis bases?* Unfortunately, the answer is no, it isn't. At times, the stronger of a pair of Brønsted bases is the weaker Lewis base or nucleophile. As a rule, however, strong Brønsted bases are strong nucleophiles, and weak Brønsted bases are weak nucleophiles.¹

Despite the enormous utility of Grignard reagents in organic chemistry, the exact mechanism of the reaction between the reagents and a carbonyl is not known. There is reason to believe that two molecules of the Grignard reagent are involved in the reaction. The magnesium atom of one molecule of the reagent acts as a Lewis acid that interacts with the oxygen atom of the carbonyl group. The alkyl group of the other reagent molecule then acts as a Lewis base, attacking the positive end of the carbonyl.



In essence, the reaction involves the attack by a negatively charged CH_3^- ion at the positively charged end of the carbonyl group. When this happens, the pair of nonbonding electrons on the CH_3^- ion are used to form a C–C bond. This, in turn, displaces the pair of electrons in the π bond onto the other end of the carbonyl group.

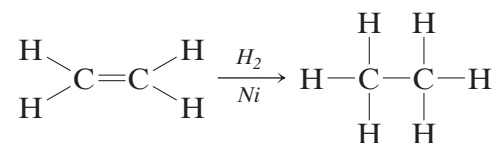
¹See T. B. McMahon, T. Heinis, G. Nicol, J. K. Hovey, and P. Kebarle, *J. Am. Chem. Soc.*, **110**, 7591 (1988).



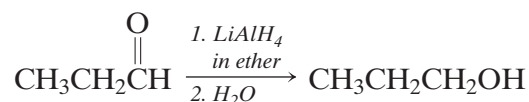
The second molecule of the Grignard reagent, which binds at the oxygen end of the carbonyl, isn't consumed in the reaction. Its function is simple. When it acts as a Lewis acid, binding to the oxygen atom in the C=O double bond, it increases the polarity of the bond. By making the bond more polar, it increases the rate at which the CH_3^- ion attacks the positive end of the C=O bond.

O3.3 THE MECHANISM OF REDUCTION REACTIONS

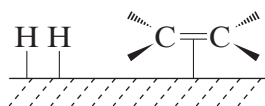
Two fundamentally different reducing agents have been used in the previous chapters on organic chemistry to add hydrogen across a double bond. In Section O1.6, a metal was used to catalyze the reaction between hydrogen gas and the C=C double bond in an alkene.



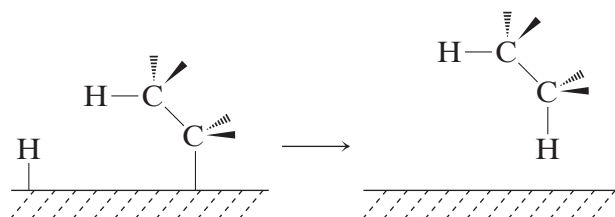
A source of the hydride ion (H^-), on the other hand, was used to reduce C=O double bonds in Section O2.6.



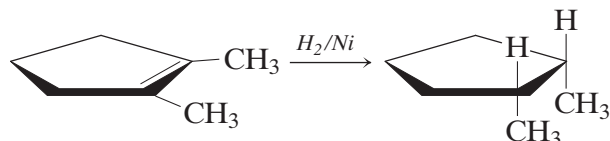
The first step toward understanding the difference between these reactions involves noting that the first reaction uses a nonpolar reagent to reduce a nonpolar double bond. The atoms on the surface of a metal are different from those buried in the body of the solid because they cannot satisfy their tendency to form strong metal-metal bonds. Some metals can satisfy a portion of their combining power by binding hydrogen atoms and/or alkenes to the surface.



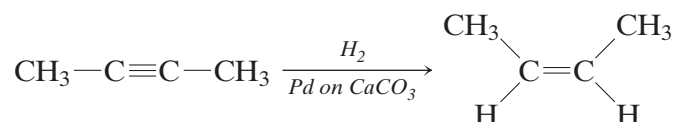
Transferring one of the hydrogen atoms on the metal surface to the alkene bound to the metal surface forms an alkyl group, which can bond to the metal until the second hydrogen atom can be added to form the alkane.



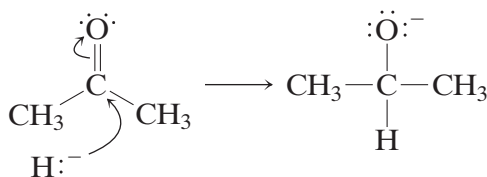
Although the hydrogen atoms are transferred one at a time, the reaction is fast enough that both of the atoms usually end up on the same side of the C=C double bond. This can't be seen in most alkanes produced by the reaction because of the free rotation around C—C bonds. Reduction of a cycloalkene, however, gives a stereoselective product.



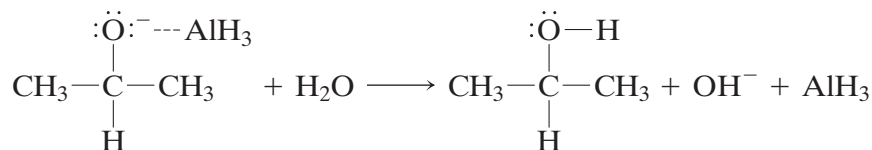
Reduction of an alkyne with hydrogen on a metal catalyst gives the corresponding alkane. By selectively “poisoning” the catalyst it is possible to reduce an alkyne to an alkene. Once again, the reaction is stereoselective, adding both hydrogen atoms from the same side of the C≡C bond to form the *cis*-alkene.



Because it is a polar reagent, LiAlH₄ won't react with a C=C double bond. It acts as a source of the H[−] ion, however, which is a strong Brønsted base and a strong nucleophile. The H[−] ion can therefore attack the δ⁺ end of a polar C=O double bond.

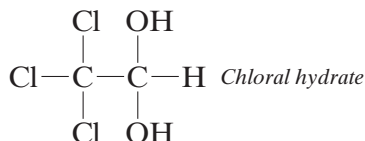


The neutral AlH₃ molecule formed when an AlH₄[−] ion acts as a hydride donor is a Lewis acid that coordinates to the negatively charged oxygen atom in the product of the reaction. When a protic solvent is added to the reaction in a second step, an alcohol is formed.



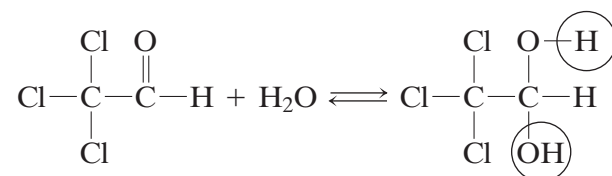
O3.4 NUCLEOPHILIC ATTACK BY WATER

In the 1930s and 1940s, Dashiell Hammett (1894–1961) created the genre of the “hard-boiled” detective novel with books such as *The Maltese Falcon* and *The Thin Man*. A common occurrence in this literature was a character who “slipped someone a Mickey Finn”—a dose of the sedative known as chloral hydrate dissolved in a drink that contains alcohol.



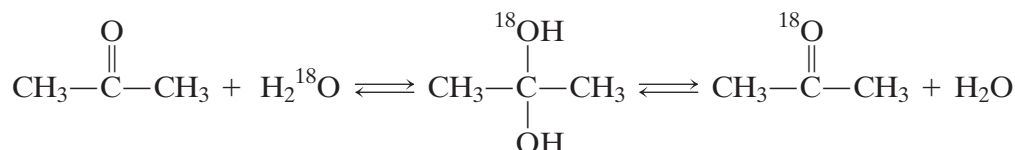
10 ORGANIC REACTION MECHANISMS

Chloral hydrate is a white solid formed by adding a molecule of water across the C=O double bond in the corresponding aldehyde.



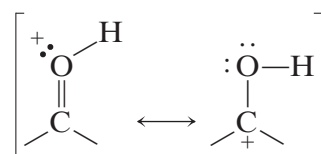
The equilibrium constant for the reaction is sensitive to the substituents on the carbonyl carbon. Electron-withdrawing substituents, such as the Cl_3C group in chloral, drive the reaction toward the dialcohol, or **diol** ($K \gg 1$). Electron-donating substituents, such as the pair of CH_3 groups in acetone, pull the equilibrium back toward the aldehyde ($K = 2 \times 10^{-3}$).

The rate of the reaction can be studied by following the incorporation of isotopically labeled water. The vast majority (99.76%) of water molecules contain ^{16}O , but some contain ^{17}O (0.04%) or ^{18}O (0.2%). When acetone is dissolved in a sample of water that has been enriched in ^{18}O , it gradually picks up the ^{18}O isotope.

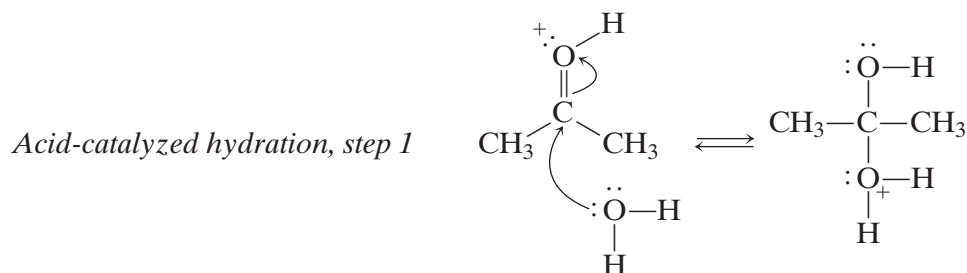


The rate of the reaction is infinitesimally slow in a neutral solution ($\text{pH} \approx 7$). But in the presence of a trace of acid (or base), the reaction occurs very rapidly.

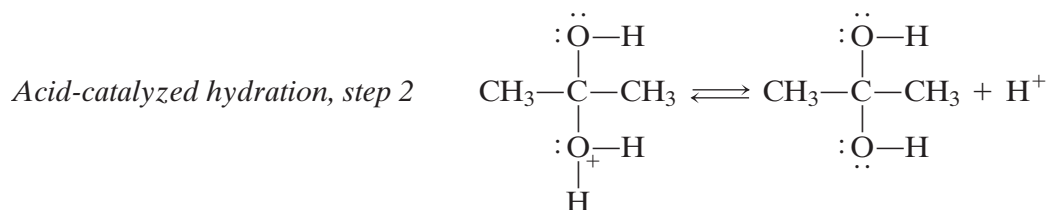
The role of the acid catalyst can be understood by noting that protonation of the oxygen atom increases the polarity of the carbonyl bond.



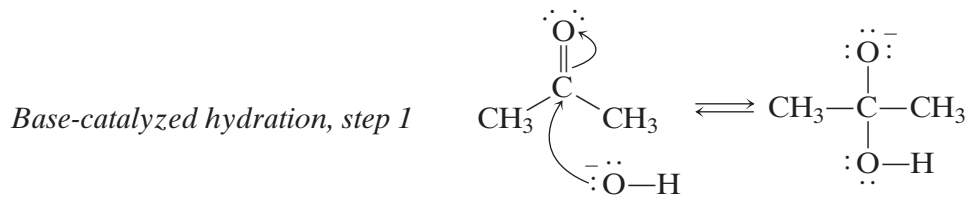
This increases the rate at which a water molecule can act as a nucleophile toward the positive end of the C=O double bond.



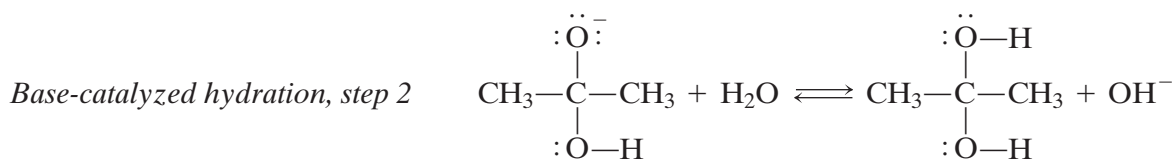
The product of the reaction then loses an H^+ ion to form the diol.



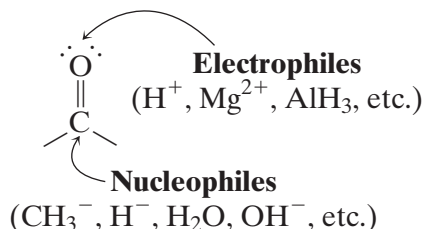
The role of the base catalyst can be understood by noting that the OH^- ion is a much stronger nucleophile than water, strong enough to attack the carbonyl by itself.



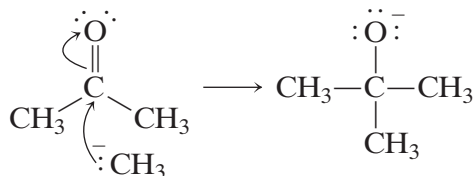
The product of the reaction then picks up a proton from a water molecule to form the diol and regenerate the OH^- ion.



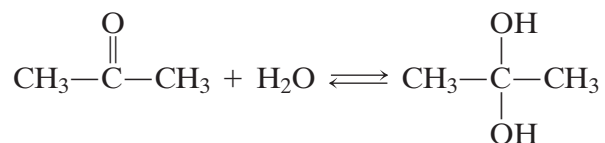
There is a fundamental relationship between the mechanisms of the reactions at the carbonyl group introduced so far. In each case, a nucleophile or Lewis base attacks the positive end of the carbonyl group. And, in each case, the rate of reaction can be increased by coordinating a Lewis acid or electrophile at the other end of the carbonyl.



There is a subtle difference between the reactions, however. Very strong nucleophiles, such as Grignard reagents and the hydride ion, add to the carbonyl in an irreversible reaction.

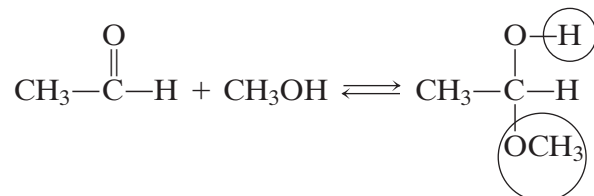


Attack by a weaker nucleophile, such as water, is a reversible reaction that can occur in either direction.



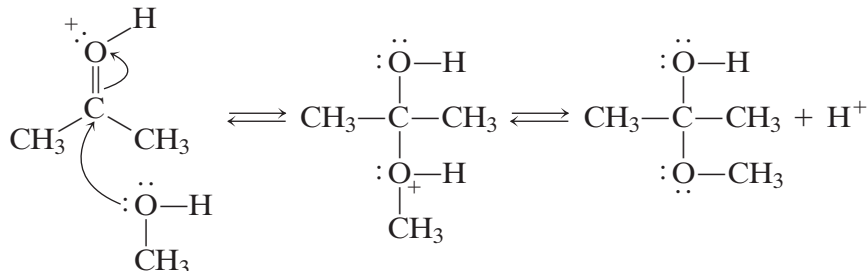
O3.5 NUCLEOPHILIC ATTACK BY AN ALCOHOL

What would happen if we dissolved an aldehyde or ketone in an alcohol, instead of water? We would get a similar reaction, but now an ROH molecule is added across the C=O double bond.

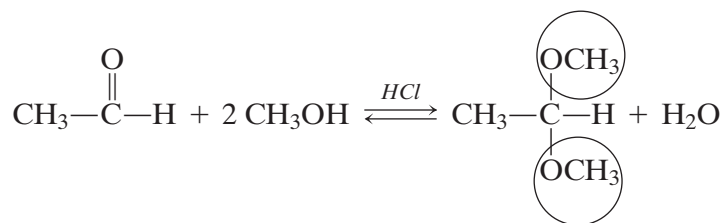


Once again, the reaction is relatively slow in the absence of an acid or base catalyst. If we bubble HCl gas through the solution, or add a small quantity of concentrated H₂SO₄, we get an acid-catalyzed reaction that occurs by a mechanism analogous to that described in the previous section.²

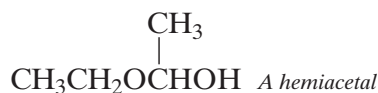
Acid-catalyzed reaction of an alcohol with a carbonyl



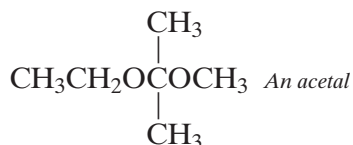
The product of the reaction is known as a **hemiacetal** (literally, “half of an acetal”). If an anhydrous acid is added to a solution of the aldehyde in a large excess of alcohol, the reaction continues to form an **acetal**.



Hemiacetals can be recognized by looking for a carbon atom that has both an —OH and an —OR group.

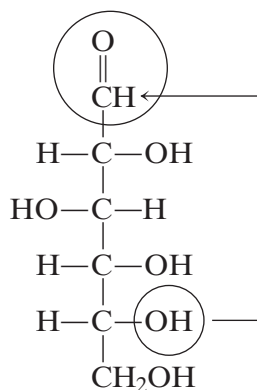


Acetals, on the other hand, contain a carbon atom that has two —OR groups.

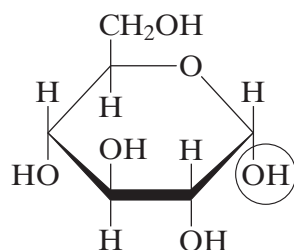


²Gaseous HCl and concentrated H₂SO₄ give an acidic solution without contaminating the solution with water, which could react with the carbonyl.

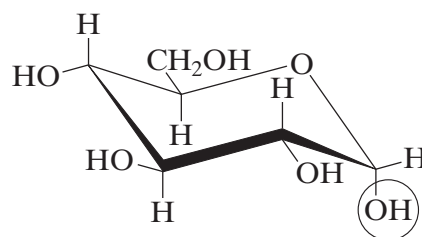
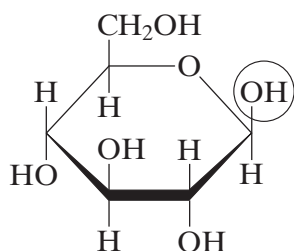
Hemiacetals and acetals play an important role in the chemistry of carbohydrates. Consider what would happen, for example, if the —OH group on the fifth carbon atom in a glucose molecule attacked the aldehyde at other end of the molecule.



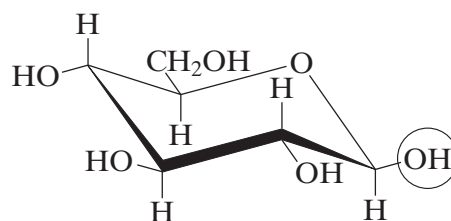
The product of the reaction is a hemiacetal that contains a six-membered ring known as a pyranose. Two isomers of glucopyranose can be formed, depending on whether the —OH group attacks from above or below the C=O group.



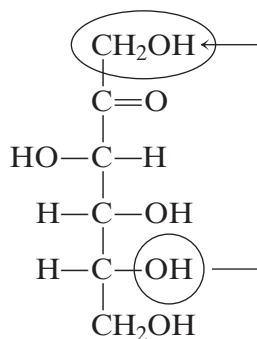
or

*α-D-Glucopyranose*

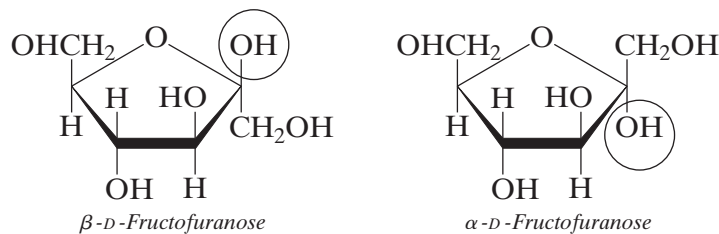
or

*β-D-Glucopyranose*

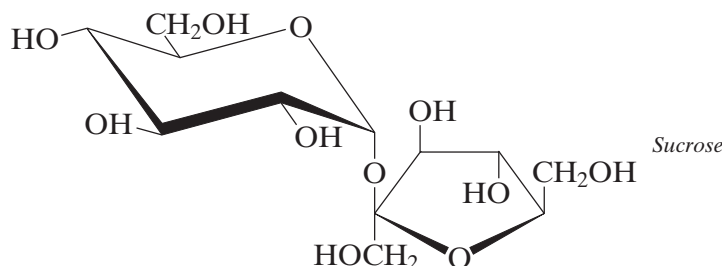
An analogous intramolecular reaction can occur within a fructose molecule.



In this case, a hemiacetal is formed that contains a five-membered furanose ring. Once again, there are two isomers, depending on how the —OH group attacks the C=O group.

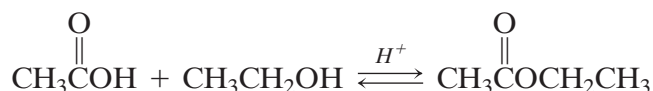


Sugars, such as glucose and fructose, can be linked to form complex carbohydrates by forming an acetal linkage between the —OH group on one sugar and the hemiacetal on the other. Sucrose, or cane sugar, for example, is an acetal formed by linking α -D-glucopyranose and β -D-fructofuranose residues.



O3.6 ADDITION/ELIMINATION REACTIONS OF CARBOXYLIC ACID DERIVATIVES

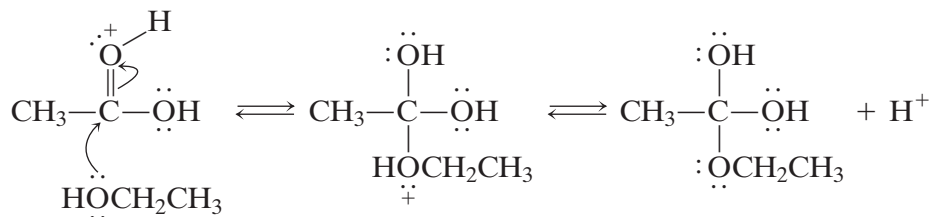
The following reaction was used in Section O2.8 to illustrate the synthesis of an ester from a carboxylic acid.



These reactions occur very slowly in the absence of a strong acid. When gaseous HCl is bubbled through the solution, or a small quantity of concentrated H_2SO_4 is added, the reactions reach equilibrium within a few hours. Once again, the acid protonates the oxygen of the C=O double bond, thereby increasing the polarity of the carbonyl group, which makes it more susceptible to attack by a nucleophile.

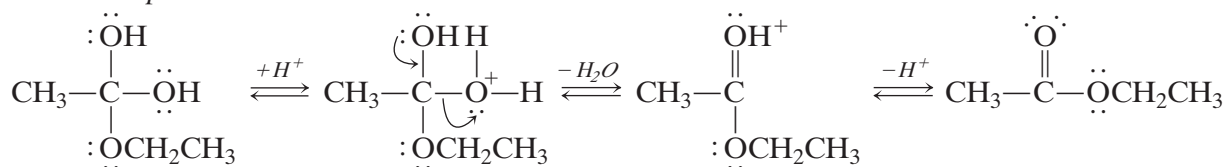
As might be expected, the first step in the reaction involves attack by a nucleophile at the positively charged end of the C=O double bond. A pair of nonbonding electrons on the oxygen atom of the alcohol is donated to the carbon atom of the carbonyl to form a C—O bond. As the bond forms, the electrons in the π bond of the carbonyl are displaced onto the oxygen atom. A proton is then transferred back to the solvent to give a tetrahedral addition intermediate.

Nucleophilic addition

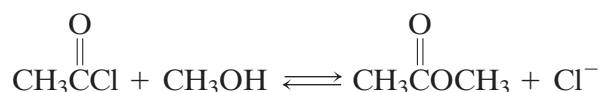


One of the —OH groups in the intermediate picks up a proton, loses a molecule of water, and then transfers a proton back to the solvent to give the ester.

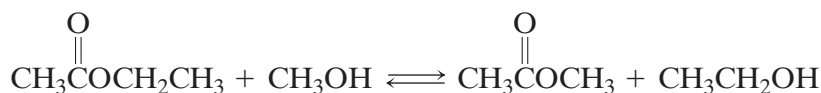
Nucleophilic elimination



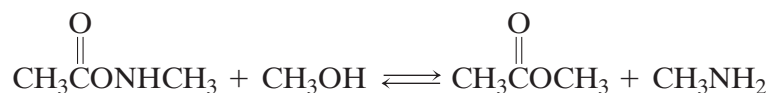
The combination of addition and elimination reactions has the overall effect of substituting one nucleophile for another—in this case, substituting an alcohol for water. The rate of these **nucleophilic substitution reactions** is determined by the ease with which the elimination step occurs. *As a rule, the best leaving groups in nucleophilic substitution reactions are weak bases.* The most reactive of the carboxylic acid derivatives are the acyl chlorides because the **leaving group** is a chloride ion, which is a very weak base ($K_b \approx 10^{-20}$).



Esters are less reactive because the leaving group is an alcohol, which is a slightly better base ($K_b \approx 10^{-14}$).

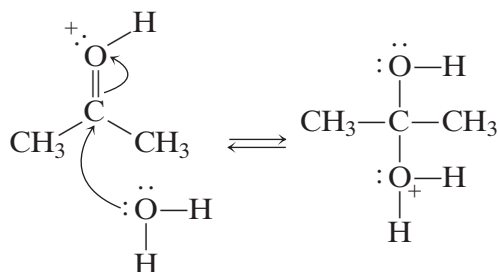


Amides are even less reactive because the leaving group is ammonia or an amine, which are significantly more basic ($K_b \approx 10^{-5}$).

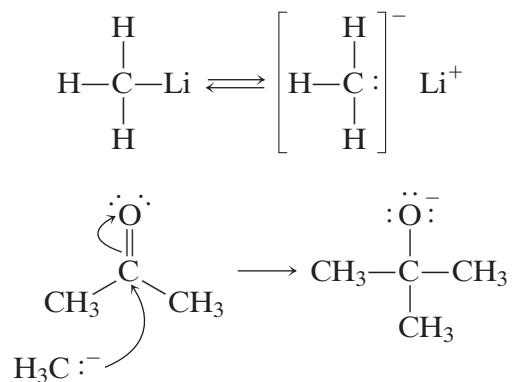


O3.7 FREE RADICAL REACTIONS

The starting point for reactions at a carbonyl involves attack by a nucleophile on the carbon atom of the C=O double bond.



Or it involves the **heterolytic** splitting of a bond to form a nucleophile that can attack the carbonyl group.

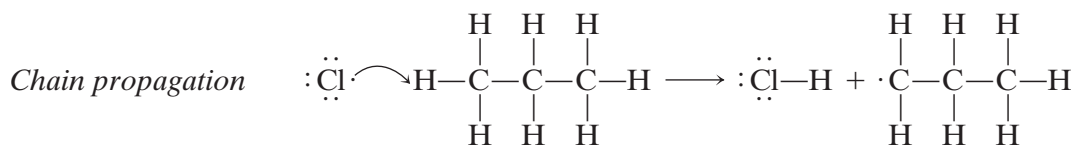


In either case, the reaction is carried out by a reagent that donates a pair of electrons to a carbon atom to form a new covalent bond.

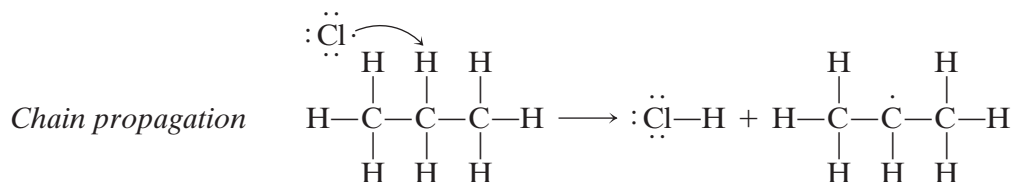
Section O2.3 introduced a reaction that occurs by a very different mechanism: free radical halogenation of an alkane. The first step in these reactions is the **homolytic** splitting of a bond to give a pair of free radicals.



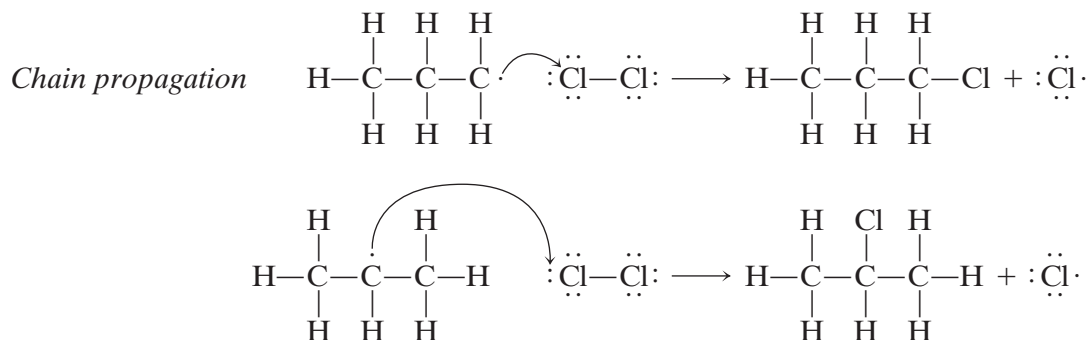
A series of reactions then occurs that involves a chain reaction. Consider the chlorination of propane, for example. A $\text{Cl}\cdot$ atom can attack the CH_3 group at one end of the molecule.



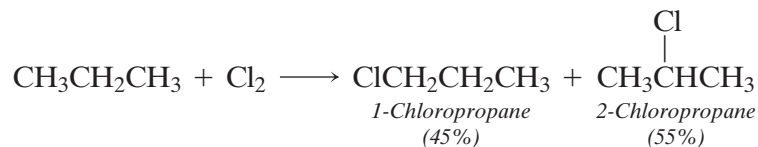
Or it can attack the CH_2 group in the center of the molecule.



The free radicals generated in the reactions then react with chlorine to form either 1-chloropropane or 2-chloropropane and regenerate a $\text{Cl}\cdot$ radical.

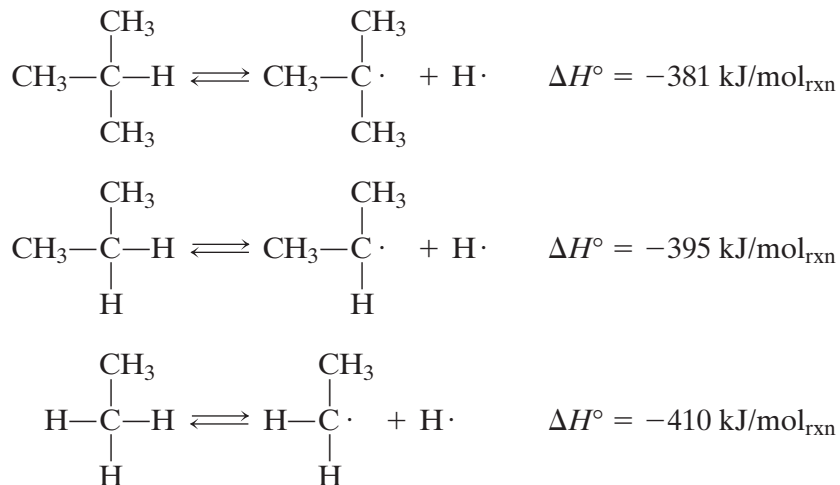


There are six hydrogen atoms in the two CH₃ groups and two hydrogens in the CH₂ group in propane. If attack occurred randomly, six-eighths (or three-quarters) of the product of the reaction would be 1-chloropropane. The distribution of products of the reaction, however, suggests that 1-chloropropane is formed slightly *less often* than 2-chloropropane.

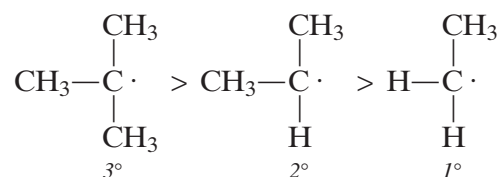


This can be explained by noting that the 2° radical formed by removing a hydrogen atom from the CH₂ group in the center of the molecule is slightly more stable than the 1° radical produced when a hydrogen atom is removed from one of the CH₃ groups at either end of the molecule.

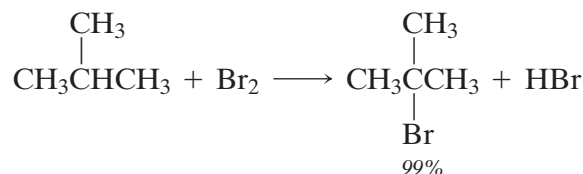
The difference between the radicals can be appreciated by considering the energy it takes to break the C—H bond in the following compounds.



These data suggest that it takes *less energy* to break a C—H bond as the number of alkyl groups on the carbon atom that contains the bond increases. This can be explained by assuming that the products of the bond-breaking reaction become *more stable* as the number of alkyl groups increases. In other words, 3° radicals are more stable than 2° radicals, which are more stable than 1° radicals.



The activation energy for the chain propagation steps in free radical bromination reactions is significantly larger than the activation energy for the steps during chlorination. As a result, free radical bromination reactions are more selective than chlorination reactions. Bromination reactions are far more likely to give the product predicted from the relative stability of the free radical intermediate. Bromination of 2-methylpropane, for example, gives almost exclusively 2-bromo-2-methylpropane, not the statistically more likely 1-bromo-2-methylpropane.



O3.8 BIMOLECULAR NUCLEOPHILIC SUBSTITUTION OR S_N2 REACTIONS

Most of our knowledge of the mechanisms of chemical reactions has come from the study of the factors that influence the rate of these reactions. The type of reaction that has been studied more than any other involves attack by a nucleophile on a saturated carbon atom. Consider the following reaction, for example, which converts an alkyl bromide into an alcohol.



In the course of the reaction, one nucleophile (the OH⁻ ion) is substituted for another (the Br⁻ ion). This is therefore a **nucleophilic substitution reaction**.

The rate of the reaction is first-order in both CH₃Br and the OH⁻ ion, and second-order overall.

$$\text{Rate} = k(\text{CH}_3\text{Br})(\text{OH}^-)$$

In the 1930s, Sir Christopher Ingold proposed a mechanism for the reaction in which both the alkyl halide and the hydroxyl ion are involved in the rate-limiting or slowest step of the reaction. The OH⁻ ion attacks the “backside” of the CH₃Br molecule. (It attacks the carbon atom at a point directly opposite the Br substituent or leaving group.) When this happens, a pair of nonbonding electrons on the OH⁻ ion are used to form a covalent bond to the carbon atom at the same time that the carbon–bromine is broken, as shown in Figure O3.2. Because the rate-limiting step in the reaction involves both the CH₃Br and OH⁻ molecules, it is called a **bimolecular nucleophilic substitution reaction**, or **S_N2 reaction**.

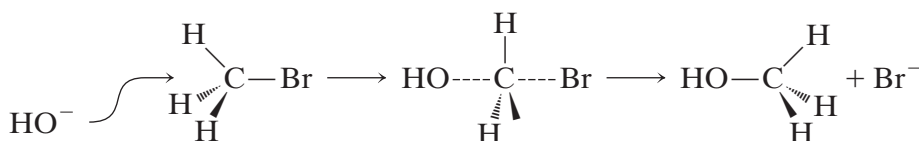
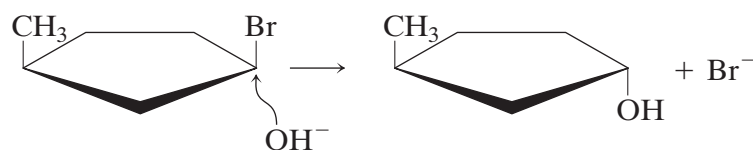


FIGURE O3.2 The mechanism for nucleophilic attack on CH₃Br.

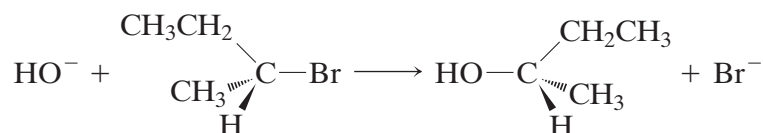
The most important point to remember about the mechanism of S_N2 reactions is that they occur in a single step. The species in the middle of Figure O3.2 is known as a **transition state**. If you envision the reaction as an endless series of snapshots that capture the infinitesimally small changes which occur as one bond forms and the other bond breaks, the transition state is the snapshot in the series that has the highest energy—and is therefore the least stable. The transition state has an infinitesimally short lifetime, on the order of 10⁻¹² second.

In the course of an S_N2 reaction, the other three substituents on the carbon atom are “flipped” from one side of the atom to the other. This inevitably leads to inversion of the

configuration at a stereocenter. Consider the following reaction, for example, in which *cis*-1-bromo-3-methylcyclopentane is converted to *trans*-3-methylcyclopentanol.

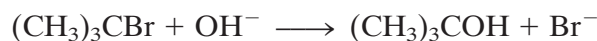


Or consider the reaction in which the *R* isomer of 2-bromobutane is transformed into the *S* isomer of 2-butanol.



O3.9 UNIMOLECULAR NUCLEOPHILIC SUBSTITUTION OR S_N1 REACTIONS

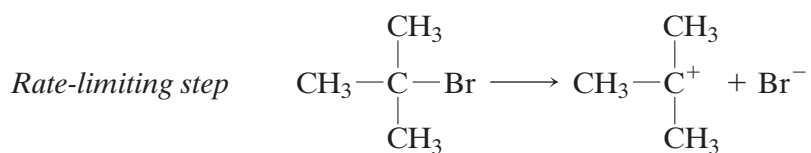
The kinetics of nucleophilic substitution reactions have been studied in greater detail than any other type of reaction because they don't always proceed through the same mechanism. Consider the reaction between the OH^- ion and *t*-butyl bromide, for example.



The rate of the reaction depends only on the concentration of the alkyl bromide. (Adding more OH^- ion to the solution has no effect on the rate of reaction.)

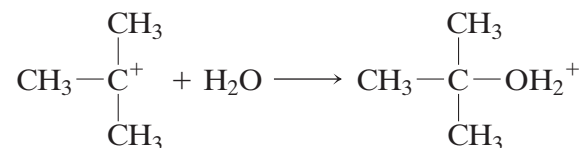
$$\text{Rate} = k((\text{CH}_3)_3\text{CBr})$$

Ingold and co-workers argued that this rate law is consistent with a mechanism in which the rate-limiting or slowest step involves the breaking of the carbon–bromine bond to form a pair of ions. As one might expect, the pair of electrons in the C–Br bond end up on the more electronegative bromine atom.

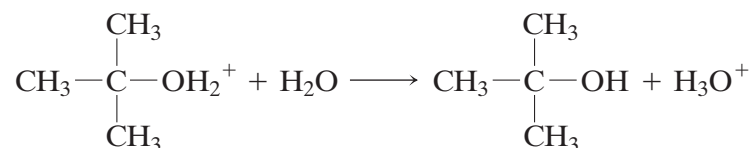


Because the bromine atom has formally gained an electron from the carbon atom, it is now a negatively charged Br^- ion. Because the carbon atom has formally lost an electron, it is now a “carbocation.”

The first step in the mechanism is a relatively slow reaction because the activation energy for this step is roughly $80 \text{ kJ/mol}_{\text{rxn}}$. If the reaction is done in water, the next step is extremely fast. The $(\text{CH}_3)_3\text{C}^+$ ion is a Lewis acid because it has an empty orbital that can be used to accept a pair of electrons. Water, on the other hand, is a reasonably good Lewis base. A Lewis acid–base reaction therefore rapidly occurs in which a pair of nonbonding electrons on a water molecule are donated to the carbocation to form a covalent C–O bond.



The product of the reaction is a stronger acid than water. As a result, it transfers a proton to water.



Because the slowest step of the reaction only involves *t*-butyl bromide, the overall rate of reaction depends only on the concentration of that species. The reaction is therefore a **uni-molecular nucleophilic substitution reaction**, or **S_N1 reaction**.

The central carbon atom in the *t*-butyl carbocation formed in the first step of the reaction is planar, as shown in Figure O3.3. This means that water can attack the carbocation in the second step with equal probability from either side of the carbon atom. This has no effect on the products of the reaction, because the starting material is not optically active. But what would happen if we started with an optically active halide, such as *trans*-2-bromobutane?

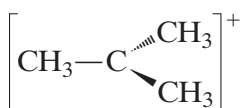
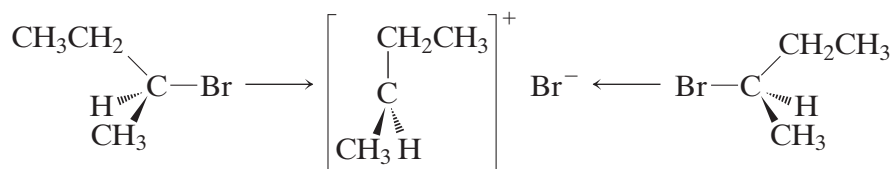


FIGURE O3.3 The geometry of the (CH₃)₃C⁺ ion.

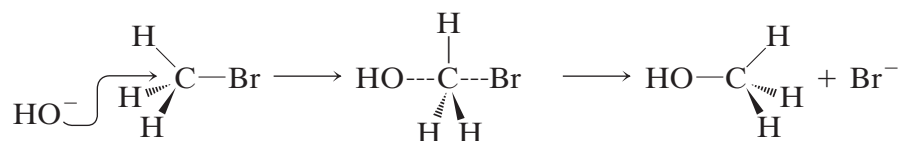
Regardless of whether we start with the *R* or *S* isomer of 2-bromobutane, we get the same intermediate when the C—Br bond breaks.



The intermediate formed in the first step in the S_N1 mechanism is therefore *achiral*.

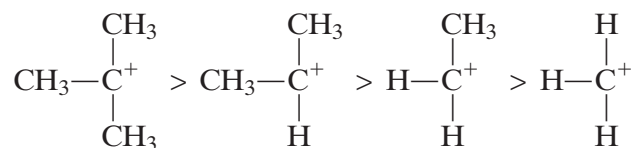
Mixtures of equal quantities of the *+/−* or *R/S* stereoisomers of a compound are said to be **racemic**. The term traces back to the Latin word *racemus*, which means “a cluster of grapes.” Just as there is an equal probability of finding grapes on either side of the stem in a cluster of grapes, there is an equal probability of finding the *R* and *S* enantiomers in a racemic mixture. S_N1 reactions are therefore said to *proceed with racemization*. If we start with a pure sample of (*R*)-2-bromobutane, for example, we expect the product of the S_N1 reaction with the OH[−] ion to be a racemic mixture of the two enantiomers of 2-butanol.

We are now ready to address a pair of important questions. First, why does CH₃Br react with the OH[−] ion by the S_N2 mechanism if (CH₃)₃CBr does not? The S_N2 mechanism requires direct attack by the OH[−] ion on the carbon atom that carries the C—Br bond. It is much easier for the OH[−] ion to get past the small hydrogen atoms in CH₃Br than it is for the ion to get past the bulkier CH₃ groups in (CH₃)₃CBr.



Thus, $\text{S}_{\text{N}}2$ reactions at the 1° carbon atom in CH_3Br are much faster than the analogous reaction at the 3° carbon atom in $(\text{CH}_3)_3\text{CBr}$.

Why, then, does $(\text{CH}_3)_3\text{CBr}$ react with the OH^- ion by the $\text{S}_{\text{N}}1$ mechanism if CH_3Br does not? The $\text{S}_{\text{N}}1$ reaction proceeds through a carbocation intermediate, and the stability of such ions decreases in the following order.



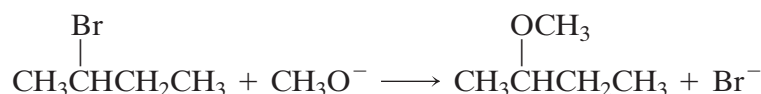
Organic chemists explain this by noting that alkyl groups are slightly “electron releasing.” They can donate electron density to a neighboring group. This tends to delocalize the charge over a larger volume of the molecule, which stabilizes the carbocation.

When we encountered a similar phenomenon in the chemistry of free radicals in Section O3.7 we noted that 3° radicals are roughly 30 kJ/mol more stable than 1° radicals. In this case, the difference is much larger. A 3° carbocation is 340 kJ/mol more stable than a 1° carbocation!³ As a result, it is much easier for $(\text{CH}_3)_3\text{CBr}$ to form a carbocation intermediate than it is for CH_3Br to undergo a similar reaction.

In theory, both starting materials could undergo both reaction mechanisms. But the rate of $\text{S}_{\text{N}}2$ reactions for CH_3Br are much faster than the corresponding $\text{S}_{\text{N}}1$ reactions, whereas the rate of $\text{S}_{\text{N}}1$ reactions for $(\text{CH}_3)_3\text{CBr}$ are very much faster than $\text{S}_{\text{N}}2$ reactions.

O3.10 ELIMINATION REACTIONS

Why do we need to worry about whether a nucleophilic substitution reaction occurs by an $\text{S}_{\text{N}}1$ or $\text{S}_{\text{N}}2$ mechanism? At first glance, it would appear that the same product is obtained regardless of the mechanism of the reaction. Consider the following substitution reaction, for example.

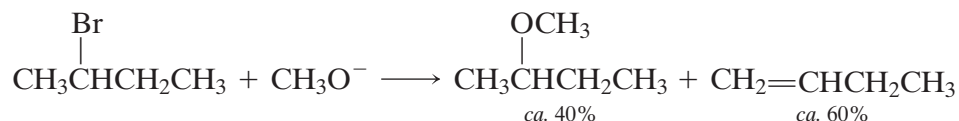


The only apparent difference between the two mechanisms is the stereochemistry of the product. If the reaction proceeds through an $\text{S}_{\text{N}}2$ mechanism, it gives inversion of configuration—conversion of an *R* starting material into an *S* product, or vice versa. If the reaction proceeds through a carbocation intermediate via an $\text{S}_{\text{N}}1$ mechanism, we get a racemic mixture.

The importance of understanding the mechanism of nucleophilic substitution reactions can best be appreciated by studying the distribution of products of the example given above.

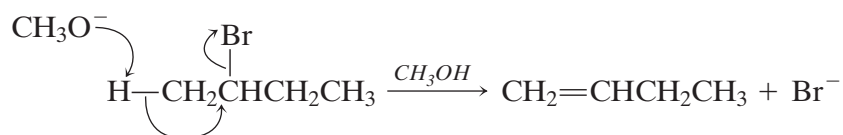
³J. E. Bartmess, *Mass Spectrometry Review*, **8**, 297–343 (1989).

When 2-bromobutane is allowed to react with the methoxide ion in methanol, less than half of the starting material is converted into methyl isopropyl ether; the rest is transformed into 2-propene.

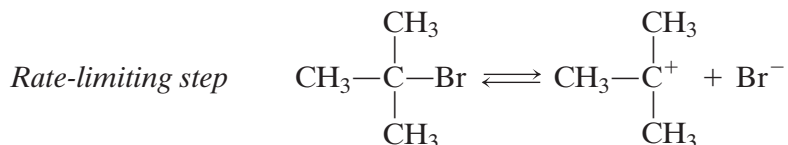


The reaction that produces the alkene involves the loss of an HBr molecule to form a C=C double bond. It is therefore an example of an **elimination reaction**.

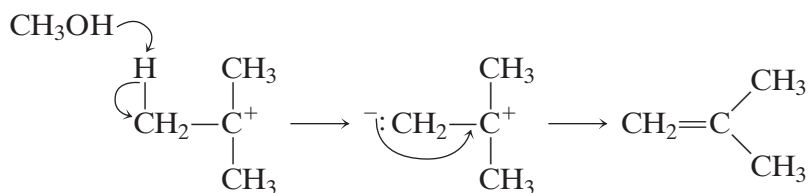
Starting materials that are likely to undergo a bimolecular S_N2 reaction undergo elimination reactions by a *bimolecular elimination mechanism*, or **E₂ reaction**. This is a one-step reaction in which the nucleophile attacks a C—H bond on the carbon atom adjacent to the site of S_N2 reaction.



Starting materials that are likely to undergo a unimolecular S_N1 reaction undergo elimination reactions by a *unimolecular elimination mechanism*, or **E₁ reaction**. As might be expected, the rate-limiting step is the formation of the carbocation.



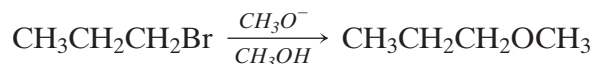
The solvent then acts as a base, removing an H⁺ ion from one of the alkyl groups adjacent to the carbocation. The electrons in the C—H bond that is broken are donated to the empty orbital on the carbocation to form a double bond.



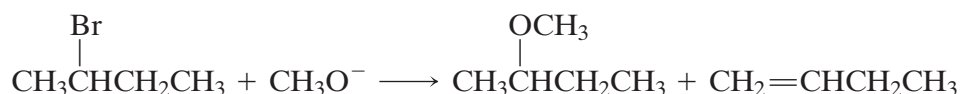
O3.11 SUBSTITUTION VERSUS ELIMINATION REACTIONS

There are three ways of pushing the reaction between an alkyl halide and a nucleophile toward elimination instead of substitution.

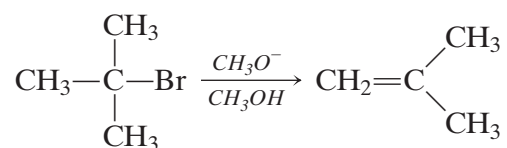
- Start with a highly substituted substrate, which is more likely to undergo elimination. Only 10% of a primary alkyl bromide undergoes elimination to form an alkene, for example, when it reacts with an alkoxide ion dissolved in alcohol. The vast majority of the starting material goes on to form the product expected for an S_N2 reaction.



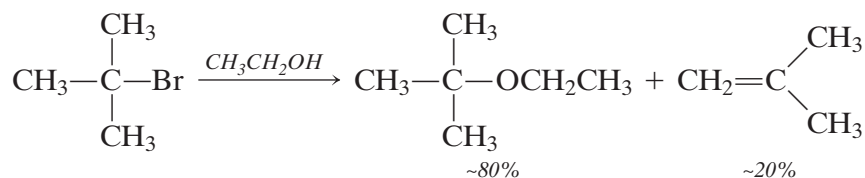
More than half of a secondary alkyl bromide undergoes elimination under the same conditions, as we have already seen.



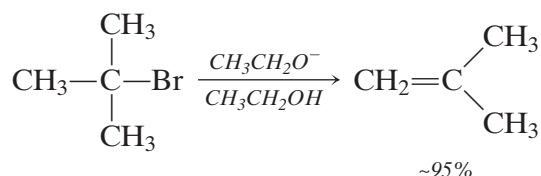
When the starting material is a tertiary alkyl halide, more than 90% of the product is formed by an E₁ elimination reaction.



- Use a very strong base as the nucleophile. When we use a relatively weak base, such as ethyl alcohol, only about 20% of *t*-butyl bromide undergoes elimination.



In the presence of the ethoxide ion, which is a much stronger base, the product of the reaction is predominantly the alkene.



- Increase the temperature at which the reaction is run. Because both E₁ and E₂ reactions lead to an increase in the number of particles in the system, they are associated with a positive entropy term. Thus, increasing the temperature of the reaction makes the overall free energy of reaction more negative, and the reaction becomes more favorable.

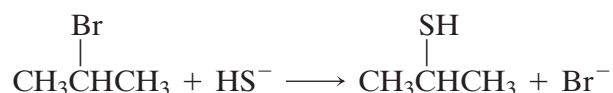
Summary of Substitution/Elimination Reactions

- Methyl halides and primary alkyl halides such as CH₃CH₂Br undergo nucleophilic substitution reactions.

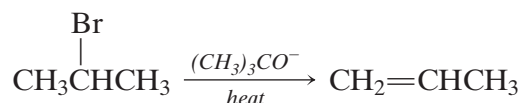


24 ORGANIC REACTION MECHANISMS

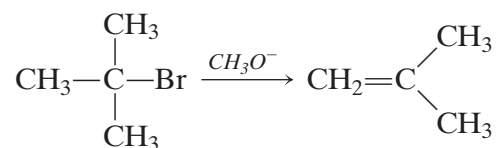
- Secondary alkyl halides undergo S_N2 reactions when handled gently—at low temperatures and with moderately strong nucleophiles.



- At high temperatures, or in the presence of a strong base, secondary alkyl halides undergo E_2 elimination reactions.



- Tertiary alkyl halides undergo a combination of S_N1 and E_1 reactions. If the reaction is kept cool, and the nucleophile is a relatively weak base, it is possible to get nucleophilic substitution. At high temperatures, or with strong bases, elimination reactions predominate.



KEY TERMS

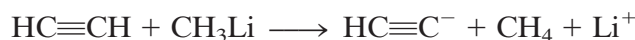
Acetal	Brønsted base	Lewis acid
Acid	Diol	Lewis base
Acid dissociation equilibrium constant, K_a	E_1 reaction	Nucleophilic substitution reaction
Alkali	E_2 reaction	S_N1 reaction
Base	Elimination reaction	S_N2 reaction
Bimolecular nucleophilic substitution reaction	Hemiacetal	Transition state
Brønsted acid	Heterolytic	Unimolecular nucleophilic substitution reaction
	Homolytic	
	Leaving group	

PROBLEMS

Acids and Bases

- Predict the products of the reaction between ethanol ($\text{CH}_3\text{CH}_2\text{OH}$) and sodium hydride (NaH).
- Write the Lewis structure for the conjugate *base* of ethanol ($\text{CH}_3\text{CH}_2\text{OH}$).
- Which of the following is the conjugate *acid* of ethanol ($\text{CH}_3\text{CH}_2\text{OH}$)?
(a) $\text{CH}_3\text{CH}_2\text{OH}$ (b) $\text{CH}_3\text{CH}_2\text{O}^-$ (c) $\text{CH}_3\text{CH}_2\text{OH}_2^+$ (d) CH_3CH_2^+ (e) H_3O^+
- Some beginning chemistry students get confused when acetic acid is described as a weak acid because they see four hydrogen atoms in a $\text{CH}_3\text{CO}_2\text{H}$ molecule. Explain why only one of the H atoms dissociates when acetic acid is dissolved in water.

5. Which of the following are Lewis acids but not a Brønsted acid?
 (a) H^+ (b) NH_4^+ (c) BF_3 (d) $\text{CH}_3\text{CH}_2\text{OH}$ (e) Mg^{2+}
6. Arrange the following compounds in order of increasing basicity.
 (a) NH_3 (b) NH_2^- (c) NH_4^+ (d) N^{3-}
7. Identify the Brønsted acids in the following reaction.



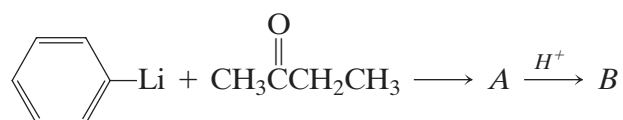
8. Arrange the following hydrocarbons in order of increasing acidity.
 (a) C_2H_2 (b) C_2H_4 (c) C_2H_6
9. Which of the following reagents is a strong enough base to generate the ethoxide ion ($\text{CH}_3\text{CH}_2\text{O}^-$) from ethanol ($\text{CH}_3\text{CH}_2\text{OH}$)?
 (a) NaOH (b) NaH (c) NaNH_2 (d) CH_3MgBr (e) $\text{HC}\equiv\text{CNa}$
10. Which of the following acid–base reactions should occur as written?
 (a) $\text{CH}_3\text{CH}_2\text{OH} + \text{NaOH} \rightarrow \text{Na}^+ + \text{CH}_3\text{CH}_2\text{O}^- + \text{H}_2\text{O}$
 (b) $\text{CH}_4 + \text{NaNH}_2 \rightarrow \text{CH}_3^- + \text{Na}^+ + \text{NH}_3$
 (c) $\text{CH}_3\text{Li} + \text{HC}\equiv\text{CH} \rightarrow \text{CH}_4 + \text{HC}\equiv\text{CLi}$
 (d) $\text{CH}_3\text{CH}_2\text{OH} + \text{HS}^- \rightarrow \text{CH}_3\text{CH}_2\text{O}^- + \text{H}_2\text{S}$

Attack at a Carbonyl

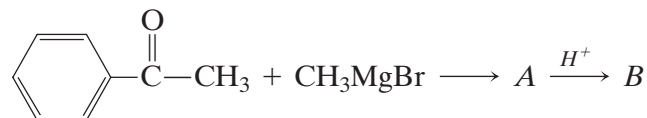
11. Use Lewis structures and the concept of oxidation–reduction reactions to explain why it takes two moles of lithium metal to reduce a mole of methyl bromide to form methyl-lithium.



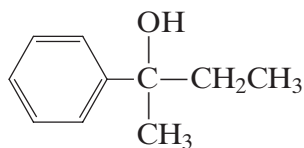
12. Explain why ethers, but not alcohols, are used as solvents for reactions that involve Grignard or alkyllithium reagents.
13. Explain why the bonding of a Lewis acid at the oxygen atom of a carbonyl group increases the rate at which nucleophilic attack occurs at the carbon atom.
14. Predict the products of the following reactions.



15. Predict the products of the following reactions.

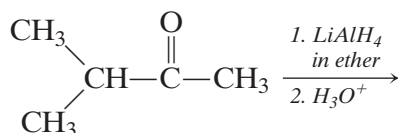


16. Design a two-step reaction sequence using either a Grignard or alkyllithium reagent that could be used to produce the following compound.

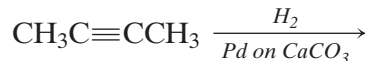


The Mechanism of Reduction Reactions

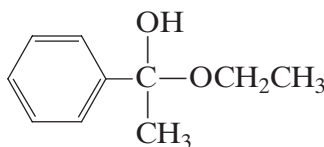
- Both H_2 on a metal catalyst and LiAlH_4 , can be used to reduce a carbonyl to an alcohol. Explain why H_2 on a metal catalyst can be used to reduce a $\text{C}=\text{C}$ double bond but not LiAlH_4 .
- Explain why the yield of reactions that try to reduce a carbonyl with LiAlH_4 in ethanol is effectively zero.
- Reduction of a $\text{C}=\text{C}$ double bond with H_2 gas on a metal catalyst gives a product in which the two hydrogen atoms are added to the same side of the double bond. What does this tell us about the relative rates of the first and second steps in the reaction?
- Why is it important to “poison” the metal catalyst before trying to reduce an alkyne to an alkene with H_2 ?
- The reagent that attacks the carbon atom is the same when either LiAlH_4 or NaBH_4 is used to reduce a $\text{C}=\text{O}$ double bond. (In each case, it is the H^- ion.) What does the fact that LiAlH_4 is significantly more reactive than NaBH_4 tell us about the relative acidity of AlH_3 and BH_3 as Lewis acids?
- Predict the product of the following reaction.



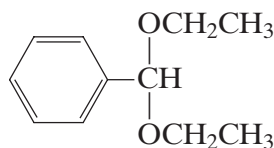
- Predict the product of the following reaction.

**Nucleophilic Attack by Water or an Alcohol**

- Explain why the rate of nucleophilic attack on a carbonyl by either water or an alcohol is relatively slow in the absence of an acid or base catalyst.
- Identify the starting materials that would give the following product.



- Identify the starting materials that would give the following acetal, which has a delightful odor of ‘Bing’ cherries.



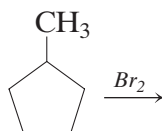
- Maltose, or malt sugar, is an important component of the barley malt used to brew beer. This disaccharide is formed when the $-\text{OH}$ group on C-4 of one α -D-glucopyranose forms an acetal by reacting with C-1 of a second α -D-glucopyranose residue. Draw the structure of the compound.

Addition/Elimination Reactions

28. Explain why acyl chlorides are more reactive than carboxylic acid esters toward addition/elimination reactions.
29. Use the fact that the best leaving groups for addition/elimination reactions are weak bases to explain why attack on a carbonyl by the H^- ion or a source of the CH_3^- ion are not reversible reactions.
30. Which of the following would be the best leaving group?
 (a) NH_2^- ($\text{p}K_{\text{b}} = -19$) (b) CH_3O^- ($\text{p}K_{\text{b}} = -4$) (c) HS^- ($\text{p}K_{\text{b}} = 7$)
 (d) CH_3CO_2^- ($\text{p}K_{\text{b}} = 9.3$)

Free Radical Reactions

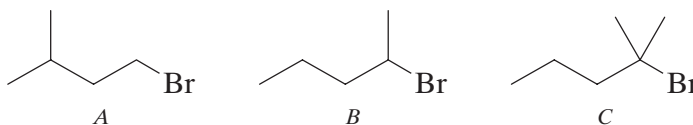
31. Draw the structures of all possible products of the free radical chlorination of 2-methylbutane. Predict the relative abundance of the products if the reaction is so fast that it is not selective.
32. Draw the structures of all possible products of the free radical bromination of methylcyclobutane. Predict the relative abundance of the products if the reaction is equally likely to occur at each of the hydrogen atoms.



33. Assume that the reaction in the previous problem is slow enough to give almost exclusively the product that would be formed from the most stable free radical intermediate. Predict the structure of the product.
34. Calculate the value of ΔH° for the reaction in which H_2 , F_2 , Cl_2 , Br_2 , and I_2 dissociate to form free radicals.

Nucleophilic Substitution Reactions

35. Which of the following starting materials is most likely to undergo an $\text{S}_{\text{N}}2$ reaction with the OCH_3^- ion?

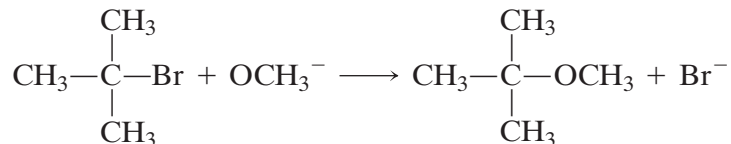


36. Predict the products of the following reactions.
 (a) $\text{CH}_3\text{CH}_2\text{CH}_2\text{I} + \text{OH}^- \rightarrow$ (b) $(\text{CH}_3)_2\text{CHBr} + \text{I}^- \rightarrow$
 (c) $\text{CH}_3\text{Br} + \text{CN}^- \rightarrow$ (d) $\text{CH}_3\text{CH}_2\text{I} + \text{HS}^- \rightarrow$
37. The relative rates of nucleophilic substitution reactions often decrease in the order $\text{CH}_3^- > \text{OH}^- > \text{Cl}^-$. Is this consistent with what we know about the relative strengths of the ions as Brønsted bases?
38. The relative rates of nucleophilic substitution reactions often decrease in the order $\text{I}^- > \text{Br}^- > \text{Cl}^- > \text{F}^-$. Is this consistent with what we know about the relative acidities of HI ($K_{\text{a}} = 3 \times 10^9$), HBr ($K_{\text{a}} = 1 \times 10^9$), HCl ($K_{\text{a}} = 10^6$), and HF ($K_{\text{a}} = 7.2 \times 10^{-4}$)?

28 ORGANIC REACTION MECHANISMS

Or does it suggest that there is a difference between trends in nucleophilicity and basicity as we go down a column of the periodic table? (In other words, the X^- ion becomes less basic and more nucleophilic as we go down the column.)

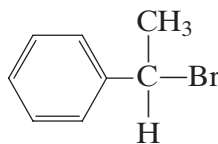
39. Write the mechanism for the following reaction.



40. Identify a set of starting materials that would give the following compound as the product of a nucleophilic substitution reaction.



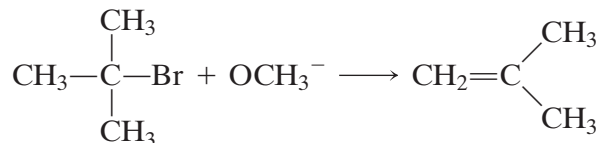
41. Assume that you had a choice of two reagents to react with the following starting material, CH_3OH and the CH_3O^- ion.



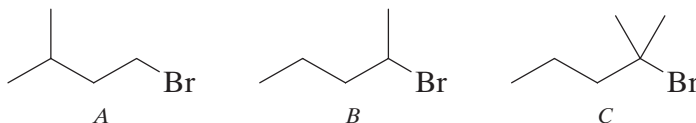
Which nucleophile would be more likely to give a racemized product?

Elimination Reactions

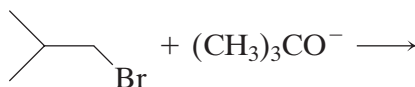
42. Write the mechanism for the following reaction.



43. Which of the following would be the most likely to undergo an E_1 elimination reaction with a very strong base, such as the $(\text{CH}_3)_3\text{CO}^-$ ion?

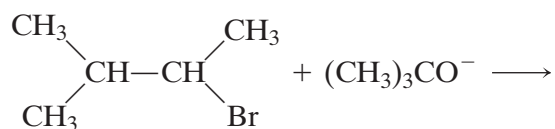


44. Predict the product of the following elimination reaction.



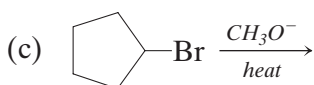
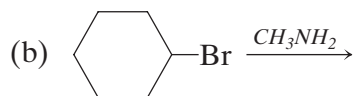
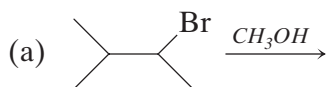
45. Elimination reactions can often give two different products, depending on which carbon atom adjacent to the $\text{C}-\text{X}$ bond is attacked. As a rule, the dominant product of

the reactions is the most highly substituted alkene. Predict the product of the following elimination reaction.

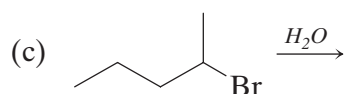
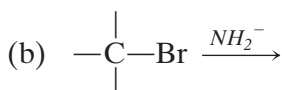
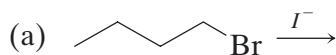


Substitution versus Elimination Reactions

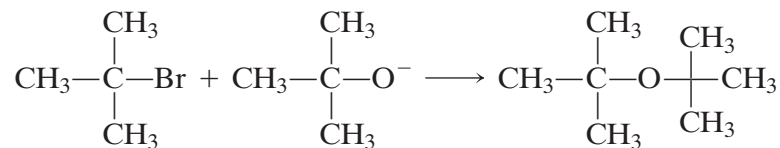
46. Assume that 2-bromopropane undergoes a combination of E_2 and $\text{S}_{\text{N}}2$ reactions when it reacts with the CH_3O^- ion in methanol. Predict the products of the reactions.
47. Predict the most likely product or products of the following reactions.



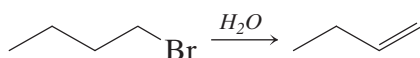
48. Predict whether the following reactions are more likely to undergo elimination or substitution. Identify the mechanism of the dominant reaction (E_1 versus E_2 ; $\text{S}_{\text{N}}1$ versus $\text{S}_{\text{N}}2$).



49. Explain why the following reaction will not give the indicated product. Predict the product that would form.



50. Explain why the following reaction will not give the indicated product. Predict the product that would form.



Integrated Problems

51. The following Lewis structures were drawn correctly by an organic chemistry student who forgot to indicate whether the molecules carry a positive or negative charge. Correct the work by specifying whether each molecule is negatively charged, positively charged, or neutral.

