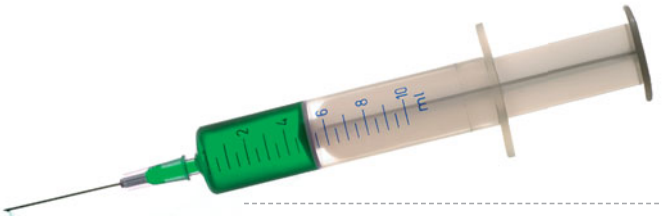
Organic Chemistry

SECOND EDITION

DAVID KLEIN

WILEY

7 Substitution Reactions

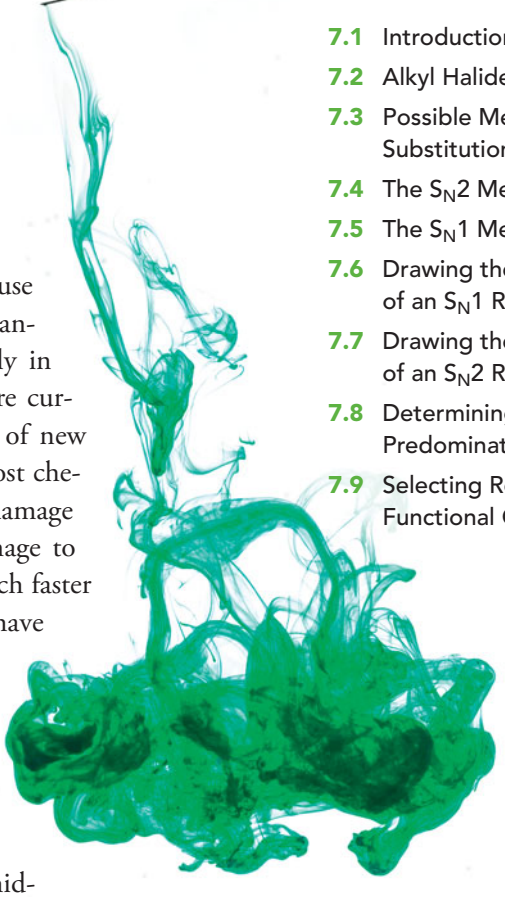


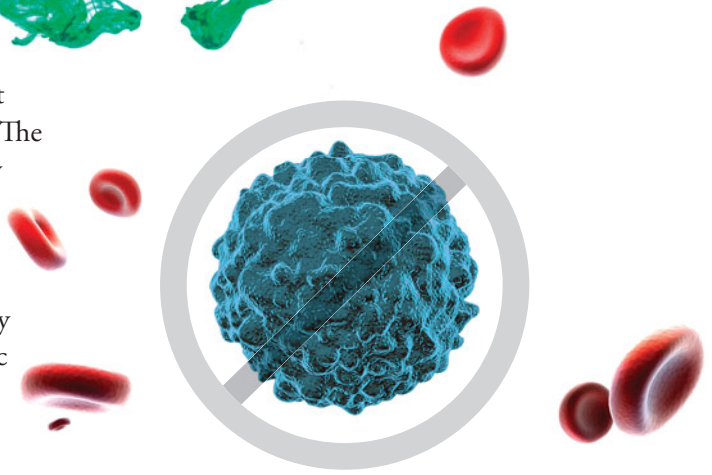
DID YOU EVER WONDER . . .

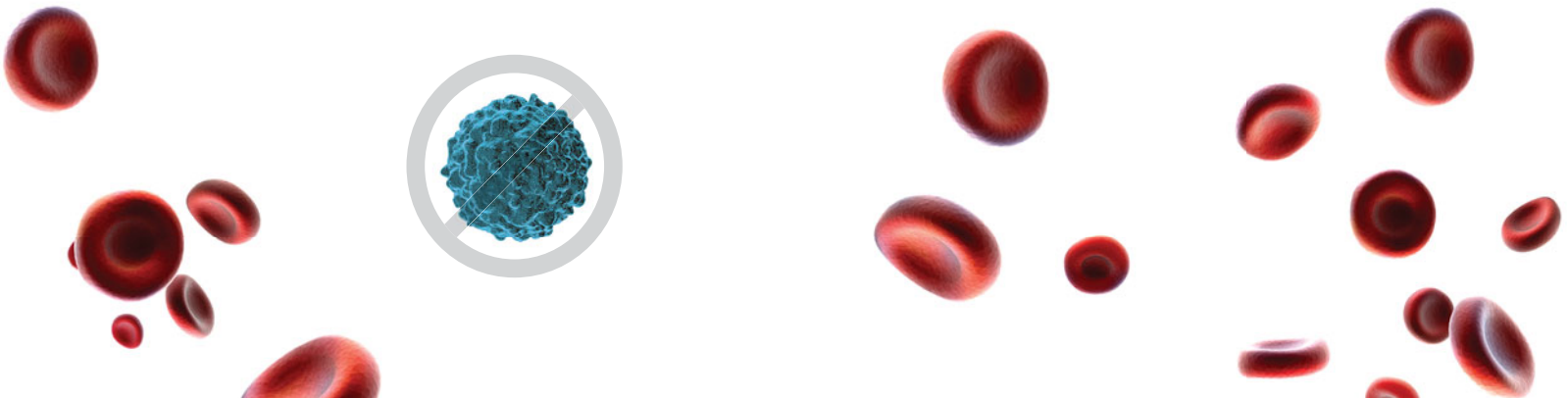
what chemotherapy is?

As its name implies, chemotherapy is the use of chemical agents in the treatment of cancer. Dozens of chemotherapy drugs are currently in clinical use, and researchers around the world are currently working on the design and development of new drugs for treating cancer. The primary goal of most chemotherapeutic agents is to cause irreparable damage to cancer cells while causing only minimal damage to normal, healthy cells. Since cancer cells grow much faster than most other cells, many anticancer drugs have been designed to interrupt the growth cycle of fast-growing cells. Unfortunately, some healthy cells are also fast growing, such as hair follicles and skin cells. For this reason, chemotherapy patients often experience a host of side effects, including hair loss and rashes.

The field of chemotherapy began in the mid-1930s, when scientists realized that a chemical warfare agent (sulfur mustard) could be modified and used to attack tumors. The action of sulfur mustard (and its derivatives) was thoroughly investigated and was found to involve a series of reactions called substitution reactions. Throughout this chapter, we will explore many important features of substitution reactions. At the end of the chapter, we will revisit the topic of chemotherapy by exploring the rational design of the first chemotherapeutic agents.







DO YOU REMEMBER?

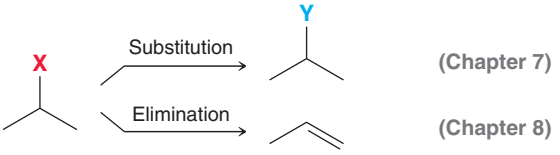
Before you go on, be sure you understand the following topics.
If necessary, review the suggested sections to prepare for this chapter.

- The Cahn-Ingold-Prelog System (Section 5.3)
- Kinetics and Energy Diagrams (Sections 6.5, 6.6)
- Nucleophiles and Electrophiles (Section 6.7)
- Arrow Pushing and Carbocation Rearrangements (Sections 6.8–6.11)

Take the DO YOU REMEMBER? QUIZ in **WileyPLUS** to check your understanding.

7.1 Introduction to Substitution Reactions

This chapter introduces a class of reactions, called **substitution reactions**, in which one group is exchanged for another, while Chapter 8 introduces **elimination** reactions, characterized by the formation of a π bond:



Substitution and elimination reactions often compete with each other; in fact, the last three sections of Chapter 8 will explore the main factors that govern this competition. In this chapter, we will focus our attention exclusively on substitution reactions, and then we will broaden our discussion in Chapter 8 to include elimination reactions.

A substitution reaction can occur when a suitable electrophile is treated with a nucleophile, as in the following example:

LOOKING BACK
For a review of nucleophiles and electrophiles see Section 6.7.

Organic chemists often use the term **substrate** when referring to the electrophile in a substitution reaction. In order for an electrophile to function as a substrate in a substitution reaction, it must contain a **leaving group**, which is a group capable of separating from the substrate. In the example above, chloride functions as the leaving group. A leaving group serves two critical functions:

1. The leaving group withdraws electron density via induction, rendering the adjacent carbon atom electrophilic. This can be visualized with electrostatic potential maps of various methyl halides (Figure 7.1). In each image, the blue color indicates a region of low electron density.

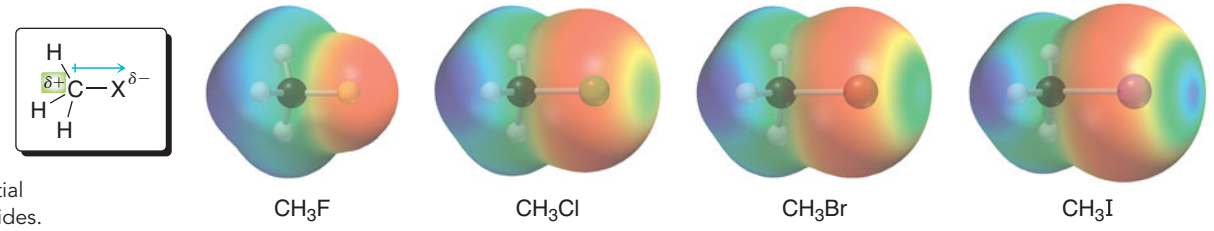
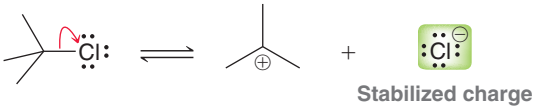


FIGURE 7.1
Electrostatic potential maps of methyl halides.

2. The leaving group can stabilize any negative charge that may develop as the result of the leaving group separating from the substrate:



Halogens (Cl, Br, and I) are very common leaving groups.

7.2 Alkyl Halides

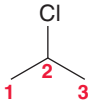
Halogenated organic compounds are commonly used as electrophiles in substitution reactions. Although other compounds can also serve as electrophiles, we will focus our attention for now on compounds containing halogens.

Naming Halogenated Organic Compounds

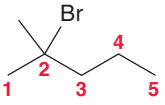
Recall from Section 4.2 that systematic (IUPAC) names of alkanes are assigned using four discrete steps:

1. Identify and name the parent.
2. Identify and name the substituents.
3. Number the parent chain and assign a locant to each substituent.
4. Assemble the substituents alphabetically.

The same exact four-step procedure is used to name compounds that contain halogens, and all of the rules discussed in Chapter 4 apply here as well. Halogens are simply treated as substituents and receive the following names: fluoro-, chloro-, bromo-, and iodo-. Below are two examples:



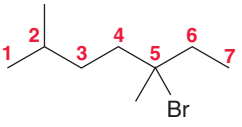
2-Chloropropane



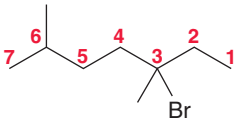
2-Bromo-2-methylpentane

As we saw in Chapter 4, the parent is the longest chain, and it should be numbered so that the first substituent receives the lower number:

Correct



Incorrect

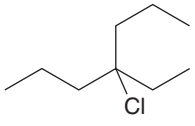


2, 5, 5 beats 3, 3, 6

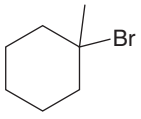
CONCEPTUAL CHECKPOINT

7.1 Assign a systematic name for each of the following compounds:

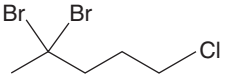
(a)



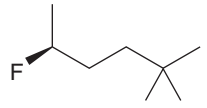
(b)



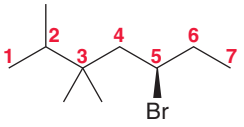
(c)



(d)

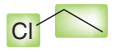


When a chirality center is present in the compound, the configuration must be indicated at the beginning of the name:



(*R*)-5-Bromo-2,3,3-trimethylheptane

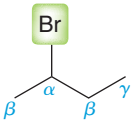
In addition to systematic names, IUPAC nomenclature also recognizes common names for many halogenated organic compounds.

Systematic name	Common name
	
Halo alkane	Alkyl halide
Chloroethane	Ethyl chloride

The systematic name treats a halogen as a substituent, calling the compound a **haloalkane**. The common name treats the compound as an alkyl substituent connected to a halide, and the compound is called an **alkyl halide** or an **organohalide**.

Structure of Alkyl Halides

Each carbon atom is described in terms of its proximity to the halogen using letters of the Greek alphabet. The **alpha (α) position** is the carbon atom connected directly to the halogen, while the **beta (β) positions** are the carbon atoms connected to the alpha position:



An alkyl halide will have only one α position, but there can be as many as three β positions. This chapter focuses on reactions that occur at the α position, and the next chapter will focus on reactions involving the β position.

Alkyl halides are classified as **primary** (1°), **secondary** (2°), or **tertiary** (3°) based on the number of alkyl groups connected to the α position (Figure 7.2).

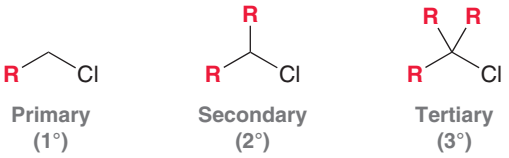
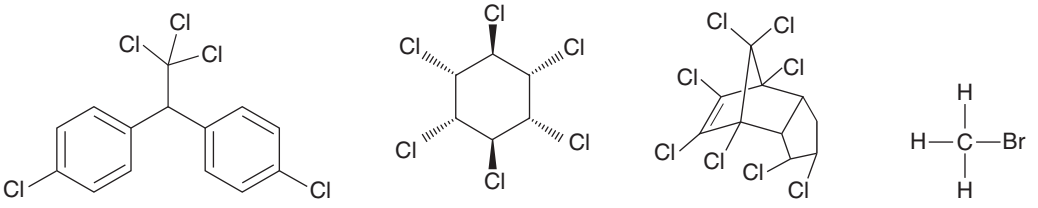


FIGURE 7.2
Classification of alkyl halides as primary, secondary, or tertiary.

Uses of Organohalides

Many organohalides are toxic and have been used as insecticides:

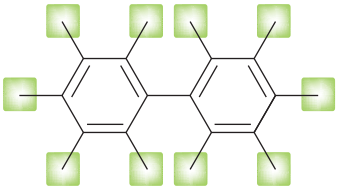


DDT (dichlorodiphenyltrichloroethane) was developed in the late 1930s and became one of the first insecticides to be used around the globe. It was found to exhibit strong toxicity for insects but rather low toxicity for mammals. DDT was used as an insecticide for many decades and has been credited with saving more than half a billion lives by killing mosquitos that carry deadly diseases. Unfortunately, it was found that DDT does not degrade quickly and persists in the environment.

Rising concentrations of DDT in wildlife began to threaten the survival of many species. In response, the Environmental Protection Agency (EPA) banned the use of DDT in 1972, and it was replaced with other, environmentally safer, insecticides.

Lindane is used in shampoos designed to treat head lice, while chlordane and methyl bromide have been used to prevent and treat termite infestations. The use of methyl bromide has recently been regulated due to its role in the destruction of the ozone layer (for more on the hole in the ozone layer, see Section 11.8).

Organohalides are particularly stable compounds, and many of them, like DDT, persist and accumulate in the environment. PCBs (polychlorinated biphenyls) represent another well-known example. Biphenyl is a compound that can have up to 10 substituents:

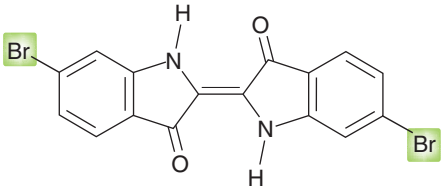


Biphenyl

PCBs are compounds in which many of these positions contain chlorine atoms. PCBs were originally produced as coolants and insulating fluids for industrial transformers and capacitors. They were also used as hydraulic fluids and as flame retardants. But their accumulation in the environment began to threaten wildlife, and their use was banned.

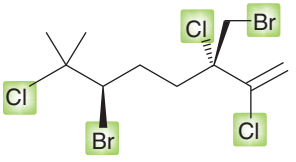
The above examples have contributed to the bad reputation of organohalides. As a result, organohalides are often viewed as man-made poisons. However, research over the last 20 years has indicated that organohalides are actually more common in nature than had previously been thought. For example, methyl chloride is the most abundant organohalide in the atmosphere. It is produced in large quantities by evergreen trees and marine organisms, and it is consumed by many bacteria, such as *Hyphominocrobium* and *Methylobacterium*, that convert methyl chloride into CO_2 and Cl^-.

Many organohalides are also produced by marine organisms. Over 5000 such compounds have already been identified, and several hundred new compounds are discovered each year. Here are two examples:



Tyrian purple

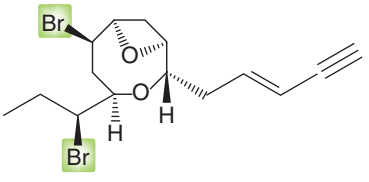
Isolated from the sea snail *Hexaplex trunculus*, this compound is one of the oldest known dyes and was used to make royal clothing thousands of years ago.



Halomon

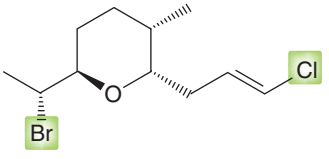
Isolated from the red algae *Portieria hornemannii*, this compound is currently in clinical trials for use as an antitumor agent.

Organohalides serve a variety of functions in living organisms. In sponges, corals, snails, and seaweeds organohalides are used as a defense mechanism against predators (a form of chemical warfare). Here are two such examples:



(*3E*)-Laureatin

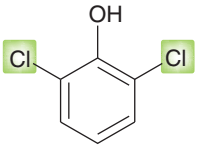
Used by the red algae *Laurencia nipponina*



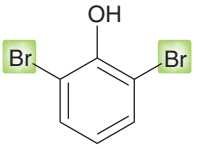
Kumepaloxane

Used by the snail *Haminoea cymbalum*

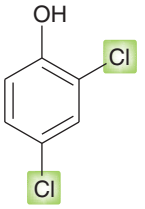
Both of these compounds are used to ward off predators. In many kinds of organisms organohalides act as hormones (chemical messengers that act only on specific target cells). Examples include the following:



2,6-Dichlorophenol
Used as a sex hormone by the lone star tick *Amblyomma americanum*

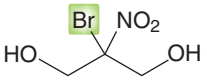


2,6-Dibromophenol
Isolated from the acorn worm *Balanoglossus biminiensis*, likely used as a hormone

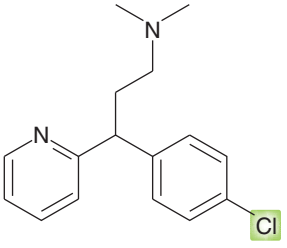


2,4-Dichlorophenol
Used as a growth hormone by *Penicillium* molds

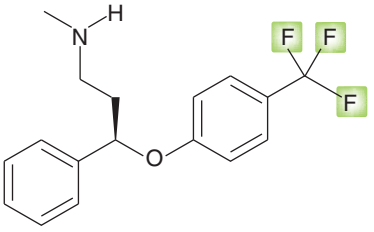
Not all halogenated compounds are toxic. In fact, many organohalides have clinical applications. For example, the following compounds are widely used and have contributed much to the improvement of physical and psychological health:



Bronopol
(2-Bromo-2-nitropropane-1,3-diol)
A powerful antimicrobial compound safe enough to use in baby-wipes



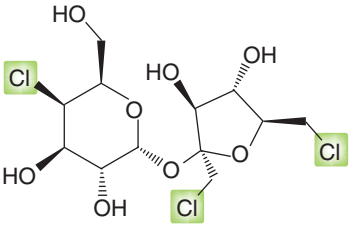
Chlorpheniramine
An antihistamine, sold under the trade name Chlor-Trimeton



(*R*)-Fluoxetine
An antidepressant, sold under the trade name Prozac

BY THE WAY
Sucralose was discovered by accident in 1976 when a British company (Tate and Lyle) was conducting research on potential uses of chlorinated sugars. A foreign graduate student participating in the research misunderstood a request to "test" one of the compounds and instead thought he was being asked to "taste" the compound. The graduate student reported an intensely sweet taste, and it was later found to be safe to consume.

Some organohalides have even been used in the food industry. Consider, for example, the structure of sucralose, shown here. Sucralose contains three chlorine atoms, but it is known not to be toxic. It is several hundred times sweeter than sugar and is sold as an artificial, low-calorie sweetener under the trade name Splenda.



Sucralose
An artificial sweetener, sold under the trade name Splenda

7.3 Possible Mechanisms for Substitution Reactions

Recall from Chapter 6 that ionic mechanisms are comprised of only four types of arrow-pushing patterns (Figure 7.3). All four of these steps will be used in this chapter, so it might be wise to review Sections 6.7–6.10.

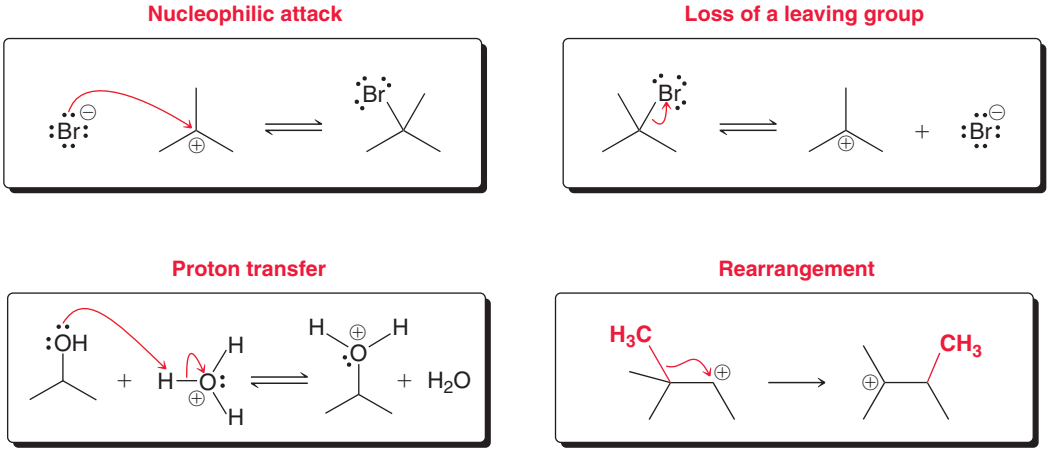
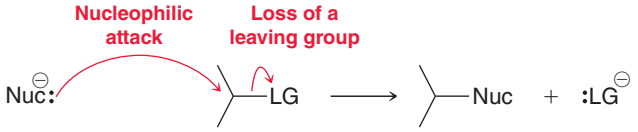
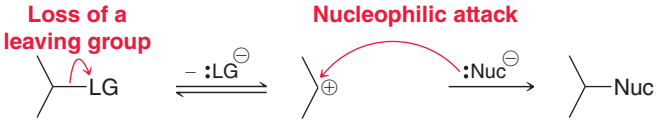


FIGURE 7.3
The four arrow-pushing patterns for ionic processes.

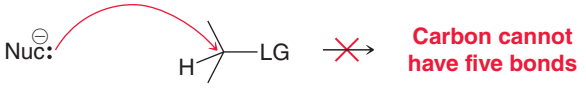
Every substitution reaction exhibits at least two of the four patterns—nucleophilic attack and loss of a leaving group:



But consider the order of these events. Do they occur simultaneously (in a concerted fashion), as shown above, or do they occur in a stepwise fashion, as shown below?



In the stepwise mechanism, the leaving group leaves, generating an intermediate carbocation, which is then attacked by the nucleophile. The nucleophile cannot attack before the leaving group leaves, because that would violate the octet rule:



Therefore, there are two possible mechanisms for a substitution reaction:

- In a *concerted process*, nucleophilic attack and loss of the leaving group occur simultaneously.
- In a *stepwise process*, loss of the leaving group occurs first followed by nucleophilic attack.

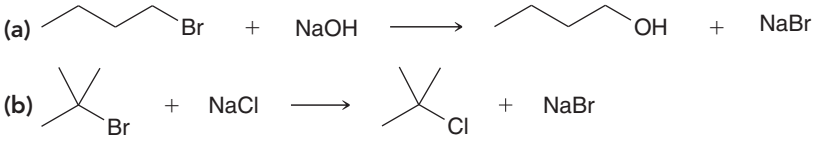
We will see that both of these mechanisms do occur, but under different conditions. We will explore each mechanism in the next section, but first let's practice drawing the curved arrows for the two mechanisms.

SKILLBUILDER

7.1 DRAWING THE CURVED ARROWS OF A SUBSTITUTION REACTION

LEARN the skill

Below are two substitution reactions. Experimental evidence suggests that the first reaction proceeds via a concerted process, while the second reaction proceeds via a stepwise process. Draw a mechanism for each reaction:



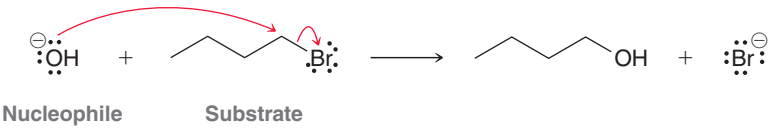
SOLUTION

(a) First identify the substrate, the leaving group, and the nucleophile. Here, the substrate is butyl bromide, the leaving group is bromide, and the nucleophile is a hydroxide ion:

STEP 1 Identify the substrate, leaving group, and nucleophile.

When you see NaOH, remember that the reagent is a hydroxide ion ($HO^{\ominus}$). Na^{+} is the counter-ion, and its role in the reaction does not concern us in most cases. In a concerted process, nucleophilic attack and loss of a leaving group occur simultaneously. This process requires two curved arrows—one to show the nucleophilic attack and one to show the loss of the leaving group. When drawing the first curved arrow, place the tail on a lone pair of the nucleophile and place the head on the carbon atom bearing the leaving group:

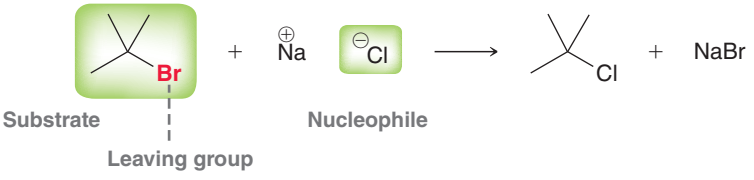
STEP 2 Draw two curved arrows, showing nucleophilic attack and loss of the leaving group.



WATCH OUT Be very precise in placing the head and tail of every curved arrow.

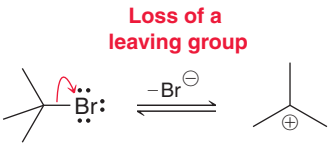
(b) A stepwise process involves two separate mechanistic steps: (1) loss of a leaving group to form a carbocation intermediate followed by (2) nucleophilic attack. To draw these steps, we must identify the substrate, leaving group, and nucleophile. Here, the substrate is *tert*-butyl bromide, the leaving group is a bromide ion, and the nucleophile is a chloride ion:

STEP 1 Identify the substrate, leaving group, and nucleophile.



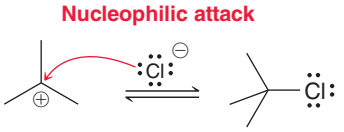
STEP 2 Draw a curved arrow showing loss of the leaving group and then draw the resulting carbocation.

The first step of the mechanism requires one curved arrow showing the loss of the leaving group. The tail of this curved arrow is placed on the bond that is broken (the C—Br bond); the head of the arrow is placed on the bromine atom.

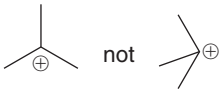


STEP 3
Draw a curved arrow showing a nucleophilic attack.

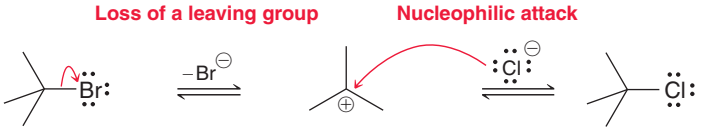
The second step of the mechanism requires one curved arrow showing the nucleophilic attack in which the carbocation intermediate is captured by the nucleophile (chloride):



BY THE WAY
Draw all three groups of a tertiary carbocation as far apart from each other as possible:

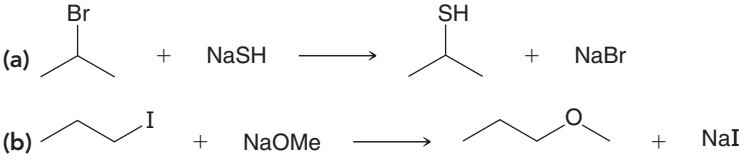


The complete mechanism can therefore be drawn like this:

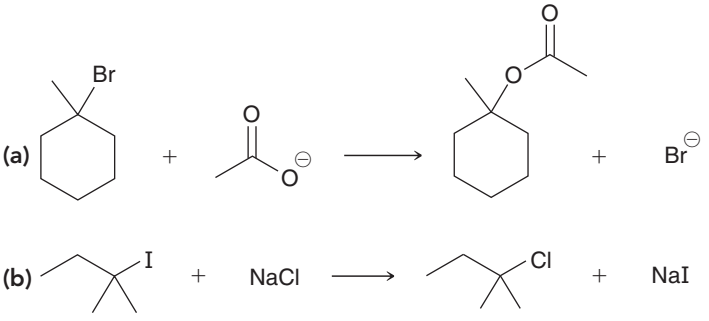


PRACTICE the skill

7.2 For each of the following reactions, assume a concerted process is taking place and draw the mechanism:



7.3 For each of the following reactions assume a stepwise process is taking place and draw the mechanism:



APPLY the skill

7.4 When a nucleophile and electrophile are tethered to each other (that is, both present in the same compound), an *intramolecular substitution reaction* can occur, as shown. Assume that this reaction occurs via a concerted process and draw the mechanism.

7.5 For the substitution reaction shown below, assume a stepwise process is taking place and draw the mechanism. (**Hint:** Review the rules for drawing resonance structures, Section 2.10.)

need more **PRACTICE?** **Try Problem 7.64a**

7.4 The S_N2 Mechanism

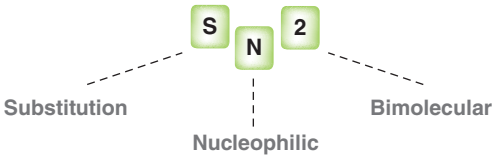
During the 1930s, Sir Christopher Ingold and Edward D. Hughes (University College, London) investigated substitution reactions in an effort to elucidate their mechanism. Based on kinetic and stereochemical observations, Ingold and Hughes proposed a concerted mechanism for many of the substitution reactions that they investigated. We will now explore the observations that led them to propose a concerted mechanism.

Kinetics

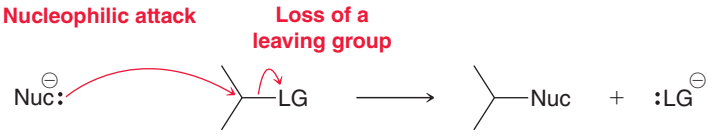
For most of the reactions that they investigated, Ingold and Hughes found the rate of reaction to be dependent on the concentrations of both the substrate and the nucleophile. This observation is summarized in the following rate equation:

$$\text{Rate} = k\,[\text{substrate}]\,[\text{nucleophile}]$$

Specifically, they found that doubling the concentration of the nucleophile caused the reaction rate to double. Similarly, doubling the concentration of the substrate also caused the rate to double. The rate equation above is described as **second order**, because the rate is linearly dependent on the concentrations of two different compounds. Based on their observations, Ingold and Hughes concluded that the mechanism must exhibit a step in which the substrate and the nucleophile collide with each other. Because that step involves two chemical entities, it is said to be **bimolecular**. Ingold and Hughes coined the term **S_N2** to refer to bimolecular substitution reactions:



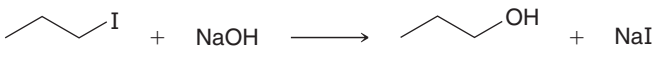
The experimental observations for S_N2 reactions are consistent with a concerted mechanism, because a concerted mechanism exhibits only one mechanistic step, involving both the nucleophile and the substrate:



It makes sense that the rate should be dependent on the concentrations of both the nucleophile and the substrate.

CONCEPTUAL CHECKPOINT

7.6 The reaction below exhibits a second-order rate equation:



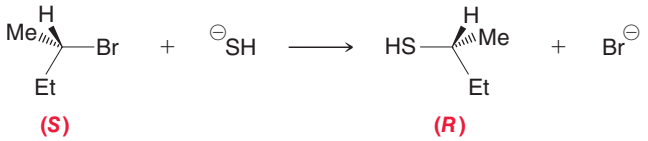
(a) What happens to the rate if the concentration of 1-iodopropane is tripled and the concentration of sodium hydroxide remains the same?

(b) What happens to the rate if the concentration of 1-iodopropane remains the same and the concentration of sodium hydroxide is doubled?

(c) What happens to the rate if the concentration of 1-iodopropane is doubled and the concentration of sodium hydroxide is tripled?

Stereospecificity of S_N2 Reactions

There is another crucial piece of evidence that led Ingold and Hughes to propose the concerted mechanism. When the α position is a chirality center, a change in configuration is generally observed, as illustrated in the following example:



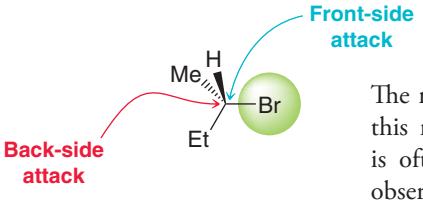


FIGURE 7.4
The front and back sides of a substrate.

The reactant exhibits the *S* configuration, while the product exhibits the *R* configuration. That is, this reaction is said to proceed with **inversion of configuration**. This stereochemical outcome is often called a Walden inversion, named after Paul Walden, the German chemist who first observed it.

The requirement for inversion of configuration means that the nucleophile can only attack from the back side (the side opposite the leaving group) and never from the front side (Figure 7.4). There are two ways to explain why the reaction proceeds through **back-side attack**:

1. The lone pairs of the leaving group create regions of high electron density that effectively block the front side of the substrate, so the nucleophile can only approach from the back side.
2. Molecular orbital (MO) theory provides a more sophisticated answer. Recall that molecular orbitals are associated with the entire molecule (as opposed to *atomic* orbitals, which are associated with individual atoms). According to MO theory, the electron density flows from the HOMO of the nucleophile into the LUMO of the electrophile. As an example let's focus our attention on the LUMO of methyl bromide (Figure 7.5). If a nucleophile attacks methyl bromide from the front side, the nucleophile will encounter a node, and as a result, no net bonding will result from the overlap between the HOMO of the nucleophile and the LUMO of the electrophile. In contrast, nucleophilic attack from the back side allows for efficient overlap between the HOMO of the nucleophile and the LUMO of the electrophile.

LOOKING BACK
For a review of molecular orbital theory and the terms HOMO and LUMO, see Section 1.8.

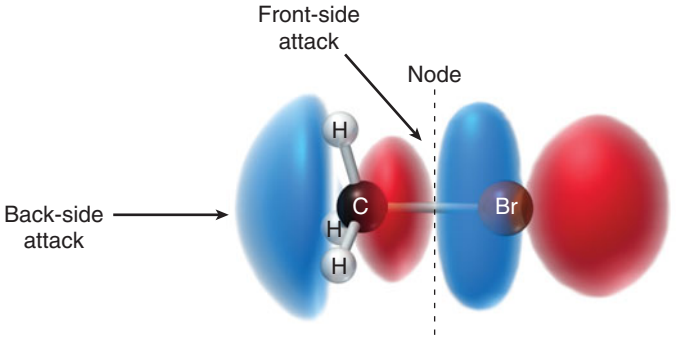
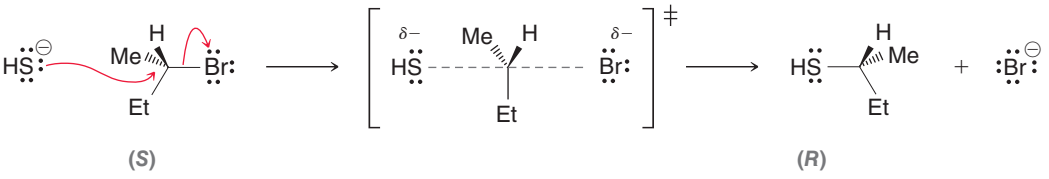


FIGURE 7.5
The lowest unoccupied molecular orbital (LUMO) of methyl bromide.

The observed stereochemical outcome for an S_N2 process (inversion of configuration) is consistent with a concerted mechanism. The nucleophile attacks with simultaneous loss of the leaving group. This causes the chirality center to behave like an umbrella flipping in the wind:



The transition state (drawn in brackets) will be discussed in more detail in the coming section. This reaction is said to be **stereospecific**, because the configuration of the product is dependent on the configuration of the starting material.

SKILLBUILDER

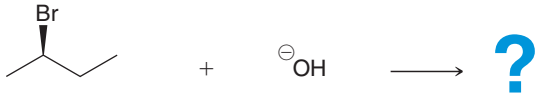
7.2 DRAWING THE PRODUCT OF AN S_N2 PROCESS

LEARN the skill

When (*R*)-2-bromobutane is treated with a hydroxide ion, a mixture of products is obtained. An S_N2 process is responsible for generating one of the minor products, while the major product is generated via an elimination process, as will be discussed in the next chapter. Draw the S_N2 product that is obtained when (*R*)-2-bromobutane reacts with a hydroxide ion.

SOLUTION

First draw the reagents described in the problem:

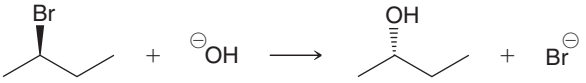


(*R*)-2-Bromobutane Hydroxide

Now identify the nucleophile and the substrate. Bromobutane is the substrate and hydroxide is the nucleophile. When hydroxide attacks, it will eject the bromide ion as a leaving group. The net result is that the Br will be replaced with an OH group:

WATCH OUT
In an S_N2 reaction, if the α position is a chirality center, make sure to draw an inversion of configuration in the product.

In this case, the α position is a chirality center, so we expect inversion:



PRACTICE the skill

7.7 Draw the product for each of the following S_N2 reactions:

(a) (*S*)-2-Chloropentane and NaSH **(b)** (*R*)-3-Iodohexane and NaCl

(c) (*R*)-2-Bromohexane and sodium hydroxide

APPLY the skill

7.8 When (*S*)-1-bromo-1-fluoroethane reacts with sodium methoxide, an S_N2 reaction takes place in which the bromine atom is replaced by a methoxy group (OMe). The product of this reaction is (*S*)-1-fluoro-1-methoxyethane. How can it be that the starting material and the product both have the *S* configuration? Shouldn't S_N2 involve a change in the configuration? Draw the starting material and the product of inversion, and then explain the anomaly.

need more **PRACTICE?** **Try Problems 7.45, 7.56, 7.61**

Structure of the Substrate

For S_N2 reactions, Ingold and Hughes also found the rate to be sensitive to the nature of the starting alkyl halide. In particular, methyl halides and primary alkyl halides react most quickly with nucleophiles. Secondary alkyl halides react more slowly, and tertiary alkyl halides are essentially unreactive toward S_N2 (Figure 7.6). This trend is consistent with a concerted process in which the nucleophile is expected to encounter steric hindrance as it approaches the substrate.

To understand the nature of the steric effects that govern S_N2 reactions, we must explore the transition state for a typical S_N2 reaction, shown in general form in Figure 7.7. Recall that a transition state is represented by a peak in an energy diagram. Consider, for example, an energy diagram showing the reaction between a cyanide ion and methyl bromide (Figure 7.8). The highest point on the curve represents the transition state. The superscript symbol that looks like a telephone pole outside the brackets indicates that the drawing shows a transition state rather than an intermediate. The relative energy of this transition state determines the rate of the reaction. If the transition state is high in energy, then E_a

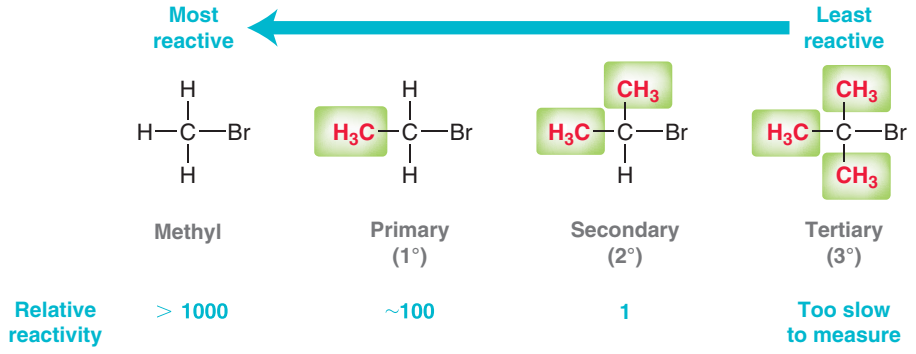


FIGURE 7.6
The relative reactivity of various substrates toward S_N2.

will be large, and the rate will be slow. If the transition state is low in energy, then E_a will be small, and the rate will be fast. With this in mind, we can now explore the effects of steric hindrance in slowing down the reaction rate and explain why tertiary substrates are unreactive.

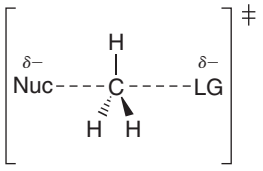


FIGURE 7.7
The generic form of a transition state in an S_N2 process.

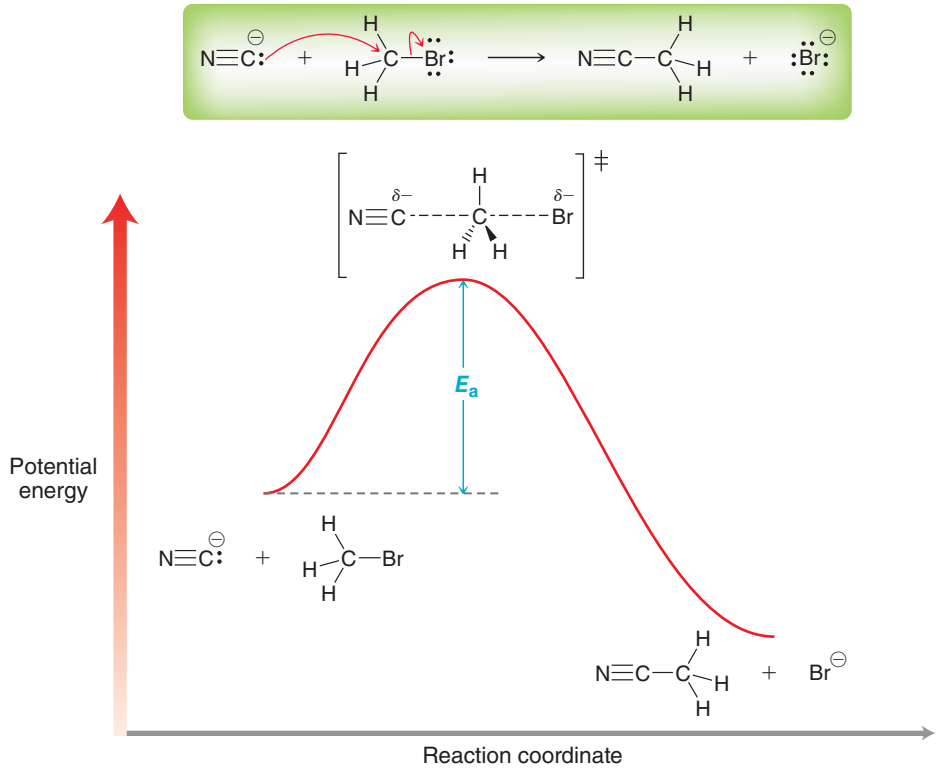


FIGURE 7.8
An energy diagram of the S_N2 reaction that occurs between methyl bromide and a cyanide ion.

Take a close look at the transition state. The nucleophile is in the process of forming a bond with the substrate, and the leaving group is in the process of breaking its bond with the substrate. Notice that there is a partial negative charge on either side of the transition state. This can be seen more clearly in an electrostatic potential map of the transition state (Figure. 7.9). If the hydrogen atoms

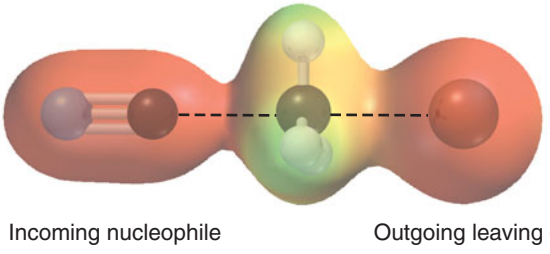


FIGURE 7.9
An electrostatic potential map of the transition state from Figure 7.7. The red areas represent regions of high electron density.

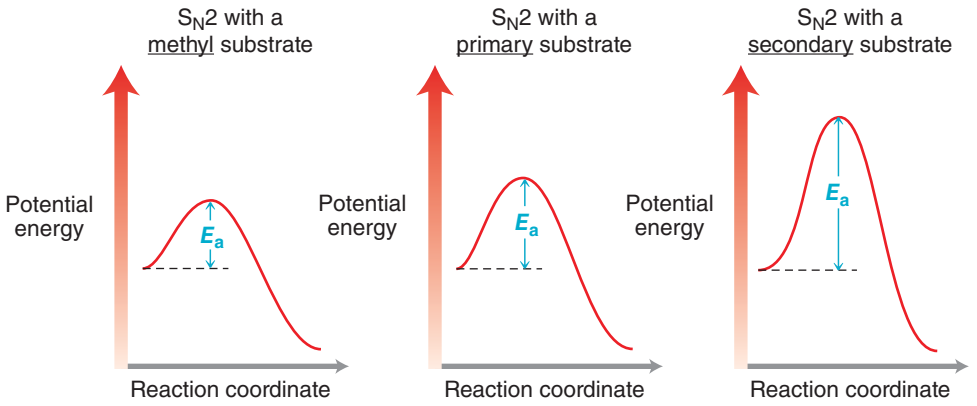
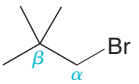


FIGURE 7.10
Energy diagrams comparing S_N2 processes for methyl, primary, and secondary substrates.

in Figure 7.9 are replaced with alkyl groups, steric interactions cause the transition state to be higher in energy, raising E_a for the reaction. Compare the energy diagrams for reactions involving methyl, primary, and secondary substrates (Figure 7.10). With a tertiary substrate, the transition state is so high in energy that the reaction occurs too slowly to observe.

Steric hindrance at the beta position can also decrease the rate of reaction. For example, consider the structure of neopentyl bromide:



Neopentyl bromide

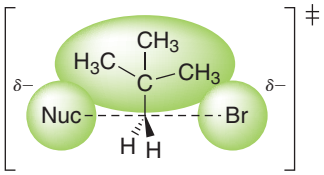
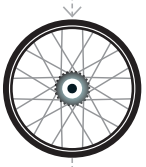


FIGURE 7.11
The transition state for an S_N2 process involving a neopentyl substrate.

This compound is a primary alkyl halide, but it has three methyl groups attached to the beta position. These methyl groups provide steric hindrance that causes the energy of the transition state to be very high (Figure 7.11). Once again, the rate is very slow. In fact, the rate of a neopentyl substrate is similar to the rate of a tertiary substrate in S_N2 reactions. This is an interesting example, because the substrate is a primary alkyl halide that essentially does not undergo an S_N2 reaction. This example illustrates why it is best to understand concepts in organic chemistry rather than memorize rules without knowing what they mean.

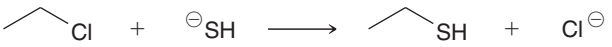
SKILLBUILDER

7.3 DRAWING THE TRANSITION STATE OF AN S_N2 PROCESS



LEARN the skill

Draw the transition state of the following reaction:



SOLUTION

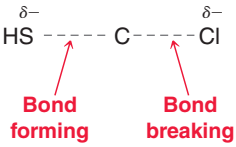
STEP 1
Identify the nucleophile and the leaving group.

First identify the nucleophile and the leaving group. These are the two groups that will be on either side of the transition state:

Nucleophile **Leaving group**

STEP 2
Draw a carbon atom connected by dotted lines to the nucleophile and the leaving group.

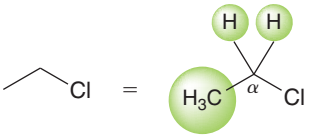
The transition state will need to show a bond forming with the nucleophile and a bond breaking with the leaving group. Dotted lines are used to show the bonds that are breaking and forming:



The δ− symbol is placed on both the incoming nucleophile and the outgoing leaving group to indicate that the negative charge is spread out over both locations.

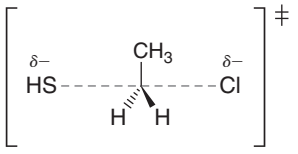
Now we must draw all of the alkyl groups connected to the α position. In our example, the α position has one CH_3 group and two H's:

STEP 3
Draw the three groups attached to the carbon atom.



So we draw these groups in the transition state connected to the α position. One group is placed on a straight line, and the other two groups are placed on a wedge and on a dash:

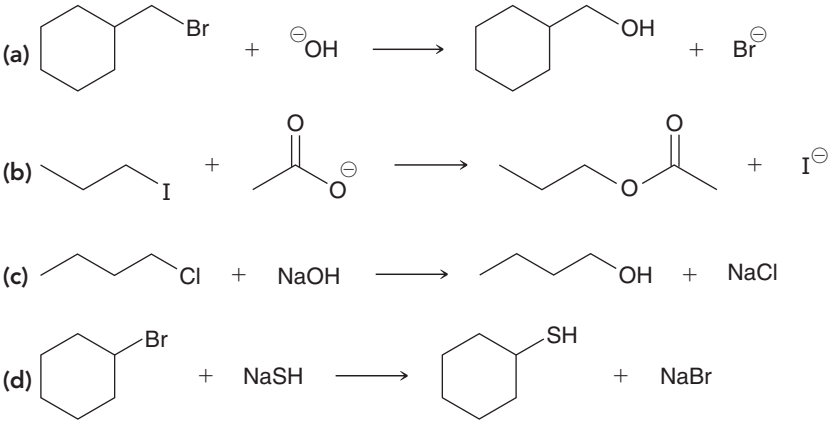
STEP 4
Place brackets as well as the symbol that indicates a transition state.



It does not matter whether the CH_3 group is placed on the line, wedge, or dash. But don't forget to indicate that the drawing is a transition state by surrounding it with brackets and using the symbol that indicates a transition state.

PRACTICE the skill

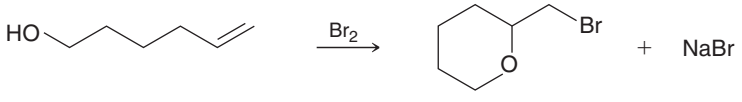
7.9 Draw the transition state for each of the following S_N2 reactions:



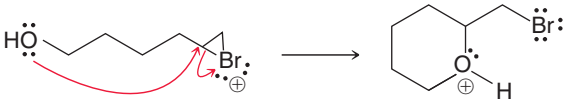
APPLY the skill

7.10 In Problem 7.4, we saw that an *intramolecular* substitution reaction can occur when the nucleophilic center and electrophilic center are present in the same compound. Draw the transition state of the reaction in Problem 7.4.

7.11 Treatment of 5-hexen-1-ol with bromine affords a cyclic product:



The mechanism of this reaction involves several steps, one of which is an intramolecular S_N2-like process:



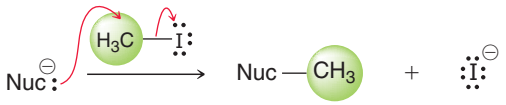
In this step, a bond is in the process of breaking, while another bond is in the process of forming. Draw the transition state of this S_N2-like process, and identify which bond is being broken and which bond is being formed. Can you offer an explanation as to why this step is favorable?

need more **PRACTICE?** **Try Problems 7.46, 7.64e**

practically speaking

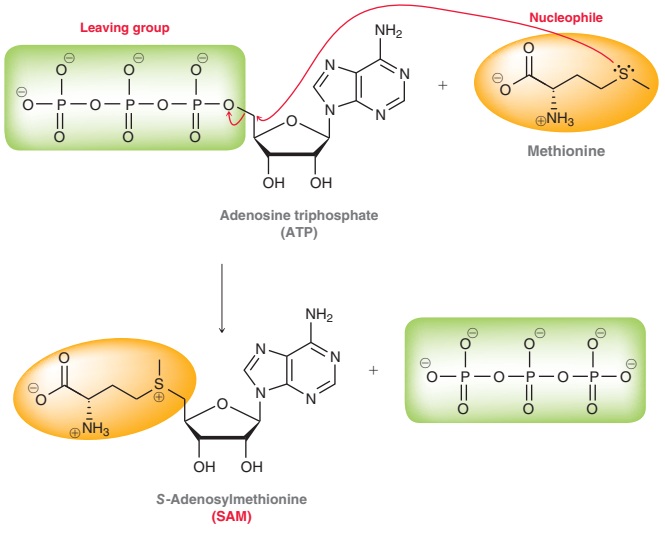
S_N2 Reactions in Biological Systems—Methylation

In the laboratory, the transfer of a methyl group is accomplished via an S_N2 process using methyl iodide:



This process is called *alkylation*, because an alkyl group has been transferred to the nucleophile. It is an S_N2 process, which means there are limitations on the type of alkyl group that can be used. Tertiary alkyl groups cannot be transferred. Secondary alkyl groups can be transferred, but slowly. Primary alkyl groups and methyl groups are transferred most readily. The alkylation process shown above is the transfer of a methyl group and is therefore called *methylation*. Methyl iodide is ideally suited for this task, because iodide is an excellent leaving group and because methyl iodide is a liquid at room temperature. This makes it easier to work with than methyl chloride or methyl bromide, which are gases at room temperature.

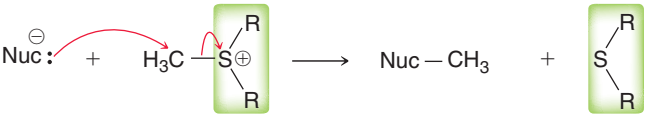
Methylation reactions also occur in biological systems, but instead of CH_3I, the methylating agent is a compound called SAM (*S*-adenosylmethionine). Your body produces SAM via an S_N2 reaction between ATP and the amino acid methionine:



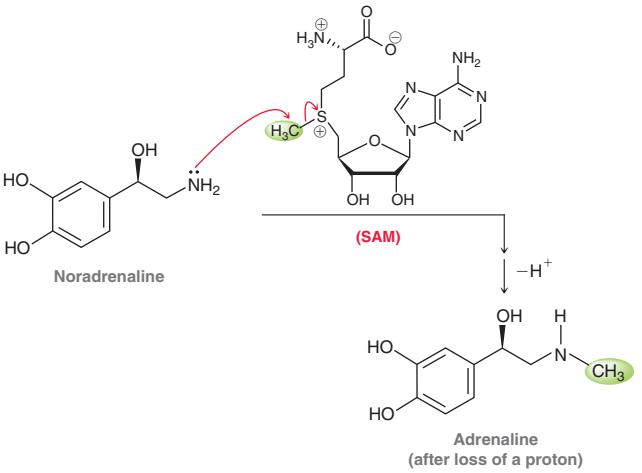
In this reaction, methionine acts as a nucleophile and attacks adenosine triphosphate (ATP), kicking off a triphosphate leaving group. The resulting product, called SAM, is able to function as a methylating agent, very much like CH_3I. Both CH_3I and SAM exhibit a methyl group attached to an excellent leaving group.

Methyl iodide	*S*-Adenosylmethionine (SAM)
H_3C-I Iodide is a relatively simple leaving group.	This leaving group is more complex.

SAM is the biological equivalent of CH_3I. The leaving group is much larger, but SAM functions in the same way as CH_3I. When SAM is attacked by a nucleophile, an excellent leaving group is expelled:



SAM plays a role in the biosynthesis of many compounds, such as adrenaline, which is released into the bloodstream in response to danger or excitement. Adrenaline is produced via a methylation reaction that takes place between noradrenaline and SAM in the adrenal gland:



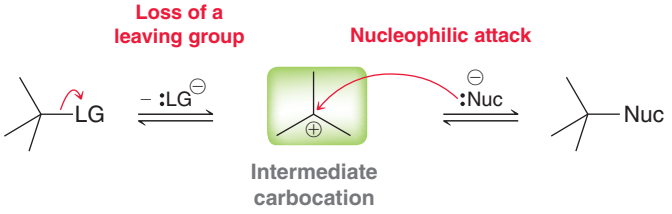
After being released into the bloodstream, adrenaline increases heart rate, elevates sugar levels to provide a boost of energy, and increases levels of oxygen reaching the brain. These physiological responses prepare the body for "fight or flight."

CONCEPTUAL CHECKPOINT

7.12 Nicotine is an addictive compound found in tobacco, and choline is a compound involved in neurotransmission. The biosynthesis of each of these compounds involves the transfer of a methyl group from SAM. Draw a mechanism for both of these transformations:

7.5 The S_N1 Mechanism

The second possible mechanism for a substitution reaction is a stepwise process in which there is (1) loss of the leaving group to form a carbocation intermediate followed by (2) nucleophilic attack on the carbocation intermediate:



An energy diagram for this type of process (Figure 7.12) is expected to exhibit two humps, one for each step. Notice that the first hump is taller than the second hump, indicating that the transition state for the first step is higher in energy than the transition state for the second step. This is extremely important, because for any process, the step with the highest energy transition state determines the rate of the overall process. That step is therefore called the **rate-determining step** (RDS). In Figure 7.12, we can see that the rate-determining step is loss of the leaving group.

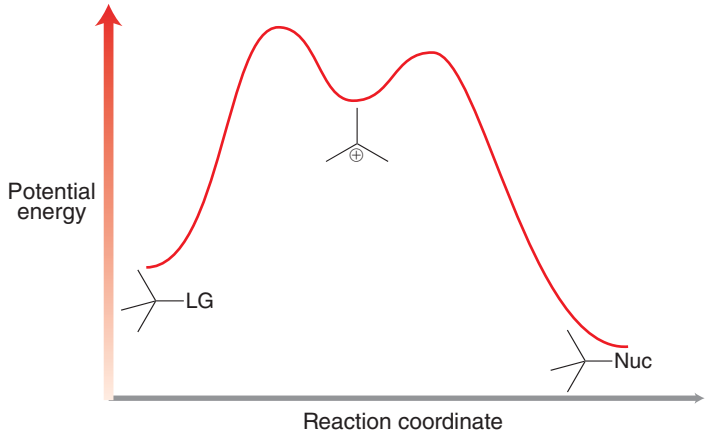
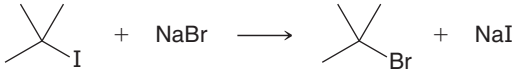


FIGURE 7.12
An energy diagram of an S_N1 process.

Many substitution reactions appear to follow this stepwise mechanism. There are several pieces of evidence that support this stepwise mechanism in those cases. This evidence will now be explored.

Kinetics

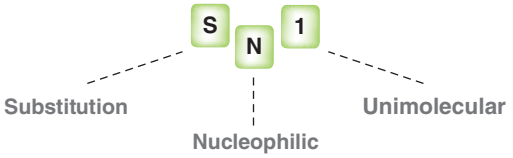
Many substitution reactions do not exhibit second-order kinetics. Consider the following example:



In the reaction above, the rate is dependent only on the concentration of the substrate. The rate equation has the following form:

$$\text{Rate} = k\,[\text{substrate}]$$

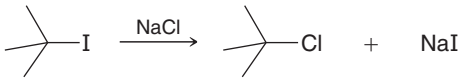
Increasing or decreasing the concentration of the nucleophile has no measurable effect on the rate. The rate equation is said to be **first order**, because the rate is linearly dependent on the concentration of only one compound. In such cases, the mechanism must exhibit a rate-determining step in which the nucleophile does not participate. Because that step involves only one chemical entity, it is said to be **unimolecular**. Ingold and Hughes coined the term **S_N1** to refer to unimolecular substitution reactions:



When we use the term unimolecular, we don't mean that the nucleophile is completely irrelevant. Clearly, the nucleophile is necessary, or there won't be a reaction. The term *unimolecular* simply describes the fact that only one chemical entity participates in the rate-determining step of the reaction, and as a result, the rate of the reaction is not affected by how much nucleophile is present. That is, the rate of an S_N1 process is dependent only on the rate at which the leaving group leaves. As a result, the rate of an S_N1 process will only be affected by factors that affect the rate of that step. Increasing the concentration of the nucleophile has no impact on the rate at which the leaving group leaves. It is true that the nucleophile must be present in order to obtain the product, but an excess of nucleophile will not speed up the reaction. A unimolecular substitution reaction is therefore consistent with a stepwise mechanism in which the first step is the rate-determining step.

CONCEPTUAL CHECKPOINT

7.13 The following reaction occurs via an S_N1 mechanistic pathway:



(a) What happens to the rate if the concentration of *tert*-butyl iodide is doubled and the concentration of sodium chloride is tripled?

(b) What happens to the rate if the concentration of *tert*-butyl iodide remains the same and the concentration of sodium chloride is doubled?

Structure of Substrate

The rate of an S_N1 reaction is highly dependent on the nature of the substrate, but the trend is the reverse of the trend we saw for S_N2 reactions. With S_N1 reactions, tertiary substrates react most quickly, while methyl and primary substrates are mostly unreactive (Figure 7.13). This observation supports a stepwise mechanism (S_N1). Why? With S_N2 reactions, steric hindrance was the issue

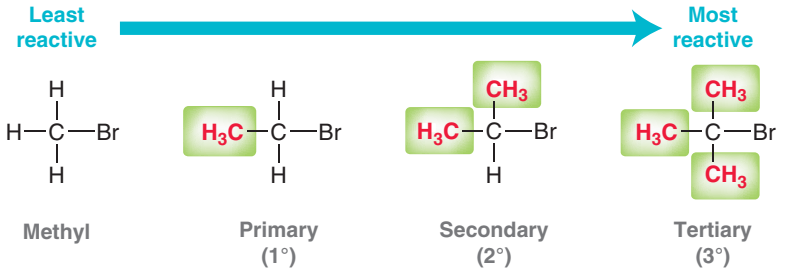


FIGURE 7.13
The relative reactivity of various substrates toward S_N1.

because the nucleophile was directly attacking the substrate. In contrast, in S_N1 reactions the nucleophile does not attack the substrate directly. Instead, the leaving group leaves first, resulting in the formation of a carbocation, and that step is the rate-determining step. Once the carbocation forms, the nucleophile captures it very quickly. The rate is only dependent on how quickly the leaving group leaves to form a carbocation. Steric hindrance is not at play, because the rate-determining step does not involve nucleophilic attack. The dominant factor now becomes carbocation stability.

Recall that carbocations are stabilized by neighboring alkyl groups (Figure 7.14).

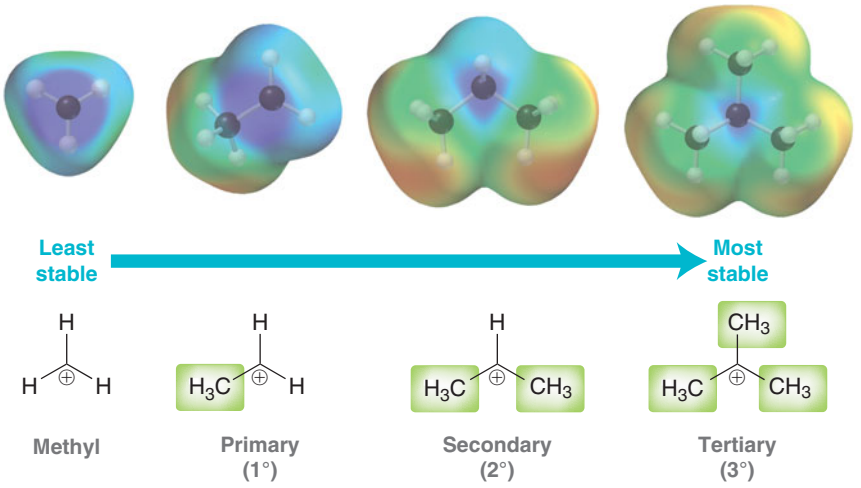


FIGURE 7.14
Electrostatic potential maps of various carbocations. The alkyl groups help spread the positive charge, thereby stabilizing the charge.

Tertiary carbocations are more stable than secondary carbocations, which are more stable than primary carbocations. Therefore, formation of a tertiary carbocation will have a smaller E_a than formation of a secondary carbocation (Figure 7.15). The larger E_a associated with formation of a secondary carbocation can be explained by the Hammond postulate (Section 6.6). Specifically, the transition state for formation of a tertiary carbocation will be close in energy to a tertiary carbocation, while the transition state for formation of a secondary carbocation will be close in energy to a secondary carbocation. Therefore, formation of a tertiary carbocation will involve a smaller E_a.

The bottom line is that tertiary substrates generally undergo substitution via an S_N1 process, while primary substrates generally undergo substitution via an S_N2 process. Secondary substrates can proceed via either pathway (S_N1 *or* S_N2) depending on other factors, which are discussed later in this chapter.

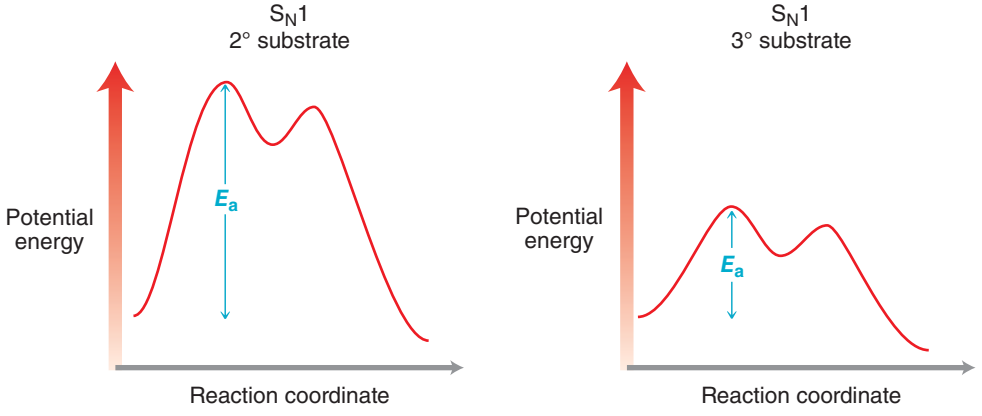


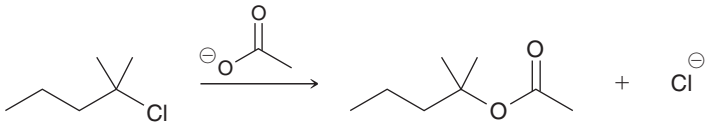
FIGURE 7.15
Energy diagrams comparing S_N1 processes for secondary and tertiary substrates.

SKILLBUILDER

7.4 DRAWING THE CARBOCATION INTERMEDIATE OF AN S_N1 PROCESS

LEARN the skill

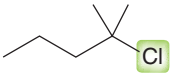
Draw the carbocation intermediate of the following S_N1 reaction:



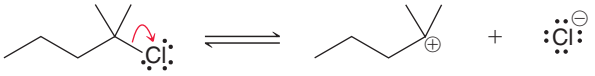
SOLUTION

First identify the leaving group:

STEP 1 Identify the leaving group.

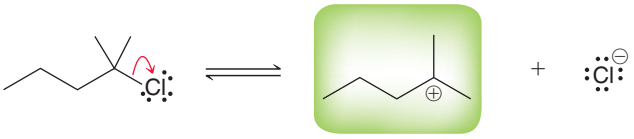


Loss of the leaving group will produce a carbocation and a chloride ion. To keep track of the electrons, it is helpful to draw the curved arrow that shows the flow of electrons:



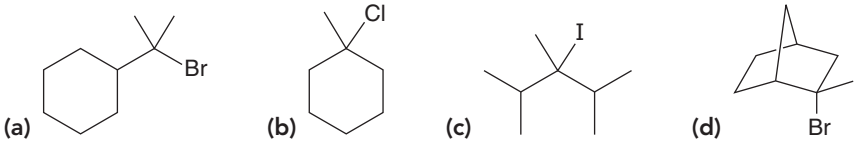
When drawing the carbocation intermediate, make sure that all three groups on the carbocation are drawn as far apart as possible. Remember that a carbocation has trigonal planar geometry, and the drawing should reflect that:

STEP 2 Draw all three groups pointing away from each other.



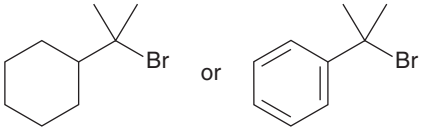
PRACTICE the skill

7.14 Draw the carbocation intermediate generated by each of the following substrates in an S_N1 reaction:



APPLY the skill

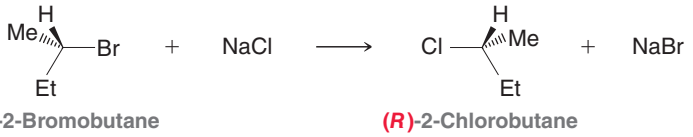
7.15 Identify which of the following substrates will undergo an S_N1 reaction more rapidly. Explain your choice.



need more **PRACTICE?** **Try Problems 7.50, 7.51**

Stereochemistry of S_N1 Reactions

Recall that S_N2 reactions proceed via an inversion of configuration:



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

In contrast, S_N1 reactions involve formation of an intermediate carbocation, which can then be attacked from either side (Figure 7.16), leading to both inversion of configuration and **retention of configuration**.

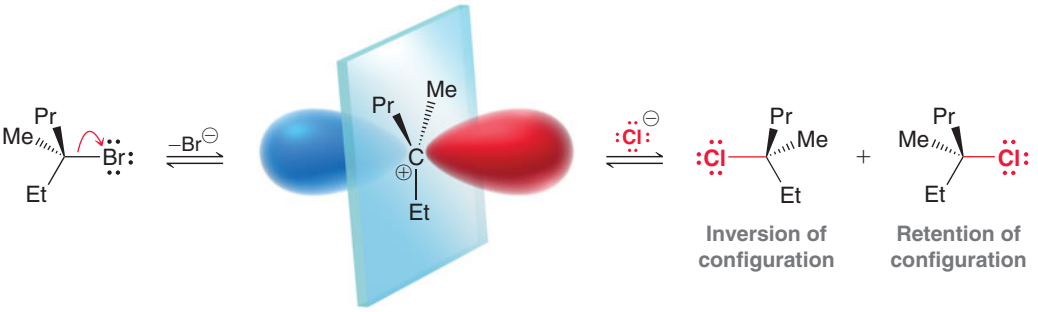


FIGURE 7.16
The intermediate of an S_N1 process is a planar carbocation.

Since the carbocation can be attacked on either side with equal likelihood, we should expect S_N1 reactions to produce a racemic mixture (equal mixture of inversion and retention). In practice, though, S_N1 reactions rarely produce exactly equal amounts of inversion and retention products. There is usually a slight preference for the inversion product. The accepted explanation involves the formation of ion pairs. When the leaving group first leaves, it is initially very close to the intermediate carbocation, forming an intimate ion pair (Figure 7.17). If the nucleophile attacks the carbocation while it is still participating in an ion pair, then the leaving group effectively blocks one face of the carbocation. The other side of the carbocation can experience unhindered attack by a nucleophile. As a result, the nucleophile will attack more often on the side opposite the leaving group, leading to a slight preference for inversion over retention.

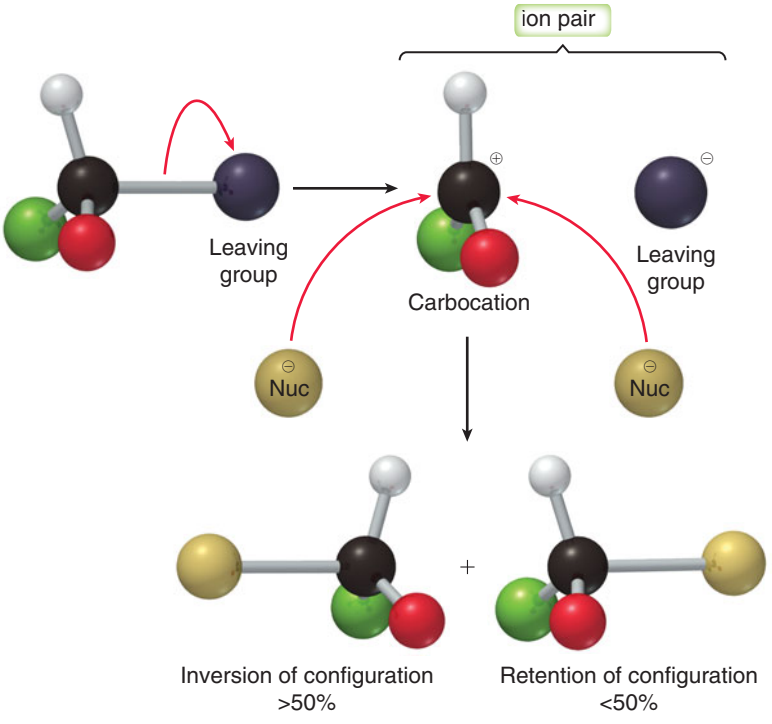


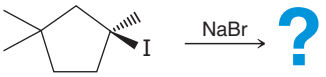
FIGURE 7.17
Loss of a leaving group initially forms an ion pair, which hinders attack on one face of the carbocation.

SKILLBUILDER

7.5 DRAWING THE PRODUCTS OF AN S_N1 PROCESS

LEARN the skill

Draw the products of the following S_N1 reaction:



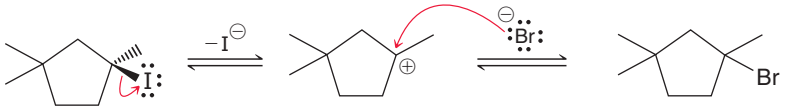
SOLUTION

First identify the leaving group and the nucleophile that will attack once the leaving group has left:

STEP 1
Identify the nucleophile and the leaving group.

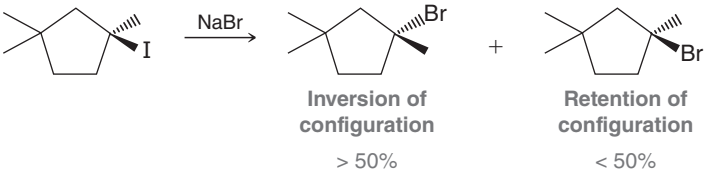
In an S_N1 process, the leaving group leaves first, generating a carbocation that is then attacked by the nucleophile:

STEP 2
Replace the leaving group with the nucleophile.



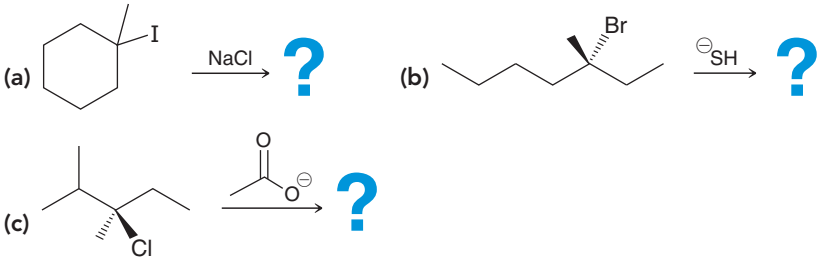
In this example, substitution is taking place at a chirality center, so we must consider the stereochemical outcome. In an S_N1 process, both enantiomers are expected as products, with a slight preference for the enantiomer resulting from inversion of configuration:

STEP 3
If the reaction takes place at a chirality center, draw both possible enantiomers.



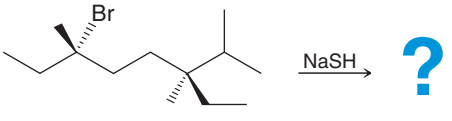
PRACTICE the skill

7.16 Draw the products that you expect in each of the following S_N1 reactions:



APPLY the skill

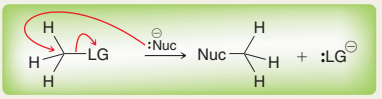
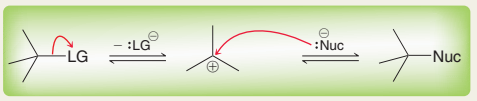
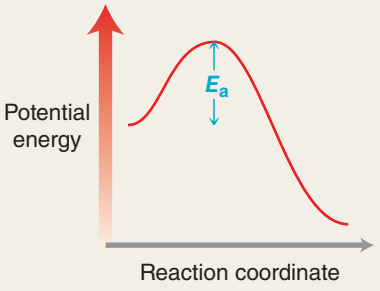
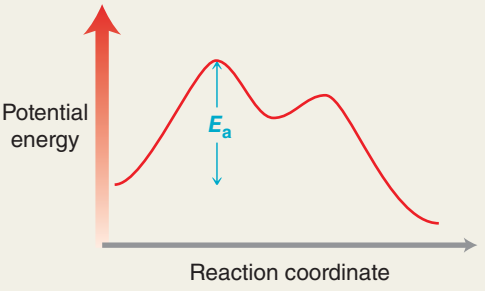
7.17 Draw the two products that you expect in the following S_N1 reaction and describe their stereoisomeric relationship:



need more **PRACTICE?** **Try Problem 7.54b**

Let's now summarize the differences that we have seen between S_N2 and S_N1 processes (Table 7.1).

TABLE 7.1 A COMPARISON OF S_N2 AND S_N1 PROCESSES

	S_N2	S_N1
Mechanism		
Energy diagram		
Rate equation	Rate = *k* [substrate] [nucleophile]	Rate = *k* [substrate]
Rate of reaction	Methyl > 1° > 2° > 3°	3° > 2° > 1° > methyl
Stereochemistry	Inversion of configuration	Racemization (with slight preference for inversion due to ion pairs)

7.6 Drawing the Complete Mechanism of an S_N1 Reaction

We have now seen that substitution reactions can occur through either a concerted mechanism (S_N2) or a stepwise mechanism (S_N1) (Figure 7.18). When drawing the mechanism of an S_N2 or S_N1 process, additional mechanistic steps will sometimes be required. In this section, we will focus on the additional steps that can accompany an S_N1 process. Recall from Chapter 6 that ionic mechanisms are constructed using only four different types of arrow-pushing patterns. This will now be important, as all four patterns can play a role in S_N1 processes.

FIGURE 7.18
The mechanistic steps in S_N2 and S_N1 processes.

As seen in Figure 7.18, every S_N1 mechanism exhibits two separate steps: (1) loss of a leaving group and (2) nucleophilic attack. In addition to these two core steps, some S_N1 processes are also accompanied by additional steps (highlighted in blue in Figure 7.19), which can occur before, between, or after the two core steps:

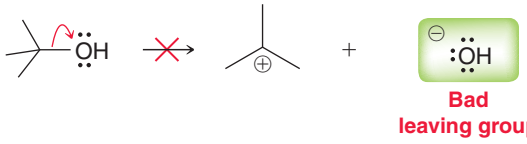
1. *Before the two core steps*—a proton transfer step is possible.
2. *Between the two core steps*—a carbocation rearrangement is possible.
3. *After the two core steps*—a proton transfer step is possible.

FIGURE 7.19
The two core steps (gray) and the three possible additional steps (blue) that can accompany an S_N1 process.

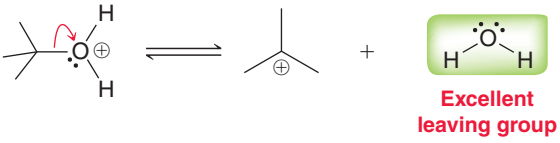
We will now explore each of these three possibilities, and we will learn how to determine whether any of the three additional steps should be included when proposing the mechanism for a transformation that occurs via an S_N1 process.

Proton Transfer at the Beginning of an S_N1 Process

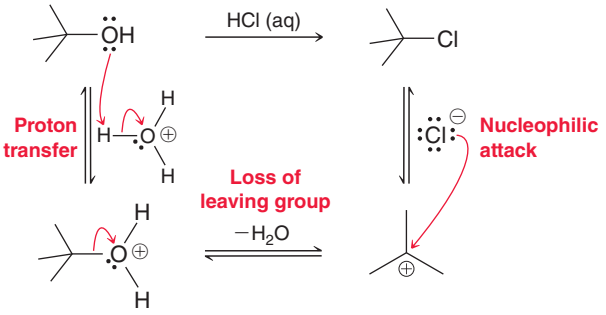
Before the two core steps of an S_N1 mechanism, a proton transfer will be necessary whenever the substrate is an alcohol (ROH). Hydroxide is a bad leaving group and will not leave by itself (as will be discussed later in this chapter):



However, once an OH group is protonated, it becomes an excellent leaving group because it can leave as a neutral species (no net charge):



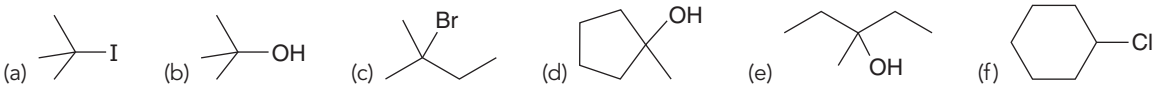
If a substrate has no leaving group other than an OH group, then acidic conditions will be required in order to allow an S_N1 reaction. In the following example, aqueous HCl supplies the hydronium ion (H_3O^+) that protonates the OH group as well as the chloride ion that functions as a nucleophile:



Notice that the two core steps of this S_N1 process are preceded by a proton transfer, giving a total of three mechanistic steps:

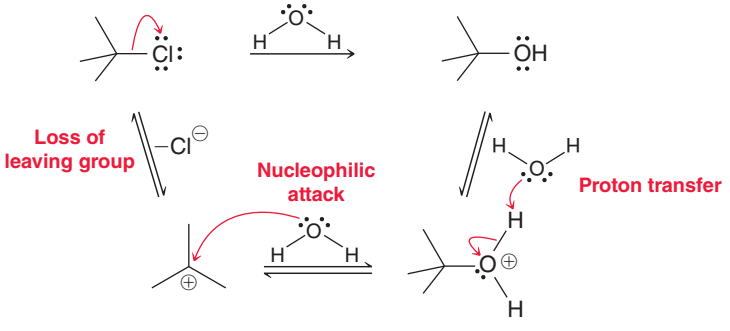
CONCEPTUAL CHECKPOINT

7.18 For each of the following substrates, determine whether an S_N1 process will require a proton transfer at the beginning of the mechanism:



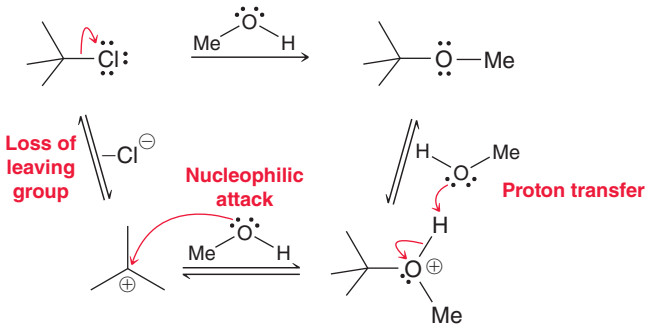
Proton Transfer at the End of an S_N1 Process

After the two core steps of an S_N1 mechanism, a proton transfer will be necessary whenever the nucleophile is neutral (not negatively charged). For example:



In this case, the nucleophile is water (H_2O), which does not possess a negative charge. In such a case, nucleophilic attack of the carbocation will produce a positively charged species. Removal of the positive charge requires a proton transfer. Notice that the mechanism above has three steps:

Any time the attacking nucleophile is neutral, a proton transfer is necessary at the end of the mechanism. Below is one more example. Reactions like this, in which the solvent functions as the nucleophile, are called **solvolysis** reactions.



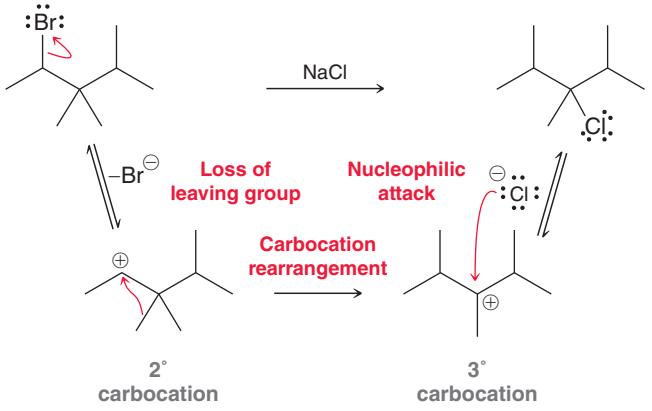
CONCEPTUAL CHECKPOINT

7.19 Will an S_N1 process involving each of the following nucleophiles require a proton transfer at the end of the mechanism?

(a) NaSH (b) H_2S (c) H_2O (d) EtOH (e) NaCN (f) NaCl
(g) $NaNH_2$ (h) NH_3 (i) NaOMe (j) NaOEt (k) MeOH (l) KBr

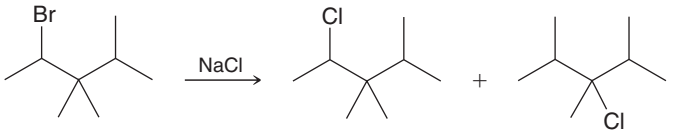
Carbocation Rearrangements during an S_N1 Process

The first core step of an S_N1 process is loss of a leaving group to generate a carbocation. Recall from Chapter 6 that carbocations are susceptible to rearrangement via either a hydride shift or a methyl shift. Here is an example of an S_N1 mechanism with a carbocation rearrangement:



Notice that the carbocation rearrangement occurs between the two core steps of the S_N1 process:

In reactions where a carbocation rearrangement is possible, a mixture of products is generally obtained. The following products are obtained from the above reaction:



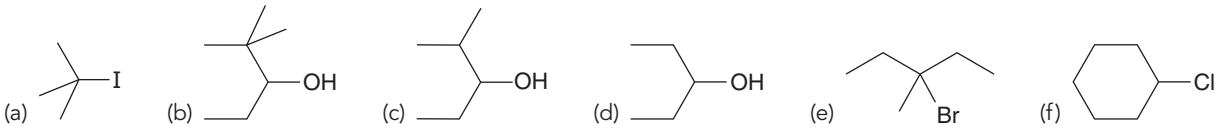
This is the product if the carbocation is captured by the nucleophile *before* rearrangement.

This is the product if the carbocation is captured by the nucleophile *after* rearrangement.

The product distribution (ratio of products) depends on how fast the rearrangement takes place and how fast the nucleophile attacks the carbocation. If the rearrangement occurs faster than attack by the nucleophile, then the rearranged product will predominate. However, if the nucleophile attacks the carbocation faster than rearrangement (if it attacks before rearrangement occurs), then the unrearranged product will predominate. In most cases, the rearranged product predominates. Why? A carbocation rearrangement is an intramolecular process, while nucleophilic attack is an intermolecular process. In general, intramolecular processes occur more rapidly than intermolecular processes.

CONCEPTUAL CHECKPOINT

7.20 For each of the following substrates, determine whether an S_N1 process is likely to involve a carbocation rearrangement or not:

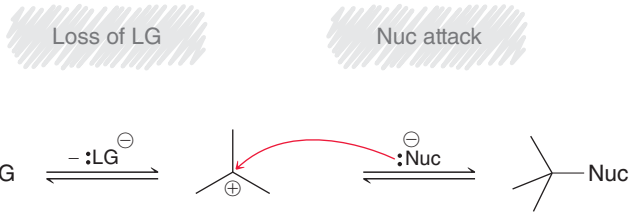


Summary of the S_N1 Process and Its Energy Diagram

We have seen that an S_N1 process has two core steps and can be accompanied by three additional steps, as summarized in Mechanism 7.1.

MECHANISM 7.1 THE S_N1 PROCESS

Two core steps



In the first core step of an S_N1 process, the leaving group leaves to form a carbocation.

In the second core step of an S_N1 process, a nucleophile attacks the carbocation.

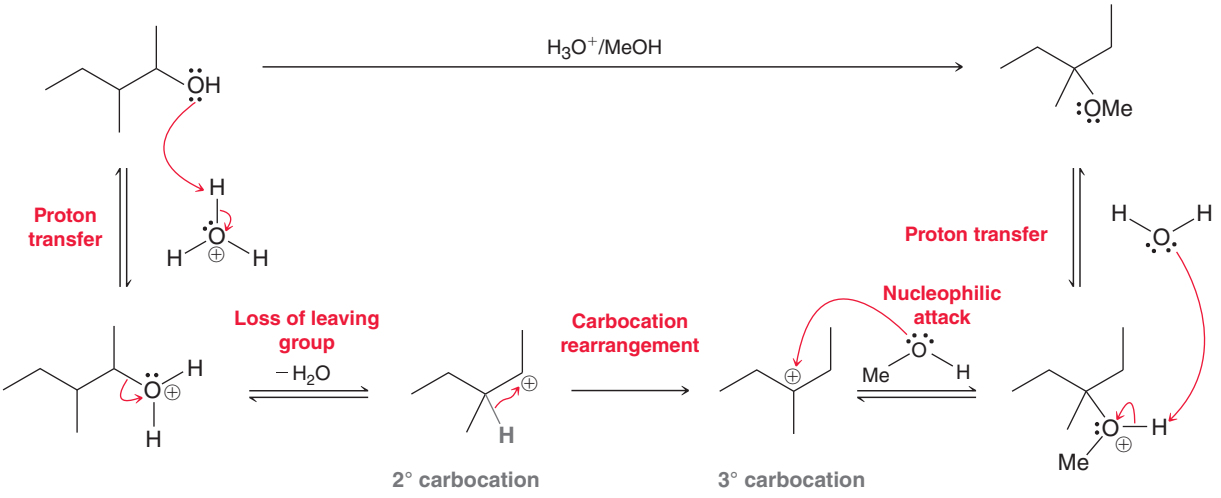
Possible additional steps

If the substrate is an alcohol, then the OH group must be protonated before it can leave.

If the carbocation initially formed can rearrange to generate a more stable carbocation, then a rearrangement will occur.

If the nucleophile is neutral, a proton transfer is required to remove the positive charge that is generated.

Here is an example of an S_N1 process that is accompanied by all three additional steps:



Since this mechanism has five steps, we expect the energy diagram for this reaction to exhibit five humps (Figure 7.20). The number of humps in the energy diagram of an S_N1 process will always be equal to the number of steps in the mechanism. Since the number of steps can range anywhere from two to five, the energy diagram of an S_N1 process can have anywhere from two to five humps. The S_N1 processes encountered most frequently will have two or three steps.

A few aspects of the energy diagram in Figure 7.21 are worth special mention:

- The tertiary carbocation is lower in energy than the secondary carbocation.
- The E_a for the carbocation rearrangement is shown to be very small because a carbocation rearrangement is generally a very fast process.
- Oxonium ions (intermediates with a positively charged oxygen atom) are generally lower in energy than carbocations (because the oxygen atom of an oxonium ion has an octet of electrons, while the carbon atom of a carbocation does not have an octet).

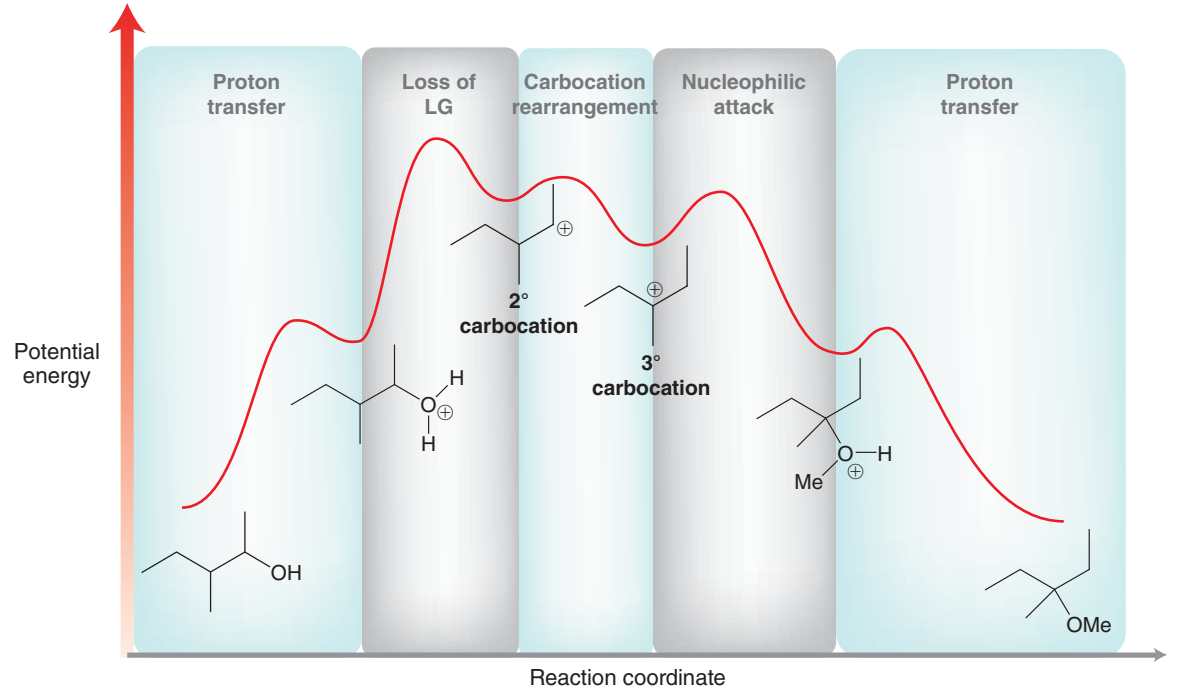


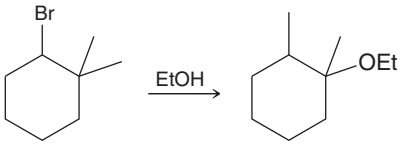
FIGURE 7.20
An energy diagram of an S_N1 process that is accompanied by three additional steps. In total, there are five steps, giving an energy diagram with five humps.

SKILLBUILDER

7.6 DRAWING THE COMPLETE MECHANISM OF AN S_N1 PROCESS

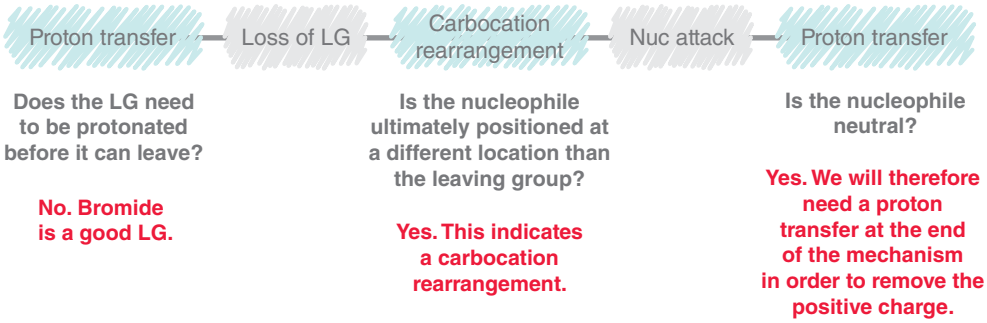
LEARN the skill

Draw the mechanism of the following S_N1 process:



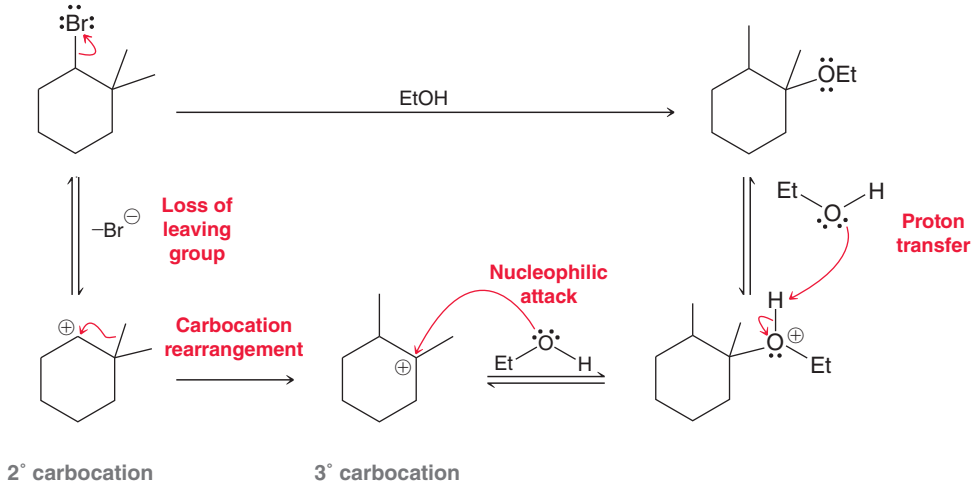
SOLUTION

An S_N1 process must always exhibit two core steps: loss of a leaving group and nucleophilic attack. But we must consider whether any of the other three possible steps will occur:



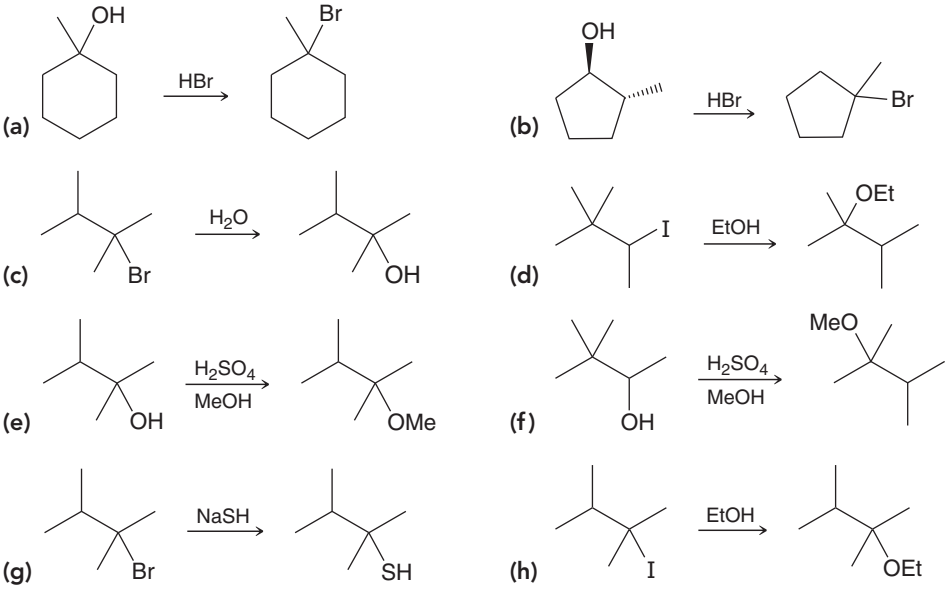
The mechanism will not begin with a proton transfer, but there will be a carbocation rearrangement, and there will be a proton transfer at the end of the mechanism. Therefore, the mechanism will have four steps:

Notice that this sequence utilizes each of the four arrow-pushing patterns that are possible for an ionic reaction. To draw these steps, we will rely on the skills we learned in Chapter 6:



PRACTICE the skill

7.21 Draw the mechanism for each of the following S_N1 processes:



APPLY the skill

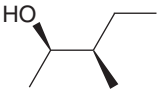
7.22 Identify the number of steps (patterns) for the mechanisms in Problems 7.21a–h. For example, the patterns for the first two are:

7.21a: +H⁺ — –LG — Nuc attack This mechanism exhibits a proton transfer before the two core steps.

7.21b: +H⁺ — –LG — C+ rearrangement — Nuc attack This mechanism exhibits a proton transfer before the two core steps as well as a carbocation rearrangement in between the two core steps.

These patterns are not identical. Draw patterns for the other six problems. Then compare the patterns. There is only one pattern that is repeated. Identify the two problems that exhibit the same pattern and then describe in words why those two reactions are so similar.

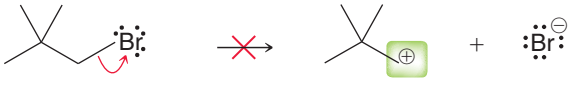
7.23 Treatment of (*2R,3R*)-3-methyl-2-pentanol with H_3O^+ affords a compound with no chirality centers. Predict the product of this reaction and draw the mechanism of its formation. Use your mechanism to explain how both chirality centers are destroyed.



(2*R*,3*R*)-3-methyl-2-pentanol

need more **PRACTICE?** **Try Problems 7.48, 7.49, 7.52, 7.54, 7.65**

In some rare cases, loss of the leaving group and carbocation rearrangement can occur in a concerted fashion (Figure 7.21). For example, neopentyl bromide cannot directly lose its leaving group, as that would generate a primary carbocation, which is too high in energy to form:



Neopentyl bromide **Primary carbocation**

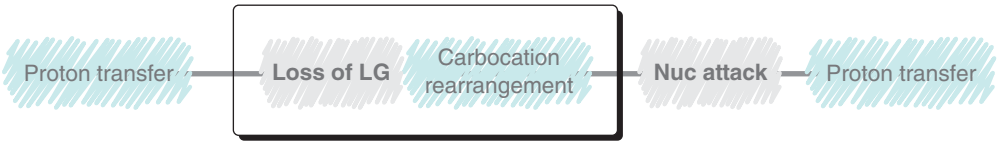
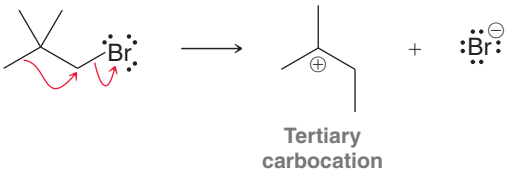


FIGURE 7.21
In an S_N1 process, loss of the leaving group and carbocation rearrangement can occur in a concerted fashion.

But it is possible for the leaving group to leave as a result of a methyl shift:



This is essentially a concerted process in which loss of the leaving group occurs simultaneously with a carbocation rearrangement. Examples like this are less common. In the vast majority of cases, each step of an S_N1 process occurs separately.

7.7 Drawing the Complete Mechanism of an S_N2 Reaction

FIGURE 7.22
The one concerted step of an S_N2 process.

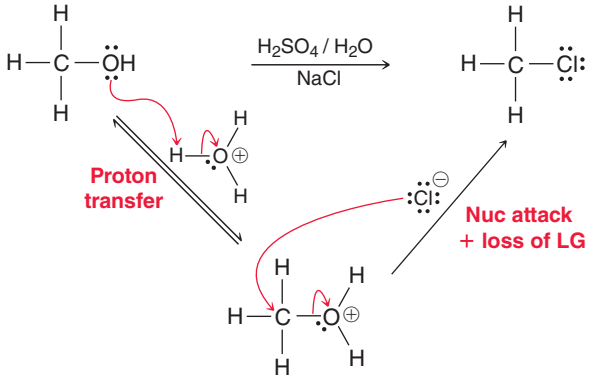
In the previous section, we analyzed the additional steps that can accompany an S_N1 process. In this section, we analyze the additional steps that can accompany an S_N2 process. Recall that an S_N2 reaction is a concerted process in which nucleophilic attack and loss of the leaving group occur simultaneously (Figure 7.22). No carbocation is formed, so there can be no carbocation rearrangement. In an S_N2 process, the only two possible additional steps are proton transfers (Figure 7.23). There can be a proton transfer before and/or after the concerted step. Proton transfers will accompany S_N2 processes for the same reasons that they accompany S_N1 processes.

FIGURE 7.23
The concerted step and the two possible additional steps of an S_N2 process.

Specifically, a proton transfer is required at the beginning of a mechanism if the substrate is an alcohol, and a proton transfer is required at the end of the mechanism if the nucleophile is neutral. Let's see examples of each.

Proton Transfer at the Beginning of an S_N2 Process

A proton transfer is necessary at the beginning of an S_N2 process if the substrate is an alcohol, although this type of process will rarely be encountered throughout the remainder of this textbook. An example of this reaction is the conversion of methanol to methyl chloride, a reaction first performed by the French chemists Jean-Baptiste Dumas and Eugene Peligot in 1835. This transformation was achieved by boiling a mixture of methanol, sulfuric acid, and sodium chloride.



The OH group is first protonated, converting it into a good leaving group, and then the chloride ion attacks in an S_N2 process, displacing the leaving group. This type of process, in which an alcohol is used as a substrate in an S_N2 reaction, has very limited utility and is generally only utilized in certain

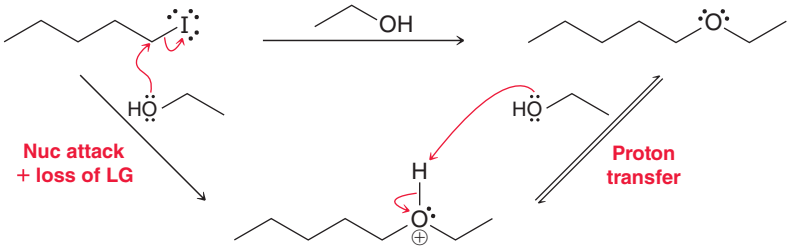
industrial applications. Methyl chloride is prepared commercially by such a process (using aqueous HCl as the source of H_3O^+ and Cl^-):

$$CH_3OH \xrightarrow{HCl} CH_3Cl$$

Proton Transfer at the End of an S_N2 Process

S_N2 —$-H^+$

A proton transfer will occur at the end of an S_N2 process if the nucleophile is neutral. For example, consider the following solvolysis reaction:

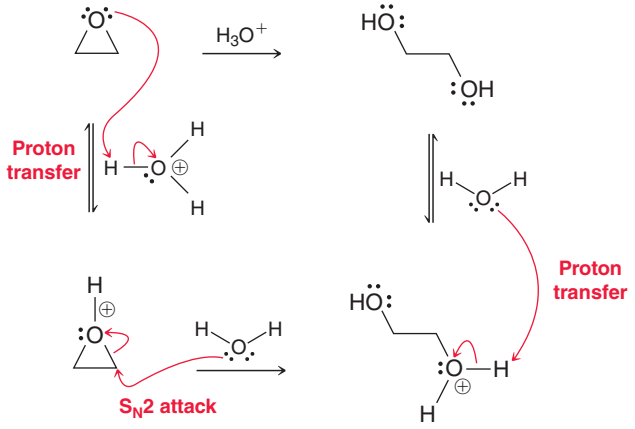


The substrate is primary, and therefore, the reaction must proceed via an S_N2 process. In this case, the solvent (ethanol) is functioning as the nucleophile, so this is a solvolysis reaction. Since the nucleophile is neutral, a proton transfer is required at the end of the mechanism in order to remove the positive charge from the compound.

Proton Transfer Before and After an S_N2 Process

$+H^+$ —S_N2 —$-H^+$

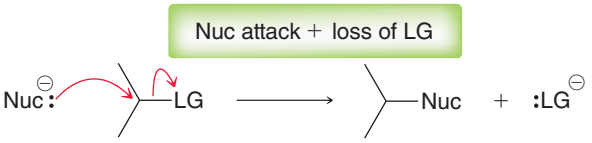
Throughout this course, we will see other examples of S_N2 processes that are accompanied by proton transfers. For example, the following reaction will be explored in Sections 9.16 and 14.10:



This reaction involves two proton transfer steps—one before and one after the S_N2 attack—as seen in Mechanism 7.2.

MECHANISM 7.2 THE S_N2 PROCESS

One concerted step



An S_N2 process is comprised of just one concerted step in which the nucleophile attacks with simultaneous loss of the leaving group.

Possible additional steps

If the substrate is an alcohol, then the OH group must be protonated before it can leave.

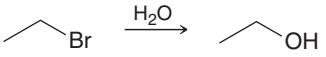
If the nucleophile is neutral, a proton transfer is required to remove the positive charge that is generated.

SKILLBUILDER

7.7 DRAWING THE COMPLETE MECHANISM OF AN S_N2 PROCESS

LEARN the skill

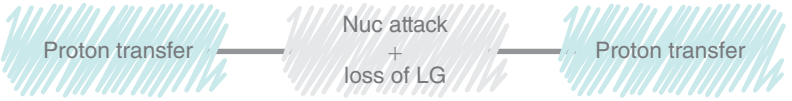
Ethyl bromide was dissolved in water and heated, and the following solvolysis reaction was observed to occur slowly, over a long period of time. Propose a mechanism for this reaction.



SOLUTION

The substrate is primary, so the reaction must proceed via an S_N2 process, rather than S_N1. An S_N1 mechanism cannot be invoked in this case, because a primary carbocation would be too unstable to form.

In an S_N2 process, there is one concerted step, and we must determine whether a proton transfer will be necessary either before or after the concerted step:



Does the LG need to be protonated first?

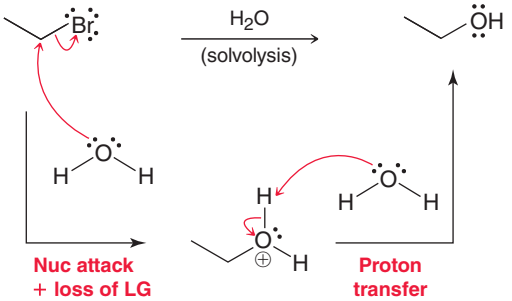
No. Bromide is a good LG.

Is the nucleophile neutral?

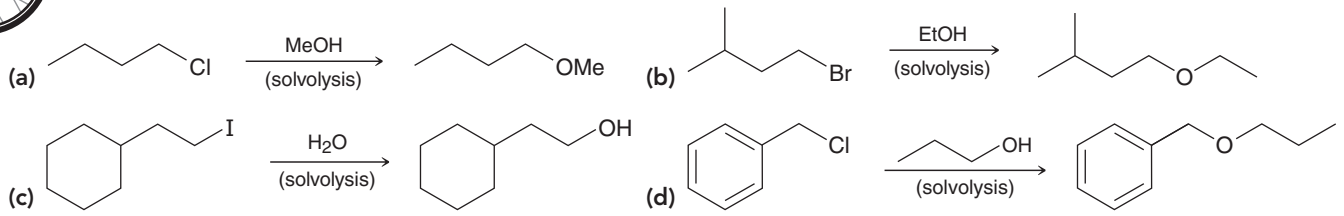
Yes. We will therefore need a proton transfer at the end of the mechanism in order to remove the positive charge.

The mechanism does not require a proton transfer before the concerted step, and even if it did, the reagents are not acidic and could not donate a proton anyway. In order to have a proton transfer at the beginning of a mechanism, an acid is required to serve as a proton source. At the end of the mechanism, there will be a proton transfer because the attacking nucleophile (H_2O) is neutral. Therefore, the mechanism will have two steps:

The first step involves a simultaneous nucleophilic attack and loss of leaving group, and the second step is a proton transfer:

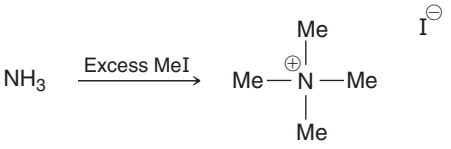


PRACTICE the skill **7.24** Draw the mechanism for each of the following solvolysis reactions:



APPLY the skill

7.25 In Chapter 23, we will learn that treatment of ammonia with excess methyl iodide produces a quaternary ammonium salt. This transformation is the result of four sequential S_N2 reactions. Use the tools we have learned in this chapter to draw the mechanism of this transformation. Your mechanism should have seven steps.



Quaternary ammonium salt

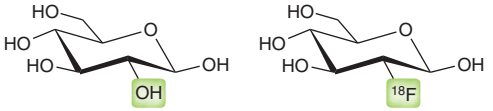
need more **PRACTICE?** **Try Problems 7.53, 7.64, 7.66**

medically speaking — Radiolabeled Compounds in Diagnostic Medicine

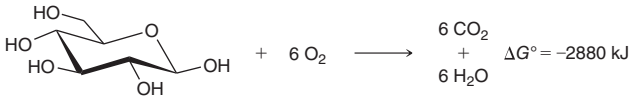
Recall from your general chemistry course that isotopes are atoms of the same element that differ from each other only in the number of neutrons. For example, carbon has three isotopes that are found in nature: ^{12}C (called carbon 12), ^{13}C (called carbon 13), and ^{14}C (called carbon 14). Each of these isotopes has six protons and six electrons, but they differ in their number of neutrons. They have six, seven, and eight neutrons, respectively. Of these isotopes, ^{12}C is the most abundant, constituting 98.9% of all carbon atoms found on Earth. The second most abundant isotope of carbon is ^{13}C, constituting approximately 1.1% of all carbon atoms. The amount of ^{14}C found in nature is very small (0.0000000001%).

The element fluorine (F) has many isotopes, although only one is found to be stable (^{19}F). Other isotopes of fluorine can be produced, but they are unstable and will undergo radioactive decay. One such example is ^{18}F, which has a half-life ($t_{1/2}$) of approximately 110 minutes. If a compound possesses ^{18}F, then the location of that compound can be tracked by observing the decay process. For this reason, *radiolabeled compounds* (compounds containing an unstable isotope, such as ^{18}F) have found great utility in the field of medicine. One such application will now be described.

Consider the structure of glucose as well as the radiolabeled glucose derivative, called ^{18}F-2-fluorodeoxyglucose (FDG):

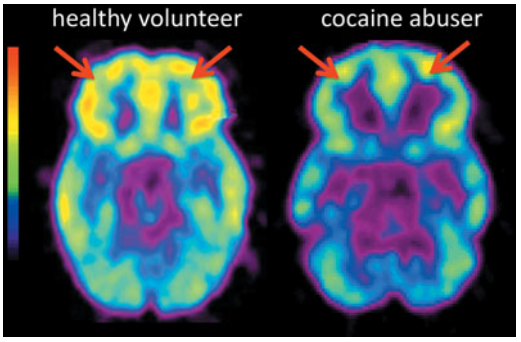


Glucose is an important compound that represents the primary source of energy for our bodies. Our bodies are capable of metabolizing glucose molecules in a series of enzymatic steps called *glycolysis*, a process in which the high-energy C—C and C—H bonds in glucose are broken and converted into lower energy C—O and C=O bonds. The difference in energy is significant, and our bodies are capable of capturing that energy and storing it for later use:



FDG is a radiolabeled compound that is a derivative of glucose (an OH group has been replaced with ^{18}F). In our bodies, the first step of glycolysis occurs with FDG just as it does with glucose. But in the case of FDG, the second step of glycolysis does not proceed at an appreciable rate. Therefore, *areas of the body that utilize glucose will also accumulate FDG*. This accumulation can be monitored, because ^{18}F decays via a process that ultimately releases high-energy photons (gamma rays) that can be detected. The details of the decay process are beyond the scope of our discussion, but for our purposes, it can be summarized in the following way: ^{18}F decays via a process called *positron emission* (β^+ decay), in which an antiparticle called a *positron* is created, travels a short distance, and then encounters an electron and annihilates it, causing two coincident gamma (γ) rays to be emitted from the body. These γ rays are then detected using special instrumentation, resulting in an image. This imaging technique is called positron emission tomography (PET).

As an example, the brain metabolizes glucose, so administering FDG to a patient will cause an accumulation of FDG in specific locations of the brain corresponding to the level of metabolic activity. Consider the following PET/^{18}FDG scans of a healthy volunteer and a cocaine abuser:

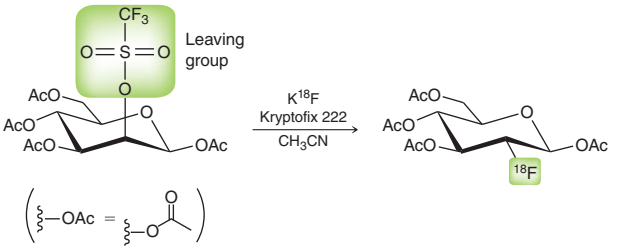


Red/orange indicates regions of high metabolism, while purple/blue indicates regions of low metabolism.

Notice that the cocaine abuser shows less accumulation of FDG in the orbitofrontal cortex (indicated with red arrows). This indicates a lower metabolism in that region, which is known to play a large role in cognitive function and decision making. This example demonstrates how neurologists can use radiolabeled compounds, such as FDG, to explore the brain and learn more about its function in normal and disease states. This technique has found great utility in diagnostic medicine, because cancerous tissues exhibit enhanced metabolic rates of glucose relative to surrounding normal tissues and therefore will also accumulate more FDG. As a result, cancerous tissues can be visualized and monitored with a PET/^{18}FDG scan.

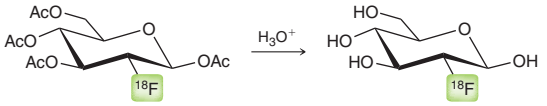
FDG has been approved by the U.S. Food and Drug Administration (FDA) to assist oncologists in the diagnosis and staging of cancer, in addition to monitoring the response to therapy. The increasing role of FDG in the field of medicine has fueled the demand for the daily production of FDG. Because ^{18}F is a short-lived radionuclide, a fresh batch of FDG must be made on a daily basis. Fortunately, the rate of decay is slow enough to permit synthesis at a regional radiopharmacy followed by distribution to regional hospitals for imaging studies.

The synthesis of FDG utilizes many of the principles covered in this chapter, because one important step in the process is an S_N2 reaction:



This reaction has a few important features worthy of our attention:

- KF is the source of fluoride ions, which function as the nucleophilic agent in this reaction. Generally, fluoride ions are not good nucleophiles, but Kryptofix interacts with the K^+ ions, thereby freeing the fluoride ions to function as nucleophiles. The ability of Kryptofix to enhance the nucleophilicity of fluoride ions is consistent with the action of crown ethers (a topic that will be explored in more detail in Section 14.4).
- This reaction proceeds with inversion of configuration, as expected for an S_N2 process.
- The solvent used for this reaction, acetonitrile (CH_3CN), is a polar aprotic solvent, and it is used to speed up the rate of the process (as described in Section 7.8).
- Notice that the OH groups (normally found in glucose) have been converted into acetate groups (OAc). This was done in order to minimize side reactions. These acetate groups can be removed easily upon treatment with aqueous acid (we will explore this process, called hydrolysis, in more detail in Section 21.11).



The effective application of FDG in PET scans certainly requires the contribution from many different disciplines, but organic chemistry has played the most critical role: The synthesis of FDG is achieved via an S_N2 process!

7.8 Determining Which Mechanism Predominates

In order to draw the products of a specific substitution reaction, we must first identify the reaction mechanism as either S_N2 or S_N1. This information is important in the following two ways:

- If substitution is taking place at a chirality center, then we must know whether to expect inversion of configuration (S_N2) or racemization (S_N1).
- If the substrate is susceptible to carbocation rearrangement, then we must know whether to expect rearrangement (S_N1) or whether rearrangement is not possible (S_N2).

Four factors have an impact on whether a particular reaction will occur via an S_N2 or an S_N1 mechanism: (1) the substrate, (2) the leaving group, (3) the nucleophile, and (4) the solvent (Figure 7.24). We must learn to look at all four factors, one by one, and to determine whether the factors favor S_N1 or S_N2.

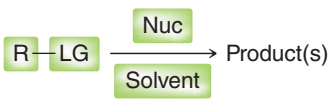


FIGURE 7.24
The four factors that determine which mechanism predominates.

The Substrate

The identity of the substrate is the most important factor in distinguishing between S_N2 and S_N1. Earlier in the chapter, we saw different trends for S_N2 and S_N1 reactions. These trends are compared in the charts in Figure 7.25.

The trend in S_N2 reactions is due to issues of steric hindrance in the transition state, while the trend in S_N1 reactions is due to carbocation stability. The bottom line is that methyl and primary substrates favor S_N2, while tertiary substrates favor S_N1. Secondary substrates can proceed via either mechanism, so a secondary substrate does not indicate which mechanism will predominate. In such a case, you must move on to the next factor, the nucleophile (covered in the next section).

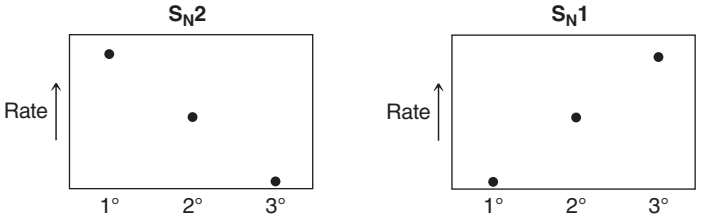
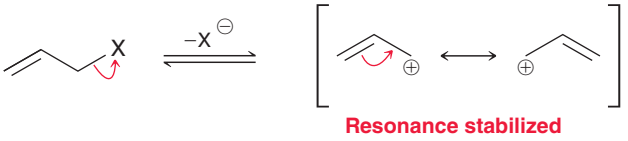
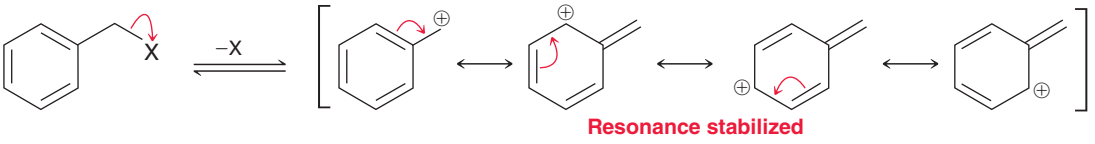


FIGURE 7.25
Substrate effects on the rates of S_N2 and S_N1 processes.

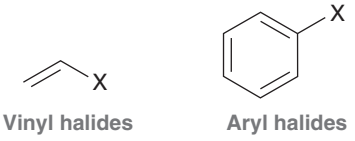
Allylic halides and *benzylic halides* can react either via S_N2 or via S_N1 processes:

These substrates can react via an S_N2 mechanism because they are relatively unhindered, and they can react via an S_N1 mechanism because loss of a leaving group generates a resonance-stabilized carbocation:

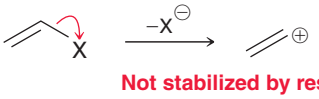


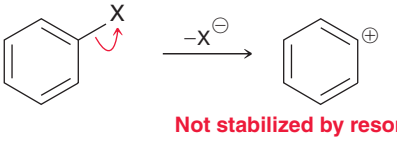


In contrast, *vinyl halides* and *aryl halides* are unreactive in substitution reactions:



S_N2 reactions are generally not observed at sp^2-hybridized centers, because back-side attack is sterically encumbered. In addition, vinyl halides and aryl halides are also unreactive toward S_N1, because loss of a leaving group would generate an unstable carbocation:



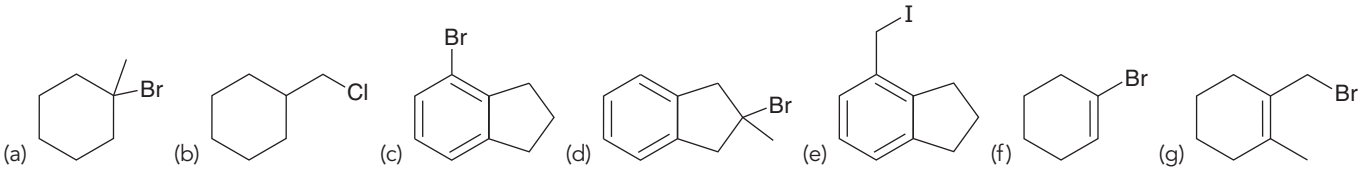


To summarize:

- Methyl and primary substrates favor S_N2.
- Tertiary substrates favor S_N1.
- Secondary substrates and allylic and benzylic substrates can often react via either mechanism.
- Vinyl and aryl substrates do not react via either mechanism.

CONCEPTUAL CHECKPOINT

7.26 Identify whether each of the following substrates favors S_N2, S_N1, both, or neither:



The Nucleophile

Recall that the rate of an S_N2 process is dependent on the concentration of the nucleophile. For the same reason, S_N2 processes are also dependent on the *strength* of the nucleophile. A strong nucleophile will speed up the rate of an S_N2 reaction, while a weak nucleophile will slow down the rate of an S_N2 reaction. In contrast, an S_N1 process is not affected by the concentration or strength of the nucleophile because the nucleophile does not participate in the rate-determining step. In summary, the nucleophile has the following effect on the competition between S_N2 and S_N1:

- A strong nucleophile favors S_N2.
- A weak nucleophile disfavors S_N2 (and thereby allows S_N1 to compete successfully).

We must therefore learn to identify nucleophiles as strong or weak. The strength of a nucleophile is determined by many factors that were first discussed in Section 6.7. Figure 7.26 shows some strong and weak nucleophiles that we will encounter.

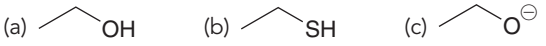
FIGURE 7.26
Some common nucleophiles grouped according to strength. Note: The designation of fluoride as a weak nucleophile is only accurate in protic solvents. In polar aprotic solvents, fluoride is in fact a strong nucleophile. This issue will be discussed in more detail later in this section, just before Table 7.3.

Common nucleophiles

Strong			Weak
$I^{\ominus}$	$HS^{\ominus}$	$HO^{\ominus}$	$F^{\ominus}$
$Br^{\ominus}$	H_2S	$RO^{\ominus}$	H_2O
$Cl^{\ominus}$	RSH	$N{\equiv}C^{\ominus}$	ROH

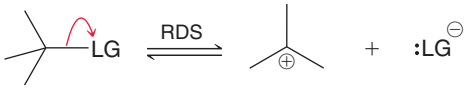
CONCEPTUAL CHECKPOINT

7.27 Does each of the following nucleophiles favor S_N2 or S_N1?



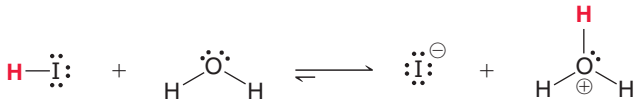
The Leaving Group

Both S_N1 and S_N2 mechanisms are sensitive to the identity of the leaving group. If the leaving group is bad, then neither mechanism can operate, but S_N1 reactions are generally more sensitive to the leaving group than S_N2 reactions. Why? Recall that the rate-determining step of an S_N1 process is loss of a leaving group to form a carbocation and a leaving group:



We have already seen that the rate of this step is very sensitive to the stability of the carbocation, but it is also sensitive to the stability of the leaving group. The leaving group must be highly stabilized in order for an S_N1 process to be effective.

What determines the stability of a leaving group? As a general rule, good leaving groups are the conjugate bases of strong acids. For example, iodide (I^-) is the conjugate base of a very strong acid (HI):



Iodide is a very weak base because it is highly stabilized. As a result, iodide can function as a good leaving group. In fact, iodide is one of the best leaving groups. Figure 7.27 shows a list of good leaving groups, all of which are the conjugate bases of strong acids. In contrast, hydroxide is a bad leaving group, because it is not a stabilized base. In fact, hydroxide is a relatively strong base, and therefore, it rarely functions as a leaving group. It is a bad leaving group.

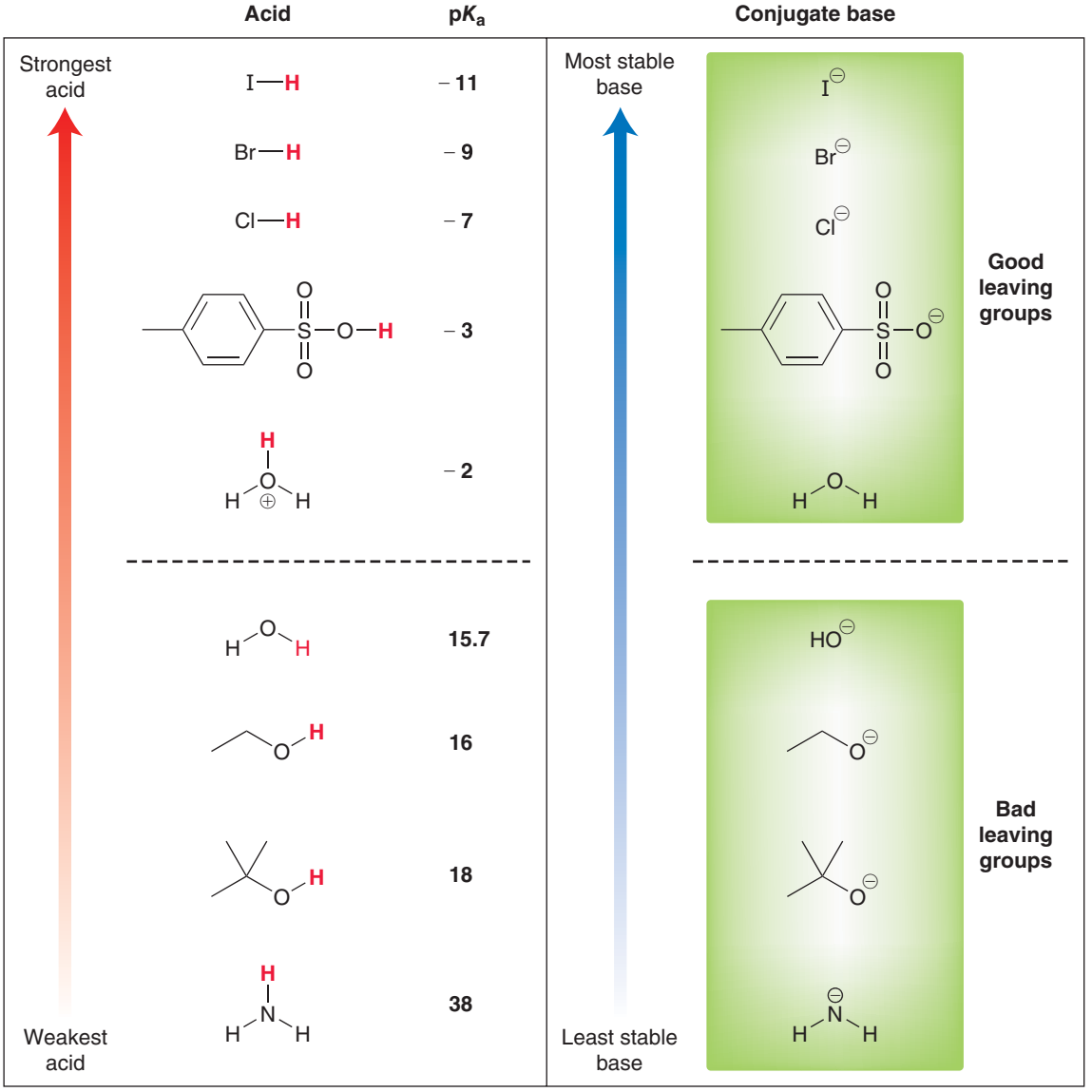


FIGURE 7.27
The conjugate base of a strong acid will generally be a good leaving group. The conjugate base of a weak acid will not be a good leaving group.

The most commonly used leaving groups are halides and **sulfonate ions** (Figure 7.28). Among the halides, iodide is the best leaving group because it is a weaker base (more stable) than bromide or chloride. Among the sulfonate ions, the best leaving group is the triflate group, but the most commonly used is the **tosylate** group. It is abbreviated as OTs. When you see OTs connected to a compound, you should recognize the presence of a good leaving group.

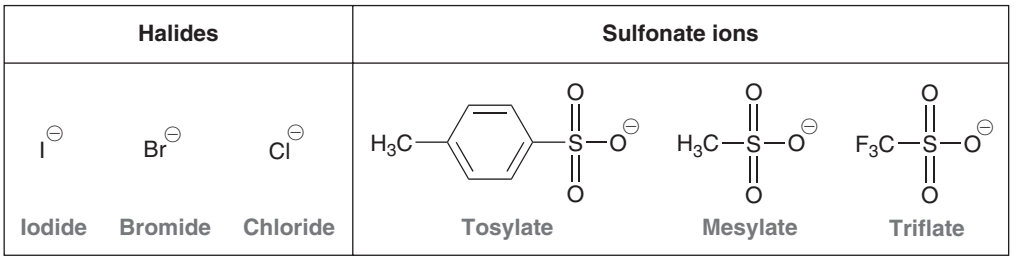


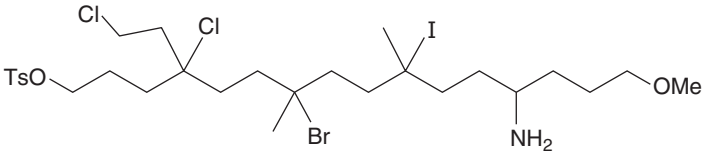
FIGURE 7.28
Common leaving groups.

CONCEPTUAL CHECKPOINT

7.28 Consider the structure of the compound below.

(a) Identify each position where an S_N2 reaction is likely to occur if the compound were treated with hydroxide.

(b) Identify each position where an S_N1 reaction is likely to occur if the compound were treated with water.

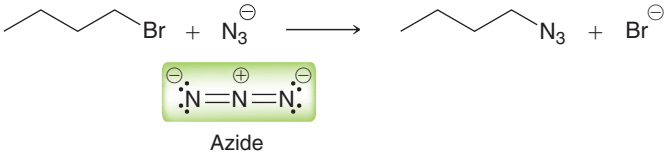


Solvent Effects

The choice of solvent can have a profound effect on the rates of S_N1 and S_N2 reactions. We will focus specifically on the effects of protic and polar aprotic solvents. **Protic solvents** contain at least one hydrogen atom connected directly to an electronegative atom. **Polar aprotic solvents** contain no hydrogen atoms connected directly to an electronegative atom. These two different kinds of solvents have different effects on the rates of S_N1 and S_N2 processes. Table 7.2 summarizes these effects.

The bottom line is that protic solvents are used for S_N1 reactions, while polar aprotic solvents are used to favor S_N2 reactions.

The effect of polar aprotic solvents on the rate of S_N2 reactions is significant. For example, consider the reaction between bromobutane and an azide ion:



The rate of this reaction is highly dependent on the choice of solvent. Figure 7.29 shows the relative rates of this S_N2 reaction in various solvents. From these data, we see that S_N2 reactions are significantly faster in polar aprotic solvents than in protic solvents.

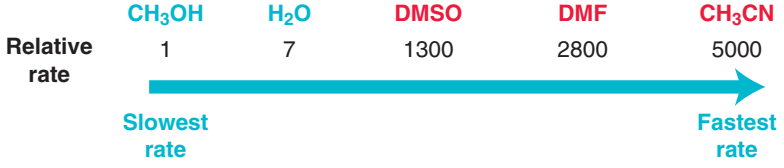
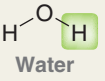
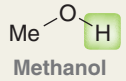
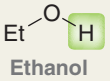
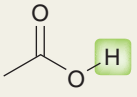
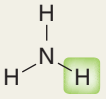
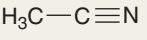
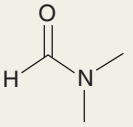
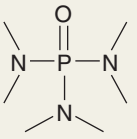
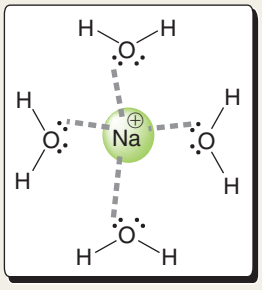
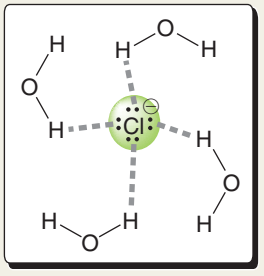
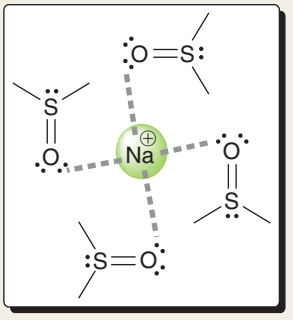
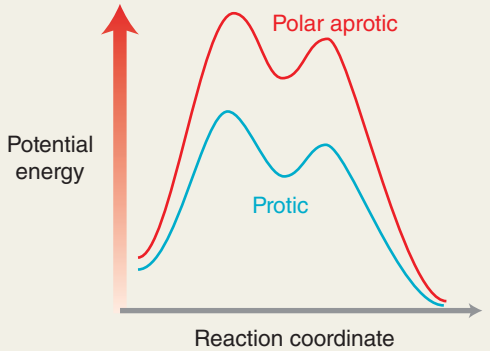
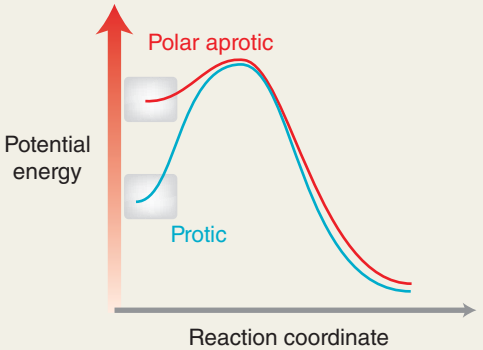


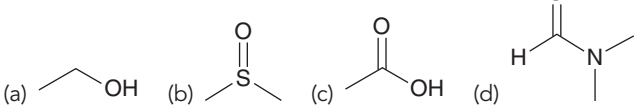
FIGURE 7.29
Relative rates of an S_N2 process in a variety of solvents. Protic solvents are shown in blue. Polar aprotic solvents are shown in red.

TABLE 7.2 THE EFFECTS OF PROTIC SOLVENTS AND POLAR APROTIC SOLVENTS

	PROTIC	POLAR APROTIC
Definition	Protic solvents contain at least one hydrogen atom connected directly to an electronegative atom.	Polar aprotic solvents contain no hydrogen atoms connected directly to an electronegative atom.
Examples	 Water  Methanol  Ethanol  Acetic acid  Ammonia	 Dimethylsulfoxide (DMSO)  Acetonitrile  Dimethylformamide (DMF)  Hexamethyl-phosphoramide (HMPA)
Function	Protic solvents stabilize cations and anions. Cations are stabilized by lone pairs from the solvent, while anions are stabilized by H-bonding interactions with the solvent:  The lone pairs on the oxygen atoms of H_2O stabilize the cation.  Hydrogen-bonding interactions stabilize the anion. As a result, anions and cations are both solvated and surrounded by a solvent shell.	Polar aprotic solvents stabilize cations, but not anions. Cations are stabilized by lone pairs from the solvent, while anions are not stabilized by the solvent:  The lone pairs on the oxygen atoms of DMSO stabilize the cation.  The anion is not stabilized by the solvent. Cations are solvated and surrounded by a solvent shell, but anions are not. As a result, nucleophiles are higher in energy when placed in a polar aprotic solvent.
Effects	Favors S_N1. Protic solvents favor S_N1 by stabilizing polar intermediates and transition states: 	Favors S_N2. Polar aprotic solvents favor S_N2 by raising the energy of the nucleophile, giving a smaller E_a: 

CONCEPTUAL CHECKPOINT

7.29 Does each of the following solvents favor an S_N2 reaction or an S_N1 reaction? (See Table 7.2.)



(e) MeOH (f) CH_3CN (g) HMPA (h) NH_3

7.30 When used as a solvent, will acetone favor an S_N2 or an S_N1 mechanism? Explain.

Acetone

The choice of solvent can also have an impact on the order of reactivity of the halides. If we compare the nucleophilicity of the halides, we find that it is dependent on the solvent. In protic solvents, the following order is observed:

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

Iodide is the strongest nucleophile, and fluoride is the weakest. However, in polar aprotic solvents, the order is reversed:

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

Why the reversal of order? Fluoride is the strongest because it is the least stable anion. In protic solvents, fluoride is the most tightly bound to its solvent shell and is the least available to function as a nucleophile (it would have to shed part of its solvent shell, which it does not do often). In such an environment, it is a weak nucleophile. However, when a polar aprotic solvent is used, there is no solvent shell, and fluoride is free to function as a strong nucleophile.

Summary of Factors Affecting S_N2 and S_N1 Mechanisms

Table 7.3 summarizes what we have learned in this section about the four factors that affect S_N2 and S_N1 processes. Now let's get some practice analyzing all four factors:

TABLE 7.3 FACTORS THAT FAVOR S_N2 AND S_N1 PROCESSES

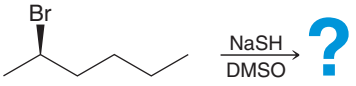
FACTOR	FAVORS S_N2	FAVORS S_N1
Substrate	Methyl or primary	Tertiary
Nucleophile	Strong nucleophile	Weak nucleophile
Leaving group	Good leaving group	Excellent leaving group
Solvent	Polar aprotic	Protic

SKILLBUILDER

7.8 DETERMINING WHETHER A REACTION PROCEEDS VIA AN S_N1 OR S_N2 MECHANISM

LEARN the skill

Determine whether the following reaction proceeds via an S_N1 or an S_N2 mechanism and then draw the product(s) of the reaction:



SOLUTION

Analyze the four factors one by one:

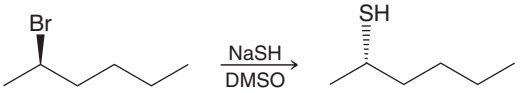
(a) *Substrate.* The substrate is secondary. If it were primary, we would predict S_N2, and if it were tertiary, we would predict S_N1. But with a secondary substrate, it could be either, so we move on to the next factor.

(b) *Nucleophile.* NaSH indicates that the nucleophile is HS^- (remember that Na^+ is just the counter ion). HS^- is a strong nucleophile, which favors S_N2.

(c) *Leaving Group.* Br^- is a good leaving group. This factor alone does not indicate a preference for either S_N1 or S_N2.

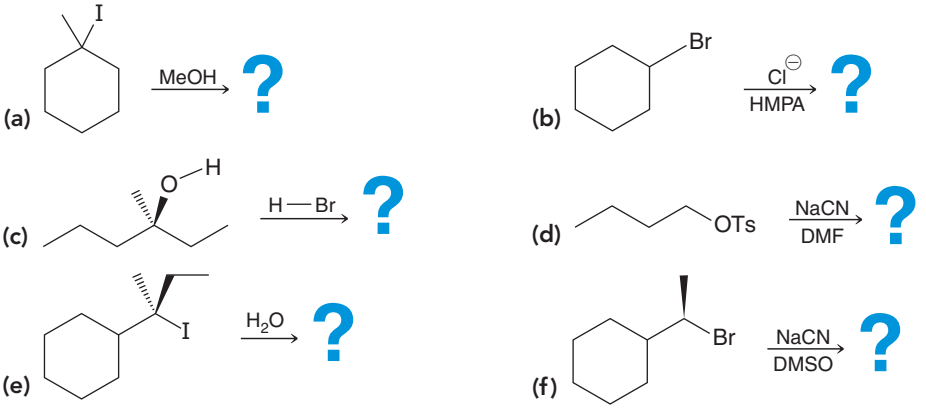
(d) *Solvent.* DMSO is a polar aprotic solvent, which favors S_N2.

Weighing all four factors, there is a preference for S_N2 because both the nucleophile and the solvent favor S_N2. Therefore, we expect inversion of configuration:



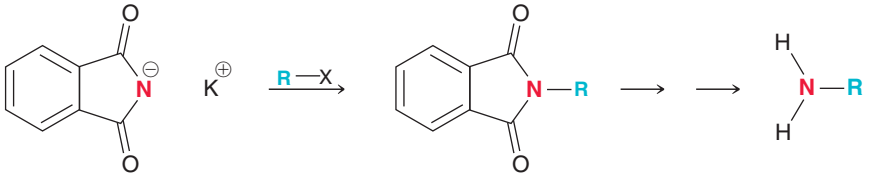
PRACTICE the skill

7.31 Determine whether each of the following reactions proceeds via an S_N1 or S_N2 mechanism and then draw the product(s) of the reaction:

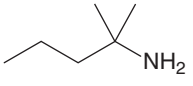


APPLY the skill

7.32 In Chapter 23, we will learn several methods for making primary amines (RNH_2). Each of these methods utilizes a different approach for forming the C—N bond. One of these methods, called the Gabriel synthesis, forms the C—N bond by treating potassium phthalimide with an alkyl halide:



The first step of this process occurs via an S_N2 mechanism. Using this information, determine whether the Gabriel synthesis can be used to prepare the following amine. Explain your answer.



need more PRACTICE? **Try Problems 7.37, 7.38, 7.40, 7.41, 7.44, 7.55, 7.57, 7.58**

7.9 Selecting Reagents to Accomplish Functional Group Transformation

As mentioned at the beginning of the chapter, substitution reactions can be utilized to accomplish functional group transformation:

A wide range of nucleophiles can be used, providing a great deal of versatility in the type of products that can be formed with substitution reactions. Figure 7.30 shows some of the types of compounds

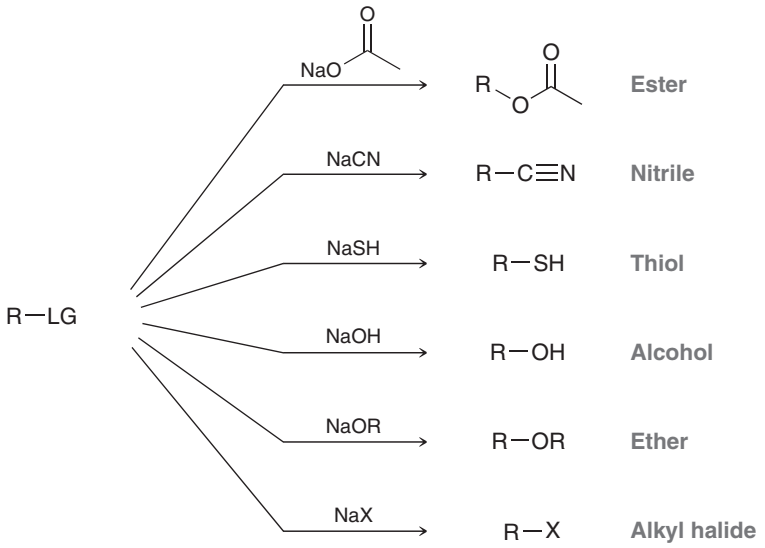
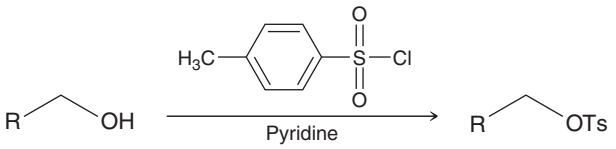


FIGURE 7.30
Various products that can be obtained via substitution reactions.

that can be prepared using substitution reactions. When selecting reagents for a substitution reaction, remember the following tips:

- *Substrate*. The identity of the substrate indicates which process to use. If the substrate is methyl or primary, an S_N2 process must be used. If the substrate is tertiary, an S_N1 process must be used. If the substrate is secondary, generally try to use an S_N2 process because it avoids the issue of carbocation rearrangement and provides greater control over the stereochemical outcome.
- *Nucleophile and Solvent*. Once you have decided whether you want to use an S_N1 or an S_N2 process (based on the substrate), make sure to choose a nucleophile and solvent that are consistent with that mechanism. For an S_N1 reaction, use a weak nucleophile in a protic solvent. For an S_N2 reaction, use a strong nucleophile in a polar aprotic solvent.
- *Leaving Group*. Remember that OH is a bad leaving group and will not leave as is. It must first be converted into a good leaving group. In an S_N1 process, use an acid to protonate the OH group, converting it into an excellent leaving group. In an S_N2 reaction, the OH group is generally converted into a tosylate, an excellent leaving group, rather than protonating the OH group. This transformation is accomplished with tosyl chloride and pyridine (and is discussed in more detail in Chapter 13):



SKILLBUILDER

7.9 IDENTIFYING REAGENTS NECESSARY FOR A SUBSTITUTION REACTION

LEARN the skill

Identify the reagents you would use to accomplish the following transformation:

SOLUTION

First determine which mechanism to use by looking at the substrate: