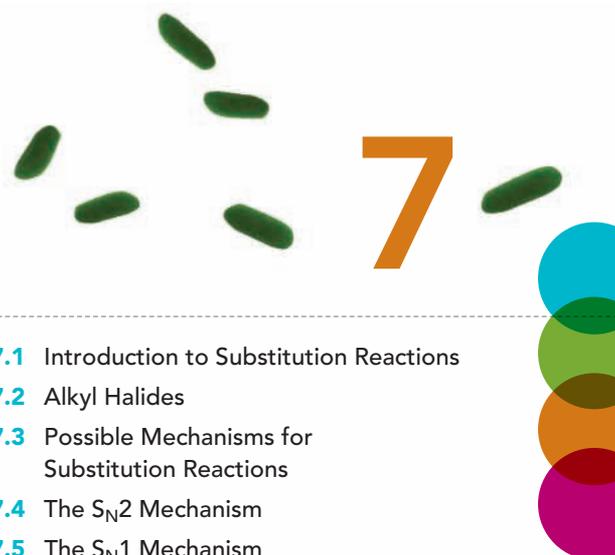


# Substitution Reactions

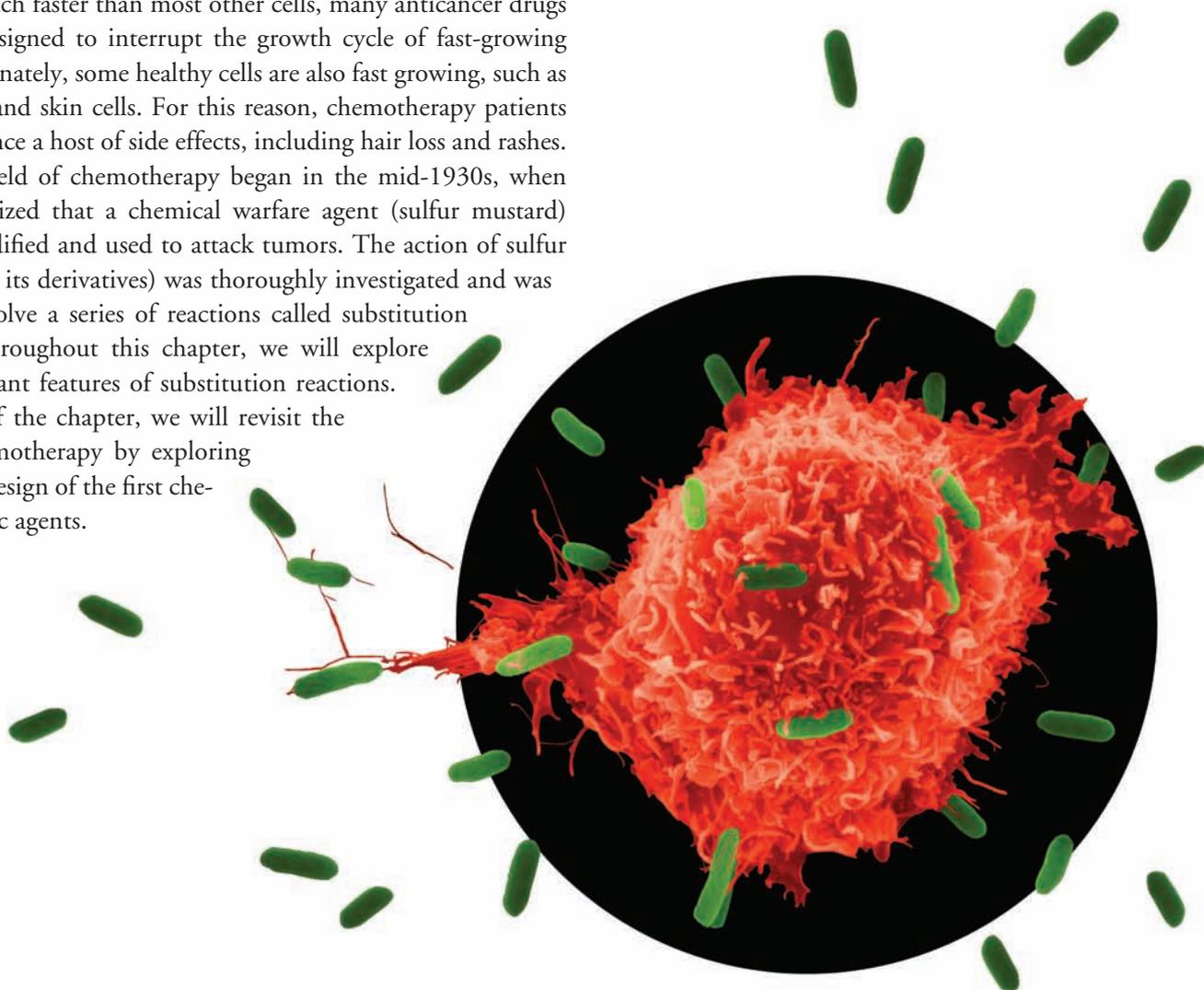
**DID YOU EVER WONDER...**  
what chemotherapy is?

**A**s its name implies, chemotherapy is the use of chemical agents in the treatment of cancer. The picture below shows a cancer cell (red) surrounded by many smaller cells (green) that scientists have filled with a cocktail of chemotherapeutic agents. These smaller cells have been engineered to function as transport vehicles that will deliver their cargo to the cancer cell. 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.



- 7.1 Introduction to Substitution Reactions
- 7.2 Alkyl Halides
- 7.3 Possible Mechanisms for Substitution Reactions
- 7.4 The  $S_N2$  Mechanism
- 7.5 The  $S_N1$  Mechanism
- 7.6 Drawing the Complete Mechanism of an  $S_N1$  Reaction
- 7.7 Drawing the Complete Mechanism of an  $S_N2$  Reaction
- 7.8 Determining Which Mechanism Predominates
- 7.9 Selecting Reagents to Accomplish Functional Group Transformation



## 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)



Visit [www.wileyplus.com](http://www.wileyplus.com) to check your understanding and for valuable practice.

## 7.1 Introduction to Substitution Reactions

**Substitution reactions** involve the exchange of one functional group for another:

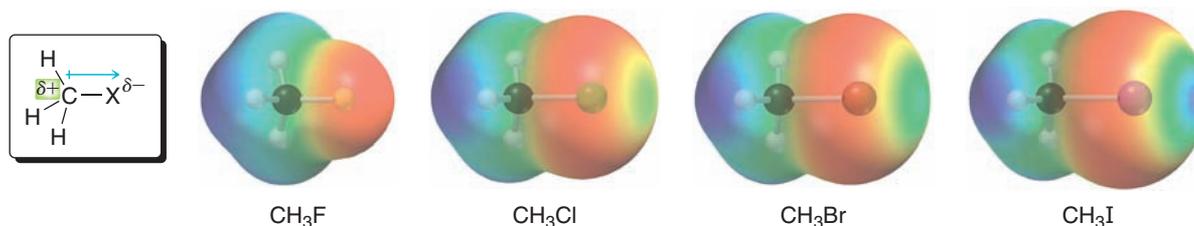


In every substitution reaction, there is an electrophile and a nucleophile:



Organic chemists often use the term **substrate** when referring to the electrophile. 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.

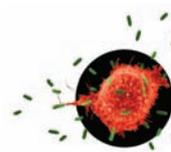


**FIGURE 7.1**  
Electrostatic potential maps of methyl halides.

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

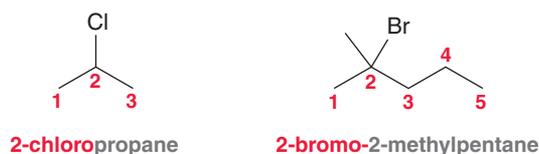
Halogenated organic compounds are commonly used as electrophiles in substitution reactions. Although other compounds can also serve as electrophiles, we will focus our attention for now on compounds containing halogens.

### Naming Halogenated Organic Compounds

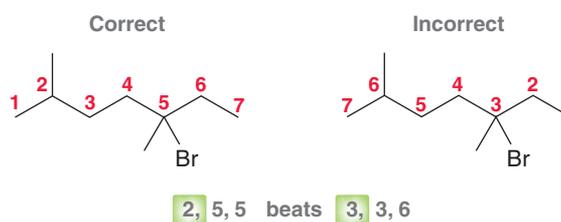
Recall from Section 4.2 that systematic (IUPAC) names of alkanes are assigned using four discrete steps:

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:

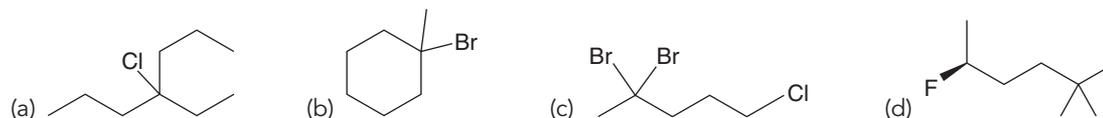


As we saw in Chapter 4, the parent is the longest chain, and it should be numbered so that the first substituent receives the lower number:

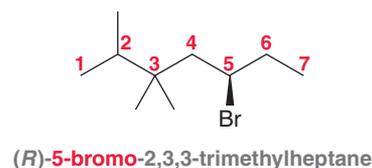


### CONCEPTUAL CHECKPOINT

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



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



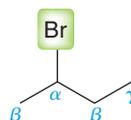
In addition to systematic names, IUPAC nomenclature also recognizes common names for many halogenated organic compounds.

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**.

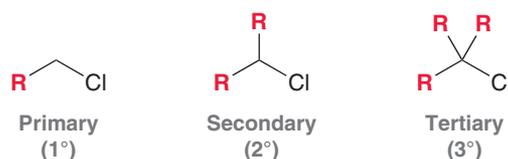
### Structure of Alkyl Halides

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



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

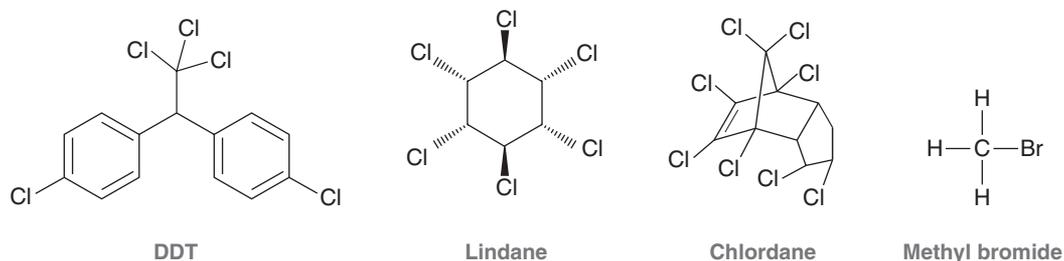
Alkyl halides are classified as **primary**, **secondary**, or **tertiary** based on the number of alkyl groups connected to the  $\alpha$  position.



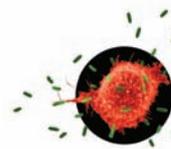
**FIGURE 7.2**  
Classification of alkyl halides as primary, secondary, or tertiary.

### Uses of Organohalides

Many organohalides are toxic and have been used as insecticides:



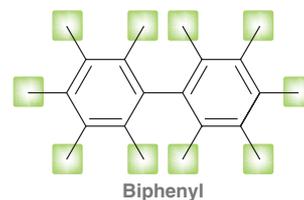
DDT (dichlorodiphenyltrichloroethane) was developed in the late 1930s and became one of the first insecticides to be used around the globe. It was found to exhibit strong toxicity for insects but rather low toxicity for mammals. DDT was used as an insecticide for many decades and has been credited with 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).

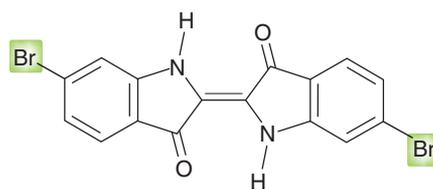
Organohalides are particularly stable compounds, and many of them, like DDT, persist and accumulate in the environment. PCBs (polychlorinated biphenyls) represent another well-known example. Biphenyl is a compound that can have up to 10 substituents:



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.

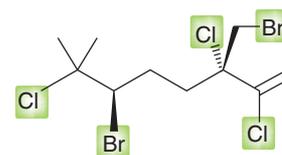
The above examples have contributed to the bad reputation of organohalides. As a result, organohalides are often viewed as man-made poisons. However, research over the last 20 years has indicated that organohalides are actually more common in nature than had previously been thought. For example, methyl 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 *Hyphomicrobium* and *Methylobacterium*, that convert methyl chloride into  $\text{CO}_2$  and  $\text{Cl}^-$ .

Many organohalides are also produced by marine organisms. Over 4000 such compounds have already been identified, and several hundred new compounds are discovered each year. Here are two examples:



**Tyrian purple**

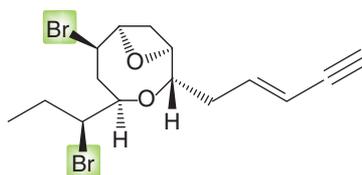
Isolated from the sea snail *Hexaplex trunculus*, this compound is one of the oldest known dyes and was used to make royal clothing thousands of years ago



**Halomon**

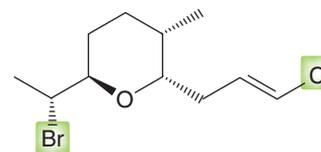
Isolated from the red algae *Portieria hornemann* this compound is currently in clinical trials for use as an antitumor agent

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**

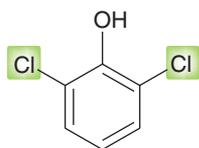
Used by the red algae *Laurencia nipponina*



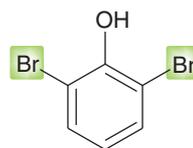
**Kumepaloxane**

Used by the snail *Haminoea cymbalum*

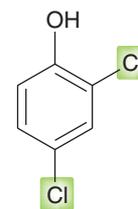
Both of these compounds are used to ward off predators. In many kinds of organisms organohalides act as hormones (chemical messengers that act only on specific target cells). Examples include the following:



**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



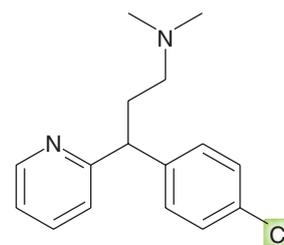
**2,4-Dichlorophenol**  
Used as a growth hormone  
by *Penicillium* molds

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:



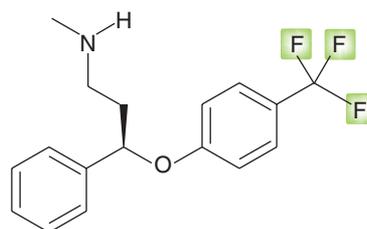
**Bronopol**  
(2-Bromo-2-nitropropane-1,3-diol)

A powerful antimicrobial compound  
safe enough to use in baby-wipes



**Chlorpheniramine**

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



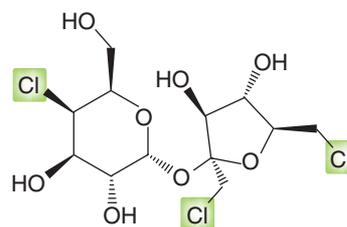
**(R)-Fluoxetine**

An antidepressant, sold under  
the trade name Prozac®

### BY THE WAY

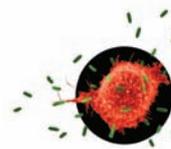
Sucralose was discovered by accident in 1976 when a British company (Tate and Lyle) was conducting research on potential uses of chlorinated sugars. A foreign graduate student participating in the research misunderstood a request to “test” one of the compounds and instead thought he was being asked to “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®.



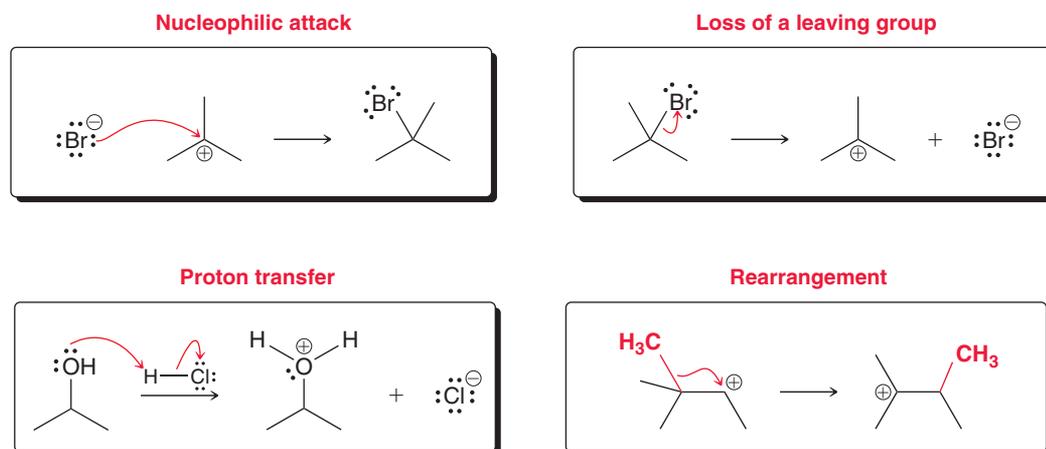
**Sucralose**

An artificial sweetener, sold  
under the trade name Splenda®



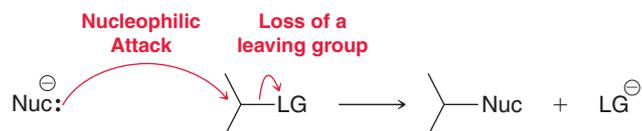
## 7.3 Possible Mechanisms for Substitution Reactions

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.

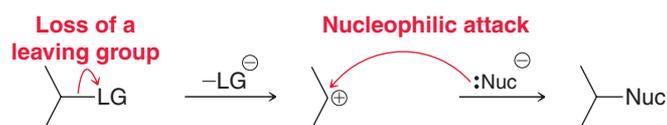


**FIGURE 7.3**  
The four arrow-pushing patterns for ionic processes.

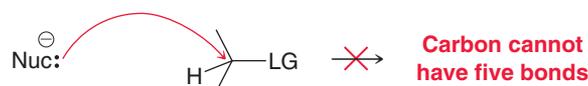
Every substitution reaction exhibits at least two of the four patterns—nucleophilic attack and loss of a leaving group:



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 only 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

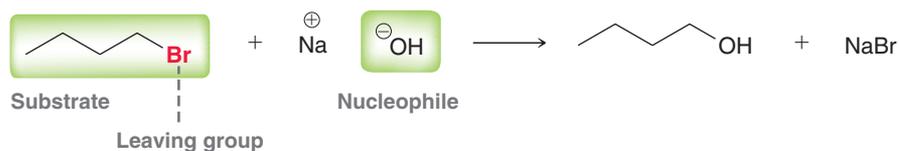
Below are two substitution reactions. Experimental evidence suggests that the first reaction proceeds via a concerted process, while the second reaction proceeds via a stepwise process. Draw a mechanism for each reaction:



## SOLUTION

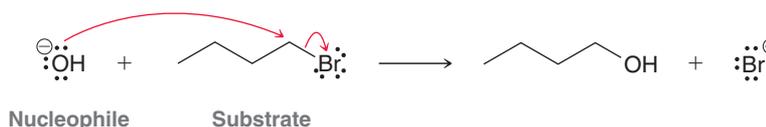
(a) First identify the substrate, the leaving group, and the nucleophile. Here, the substrate is butyl bromide, the leaving group is bromide, and the nucleophile is a hydroxide ion:

**Step 1**  
Identify the substrate, leaving group, and nucleophile.



When you see NaOH, remember that the reagent is a hydroxide ion ( $\text{HO}^-$ ).  $\text{Na}^+$  is the counterion, 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:

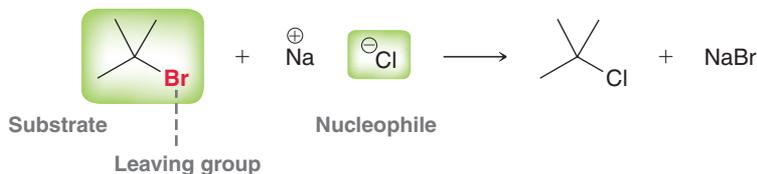
**Step 2**  
Draw two curved arrows, showing nucleophilic attack and loss of the leaving group.



## WATCH OUT

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

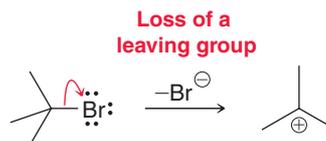
**Step 1**  
Identify the substrate, leaving group, and nucleophile.

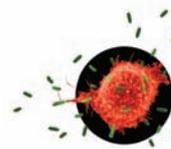


(b) A stepwise process involves two separate mechanistic steps: (1) loss of a leaving group to form a carbocation intermediate followed by (2) nucleophilic attack. To draw these steps, we must identify the substrate, leaving group, and nucleophile. Here, the substrate is *tert*-butyl bromide, the leaving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

**Step 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.

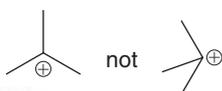


**Step 3**

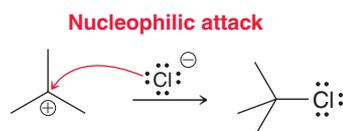
Draw a curved arrow showing a nucleophilic attack.

**BY THE WAY**

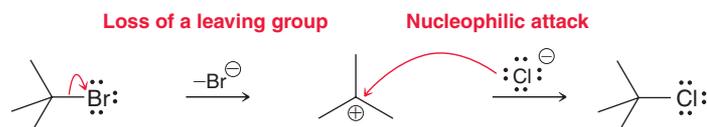
Draw all three groups of a tertiary carbocation as far apart from each other as possible:

**PRACTICE the skill**

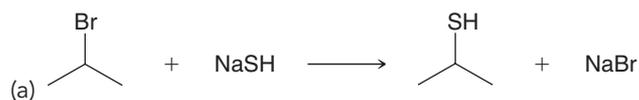
The second step of the mechanism requires one curved arrow showing the nucleophilic attack in which the carbocation intermediate is captured by the nucleophile (chloride):



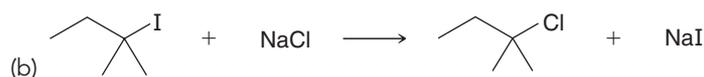
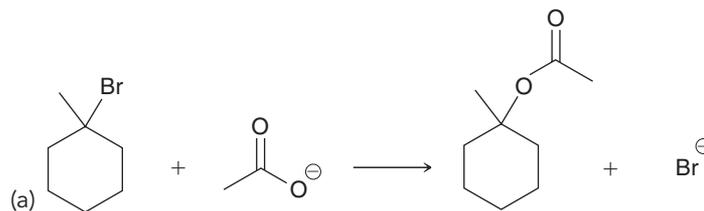
The complete mechanism can therefore be drawn like this:



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



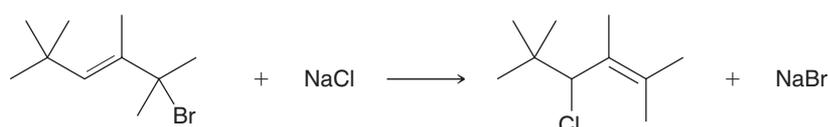
**7.3** For each of the following reactions assume a stepwise process is taking place and draw the mechanism:

**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<sub>N</sub>2 Mechanism

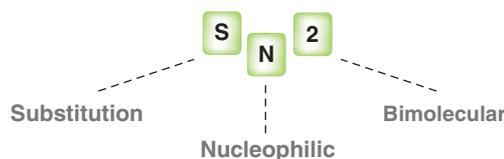
During the 1930s, Sir Christopher Ingold and Edward D. Hughes (University College, London) investigated substitution reactions in an effort to elucidate their mechanism. Based on kinetic and stereochemical observations, Ingold and Hughes proposed a concerted mechanism for many of the substitution reactions 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<sub>N</sub>2** to refer to bimolecular substitution reactions:



The experimental observations for S<sub>N</sub>2 reactions are consistent with a concerted mechanism, because a concerted mechanism exhibits only one mechanistic step, involving both the nucleophile and the substrate:



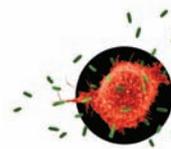
It makes sense that the rate should be dependent on the concentrations of both the nucleophile and the substrate.

### CONCEPTUAL CHECKPOINT

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

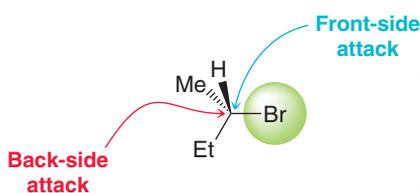
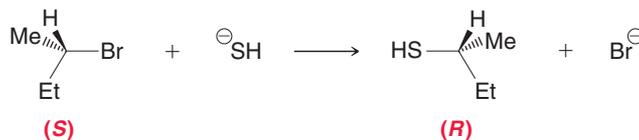


- (a) What happens to the rate if the concentration of 1-iodopropane is tripled and the concentration of sodium hydroxide remains the same?
- (b) What happens to the rate if the concentration of 1-iodopropane remains the same and the concentration of sodium hydroxide is doubled?
- (c) What happens to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



## Stereospecificity of S<sub>N</sub>2 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:



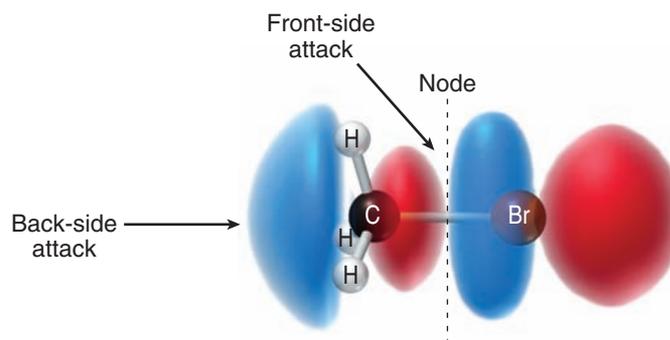
**FIGURE 7.4**  
The front and back sides of a substrate.

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.

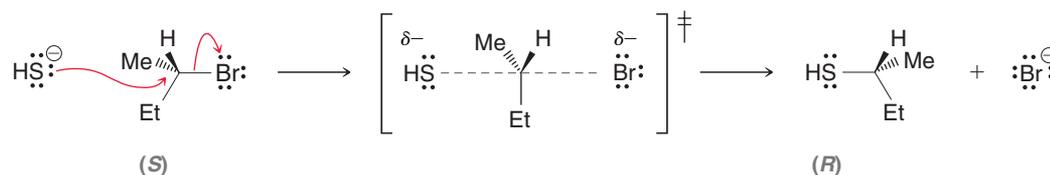
The requirement for inversion of configuration means that the nucleophile can only attack from the back side (the side opposite the leaving group), and never from the front side (Figure 7.4). There are two ways to explain why the reaction proceeds through **back-side attack**:

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.

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



The observed stereochemical outcome for an S<sub>N</sub>2 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

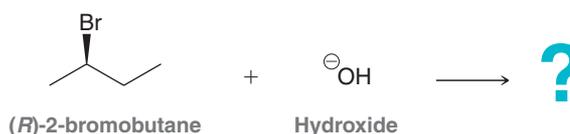
7.2 DRAWING THE PRODUCT OF AN S<sub>N</sub>2 PROCESS

## LEARN the skill

When (*R*)-2-bromobutane is treated with a hydroxide ion, a mixture of products is obtained. An S<sub>N</sub>2 process is responsible for generating one of the products, while the other products are generated via other processes that will be discussed in the next chapter. Draw the S<sub>N</sub>2 product that is obtained when (*R*)-2-bromobutane reacts with a hydroxide ion.

## SOLUTION

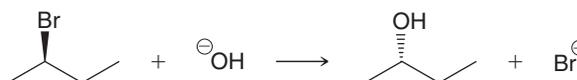
First draw the reagents described in the problem:



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:



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



## WATCH OUT

In an S<sub>N</sub>2 reaction, if the α position is a chirality center, make sure to draw an inversion of configuration in the product.

## PRACTICE the skill

7.7 Draw the product for each of the following S<sub>N</sub>2 reactions:

(a) (*S*)-2-Chloropentane and NaSH

(b) (*R*)-3-Iodohexane and NaCl

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

## APPLY the skill

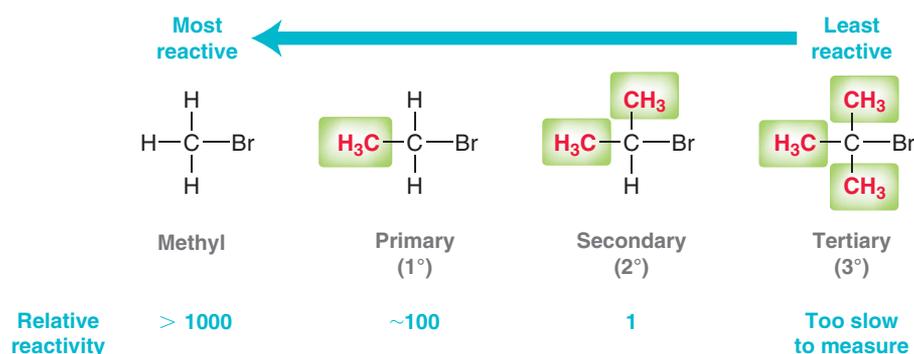
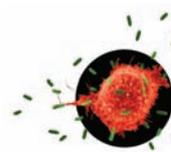
7.8 When (*S*)-1-chloro-1-fluoroethane reacts with a hydroxide ion, an S<sub>N</sub>2 reaction takes place in which the chlorine atom is replaced by the OH group. The product of this reaction is (*S*)-1-fluoro-1-ethanol. How can it be that the starting material and the product both have the *S* configuration? Shouldn't S<sub>N</sub>2 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, 7.46, 7.56, 7.61

## Structure of the Substrate

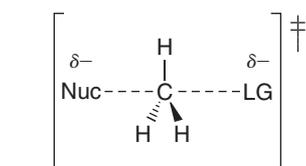
For S<sub>N</sub>2 reactions, Ingold and Hughes also found the rate to be sensitive to the nature of the starting alkyl halide. In particular, methyl halides and primary alkyl halides react most quickly with nucleophiles. Secondary alkyl halides react more slowly, and tertiary alkyl halides are essentially unreactive toward S<sub>N</sub>2 (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<sub>N</sub>2 reactions, we must explore the transition state for a typical S<sub>N</sub>2 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



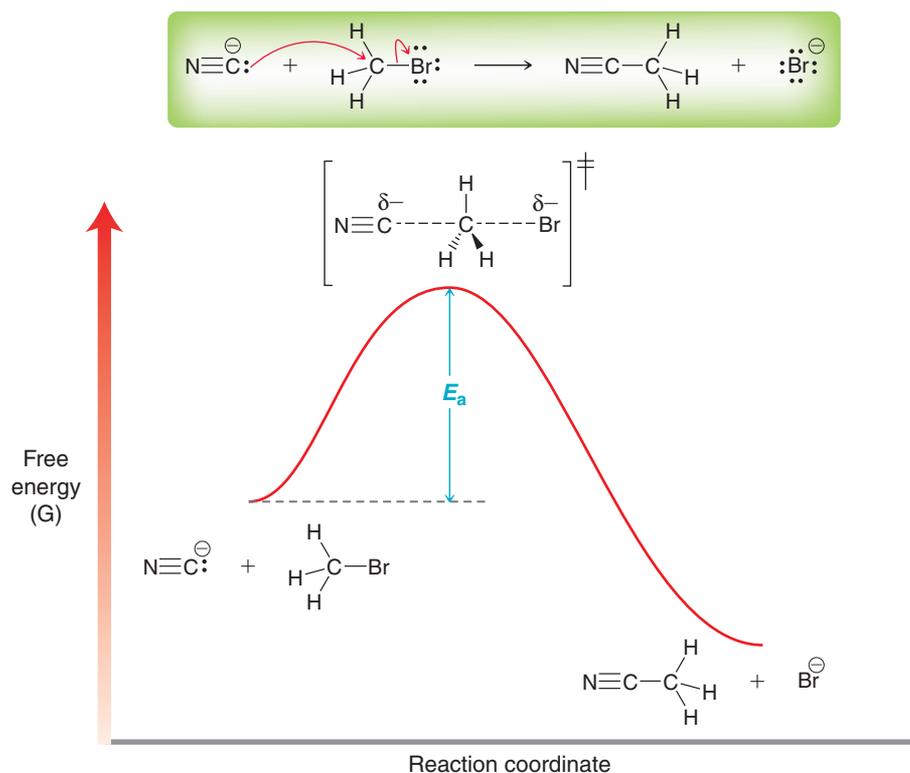
**FIGURE 7.6**  
The relative reactivity of various substrates toward S<sub>N</sub>2.

state is high in energy, then  $E_a$  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.

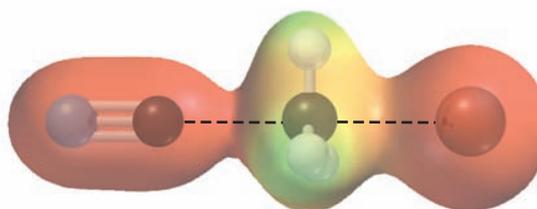


**FIGURE 7.7**  
The generic form of a transition state in an S<sub>N</sub>2 process.

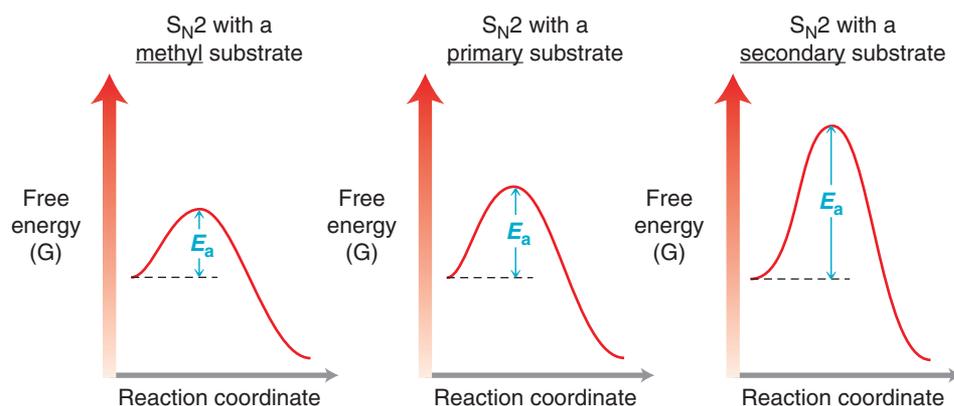
**FIGURE 7.8**  
An energy diagram of the S<sub>N</sub>2 reaction that occurs between methyl bromide and a cyanide ion.



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).



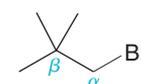
**FIGURE 7.9**  
An electrostatic potential map of the transition state from Figure 7.7.



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

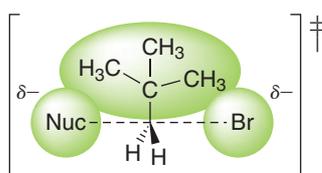
If the hydrogen atoms in Figure 7.9 are replaced with alkyl groups, steric interactions cause the transition state to be higher in energy, raising  $E_a$  for the reaction. Compare the energy diagrams for reactions involving methyl, primary, and secondary substrates (Figure 7.10). With a tertiary substrate, 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

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.



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

## SKILLBUILDER

### 7.3 DRAWING THE TRANSITION STATE OF AN $S_N2$ PROCESS



#### LEARN the skill

Draw the transition state of the following reaction:

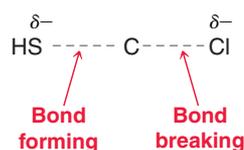


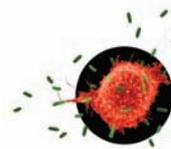
#### SOLUTION

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



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:



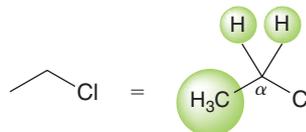


**Step 3**  
Draw the three groups attached to the carbon atom.

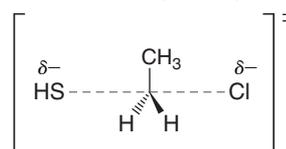
**Step 4**  
Place brackets as well as the symbol that indicates a transition state.

The δ<sup>-</sup>-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<sub>3</sub> group and two H's:



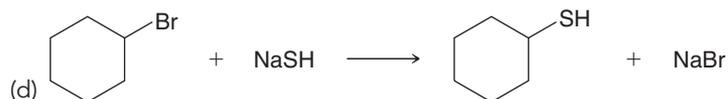
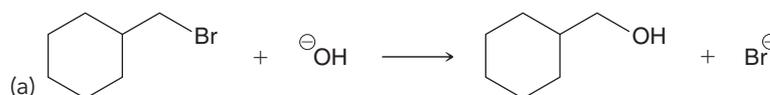
So we draw these groups in the transition state connected to the α position. One group is placed on a straight line, and the other two groups are placed on a wedge and on a dash:



In this case, there is no chirality center, so it does not matter whether the CH<sub>3</sub> 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 (the telephone pole).



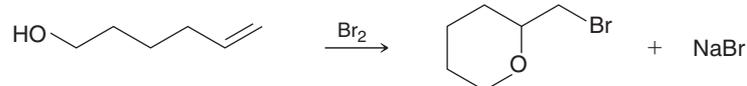
**PRACTICE the skill** 7.9 Draw the transition state for each of the following S<sub>N</sub>2 reactions:



**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<sub>N</sub>2 process:



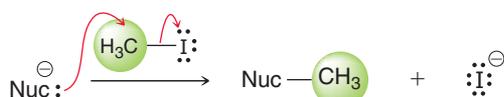
In this step, a bond is in the process of breaking, while another bond is in the process of forming. Draw the transition state of this S<sub>N</sub>2 process, and identify which bond is being broken and which bond is being formed. Can you offer an explanation as to why this step is favorable?

need more PRACTICE? Try Problems 7.46, 7.64e

## PRACTICALLY SPEAKING )))

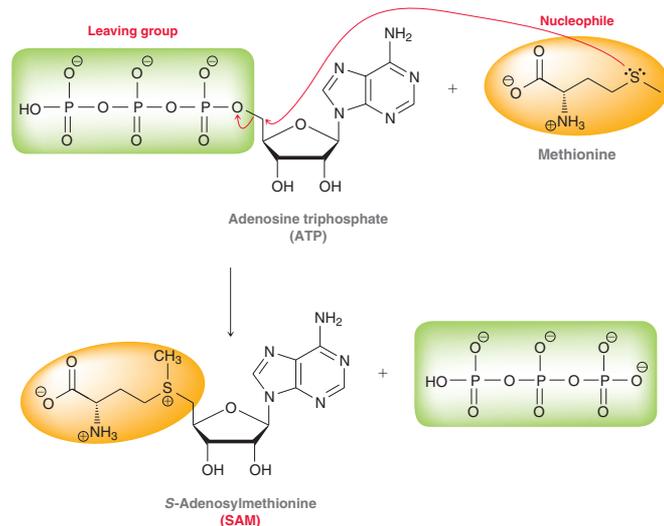
### S<sub>N</sub>2 Reactions in Biological Systems—Methylation

In the laboratory, the transfer of a methyl group is accomplished via an S<sub>N</sub>2 process using methyl iodide:



This process is called *alkylation*, because an alkyl group has been transferred to the nucleophile. It is an S<sub>N</sub>2 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<sub>3</sub>I, the methylating agent is a compound called SAM (S-adenosylmethionine). Your body produces SAM via an S<sub>N</sub>2 reaction between ATP and the amino acid methionine:



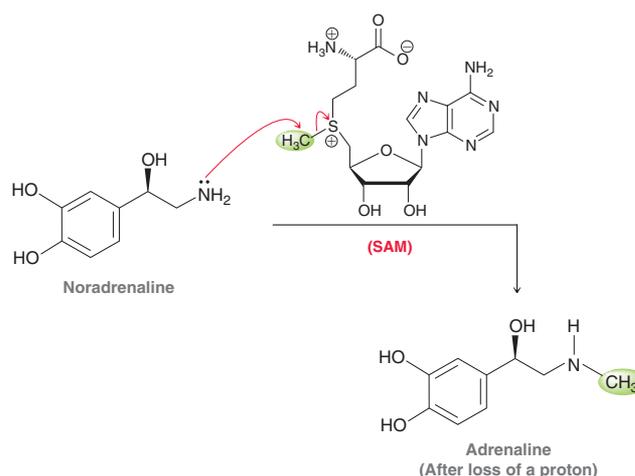
In this reaction, methionine acts as a nucleophile and attacks adenosine triphosphate (ATP), kicking off a triphosphate leaving group. The resulting product, called SAM, is able to function as a methylating agent, very much like CH<sub>3</sub>I. Both CH<sub>3</sub>I and SAM exhibit a methyl group attached to an excellent leaving group.

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

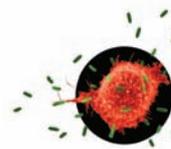
SAM is the biological equivalent of CH<sub>3</sub>I. The leaving group is much larger, but SAM functions in the same way as CH<sub>3</sub>I. When SAM is attacked by a nucleophile, the leaving group can leave as a neutral compound and is therefore a good leaving group:



SAM plays a role in the biosynthesis of many compounds, including adrenaline. 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."



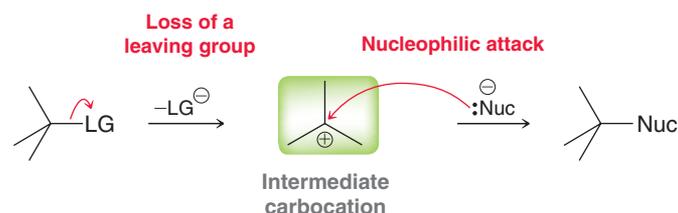
### CONCEPTUAL CHECKPOINT

**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<sub>N</sub>1 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:



Many reactions appear to follow this stepwise mechanism. Once again, there are several pieces of evidence that support this stepwise mechanism in those cases.

### Kinetics

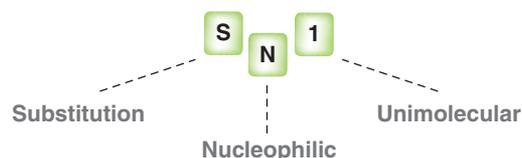
Many substitution reactions do not exhibit second-order kinetics. Consider the following example:



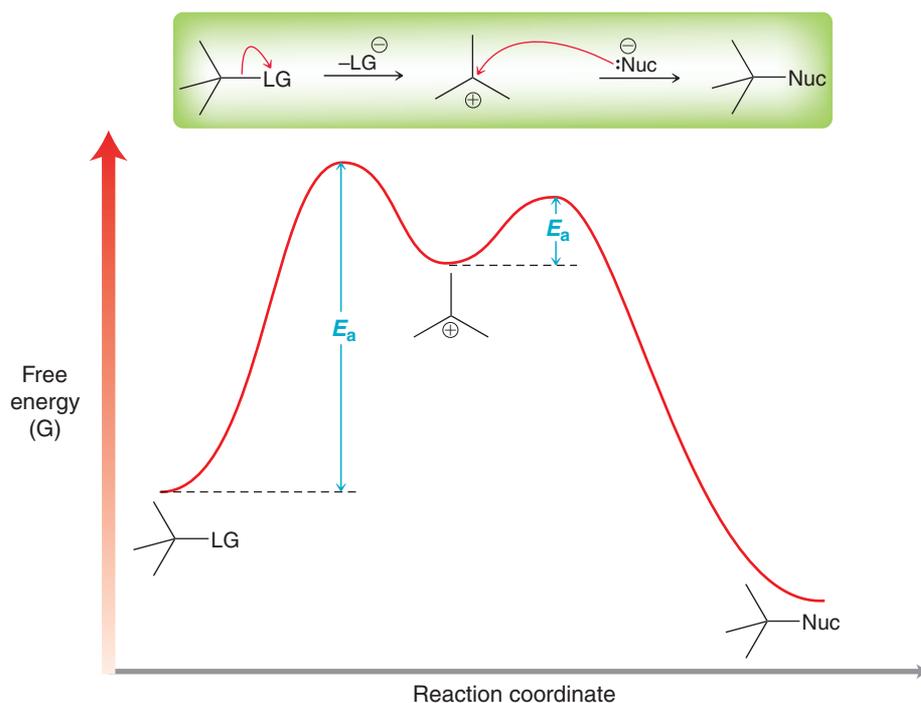
In the reaction above, the rate is dependent only on the concentration of the substrate. The rate equation has the following form:

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

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 slow 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<sub>N</sub>1** to refer to unimolecular substitution reactions:

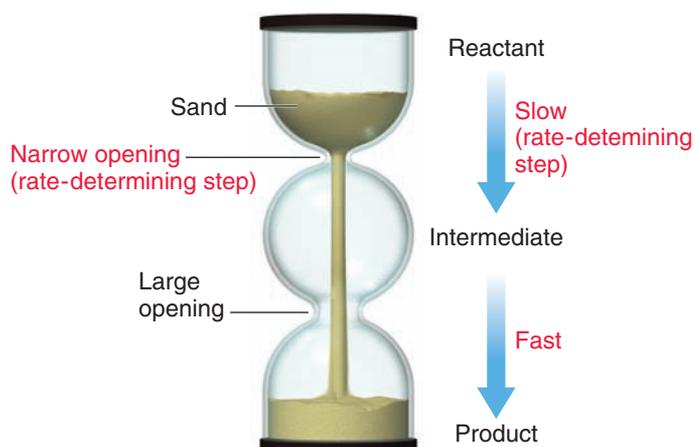


When we use the term unimolecular, we don't mean that the nucleophile is completely irrelevant. Clearly, the nucleophile is necessary, or there won't be a reaction. The term *unimolecular* simply describes the fact that only one chemical entity participates in the slowest step of the reaction, and as a result, the rate of the reaction is not affected by how much nucleophile is present.

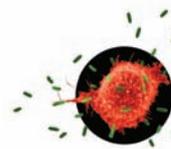


**FIGURE 7.12**  
An energy diagram of an  $S_N1$  process.

To understand why this is the case, consider the energy diagram of an  $S_N1$  mechanism (Figure 7.12). The mechanism has two steps, so we expect two humps. Compare the activation energy ( $E_a$ ) for each of these steps. The first step has a larger  $E_a$ , and therefore, the first step is slower. The rate of the entire reaction cannot be any faster than the rate of the slow step. The slow step is therefore called the **rate-determining step** (RDS). To illustrate this concept, consider the modified hourglass in Figure 7.13. As the sand falls, it passes through two passageways. The first passageway is a narrow opening; it represents the slower step. The second passageway has a larger opening and therefore has no effect on the rate at which the sand falls. If the second passageway is further widened, it will not impact the overall rate in any way. The same idea is true for reactions as well. The rate of an  $S_N1$  process is dependent only on the rate of the slow step, the loss of the leaving group. As a result, the rate of an  $S_N1$  process will only be affected by factors that affect the rate at which the leaving group leaves. Increasing the concentration of the nucleophile has no impact on the rate of the slow step. 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.

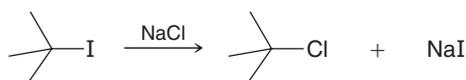


**FIGURE 7.13**  
A modified hourglass with two passageways. The narrow passageway is the rate-determining step.



### CONCEPTUAL CHECKPOINT

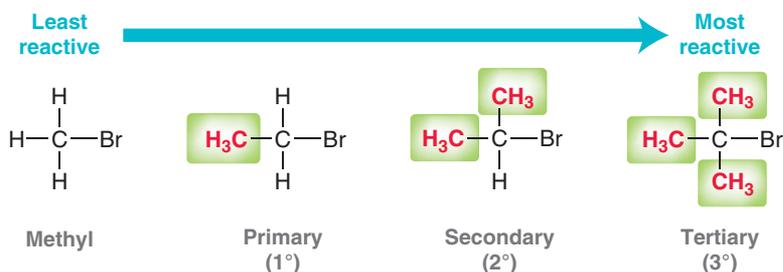
7.13 The following reaction occurs via an S<sub>N</sub>1 mechanistic pathway:



- (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?

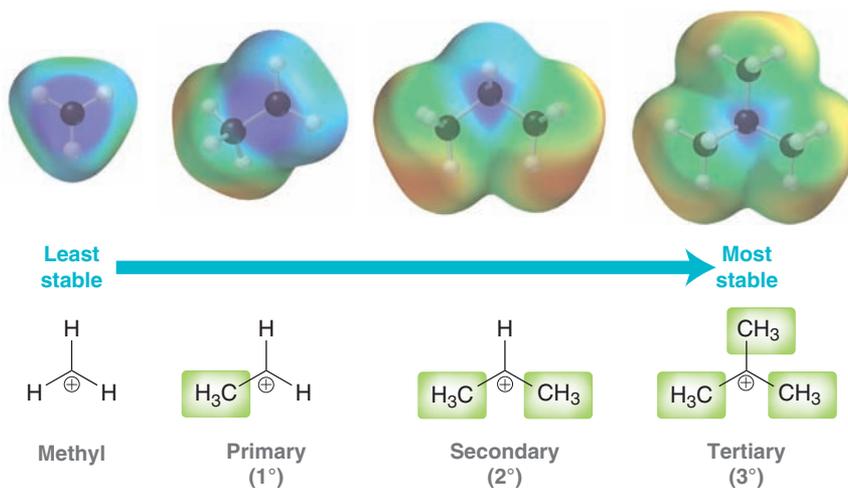
### Structure of Substrate

The rate of an S<sub>N</sub>1 reaction is highly dependent on the nature of the substrate, but the trend is the reverse of the trend we saw for S<sub>N</sub>2 reactions. With S<sub>N</sub>1 reactions, tertiary substrates react most quickly, while methyl and primary substrates are mostly unreactive (Figure 7.14). This observation supports a stepwise mechanism (S<sub>N</sub>1). Why? With S<sub>N</sub>2 reactions, steric hindrance was the issue because the nucleophile was directly attacking the substrate. In contrast, in S<sub>N</sub>1 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.

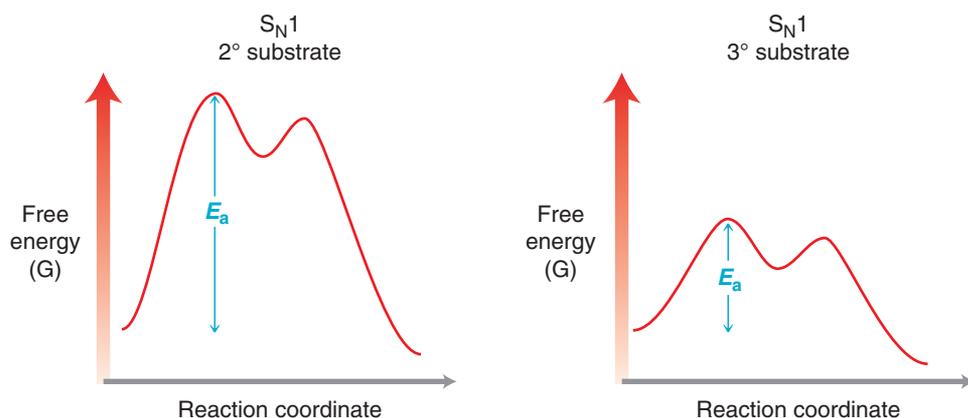


**FIGURE 7.14**  
The relative reactivity of various substrates toward S<sub>N</sub>1.

Recall that carbocations are stabilized by neighboring alkyl groups (Figure 7.15). 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



**FIGURE 7.15**  
Electrostatic potential maps of various carbocations. The alkyl groups help spread the positive charge, thereby stabilizing the charge.



**FIGURE 7.16**  
Energy diagrams comparing  $S_N1$  processes for secondary and tertiary substrates.

formation of a secondary carbocation (Figure 7.16). 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.

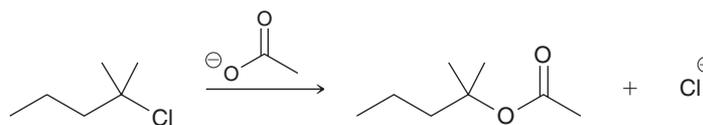
## SKILLBUILDER



### 7.4 DRAWING THE CARBOCATION INTERMEDIATE OF AN $S_N1$ PROCESS

#### LEARN the skill

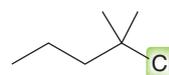
Draw the carbocation intermediate of the following  $S_N1$  reaction:



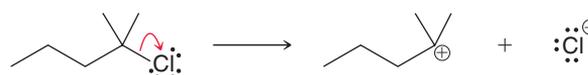
#### SOLUTION

First identify the leaving group:

**Step 1**  
Identify the leaving group.

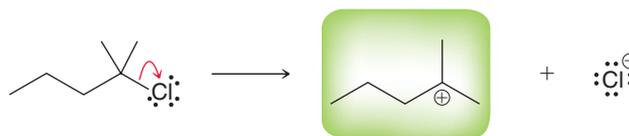
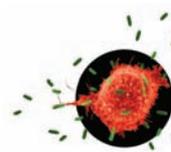


Loss of the leaving group will produce a carbocation and a chloride ion. To keep track of the electrons, it is helpful to draw the curved arrow that shows the flow of electrons:

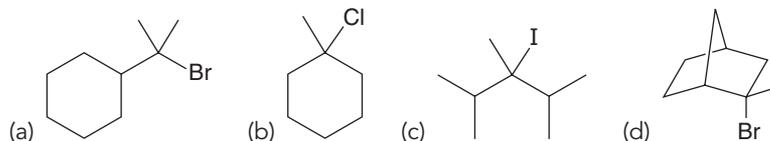


**Step 2**  
Draw all three groups pointing away from each other.

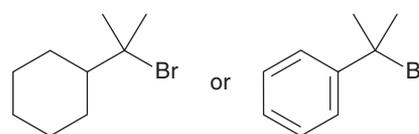
When drawing the carbocation intermediate, make sure that all three groups on the carbocation are drawn as far apart as possible. Remember that a carbocation has trigonal planar geometry, and the drawing should reflect that:



**PRACTICE the skill** 7.14 Draw the carbocation intermediate generated by each of the following substrates in an S<sub>N</sub>1 reaction:



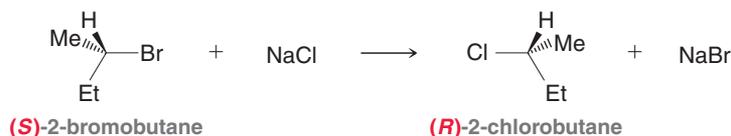
**APPLY the skill** 7.15 Identify which of the following substrates will undergo an S<sub>N</sub>1 reaction more rapidly. Explain your choice.



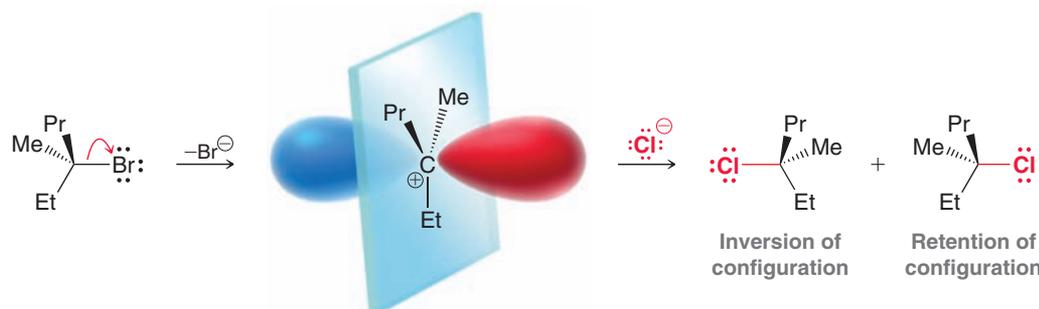
need more PRACTICE? Try Problems 7.50, 7.51

### Stereochemistry of S<sub>N</sub>1 Reactions

Recall that S<sub>N</sub>2 reactions proceed via an inversion of configuration:



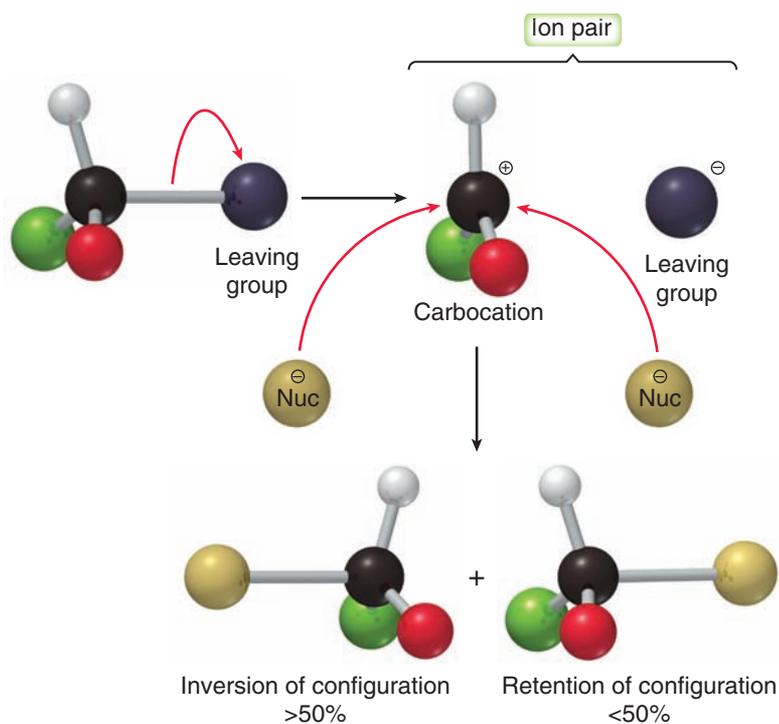
In contrast, S<sub>N</sub>1 reactions involve formation of an intermediate carbocation, which can then be attacked from either side (Figure 7.17), leading to both inversion of configuration and **retention of configuration**.



**FIGURE 7.17**  
The intermediate of an S<sub>N</sub>1 process is a planar carbocation.

A carbocation is planar, and either side of the plane can be attacked by the nucleophile with equal likelihood.

Since the carbocation can be attacked on either side with equal likelihood, we should expect S<sub>N</sub>1 reactions to produce a racemic mixture (equal mixture of inversion and retention). In practice, though, S<sub>N</sub>1 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 7.18). 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 7.18**

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:

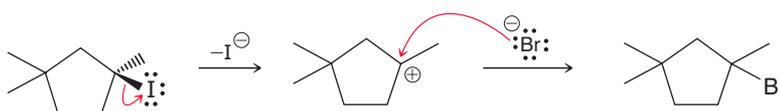


#### SOLUTION

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



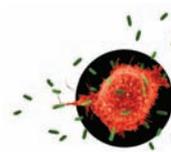
In an  $S_N1$  process, the leaving group leaves first, generating a carbocation that is then attacked by the nucleophile:



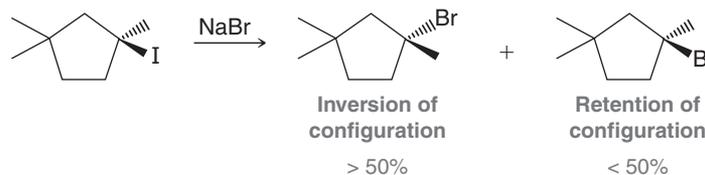
In this example, substitution is taking place at a chirality center, so we must consider the stereochemical outcome. In an  $S_N1$  process, both enantiomers are expected as products, with a slight preference for the enantiomer resulting from inversion of configuration:

**Step 1**  
Identify the nucleophile and the leaving group.

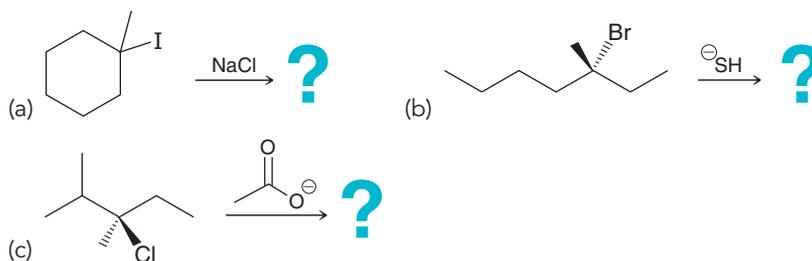
**Step 2**  
Replace the leaving group with the nucleophile.



**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<sub>N</sub>1 reactions:



**APPLY the skill**

7.17 Draw the two products that you expect in the following S<sub>N</sub>1 reaction and describe their stereoisomeric relationship:



need more PRACTICE? Try Problems 7.48, 7.49, 7.55

Let's now summarize the differences that we have seen between S<sub>N</sub>2 and S<sub>N</sub>1 processes (Table 7.1).

	S <sub>N</sub> 2	S <sub>N</sub> 1
<b>TABLE 7.1 A COMPARISON OF S<sub>N</sub>2 AND S<sub>N</sub>1 PROCESSES</b>		
<i>Mechanism</i>		
<i>Energy diagram</i>		
<i>Rate equation</i>	Rate = $k$ [substrate] [nucleophile]	Rate = $k$ [substrate]
<i>Rate of reaction</i>	Methyl > 1° > 2° > 3°	3° > 2° > 1° > methyl
<i>Stereochemistry</i>	Inversion of configuration	Racemization (with slight preference for inversion due to ion pairs)

## 7.6 Drawing the Complete Mechanism of an S<sub>N</sub>1 Reaction

We have now seen that substitution reactions can occur through either a concerted mechanism (S<sub>N</sub>2) or a stepwise mechanism (S<sub>N</sub>1) (Figure 7.19). When drawing the mechanism of an S<sub>N</sub>2 or S<sub>N</sub>1 process, additional mechanistic steps will sometimes be required. In this section, we will focus on the additional steps that can accompany an S<sub>N</sub>1 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<sub>N</sub>1 processes.



**FIGURE 7.19**  
The mechanistic steps in  $S_N2$  and  $S_N1$  processes.

As seen in Figure 7.19, 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 7.20), which can occur before, between, or after the two core steps:



**FIGURE 7.20**  
The two core steps (gray) and the three possible additional steps (blue) that can accompany an  $S_N1$  process.

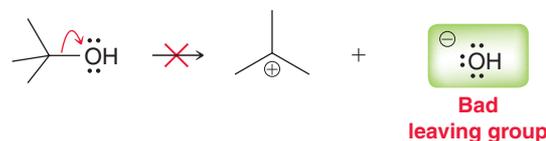
1. *Before the two core steps*—a proton transfer step is possible.
2. *Between the two core steps*—a carbocation rearrangement is possible.
3. *After the two core steps*—a proton transfer step is possible.

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.

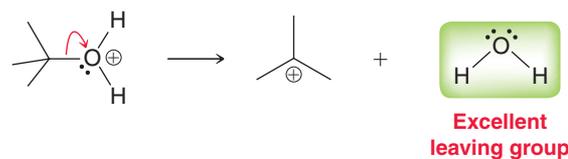
### Proton Transfer at the Beginning of an $S_N1$ Process



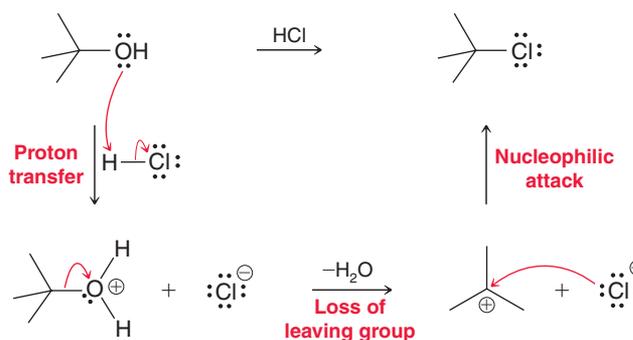
Before the two core steps of an  $S_N1$  mechanism, a proton transfer will be necessary whenever the leaving group is an OH group. Hydroxide is a bad leaving group and will not leave by itself (as will be discussed later in this chapter):

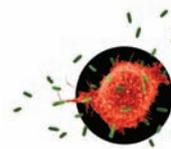


However, once an OH group is protonated, it becomes an excellent leaving group because it can leave as a neutral species (no net charge):



If a substrate has no leaving group other than an OH group, then acidic conditions will be required in order to perform an  $S_N1$  reaction. In the following example, HCl supplies the  $H^+$  necessary to protonate the OH group as well as the chloride ion that functions as the nucleophile:



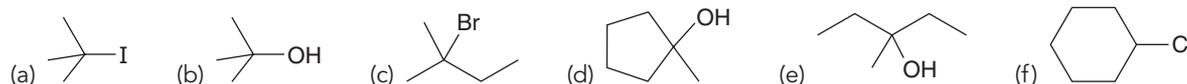


Notice that the two core steps of this  $S_N1$  process are preceded by a proton transfer, giving a total of three mechanistic steps:

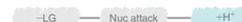


### CONCEPTUAL CHECKPOINT

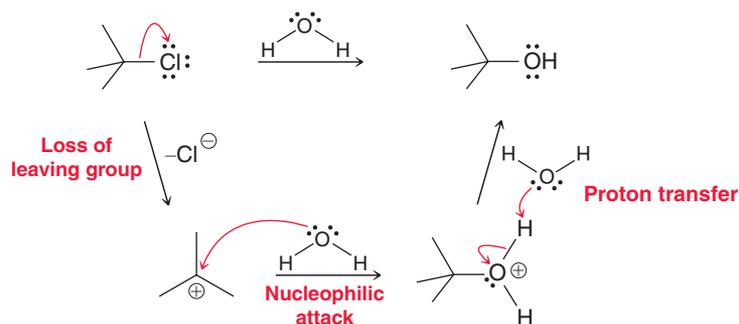
**7.18** For each of the following substrates, determine whether an  $S_N1$  process will require a proton transfer at the beginning of the mechanism:



### Proton Transfer at the End of an $S_N1$ Process



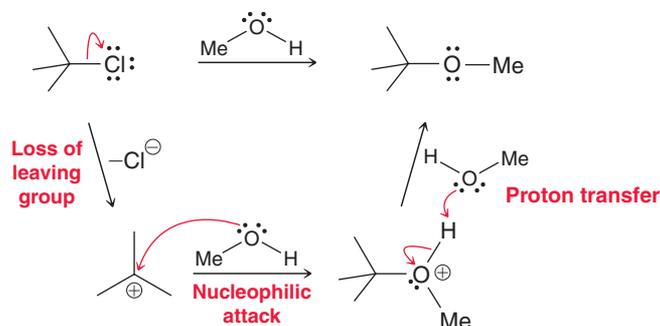
After the two core steps of an  $S_N1$  mechanism, a proton transfer will be necessary whenever the nucleophile is neutral (not negatively charged). For example:



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

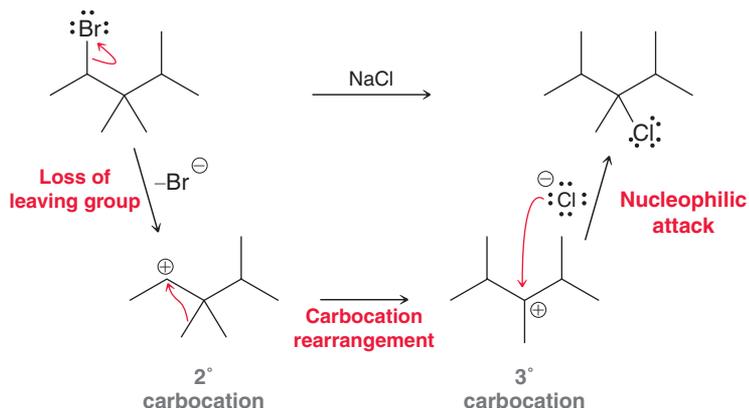
7.19 Will an  $S_N1$  process involving each of the following nucleophiles require a proton transfer at the end of the mechanism?

- (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



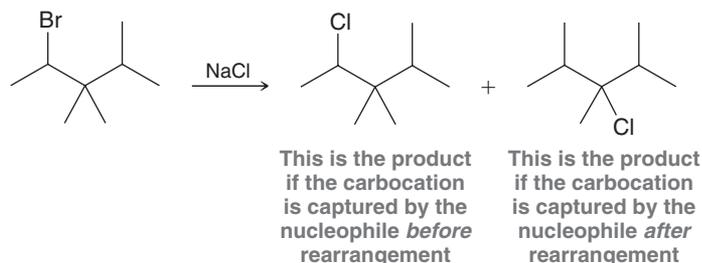
The first core step of an  $S_N1$  process is loss of a leaving group to generate a carbocation. Recall from Chapter 6 that carbocations are susceptible to rearrangement via either a hydride shift or a methyl shift. Here is an example of an  $S_N1$  mechanism with a carbocation rearrangement:



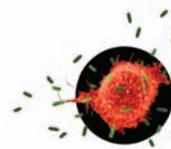
Notice that the carbocation rearrangement occurs between the two core steps of the  $S_N1$  process:



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

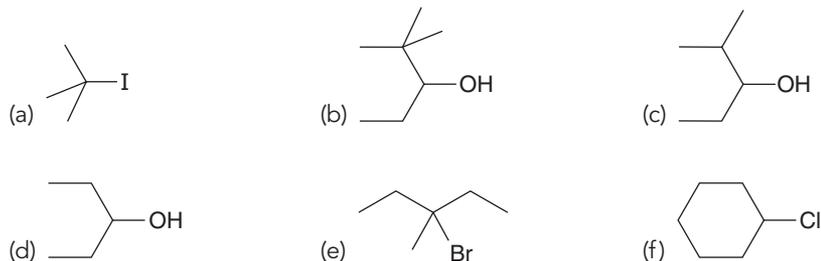


The product distribution (ratio of products) depends on how fast the rearrangement takes place and how fast the nucleophile attacks the carbocation. If the rearrangement occurs faster than attack by the nucleophile, then the rearranged product will predominate. However, if the nucleophile attacks the 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<sub>N</sub>1 process will involve a carbocation rearrangement or not:



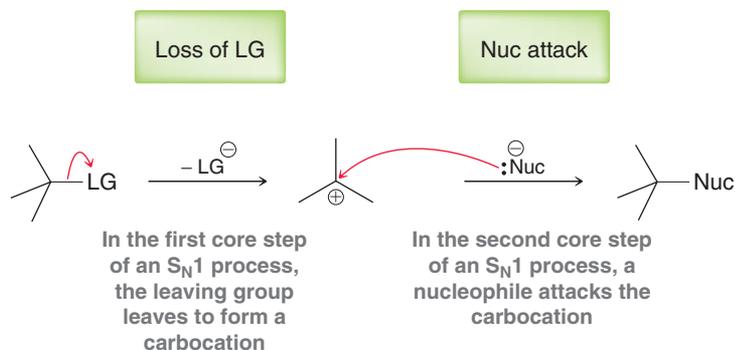
### Summary of the S<sub>N</sub>1 Process and Its Energy Diagram



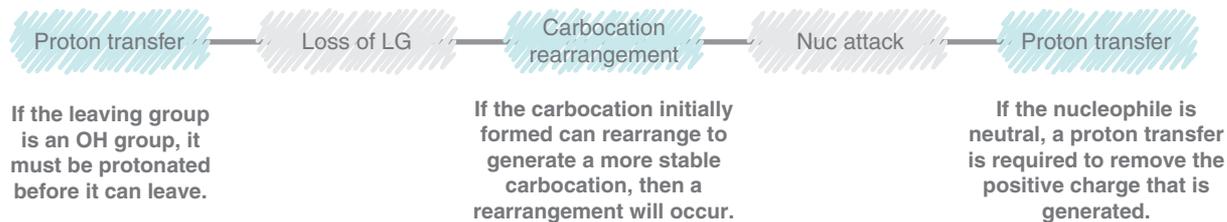
We have seen that an S<sub>N</sub>1 process has two core steps and can be accompanied by three additional steps, as summarized in Mechanism 7.1.

### MECHANISM 7.1 THE S<sub>N</sub>1 PROCESS

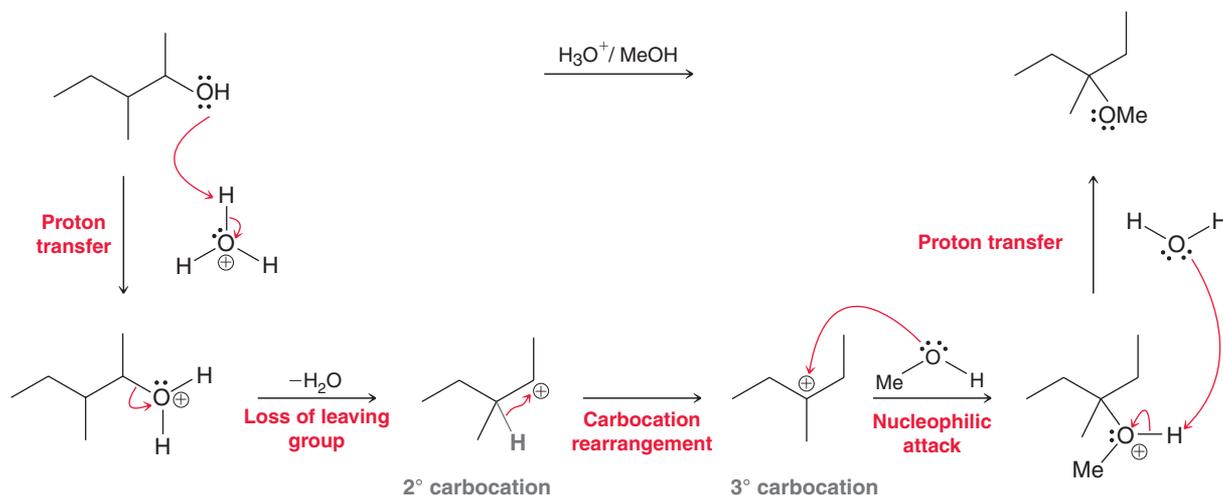
#### Two core steps



#### Possible additional steps



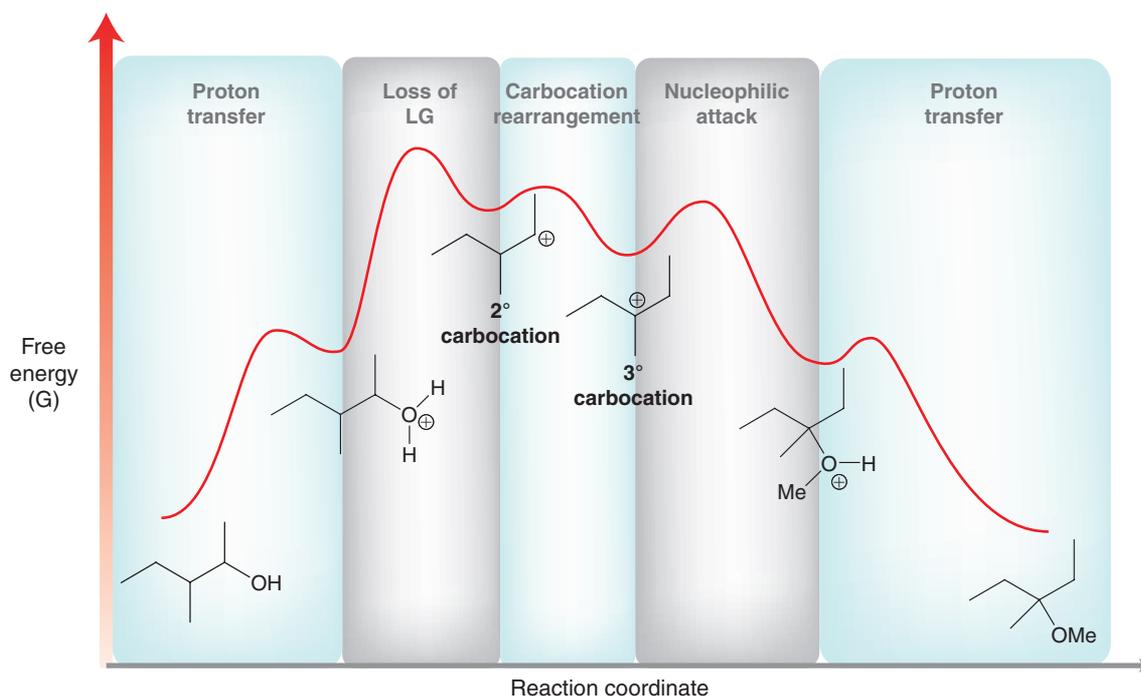
Here is an example of an  $S_N1$  process that is accompanied by all three additional steps:



Since this mechanism has five steps, we expect the energy diagram for this reaction to exhibit five humps (Figure 7.21). 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 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 7.21**

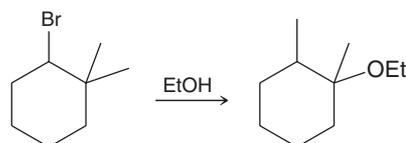
An energy diagram of an  $S_N1$  process that is accompanied by three additional steps. In total, there are five steps, giving an energy diagram with five humps.

## SKILLBUILDER

7.6 DRAWING THE COMPLETE MECHANISM OF AN S<sub>N</sub>1 PROCESS

## LEARN the skill

Draw the mechanism of the following S<sub>N</sub>1 process:



## SOLUTION

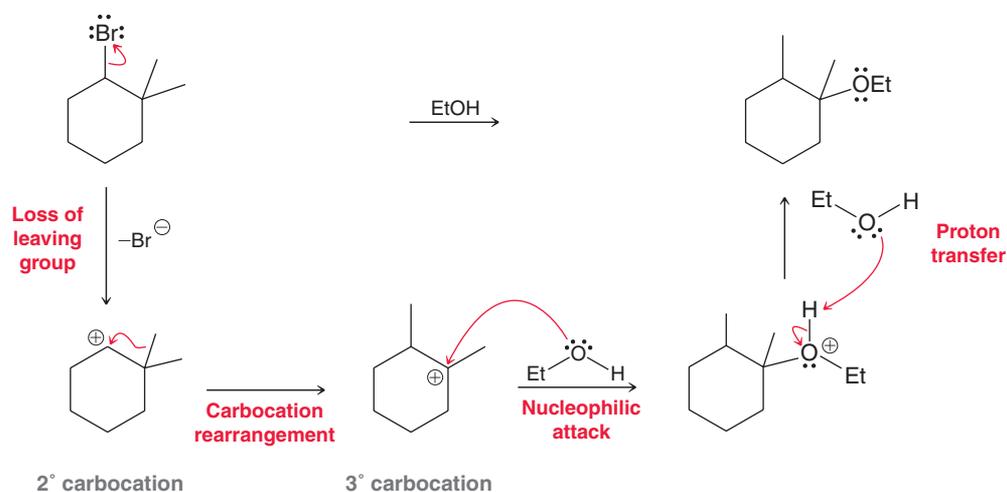
An S<sub>N</sub>1 process must always exhibit two core steps: loss of a leaving group and nucleophilic attack. But we must consider whether any of the other three possible steps will occur:



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:

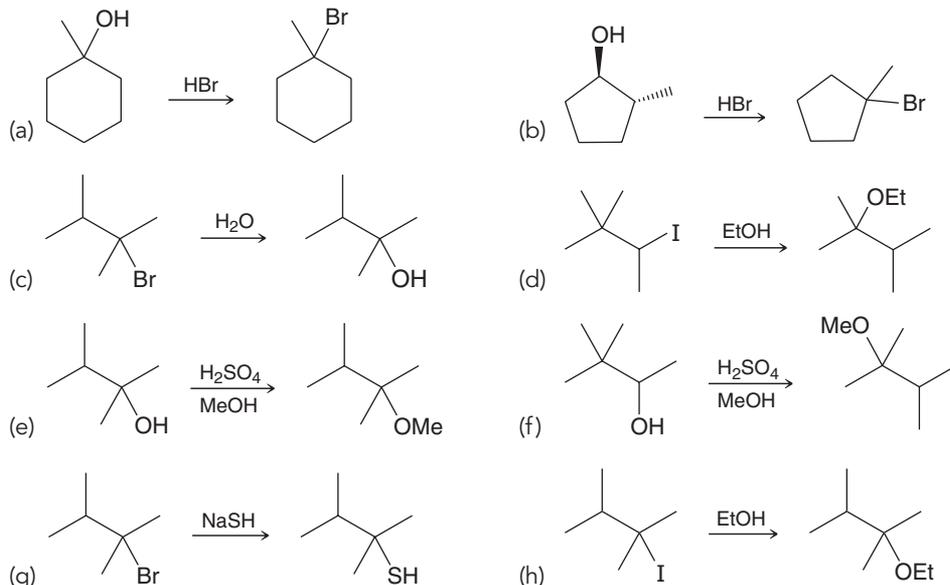


Notice that this sequence utilizes each of the four arrow-pushing patterns that are possible for an ionic reaction. To draw these steps, we will rely on the skills we learned in Chapter 6:





**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.

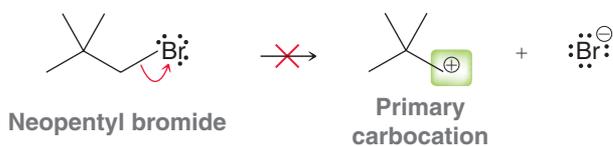
7.21b:  $+H^+$  —  $-LG$  —  $C^+$  rearrangement — Nuc attack This mechanism exhibits a proton transfer before the two core steps as well as a carbocation rearrangement in between the two core steps.

These patterns are not identical. Draw patterns for the other six problems. Then compare the patterns. There is only one pattern that is repeated in Problem 7.21. 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.

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

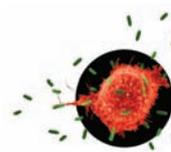
In some rare cases, loss of the leaving group and carbocation rearrangement can occur in a concerted fashion (Figure 7.22). For example, neopentyl bromide cannot directly lose its leaving group, as that would generate a primary carbocation, which is too high in energy to form:



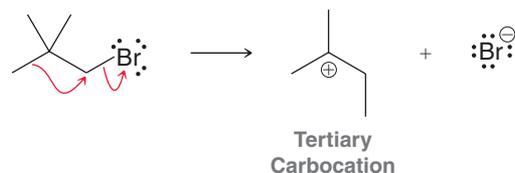
**FIGURE 7.22**

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



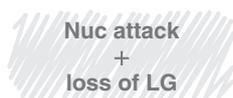


But it is possible for the leaving group to leave as a result of a methyl shift:



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<sub>N</sub>1 process occurs separately.

## 7.7 Drawing the Complete Mechanism of an S<sub>N</sub>2 Reaction

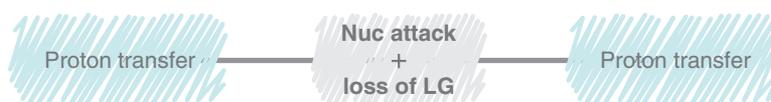


**FIGURE 7.23**

The one concerted step of an S<sub>N</sub>2 process.

**FIGURE 7.24**

The concerted step and the two possible additional steps of an S<sub>N</sub>2 process.

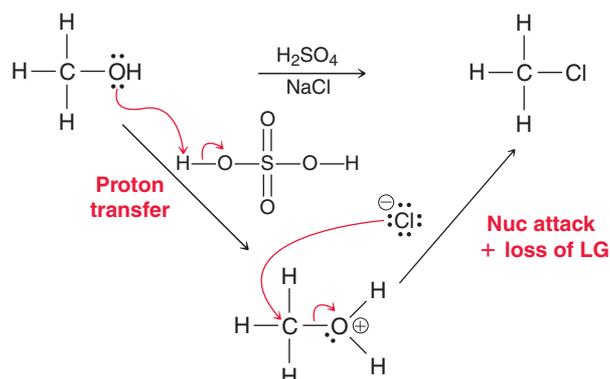


Specifically, a proton transfer is required at the beginning of a mechanism if the leaving group is an OH group, and it is required at the end of the mechanism if the nucleophile is neutral. Let's see examples of each.

### Proton Transfer at the Beginning of an S<sub>N</sub>2 Process



A proton transfer is necessary at the beginning of an S<sub>N</sub>2 process if the leaving group is an OH group. 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.



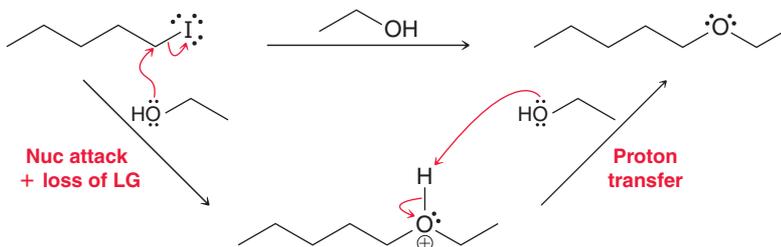
The OH group is first protonated, converting it into a good leaving group, and then the chloride ion attacks in an S<sub>N</sub>2 process, displacing the leaving group. Methyl chloride is prepared commercially by a similar process (using HCl as the source of H<sup>+</sup> and Cl<sup>-</sup>):



### 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:

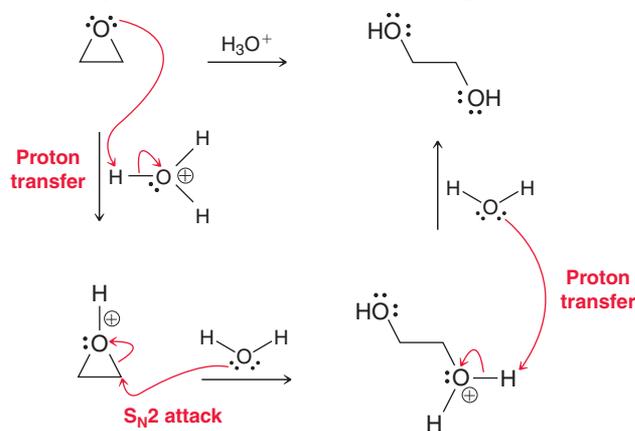


The substrate is primary, and therefore, the reaction must proceed via an  $S_N2$  process. In this case, the solvent (ethanol) is functioning as the nucleophile, so this is a solvolysis reaction. Since the nucleophile is neutral, a proton transfer is required at the end of the mechanism in order to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

### Proton Transfer Before and After an $S_N2$ Process

 $+H^+$  —  $S_N2$  —  $-H^+$ 

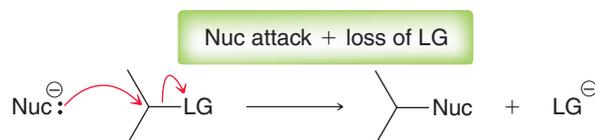
Throughout this course, we will see other examples of  $S_N2$  processes that are accompanied by proton transfers. For example, the following reaction will be explored in Sections 9.16 and 14.10:



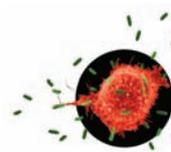
This reaction involves two proton transfer steps—one before and one after the  $S_N2$  attack—as seen in Mechanism 7.2.

## MECHANISM 7.2 THE $S_N2$ PROCESS

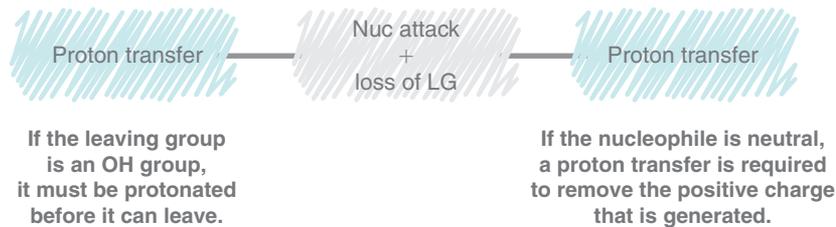
### One concerted step



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

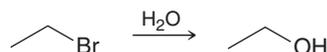


## SKILLBUILDER

7.7 DRAWING THE COMPLETE MECHANISM OF AN S<sub>N</sub>2 PROCESS

## LEARN the skill

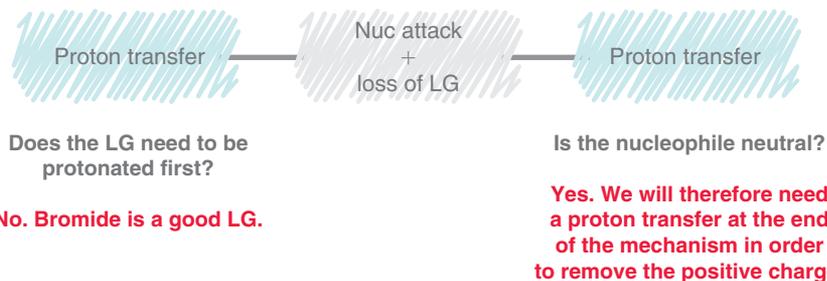
Ethyl bromide was dissolved in water and heated, and the following solvolysis reaction was observed to occur slowly, over a long period of time: Propose a mechanism for this reaction.



## SOLUTION

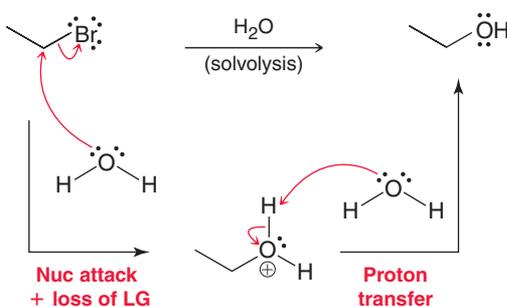
The substrate is primary, so the reaction must proceed via an S<sub>N</sub>2 process, rather than S<sub>N</sub>1. An S<sub>N</sub>1 mechanism cannot be invoked in this case, because a primary carbocation would be too unstable to form.

In an S<sub>N</sub>2 process, there is one concerted step, and we must determine whether a proton transfer will be necessary either before or after the concerted step:



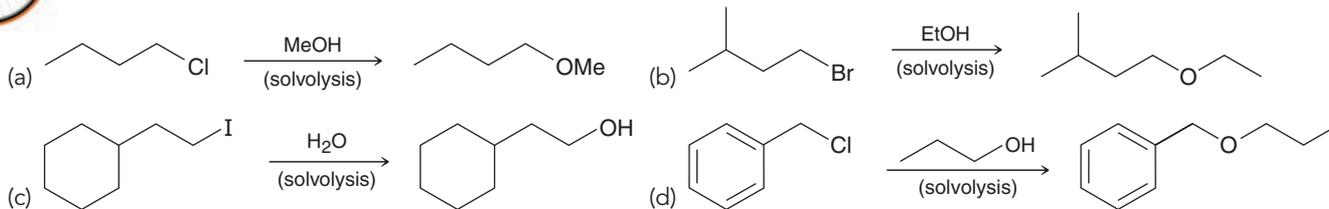
The mechanism does not require a proton transfer before the concerted step, and even if it did, the reagents are not acidic and could not donate a proton anyway. In order to have a proton transfer at the beginning of a mechanism, an acid is required to serve as a proton source. At the end of the mechanism, there will be a proton transfer because the attacking nucleophile (H<sub>2</sub>O) 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:



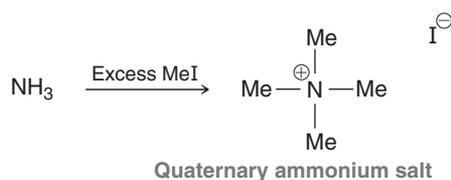


**PRACTICE the skill 7.24** Draw the mechanism for each of the following solvolysis reactions:



**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.



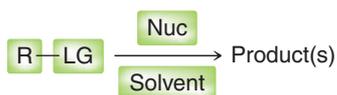
need more PRACTICE? Try Problems 7.53, 7.64, 7.66

## 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 7.25). We must learn to look at all four factors, one by one, and to determine whether the factors favor  $S_N1$  or  $S_N2$ .



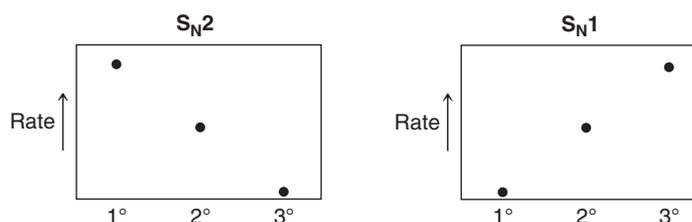
**FIGURE 7.25**

The four factors that determine which mechanism predominates.

### The Substrate

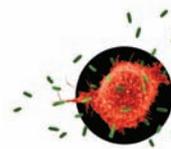
The identity of the substrate is the most important factor in distinguishing between  $S_N2$  and  $S_N1$ . Earlier in the chapter, we saw different trends for  $S_N2$  and  $S_N1$  reactions. These trends are compared in the charts in Figure 7.26.

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 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 7.26**

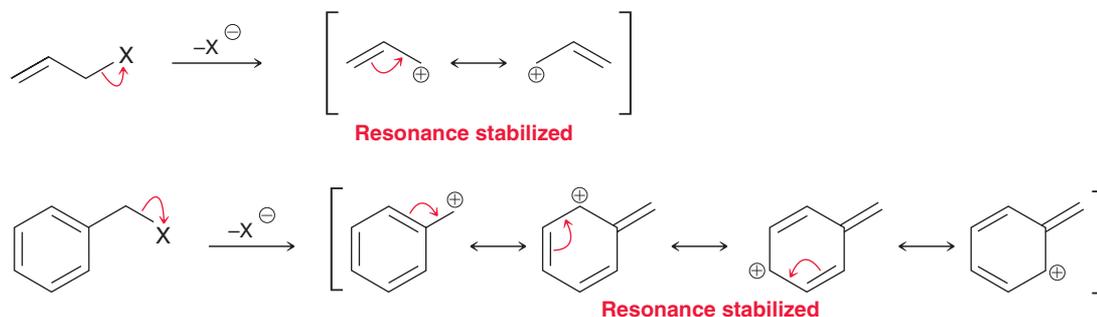
Substrate effects on the rates of  $S_N2$  and  $S_N1$  processes.



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



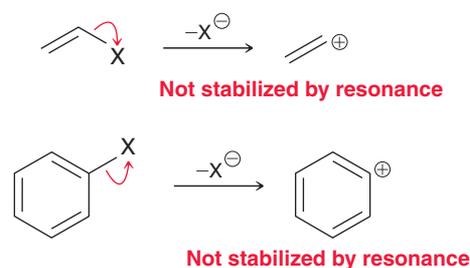
These substrates can react via an  $S_N2$  mechanism because they are relatively unhindered, and they can react via an  $S_N1$  mechanism because loss of a leaving group generates a resonance-stabilized carbocation:



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:



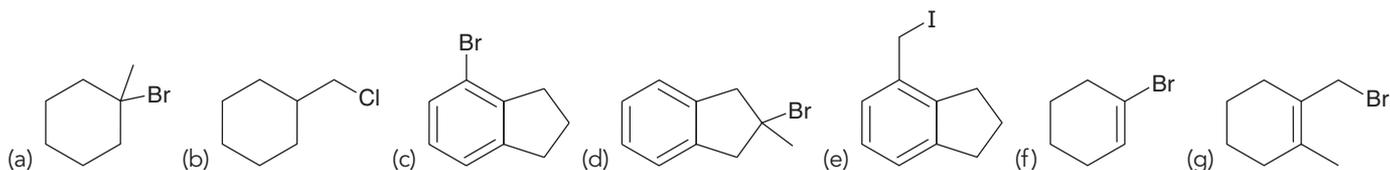
To summarize:

- Primary substrates favor  $S_N2$ .
- Tertiary substrates favor  $S_N1$ .
- Secondary substrates and allylic and benzylic substrates can 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 (remember the hourglass analogy from Section 7.5). 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).

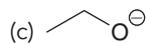
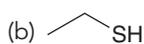
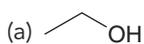
We must therefore learn to identify nucleophiles as strong or weak. The strength of a nucleophile is determined by many factors that were first discussed in Section 6.7. Figure 7.27 shows some strong and weak nucleophiles that we will encounter.

**FIGURE 7.27**  
Some common nucleophiles grouped according to strength.

Common nucleophiles			
Strong			Weak
$I^-$	$HS^-$	$HO^-$	$F^-$
$Br^-$	$H_2S$	$RO^-$	$H_2O$
$Cl^-$	$RSH$	$N\equiv C^-$	$ROH$

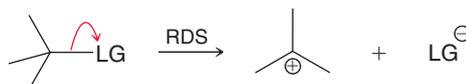
### CONCEPTUAL CHECKPOINT

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



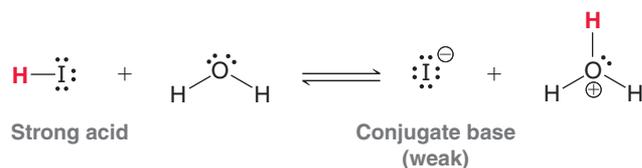
### The Leaving Group

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:

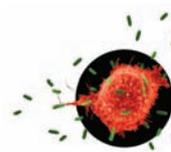


We have already seen that the rate of this step is very sensitive to the stability of the carbocation, but it is also sensitive to the stability of the leaving group. The leaving group must be highly stabilized in order for an  $S_N1$  process to be effective.

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 7.28 shows a list of good leaving groups, all of which are the conjugate bases of strong acids. In contrast, hydroxide



	Acid	pK <sub>a</sub>	Conjugate base	
Strongest acid ↑	I—H	−11	I <sup>−</sup>	Good leaving groups
	Br—H	−9	Br <sup>−</sup>	
	Cl—H	−7	Cl <sup>−</sup>	
		−3		
		−2		
-----				
Weakest acid ↓		15.7	HO <sup>−</sup>	Bad leaving groups
		16		
		18		
		38		
			Least stable base ↑	

FIGURE 7.28

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.

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.

The most commonly used leaving groups are halides and **sulfonate ions** (Figure 7.29). 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.

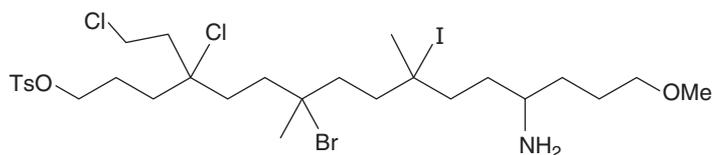
Halides			Sulfonate ions		
Iodide	Bromide	Chloride	Tosylate	Mesylate	Triflate

FIGURE 7.29  
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.  
 (b) Identify each position where an  $S_N1$  reaction is likely to occur.

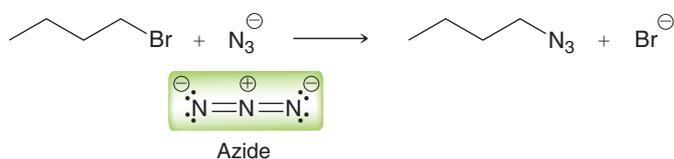


### Solvent Effects

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 polar protic and polar aprotic solvents. **Polar 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 polar protic solvents are used for  $S_N1$  reactions, while polar aprotic solvents are used to favor  $S_N2$  reactions.

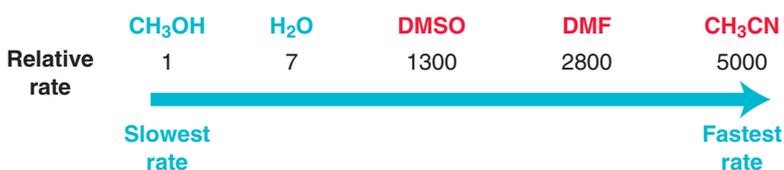
The effect of polar aprotic solvents on the rate of  $S_N2$  reactions is significant. For example, consider the reaction between bromobutane and an azide ion:



The rate of this reaction is highly dependent on the choice of solvent. Figure 7.30 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 polar protic solvents.

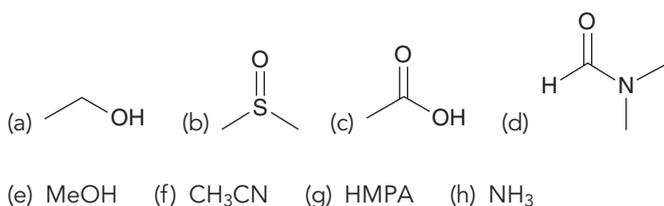
**FIGURE 7.30**

Relative rates of an  $S_N2$  process in a variety of solvents. Polar protic solvents are shown in blue. Polar aprotic solvents are shown in red.

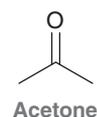


**CONCEPTUAL CHECKPOINT**

**7.29** Does each of the following solvents favor an  $S_N2$  reaction or an  $S_N1$  reaction?



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



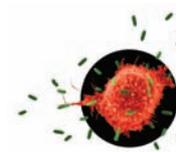
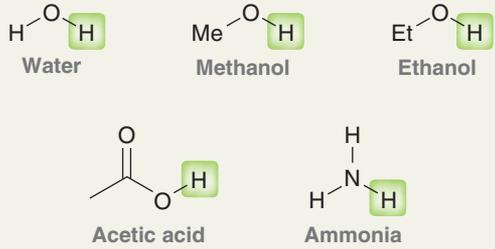
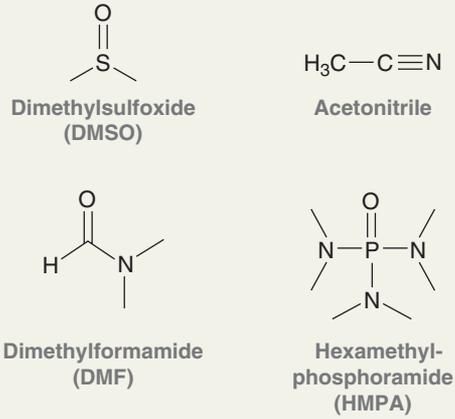
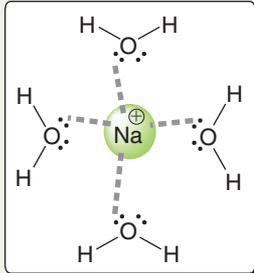
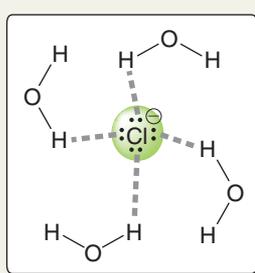
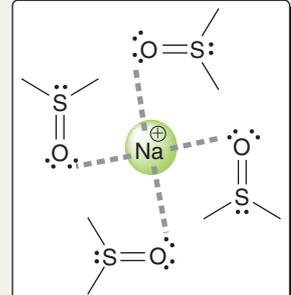
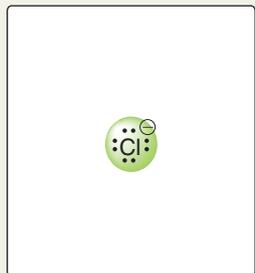
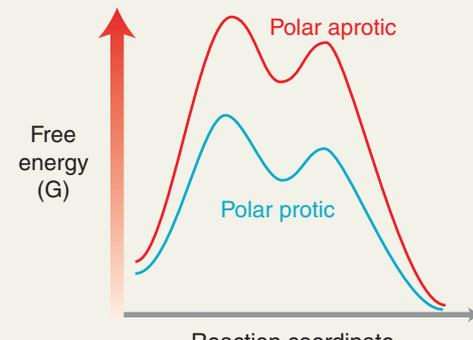
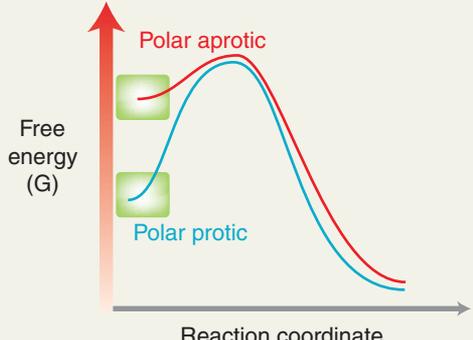
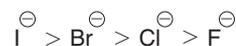


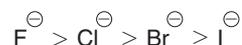
TABLE 7.2 THE EFFECTS OF POLAR PROTIC SOLVENTS AND POLAR APROTIC SOLVENTS

	POLAR PROTIC	POLAR APROTIC
Definition	Polar 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	 <p>Water      Methanol      Ethanol</p> <p>Acetic acid      Ammonia</p>	 <p>Dimethylsulfoxide (DMSO)      Acetonitrile</p> <p>Dimethylformamide (DMF)      Hexamethylphosphoramide (HMPA)</p>
Function	<p>Polar 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:</p> <div style="display: flex; justify-content: space-around;"> <div style="text-align: center;">  <p>The lone pairs on the oxygen atoms of H<sub>2</sub>O stabilize the cation.</p> </div> <div style="text-align: center;">  <p>Hydrogen-bonding interactions stabilize the anion.</p> </div> </div> <p>As a result, anions and cations are both solvated and surrounded by a solvent shell.</p>	<p>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:</p> <div style="display: flex; justify-content: space-around;"> <div style="text-align: center;">  <p>The lone pairs on the oxygen atoms of DMSO stabilize the cation.</p> </div> <div style="text-align: center;">  <p>The anion is not stabilized by the solvent.</p> </div> </div> <p>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.</p>
Effects	<p>Favors S<sub>N</sub>1. Polar protic solvents favor S<sub>N</sub>1 by stabilizing polar intermediates and transition states:</p> 	<p>Favors S<sub>N</sub>2. Polar aprotic solvents favor S<sub>N</sub>2 by raising the energy of the nucleophile, giving a smaller E<sub>a</sub>:</p> 

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 polar protic solvents, the following order is observed:



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



Why the reversal of order? Fluoride is the strongest because it is the least stable anion. In polar 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	Polar protic

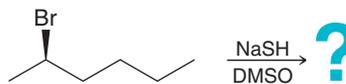
## SKILLBUILDER



### 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:

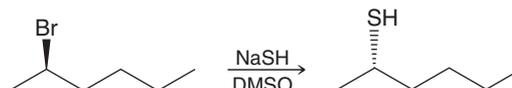


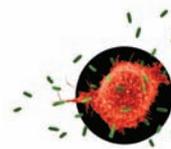
#### SOLUTION

Analyze the four factors one by one:

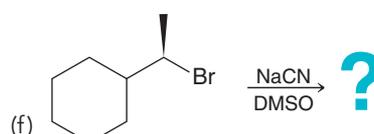
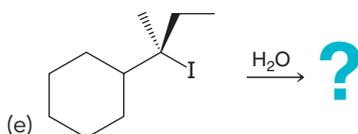
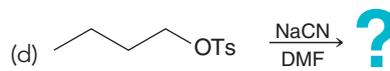
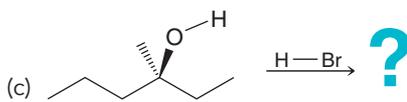
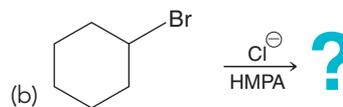
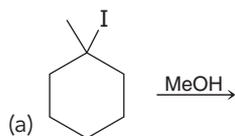
- Substrate.** The substrate is secondary. If it were primary, we would predict  $S_N2$ , and if it were tertiary, we would predict  $S_N1$ . But with a secondary substrate, it could be either, so we move on to the next factor.
- Nucleophile.** NaSH indicates that the nucleophile is  $HS^-$  (remember that  $Na^+$  is just the counter ion).  $HS^-$  is a strong nucleophile, which favors  $S_N2$ .
- Leaving Group.**  $Br^-$  is a good leaving group. This factor alone does not indicate a preference for either  $S_N1$  or  $S_N2$ .
- 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:



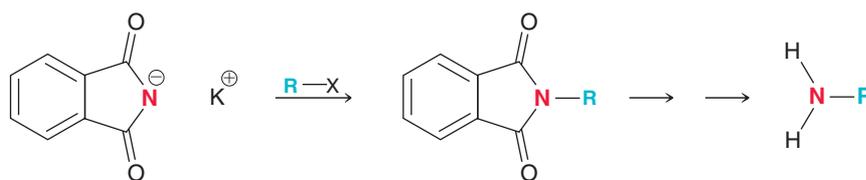


**PRACTICE the skill** 7.31 Determine whether each of the following reactions proceeds via an  $S_N1$  or  $S_N2$  mechanism and then draw the product(s) of the reaction:

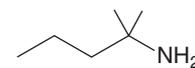


**APPLY the skill**

7.32 In Chapter 23, we will learn several methods for making primary amines ( $\text{RNH}_2$ ). 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

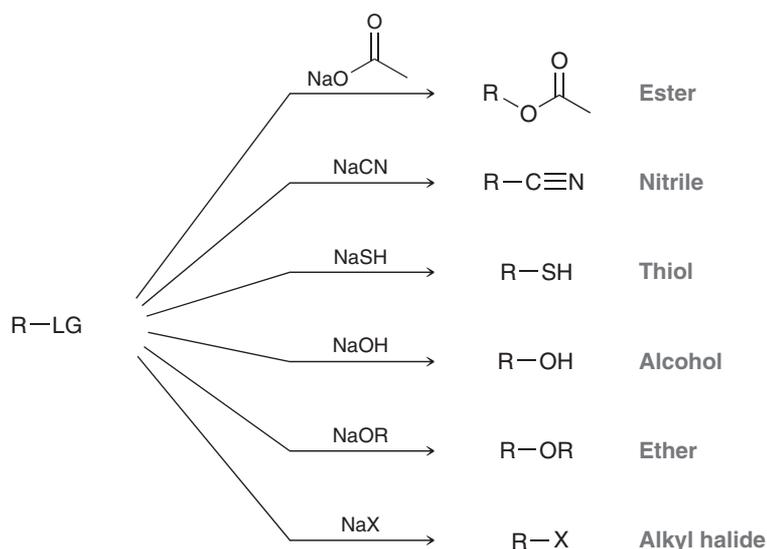
## 7.9 Selecting Reagents to Accomplish Functional Group Transformation

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



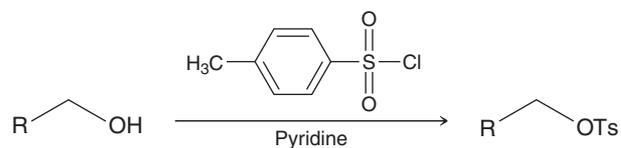
A wide range of nucleophiles can be used, providing a great deal of versatility in the type of products that can be formed with substitution reactions. Figure 7.31 shows some of the types of compounds that can be synthesized using substitution reactions. When selecting reagents for a substitution reaction, remember the following tips:

- **Substrate.** The identity of the substrate indicates which mechanism to use. If the substrate is primary, the reaction must proceed via an  $S_N2$  process. If the substrate is tertiary, the reaction must proceed via an  $S_N1$  process. 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  $S_N2$  mechanism (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 polar protic solvent. For an  $S_N2$  reaction, use a strong nucleophile in a polar aprotic solvent.

**FIGURE 7.31**

Various products that can be obtained via substitution reactions.

- *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):



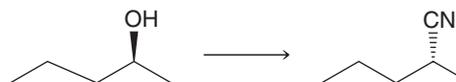
## SKILLBUILDER

### 7.9 IDENTIFYING REAGENTS NECESSARY FOR A SUBSTITUTION REACTION



#### LEARN the skill

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

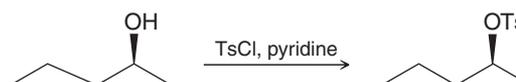


#### SOLUTION

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

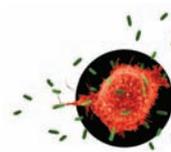
(a) *Substrate.* The substrate is secondary, so it could go either way. In general, choose  $S_N2$ , because it gives greater control. In this particular case, an  $S_N2$  pathway must be used because the product is formed only through inversion of configuration. Now choose reagents that favor  $S_N2$ .

(b) *Leaving Group.* The OH is a bad leaving group and must be converted into a better leaving group. When performing an  $S_N2$  reaction, the OH should be converted into a tosylate by using TsCl and pyridine:



**Step 1**  
Analyze the substrate and the stereochemical outcome.

**Step 2**  
Analyze the leaving group.

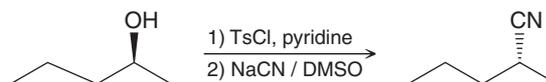


Notice that the stereoisomerism does not change when the OH group is converted into a tosylate group. If the OH is on a wedge, then the tosylate group will also be on a wedge.

**Step 3**  
Choose conditions that favor the required mechanism.

(c) *Nucleophile*. In order to accomplish the desired transformation, the nucleophile needs to be cyanide ( $\text{CN}^-$ ). Cyanide is a strong nucleophile, which supports an  $\text{S}_{\text{N}}2$  process.

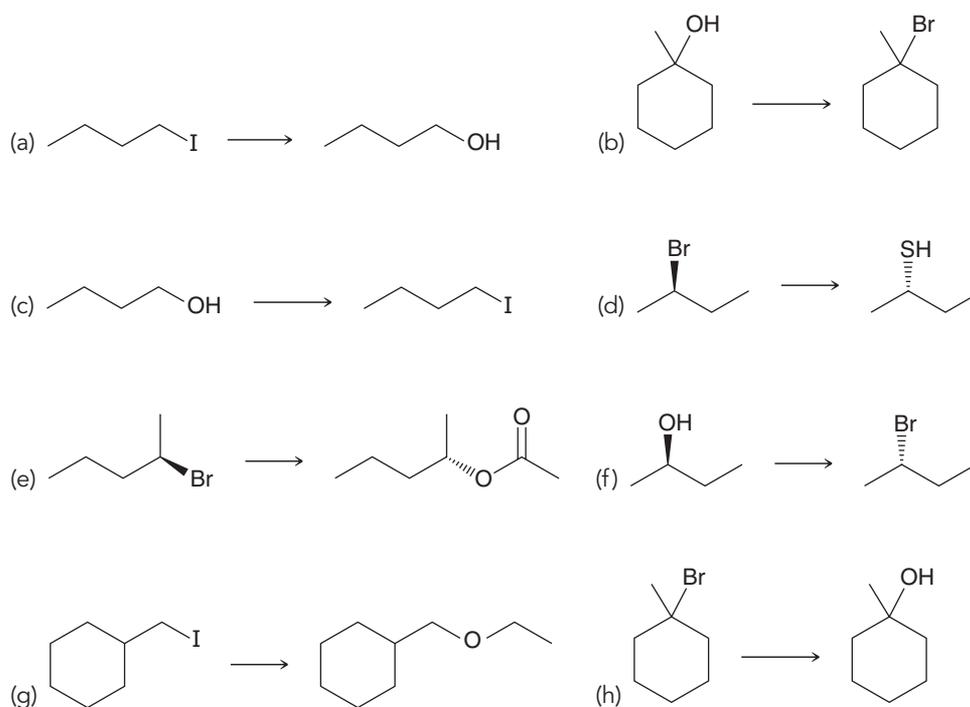
(d) *Solvent*. In order to favor an  $\text{S}_{\text{N}}2$  process, a polar aprotic solvent such as DMSO should be used:



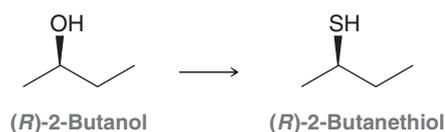
Notice that the conversion of the OH into a tosylate and the  $\text{S}_{\text{N}}2$  reaction are two separate synthetic steps, so we place the numbers 1 and 2 before the sets of reagents to indicate that they are separate reactions.



**PRACTICE the skill** 7.33 Identify the reagents you would use to accomplish each of the following transformations:



**APPLY the skill** 7.34 What reagents would you use to accomplish a substitution with retention of configuration; for example:

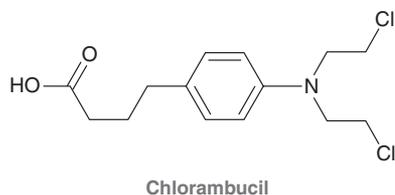


**need more PRACTICE?** Try Problems 7.59, 7.60, 7.63

## MEDICALLY SPEAKING )))

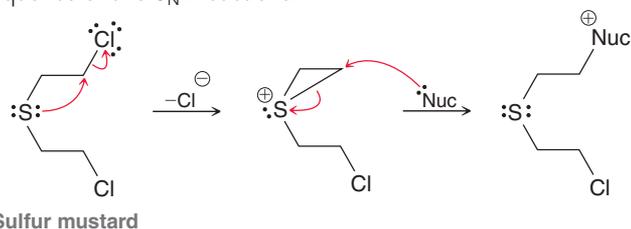
### Pharmacology and Drug Design

*Pharmacology* is the study of how drugs interact with biological systems, including the mechanisms that explain drug action. Pharmacology is a very important field of study because it serves as the basis for the design of new drugs. In this section, we will explore one specific example, the design and development of chlorambucil, an antitumor agent:

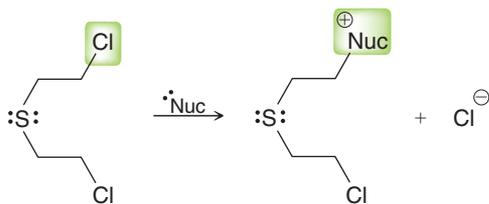


Chlorambucil was designed by chemists using principles that we have learned in this and previous chapters. The story of chlorambucil begins with a toxic compound called sulfur mustard.

This compound was first used as a chemical weapon in World War I. It was sprayed as an aerosol mixture with other chemicals and exhibited a characteristic odor similar to that of mustard plants, thus the name *mustard gas*. Sulfur mustard is a powerful alkylating agent. The mechanism of alkylation involves a sequence of two  $S_N2$  reactions:

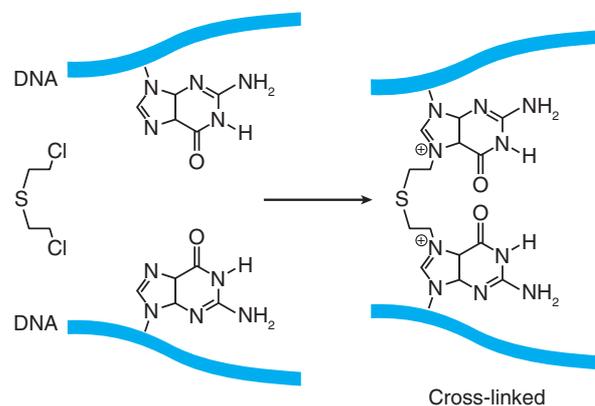


The first substitution reaction is an intramolecular  $S_N2$  process in which a lone pair on the sulfur serves as a nucleophile, expelling chloride as a leaving group. The second reaction is another  $S_N2$  process involving attack of an external nucleophile. The net result is the same as if the nucleophile had attacked directly:



The reaction occurs much more rapidly than a regular  $S_N2$  process on a primary alkyl chloride because the sulfur atom assists in ejecting chloride as a leaving group. The role that sulfur plays in this reaction is called *anchimeric assistance*.

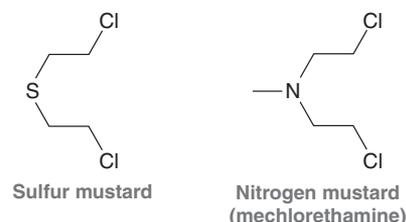
Each molecule of sulfur mustard has two chloride ions and is, therefore, capable of alkylating DNA two times. This causes individual strands of DNA to cross-link (Figure 7.32). Cross-linking of DNA prevents the DNA from replicating and ultimately leads to cell death. The profound impact of sulfur mustard on cell function inspired research on the use of this compound as an antitumor agent. In 1931, sulfur mustard was injected directly into tumors



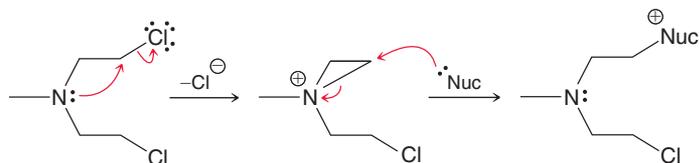
**FIGURE 7.32**

Sulfur mustard can alkylate two different strands of DNA, causing cross-linking.

with the intention of stopping tumor growth by interrupting the rapid division of the cancerous cells. Ultimately, sulfur mustard was found to be too toxic for clinical use, and the search began for a similar, less toxic, compound. The first such compound to be produced was a nitrogen analogue called mechlorethamine:

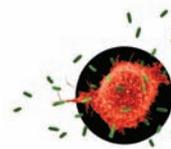


Mechlorethamine is a “nitrogen mustard” that reacts with nucleophiles in the same way as sulfur mustard, via two successive substitution reactions. The first reaction is an intramolecular  $S_N2$  process involving anchimeric assistance from the nitrogen atom; the second reaction is another  $S_N2$  process involving attack of an external nucleophile:

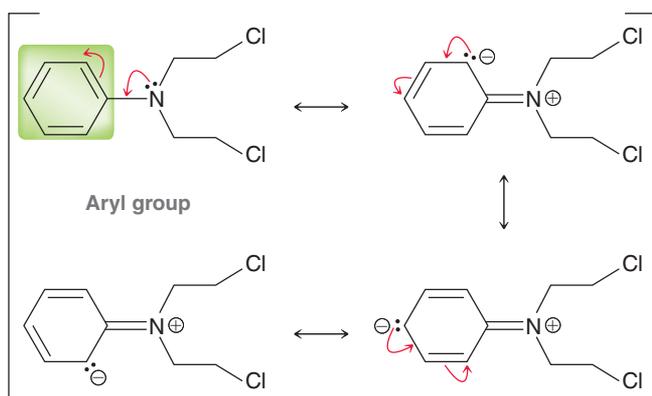


This nitrogen mustard is also capable of alkylating DNA, causing cell death, but is less toxic than sulfur mustard. The discovery of mechlorethamine launched the field of chemotherapy, the use of chemical agents to treat cancer.

Mechlorethamine is still in use today, in combination with other agents, for the treatment of advanced Hodgkin’s lymphoma and chronic lymphocytic leukemia (CLL). The use of mechlorethamine is limited, though, by its high rate of reactivity with water. This limitation led to a search for other analogues. Specifically, it was found that replacing the methyl group with an aryl group had

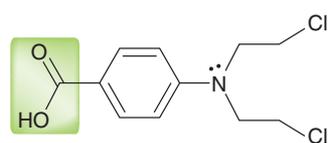


the effect of delocalizing the lone pair through resonance, rendering the lone pair less nucleophilic:



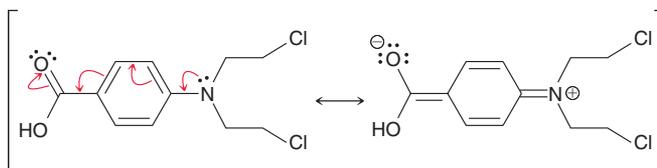
The resonance structures above all exhibit a negative charge on a carbon atom, and therefore, these resonance structures do not contribute very much to the overall resonance hybrid. Nevertheless, they are valid resonance structures, and they do contribute some character. As a result, the lone pair on the nitrogen atom is delocalized (it is spread out over the aryl group) and less nucleophilic. This decreased nucleophilicity is manifested in a slower rate of anchimeric assistance from the nitrogen atom. The compound can still function as an antitumor agent, but its rate of reactivity with water is reduced.

Introduction of the aryl group (in place of the methyl group) might have solved one problem, but it created another problem. Specifically, this new compound was not water soluble, which prevented intravenous administration. This problem was solved by introducing a carboxylate group, which rendered the compound water soluble:



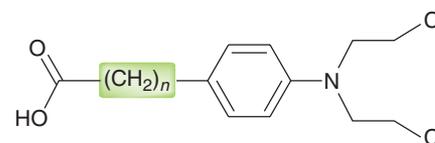
This group renders the compound water soluble

But, once again, solving one problem created another. Now, the lone pair on the nitrogen atom was too delocalized, because of the following resonance structure:

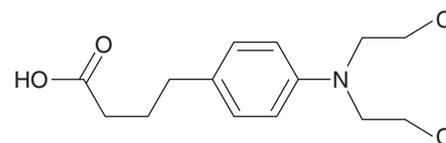


The lone pair was delocalized onto an oxygen atom, and a negative charge on an oxygen atom is much more stable than a negative charge on a carbon atom. The delocalization effect was so pronounced that the reagent no longer functioned as an antitumor agent. The lone pair on the nitrogen atom was not sufficiently nucleophilic to participate in anchimeric assistance at an appreciable rate. Solving all these problems required a way to maintain

water solubility without overly stabilizing the lone pair on the nitrogen atom. This was achieved by placing methylene groups ( $\text{CH}_2$  groups) between the carboxylate group and the aryl group:



This way, the nitrogen lone pair is no longer participating in resonance with the carboxylate group, but the presence of the carboxylate group is still able to render the compound water soluble. This final change solves all of the problems. In theory, only one methylene group is needed to ensure that the nitrogen lone pair is not overly delocalized by resonance. But in practice, research with various compounds indicated that optimal reactivity was achieved when three methylene groups were placed between the carboxylate group and the aryl group:



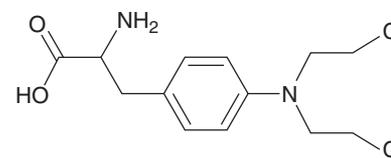
Chlorambucil

The resulting compound, called chlorambucil, was marketed under the trade name Lukeran<sup>TM</sup> by GlaxoSmithKline. It was mainly used for treatment of CLL, until other, more powerful agents were discovered.

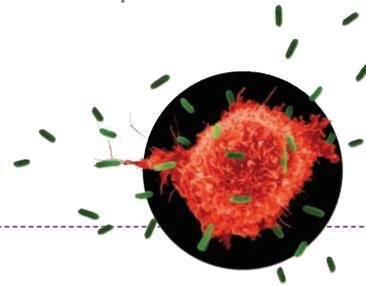
The design and development of chlorambucil is just one example of drug design, but it demonstrates how an understanding of pharmacology, coupled with an understanding of the first principles of organic chemistry, enables chemists to design and create new drugs. Each year, organic chemists and biochemists make enormous strides in the exciting fields of pharmacology and drug design.

### CONCEPTUAL CHECKPOINT

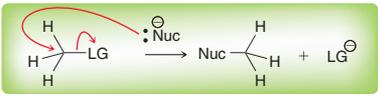
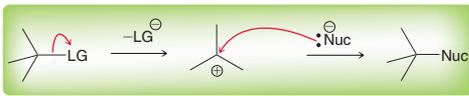
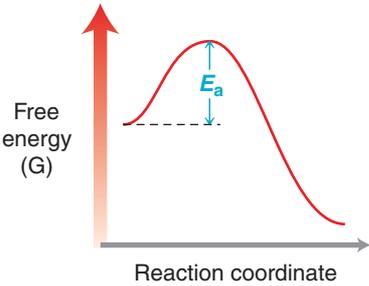
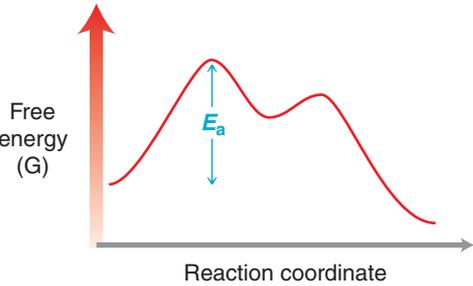
**7.35** Melphalan is a chemotherapy drug used in the treatment of multiple myeloma and ovarian cancer. Melphalan is an alkylating agent belonging to the nitrogen mustard family. Draw a likely mechanism for the alkylation process that occurs when a nucleophile reacts with melphalan:



Melphalan



## REVIEW OF REACTIONS

	S <sub>N</sub> 2	S <sub>N</sub> 1
Mechanism		
Energy diagram		
Rate equation	Rate = $k$ [substrate] [nucleophile]	Rate = $k$ [substrate]
Substrate effects	Methyl > 1° > 2° > 3°	3° > 2° > 1° > methyl
Stereochemistry	Inversion of configuration	Racemization (with slight preference for inversion due to ion pairs)

## REVIEW OF CONCEPTS AND VOCABULARY

## SECTION 7.1

- **Substitution reactions** exchange one functional group for another.
- The electrophile is called the **substrate**, and it must contain a **leaving group**.

## SECTION 7.2

- There are two ways to name halogenated organic compounds. The systematic name treats the compound as a **haloalkane**, while the common name treats the compound as an **alkyl halide**.
- 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 α position.
- Alkyl halides are classified as **primary**, **secondary**, and **tertiary** according to the number of alkyl groups connected to the α position.

## SECTION 7.3

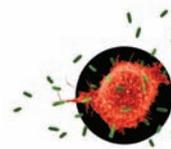
- In a **concerted process**, nucleophilic attack and loss of the leaving group occur simultaneously.
- In a **stepwise process**, first the leaving group leaves, and then the nucleophile attacks.

## SECTION 7.4

- Evidence for the concerted mechanism, called **S<sub>N</sub>2**, includes the observation of a **second-order** rate equation. The S<sub>N</sub>2 process is said to be **bimolecular**.
- Methyl halides and primary alkyl halides react most quickly, while tertiary alkyl halides are essentially unreactive toward S<sub>N</sub>2.
- When the α position is a chirality center, the reaction proceeds with **inversion of configuration**. The preference for **back-side attack** stems from the need for constructive overlap of orbitals (according to MO theory). S<sub>N</sub>2 reactions are said to be **stereospecific** because the configuration of the product is determined by the configuration of the substrate.

## SECTION 7.5

- Evidence for the stepwise mechanism, called **S<sub>N</sub>1**, includes the observation of a **first-order** rate equation. These reactions are said to be **unimolecular**.
- The first step of an S<sub>N</sub>1 process (loss of a leaving group) is the **rate-determining step**.
- The carbocation intermediate can be attacked from either side, leading to **inversion of configuration** and **retention of configuration**. There is usually a slight preference for the inversion product due to the formation of ion pairs.



### SECTION 7.6

- A proton transfer is necessary at the beginning of an  $S_N1$  mechanism if the leaving group is an OH group.
- A carbocation rearrangement can take place if it will lead to a more stable carbocation intermediate.
- A proton transfer is necessary at the end of an  $S_N1$  mechanism if the nucleophile is neutral (not negatively charged). When the solvent functions as a nucleophile, the reaction is called a **solvolysis** reaction.

### SECTION 7.7

- A proton transfer is necessary at the beginning of an  $S_N2$  mechanism if the leaving group is an OH group.
- A proton transfer must occur at the end of an  $S_N2$  mechanism if the nucleophile is neutral.

### SECTION 7.8

- There are four factors that impact the competition between the  $S_N2$  mechanism and  $S_N1$ : (1) the substrate, (2) the nucleophile, (3) the leaving group, and (4) the solvent.
- The most common leaving groups are halides and **sulfonate ions**. Of the sulfonate ions, the most common is the **tosylate** group.
- **Polar protic** solvents favor  $S_N1$ , while **polar aprotic** solvents favor  $S_N2$ .

### SECTION 7.9

- Depending on the type of nucleophile used, substitution reactions can be used to produce a wide range of different compounds.

## KEY TERMINOLOGY

alkyl halide 284  
 alpha ( $\alpha$ ) position 284  
 back-side attack 291  
 beta ( $\beta$ ) position 284  
 bimolecular 290  
 first-order 297  
 haloalkane 284

inversion of configuration 291  
 leaving group 282  
 organohalide 284  
 polar aprotic solvent 318  
 polar protic solvent 318  
 primary alkyl halide 284  
 rate-determining step 298

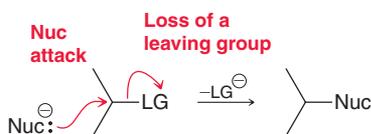
retention of configuration 301  
 secondary alkyl halide 284  
 second-order 290  
 $S_N1$  297  
 $S_N2$  290  
 solvolysis 305  
 stereospecific 291

substitution reaction 282  
 substrate 282  
 sulfonate ions 317  
 tertiary alkyl halide 284  
 tosylate 317  
 unimolecular 297

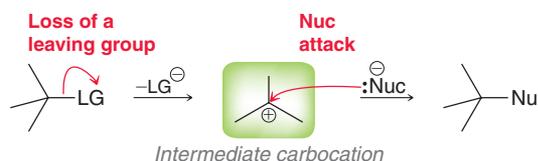
## SKILLBUILDER REVIEW

### 7.1 DRAWING THE CURVED ARROWS OF A SUBSTITUTION REACTION

**CONCERTED MECHANISM** Two curved arrows drawn in one step. Nucleophilic attack is accompanied by simultaneous loss of a leaving group.



**STEPWISE MECHANISM** Two curved arrows drawn in two separate steps. Leaving group leaves to form a carbocation intermediate, followed by a nucleophilic attack.



Try Problems 7.2–7.5, 7.6a

### 7.2 DRAWING THE PRODUCT OF AN $S_N2$ PROCESS

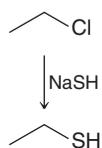
Replace the LG with the Nuc, and draw inversion of configuration.



Try Problems 7.7, 7.8, 7.45, 7.46, 7.56, 7.61

7.3 DRAWING THE TRANSITION STATE OF AN S<sub>N</sub>2 PROCESS

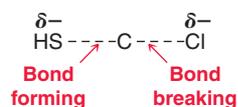
**EXAMPLE** Draw the transition state.



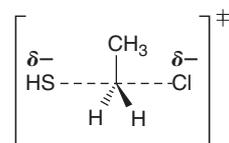
**STEP 1** Identify the nucleophile and the leaving group.



**STEP 2** Draw the carbon atom with the Nuc and LG on either side.



**STEP 3** Draw the three groups attached to the carbon atom. Place brackets and the symbol indicating a transition state.



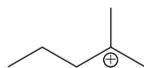
Try Problems 7.9–7.11, 7.46, 7.64e

7.4 DRAWING THE CARBOCATION INTERMEDIATE OF AN S<sub>N</sub>1 PROCESS

**STEP 1** Identify the leaving group.



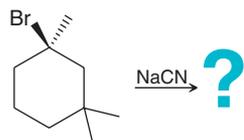
**STEP 2** Draw all three groups pointing away from each other.



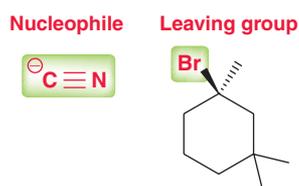
Try Problems 7.14, 7.15, 7.50, 7.51

7.5 DRAWING THE PRODUCTS OF AN S<sub>N</sub>1 PROCESS

**EXAMPLE** Predict the products.



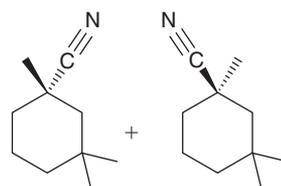
**STEP 1** Identify the nucleophile and the leaving group.



**STEP 2** Replace LG with Nuc.



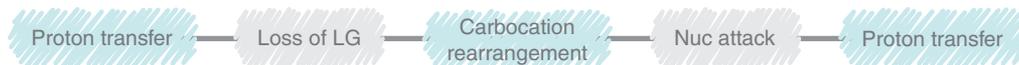
**STEP 3** If chirality center, then S<sub>N</sub>1 will produce pair of enantiomers.



Try Problems 7.16, 7.17, 7.48, 7.49, 7.55

7.6 DRAWING THE COMPLETE MECHANISM OF AN S<sub>N</sub>1 PROCESS

There are two core steps (gray) and three possible additional steps (blue).

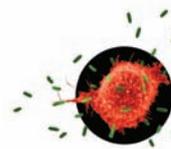


Does the LG need to be protonated before it can leave?  
If OH group, then yes.

Is the nucleophile ultimately positioned at a different location than the leaving group?  
If yes, then there is a carbocation rearrangement.

Is the nucleophile neutral?  
If yes, then there will be a proton transfer at the end of the mechanism in order to remove the positive charge.

Try Problems 7.21, 7.22, 7.23, 7.48, 7.49, 7.52, 7.54, 7.65



### 7.7 DRAWING THE COMPLETE MECHANISM OF AN $S_N2$ PROCESS

There is one core step (concerted) and two possible additional steps.



Does the LG need to be protonated first?  
If OH group, then yes.

Is the nucleophile neutral?  
If yes, then there will be a proton transfer at the end of the mechanism in order to remove the positive charge.

Try Problems 7.24, 7.25, 7.53, 7.64, 7.66

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

#### RELEVANT FACTORS

	$S_N2$	$S_N1$
Substrate	Methyl or primary	Tertiary
Nuc	Strong Nuc	Weak Nuc
LG	Good LG	Excellent LG
Solvent	Polar aprotic	Polar protic

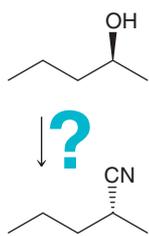
#### EXAMPLE



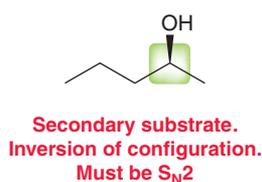
Try Problems 7.31, 7.32, 7.37, 7.38, 7.40, 7.41, 7.44, 7.55, 7.57, 7.58

### 7.9 IDENTIFYING THE REAGENTS NECESSARY FOR A SUBSTITUTION REACTION

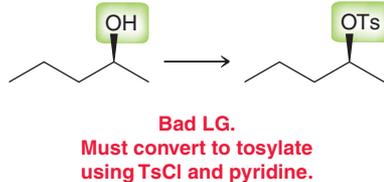
#### EXAMPLE



**STEP 1** Analyze the substrate and the stereochemistry.



**STEP 2** Analyze the LG.



**STEP 3** Use conditions that favor  $S_N2$ : strong Nuc (NaCN) and a polar aprotic solvent (DMSO).

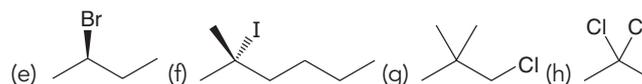
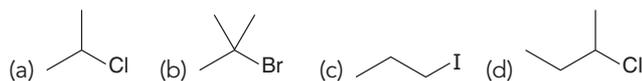
Reagents:  
1. TsCl, py  
2. NaCN, DMSO

Try Problems 7.33, 7.34, 7.59, 7.60, 7.63

## PRACTICE PROBLEMS

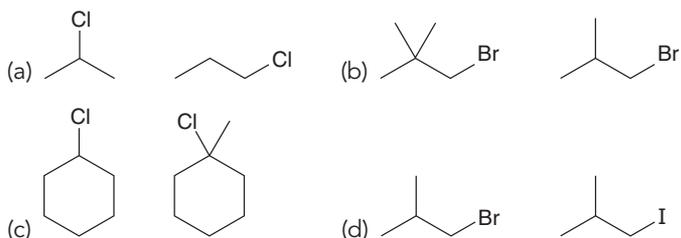
Note: Most of the Problems are available within **WILEY PLUS** WileyPLUS, an online teaching and learning solution.

**7.36** List the systematic name and common name for each of the following compounds:

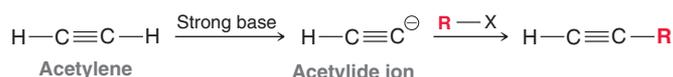


**7.37** Draw all isomers of  $C_4H_9I$ , and then arrange them in order of increasing reactivity toward an  $S_N2$  reaction.

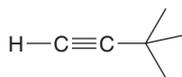
**7.38** For each of the following pairs of compounds, identify which compound would react more rapidly in an  $S_N2$  reaction. Explain your choice in each case.



**7.39** In Chapter 10, we will see that an acetylide ion (formed by treatment of acetylene with a strong base) can serve as a nucleophile in an  $S_N2$  reaction:



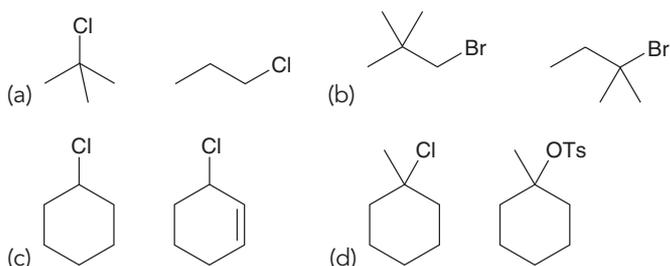
This reaction provides a useful method for making a variety of substituted alkynes. Determine whether this process can be used to make the following alkyne. Explain your answer.



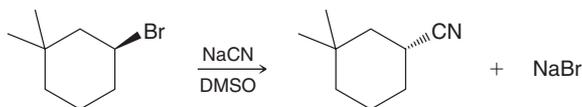
**7.40** Identify the stronger nucleophile:

- (a) NaSH vs.  $\text{H}_2\text{S}$  (c) Methoxide dissolved in methanol vs. methoxide dissolved in DMSO  
 (b) Sodium hydroxide vs. water

**7.41** For each pair of the following compounds, identify which compound would react more rapidly in an  $S_N1$  reaction. Explain your choice in each case.

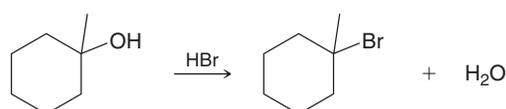


**7.42** Consider the following reaction:



- (a) How would the rate be affected if the concentration of the alkyl halide is doubled?  
 (b) How would the rate be affected if the concentration of sodium cyanide is doubled?

**7.43** Consider the following reaction:

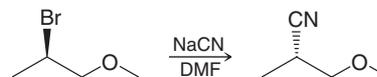


- (a) How would the rate be affected if the concentration of the alcohol is doubled?  
 (b) How would the rate be affected if the concentration of HBr is doubled?

**7.44** Classify each of the following solvents as protic or aprotic:

- (a) DMF (c) DMSO (e) Ammonia  
 (b) Ethanol (d) Water

**7.45** Consider the following  $S_N2$  reaction:

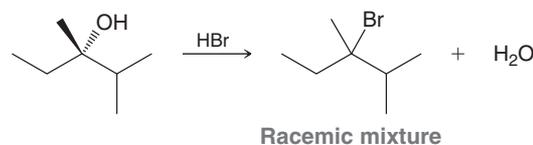


- (a) Assign the configuration of the chirality center in the substrate.  
 (b) Assign the configuration of the chirality center in the product.  
 (c) Does this  $S_N2$  process proceed with inversion of configuration? Explain.

**7.46** Draw the transition state for the reaction between ethyl iodide and sodium acetate

**7.47** (*S*)-2-Iodopentane undergoes racemization in a solution of sodium iodide in DMSO. Explain.

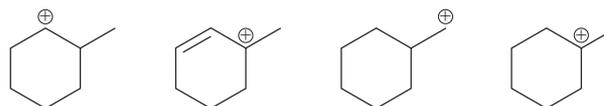
**7.48** When the following optically active alcohol is treated with HBr, a racemic mixture of alkyl bromides is obtained:



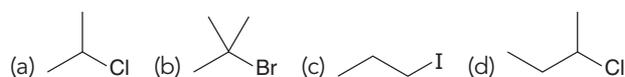
Draw the mechanism of the reaction, and explain the stereochemical outcome.

**7.49** (*R*)-2-Pentanol racemizes when placed in dilute sulfuric acid. Draw a mechanism that explains this stereochemical outcome, and draw an energy diagram of the process.

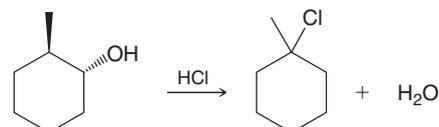
**7.50** List the following carbocations in order of increasing stability:



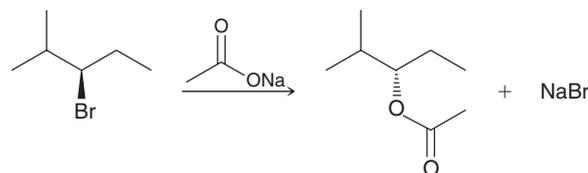
**7.51** Draw the carbocation intermediate that would be formed if each of the following substrates would participate in an  $S_N1$  reaction. In each case, identify the carbocation as being primary, secondary, or tertiary.

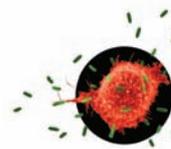


**7.52** Propose a mechanism for the following transformation:

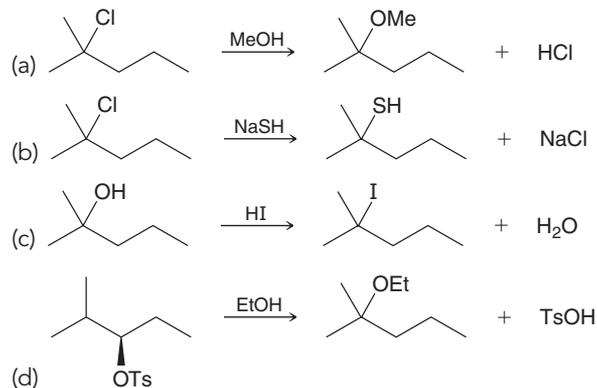


**7.53** Draw the mechanism of the following reaction:

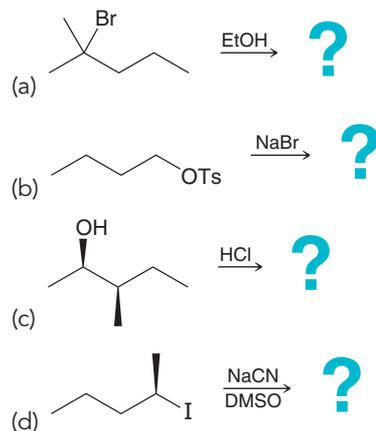




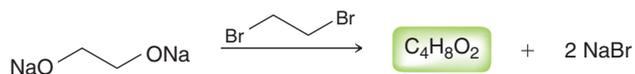
**7.54** Each of the following reactions proceeds via an  $S_N1$  mechanism and will have anywhere from two to five steps, as discussed in Section 7.6. Determine the number of steps for each reaction, and then draw the mechanism in each case:



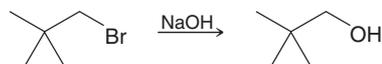
**7.55** Identify the product(s) in each of the following reactions:



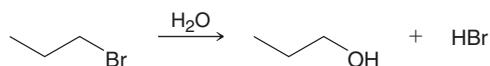
**7.56** Identify the product of the following reaction:



**7.57** The following reaction is very slow. Identify the mechanism, and explain why the reaction is so slow.

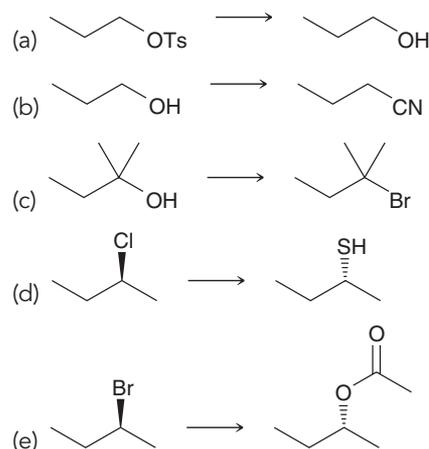


**7.58** The following reaction is very slow:

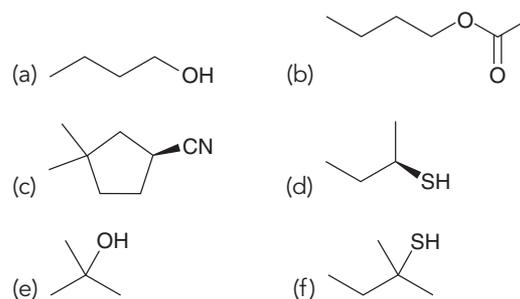


- Identify the mechanism.
- Explain why the reaction is so slow.
- When hydroxide is used instead of water, the reaction is very rapid. Draw the mechanism of this reaction, and explain why it is so fast.

**7.59** Identify the reagents you would use to achieve each of the following transformations:



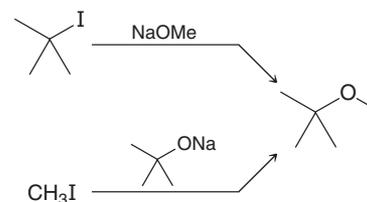
**7.60** Each of the following compounds can be prepared with an alkyl iodide and a suitable nucleophile. In each case, identify the alkyl iodide and the nucleophile that you would use.



**7.61** What products would you expect from the reaction between (S)-2-iodobutane and each of the following nucleophiles?

- (a) NaSH      (b) NaSEt      (c) NaCN

**7.62** Below are two potential methods for preparing the same ether, but only one of them is successful. Identify the successful approach and explain your choice.

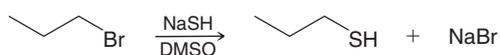


**7.63** Identify the reagent you would use to accomplish each of the following transformations:

- Cyclobutanol  $\rightarrow$  bromocyclobutane
- tert*-Butanol  $\rightarrow$  *tert*-butyl chloride
- Ethyl chloride  $\rightarrow$  ethanol

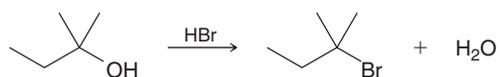
## INTEGRATED PROBLEMS

**7.64** Consider the following  $S_N2$  reaction:



- Draw the mechanism of this reaction.
- What is the rate equation of this reaction?
- What would happen to the rate if the solvent is changed from DMSO to ethanol?
- Draw an energy diagram of the reaction above.
- Draw the transition state of this reaction.

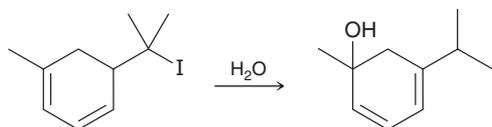
**7.65** Consider the following substitution reaction:



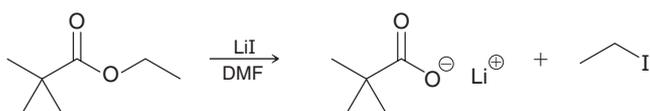
- Determine whether this reaction proceeds via an  $S_N1$  or  $S_N2$  process.

## CHALLENGE PROBLEMS

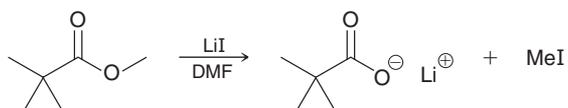
**7.67** Propose a mechanism for the following transformation:



**7.68** When the following ester is treated with lithium iodide in DMF, a carboxylate ion is obtained:

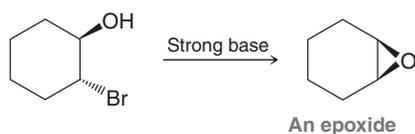


- Draw the mechanism of this reaction.
- When the methyl ester is used as the substrate, the reaction is 10 times faster:



Explain the increase in rate.

**7.69** When (1*R*,2*R*)-2-bromocyclohexanol is treated with a strong base, an epoxide (cyclic ether) is formed. Suggest a mechanism for formation of the epoxide:



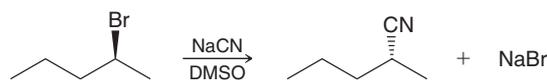
(b) Draw the mechanism of this reaction.

(c) What is the rate equation of this reaction?

(d) Would the reaction occur at a faster rate if sodium bromide were added to the reaction mixture?

(e) Draw an energy diagram of this reaction.

**7.66** Consider the following substitution reaction:



(a) Determine whether this reaction proceeds via an  $S_N1$  or  $S_N2$  process.

(b) Draw the mechanism of this reaction.

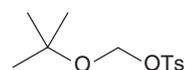
(c) What is the rate equation of this reaction?

(d) Would the reaction occur at a faster rate if the concentration of cyanide were doubled?

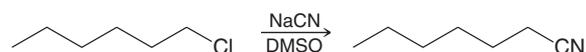
(e) Draw an energy diagram of the reaction above.

**7.70** When butyl bromide is treated with sodium iodide in ethanol, the concentration of iodide quickly decreases but then slowly returns to its original concentration. Identify the major product of the reaction.

**7.71** The following compound can react rapidly via an  $S_N1$  process. Explain why this primary substrate will undergo an  $S_N1$  reaction so rapidly.



**7.72** Consider the reaction below. The rate of this reaction is markedly increased if a small amount of sodium iodide is added to the reaction mixture. The sodium iodide is not consumed by the reaction and is therefore considered to be a catalyst. Explain how the presence of iodide can speed up the rate of the reaction.



**7.73** Propose a mechanism for the following transformation:

