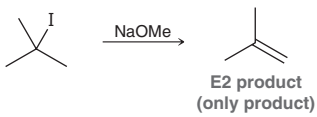
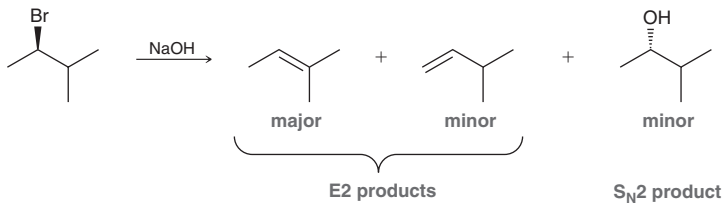
7.10 Evaluating Competing Reactions and Predicting the Major Product

Substitution and elimination reactions are very often in competition with each other. In order to predict the products of a reaction, it is necessary to determine which mechanisms are likely to occur. In some cases, only one mechanism will predominate:



In other cases, two or more mechanisms will compete, giving multiple products, as seen in the following example:



Don't fall into the trap of thinking that there must always be just one product. Sometimes there is, but that is often not the case. The goal is to predict all of the products, and to predict which products are major and which are minor. To accomplish this goal, three steps are required:

1. Determine the function of the reagent.
2. Analyze the substrate and determine the expected mechanism(s).
3. Consider any relevant regiochemical and stereochemical requirements.

Each of these three steps will now be explored individually.

Step One: Determining the Function of the Reagent

The main difference between substitution and elimination is the function of the reagent. A substitution reaction occurs when the reagent functions as a nucleophile, while an elimination reaction occurs when the reagent functions as a base. Nucleophilicity and basicity both involve electron-rich species, but they are not the same concept. While some anions, such as hydroxide, can serve as a nucleophile or a base (Section 7.8), that is not true for all anions. As first described in Section 6.7, nucleophilicity is a kinetic phenomenon and refers to the rate of reaction, while basicity is a thermodynamic phenomenon and refers to the position of equilibrium.

Nucleophilicity is determined by factors such as polarizability and the presence of high electron density (as seen in Section 7.4), while basicity is determined by the stability of a base. In Chapter 3, we saw two methods for assessing the relative stability of a base. In the first method, the strength of a base is determined by assessing the pK_a of its conjugate acid. For example, a bromide ion is an extremely weak base, because its conjugate acid (HBr) is strongly acidic ($pK_a = -9$). The other approach was described in Section 3.4 and involves the use of four factors (ARIO) for determining the relative stability of a base containing a negative charge. For example, a bromide ion has a negative charge on a large atom and is therefore highly stabilized (a weak base). Notice that both approaches provide the same prediction: that bromide is a weak base. On the other hand, bromide is a very strong nucleophile because it is large and polarizable, and it bears a negative charge. This example illustrates that nucleophilicity and basicity do not always parallel each other.

We can classify common reagents as strong bases (if the conjugate acid has a pK_a greater than ~12) or *not* strong bases (if the conjugate acid has a pK_a below 10, then the base is either weak or moderate, but not strong). If we also classify them as either strong or weak nucleophiles, then there are four categories. Each of these four categories is shown in Figure 7.19, with specific examples of each category:

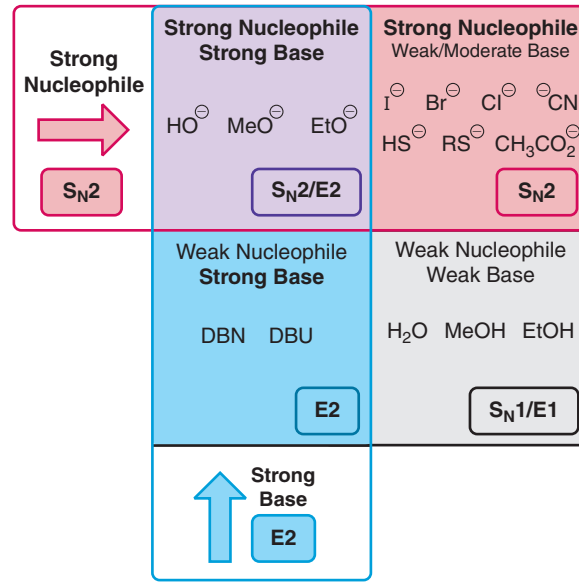


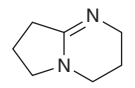
FIGURE 7.19
Classification of common reagents used for substitution and elimination reactions.

Keep in mind that some reagents do not fit perfectly into one of these four categories. For example, ammonia (NH_3) and amines (RNH_2) are excellent nucleophiles for the S_N2 reaction, but they are also fairly good bases. Therefore, they don't fit perfectly in the same category as the weakly basic chloride, and they are not basic enough to be in the same category as hydroxide. Nevertheless, the simplified classification scheme in Figure 7.19 will enable us to make useful predictions regarding the outcomes of many substitution and elimination reactions.

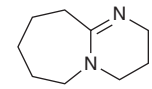
We will now briefly discuss each of the four categories in Figure 7.19. The first category shows reagents that are both strong nucleophiles and strong bases. These reagents include hydroxide (HO^-) and alkoxide ions (RO^-). Such reagents indicate bimolecular processes (S_N2 and E2). Backside attack is slowed by steric hindrance, so S_N2 reactions with hydroxide or alkoxide are efficient only with methyl and primary alkyl halides. As described in Section 7.8, E2 elimination predominates in reactions with secondary alkyl halides. Tertiary alkyl halides do not undergo S_N2 reactions, and such substrates give exclusively E2 products when treated with hydroxide or alkoxide.

The second category in Figure 7.19 shows reagents that function primarily as nucleophiles. That is, they are strong nucleophiles because they are negatively charged, but they are relatively weak bases because they are highly stabilized. Take a moment to evaluate the reagents in this category. Using the ARIO factors we learned in Chapter 3, can you identify the stabilizing feature(s) in each reagent? Some, like the halides and sulfur, are large anions, and the acetate ion (CH_3CO_2Na) is stabilized by resonance. The lone pair on carbon in cyanide is in a stable *sp* hybrid orbital, and the anion is further stabilized by inductive effects from the electronegative nitrogen atom. The use of reagents from this category are ideal for backside attack (S_N2 substitution), with minimal E2 competition.

The third category in Figure 7.19 shows reagents that function almost exclusively as bases. The use of one of these reagents (DBN or DBU) indicates that an E2 elimination reaction will occur, rather than an S_N2 backside attack:

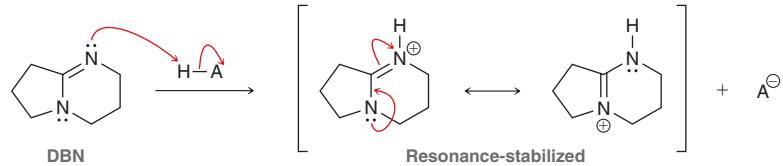


1,5-diazabicyclo[4.3.0]non-5-ene
(DBN)



1,8-diazabicyclo[5.4.0]undec-7-ene
(DBU)

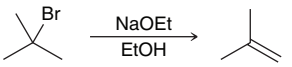
These two compounds are very similar in structure. When either of these compounds is protonated, the resulting positive charge is resonance-stabilized:



The positive charge is spread over two nitrogen atoms, rather than one, so this cation is highly stabilized and therefore weakly acidic. As a result, both DBN and DBU are strongly basic. These examples demonstrate that it is possible for a neutral compound to be a strong base. If an E2 elimination is desired, either DBN or DBU would be a suitable base to use.

The fourth and final category in Figure 7.19 shows reagents that are weak nucleophiles and weak bases. These reagents include water (H_2O) and alcohols (ROH). These compounds are very stable, unreactive molecules, so they are not suitable for bimolecular *attack* (S_N2 or E2). At the same time, their extreme polarity makes them ideal solvents to support carbocation formation. As such, these reagents are generally used for unimolecular processes (S_N1 and E1), as seen in solvolysis reactions (Section 7.9).

It should be noted that you will often encounter reactions in which the reagent is shown as NaOEt together with EtOH, as seen in the following example:



NaOEt is a strong nucleophile/strong base, while EtOH is a weak nucleophile/weak base. Which one is the reagent here? In a situation like this, the strong nucleophile/strong base (NaOEt) is the reagent, while the weak nucleophile/weak base (EtOH) is simply the solvent in which the reagent is dissolved. EtOH is not considered to be the reagent in this case. Indeed, this is the case any time a strong nucleophile/strong base (such as NaOH, or NaOMe, or NaOEt, etc.) is dissolved in a solvent such as H_2O, MeOH or EtOH. In such a case, the solvent functions as the medium in which the reaction occurs, and the strong nucleophile/strong base functions as the reagent. In some cases, the identity of the solvent may not be indicated; nevertheless, it should be understood that there is always a solvent present to ensure that the reactants can mix and react efficiently. In practice, the choice of solvent has a significant impact on reaction outcomes. The effect of solvents on reaction rates will be discussed in Section 7.13.

In summary, determining the function of the reagent (the category to which it belongs) is the first step in predicting the products of substitution and elimination reactions of alkyl halides. If a reagent with strong reactivity is used, a *bimolecular* reaction is expected (Figure 7.20).

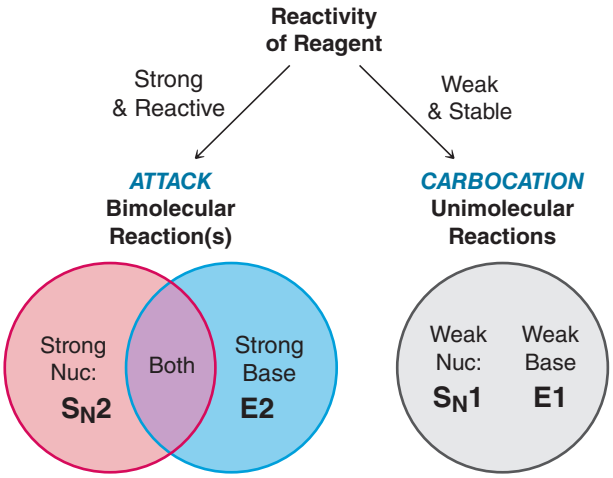


FIGURE 7.20
The decision between a bimolecular or unimolecular process is based on the reactivity of the reagent.

A strong, reactive reagent will engage in backside *attack* as a nucleophile (S_N2), or it will *attack* a beta proton as a base (E2). The amount of steric hindrance exhibited by the substrate determines which mechanism predominates (Section 7.8). In the absence of a strong nucleophile/base, there is no attack on the substrate. Instead, the leaving group leaves on its own to generate a *carbocation*. This unimolecular path leads to both S_N1 and E1 products, typically as a mixture. Once we have determined the function of the reagent, we can move on to the next step.

Step Two: Determining the Expected Mechanism(s)

After determining the function of the reagent, the next step is to analyze the substrate and identify which mechanism(s) are favored. Each of the four mechanisms has different requirements, making

it more or less likely to occur with a given alkyl halide. The S_N2 reaction requires a leaving group on an unhindered carbon atom. Therefore, backside attack is exceptionally favorable on methyl and primary alkyl halides, and reasonable on secondary substrates, but it fails if the leaving group is on a tertiary carbon atom (Figure 7.21).

	CH_3X (methyl)	1° RX (primary)	2° RX (secondary)	3° RX (tertiary)
S_N2 (no sterics)	✓	✓	okay	✗
E2	✗	rare	✓	✓
S_N1 (carbocation)	✗	✗	okay	✓
E1 (carbocation)	✗	✗	okay	✓

FIGURE 7.21
The nature of the alkyl halide substrate governs the likely mechanism(s).

The E2 mechanism cannot take place on a methyl substrate, because at least two carbon atoms are needed to form a C=C double bond! Backside (S_N2) attack is favorable on a primary alkyl halide, so a bulky base is required (such as *tert*-butoxide, DBN, or DBU) in order to favor an E2 reaction with such substrates. When secondary and tertiary alkyl halides are treated with a strong base, E2 is the predominant mechanism (Section 7.8).

The unimolecular mechanisms (S_N1 and E1) both involve a carbocation intermediate, so these processes have the same requirements. A tertiary substrate is ideal for S_N1/E1 because it is relatively easy to generate a stable, tertiary carbocation. Secondary alkyl halides are reasonable substrates, especially if the resulting carbocation can undergo a rearrangement. Primary and methyl carbocations are extremely unstable, so primary and methyl alkyl halides are not suitable for unimolecular processes.

Let's explore the expected outcome with a primary, secondary, or tertiary substrate for each of the four categories of reagents as well. These correlations are summarized in Figure 7.22.

	Strong base Weak nucleophile DBU DBN	Strong base Strong nucleophile HO^- MeO^- EtO^-	Weak base Strong nucleophile X^- RS^- CN^- $CH_3CO_2^-$	Weak base Weak nucleophile H_2O ROH
1°	E2	E2 / S_N2	S_N2	✗
2°	E2	E2 / S_N2	S_N2	S_N1 / E1
3°	E2	E2	S_N1	S_N1 / E1

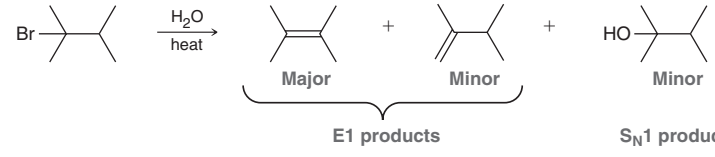
FIGURE 7.22
The operative mechanism(s) can be determined by considering the identity of the substrate (primary, secondary, or tertiary) and the identity of the reagent (nucleophile or base).

Let's begin our analysis of Figure 7.22 by focusing on the left side of the figure (the left two columns). Those two columns correspond with strong bases. Notice that these two columns appear to be dominated by the E2 mechanism, as we would expect when a strong base is used. In the first column, E2 is the only mechanism observed, regardless of the type of substrate (primary, secondary, or tertiary), because the reagent is a weak nucleophile, and S_N2 reactions are not observed. In the absence of competing S_N2 reactions, the E2 pathway dominates.

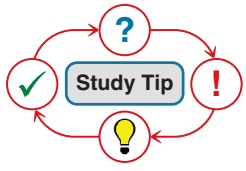
The second column in Figure 7.22 represents reagents that are both strong bases and strong nucleophiles (such as hydroxide or alkoxide ions). With such a reagent, the amount of steric hindrance presented by the substrate is the key to determining which mechanism competes most effectively. Recall from Section 7.8 that E2 predominates in all cases except for primary substrates. With a primary alkyl halide, S_N2 (backside attack) is favored with hydroxide and non-sterically hindered alkoxide reagents such as NaOMe and NaOEt.

The third column of Figure 7.22 corresponds with reagents that are strong nucleophiles and weak bases. When one of these reagents is used, all substrates yield substitution products. A substitution reaction is expected with a strongly nucleophilic reagent that is not strongly basic, because E2 processes are too slow when a weak base is used. Primary substrates react exclusively through the S_N2 mechanism, while tertiary substrates react exclusively through the S_N1 mechanism. Over the last several decades, there has been much debate/confusion over the fate of secondary alkyl halides, although there is strong evidence that such substrates react with strong nucleophiles almost exclusively via an S_N2 process, and rarely, if at all, through an S_N1 process.[9,10]

The final column in Figure 7.22 corresponds with reagents that are both weak nucleophiles and weak bases (such as water, or alcohols, ROH). In the absence of a strong base or strong nucleophile, bimolecular reactions (S_N2 and E2) do not occur. Under such conditions, unimolecular reactions (S_N1 and E1) can occur. These reactions are observed for tertiary substrates (not for primary and secondary substrates, unless they are allylic or benzylic). The product distribution (S_N1 vs. E1) is affected by the identities of the E1 products. When one or more of the possible E1 products is a tri- or tetra-substituted alkene, then E1 is generally favored over S_N1:



In this example, the first alkene is tetrasubstituted, so this E1 product is favored over the S_N1 product. However, in a case where the E1 products are not highly substituted, then S_N1 is generally favored.



There is certainly a lot of information to process when deciding which mechanism(s) will be favored in a given situation! While there are many methods to solving such problems, simply attempting to memorize Figure 7.22 is unlikely to be a successful strategy. In addition to predicting products, you should be able to draw mechanisms and explain reaction rates and outcomes—so your goal should be understanding the trends in Figure 7.22 rather than just committing it to memory. Figure 7.23 provides a systematic approach to evaluating the function of the reagent and the nature of the substrate. First, we determine whether a bimolecular (*ATTACK*) or unimolecular (*CARBOCATION*) pathway is expected, based on the reactivity of the reagent.

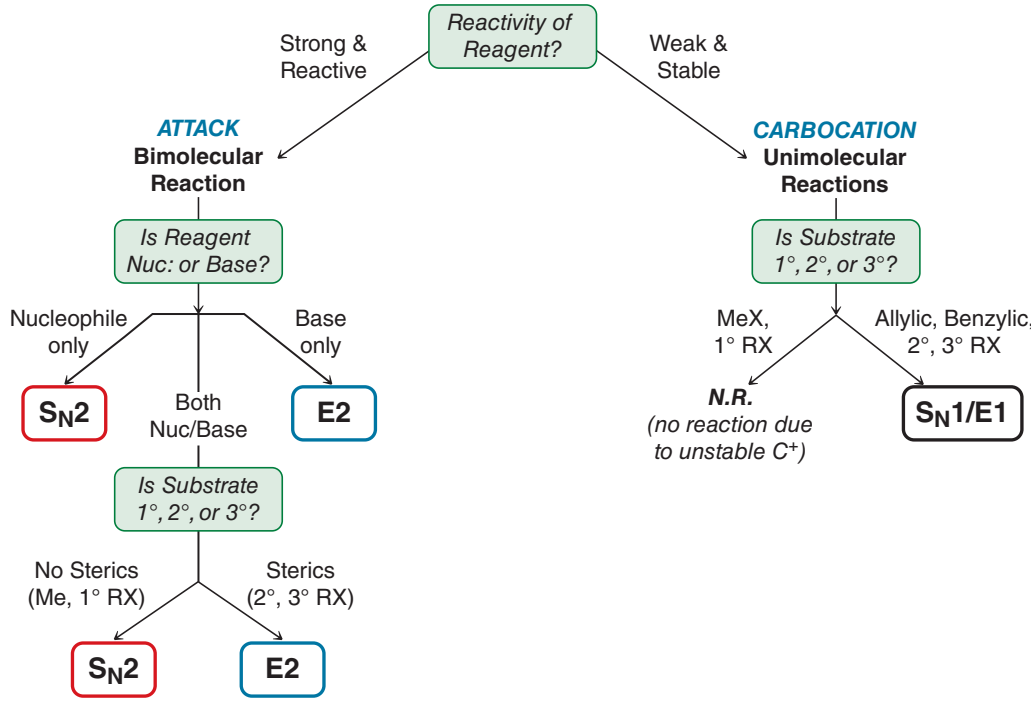


FIGURE 7.23
A decision tree examines the reactivity and function of the reagent, along with the nature of the substrate, to identify the predominant mechanism(s).

If the reagent is weakly reactive (H_2O or ROH), a carbocation is formed by loss of the leaving group, and we expect the mixture of products that results from S_N1 and E1 mechanisms. If no stable carbocation is possible, then the leaving group will not leave, and no reaction will take place (N.R.).

For a reagent with strong reactivity, we have to decide if the reagent is nucleophilic (S_N2) or basic (E2). If it is both a strong nucleophile and a strong base, then the nature of the substrate determines whether the S_N2 or E2 predominates (see Section 7.8).

In summary, when we consider both the function of the reagent and the structure of the substrate, we can make reasonable predictions regarding which mechanism(s) operate, as summarized in Figures 7.22 and 7.23. Armed with this information, we can now move on to the final step of predicting products.

Step Three: Considering Regiochemical and Stereochemical Outcomes

After determining which mechanism(s) operates, the final step is to consider the regiochemical and stereochemical outcomes for each of the expected mechanisms. Table 7.4 provides a summary of guidelines that must be followed when drawing products. All of the information in this table has already been presented in this chapter. The table is meant only as a summary of all of the relevant information, so that it is easily accessible in one location.

TABLE 7.4 THE REGIOCHEMICAL AND STEREOCHEMICAL OUTCOMES OF SUBSTITUTION AND ELIMINATION REACTIONS

	REGIOCHEMICAL OUTCOME	STEREOCHEMICAL OUTCOME
S_N2	• Nucleophile attacks the carbon atom bearing the leaving group	• Inversion of configuration (due to backside attack)
E2	• More stable alkene formed (more substituted, Zaitsev product) • If bulky base is used, less substituted alkene is favored (Hofmann product)	• Leaving group and beta proton must be *anti*-periplanar • If more than one β-H, then the more stable alkene is major product (*e.g., trans*)
S_N1	• Carbocation rearrangement is possible, so nucleophile may not be at the same position as leaving group	• Racemization of chiral center (due to planar carbocation intermediate)
E1	• Most stable alkene favored (Zaitsev) • Carbocation rearrangement is possible, so alkene may not be at the same position as leaving group	• No *anti* β-H requirement (due to stepwise mechanism) • Most stable stereoisomer is favored (if alkene product exhibits stereoisomerism)

SKILLBUILDER

7.7 PREDICTING THE PRODUCTS OF SUBSTITUTION AND ELIMINATION REACTIONS OF ALKYL HALIDES

LEARN the skill

For each of the following reactions, identify the predominant mechanism(s) and predict the major product(s).

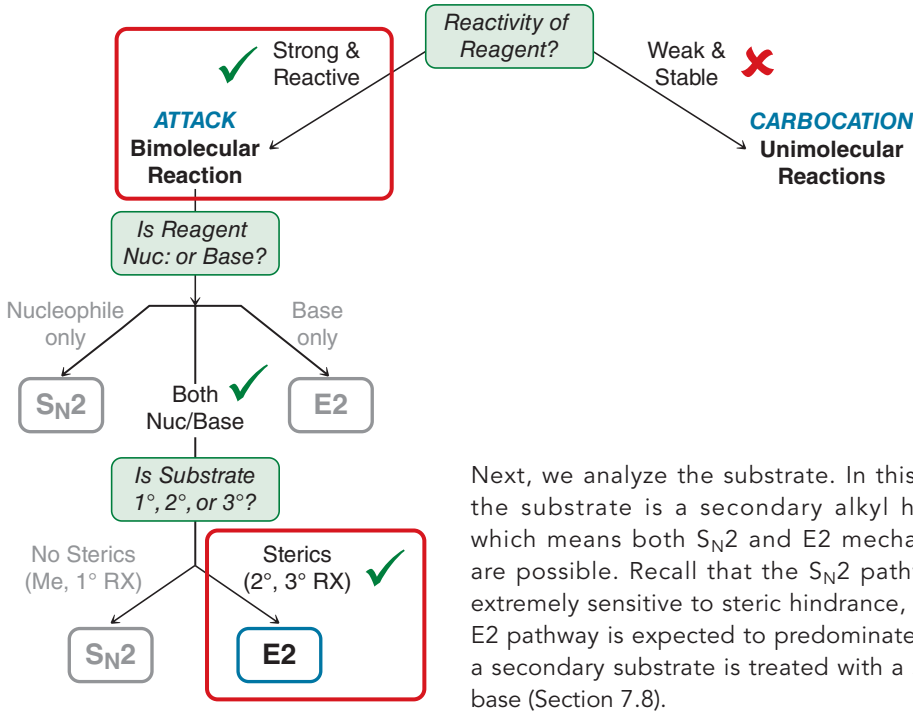
SOLUTION

(a) In order to draw the products, the following three steps must be followed:

1. Determine the function and reactivity of the reagent.
2. Analyze the substrate and determine the expected mechanism(s).
3. Consider any relevant regiochemical and stereochemical requirements.

STEP 1
Determine the function and reactivity of the reagent.

Let's approach this problem by using the decision tree (Figure 7.23). In the first step, we analyze the reagent. In the presence of ethoxide, ethanol serves only as the solvent for the reaction. The ethoxide ion is both a strong base and a strong nucleophile, so a bimolecular (*ATTACK*) pathway is expected (S_N2 or E2).



STEP 2
Analyze the substrate and determine the expected mechanism(s).

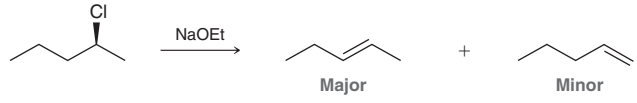
Next, we analyze the substrate. In this case, the substrate is a secondary alkyl halide, which means both S_N2 and E2 mechanisms are possible. Recall that the S_N2 pathway is extremely sensitive to steric hindrance, so the E2 pathway is expected to predominate when a secondary substrate is treated with a strong base (Section 7.8).

Therefore, we would expect the major product(s) to be generated via an E2 process. In this case, the S_N2 product will be the minor product, as summarized in Figure 7.22:

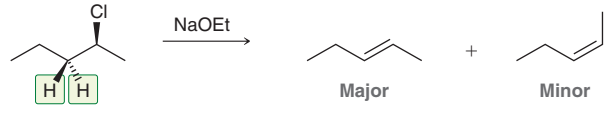
	Strong base Weak nucleophile	Strong base Strong nucleophile	Weak base Strong nucleophile	Weak base Weak nucleophile
1°	E2	E2 S_N2	S_N2	
2°	E2	E2 S_N2	S_N2	S_N1/E1
3°	E2	E2	S_N1	S_N1/E1

STEP 3
Consider regiochemical and stereochemical requirements.

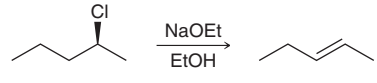
In order to draw the major product(s), we must consider the regiochemical and stereochemical outcomes for the E2 process. For the regiochemical outcome, we expect the Zaitsev product to be the major product, because the reaction does not utilize a sterically hindered base:



Finally, let's look at the stereochemistry. The β position has more than one proton. Each of these protons can be anti-periplanar to the leaving group, so we expect *cis* and *trans* isomers, with a predominance of the more stable *trans* isomer:

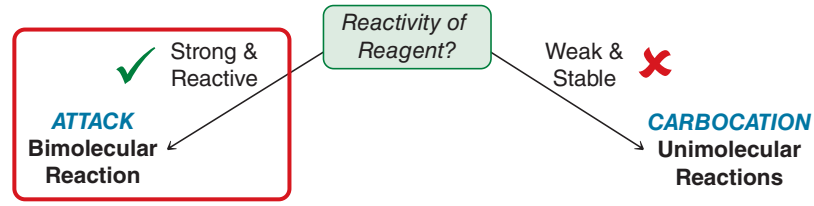


In summary, we expect the following major product, from an E2 mechanism:



STEP 1
Determine the function and strength of the reagent.

(b) Once again, we approach this problem by using the decision tree (Figure 7.23). In the first step, we analyze the reagent. Because it bears a negative charge, the cyanide ion will be strongly reactive. Therefore, a bimolecular ATTACK pathway is expected (S_N2 or E2):

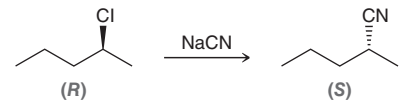


STEP 2
Analyze the substrate and determine the expected mechanism(s).

The substrate is a secondary alkyl halide, which means that both S_N2 and E2 mechanisms are possible. To decide which will be major, we need to determine whether the reagent is a nucleophile (S_N2) or a base (E2). Cyanide is a strong nucleophile because it has a negative charge, but how do we know whether or not it also a strong base? There is no need to memorize pK_a values, because the list of strong bases is quite short. If the anion is not *hydroxide* or *alkoxide*, then it is most likely *not* a strong base. There are certainly exceptions to this generalization, and we will encounter such cases in future chapters. For now, we should evaluate the anion and confirm that it has some stabilizing feature that indeed makes it less basic than hydroxide. In the case of cyanide, the anion is stabilized by being located on an *sp*-hybridized carbon atom, and by inductive withdrawal of electron density by the nearby nitrogen atom. Therefore, cyanide is not a strong base, and the S_N2 mechanism is expected to predominate.

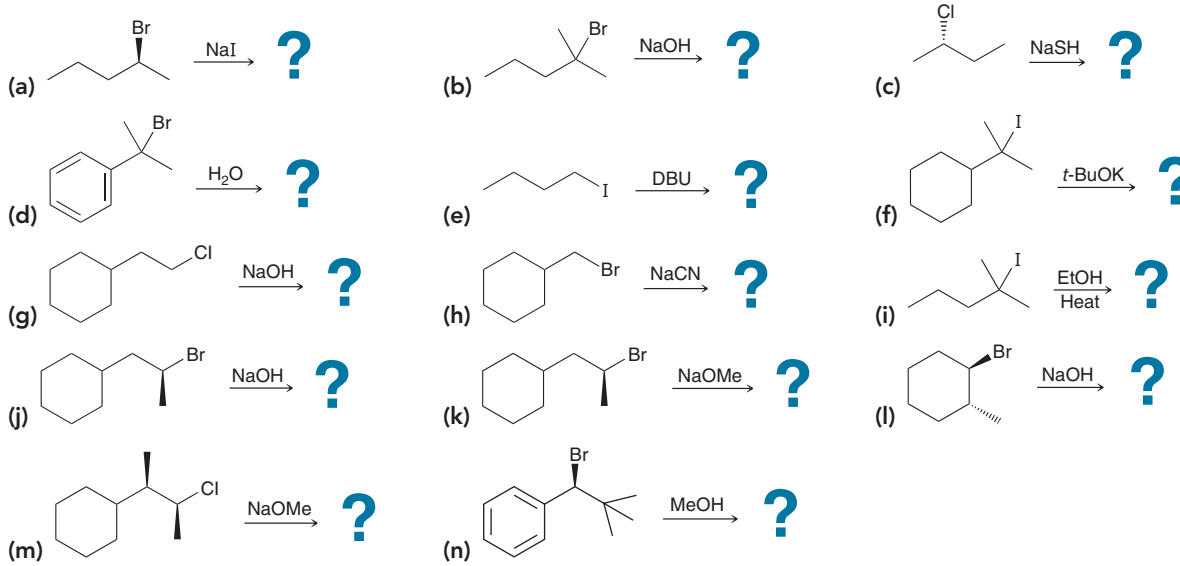
STEP 3
Consider regiochemical and stereochemical requirements.

The regiochemistry of an S_N2 reaction is straightforward: the nucleophile is simply installed at the position bearing the leaving group. Finally, we consider the stereochemistry. In this case, the backside attack occurs at a chiral center, so we expect inversion of configuration:



PRACTICE the skill

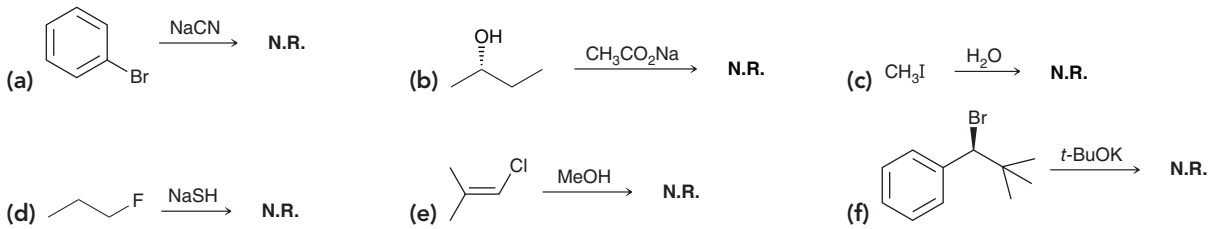
7.28 Identify the predominant mechanism(s) and predict the major product(s) that are expected for each of the following reactions.



APPLY the skill

7.29 Compound **A** and compound **B** are constitutional isomers with the molecular formula C_3H_7Cl. When compound **A** is treated with sodium methoxide (NaOMe), a substitution reaction predominates. When compound **B** is treated with sodium methoxide, an elimination reaction predominates. Propose structures for compounds **A** and **B**.

7.30 None of the following reactions produce any S_N2 or S_N1 substitution products, or any E2 or E1 elimination products. Explain why each reaction fails (N.R. = No Reaction).



7.31 An unknown compound with the molecular formula $C_6H_{13}Cl$ is treated with sodium ethoxide (NaOEt) to produce 2,3-dimethyl-2-butene (shown here) as the major product. Identify the structure of the unknown compound.

2,3-dimethyl-2-butene

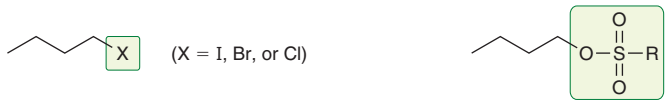
need more **PRACTICE?** **Try Problems 7.75, 7.76, 7.80, 7.83, 7.85**

7.11 Substitution and Elimination Reactions with Other Substrates

Nucleophilic substitution and beta-elimination reactions are not limited to alkyl halides. In this section, we will briefly explore the reactivity of alkyl sulfonates, and we will introduce the reactivity of alcohols (a topic further developed in Chapter 12).

Tosylates

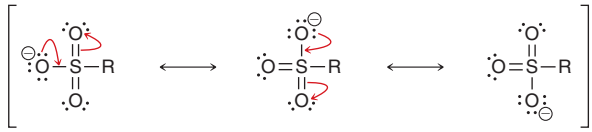
In Table 7.1, we saw that sulfonate ions (RSO_3^-) are excellent leaving groups, much like halide ions, so it should come as no surprise that alkyl halides and alkyl sulfonates undergo similar reactions:



An alkyl halide

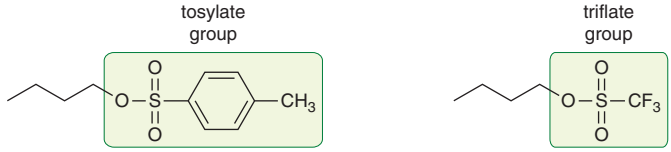
An alkyl sulfonate

With an alkyl sulfonate, the leaving group is a sulfonate ion, which is highly stabilized by resonance:



Sulfonate leaving groups are resonance-stabilized

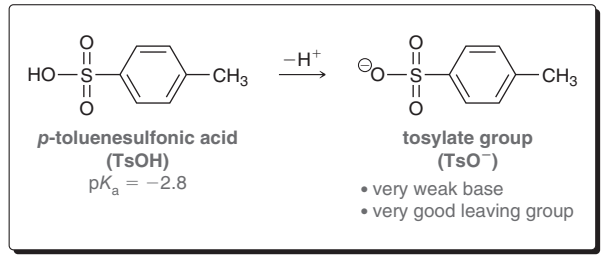
Since sulfonate ions are such good leaving groups, alkyl sulfonates undergo substitution and elimination reactions, much like alkyl halides. Many sulfonates are commonly used, including tosylates and triflates:

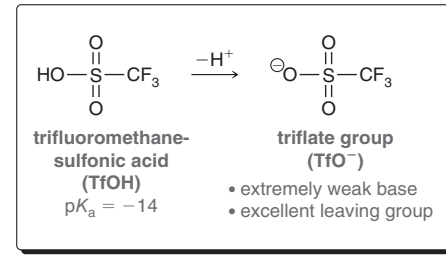


An alkyl tosylate (ROTs)

An alkyl triflate (ROTf)

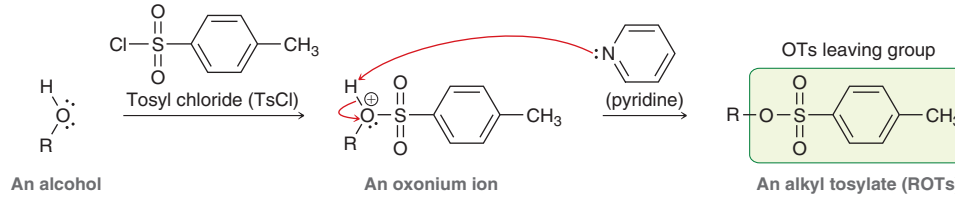
Tosylates are the most commonly used, although triflates have the best leaving group. Recall that the best leaving groups are the most stable, weakest bases. Compare the pK_a values of the following sulfonic acids (RSO_3H):



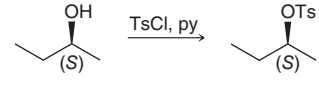


The triflate ion is one of the weakest known bases, because the TfO^- anion is stabilized by both resonance and inductive effects of the fluorine atoms (recall ARIO factors from Chapter 3). As such, it is the conjugate base of an especially strong acid. Trifluoromethanesulfonic acid has a pK_a of −14! Triflates are often used in situations that require extremely good leaving groups.

Tosylates (ROTs) can be prepared by treating the corresponding alcohol (ROH) with tosyl chloride (TsCl) in the presence of pyridine. Under these conditions, the alcohol serves as a nucleophile and displaces the chloride ion in TsCl, and the resulting oxonium ion is deprotonated by pyridine (a base) to give an alkyl tosylate:

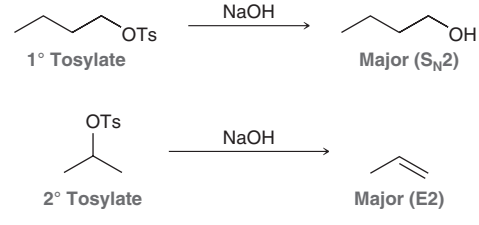


The bond between R and O (in ROH) is not broken during the process, and as a result, a chiral alcohol will retain its configuration when converted to its corresponding tosylate:



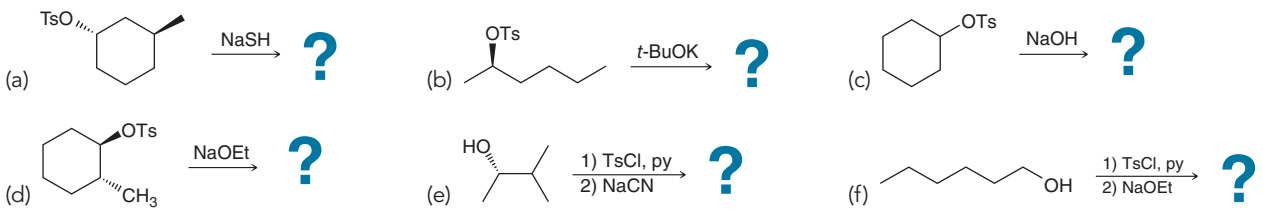
The configuration (*S*) does not change during formation of the tosylate. A common abbreviation for pyridine is "py," as shown in the reaction above.

Alkyl sulfonates undergo substitution and elimination reactions, much like the corresponding alkyl halides. For example, when treated with a strong nucleophile that is also a strong base, a primary alkyl tosylate will give backside attack (S_N2 substitution) as the major product, and a secondary alkyl tosylate will undergo predominantly E2 elimination:



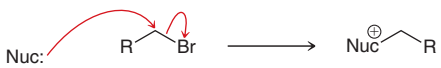
CONCEPTUAL CHECKPOINT

7.32 Predict the major product(s) for each of the following reactions.



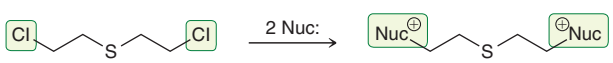
BioLinks Alkylating Agents as Chemotherapy Drugs

Consider the following substitution reaction:



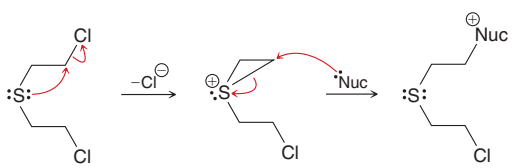
Because an alkyl group has been attached to the nucleophile, we can say that the nucleophile has been alkylated. The alkyl halide can be described as an alkylating agent. Substitution reactions are very useful in the laboratory, but the situation is quite different when they occur in living systems. For example, there are many nucleophilic sites on strands of DNA. If DNA is exposed to an alkylating agent, its structure becomes permanently altered and it can no longer replicate. As a result, alkylating agents can have toxic effects on living organisms, and they must be handled with care. Unfortunately, alkylating agents have been used as weapons of war, but their reactivity has also been harnessed to fight cancer. This example illustrates how the relationship between humans and chemistry has been a complicated one throughout history.

Sulfur mustard 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. Each molecule of sulfur mustard has *two* leaving groups, so it can react with *two* nucleophiles:



Sulfur mustard

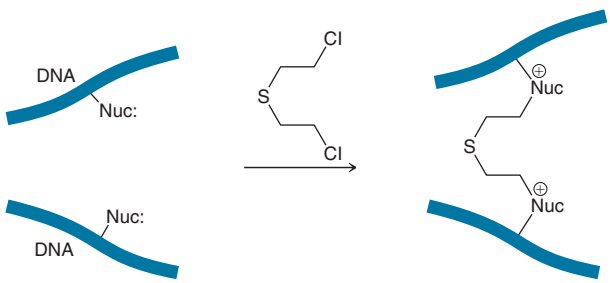
The mechanism of each alkylation involves a sequence of two substitution reactions:



Sulfur mustard

The process shown above (an *intramolecular* backside attack, followed by a *ring-opening* backside attack) will be explored further in a Chapter 13 BioLinks application.

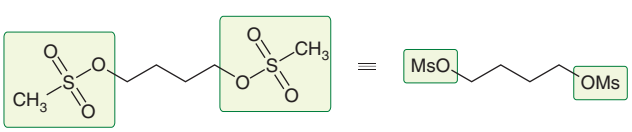
Because each molecule of sulfur mustard is capable of alkylating DNA two times, it causes individual strands of DNA to cross-link:



Cross-linked DNA

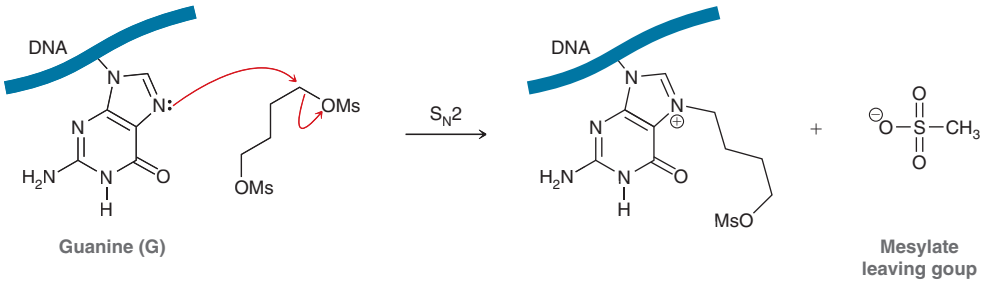
Such cross-linking prevents transcription of the DNA into RNA, ultimately leading to cell death. The profound impact of sulfur mustard on cell function inspired research on the use of this compound as an antitumor agent. In 1931, sulfur mustard was injected directly into tumors with the intention of stopping tumor growth by interrupting the rapid division of the cancerous cells. Ultimately, sulfur mustard was found to be too toxic for clinical use, but the concept of using an alkylating agent to fight a tumor had been proven and the field of chemotherapy was born. Continuous research from that point on has resulted in the development a variety of chemotherapeutic drugs that are cross-linking agents.

Busulfan (byoo-SUL-fan) was first used in 1959, and in 1999 it was approved for use in the treatment of chronic myeloid leukemia (CML). Leukemia is a cancer that starts in the blood-forming cells of the bone marrow. Busulfan destroys white blood cells and bone marrow, so it is used primarily to prepare cancer patients for stem cell or bone marrow transplantation. Like sulfur mustard, busulfan is an effective cross-linking agent because it has two leaving groups:



Busulfan **Two sulfonate leaving groups**

The sulfonate leaving group in busulfan, called methanesulfonate or mesylate (OMs), is similar to the tosylate and triflate leaving groups in Section 7.11. Alkylation with busulfan occurs at guanine (G) and adenine (A) residues in DNA, where a nucleophilic nitrogen atom can displace the mesylate leaving group via backside attack:

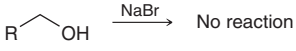


The unhindered, primary carbon atom is ideal for S_N2 reaction, and resonance delocalization of the negative charge makes the mesylate group an excellent leaving group. A second S_N2 substitution ejects the other leaving group and establishes the DNA cross-link, leading to destruction of the cell.

Alcohols

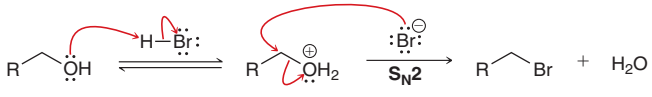
Chapter 12 covers reactions of alcohols (ROH), and in Section 12.9, we will explore a number of reactions that involve substitution and elimination processes. We will now preview two such reactions: 1) the reaction between ROH and HBr; and 2) the reaction of ROH in concentrated sulfuric acid. This current discussion is meant to reinforce the importance of the mechanisms covered in this chapter.

Unlike alkyl halides and alkyl sulfonates, alcohols do not undergo S_N2 reactions directly when treated with a strong nucleophile. For example, no reaction is observed when an alcohol is treated with sodium bromide:

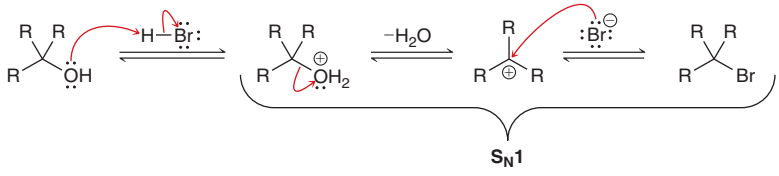


Alcohols are not suitable substrates for nucleophilic substitution reactions, because hydroxide (HO^-) is a poor leaving group. However, under strongly acidic conditions (such as HBr), a substitution reaction is indeed observed:

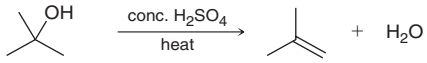
Under strongly acidic conditions, the OH group can be protonated, thereby converting a bad leaving group (HO^-) into a good leaving group (H_2O). This allows for an S_N2 reaction to occur, giving an alkyl bromide:



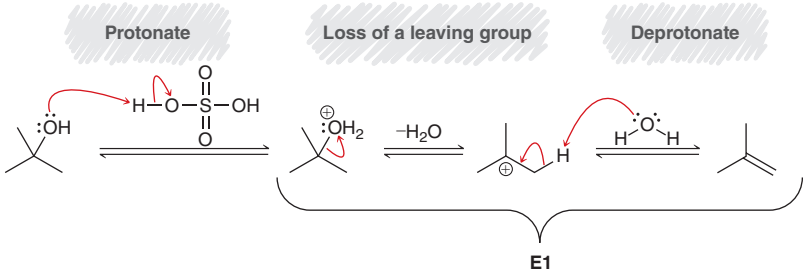
A similar reaction is also observed for secondary and tertiary alcohols, although tertiary alcohols presumably react via an S_N1 process (rather than S_N2), as shown here:



In the examples above, we see that strongly acidic conditions can activate an alcohol towards substitution (either S_N2 or S_N1, depending on the substrate). Similarly, strongly acidic conditions can also activate an alcohol towards elimination. Consider the following example:

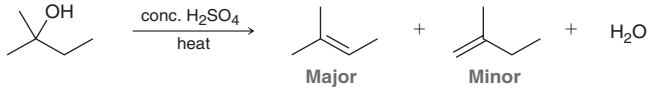


Under these strongly acidic conditions, the OH group can be protonated, thereby converting it into a good leaving group. These conditions are also favorable toward carbocation formation. Unlike HBr, which is a source of both acid (H^+) and a nucleophile (Br^-), H_2SO_4 has no strongly nucleophilic component. With no competing S_N1 mechanism, the carbocation undergoes an E1 process, giving an alkene as the product:



The overall process involves formation of an alkene via the removal of water (H and OH) and is therefore called a *dehydration* reaction. As shown in the mechanism above, dehydration of an alcohol (under acidic conditions) occurs via a three-step mechanism. The first step is protonation of the alcohol, followed by the two steps of an E1 process (loss of leaving group and deprotonation). When drawing the first step of this mechanism, notice that H_2SO_4 is shown as the source of the proton, rather than H_3O^+. Concentrated sulfuric acid is a mixture of mostly H_2SO_4 and a very small amount of water, so H_2SO_4 is the most likely acid to be encountered by the alcohol.

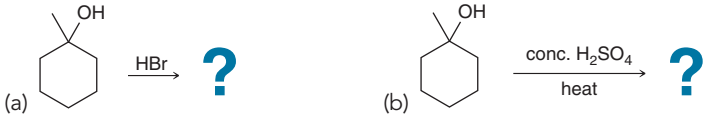
For some alcohols, dehydration can yield more than one possible alkene, and in such instances, the most stable alkene is generally favored, as we would expect for an E1 process.



These Chapter 12 reactions illustrate an important point. Specifically, the four mechanisms covered in this chapter (S_N2, E2, S_N1, and E1) will all reappear many times throughout the remaining chapters of this textbook. Even unimolecular reactions will play a prominent role in our discussions as we move forward.

CONCEPTUAL CHECKPOINT

7.33 Predict the major product for each of the following reactions.



7.34 Draw a plausible mechanism for each of the following transformations.