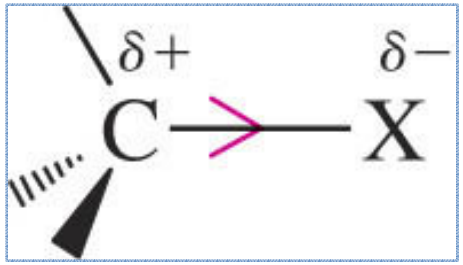
Chapter 6

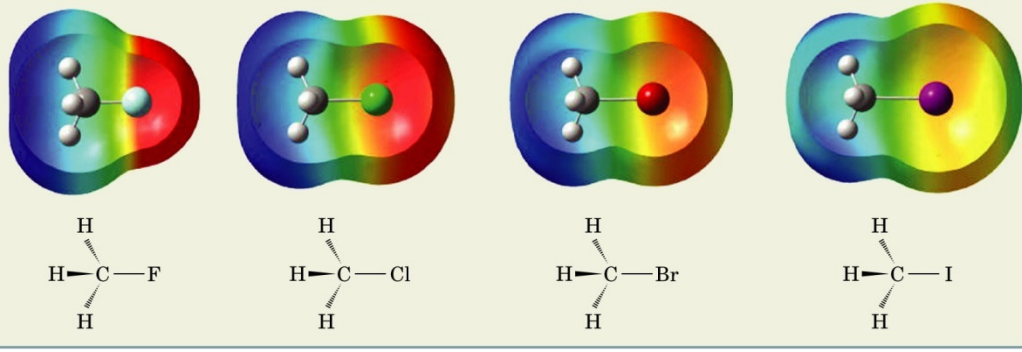
Organic Halogen Compounds

Introduction

- The polarity of a carbon-halogen bond leads to the carbon having a partial positive charge
  - In alkyl halides this polarity causes the carbon to become activated to substitution reactions with nucleophiles



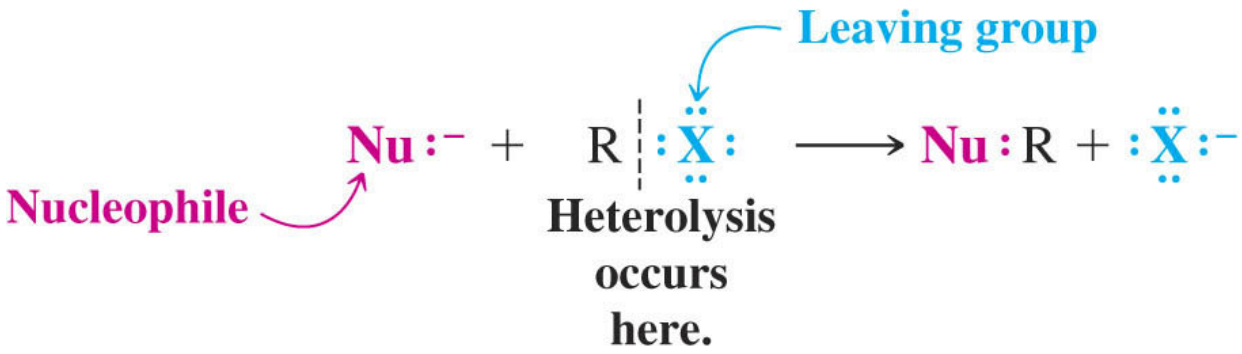
- Carbon-halogen bonds get less polar, longer and weaker in going from fluorine to iodine



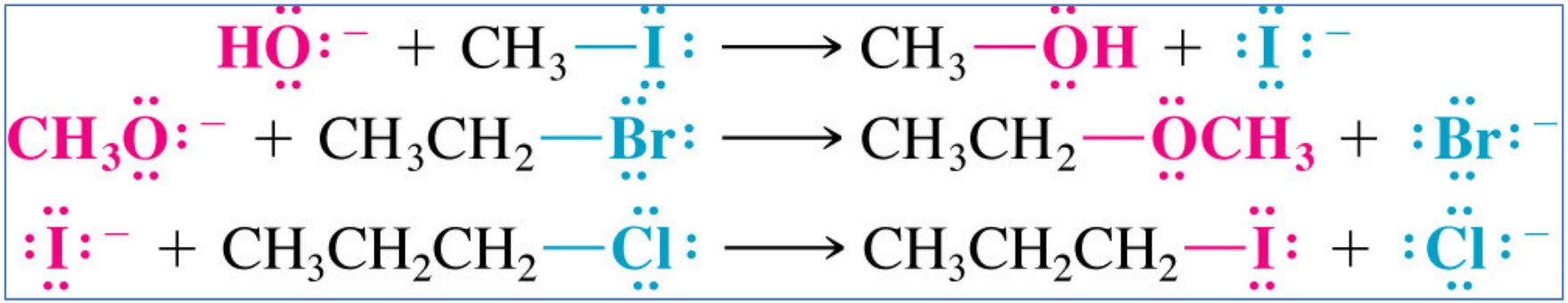
	H–C–F	H–C–Cl	H–C–Br	H–C–I
C—X Bond length (Å)	1.39	1.78	1.93	2.14
C—X Bond strength (kJ mol^{-1})	472	350	293	239

6.1 Nucleophilic Substitution Reactions

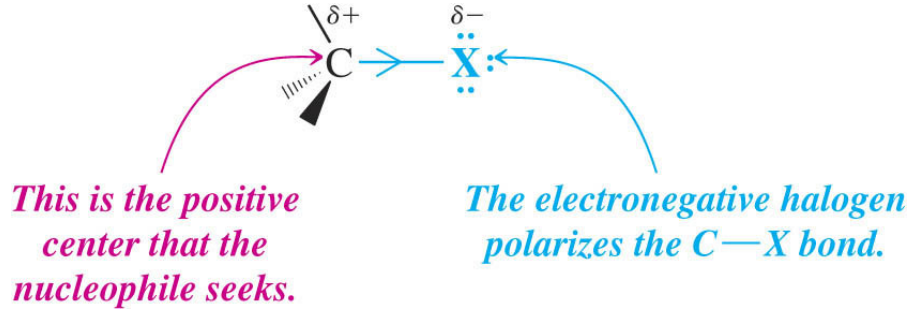
- In this reaction a nucleophile is a species with an unshared electron pair which reacts with an electron deficient carbon
- A leaving group is substituted by a nucleophile



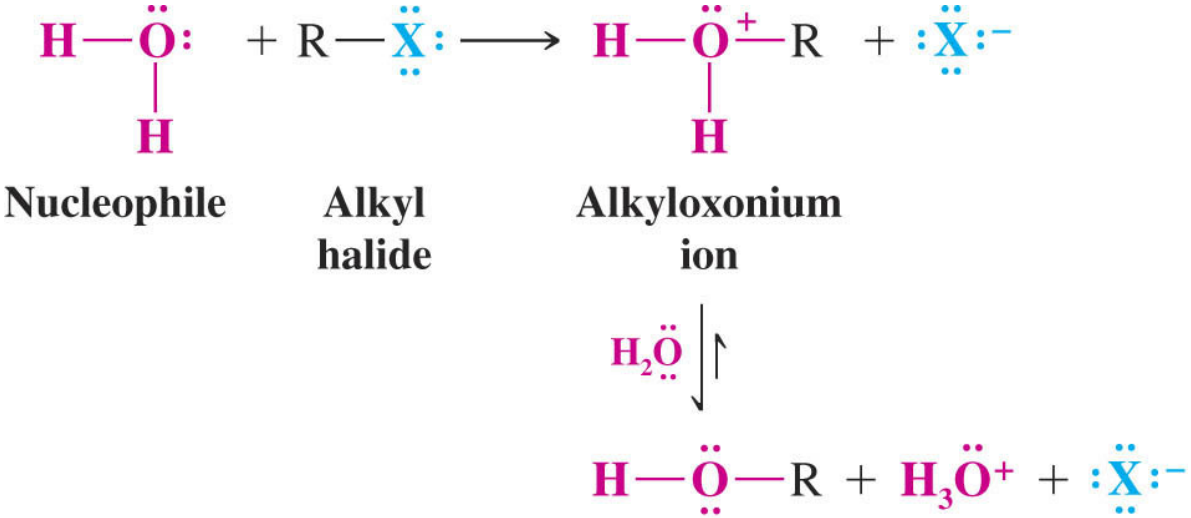
6.2 Examples of nucleophilic substitution



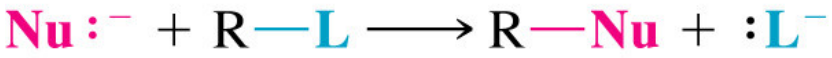
- Nucleophile
  - The nucleophile reacts at the electron deficient carbon

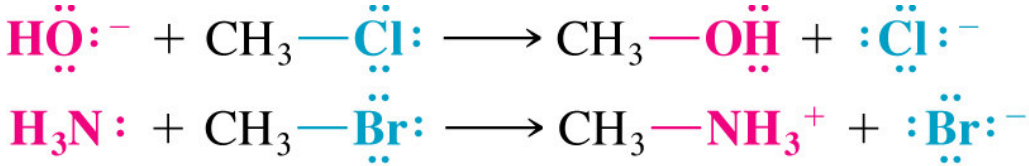


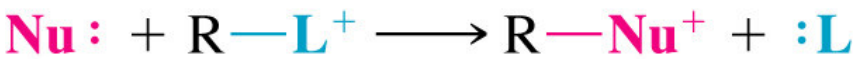
  - A nucleophile may be any molecule with an unshared electron pair



- # Leaving Group
  - A leaving group is a substituent that can leave as a relatively stable entity
  - It can leave as an anion or a neutral species







Specific Example

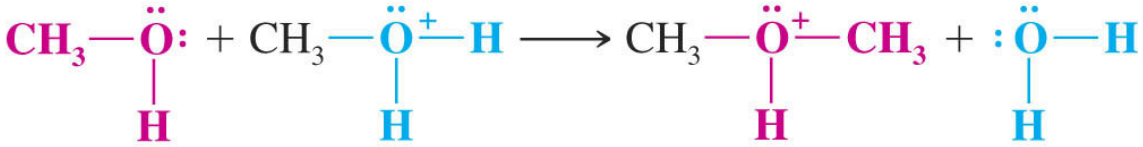


Table 6.1 Reactions of common nucleophiles with alkyl halides (eqs. 6.2 and 6.3)

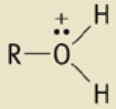
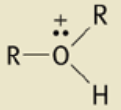
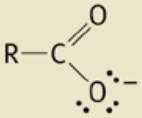
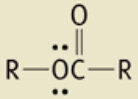
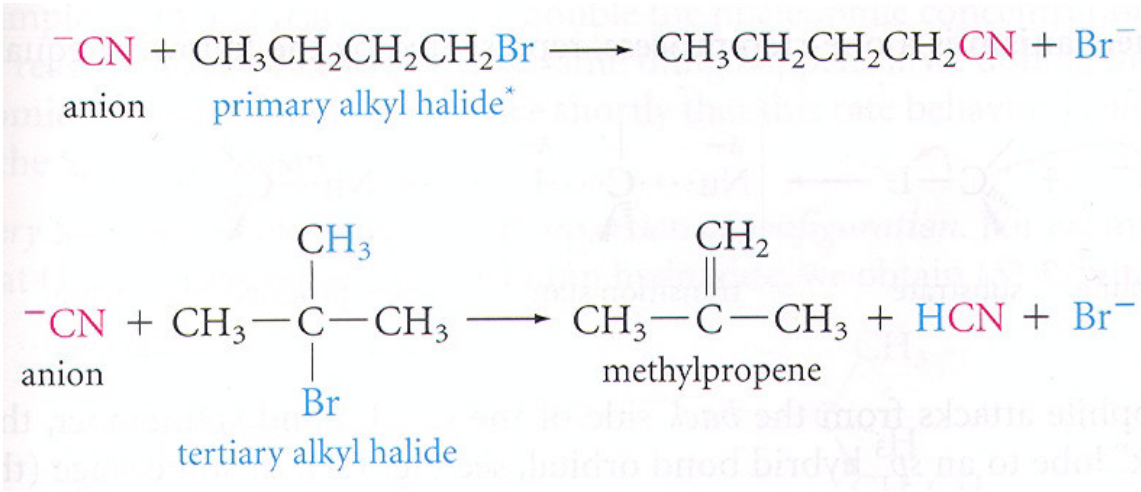
Nu		R—Nu		
Formula	**Name**	**Formula**	**Name**	**Comments**
Oxygen nucleophiles				
1. HO^-	hydroxide	R—OH	alcohol	
2. RO^-	alkoxide	R—OR	ether	
3. HOH	water		alkyloxonium ion	These ions lose a proton and the products are alcohols and ethers. $\xrightarrow{-H^+}$ ROH (alcohol)
4. ROH	alcohol		dialkyloxonium ion	$\xrightarrow{-H^+}$ ROR (ether)
5. 	carboxylate		ester	
Nitrogen nucleophiles				
6. NH_3	ammonia	$R—\overset{+}{N}H_3$	alkylammonium ion	With a base, these ions readily lose a proton to give amines. $\xrightarrow{-H^+}$ RNH_2
7. RNH_2	primary amine	$R—\overset{+}{N}H_2R$	dialkylammonium ion	$\xrightarrow{-H^+}$ R_2NH
8. R_2NH	secondary amine	$R—\overset{+}{N}HR_2$	trialkylammonium ion	$\xrightarrow{-H^+}$ R_3N:
9. R_3N	tertiary amine	$R—\overset{+}{N}R_3$	tetraalkylammonium ion	

Table 6.1 (Continued)

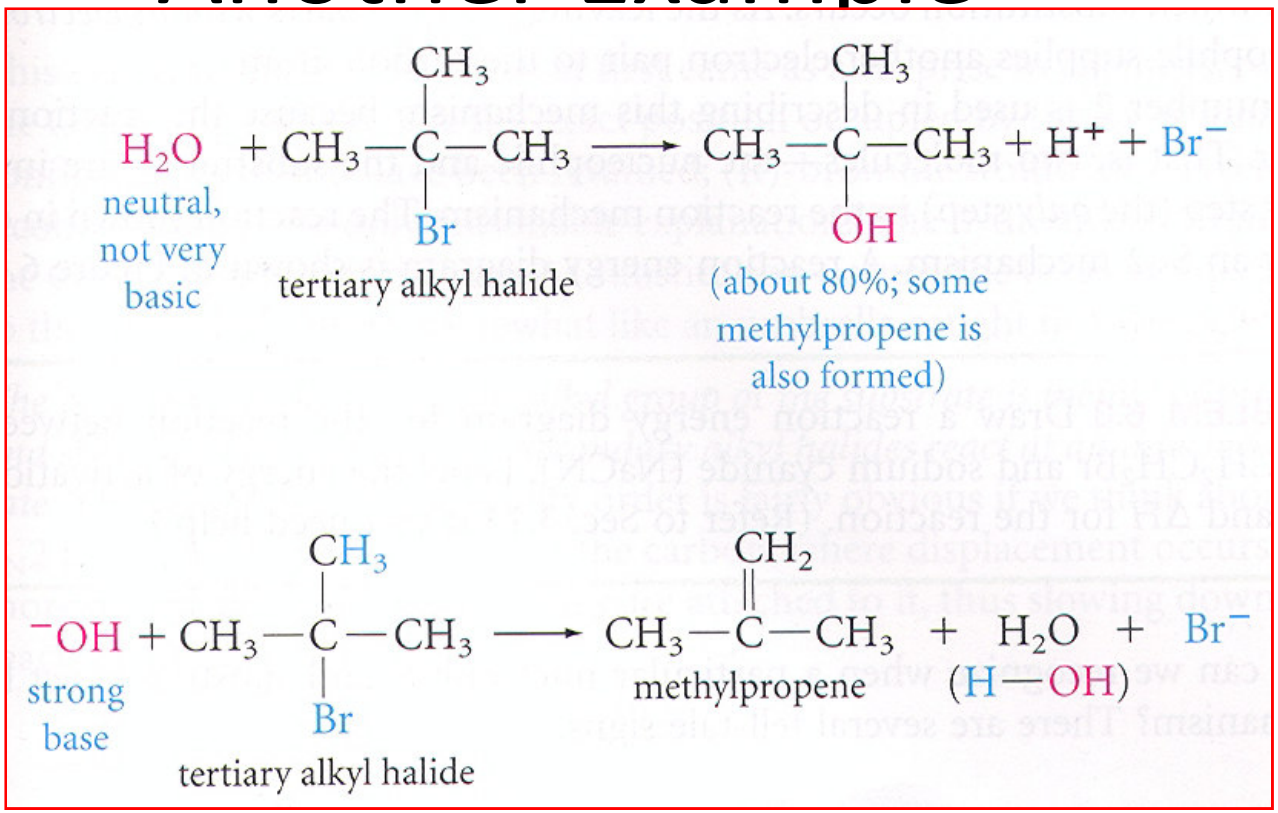
Nu		R—Nu		
Formula	**Name**	**Formula**	**Name**	**Comments**
Sulfur nucleophiles				
10. HS^-	hydrosulfide	$R-SH$	thiol ion	
11. RS^-	mercaptide	$R-SR$	thioether (sulfide) ion	
12. R_2S:	thioether	$R-SR_2^+$	trialkylsulfonium ion	
Halogen nucleophiles				
13. $:I:^-$	iodide	$R-I$:	alkyl iodide	The usual solvent is acetone. Sodium iodide is soluble in acetone, but sodium bromide and sodium chloride are not.
Carbon nucleophiles				
14. $^-:C\equiv N:$	cyanide	$R-C\equiv N:$	alkyl cyanide (nitrile)	Sometimes the isonitrile, $R-N^+\equiv C^-:$, is formed.
15. $^-:C\equiv CR$	acetylide	$R-C\equiv CR$	acetylene	

Limitations

The substitution reactions in Table 6.1 have some limitations with respect to the structure of the *R* group in the alkyl halide. For example, these are reactions of *alkyl* halides (halogen bonded to sp^3-hybridized carbon). *Aryl* halides and *vinyl* halides, in which the halogen is bonded to sp^2-hybridized carbon, do not undergo this type of nucleophilic substitution reaction. Another important limitation often occurs when the nucleophile is either an anion or a base or both. For example,



Another Example



To understand these differences, we must consider the mechanisms by which the substitutions in Table 6.1 take place.

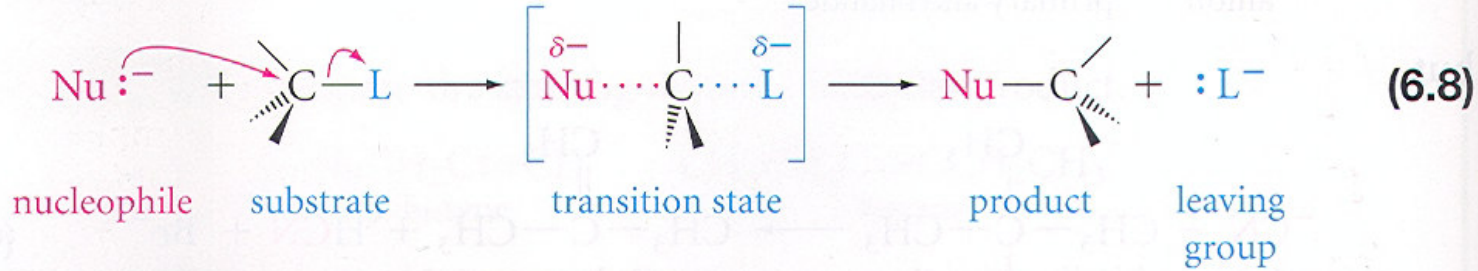
6.3 Nucleophilic Substitution Mechanisms

As a result of experiments that began more than 70 years ago, we now understand the mechanisms of nucleophilic substitution reactions rather well. We use the plural because such *nucleophilic substitutions occur by more than one mechanism.* The mechanism observed in a particular case depends on the structures of the nucleophile and the alkyl halide, the solvent, the reaction temperature, and other factors.

There are two main nucleophilic substitution mechanisms. These are described by the symbols $\mathbf{S_N2}$ and $\mathbf{S_N1}$, respectively. The S_N part of each symbol stands for "substitution, nucleophilic." The meaning of the numbers 2 and 1 will become clear as we discuss each mechanism.

6.4 The S_N2 Mechanism

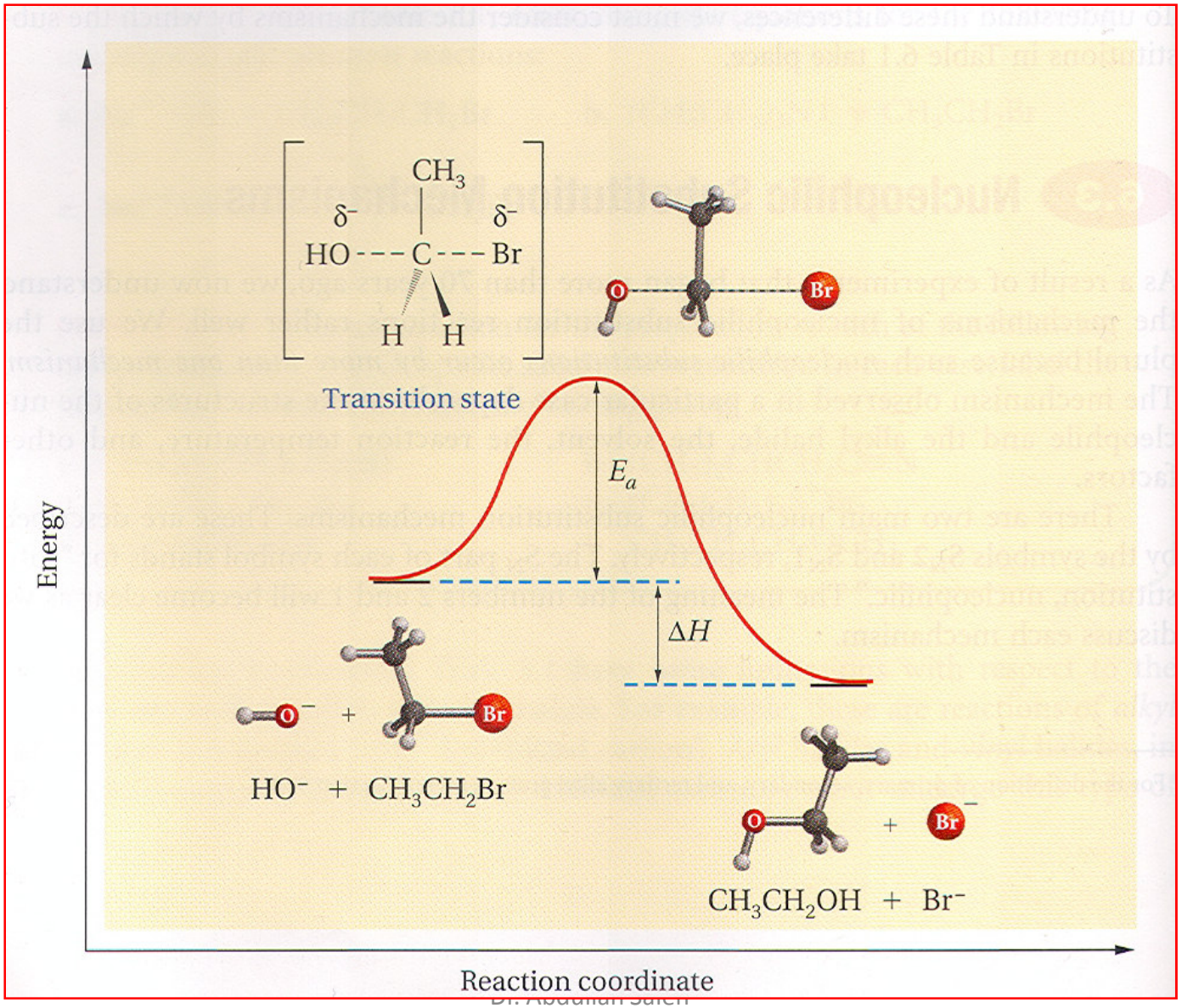
The **S_N2 mechanism** is a one-step process, represented by the following equation:



The nucleophile attacks from the *back* side of the C—L bond (remember, there is a small "back" lobe to an sp^3 hybrid bond orbital; see Fig. 1.7). At some stage (the transition state), the nucleophile *and* the leaving group are *both* partly bonded to the carbon at which substitution occurs. As the leaving group departs *with its electron pair,* the nucleophile supplies another electron pair to the carbon atom.

The number 2 is used in describing this mechanism because the reaction is *bi*molecular. That is, two molecules—the nucleophile and the substrate—are involved in the key step (the *only* step) in the reaction mechanism. The reaction shown in eq. 6.1 occurs by an S_N2 mechanism. A reaction energy diagram is shown in Figure 6.1.

Reaction energy diagram for an S_N2 reaction

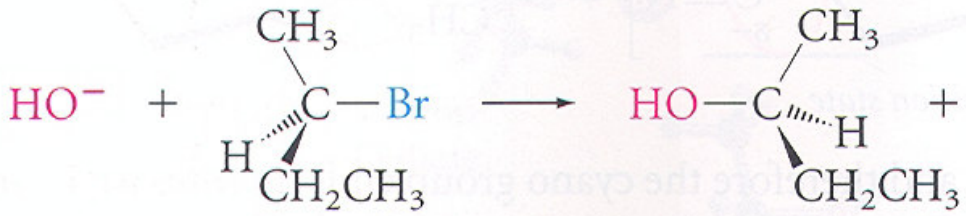


Tell-Tale Signs of S_N2

How can we recognize when a particular nucleophile and substrate react by the S_N2 mechanism? There are several tell-tale signs.

1. *The rate of the reaction depends on both the nucleophile and the substrate concentrations.* The reaction of hydroxide ion with ethyl bromide (eq. 6.1) is an example of an S_N2 reaction. If we double the nucleophile concentration (HO^-), the reaction goes twice as fast. The same thing happens if we double the ethyl bromide concentration. We will see shortly that this rate behavior is *not* observed in the S_N1 mechanism.

2. *Every S_N2 displacement occurs with inversion of configuration.* For example, if we treat (*R*)-2-bromobutane with sodium hydroxide, we obtain (*S*)-2-butanol.

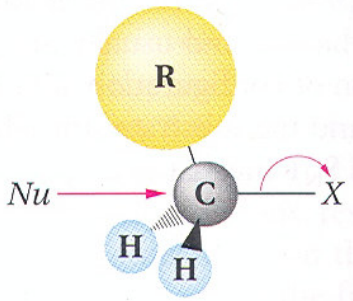


(6.9)

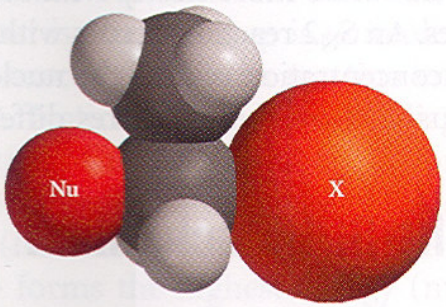
(*R*)-2-bromobutane (*S*)-2-butanol

This experimental result, which at first came as a surprise to chemists, meant that the OH group did *not* take the exact position occupied by the Br. If it had, the configuration would have been retained; (*R*)-bromide would have given (*R*)-alcohol. What is the only reasonable explanation? The hydroxide ion must attack the C—Br bond from the rear. As substitution occurs, the three groups attached to the sp^3 carbon *invert,* somewhat like an umbrella caught in a strong wind.*

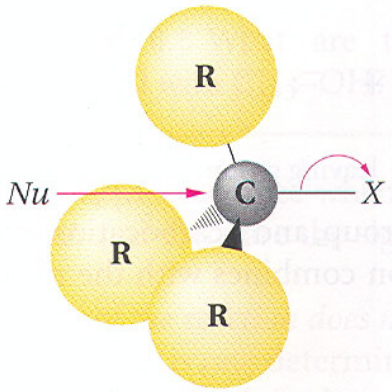
3. *The reaction is fastest when the alkyl group of the substrate is methyl or primary and slowest when it is tertiary. Secondary alkyl halides react at an intermediate rate.* The reason for this reactivity order is fairly obvious if we think about the S_N2 mechanism. The rear side of the carbon, where displacement occurs, is more crowded if more alkyl groups are attached to it, thus slowing down the reaction rate.**



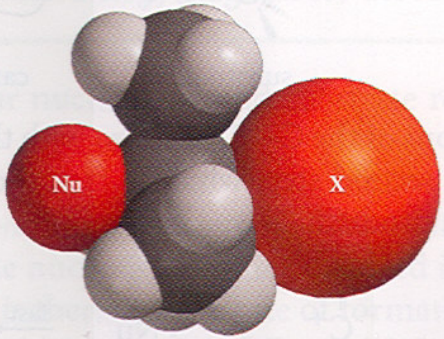
primary alkyl halide
(rear side not crowded; S_N2 fast)



(6.10)



tertiary alkyl halide
(rear side crowded; S_N2 slow or impossible)

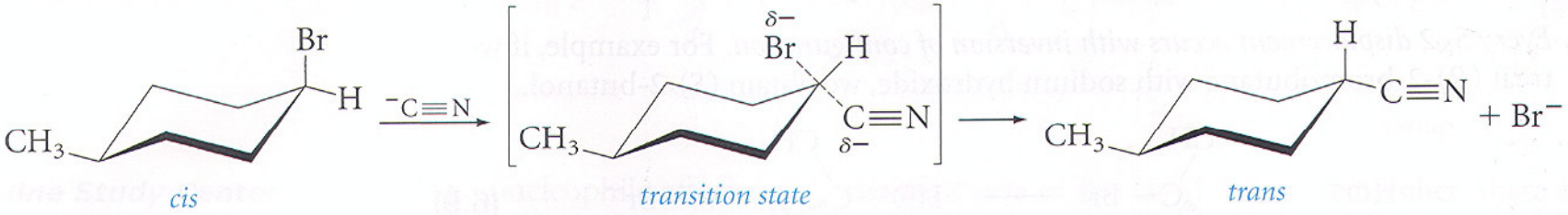


(6.11)

EXAMPLE 6.5

Predict the product from the S_N2 reaction of *cis*-4-methylcyclohexyl bromide with cyanide ion.

SOLUTION



cis *transition state* *trans*

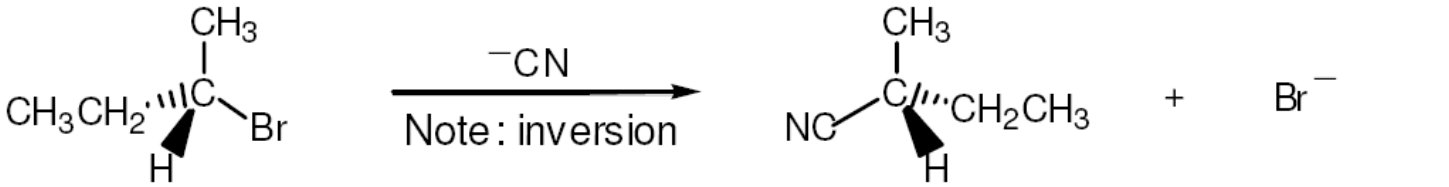
Cyanide ion attacks the C—Br bond from the rear and therefore the cyano group ends up *trans* to the methyl group.

PROBLEM 6.4 Predict the product from the S_N2 reaction of

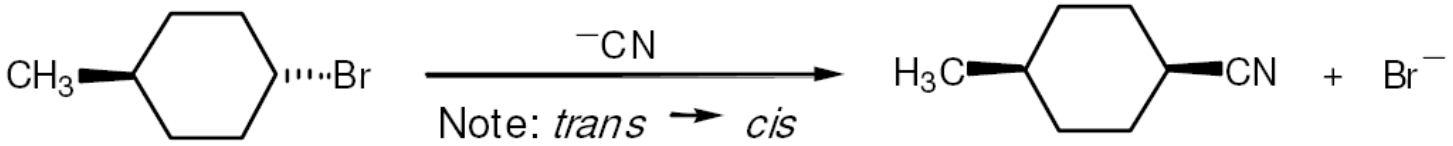
a. (*S*)-2-bromobutane with cyanide ion.
b. *trans*-4-methylcyclohexyl bromide with cyanide ion.
c. (*R*)-2-bromopentane with NaSH.

6.4

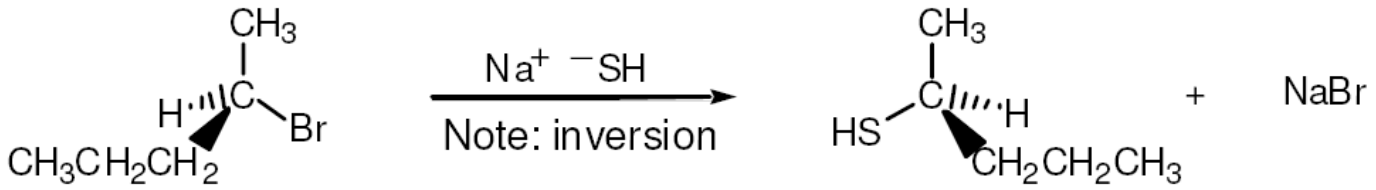
a.



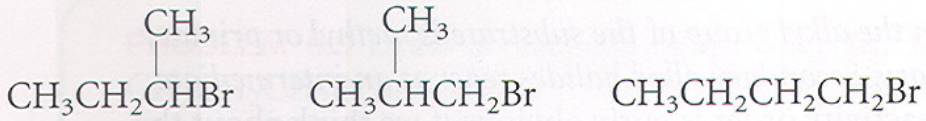
b.



c.



PROBLEM 6.5 Arrange the following compounds in order of *decreasing* S_N2 reactivity toward sodium ethoxide

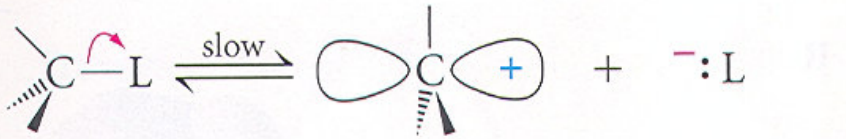


6.5 $CH_3CH_2CH_2CH_2Br > (CH_3)_2CHCH_2Br > CH_3CH_2CH(CH_3)Br$

The more crowded the carbon where displacement occurs, the slower the reaction rate.

6.5 The S_N1 Mechanism

The **S_N1 mechanism** is a two-step process. In the first step, which is slow, the bond between the carbon and the leaving group breaks as the substrate dissociates (ionizes).

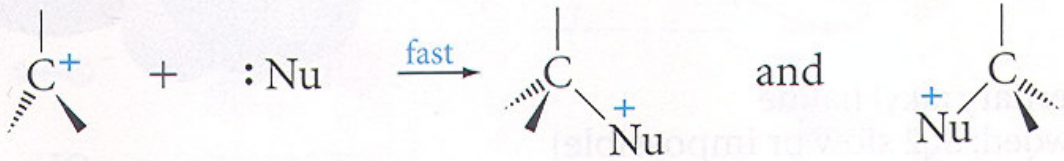


substrate carbocation leaving group

(6.12)

The electrons of the C—L bond go with the leaving group, and a carbocation is formed.

In the second step, which is fast, the carbocation combines with the nucleophile to give the product.

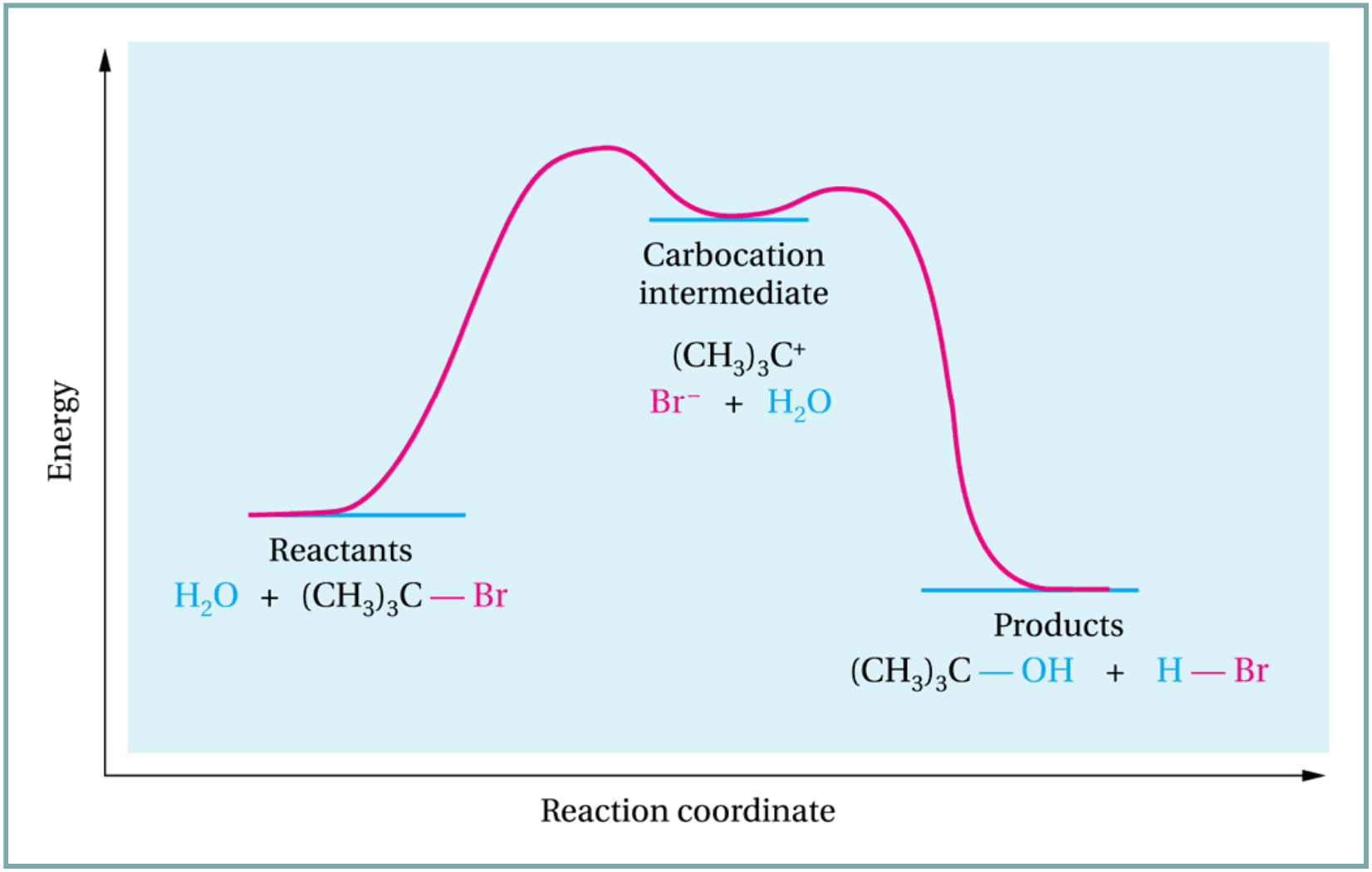


carbocation nucleophile

(6.13)

When the nucleophile is a neutral molecule, such as water or an alcohol, loss of a proton from the nucleophilic oxygen, in a third step, gives the final product.

Figure 6.2 Reaction energy diagram for an S_N1 reaction



The number 1 is used to designate this mechanism because the slow, or rate-determining, step involves *only one* of the two reactants: the substrate (eq. 6.12). It does *not* involve the nucleophile at all. That is, the first step is *uni*molecular. The reaction shown in eq. 6.6 occurs by an S_N1 mechanism and a reaction energy diagram for that reaction is shown in Figure 6.2. Notice that the energy diagram for this reaction, and all S_N1 reactions, resembles that of an electrophilic addition to an alkene (Figure 3.11), another reaction that has a carbocation intermediate. Also notice that the energy of activation for the first step (the rate-determining step) is much greater than for subsequent steps. This first step forms the highest energy (most unstable) species in the reaction energy diagram.

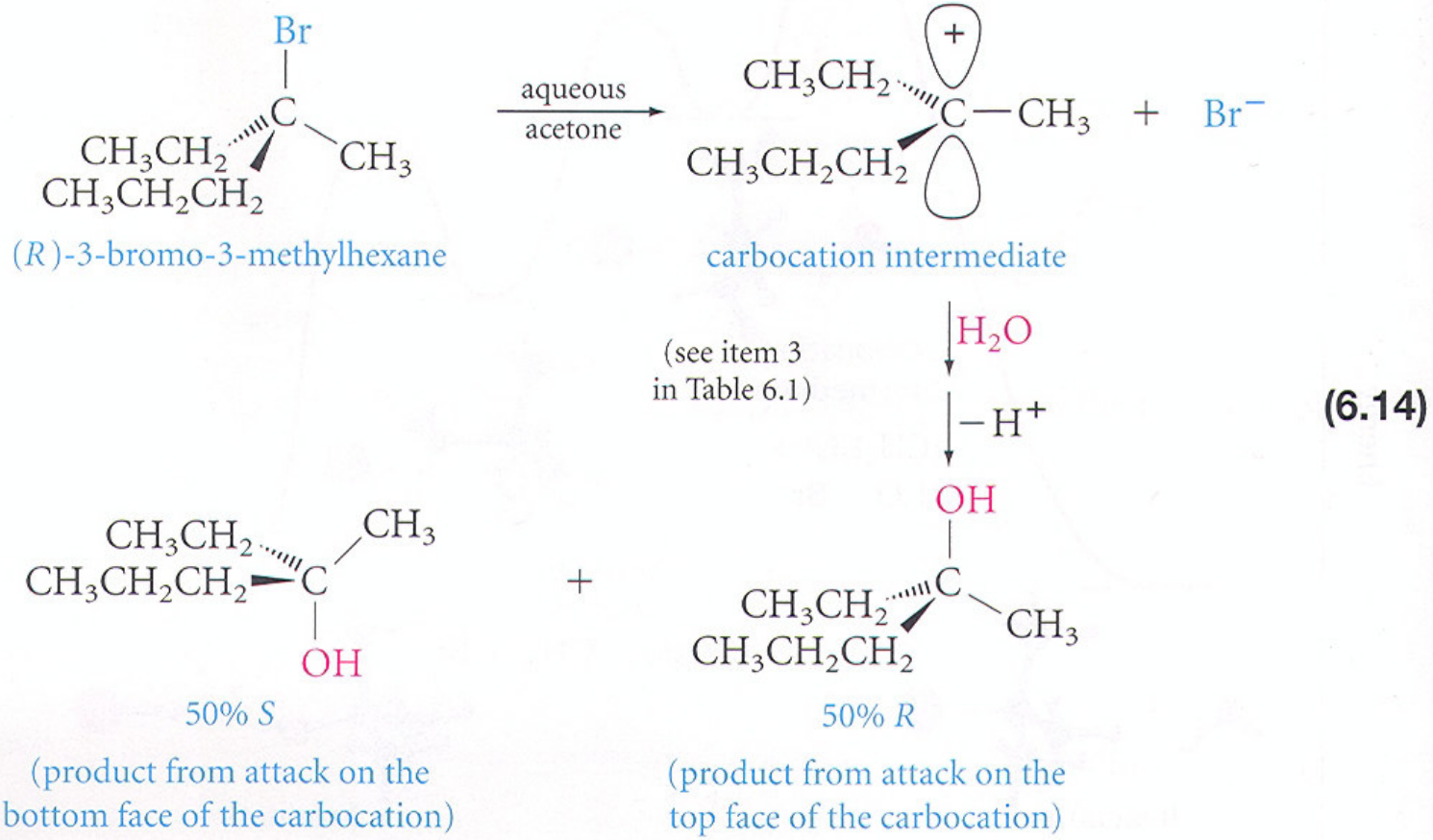
How can we recognize when a particular nucleophile and substrate react by the S_N1 mechanism? Here are the signs:

Tell-Tale Signs of S_N1

1. *The rate of the reaction does not depend on the concentration of the nucleophile.* The first step is rate determining, and the nucleophile is not involved in this step. The bottleneck in the reaction rate is therefore the rate of formation of the carbocation, not the rate of its reaction with the nucleophile, which is nearly instantaneous.

2. *If the carbon bearing the leaving group is stereogenic, the reaction occurs mainly with loss of optical activity (that is, with racemization).* In carbocations, only three groups are attached to the positively charged carbon. Therefore, the positively charged carbon is sp^2-hybridized and planar. As shown in eq. 6.13, the

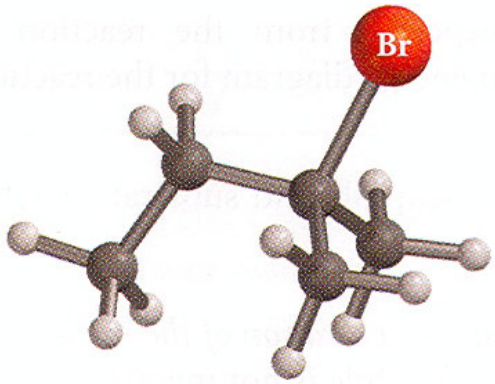
nucleophile can react at either "face" of the carbocation to give a 50:50 mixture of two enantiomers, a racemic mixture. For example, the reaction of (*R*)-3-bromo-3-methylhexane with water gives the racemic alcohol.

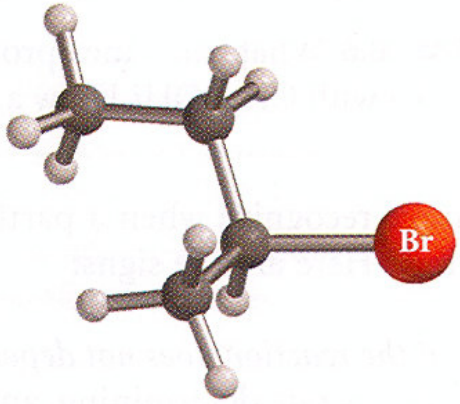


The intermediate carbocation is planar and achiral. Combination with H_2O from the "top" or "bottom" of the carbocation intermediate is equally probable, giving the *R* and *S* alcohols, respectively, in equal amounts.

3. *The reaction is fastest when the alkyl group of the substrate is tertiary and slowest when it is primary.* The reason is that S_N1 reactions proceed via carbocations, so the reactivity order corresponds to that of carbocation stability ($3° > 2° > 1°$). That is, the easier it is to form the carbocation, the faster the reaction will proceed. For this reason, S_N1 reactivity is also favored for resonance-stabilized carbocations, such as allylic carbocations (see Sec. 3.15). Likewise, S_N1 reactivity is disfavored for aryl and vinyl halides because aryl and vinyl carbocations are unstable and not easily formed.

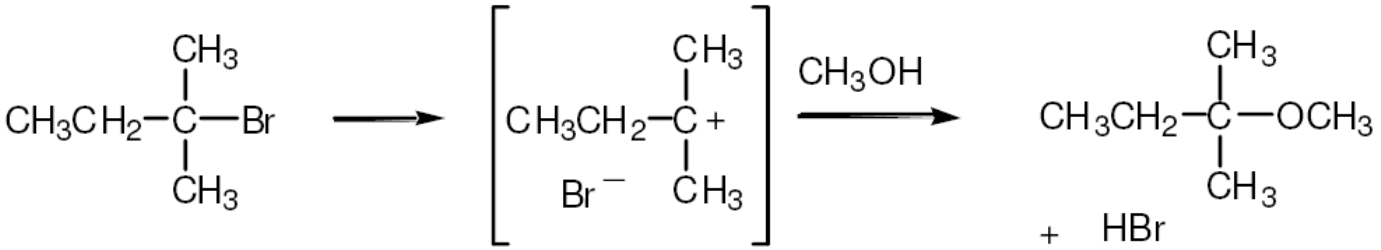
PROBLEM 6.7 Which of the following bromides will react faster with methanol (via an S_N1 reaction)? What are the reaction products in each case?

a. 

or 

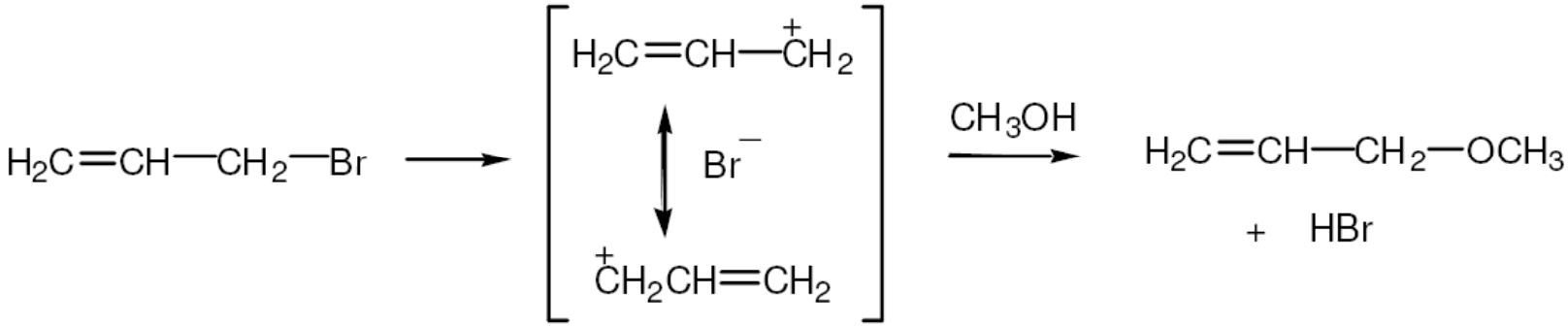
b. $CH_3CH_2CH_2Br$ or $H_2C{=}CHCH_2Br$

a. $CH_3CH_2C(CH_3)_2Br$ will react faster than $CH_3CH_2CH(CH_3)Br$ because ionization of the C–Br bond gives the more stable carbocation (tertiary versus secondary).



b. Allyl bromide, $CH_2{=}CHCH_2Br$, will react faster than $CH_3CH_2CH_2Br$ because ionization of

the C–Br bond gives the more stable carbocation (allylic versus primary).



allylic carbocation

Summary

Nucleophilic substitution may occur by two mechanisms. The **S_N2** mechanism is a one-step process. Its rate depends on the concentrations of substrate and nucleophile. If the halogen-bearing carbon is stereogenic, substitution occurs with inversion of configuration. The reaction is fastest for primary halides and slowest for tertiary halides.

The **S_N1 mechanism** is a two-step process. In the first step, the alkyl halide ionizes to a carbocation and a halide ion. In the second, fast step, the carbocation combines with the nucleophile. The overall rate is independent of nucleophile concentration. If the halogen-bearing carbon is stereogenic, substitution occurs with racemization. The reaction is fastest for tertiary halides and slowest for primary halides. The two mechanisms are compared in Table 6.2.

6.6 The S_N1 and S_N2 Mechanisms Compared

How can we tell whether a particular nucleophilic substitution reaction will proceed by an S_N2 or an S_N1 mechanism? And why do we care? We care for several reasons. When we perform a reaction in the laboratory, we want to be sure that the reaction will proceed at a rate fast enough to obtain the product in a reasonable time. If the reaction has stereochemical consequences, we want to know in advance what that outcome will be: inversion or racemization.

Table 6.2 should be helpful. It summarizes what we have said so far about the two substitution mechanisms, and it compares them with respect to two other variables, solvent and nucleophile structure, which we will discuss here.

Primary halides almost always react by the S_N2 mechanism, whereas tertiary halides react by the S_N1 mechanism. Only with secondary halides are we likely to encounter both possibilities.

Table 6.2 **Comparison of S_N2 and S_N1 substitutions**

Variables	S_N2	S_N1
Halide structure		
Primary or CH_3	Common	Rarely*
Secondary	Sometimes	Sometimes
Tertiary	Rarely	Common
Stereochemistry	Inversion	Racemization
Solvent	Rate is retarded by polar protic solvents and increased by polar aprotic solvents	Because the intermediates are ions, the rate is increased by polar solvents
Nucleophile	Rate depends on nucleophile concentration; mechanism is favored when the nucleophile is an anion	Rate is independent of nucleophile concentration; mechanism is more likely with neutral nucleophiles

*Allyl and benzyl substrates are the common exceptions (see Problem 6.7b).

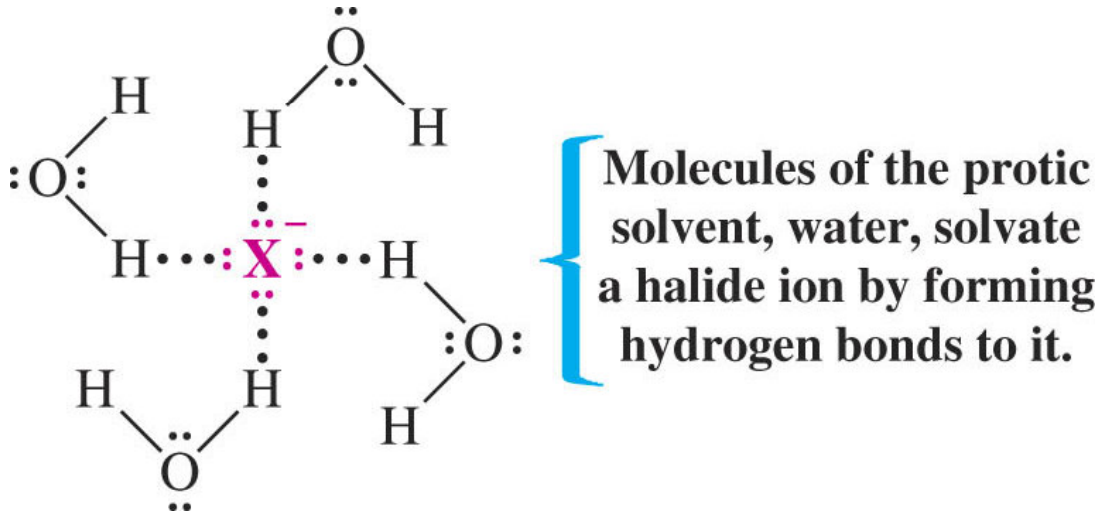
Solvent Effects

One experimental variable that we can use to help control the mechanism is the solvent polarity. Water and alcohols are **polar protic solvents** (protic because of the proton-donating ability of the hydroxyl groups). How will such solvents affect S_N1 and S_N2 reactions?

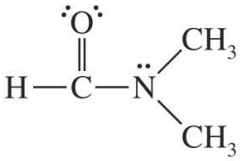
The first step of the S_N1 mechanism involves the formation of ions. Since polar solvents can solvate ions, the rate of S_N1 processes is enhanced by polar solvents. On the other hand, solvation of nucleophiles ties up their unshared electron pairs. Therefore, S_N2 reactions, whose rates depend on nucleophile effectiveness, are usually retarded by polar protic solvents. Polar but *aprotic* solvents [examples are acetone, dimethyl sulfoxide, $(CH_3)_2S{=}O$, or dimethylformamide, $(CH_3)_2NCHO$] solvate cations preferentially. These solvents *accelerate* S_N2 reactions because, by solvating the cation (say, K^+ in $K^{+-}CN$), they leave the anion more "naked" or unsolvated, thus improving its nucleophilicity.

– Solvent Effects on S_N2 Reactions: Polar Protic and Aprotic Solvents

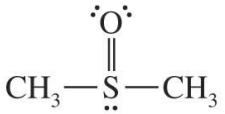
- Polar Protic Solvents
  - Polar solvents have a hydrogen atom attached to strongly electronegative atoms
  - They solvate nucleophiles and make them less reactive



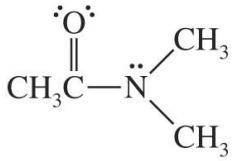
- Polar Aprotic Solvents
  - Polar aprotic solvents do not have a hydrogen attached to an electronegative atom



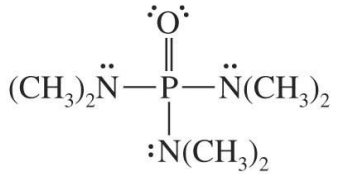
N,*N*-Dimethylformamide (DMF)



Dimethyl sulfoxide (DMSO)

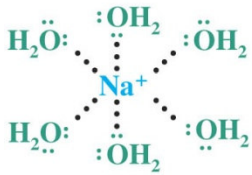


Dimethylacetamide (DMA)

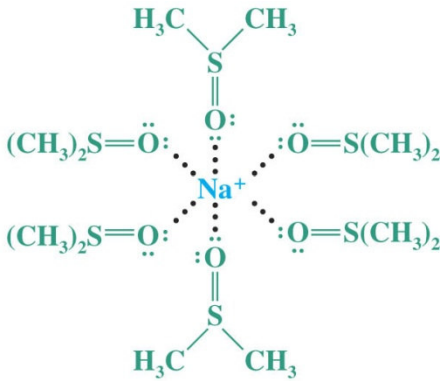


Hexamethylphosphoramide (HMPA)

  - They solvate cations well but leave anions unsolvated because positive centers in the solvent are sterically hindered



A sodium ion solvated by molecules of the protic solvent water



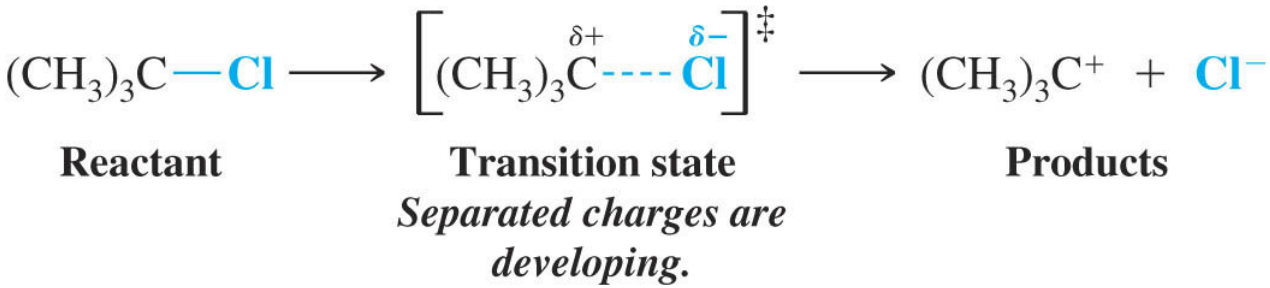
A sodium ion solvated by molecules of the aprotic solvent DMSO

  - Polar aprotic solvents lead to generation of “naked” and very reactive nucleophiles

  - They are excellent solvents for S_N2 reactions

– Solvent Effects on S_N1 Reactions: The Ionizing Ability of the Solvent

- Polar protic solvents are excellent solvents for S_N1 reactions
- Polar protic solvents stabilize the transition state
- Water-ethanol and water-methanol mixtures are most common



Nucleophile Strength

Now let us consider the other variable in Table 6.2—the nucleophile. As we have seen, the rate of an S_N2 reaction (but *not* an S_N1 reaction) depends on the nucleophile. If the nucleophile is *strong*, the S_N2 mechanism will be favored. How can we tell whether a nucleophile is strong or weak, or whether one nucleophile is stronger than another? Here are a few useful generalizations.

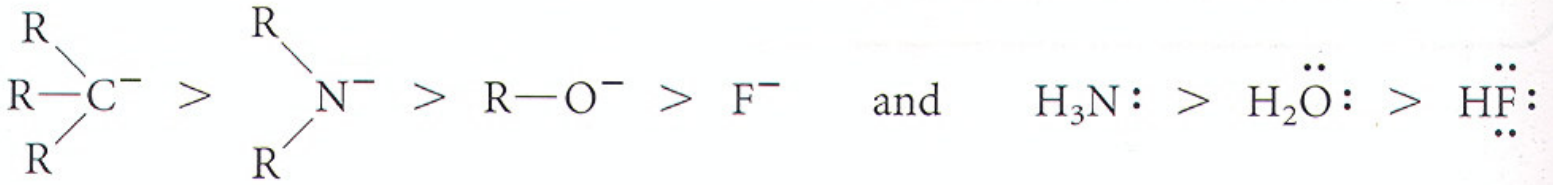
1. *Negative ions are more nucleophilic, or better electron suppliers, than the corresponding neutral molecules.* Thus,

$$HO^- > HOH \qquad RS^- > RSH \qquad RO^- > ROH$$

2. *Elements low in the periodic table tend to be more nucleophilic than elements above them in the same column.* Thus,

$$HS^- > HO^- \qquad I^- > Br^- > Cl^- > F^- \quad \text{(in protic solvents)}$$

3. *Elements in the same row in the periodic table tend to be less nucleophilic, the more electronegative the element (that is, the more tightly it holds electrons to itself).* Thus,



– Larger nucleophilic atoms are less solvated and therefore more reactive in polar protic solvents

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

– Larger nucleophiles are also more polarizable and can donate more electron density

EXAMPLE 6.6

Which mechanism, S_N1 or S_N2, would you predict for this reaction?

$$(CH_3)_3CBr + CH_3OH \longrightarrow (CH_3)_3COCH_3 + HBr$$

SOLUTION S_N1, because the substrate is a tertiary alkyl halide. Also, methanol is a weak, neutral nucleophile and, if used as the reaction solvent, rather polar. Thus, it favors ionization.

EXAMPLE 6.7

Which mechanism, S_N1 or S_N2, would you predict for this reaction?

$$CH_3CH_2—I + NaOCH_3 \longrightarrow CH_3CH_2—OCH_3 + NaI$$

SOLUTION S_N2, because the substrate is a primary halide, and methoxide (CH_3O^-), an anion, is a rather strong nucleophile.

PROBLEM 6.8 Which mechanism, S_N1 or S_N2, would you predict for each of the following reactions?

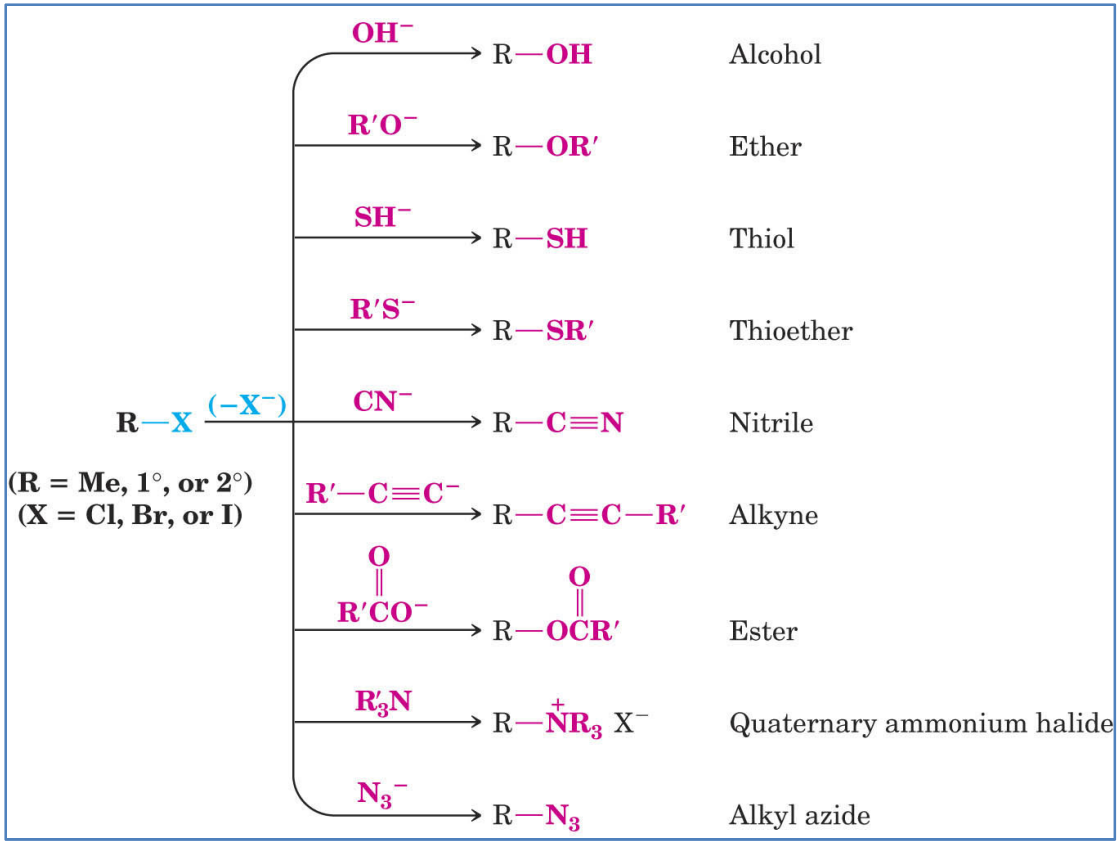
a. $CH_3\underset{\displaystyle Br}{\underset{|}{C}}HCH_2CH_2CH_3 + Na^{+-}SH \longrightarrow CH_3\underset{\displaystyle SH}{\underset{|}{C}}HCH_2CH_2CH_3 + NaBr$

b. $CH_3\underset{\displaystyle Br}{\underset{|}{C}}HCH_2CH_2CH_3 + CH_3OH \longrightarrow CH_3\underset{\displaystyle OCH_3}{\underset{|}{C}}HCH_2CH_2CH_3 + HBr$

a. S_N2. The substrate is a secondary halide and may react by either S_N2 or S_N1. The nucleophile HS^- is a strong nucleophile, favoring S_N2.

b. S_N1. The substrate is a secondary halide and may react by either mechanism. The nucleophile (CH_3OH) is relatively weak and also polar, favoring the ionization mechanism.

- Organic Synthesis: Functional Group Transformations Using S_N2 Reactions



Stereochemistry can be controlled in S_N2 reactionS