Organic Halogen Compounds; Substitution and Elimination Reactions

Chapter Summary

Alkyl halides react with **nucleophiles**, reagents that can supply an electron pair to form a covalent bond, to give a product in which the nucleophile takes the place of the halogen. Table 6.1 gives fifteen examples of such **nucleophilic substitution reactions**, which can be used to convert alkyl halides to alcohols, ethers, esters, amines, thiols, alkyl cyanides, or acetylenes.

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.

Elimination reactions often compete with substitution. They involve elimination of the halogen and a hydrogen from adjacent carbons to form an alkene. Like substitution, they occur by two main mechanisms. The **E2 mechanism** is a one-step process. The nucleophile acts as a base to remove the adjacent proton. The preferred form of the transition state is planar, with the hydrogen and the **leaving group** in an *anti* conformation. The **E1 mechanism** has the same first step as the S_N1 mechanism. The resulting carbocation then loses a proton from a carbon atom adjacent to the positive carbon to form the alkene.

Several polyhalogen compounds have useful properties. Among them, carbon tetrachloride, chloroform, and methylene chloride are useful solvents. Other important polyhalogen compounds include **Halons** ($CBrClF_2$ and $CBrF_3$) used as fire extinguishers, and **hydrochlorofluorocarbons** (HCFCs), used as refrigerants, blowing agents, aerosol propellants, and solvents. **Teflon** is a polymer of tetrafluoroethene. It is used in nonstick coatings, Gore-Tex fabrics, insulators, and many other things. Certain **perfluorochemicals** dissolve high percentages of oxygen and can be used as artificial blood. Many halogen-containing compounds are important pesticides.
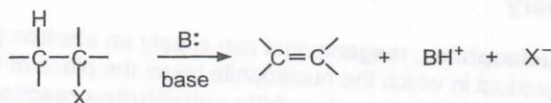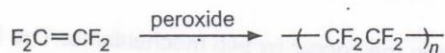
Reaction Summary

Nucleophilic Substitution

$$Nu: + R-X \longrightarrow R-Nu^+ + X^-$$

$$Nu:^- + R-X \longrightarrow R-Nu + X^-$$

(See Table 6.1 for examples)

Elimination

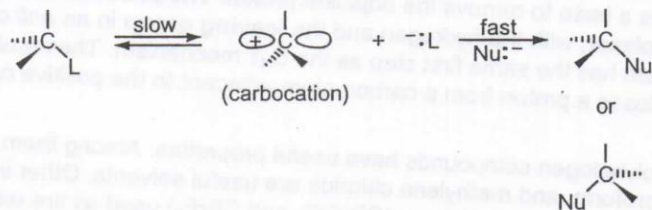
Preparation of Teflon
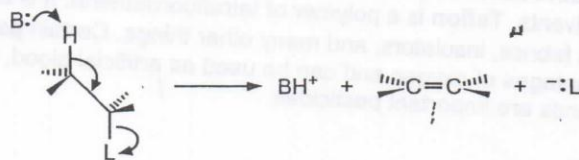
$$F_2C=CF_2 \xrightarrow{\text{peroxide}} -(CF_2CF_2)_n-$$

Mechanism Summary

S_N2 (Bimolecular Nucleophilic Substitution)
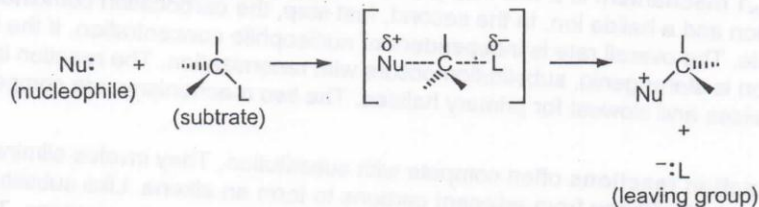
S_N1 (Unimolecular Nucleophilic Substitution)
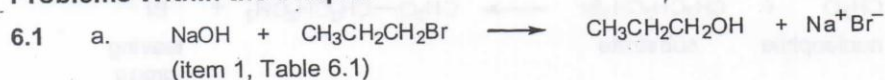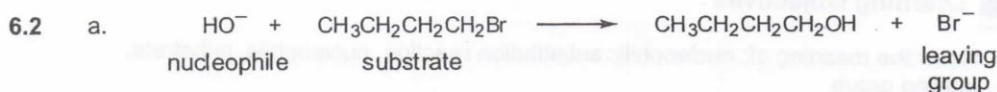

E2 (Bimolecular Elimination)

E1 (Unimolecular Elimination)

$$-\overset{\overset{H}{|}}{\underset{|}{C}}-\overset{\overset{H}{|}}{\underset{|}{C}}-L \quad \longrightarrow \quad -\overset{\overset{H}{|}}{\underset{|}{C}}-\overset{+}{C}\diagdown \quad \longrightarrow \quad \diagup C = C \diagdown$$

$$L:^- \qquad\qquad\qquad H^+$$
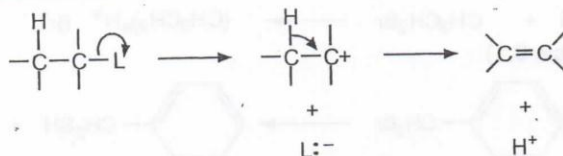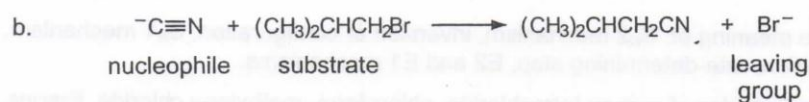
<div style="border:1px solid #000; padding:4px; display:inline-block;">   </div> **Learning Objectives**

1. Know the meaning of: nucleophilic substitution reaction, nucleophile, substrate, leaving group.

2. Be familiar with the examples of nucleophilic substitution reactions listed in Table 6.1.

3. Know the meaning of: S_N2 mechanism, inversion of configuration, S_N1 mechanism, racemization, rate-determining step, E2 and E1 mechanisms.

4. Know the formulas of carbon tetrachloride, chloroform, methylene chloride, Freons, Halons, Teflon.

5. Given the name of an alkyl halide or a polyhalogen compound, write its structural formula.

6. Given the structural formula of an alkyl halide, write a correct name for it.

7. Write the equation for the reaction of an alkyl halide with any of the nucleophiles listed in Table 6.1. Recognize the class of organic compound to which the product belongs.

8. Given the structure of an alkyl halide, predict whether it is most likely to react with nucleophiles by an S_N1 or an S_N2 mechanism.

9. Given the structure of an alkyl halide and a nucleophile, write the equations that illustrate the formation of both the substitution and elimination products and be able to predict which path is likely to be favored.

10. Know the stereochemical outcome of S_N1 and S_N2 substitutions and E1 and E2 eliminations.

11. Given an alkyl halide with a particular stereochemistry, a nucleophile, and reaction conditions, predict the stereochemistry of the product of nucleophilic substitution.

12. Combine nucleophilic substitutions with previously studied reactions to devise a multi-step synthesis of a given product.
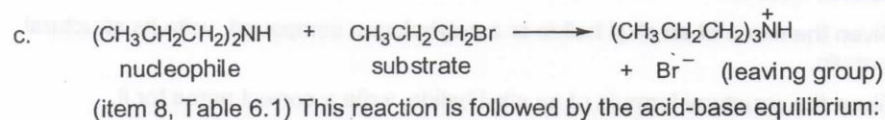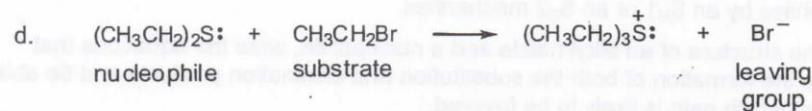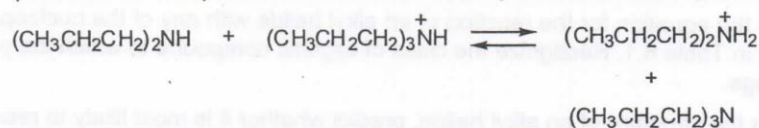
ANSWERS TO PROBLEMS

Problems Within the Chapter

6.1   a. $NaOH + CH_3CH_2CH_2Br \longrightarrow CH_3CH_2CH_2OH + Na^+Br^-$
         (item 1, Table 6.1)

b. $(CH_3CH_2)_3N$ + CH_3CH_2Br ⟶ $(CH_3CH_2)_4N^+$ Br^-
(item 9, Table 6.1)

c. $NaSH$ + ⟨benzene⟩–CH_2Br ⟶ ⟨benzene⟩–CH_2SH + $Na^+ Br^-$
(item 10, Table 6.1)

6.2 a. HO^- + $CH_3CH_2CH_2CH_2Br$ ⟶ $CH_3CH_2CH_2CH_2OH$ + Br^-
nucleophile   substrate   leaving group
(item 1, Table 6.1)

b. $^-C\equiv N$ + $(CH_3)_2CHCH_2Br$ ⟶ $(CH_3)_2CHCH_2CN$ + Br^-
nucleophile   substrate   leaving group
(item 14, Table 6.1)

c. $(CH_3CH_2CH_2)_2NH$ + $CH_3CH_2CH_2Br$ ⟶ $(CH_3CH_2CH_2)_3\overset{+}{N}H$
nucleophile   substrate   + Br^- (leaving group)
(item 8, Table 6.1) This reaction is followed by the acid-base equilibrium:
$(CH_3CH_2CH_2)_2NH$ + $(CH_3CH_2CH_2)_3\overset{+}{N}H$ ⇌ $(CH_3CH_2CH_2)_2\overset{+}{N}H_2$
+
$(CH_3CH_2CH_2)_3N$

d. $(CH_3CH_2)_2\overset{..}{S}:$ + CH_3CH_2Br ⟶ $(CH_3CH_2)_3\overset{+}{S}:$ + Br^-
nucleophile   substrate   leaving group
(item 12, Table 6.1)

e. I^- + $CH_2=CHCH_2Br$ ⟶ $CH_2=CHCH_2I$ + Br^-
nucleophile   substrate   leaving group
(item 13, Table 6.1)
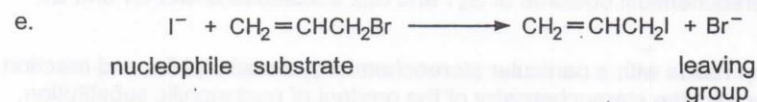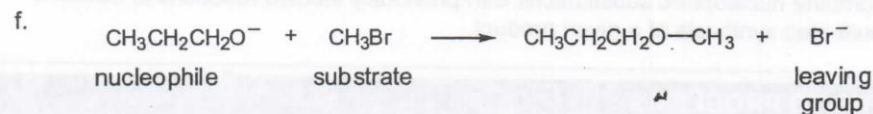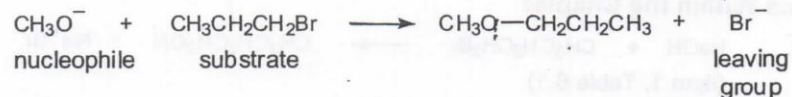
f. $CH_3CH_2CH_2O^-$ + CH_3Br ⟶ $CH_3CH_2CH_2O-CH_3$ + Br^-
nucleophile   substrate   leaving group
or
CH_3O^- + $CH_3CH_2CH_2Br$ ⟶ $CH_3O-CH_2CH_2CH_3$ + Br^-
nucleophile   substrate   leaving group
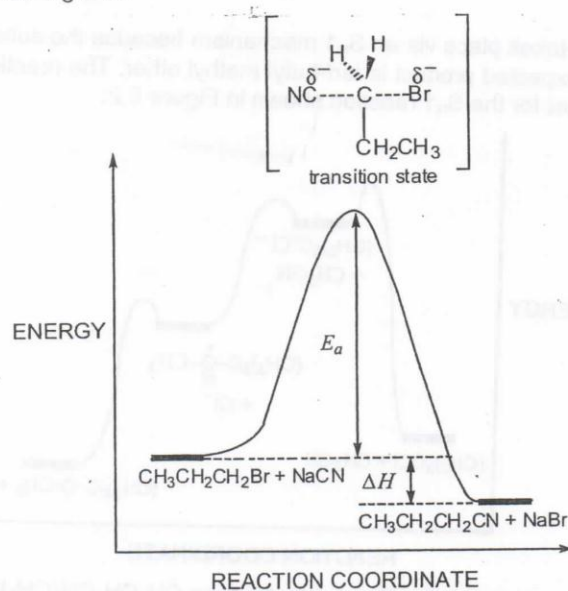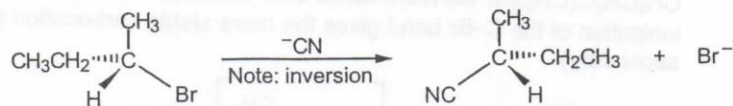(item 2, Table 6.1) Iodides or chlorides could also be used as substrates.

6.3   Use Figure 6.1 as a guide:

$$\left[\begin{array}{c} H \\ NC\underset{\delta^-}{----}C\underset{\delta^-}{----}Br \\ | \\ CH_2CH_3 \end{array}\right]$$
transition state

ENERGY

E_a

REACTION COORDINATE

$CH_3CH_2CH_2Br + NaCN$

ΔH

$CH_3CH_2CH_2CN + NaBr$

6.4   a.

$$CH_3CH_2\overset{CH_3}{\underset{H}{\text{''''}C}}Br \xrightarrow[\text{Note: inversion}]{^-CN} \overset{CH_3}{\underset{H}{C\text{''''}CH_2CH_3}} + Br^-$$
NC

b.

$$CH_3\text{-}\overset{}{\bigcirc}\text{''''}Br \xrightarrow[\text{Note: } \textit{trans} \longrightarrow \textit{cis}]{^-CN} H_3C\text{-}\overset{}{\bigcirc}\text{-}CN + Br^-$$

c.

$$H\overset{CH_3}{\underset{CH_3CH_2CH_2}{\text{''''}C}}Br \xrightarrow[\text{Note: inversion}]{Na^+ \ ^-SH} \overset{CH_3}{\underset{CH_2CH_2CH_3}{C\text{''''}H}} + Br^-$$
HS
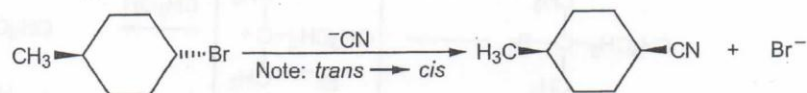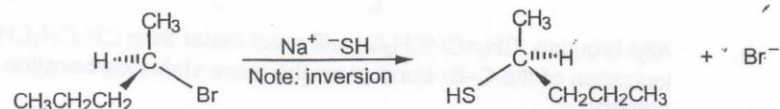
6.5 $CH_3CH_2CH_2CH_2Br > (CH_3)_2CHCH_2Br > CH_3CH_2CH(CH_3)Br$
The more crowded the carbon where displacement occurs, the slower the reaction rate.

6.6 The reaction takes place via an S_N1 mechanism because the substrate is a tertiary halide. The expected product is *tert*-butyl methyl ether. The reaction energy diagram resembles that for the S_N1 reaction shown in Figure 6.2:
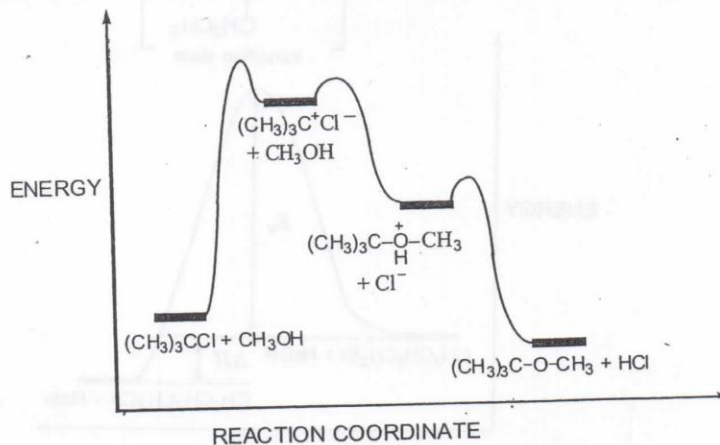
6.7 a. $CH_3CH_2C(CH_3)_2Br$ will react faster than $CH_3CH_2CH(CH_3)Br$ because ionization of the C–Br bond gives the more stable carbocation (tertiary versus secondary).
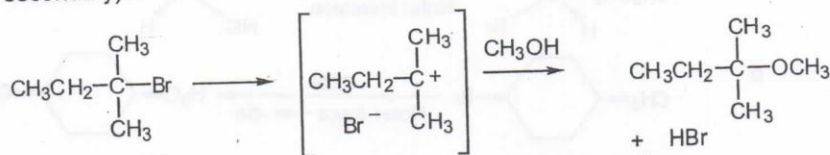

b. Allyl bromide, $CH_2=CHCH_2Br$, will react faster than $CH_3CH_2CH_2Br$ because ionization of the C–Br bond gives the more stable carbocation (allylic versus primary).
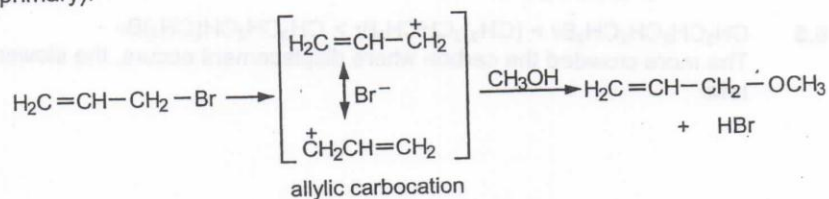
6.8 a. S_N2. The substrate is a secondary halide and may react by either S_N2 or S_N1. The nucleophile HS^- is a strong nucleophile, favoring S_N2.

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.

6.9   Two products are possible. Removal of the hydrogen from carbon-1 gives 2-methyl-1-butene. Removal of the hydrogen from carbon-3 gives 2-methyl-2-butene.
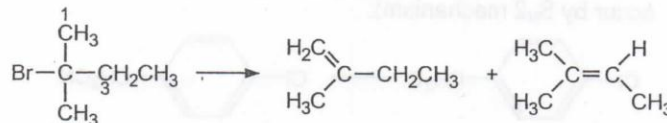

6.10
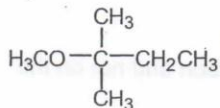
2-Bromo-2-methylbutane is a tertiary alkyl halide. It reacts with methanol, a weak nucleophile and polar solvent, to give an ether by an S_N1 mechanism.

ADDITIONAL PROBLEMS

**6.11** a.   Structures of alkyl halides can be generated by taking a hydrocarbon and replacing one of the hydrogens with a halogen. Thus, taking propane (C_3H_8) and replacing one of the hydrogens with a chlorine will generate an alkyl halide with the molecular formula C_3H_7Cl. Replacement of a primary hydrogen gives a primary halide.
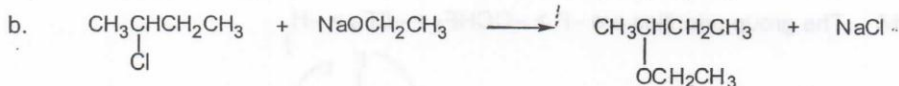
$$CH_3CH_2CH_2Cl \qquad \text{1-chloropropane}$$

b.   Start with a hydrocarbon with the molecular formula C_5H_{12} that also has a tertiary hydrogen.


2-bromo-2-methylbutane
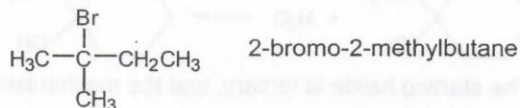
c.   In this case we must start with a hydrocarbon with the molecular formula C_6H_{12}. This formula indicates that the structure must also contain a double bond or a ring. Three of the many possibilities are shown below.

iodocyclohexane   3-iodo-1-hexene   4-iodo-1-hexene
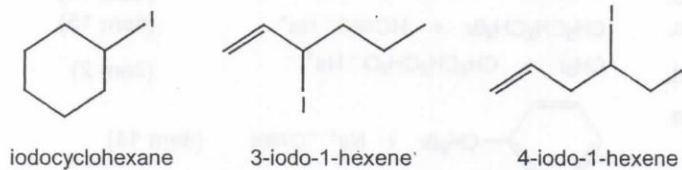
6.12   Each of these reactions involves displacement of a halogen by a nucleophile. Review Sec. 6.1 and Table 6.1.

a. $CH_3CH_2CH_2CH_2Br \ + \ NaI \longrightarrow CH_3CH_2CH_2CH_2I \ + \ NaBr$

b.

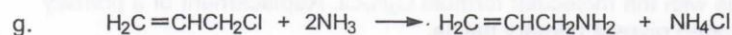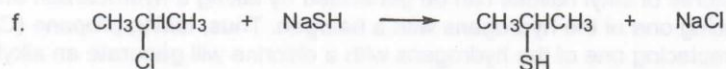c. $(CH_3)_3CBr \ + \ CH_3OH \longrightarrow (CH_3)_3COCH_3 \ + \ HBr$

The mechanism here is S_N1 (most of the other reactions in this problem occur by S_N2 mechanism).

d.
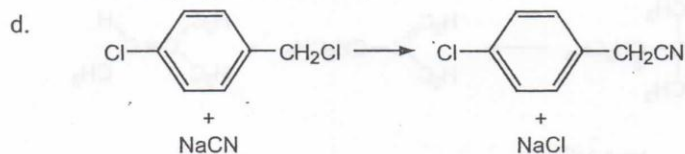
Substitution occurs only at the aliphatic (benzyl) carbon and not on the aromatic ring.

e. $CH_3CH_2CH_2I + Na^{+\;-}C\equiv CH \longrightarrow CH_3CH_2CH_2C\equiv CH + NaI$

The use of acetylides as nucleophiles is a particularly important example of nucleophilic substitution because it results in a new carbon–carbon bond. Thus, larger organic molecules can be assembled from smaller ones using this method. The same is true for cyanide ion as a nucleophile (part d).
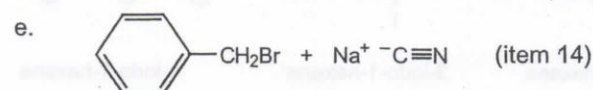
f.

g. $H_2C=CHCH_2Cl + 2NH_3 \longrightarrow H_2C=CHCH_2NH_2 + NH_4Cl$

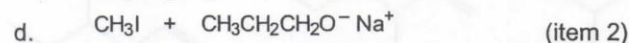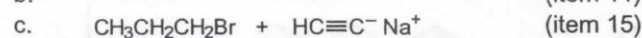h. $BrCH_2CH_2CH_2CH_2Br + 2\ NaC\equiv N \longrightarrow N\equiv CCH_2CH_2CH_2CH_2C\equiv N + 2\ NaBr$
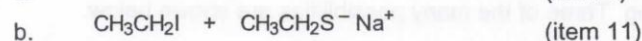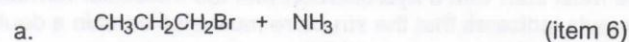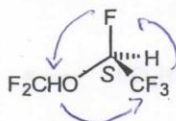
Displacement occurs at both possible positions.

i.
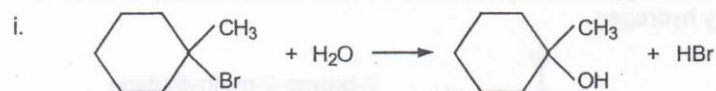
The starting halide is tertiary, and the mechanism is S_N1.

6.13 Use the equations in Table 6.1 as a guide.

a. $CH_3CH_2CH_2Br + NH_3$ (item 6)

b. $CH_3CH_2I + CH_3CH_2S^-\ Na^+$ (item 11)

c. $CH_3CH_2CH_2Br + HC\equiv C^-\ Na^+$ (item 15)

d. $CH_3I + CH_3CH_2CH_2O^-\ Na^+$ (item 2)

e.

f.
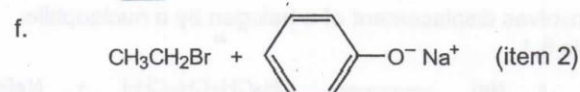
6.14 The group priorities are $-F > -OCHF_2 > -CF_3 > -H$.

6.15 The configuration inverts if the reaction occurs by an S_N2 mechanism, but if the S_N1 mechanism prevails, considerable racemization occurs.
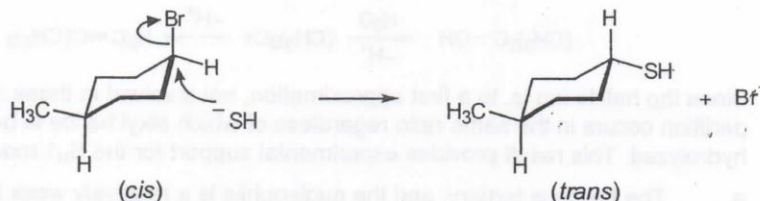
   a. The nucleophile is methoxide ion, CH_3O^-. The alkyl halide is secondary, and the mechanism is S_N2.

(inversion)

(R)-2-bromobutane   (S)-2-methoxybutane
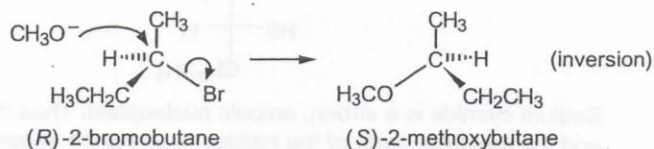
   b. The alkyl halide is tertiary and the nucleophile is methanol (a weaker nucleophile than methoxide ion). The mechanism is S_N1, and the product is a mixture of R and S isomers.

(S)-3-bromo-3-methylhexane

(R)-3-methoxy-3-methylhexane   (S)-3-methoxy-3-methylhexane
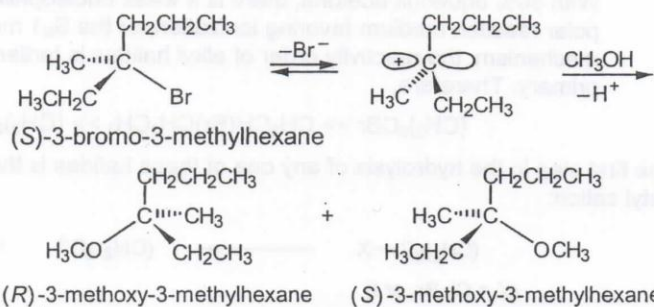
   c. The alkyl halide is secondary, and the HS^- ion is a strong nucleophile. The mechanism is S_N2.

(cis)   (trans)

6.16 An S_N2 displacement can occur. Since the leaving group and the nucleophile are identical (iodide ion), there is no change in the gross structure of the product. However, the configuration inverts every time a displacement occurs.


(R)-2-iodobutane   (S)-2-iodobutane
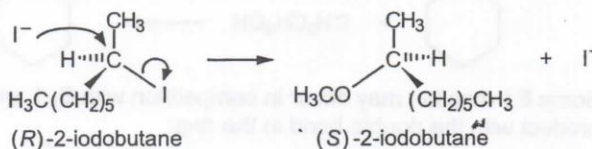
Since the enantiomer is produced, the optical rotation of the solution decreases. As the concentration of the S enantiomer builds up, it too reacts with iodide ion to form some R isomer. Eventually, an equilibrium (50:50) or racemic mixture is formed, and the solution is optically inactive.

6.17 The reaction involves a good nucleophile and a polar solvent (acetone). These conditions favor an S_N2 mechanism with inversion of configuration.
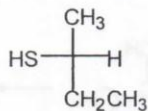

6.18 a. Sodium cyanide is a strong, anionic nucleophile. Thus the mechanism is S_N2 and the reactivity order of the halides is primary > secondary > tertiary. Therefore,

$$(CH_3)_2CHCH_2Br > CH_3CH(Br)CH_2CH_3 >> (CH_3)_3CBr$$
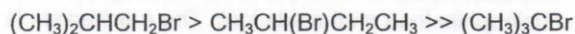
b. With 50% aqueous acetone, there is a weak nucleophile (H_2O) and a highly polar reaction medium favoring ionization, or the S_N1 mechanism. In this mechanism, the reactivity order of alkyl halides is tertiary > secondary > primary. Therefore,

$$(CH_3)_3CBr >> CH_3CH(Br)CH_2CH_3 >> (CH_3)_2CHCH_2Br$$
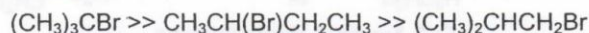
6.19 The first step in the hydrolysis of any one of these halides is the ionization to a *t*-butyl cation:

$$(CH_3)_3C{-}X \longrightarrow (CH_3)_3C^+ \ + \ X^-$$

(X = Cl, Br, or I)
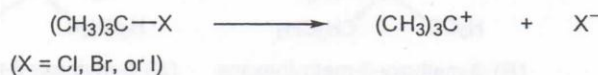
The product-determining step involves the partition of this intermediate between two paths–reaction with water and loss of a proton:

$$(CH_3)_3C{-}OH \xrightarrow[-H^+]{H_2O} (CH_3)_3C+ \xrightarrow{-H^+} H_2C{=}C(CH_3)_2$$
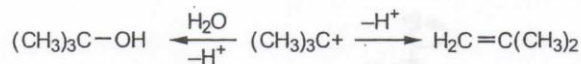
Since the halide ion is, to a first approximation, not involved in these steps, this partition occurs in the same ratio regardless of which alkyl halide is being hydrolyzed. This result provides experimental support for the S_N1 mechanism.

6.20 a. The halide is tertiary, and the nucleophile is a relatively weak base. Hence the predominant mechanism is S_N1:
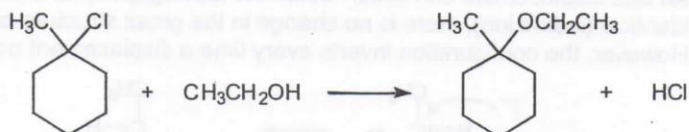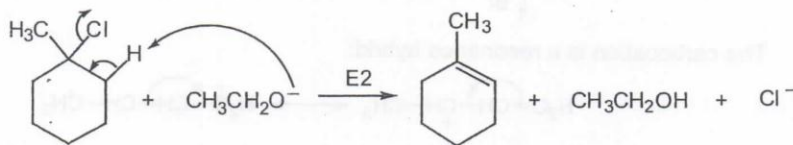

Some E1 reaction may occur in competition with S_N1, giving mainly the product with the double bond in the ring:
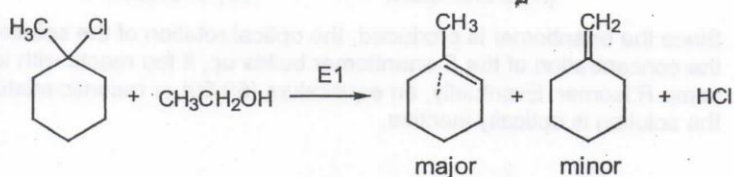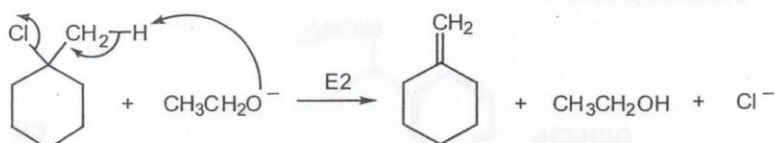

However, the main product will be the ether (S_N1).

b. The nucleophile in this case is stronger, but the S_N2 process is not possible because the alkyl halide is tertiary. This nucleophile is also a strong base. Therefore, an E2 reaction will be preferred.
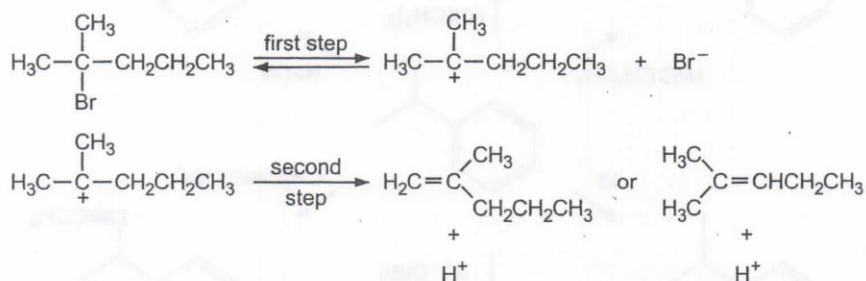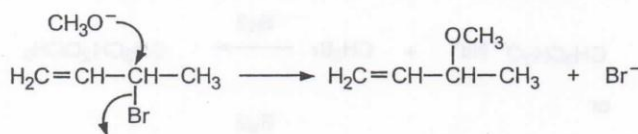

or

The predominant product is 1-methylcyclohexene, the more stable of the two possible alkenes.

6.21

In the second step, the proton may be lost from either of the methyl carbons *or* from the methylene carbon, giving the two alkenes shown.

6.22 The first reaction involves a strong nucleophile (CH_3O^-), and the S_N2 mechanism is favored. Therefore, only one product is obtained.

The second reaction involves a weak nucleophile (CH_3OH) that is also a fairly polar solvent, favoring the S_N1 mechanism:
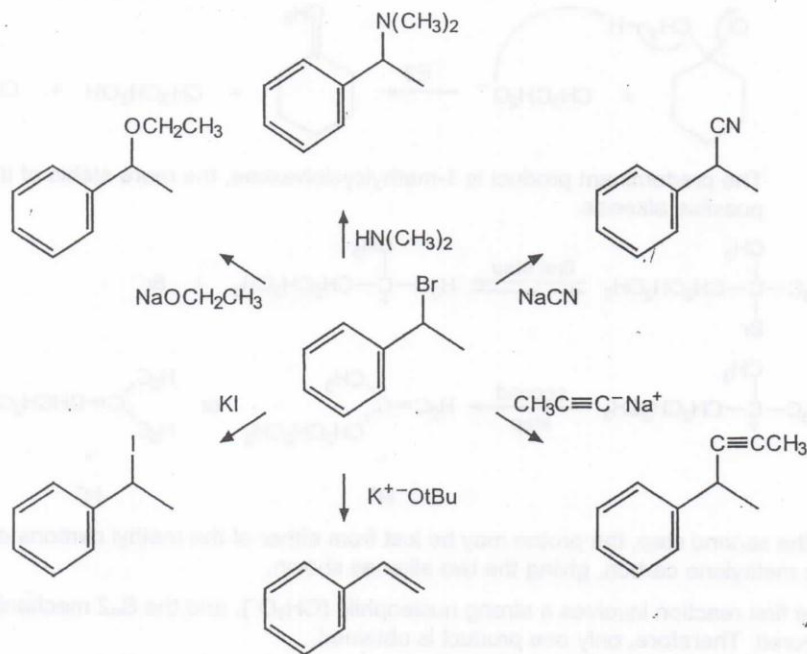
$$H_2C=CH-CH-CH_3 \rightleftharpoons H_2C=CH-\overset{+}{CH}-CH_3 + Br^-$$
$$\overset{|}{Br}$$
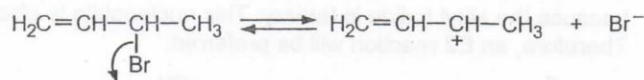
The carbocation is a resonance hybrid:

$$H_2C=CH-\overset{+}{CH}-CH_3 \longleftrightarrow H_2\overset{+}{C}-CH=CH-CH_3$$

It can react with methanol at either positively charged carbon, giving the two observed products.

6.23

6.24 a.

$$CH_3CH_2O^-Na^+ + CH_3Br \xrightarrow{S_N2} CH_3CH_2OCH_3 + Na^+Br^-$$
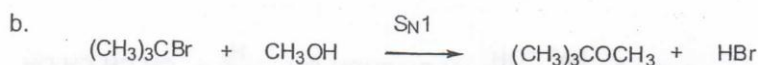
or

$$CH_3O^-Na^+ + CH_3CH_2Br \xrightarrow{S_N2} CH_3OCH_2CH_3 + Na^+Br^-$$

Both reactions would be successful. This synthesis of ethers is called the Williamson synthesis (see Sec. 8.5).

b.

$$(CH_3)_3CBr \ + \ CH_3OH \ \xrightarrow{S_N1} \ (CH_3)_3COCH_3 \ + \ HBr$$

We select this combination of reagents, *not* $(CH_3)_3COH + CH_3Br$, because methyl bromide, being primary, will not react by an S_N1 mechanism, and $(CH_3)_3COH$ is too weak a nucleophile to displace Br^- from CH_3Br in an S_N2 process. $[(CH_3)_3CO^-K^+$ would provide a strong enough nucleophile, and the reaction

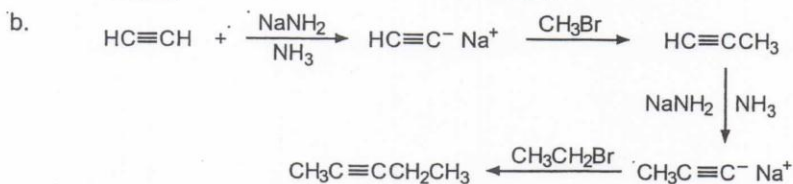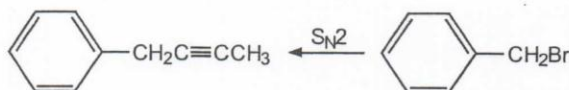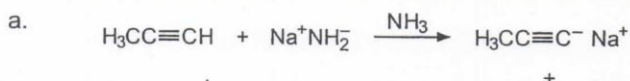$$(CH_3)_3CO^- \ K^+ \ + \ CH_3Br \ \xrightarrow{S_N2} \ (CH_3)_3COCH_3 \ + \ K^+Br^-$$

would provide an alternative synthesis of the desired product, but it uses an alkoxide rather than an alcohol as the problem specifies.]

6.25 Dehydrohalogenation of (bromomethyl)cyclohexane with potassium *tert*-butoxide, a sterically hindered and strong base, would give the desired alkene as the major product. The substitution derived from S_N2 displacement of the halide by the alkoxide might also be obtained as a minor product.
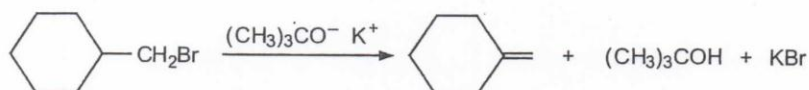
Dehydrohalogenation of 1-bromo-1-methylcyclohexane with a strong base (NaOH or potassium *tert*-butoxide) would also provide the desired alkene. This reaction, however, would be complicated by the formation of methylcyclohexene as the major product.

6.26 This type of reaction sequence is a useful method for constructing C–C bonds.

a.

$$H_3CC\equiv CH \ + \ Na^+NH_2^- \ \xrightarrow{NH_3} \ H_3CC\equiv C^- \ Na^+$$

$$+$$

b.

$$HC\equiv CH \ + \ \xrightarrow[NH_3]{NaNH_2} \ HC\equiv C^- \ Na^+ \ \xrightarrow{CH_3Br} \ HC\equiv CCH_3$$

$$\downarrow NaNH_2 \ | \ NH_3$$

$$CH_3C\equiv CCH_2CH_3 \ \xleftarrow{CH_3CH_2Br} \ CH_3C\equiv C^- \ Na^+$$

The order in which the alkyl halides were used could be reversed, with the same overall result.