

- Halogen compounds are important for several reasons. Simple alkyl and aryl halides, especially chlorides and bromides, are versatile reagents in syntheses.
- Through substitution reactions, which we will discuss in this chapter, halogens can be replaced by many other functional groups. Organic halides can be converted to unsaturated compounds through dehydrohalogenation.

6.2 Examples of Nucleophilic Substitution

- Nucleophiles can be classified according to the kind of atom that forms a new covalent bond. For example, the hydroxide ion is an *oxygen* nucleophile. In the product, a new carbon–*oxygen* bond is formed.
- *The most common nucleophiles are oxygen , nitrogen, sulfur, halogen, and carbon nucleophiles.*
- Table 6.1 shows some examples of nucleophiles and the products that they form when they react with an alkyl halide.

Table 6.1 ■ Reactions of Common Nucleophiles with Alkyl Halides (Eqs. 6.2 and 6.3)

| Nu | | R—Nu | | Comments |
|--|-----------------|--|------------------------|---|
| Formula | Name | Formula | Name | |
| Oxygen nucleophiles | | | | |
| 1. $\text{H}\ddot{\text{O}}:^-$ | hydroxide | $\text{R}-\ddot{\text{O}}\text{H}$ | alcohol | |
| 2. $\text{R}\ddot{\text{O}}:^-$ | alkoxide | $\text{R}-\ddot{\text{O}}\text{R}$ | ether | |
| 3. $\text{H}\ddot{\text{O}}\text{H}$ | water | $\text{R}-\overset{+}{\text{O}}\begin{matrix} \text{H} \\ \text{H} \end{matrix}$ | alkyloxonium ion | These ions lose a proton and the products are alcohols and ethers. $\xrightarrow{-\text{H}^+} \text{R}\ddot{\text{O}}\text{H}$ (alcohol) $\xrightarrow{-\text{H}^+} \text{R}\ddot{\text{O}}\text{R}$ (ether) |
| 4. $\text{R}\ddot{\text{O}}\text{H}$ | alcohol | $\text{R}-\overset{+}{\text{O}}\begin{matrix} \text{R} \\ \text{H} \end{matrix}$ | dialkyloxonium ion | |
| 5. $\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\overset{\ominus}{\text{O}}\ddot{\text{O}}$ | carboxylate | $\text{R}-\overset{\text{O}}{\parallel}{\ddot{\text{O}}}\text{C}-\text{R}$ | ester | |
| Nitrogen nucleophiles | | | | |
| 6. $\ddot{\text{N}}\text{H}_3$ | ammonia | $\text{R}-\overset{+}{\text{N}}\text{H}_3$ | alkylammonium ion | With a base, these ions readily lose a proton to give amines. $\xrightarrow{-\text{H}^+} \ddot{\text{N}}\text{H}_2$ $\xrightarrow{-\text{H}^+} \text{R}_2\ddot{\text{N}}\text{H}$ $\xrightarrow{-\text{H}^+} \text{R}_3\ddot{\text{N}}:$ |
| 7. $\text{R}\ddot{\text{N}}\text{H}_2$ | primary amine | $\text{R}-\overset{+}{\text{N}}\text{H}_2\text{R}$ | dialkylammonium ion | |
| 8. $\text{R}_2\ddot{\text{N}}\text{H}$ | secondary amine | $\text{R}-\overset{+}{\text{N}}\text{HR}_2$ | trialkylammonium ion | |
| 9. $\text{R}_3\ddot{\text{N}}$ | tertiary amine | $\text{R}-\overset{+}{\text{N}}\text{R}_3$ | tetraalkylammonium ion | |

Sulfur nucleophiles

10. $\text{H}\ddot{\text{S}}:^{-}$ hydrosulfide $\text{R}-\ddot{\text{S}}\text{H}$ thiol
11. $\text{R}\ddot{\text{S}}:^{-}$ mercaptide $\text{R}-\ddot{\text{S}}\text{R}$ thioether (sulfide)
12. $\text{R}_2\ddot{\text{S}}:$ thioether $\text{R}-\overset{+}{\text{S}}\text{R}_2$ trialkylsulfonium ion

Halogen nucleophiles

13. $:\ddot{\text{I}}:^{-}$ iodide $\text{R}-\ddot{\text{I}}:$ alkyl iodide

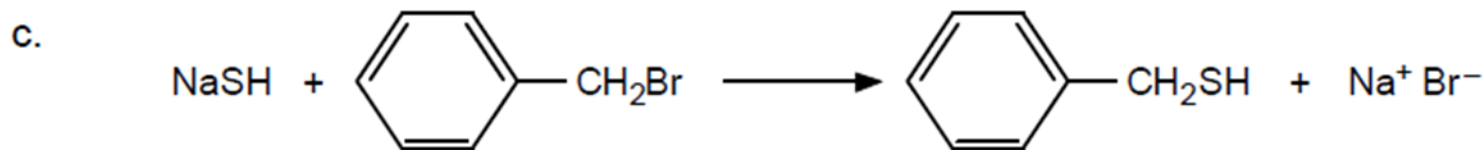
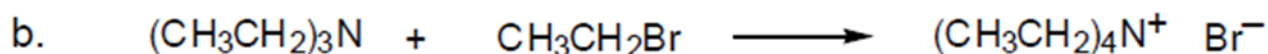
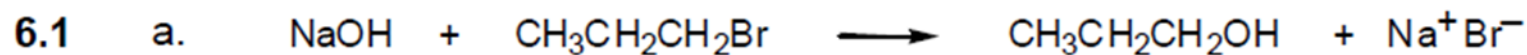
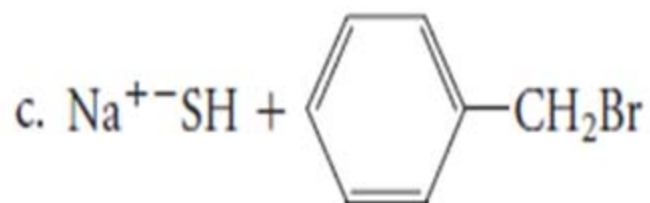
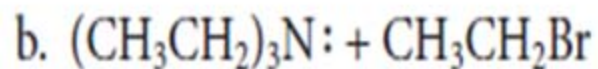
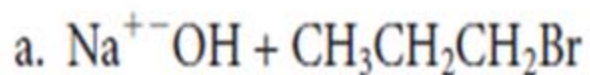
The usual solvent is acetone. Sodium iodide is soluble in acetone, but sodium bromide and sodium chloride are not.

Carbon nucleophiles

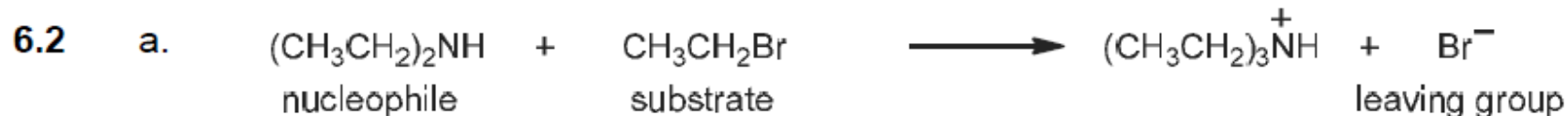
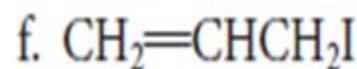
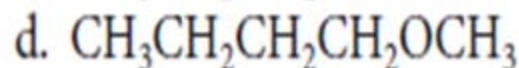
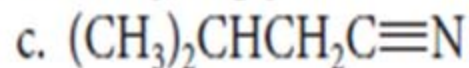
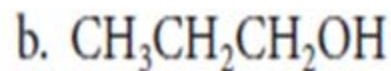
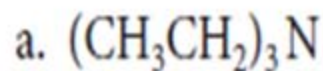
14. $^{-}:\text{C}\equiv\text{N}:$ cyanide $\text{R}-\text{C}\equiv\text{N}:$ alkyl cyanide (nitrile)
15. $^{-}:\text{C}\equiv\text{CR}$ acetylide $\text{R}-\text{C}\equiv\text{CR}$ alkyne

Sometimes the isonitrile, $\text{R}-\overset{+}{\text{N}}\equiv\text{C}^{-}:$, is formed.

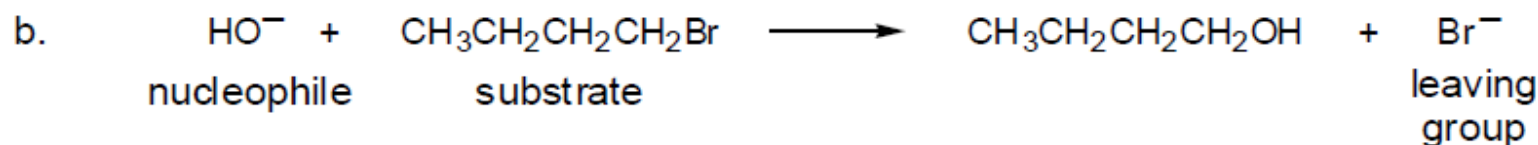
PROBLEM 6.1 Using Table 6.1, write complete equations for the following nucleophilic substitution reactions:



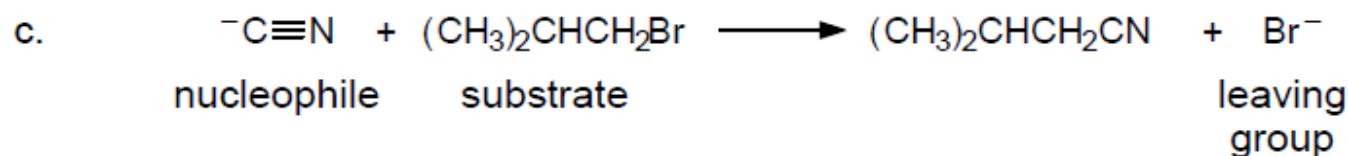
PROBLEM 6.2 Write an equation for the preparation of each of the following compounds, using a nucleophilic substitution reaction. In each case, label the nucleophile, the substrate, and the leaving group.



(item 8, Table 6.1) This reaction is followed by the acid-base equilibrium:

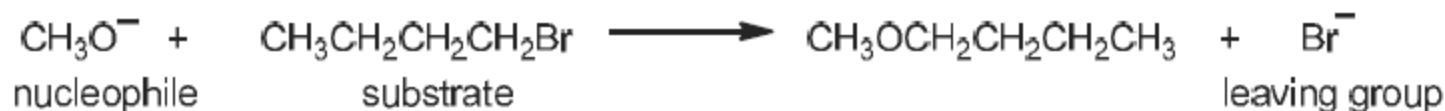
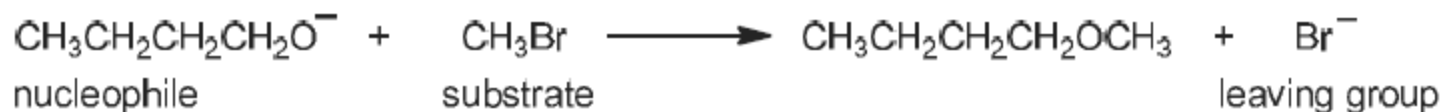


(item 1, Table 6.1)



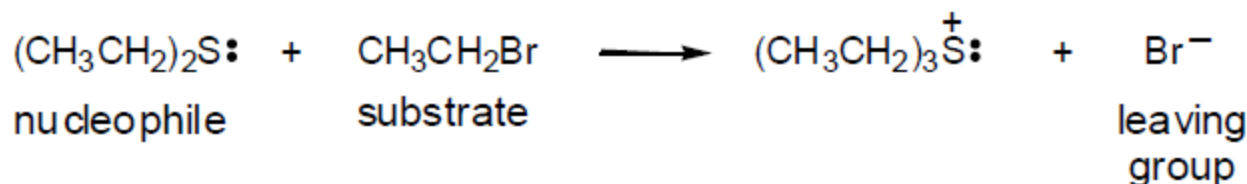
(item 14, Table 6.1)

d.



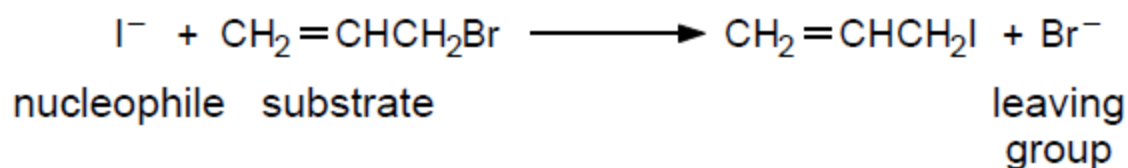
(item 2, Table 6.1) Iodides or chlorides could also be used as substrates.

e.



(item 12, Table 6.1)

f.

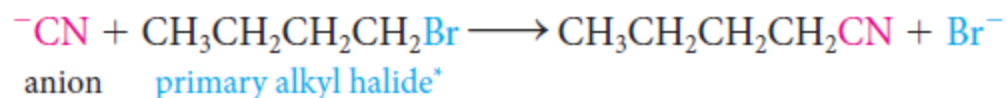


(item 13, Table 6.1)

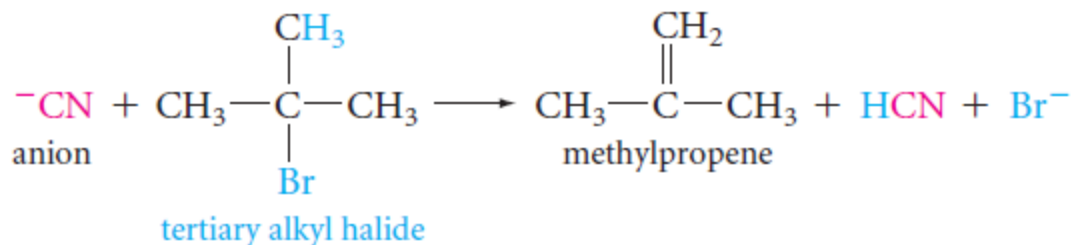
The substitution reactions have some limitations with respect to the structure of the *R* group in the alkyl halide.

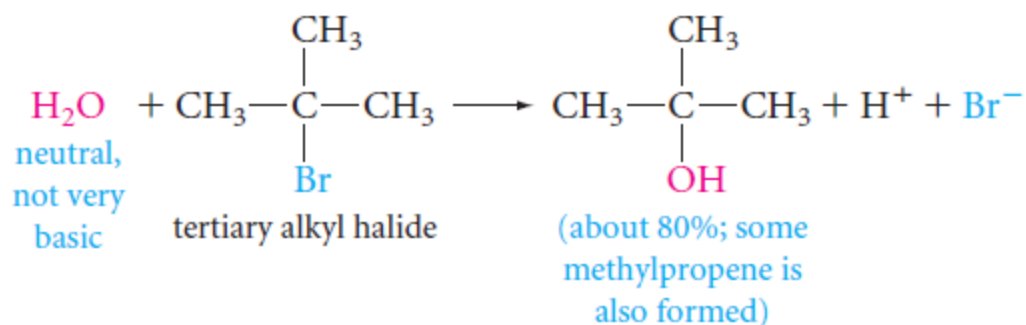
-These are reactions of alkyl halides. Aryl halides and vinyl halides, do not undergo this type of nucleophilic substitution reaction.

-Elimination rather than substitution occurs when the nucleophile is an anion or a base or both.

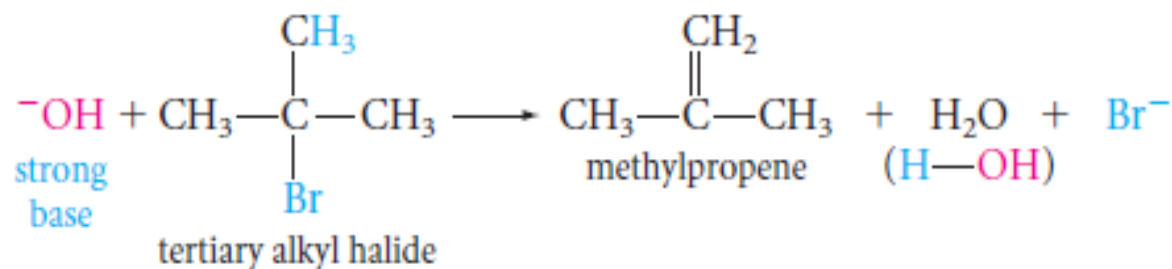


but





but

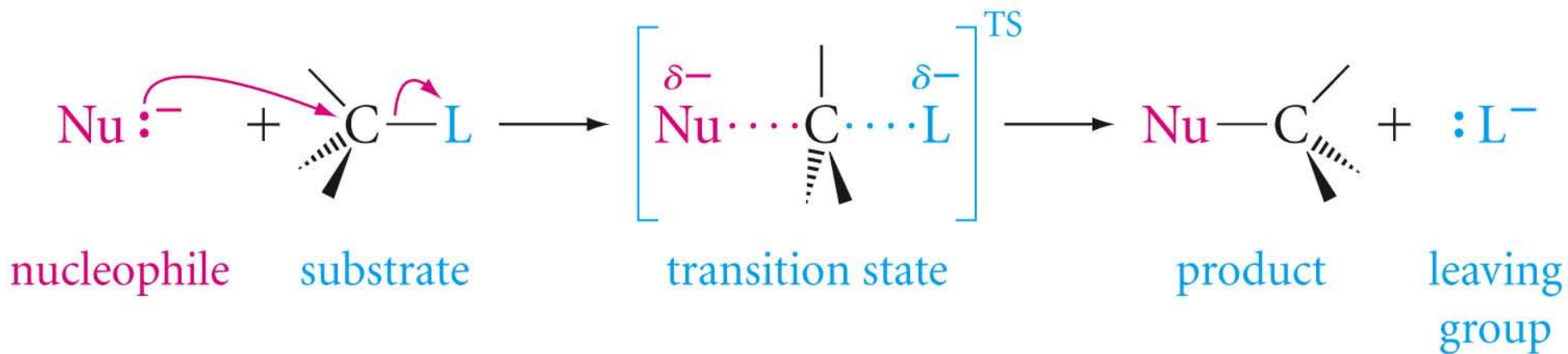


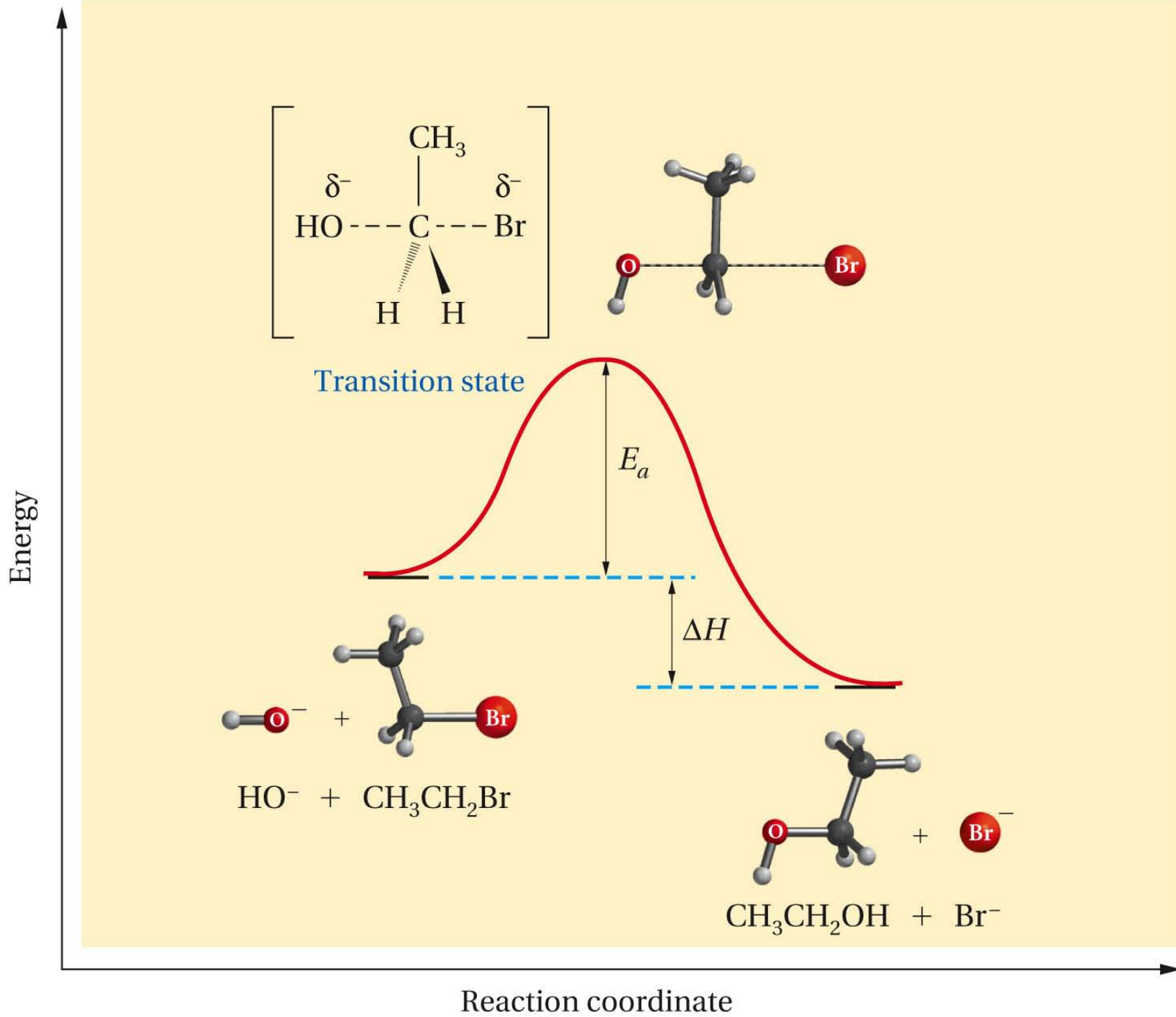
6.3 Nucleophilic Substitution Mechanisms

- There are two main nucleophilic substitution mechanisms. These are described by the symbols **S_N2** and **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

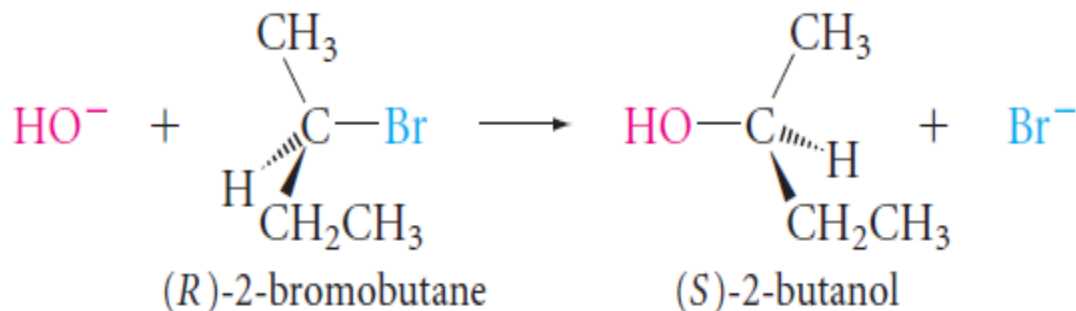
The **S_N2 mechanism** is a one-step process in which the bond to the leaving group begins to break as the bond to the nucleophile begins to form. It can be represented by the following equation:



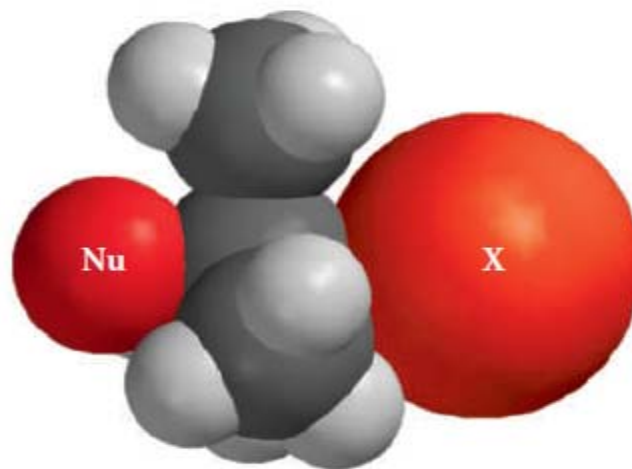
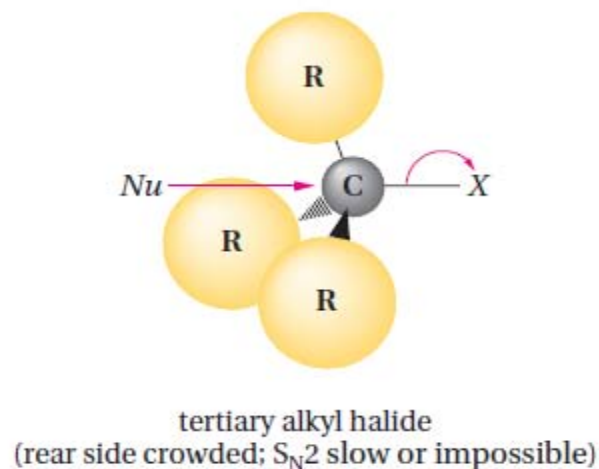
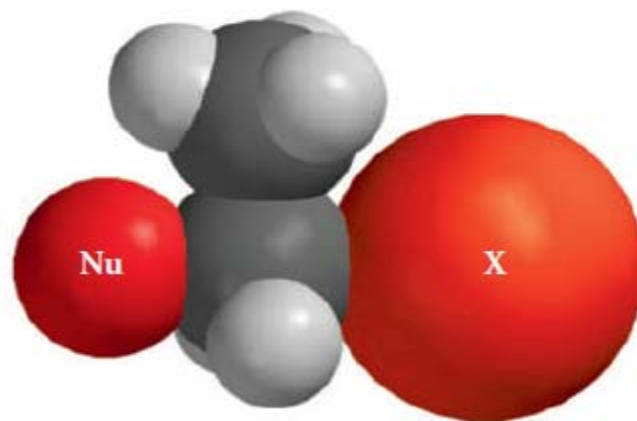
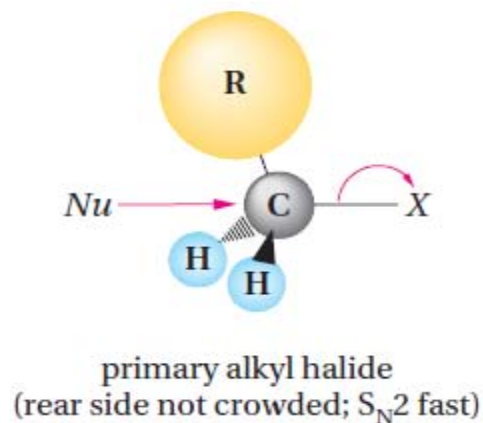


How can we recognize when a particular nucleophile and substrate react by the S_N2 mechanism?

1. *The rate of the reaction depends on both the nucleophile and the substrate concentrations.*
2. Every S_N2 displacement occurs with **inversion** of configuration.

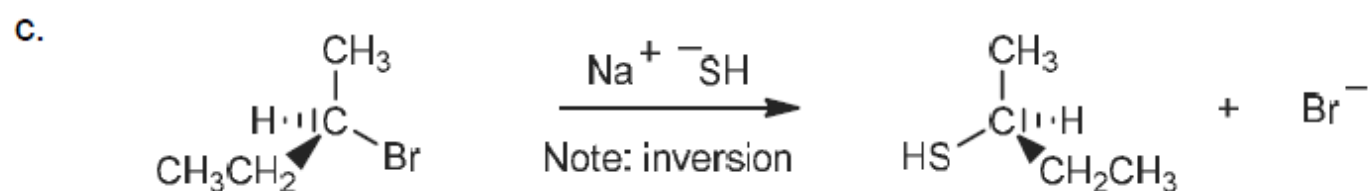
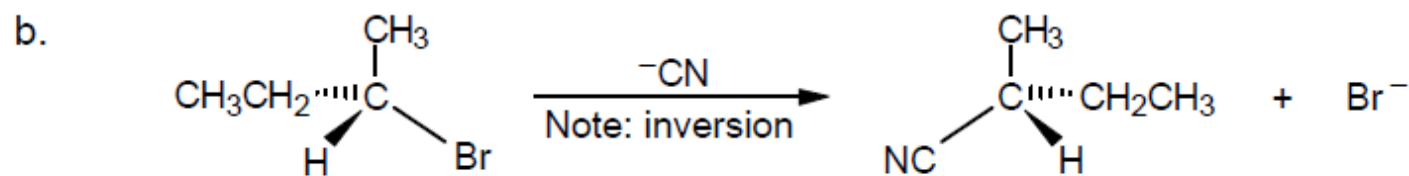
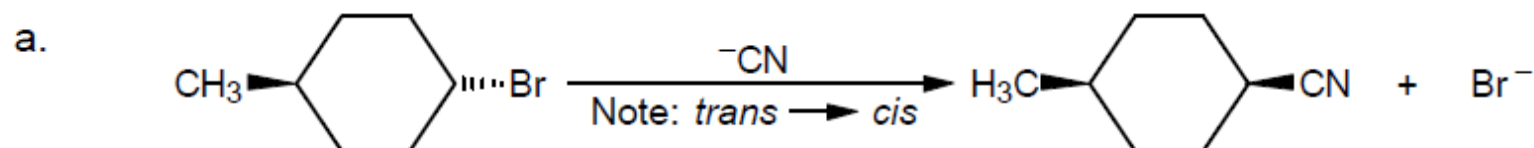


3. The reaction is fastest when the alkyl group of the substrate is methyl or primary and slowest when it is tertiary. Secondary alkyl halides react at an intermediate rate.

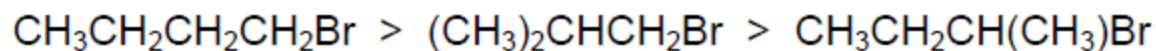
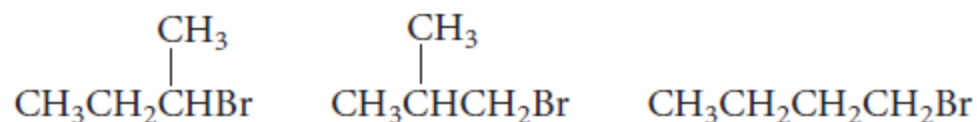


PROBLEM 6.4 Predict the product from the S_N2 reaction of

- trans*-4-methylcyclohexyl bromide with cyanide ion.
- (*S*)-2-bromopentane with cyanide ion.
- (*R*)-2-chlorobutane with NaSH.



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



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

Summary

- The S_N2 mechanism is a one-step process favored for methyl and primary halides.
- It occurs more slowly with secondary halides and usually not at all with tertiary halides.
- An S_N2 reaction occurs with inversion of configuration.
- Its rate depends on the concentration of *both* the nucleophile and the substrate (the alkyl halide).

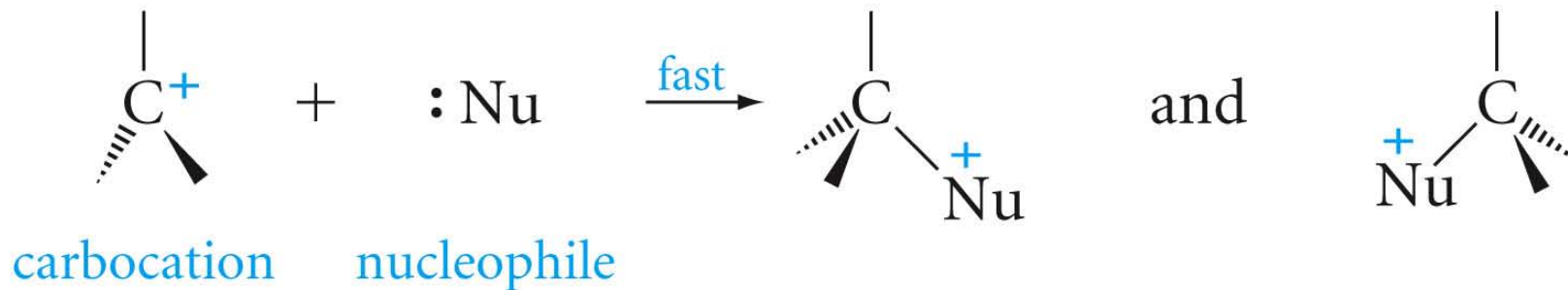
6.5 The S_N1 Mechanism

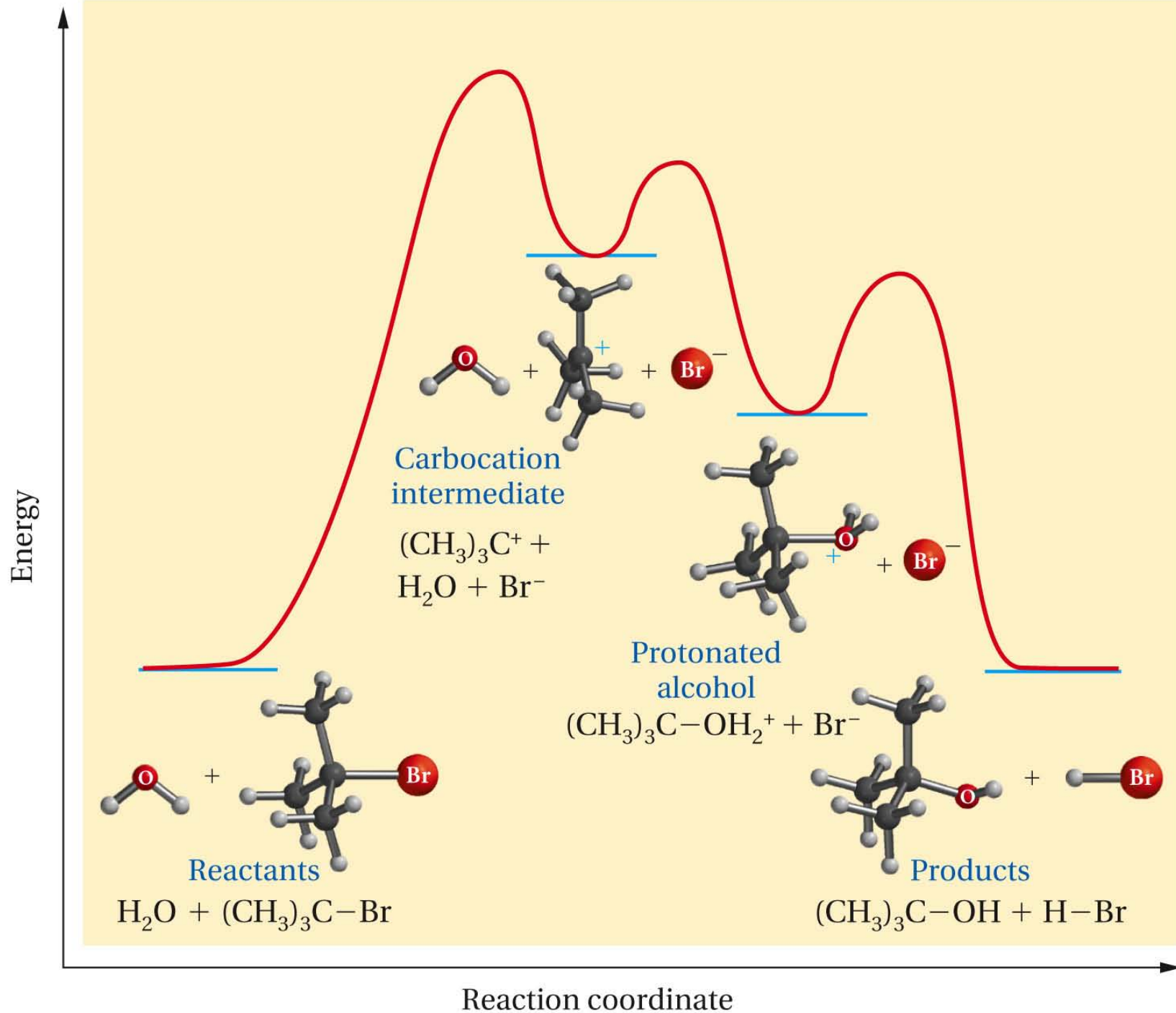
The **S_N1 mechanism** is a two step process:

The bond between the carbon and the leaving group breaks first then the



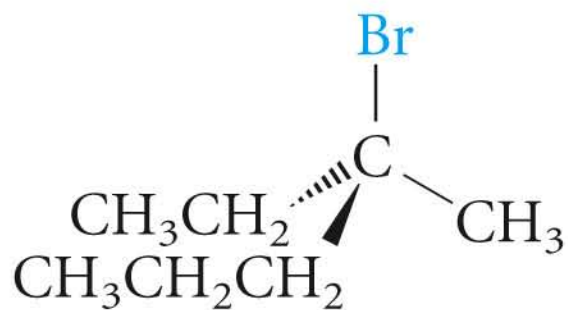
Resulting carbocation combines with the nucleophile.



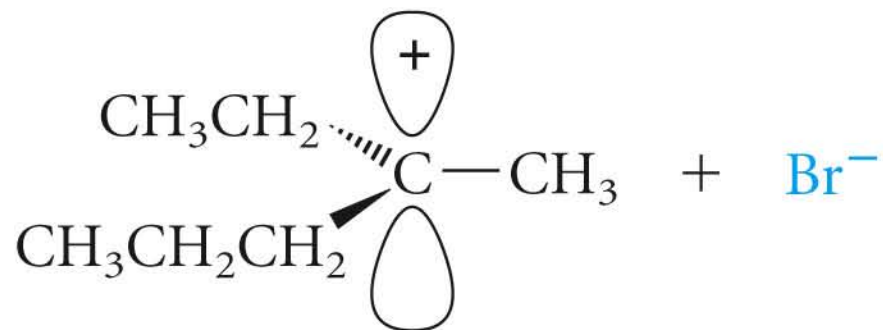
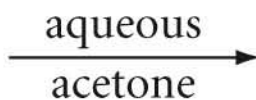


How can we recognize when a particular nucleophile and substrate react by the S_N1 mechanism?

1. The rate of the reaction does not depend on the concentration of the nucleophile.
2. If the carbon bearing the leaving group is stereogenic, the reaction occurs mainly with loss of optical activity (that is, with racemization).

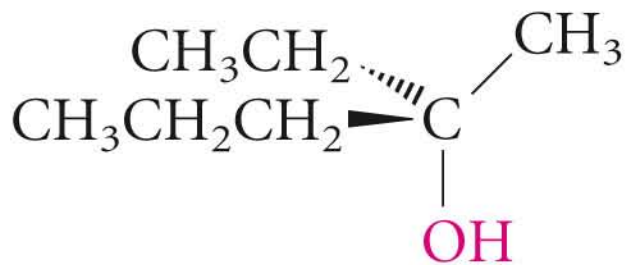


(*R*)-3-bromo-3-methylhexane



carbocation intermediate

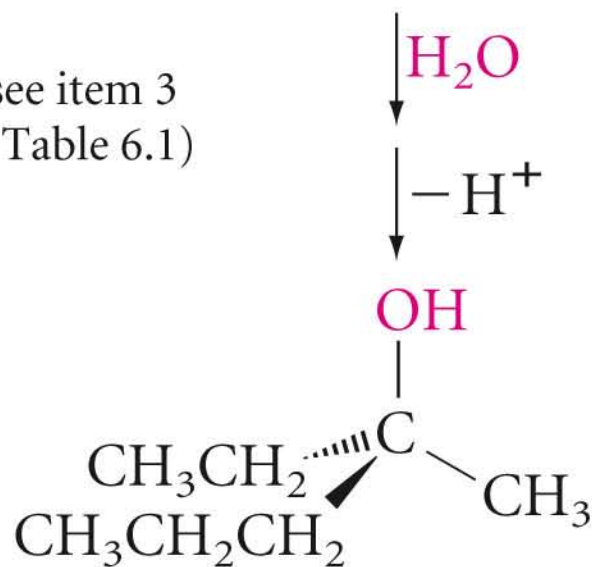
(see item 3
in Table 6.1)



50% *S*

(product from attack on the
bottom face of the carbocation)

+



50% *R*

(product from attack on the
top face of the carbocation)

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 ($3^\circ > 2^\circ > 1^\circ$).

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 |

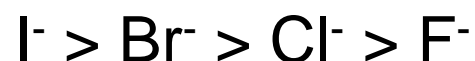
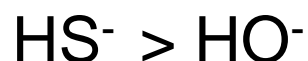
*Allyl and benzyl substrates are the common exceptions (see Problem 6.7b).

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

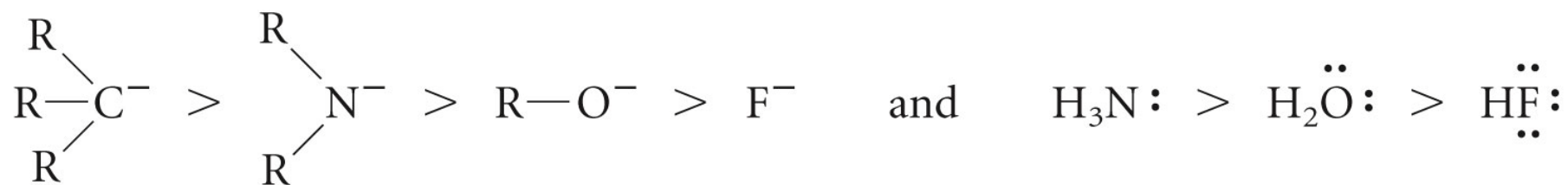
1. Negative ions are more nucleophilic, or better suppliers, than the corresponding neutral molecules.



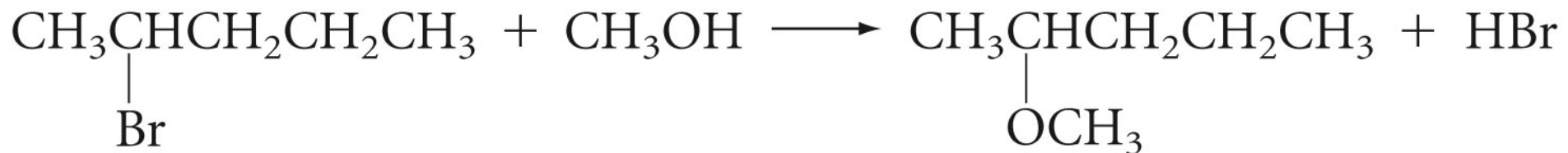
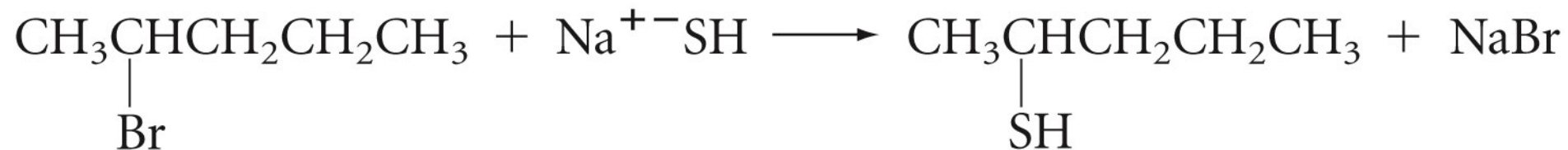
2. Elements low in the periodic table tend to be more nucleophilic than elements above them in the same column



3. Across a row in the periodic table, more electronegative elements (the more tightly an element holds electron to itself) tend to be less nucleophilic.

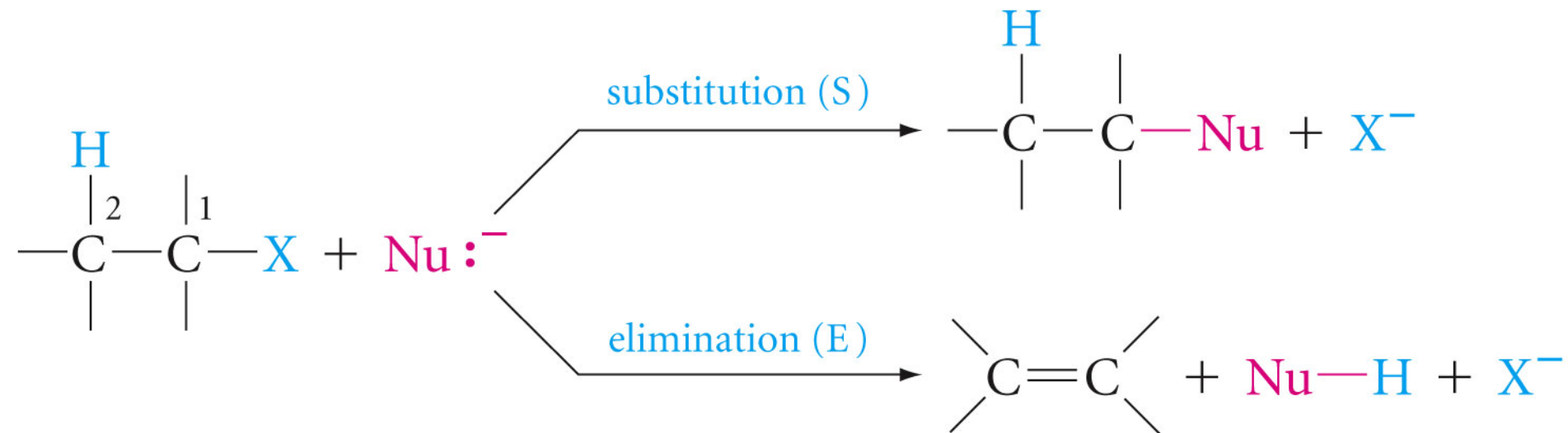


6.8 Which mechanism, S_N1 or S_N2, would you predict for each of the following reactions?



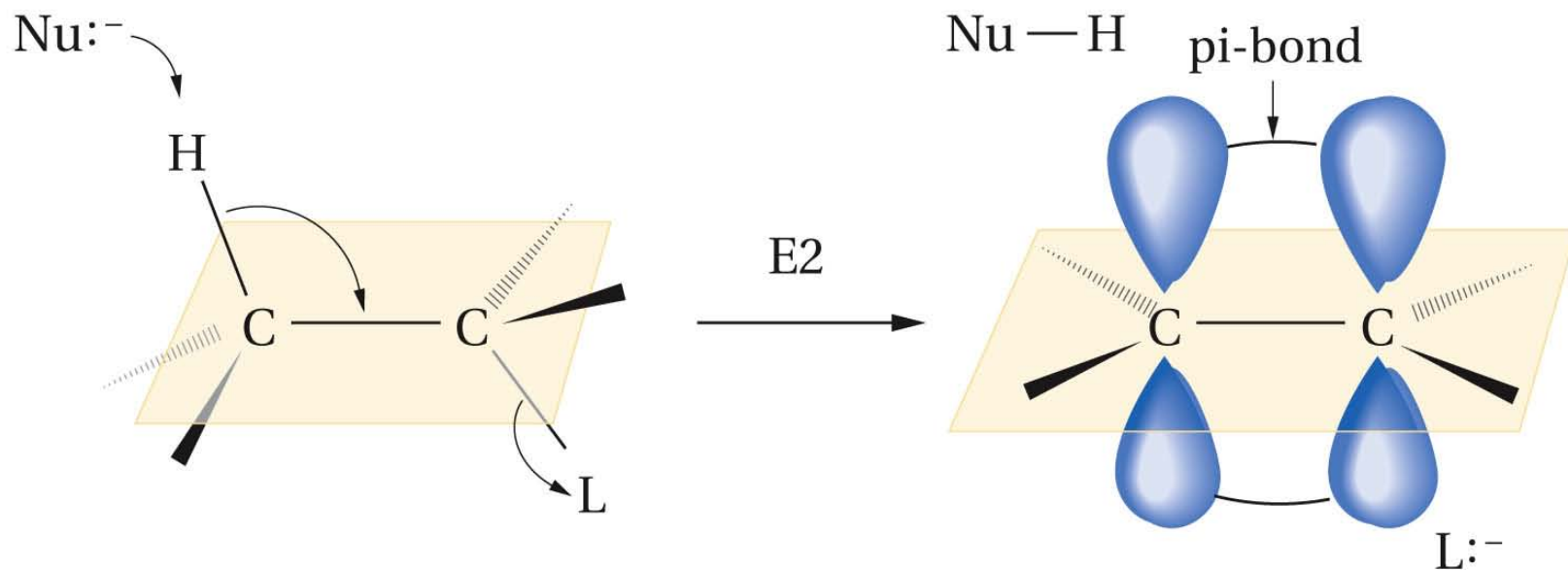
6.7 Dehydrohalogenation, and Elimination Reaction; The E2 and E1 Mechanisms

In elimination (or dehydrohalogenation) reactions of alkyl halides, a hydrogen atom and a halogen atom from adjacent carbons are eliminated and a carbon-carbon double bond is formed



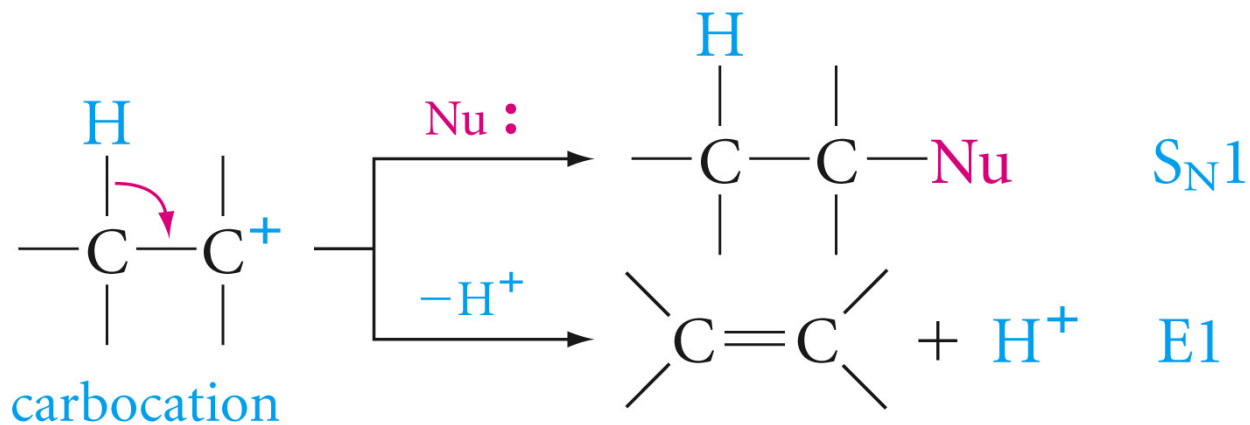
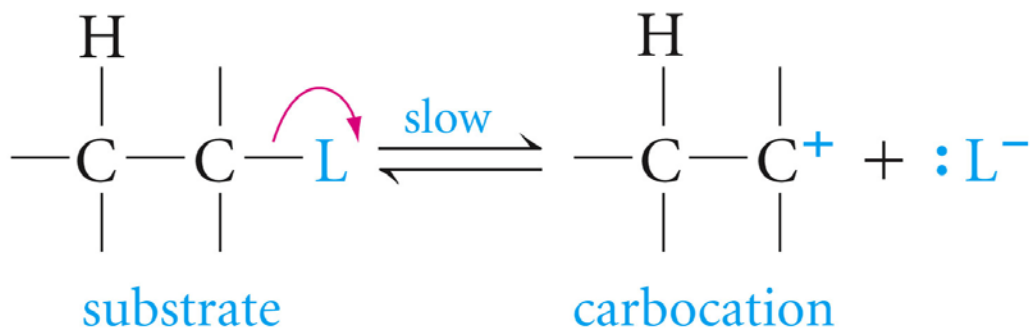
There are two main mechanisms for elimination reactions, designated E2 and E1.

- **E2 mechanism** is a process in which HX is eliminated and a C=C bond is formed in the same step.



- The preferred conformation for the substrate in an E2 reaction is :The H-C-C-L atoms lie in a single plane, with H and L in an *anti* arrangement.

• **E1 mechanism** is a two-step process with the same first step as an **S_N1** reaction.

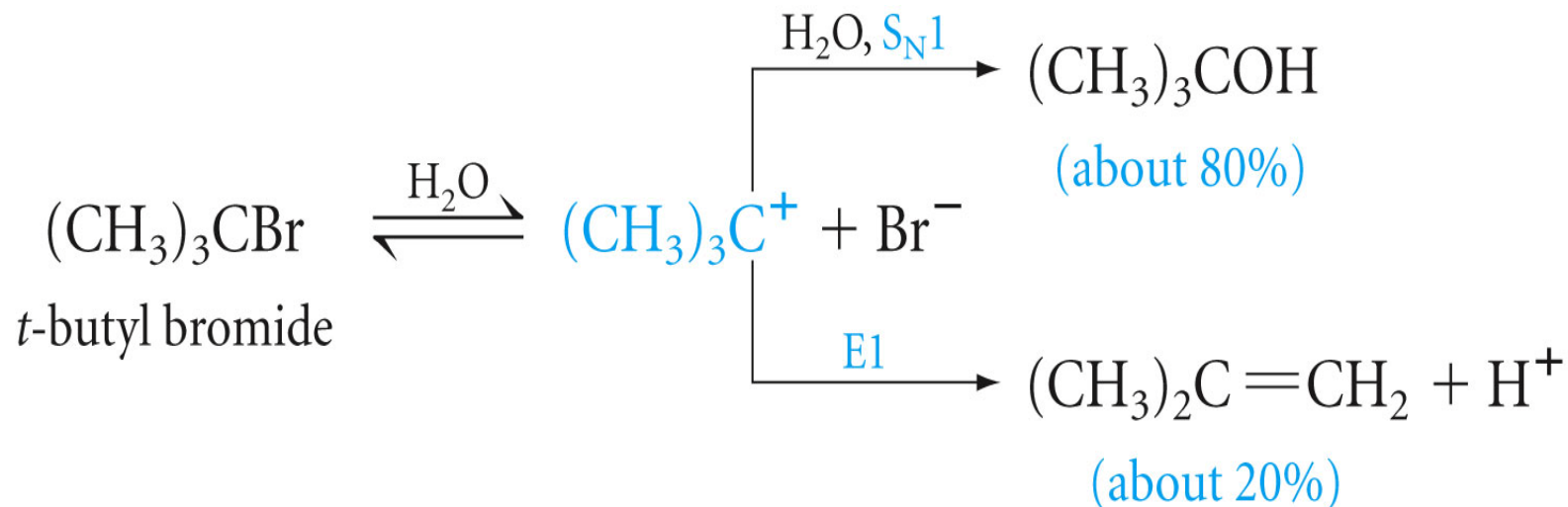


6.8 Substitution and Elimination in Competition

•Tertiary Halides

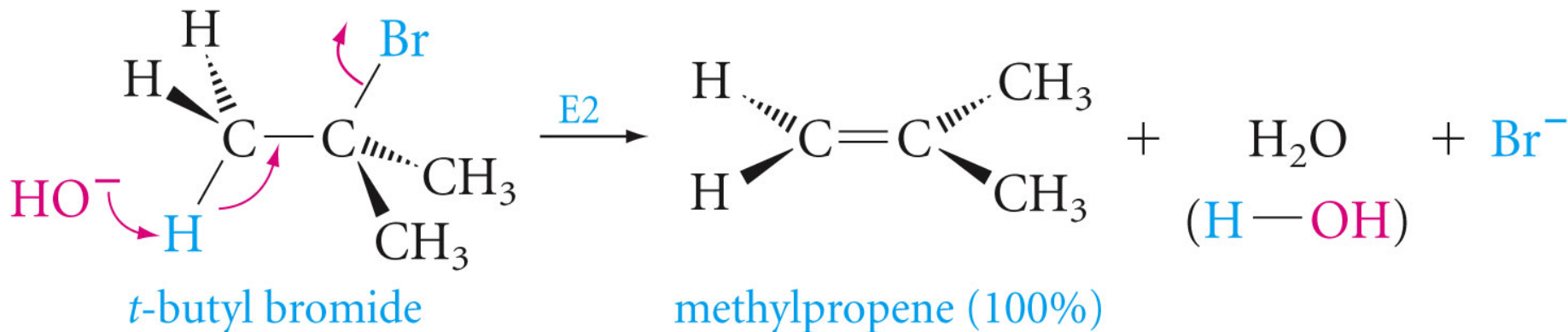
Substitution can only occur by the S_N1 mechanism, but elimination can occur by either the E1 or the E2 mechanism.

With weak nucleophiles and polar solvents, the S_N1 and E1 mechanisms compete with each other.



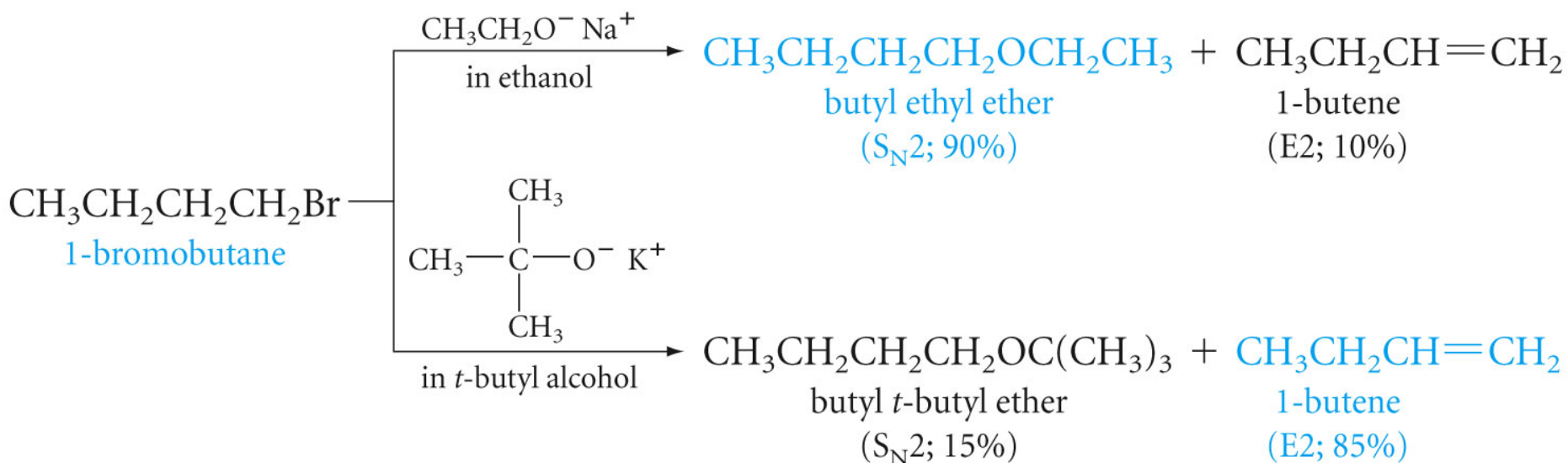
- With a strong nucleophile (which can act as a base), elimination by the E2 mechanism. is favored .

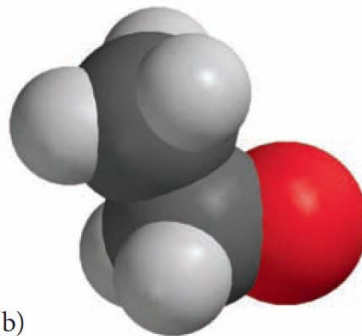
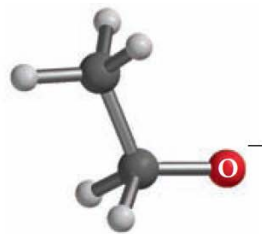
With OH^- or CN^- as nucleophiles, only elimination occurs with alkene as the exclusive product.



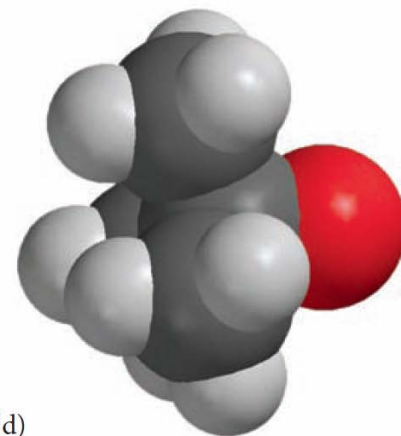
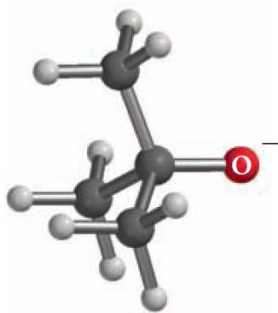
Primary Halides

With most nucleophiles, primary halides give mainly substitution products (S_N2). Only with very bulky, strongly basic nucleophiles do we see that the E2 process is favored. For example,





Ethoxide

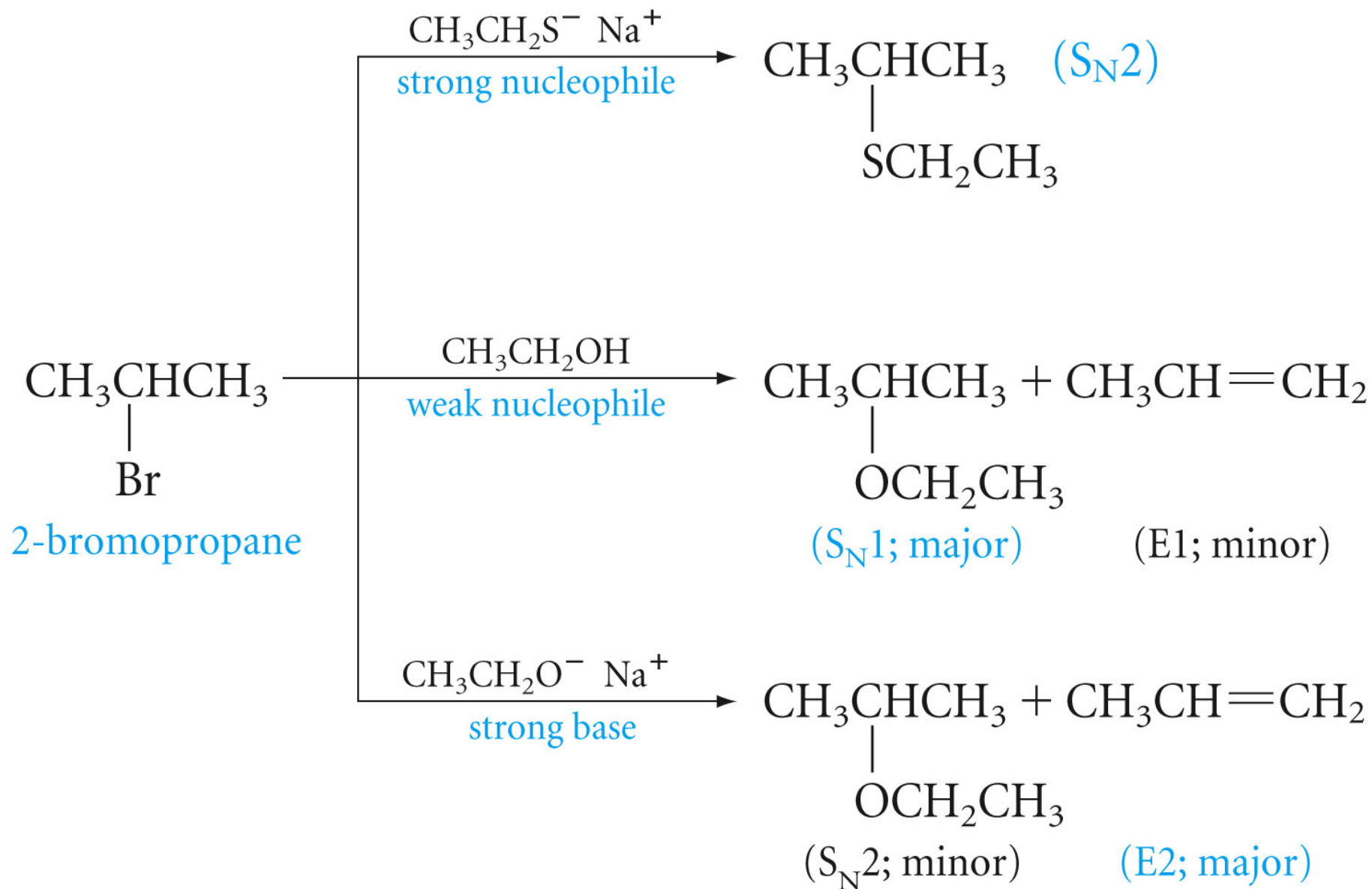


t-butoxide

Secondary Halides

All four mechanisms, S_N2 and E2 as well as S_N1 and E1, are possible. The product composition is sensitive to the nucleophile (its strength as a nucleophile and as a base) and to the reaction conditions (solvent, temperature).

Substitution is favored with stronger nucleophiles that are not strong bases (S_N2) or by weaker nucleophiles in polar solvents (S_N1), but elimination is favored by strong bases (E2).



A Summary of Substitution and Elimination Reactions

| Halide type | S_N1 | S_N2 | E1 | E2 |
|-------------------------|---|--|---|------------------------------------|
| RCH_2X (primary) | Does not occur | Highly favored | Does not occur | Occurs when strong bases are used |
| R_2CHX (secondary) | Can occur with benzylic and allylic halides | Occurs in competition with E2 reaction | Can occur with benzylic and allylic halides | Favored when strong bases are used |
| R_3CX (tertiary) | Favored in hydroxylic solvents | Does not occur | Occurs in competition with S_N1 reaction | Favored when bases are used |

Homework

13, 14, 22, 24, 25, 28, 29