3. Carbocations are stabilized by hyperconjugation: Tertiary are the most stable, followed by secondary. Primary and methyl cations are too unstable to form in solution.

4. Racemization often results when unimolecular substitution takes place at a chiral carbon.

5. Unimolecular elimination to form an alkene accompanies substitution in secondary and tertiary systems.

6. High concentrations of strong base may bring about bimolecular elimination. Expulsion of the leaving group accompanies removal of a hydrogen from the neighboring carbon by the base. The stereochemistry indicates an anti conformational arrangement of the hydrogen and the leaving group.

7. Substitution is favored by unhindered substrates and small, less basic nucleophiles.

8. Elimination is favored by hindered substrates and bulky, more basic nucleophiles.

Problems

25. What is the major substitution product of each of the following solvolysis reactions?

26. For each reaction presented in Problem 25, write out the complete, step-by-step mechanism using curved-arrow notation. Be sure to show each individual step of each mechanism separately, and show the complete structures of the products of that step before going on to the next.

27. Write the two major substitution products of the reaction shown in the margin. (a) Write a mechanism to explain the formation of each of them. (b) Monitoring the reaction mixture reveals that an isomer of the starting material is generated as an intermediate. Draw its structure and explain how it is formed.

28. Give the two major substitution products of the following reaction.

29. How would each reaction in Problem 25 be affected by the addition of each of the following substances to the solvolysis mixture?

(a) H₂O  
(b) KI  
(c) NaN₃  
(d) CH₂CH₂OCH₂CH₃ (Hint: Low polarity.)

30. Rank the following carbocations in decreasing order of stability.
31. Rank the compounds in each of the following groups in order of decreasing rate of solvolysis in aqueous acetone.

(a) \( \text{CH}_3\text{CHCH}_2\text{CH}_2\text{Cl} \)  
(b) \( \text{OCCH}_3\text{CH}_2\text{Cl} \)  
(c) \( \text{H}_3\text{C}\text{Cl} \)

32. Give the products of the following substitution reactions. Indicate whether they arise through the \( S_n1 \) or the \( S_n2 \) process. Formulate the detailed mechanisms of their generation.

(a) \( (\text{CH}_3)_2\text{CHOSO}_2\text{CF}_3 \xrightarrow{\text{CH}_3\text{CH}_2\text{OH}} \)  
(b) \( \text{CH}_3\text{Br} \xrightarrow{\text{Excess CH}_3\text{SH}, \text{CH}_3\text{OH}} \)  
(c) \( \text{CH}_3\text{CH}_2\text{CH}_2\text{Br} \xrightarrow{(\text{C}_6\text{H}_5)_3\text{P}, \text{DMSO}} \)  
(d) \( \text{CH}_3\text{CH}_2\text{CHClCH}_2\text{Br} \)

33. Give the product of each of the following substitution reactions. Which of these transformations should proceed faster in a polar, aprotic solvent (such as acetone or DMSO) than in a polar, protic solvent (such as water or \( \text{CH}_3\text{OH} \))? Explain your answer on the basis of the mechanism that you expect to be operating in each case.

(a) \( \text{CH}_3\text{CH}_2\text{C}_6\text{H}_5 + \text{Na}^+ \xrightarrow{} \text{CN} \)  
(b) \( (\text{CH}_3)_2\text{CH}_2\text{I} + \text{Na}^+ \xrightarrow{} \text{N}_3^- \)  
(c) \( (\text{CH}_3)_2\text{CBr} + \text{HSCH}_2\text{CH}_3 \)  
(d) \( (\text{CH}_3)_2\text{CHOSO}_2\text{CH}_3 + \text{HOCH(CH}_3)_2 \)

34. Propose a synthesis of \((\text{R})-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}\), starting from \((\text{R})-2\)-chlorobutane.

35. Two substitution reactions of \((\text{S})-2\)-bromobutane are shown here. Show their stereochemical outcomes.

\( (\text{S})-\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{Br} \xrightarrow{\text{HCOH}} \)

\( (\text{S})-\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{Br} \xrightarrow{\text{HCOH, Na}^+, \text{DMSO}} \)

36. Propose a stereocontrolled synthesis of cis-1-acetoxy-3-methylcyclopentane (margin), starting from trans-1-chloro-3-methylcyclopentane.

37. The two seemingly similar reactions shown below differ in their outcomes.

\( \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{Br} \xrightarrow{\text{NaOH, CH}_3\text{CH}_2\text{OH}} \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{OH} \)

\( \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{Br} \xrightarrow{\text{NaSH, CH}_3\text{CH}_2\text{OH}} \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{SH} \)

The first proceeds in high yield. The yield of the product in the second, however, is diminished by the formation of \((\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2)_2\text{S}\) in substantial quantities. Discuss the formation of this by-product mechanistically, and explain why it occurs in the second case but not in the first.

38. Write all possible E1 products of each reaction in Problem 25.

39. Formulate the complete step-by-step mechanisms for all the E1 processes that you identified in Problem 38.
Chapter 7  
Further Reactions of Haloalkanes

40. Write the products of the following elimination reactions. Specify the predominant mechanism (E1 or E2) and formulate it in detail.

(a) \( \text{CH}_3\text{CH}_2\text{CBr} \xrightarrow{\text{NaNH}_2, \text{NH}_3} \)

(b) \( \text{CH}_2\text{CH}_2\text{CH}_2\text{Cl} \xrightarrow{\text{KOC(CH}_3)_3, (\text{CH}_3)_2\text{COH}} \)

(c) \( \text{BrCH}_2\text{CH}_3 \xrightarrow{\text{Excess KOH, CH}_3\text{CH}_2\text{OH}} \)

(d) \( \text{CH}_3 \xrightarrow{\text{NaOCH}_3, \text{CH}_3\text{OH}} \)

41. From the list of reagents (a)–(f) below, choose all those that are most likely to give primarily (i) S$_2$2 reaction with primary RX; (ii) E2 reaction with primary RX; (iii) S$_2$2 reaction with secondary RX; (iv) E2 reaction with secondary RX.

(a) NaSCH$_3$ in CH$_3$OH
(b) (CH$_3$)$_2$CHCl in (CH$_3$)$_2$COH
(c) NaNH$_2$ in liquid NH$_3$
(d) KCN in DMSO
(e) NaNH$_2$ in liquid NH$_3$
(f) CH$_3$CH$_2$CH$_2$CONa in DMF

42. Predict the major product(s) that should form from reaction between 1-bromobutane and each of the following substances. By which reaction mechanism is each formed — S$_2$N$_1$, S$_2$N$_2$, E1, or E2? If it appears that a reaction will either not take place or be exceedingly slow, write “no reaction.” Assume that each reagent is present in large excess. The solvent for each reaction is given.

(a) KCl in DMF
(b) KI in DMF
(c) KCl in CH$_3$NO$_2$
(d) NH$_3$ in CH$_3$CH$_2$OH
(e) NaOCH$_3$CH$_2$ in CH$_3$CH$_2$OH
(f) CH$_3$CH$_2$OH

43. Predict the major product(s) and mechanism(s) for reaction between 2-bromobutane (sec-butyl bromide) and each of the reagents in Problem 42.

44. Predict the major product(s) and mechanism(s) for reaction between 2-bromo-2-methylpropane (tert-butyl bromide) and each of the reagents in Problem 42.

45. Three reactions of 2-chloro-2-methylpropane are shown here. (a) Write the major product of each transformation. (b) Compare the rates of the three reactions. Assume identical solution polarities and reactant concentrations. Explain mechanistically.

\[
\begin{align*}
\text{(CH}_3)_2\text{CCl} & \xrightarrow{\text{H}_2\text{S, CH}_3\text{OH}} \\
\text{(CH}_3)_2\text{CCl} & \xrightarrow{\text{O}} \text{CH}_3\text{CONa}^+ \text{CH}_3\text{OH} \\
\text{(CH}_3)_2\text{CCl} & \xrightarrow{\text{CH}_3\text{O}^- \text{K}^+, \text{CH}_3\text{OH}} \\
\end{align*}
\]

46. Give the major product(s) of the following reactions. Indicate which of the following mechanism(s) is in operation: S$_2$N$_1$, S$_2$N$_2$, E1, or E2. If no reaction takes place, write “no reaction.”

(a) \( \text{CH}_3\text{Cl} \xrightarrow{\text{KOC(CH}_3)_3, (\text{CH}_3)_2\text{COH}} \)

(b) \( \text{CH}_3\text{CHCH}_2\text{CH}_3 \xrightarrow{\text{KBr, acetone}} \)

(c) \( \text{H}_2\text{C} = \text{Br} \xrightarrow{\text{H}_2\text{O}} \)

(d) \( \text{NaNH}_2 \text{ liquid NH}_3 \)
47. Fill in the blanks in the following table with the major product(s) of the reaction of each haloalkane with the reagents shown.

<table>
<thead>
<tr>
<th>Haloalkane</th>
<th>H₂O</th>
<th>NaSeCH₃</th>
<th>NaOCH₃</th>
<th>KOC(CH₃)₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃Cl</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CH₃CH₂CH₂Cl</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(CH₃)₂CHCl</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(CH₃)₂CCl</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

48. Indicate the major mechanism(s) (simply specify S₂N₂, S₂N₁, E₂, or E₁) required for the formation of each product that you wrote in Problem 47.

49. For each of the following reactions, indicate whether the reaction would work well, poorly, or not at all. Formulate alternative products, if appropriate.

(a) CH₃CH₂CHCH₃Br → CH₃CH₂CHCH₃Br
(b) CH₃CHCH₂Cl → CH₃CHCH₂OCH₃
(c) CH₂═CH₂CH₂CH₂CH₂OH → CH₂═CH₂CH₂CH₂OCH₃
(d) CH₃—C—CH₂CH₂CH₂CH₂OH → CH₃—C—CH₂CH₂CH₂OCH₃
(e) CH₂—CH—I → CH₂—CH₂SCH₃
(f) CH₃CH₂CH₂Br → CH₃CH₂CH₂Br
(g) (CH₃)₂CCI → (CH₃)₂CI
(h) (CH₃CH₂)₂O → (CH₃CH₂)₂OCH₃ + I⁻
(i) CH₃OH → CH₃OH
(j) (CH₃CH₂)₂COCH₃ → (CH₃CH₂)₂COCH₃
Upon mixing the colorless substrate and solvent, a reddish-orange color is observed immediately, signaling the formation of an intermediate carbocation. This color fades over a period of about a minute, and analysis of the solution reveals the presence of the final product in 100% yield.

(a) There are two reasons for the buildup of a detectable concentration of carbocation in this case. One is that the carbocation derived from dissociation of this particular substrate is unusually stable (for reasons we will explore in Chapter 22). The other is that the solvent (2,2,2-trifluoroethanol) is an unusually poor nucleophile, even compared with ordinary alcohols such as ethanol. Suggest an explanation for the poor nucleophilicity of the solvent.

(b) What can you say about the relative rates of the two steps (rate1 and rate2), and how do they compare to those in the usual S_N1 reaction mechanism? (c) How might increasing carbocation stability and decreasing solvent nucleophilicity affect the relative magnitudes of rate1 and rate2 in an S_N1 process? (d) Write the complete mechanism for the reaction above.

53. Match each of the following transformations to the correct reaction profile shown here, and draw the structures of the species present at all points on the energy curves marked by capital letters.
54. Formulate the structure of the most likely product of the following reaction of 4-chloro-4-methyl-1-pentanol in neutral polar solution.

\[ (\text{CH}_3)_2\text{CCl} + (\text{C}_6\text{H}_5)_3\text{P} \rightarrow \text{HCl} + \text{C}_6\text{H}_{12}\text{O} \]

In strongly basic solution, the starting material again converts into a molecule with the molecular formula \( \text{C}_6\text{H}_{12}\text{O} \), but with a completely different structure. What is it? Explain the difference between the two results.

55. The following reaction can proceed through both E1 and E2 mechanisms.

\[ \text{CH}_3 \]
\[ \text{C}_6\text{H}_5\text{CH}_2\text{CCl} + \text{NaOCH}_3\text{CH}_2\text{OH} \rightarrow \text{C}_6\text{H}_5\text{CH} = \text{C}(\text{CH}_3)_2 + \text{C}_6\text{H}_5\text{CH}_2\text{C} = \text{CH}_2 \]

The E1 rate constant \( k_{\text{E1}} = 1.4 \times 10^{-4} \text{ s}^{-1} \) and the E2 rate constant \( k_{\text{E2}} = 1.9 \times 10^{-4} \text{ L mol}^{-1} \text{ s}^{-1} \); 0.02 M haloalkane. (a) What is the predominant elimination mechanism with 0.5 M NaOCH\(_3\)? (b) What is the predominant elimination mechanism with 2.0 M NaOCH\(_3\)? (c) At what concentration of base does exactly 50% of the starting material react by an E1 route and 50% by an E2 pathway?

56. The compound below is an example of a methyl ester. Methyl esters react with lithium iodide to give lithium carboxylate salts. The solvent in this example is pyridine (margin).

\[ \text{O} = \text{C} = \text{O} \text{CH}_3 \]
\[ \text{O} = \text{C} = \text{O}^{-\text{Li}^+} + \text{CH}_3\text{I} \]

Suggest several experiments that would allow you to determine the likely mechanism of this process.
57. **CHALLENGE**  Ethers containing the 1,1-dimethylethyl (tert-butyl) group are readily cleaved with dilute, strong acid, as shown in the example below.

\[
\text{CH}_3\text{O} -\text{C} -\text{CH}_3 \xrightarrow{\text{CF}_3\text{CO}_2\text{H, H}_2\text{O}} \text{CH}_3\text{OH} + \text{CH}_2\text{C} = \text{CH}_2
\]

Suggest a plausible mechanism for this process. What role might the strong acid play?

58. Give the mechanism and major product for the reaction of a secondary haloalkane in a polar aprotic solvent with the following nucleophiles. The \( pK_a \) value of the conjugate acid of the nucleophile is given in parentheses.

(a) \( \text{N}_3^- \) (4.6)  
(b) \( \text{H}_2\text{N}^- \) (35)  
(c) \( \text{NH}_3 \) (9.5)

(d) \( \text{HSe}^- \) (3.7)  
(e) \( \text{F}^- \) (3.2)  
(f) \( \text{C}_6\text{H}_5\text{O}^- \) (9.9)

(g) \( \text{PH}_3 \) (12)  
(h) \( \text{NH}_2\text{OH} \) (6.0)  
(i) \( \text{NCS}^- \) (0.7)

59. Cortisone is an important steroidal anti-inflammatory agent. Cortisone can be synthesized efficiently from the alkene shown here.

Of the following three chlorinated compounds, two give reasonable yields of the alkene shown above by E2 elimination with base, but one does not. Which one does not work well, and why? What does it give during attempted E2 elimination? (Hint: Consider the geometry of each system.)

60. **CHALLENGE**  The chemistry of derivatives of trans-decalin is of interest because this ring system is part of the structure of steroids. Make models of the brominated systems (i and ii) to help you answer the following questions.

(a) One of the molecules undergoes E2 reaction with \( \text{NaOCH}_2\text{CH}_3 \) in \( \text{CH}_3\text{CH}_2\text{OH} \) considerably faster than does the other. Which molecule is which? Explain.  
(b) The following deuterated analogs of systems i and ii react with base to give the products shown.
Specify whether \textit{anti} or \textit{syn} eliminations have taken place. Draw the conformations that the molecules must adopt for elimination to occur. Does your answer to (b) help you in solving (a)?

Team Problem

61. Consider the general substitution-elimination reactions of the bromoalkanes.

\[
\begin{align*}
R-\text{Br} & \xrightarrow{\text{Nu/base}} R-\text{Nu} + \text{alkene}
\end{align*}
\]

How do the reaction mechanisms and product formation differ when the structure of the substrate and reaction conditions change? To begin to unravel the nuances of bimolecular and unimolecular substitution and elimination reactions, focus on the treatment of bromoalkanes A through D under conditions (a) through (e). Divide the problem evenly among yourselves so that each of you tackles the questions of reaction mechanism(s) and qualitative distribution of product(s), if any. Reconvéné to discuss your conclusions and come to a consensus. When you are explaining a reaction mechanism to the rest of the team, use curved arrows to show the flow of electrons. Label the stereochemistry of starting materials and products as \( R \) or \( S \), as appropriate.

\[
\begin{align*}
\text{A} & \quad \text{B} & \quad \text{C} & \quad \text{D} \\
\text{Br} & \quad \text{Br} & \quad \text{Br} & \quad \text{Br}
\end{align*}
\]

(a) \( \text{NaN}_3, \text{DMF} \) \quad (b) \( \text{LDA, DMF} \) \quad (c) \( \text{NaOH, DMF} \) \quad (d) \( \text{CH}_3\text{CO}^+\text{Na}^-, \text{CH}_3\text{COH} \) \quad (e) \( \text{CH}_3\text{OH} \)

Preprofessional Problems

62. Which of the following haloalkanes will undergo hydrolysis most rapidly?

(a) \((\text{CH}_3)_3\text{CF}\) \quad (b) \((\text{CH}_3)_3\text{CCl}\) \quad (c) \((\text{CH}_3)_3\text{CBr}\) \quad (d) \((\text{CH}_3)_3\text{Cl}\)

63. The reaction

\[
(\text{CH}_3)_3\text{CCl} \xrightarrow{\text{CH}_3\text{CO}} \text{H}_3\text{C} \quad \text{C} = \text{CH}_2
\]

is an example of which of the following processes?

(a) \( \text{E1} \) \quad (b) \( \text{E2} \) \quad (c) \( \text{S}_\text{N}1 \) \quad (d) \( \text{S}_\text{N}2 \)
64. In this transformation,

\[ A \xrightarrow{\text{H}_2\text{O, acetone}} \text{CH}_3\text{CH}_2\text{C(CH}_3\text{)}_2\text{OH} \]

what is the best structure for \( A \)?

(a) \( \text{BrCH}_2\text{CH}_2\text{CH} \text{(CH}_3\text{)}_2 \) 
(b) \( \text{CH}_3\text{CH}_2\text{CBr} \)
(c) \( \text{CH}_3\text{CH}_2\text{CH} \text{CH} \text{(CH}_3\text{)}_2 \text{Br} \)
(d) \( \text{CH}_3\text{CHCH} \text{(CH}_3\text{)}_2 \text{Br} \)

65. Which of the following isomeric carbocations is the most stable?

(a) \( \text{CH}_2\text{CH}_2\text{+} \) 
(b) \( \text{CH}_3\text{CH}_3\text{+} \)
(c) \( \text{CH}_3\text{CH}_3\text{+} \) 
(d) \( \text{CH}_3\text{CH}_3\text{+} \)

66. Which reaction intermediate is involved in the following reaction?

\[ \text{2-Methylbutane} \xrightarrow{\text{Br}_2, \text{hv}} \text{2-bromo-3-methylbutane} \text{ (not the major product)} \]

(a) A secondary radical  
(b) A tertiary radical  
(c) A secondary carbocation  
(d) A tertiary carbocation