

Chapter 11 – Reactions of Alkyl Halides: Nucleophilic Substitutions and Eliminations

Chapter Outline

- I. Substitution Reactions (Sections 11.1 – 11.6).
 - A. S_N2 reactions (Sections 11.1 – 11.3).
 1. The discovery of S_N2 reactions (Section 11.1).
 - a. Walden discovered that (+) malic acid and (–) malic acid could be interconverted (Section 11.1).
 - b. This discovery meant that one or more reactions must have occurred with inversion of configuration at the chirality center.
 - c. Nucleophilic substitution of tosylate ion by acetate ion occurs with inversion of configuration.

Nucleophilic substitution reactions of primary and secondary alkyl halides always proceed with inversion of configuration.
 2. The S_N2 reaction (Section 11.2).
 - a. Kinetics.
 - i. The kinetics of a reaction measure the relationship between reactant concentrations and product concentrations.
 - ii. In an S_N2 reaction, reaction rate depends on the concentration of both alkyl halide and nucleophile.

This type of reaction is a second-order reaction.
 - iii. In a second-order reaction, rate = $k \times [\text{RX}] \times [\text{Nu}]$.

The constant k is the rate constant; its units are (L/mol·s).
 - b. Mechanism.
 - i. The reaction takes place in a single step, without intermediates.
 - ii. The nucleophile attacks the substrate from a direction directly opposite to the leaving group.

This type of attack accounts for inversion of configuration.
 - iii. In the transition state, the new bond forms at the same time as the old bond breaks.
 - iv. Negative charge is shared between the attacking nucleophile and the leaving group.
 - v. The three remaining bonds to carbon are in a planar arrangement.
 - vi. Both substrate and nucleophile are involved in the step whose rate is measured.
 3. Characteristics of the S_N2 reaction (Section 11.3).
 - a. Changes in the energy levels of reactants or of the transition state affect the reaction rate.
 - b. Changes in the substrate.
 - i. Reaction rate is decreased if the substrate is bulky.
 - ii. Substrates, in order of increasing reactivity: tertiary, neopentyl, secondary, primary, methyl.
 - iii. S_N2 reactions can occur only at relatively unhindered sites.
 - iv. Vinylic and aryl halides are unreactive to S_N2 substitutions.

- c. Changes in the nucleophile.
 - i. Any species can act as a nucleophile if it has an unshared electron pair.
 If the nucleophile has a negative charge, the product is neutral.
 If the nucleophile is neutral, the product is positively charged.
 - ii. The reactivity of a nucleophile is dependent on reaction conditions.
 - iii. In general, nucleophilicity parallels basicity.
 - iv. Nucleophilicity increases going down a column of the periodic table.
 - v. Negatively charged nucleophiles are usually more reactive than neutral nucleophiles.
 - d. Changes in the leaving group.
 - i. In general, the best leaving groups are best able to stabilize negative charge.
 - ii. Usually, the best leaving groups are the weakest bases.
 - iii. Good leaving groups lower the energy of the transition state.
 - iv. Poor leaving groups include F^- , HO^- , RO^- , and H_2N^- .
 Poor leaving groups can be converted to better leaving groups.
 - e. Changes in the solvent.
 - i. Polar, protic solvents slow S_N2 reactions by lowering the reactivity of the nucleophile.
 - ii. Polar, aprotic solvents raise the ground-state energy of the nucleophile and make it more reactive.
 - f. A summary:
 - i. Steric hindrance in the substrate raises the energy of the transition state, increasing ΔG^\ddagger , and decreasing the reaction rate.
 - ii. More reactive nucleophiles have a higher ground-state energy, decreasing ΔG^\ddagger , and increasing the reaction rate.
 - iii. Good leaving groups decrease the energy of the transition state, decreasing ΔG^\ddagger , and increasing the reaction rate.
 - iv. Polar protic solvents solvate the nucleophile, lowering the ground-state energy, increasing ΔG^\ddagger , and decreasing the reaction rate. Polar aprotic solvents don't solvate the nucleophile, raising the ground-state energy, decreasing ΔG^\ddagger , and increasing the reaction rate.
- B. S_N1 Reactions (Sections 11.4 – 11.5).
- 1. The S_N1 reaction (Section 11.4).
 - a. Under certain reaction conditions, tertiary halides are much more reactive than primary and methyl halides.
 These reactions must be occurring by a different mechanism.
 - b. Kinetics of the S_N1 reaction.
 - i. The rate of reaction of a tertiary alkyl halide with water depends only on the concentration of the alkyl halide.
 - ii. The reaction is a first order process, with reaction rate = $k \times [RX]$.
 - iii. The rate expression shows that only RX is involved in the slowest, or rate-limiting, step, and the nucleophile is involved in a different, faster step.
 - iv. The rate expression also shows that there must be at least two steps in the reaction.
 - v. In an S_N1 reaction, slow dissociation of the substrate is followed by rapid reaction with the nucleophile.
 - c. Stereochemistry of S_N1 reactions.
 - i. An S_N1 reaction of an enantiomer produces racemic product because an S_N1 reaction proceeds through a planar, achiral intermediate.

- ii. Few S_N1 reactions proceed with complete racemization.
 - iii. The ion pair formed by the leaving group and the carbocation sometimes shields one side of the carbocation from attack before the leaving group can diffuse away.
2. Characteristics of the S_N1 reaction (Section 11.5).
- a. As in S_N2 reactions, factors that lower ΔG^\ddagger favor faster reactions.
 - b. Changes in the substrate.
 - i. The more stable the carbocation intermediate, the faster the S_N1 reaction.
 - ii. Substrates, in order of increasing reactivity: methyl, primary, secondary and allyl and benzyl, tertiary.
 - iii. Allylic and benzylic substrates are also reactive in S_N2 reactions.
 - c. Changes in the leaving group.
 - i. The best leaving groups are the conjugate bases of strong acids.
 - ii. In S_N1 reactions, water can act as a leaving group.
 - d. Changes in the nucleophile have no effect on S_N1 reactions.
 - e. Changes in the solvent.
 - i. Polar solvents (high dielectric constant) increase the rates of S_N1 reactions.
 - ii. Polar solvents stabilize the carbocation intermediate more than the reactants and lower ΔG^\ddagger .
 - iii. Polar solvents stabilize by orienting themselves around the carbocation, with electron-rich ends facing the positive charge.
 - f. A summary:
 - i. The best substrates are those that form stable carbocations.
 - ii. Good leaving groups lower the energy of the transition state leading to carbocation formation and increase the reaction rate.
 - iii. The nucleophile doesn't affect the reaction rate, but it must be nonbasic.
 - iv. Polar solvents stabilize the carbocation intermediate and increase the reaction rate.
- C. Biological substitution reactions (Section 11.6).
- 1. Both S_N1 and S_N2 reactions occur often in biochemical pathways.
 - 2. In S_N1 reactions, the leaving group is often an organodiphosphate.
 - 3. S_N2 reactions are involved in biological methylations.
- II. Elimination reactions (Sections 11.7 – 11.11).
- A. Introduction (Section 11.7).
- 1. In addition to bringing about substitution, a basic nucleophile can also cause elimination of HX from an alkyl halide to form a carbon-carbon double bond.
 - 2. A mixture of double-bond products is usually formed, but the product with the more substituted double bond is the major product.

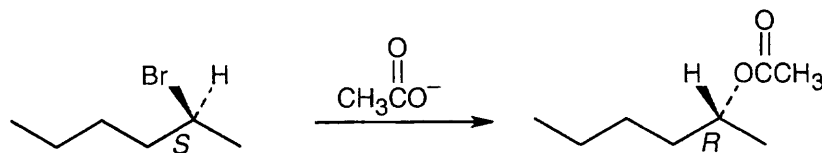
This observation is the basis of Zaitsev's rule.
 - 3. Double-bond formation can occur by several mechanistic routes, but at this point, we will study only three mechanisms.
- B. The E2 reaction (Sections 11.8 – 11.9).
- 1. General features (Section 11.8).
 - a. An E2 reaction occurs when an alkyl halide is treated with strong base.
 - b. The reaction occurs in one step, without intermediates.
 - c. E2 reactions follow second-order kinetics.
 - d. E2 reactions show the deuterium isotope effect.
 - i. In a reaction in which a C-H bond is cleaved in the rate-limiting step, substitution of -D for -H results in a decrease in rate.
 - ii. Because this effect is observed in E2 reactions, these reactions must involve C-H bond breaking in the rate-limiting step.

- e. E2 reactions always occur with periplanar geometry.
 - i. Periplanar geometry is required because of the need for overlap of the sp^3 orbitals of the reactant as they become π orbitals in the product.
 - ii. Anti periplanar geometry is preferred because it allows the substituents of the two carbons to assume a staggered relationship.
 - iii. Syn periplanar geometry occurs only when anti periplanar geometry isn't possible.
- f. The preference for anti periplanar geometry results in the formation of double bonds with specific *E,Z* configurations.
2. Elimination reactions and cyclohexane conformations (Section 11.9).
 - a. The chemistry of substituted cyclohexanes is controlled by their conformations.
 - b. The preference for anti periplanar geometry for E2 reactions can be met only if the atoms to be eliminated have a trans-diaxial relationship.
 - c. Neomenthyl chloride reacts 200x faster than menthyl chloride because the groups to be eliminated are trans diaxial in the most favorable conformation, and the Zaitsev product is formed.
 - d. For menthyl chloride, reaction must proceed through a higher energy conformation, and non-Zaitsev product is formed.
- C. The E1 reaction (Section 11.10).
 1. An E1 reaction occurs when the intermediate carbocation of an S_N1 loses H^+ to form a $C=C$ bond.
 2. E1 reactions usually occur in competition with S_N1 reactions.
 3. E1 reactions show first-order kinetics.
 4. There is no geometric requirement for the groups to be eliminated, and the most stable (Zaitsev) product is formed.
- D. The E1cB reaction.
 1. The E1cB reaction takes place through a carbanion.
 2. The rate-limiting step involves base-induced abstraction of a proton.
 3. Often the leaving group is poor.
 4. A carbonyl group stabilizes the anion.
 5. The E1cB is fairly common in biochemical pathways (Section 11.11).
- III. Summary of reactivity (Section 11.12).
 - A. Primary halides.
 1. S_N2 reaction is usually observed.
 2. E1 reaction occurs if a strong, bulky base is used.
 3. E1cB reaction occurs if the leaving group is two carbons away from a carbonyl group.
 - B. Secondary halides.
 1. S_N2 and E2 reactions occur in competition.
 2. Strong bases promote E2 elimination.
 3. Secondary halides (especially allylic and benzylic halides) can react by S_N1 and E1 routes if weakly basic nucleophiles and protic solvents are used.
 4. E1cB reaction occurs if the leaving group is two carbons away from a carbonyl group.
 - C. Tertiary halides.
 1. Under basic conditions, E2 elimination is favored.
 2. S_N1 and E1 products are formed under nonbasic conditions.
 3. E1cB reaction occurs if the leaving group is two carbons away from a carbonyl group.

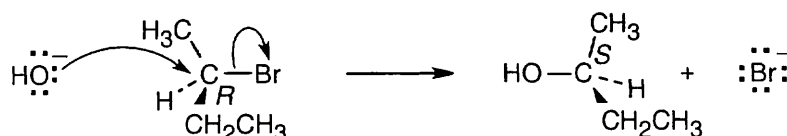
Solutions to Problems

- 11.1 Strategy:** As described in Worked Example 11.1, identify the leaving group and the chirality center. Draw the product carbon skeleton, inverting the configuration at the chirality center, and replace the leaving group with the nucleophilic reactant.

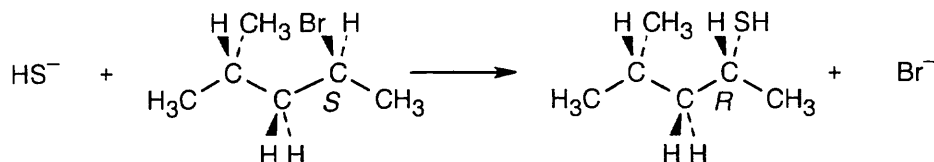
Solution:



- 11.2** Use the suggestions in the previous problem to draw the correct product.



11.3



- 11.4** All of the nucleophiles in this problem are relatively reactive.

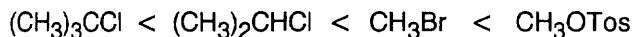
- (a) $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{Br} + \text{NaI} \longrightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{I} + \text{NaBr}$
- (b) $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{Br} + \text{KOH} \longrightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{OH} + \text{KBr}$
- (c) $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{Br} + \text{HC}\equiv\text{C}^- \text{Li}^+ \longrightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{C}\equiv\text{CH} + \text{LiBr}$
- (d) $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{Br} + \text{NH}_3 \longrightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_3^+ \text{Br}^-$

- 11.5** (a) $(\text{CH}_3)_2\text{N}^-$ is more nucleophilic because it is more basic than $(\text{CH}_3)_2\text{NH}$ and because a negatively charged nucleophile is more nucleophilic than a neutral nucleophile.
- (b) $(\text{CH}_3)_3\text{N}$ is more nucleophilic than $(\text{CH}_3)_3\text{B}$. $(\text{CH}_3)_3\text{B}$ is non-nucleophilic because it has no lone electron pair.
- (c) H_2S is more nucleophilic than H_2O because nucleophilicity increases in going down a column of the periodic table.

11.6 Strategy: In this problem, we are comparing two effects – the effect of the substrate and the effect of the leaving group. Tertiary substrates are less reactive than secondary substrates, which are less reactive than primary substrates.

Solution:

Least reactive \longrightarrow Most reactive



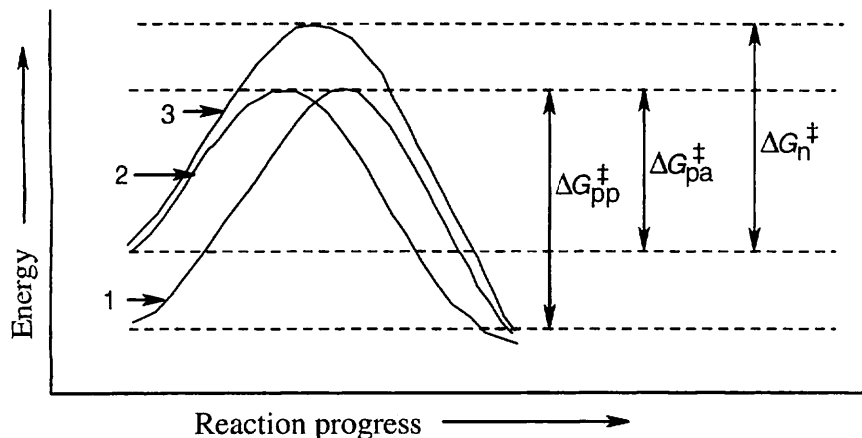
tertiary
carbon

secondary
carbon

good
leaving
group

excellent
leaving
group

11.7

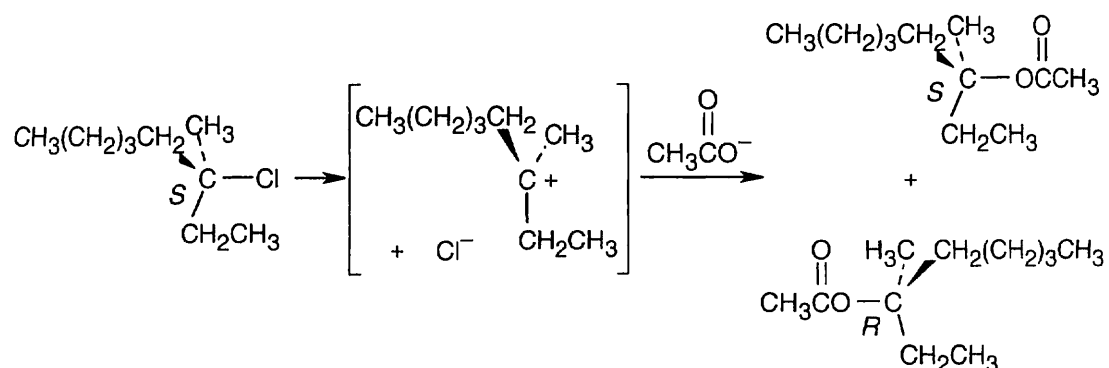


Polar protic solvents (curve 1) stabilize the charged transition state by solvation and also stabilize the nucleophile by hydrogen bonding.

Polar aprotic solvents (curve 2) stabilize the charged transition state by solvation, but do not hydrogen-bond to the nucleophile. Since the energy level of the nucleophile is higher, ΔG^\ddagger is smaller and the reaction is faster in polar aprotic solvents than in polar protic solvents.

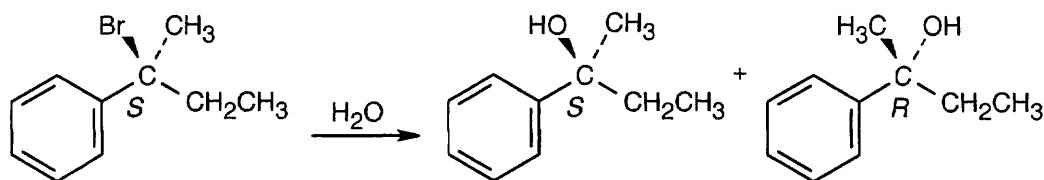
Nonpolar solvents (curve 3) stabilize neither the nucleophile nor the transition state. ΔG^\ddagger is therefore higher in nonpolar solvents than in polar solvents, and the reaction rate is slower.

11.8

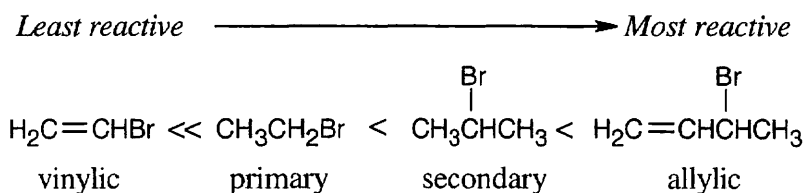


Attack by acetate can occur on either side of the planar, achiral carbocation intermediate, resulting in a mixture of both the *R* and *S* enantiomeric acetates. The ratio of enantiomers is probably close to 50:50.

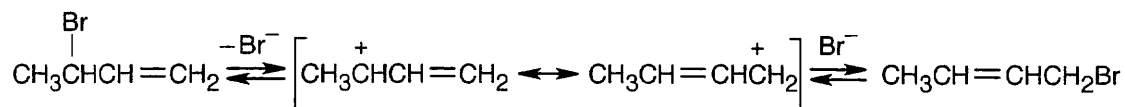
- 11.9** If reaction had proceeded with complete inversion, the product would have had a specific rotation of $+53.6^\circ$. If complete racemization had occurred, $[\alpha]_D$ would have been zero. The observed rotation was $+5.3^\circ$. Since $\frac{+5.3^\circ}{+53.6^\circ} = 0.099$, 9.9% of the original tosylate was inverted. The remaining 90.1% of the product must have been racemized.
- 11.10** The *S* substrate reacts with water to form a mixture of *R* and *S* alcohols. The ratio of enantiomers is close to 50:50.



- 11.11** $\text{S}_{\text{N}}1$ reactivity is related to carbocation stability. Thus, substrates that form the most stable carbocations are the most reactive in $\text{S}_{\text{N}}1$ reactions.



11.12



The two bromobutenes form the same allylic carbocation in the rate-limiting step.

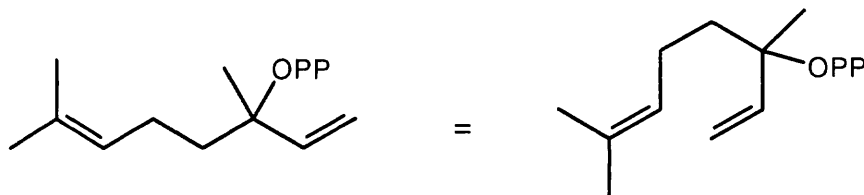
- 11.13 Strategy:** Both substrates have allylic groups and might react either by an $\text{S}_{\text{N}}1$ or an $\text{S}_{\text{N}}2$ route. The reaction mechanism is determined by the leaving group, the solvent, or the nucleophile.

Solution:

(a) This reaction probably occurs by an $\text{S}_{\text{N}}1$ mechanism. HCl converts the poor $-\text{OH}$ leaving group into an excellent $-\text{OH}_2^+$ leaving group, and the polar solvent stabilizes the carbocation intermediate.

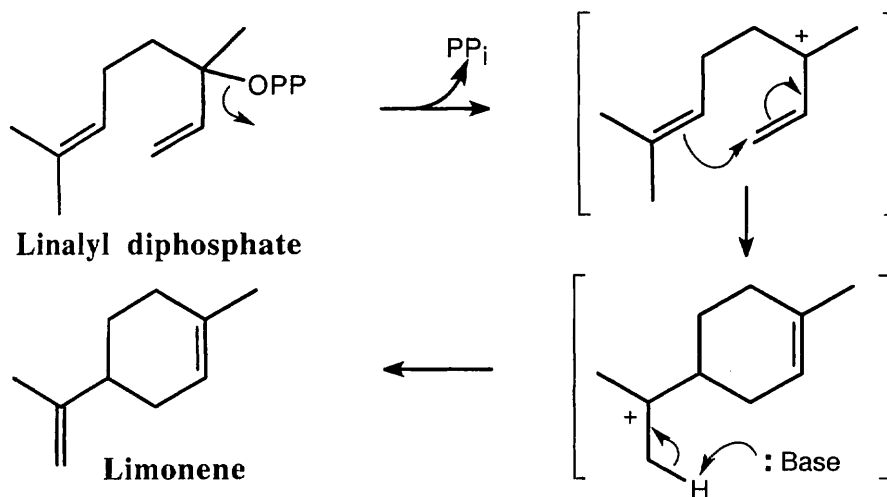
(b) This reaction takes place with a negatively charged nucleophile in a polar, aprotic solvent. It is very likely that the reaction occurs by an $\text{S}_{\text{N}}2$ mechanism.

11.14 Strategy: Redraw linalyl diphosphate so that has the same orientation as limonene.



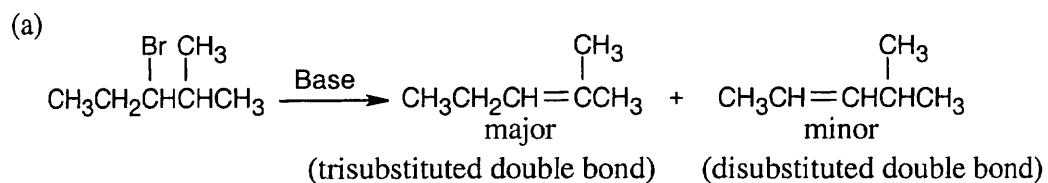
After dissociation of PP_i , the cation cyclizes by attack of the double bond π electrons. Removal of an -H yields limonene.

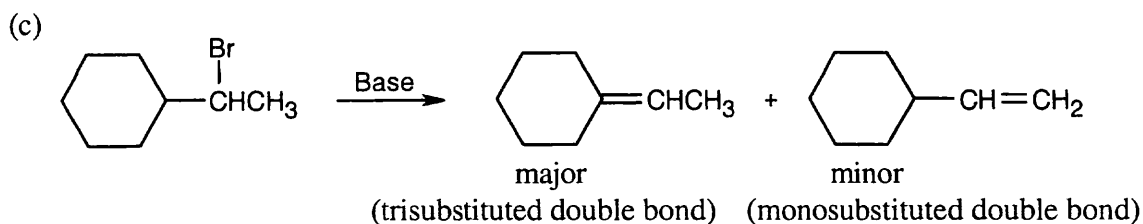
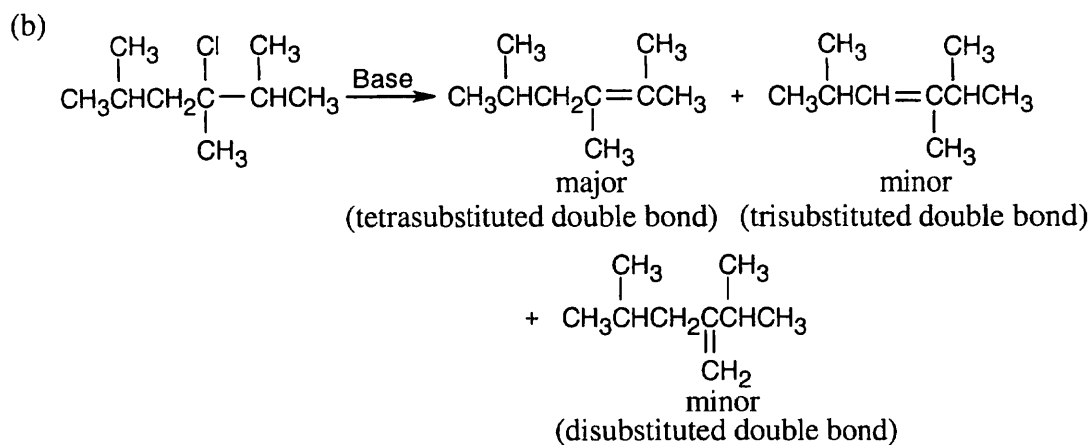
Solution:



11.15 Strategy: Form the double bond by removing HX from the alkyl halide reactant in as many ways as possible. The major elimination product in each case has the most substituted double bond.

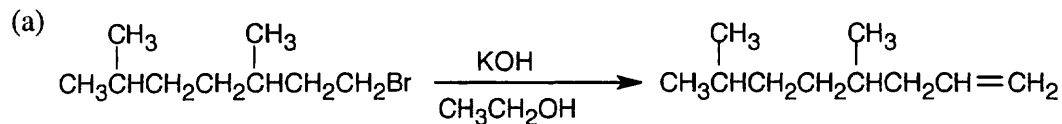
Solution:



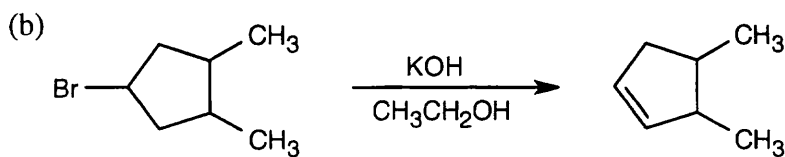


11.16 Strategy: For maximum yield, the alkyl halide reactant should not give a mixture of products on elimination.

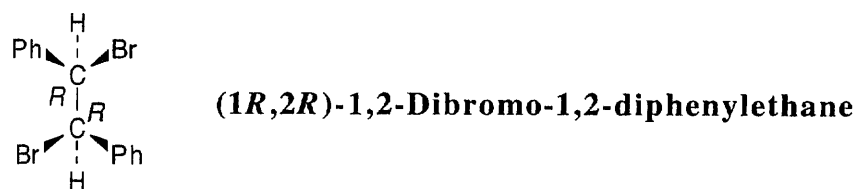
Solution:



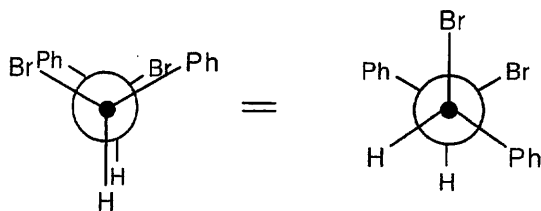
The 2-bromo isomer yields a mixture of alkene products.



11.17 Strategy: Draw the reactant with correct stereochemistry.

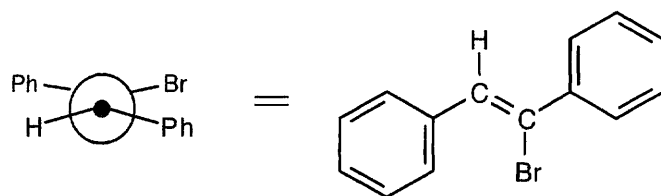


Convert this drawing into a Newman projection, and draw the conformation having anti periplanar geometry for -H and -Br .

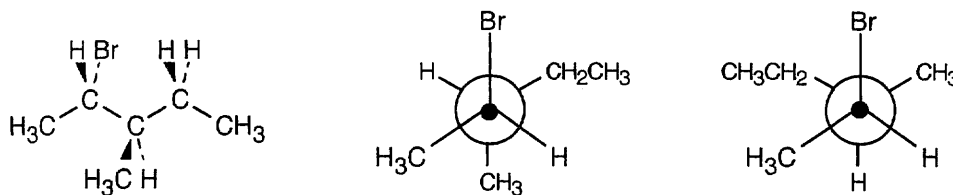


The alkene resulting from E2 elimination is (*Z*)-1-bromo-1,2-diphenylethylene.

Solution:

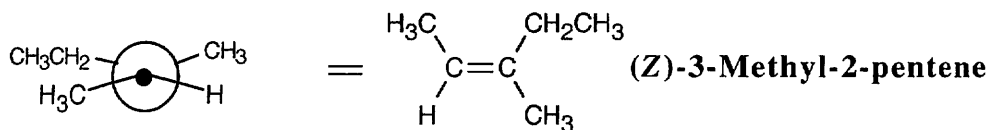


11.18 Strategy: As in the previous problem, draw the structure, convert it to a Newman projection, and rotate the groups so that the -H and -Br to be eliminated have an anti periplanar relationship.

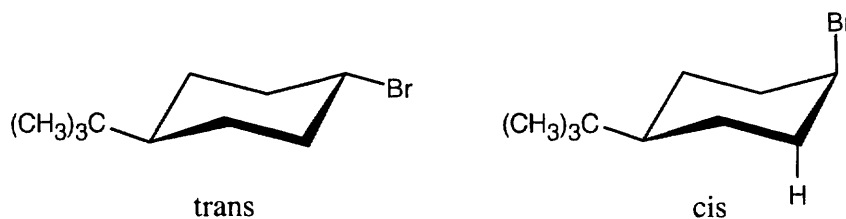


The major product is (*Z*)-3-methyl-2-pentene. A small amount of 3-methyl-1-pentene is also formed.

Solution:

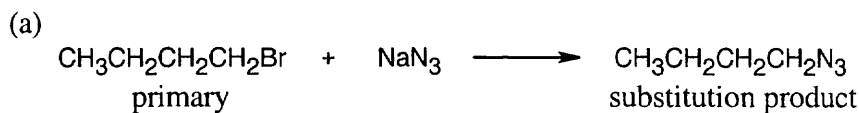


11.19

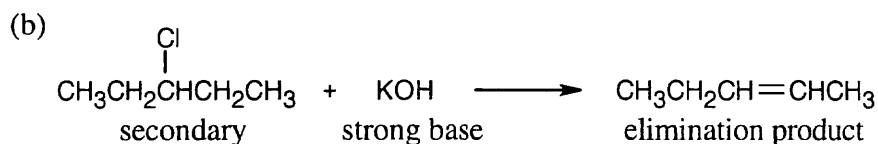


The more stable conformations of each of the two isomers are pictured above; the larger *tert*-butyl group is always equatorial in the more stable conformation. The cis isomer reacts faster under E2 conditions because $-\text{Br}$ and $-\text{H}$ are in the anti periplanar arrangement that favors E2 elimination.

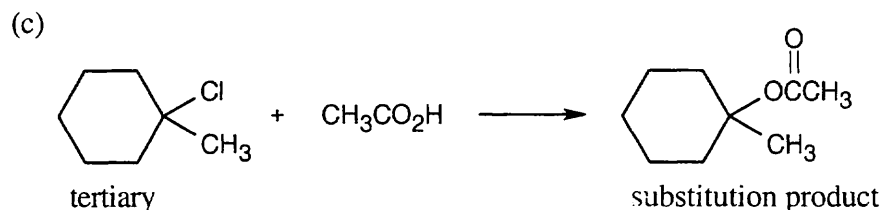
11.20



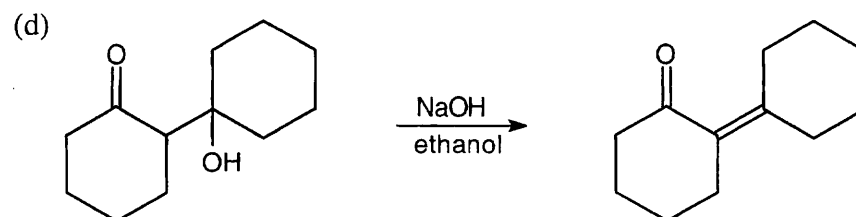
The reaction occurs by an $\text{S}_{\text{N}}2$ mechanism because the substrate is primary, the nucleophile is nonbasic, and the product is a substitution product.



This is an E2 reaction since a secondary halide reacts with a strong base to yield an elimination product.



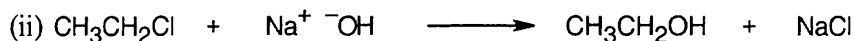
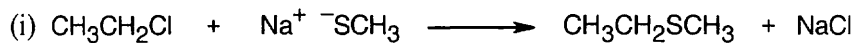
This is an $\text{S}_{\text{N}}1$ reaction. Tertiary substrates form substitution products only by the $\text{S}_{\text{N}}1$ route.



This is an E1cB reaction because the leaving group is two carbons away from a carbonyl group.

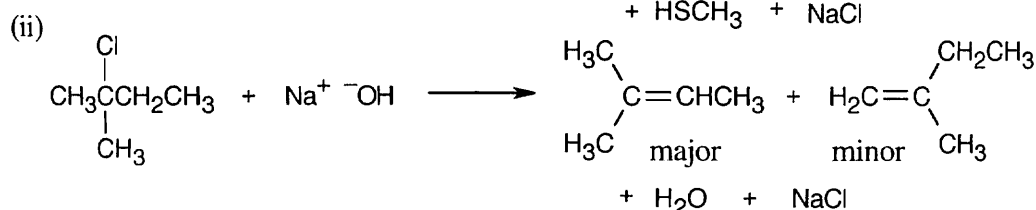
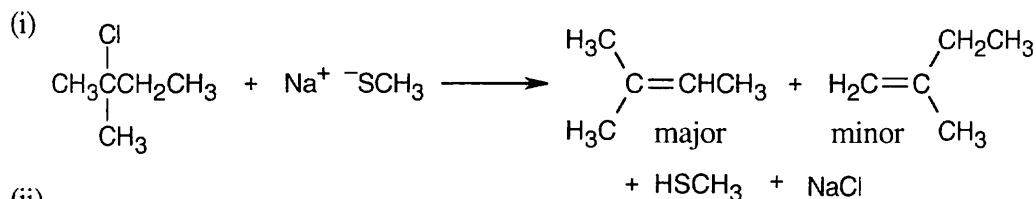
Visualizing Chemistry

11.21 (a)



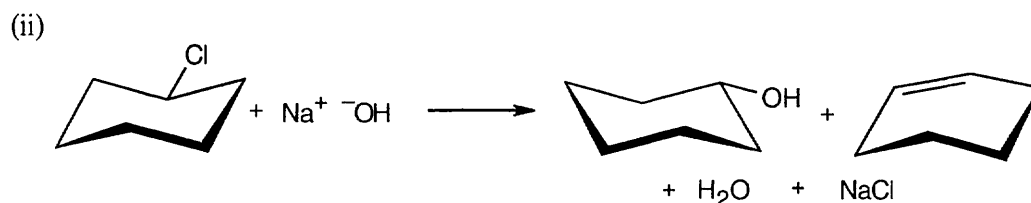
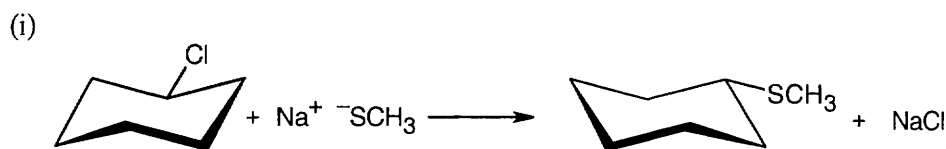
Both reactions yield $\text{S}_{\text{N}}2$ substitution products because the substrate is primary and both nucleophiles are good.

(b)



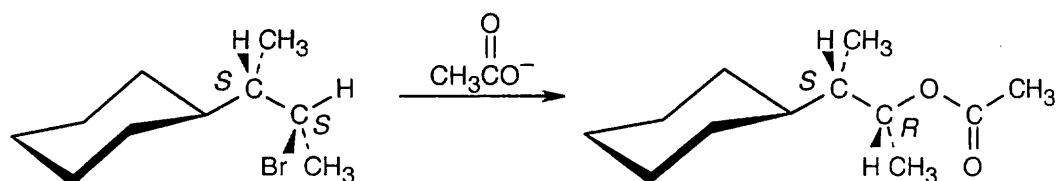
The substrate is tertiary, and the nucleophiles are basic. Two elimination products are expected; the major product has the more substituted double bond, in accordance with Zaitsev's rule.

(c)



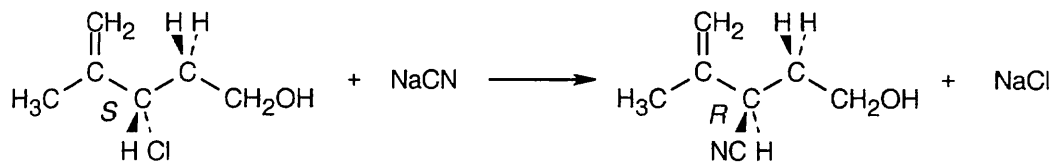
In (i), the secondary substrate reacts with the good, but weakly basic, nucleophile to yield substitution product. In (ii), NaOH is a poorer nucleophile but a stronger base, and both substitution and elimination product are formed.

11.22



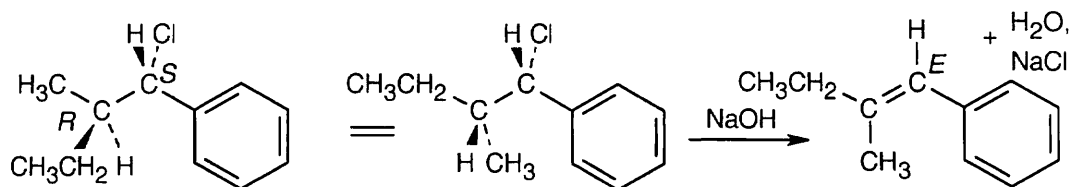
Reaction of the secondary bromide with the weakly basic acetate nucleophile occurs by an $\text{S}_{\text{N}}2$ route, with inversion of configuration, to produce the *R* acetate.

11.23



The *S* substrate has a secondary allylic chloride group and a primary hydroxyl group. $\text{S}_{\text{N}}2$ reaction occurs at the secondary carbon to give the *R* cyano product because hydroxide is a poor leaving group.

11.24

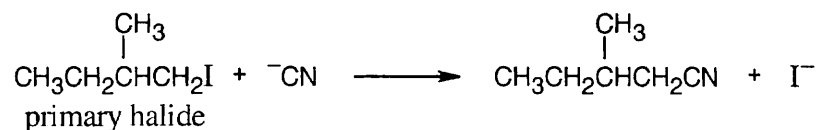


Rotate the left side of the molecule so that the groups to be eliminated have an anti periplanar relationship. The double bond in the product has the *E* configuration.

Additional Problems

- 11.25 (a) CH_3I reacts faster than CH_3Br because I^- is a better leaving group than Br^- .
 (b) $\text{CH}_3\text{CH}_2\text{I}$ reacts faster with OH^- in dimethylsulfoxide (DMSO) than in ethanol. Ethanol, a protic solvent, hydrogen-bonds with hydroxide ion and decreases its reactivity.
 (c) Under the $\text{S}_{\text{N}}2$ conditions of this reaction, CH_3Cl reacts faster than $(\text{CH}_3)_3\text{CCl}$. Approach of the nucleophile to the bulky $(\text{CH}_3)_3\text{CCl}$ molecule is hindered.
 (d) $\text{H}_2\text{C}=\text{CHCH}_2\text{Br}$ reacts faster because vinylic halides such as $\text{H}_2\text{C}=\text{CHBr}$ are unreactive to substitution reactions.

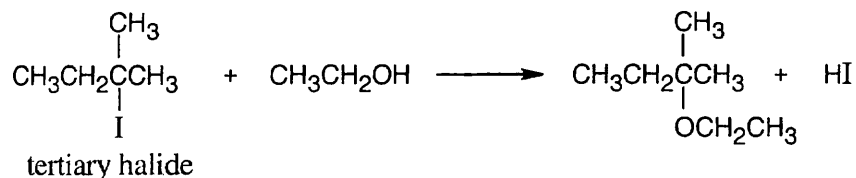
11.26



This is an $\text{S}_{\text{N}}2$ reaction, whose rate depends on the concentration of both alkyl halide and nucleophile. $\text{Rate} = k \times [\text{RX}] \times [\text{Nu}:^-]$

- (a) Halving the concentration of cyanide ion and doubling the concentration of alkyl halide doesn't change the reaction rate.
 (b) Tripling the concentrations of both cyanide ion and alkyl halide causes a ninefold increase in reaction rate.

11.27

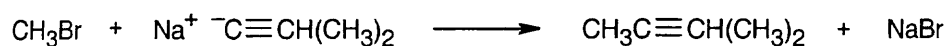


This is an $\text{S}_{\text{N}}1$ reaction, whose rate depends only on the concentration of 2-iodo-2-methylbutane. $\text{Rate} = k \times [\text{RX}]$.

- (a) Tripling the concentration of alkyl halide triples the rate of reaction.
 (b) Halving the concentration of ethanol by dilution with diethyl ether reduces the polarity of the solvent and decreases the rate.

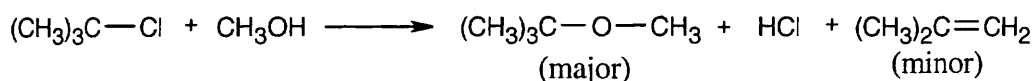
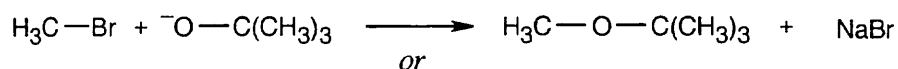
11.28

(a)

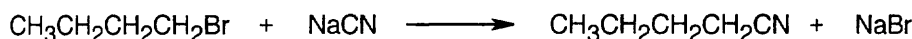


Not $\text{CH}_3\text{C}\equiv\text{C}^- \text{Na}^+ + \text{BrCH}(\text{CH}_3)_2$. The strong base $\text{CH}_3\text{C}\equiv\text{C}^-$ brings about elimination, producing $\text{CH}_3\text{C}\equiv\text{CH}$ and $\text{H}_2\text{C}=\text{CHCH}_3$.

(b)



(c)



(d)



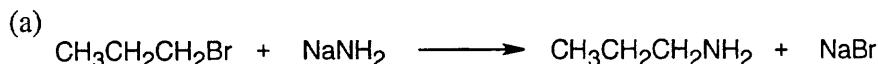
11.29 (a) The difference in this pair of reactions is in the *leaving group*. Since $^-\text{OTos}$ is a better leaving group than ^-Cl (see Section 11.5), $\text{S}_{\text{N}}2$ displacement by iodide on $\text{CH}_3\text{--OTos}$ proceeds faster.

(b) The *substrates* in these two reactions are different. Bromoethane is a primary bromoalkane, and bromocyclohexane is a secondary bromoalkane. Since $\text{S}_{\text{N}}2$ reactions proceed faster at primary than secondary carbon atoms, $\text{S}_{\text{N}}2$ displacement on bromoethane is a faster reaction.

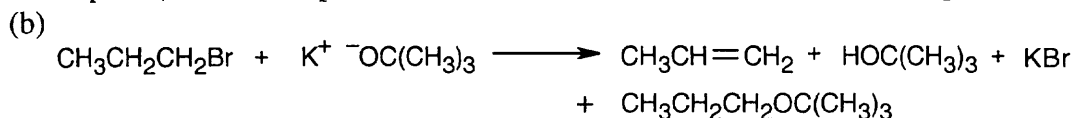
(c) Ethoxide ion and cyanide ion are different *nucleophiles*. Since CN^- is more reactive than $\text{CH}_3\text{CH}_2\text{O}^-$ in $\text{S}_{\text{N}}2$ reactions, $\text{S}_{\text{N}}2$ displacement on 2-bromopropane by CN^- proceeds at a faster rate.

(d) The *solvent* in each reaction is different. The $\text{S}_{\text{N}}2$ reaction on bromoethane in polar, aprotic acetonitrile proceeds faster than the reaction in nonpolar benzene.

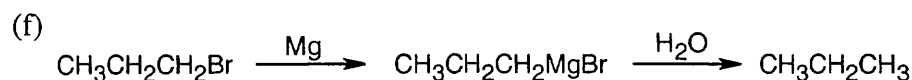
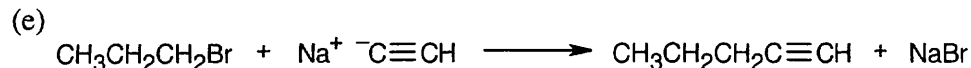
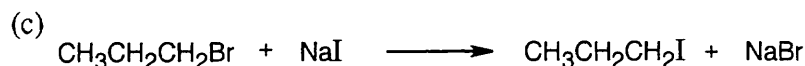
11.30 Because 1-bromopropane is a primary haloalkane, the reaction proceeds by either a S_N2 or $E2$ mechanism, depending on the basicity and the amount of steric hindrance in the nucleophile.



Propene (elimination product) is also formed because NaNH_2 is a strong base.



$\text{K}^+ \text{ } ^-\text{OC}(\text{CH}_3)_3$ is a strong, bulky base that brings about elimination as well as some substitution.

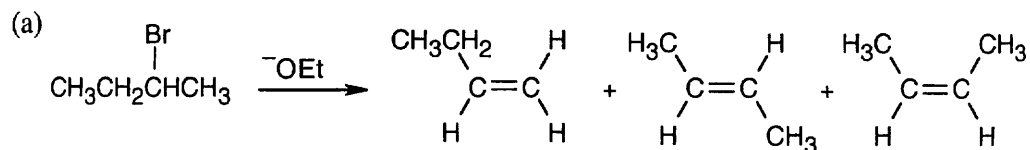


11.31 To predict nucleophilicity, remember these guidelines:

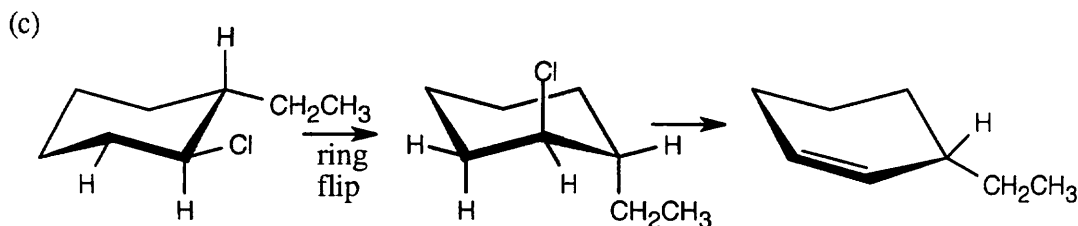
- (1) In comparing nucleophiles that have the same attacking atom, nucleophilicity parallels basicity. In other words, a more basic nucleophile is a more effective nucleophile.
- (2) Nucleophilicity increases in going down a column of the periodic table.
- (3) A negatively charged nucleophile is usually more reactive than a neutral nucleophile.

<i>More Nucleophilic</i>	<i>Less Nucleophilic</i>	<i>Reason</i>
(a) $\text{ } ^-\text{NH}_2$	NH_3	Rule 1 or 3
(b) CH_3CO_2^-	H_2O	Rule 1 or 3
(c) F^-	BF_3	BF_3 is not a nucleophile
(d) $(\text{CH}_3)_3\text{P}$	$(\text{CH}_3)_3\text{N}$	Rule 2
(e) I^-	Cl^-	Rule 2
(f) $\text{ } ^-\text{C}\equiv\text{N}$	$\text{ } ^-\text{OCH}_3$	Reactivity chart, Section 11.3

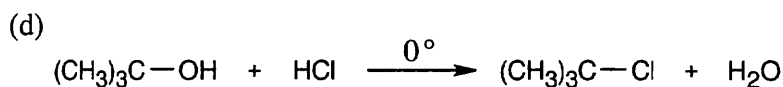
11.32



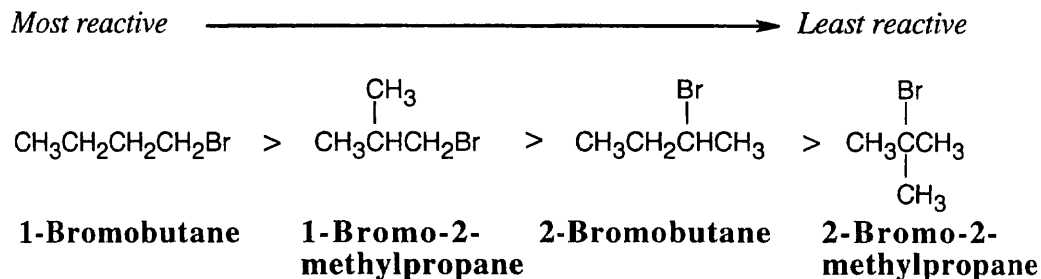
(b) $\text{H}_2\text{C}=\text{CHBr}$, like other vinylic organohalides, does not undergo nucleophilic substitutions.



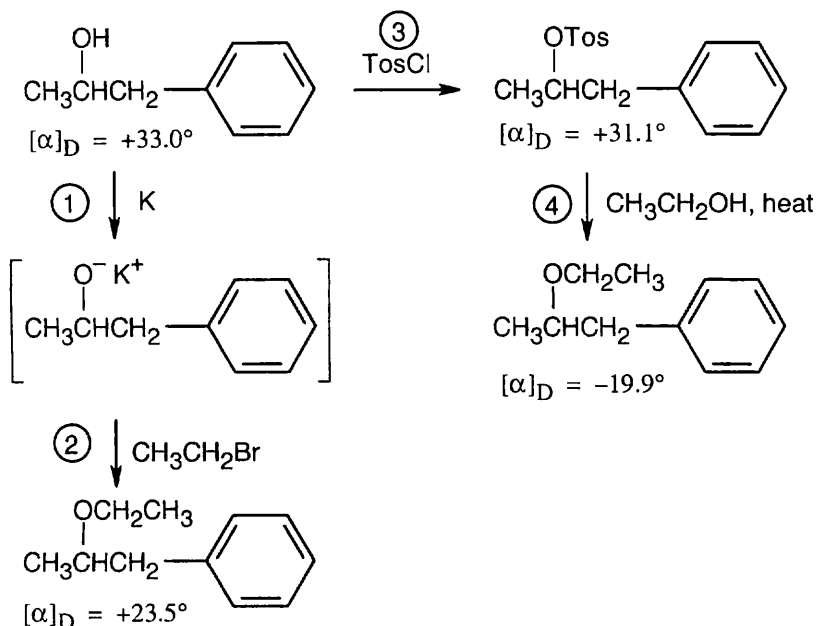
This alkyl halide gives the less substituted cycloalkene (non-Zaitsev product). Elimination to form the Zaitsev product does not occur because the $-\text{Cl}$ and $-\text{H}$ involved cannot assume the anti periplanar geometry preferred for E2 elimination.



11.33



11.34 An alcohol is converted to an ether by two different routes in this series of reactions. The two resulting ethers have identical structural formulas but differ in the sign of specific rotation. Therefore, at some step or steps in these reaction sequences, inversion of configuration at the chiral carbon must have occurred. Let's study each step of the Phillips and Kenyon series to find where inversion is occurring.



In step 1, the alcohol reacts with potassium metal to produce a potassium alkoxide. Since the bond between carbon and oxygen has not been broken, no inversion occurs in this step.

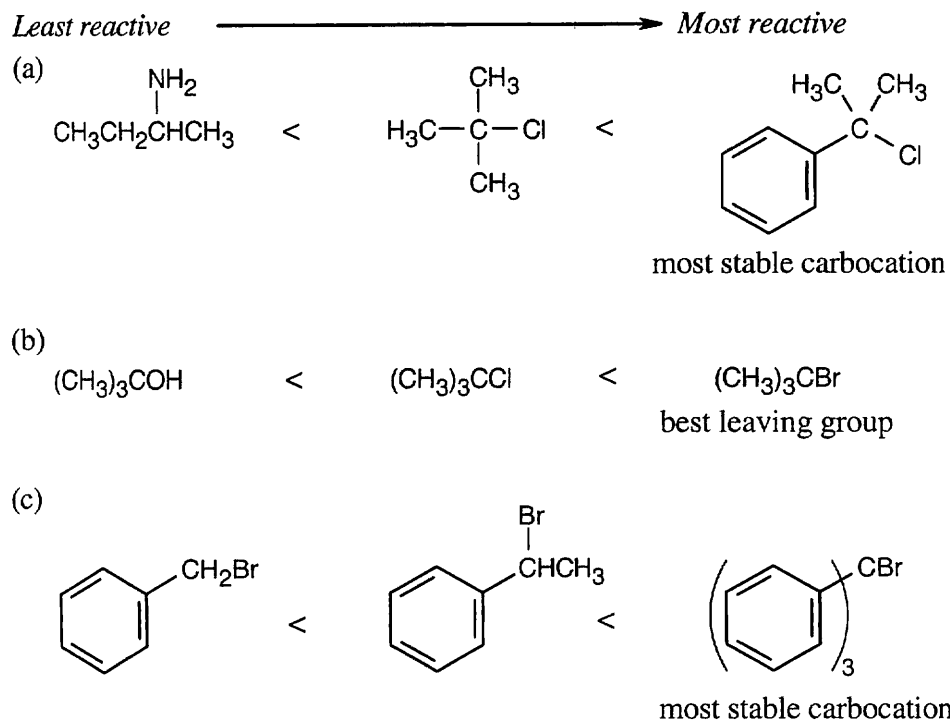
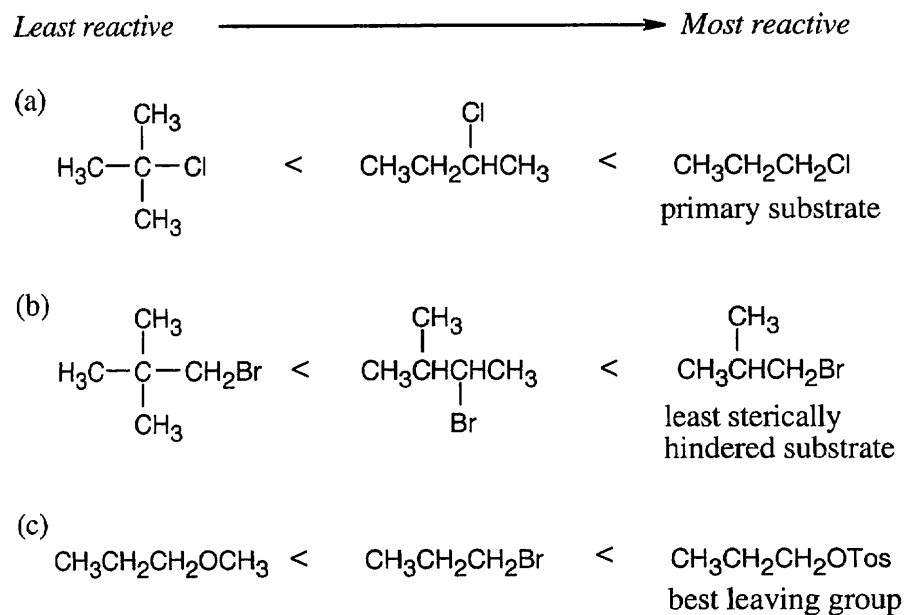
The potassium alkoxide acts as a nucleophile in the S_N2 displacement on $\text{CH}_3\text{CH}_2\text{Br}$ in step 2. It is the C–Br bond of bromoethane, however, not the C–O bond of the alkoxide, that is broken. No inversion at the carbon chirality center occurs in step 2.

The starting alcohol reacts with tosyl chloride in step 3. Again, because the O–H bond, rather than the C–O bond, of the alcohol is broken, no inversion occurs at this step.

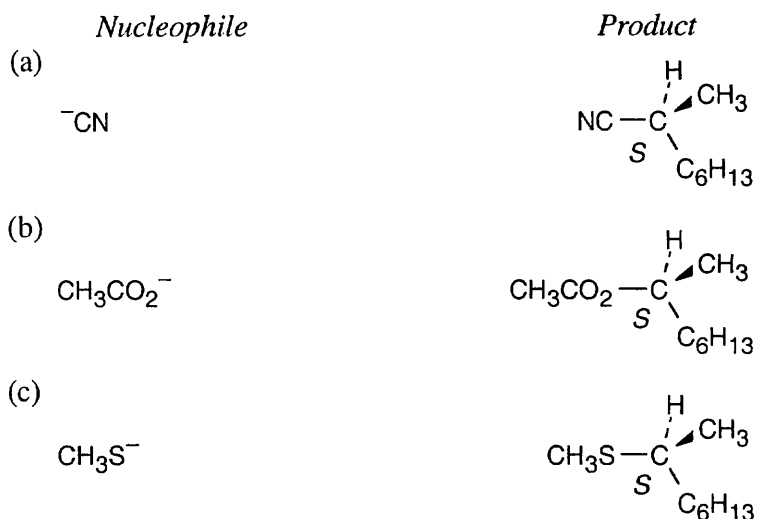
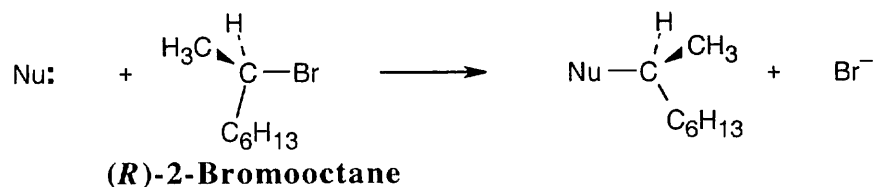
Inversion must therefore occur at step 4 when the $^-\text{OTos}$ group is displaced by $\text{CH}_3\text{CH}_2\text{OH}$. The C–O bond of the tosylate ($-\text{OTos}$) is broken, and a new C–O bond is formed.

Notice the specific rotations of the two enantiomeric products. The product of steps 1 and 2 should be enantiomerically pure because neither reaction has affected the C–O bond. Reaction 4 proceeds with some racemization at the chirality center to give a smaller absolute value of $[\alpha]_D$.

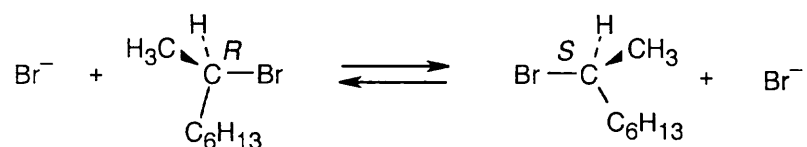
- 11.35** (a) Substitution does not take place with secondary alkyl halides when a strong, bulky base is used. Elimination occurs instead and produces $\text{H}_2\text{C}=\text{CHCH}_2\text{CH}_3$ and $\text{CH}_3\text{CH}=\text{CHCH}_3$.
 (b) Fluoroalkanes don't undergo S_N2 reactions because F^- is a poor leaving group.
 (c) SOCl_2 in pyridine converts primary and secondary alcohols to chlorides by an S_N2 mechanism. 1-Methyl-1-cyclohexanol is a tertiary alcohol and does not undergo S_N2 substitution. Instead, E2 elimination occurs to give 1-methylcyclohexene.

11.36 S_N1 reactivity:11.37 S_N2 reactivity:

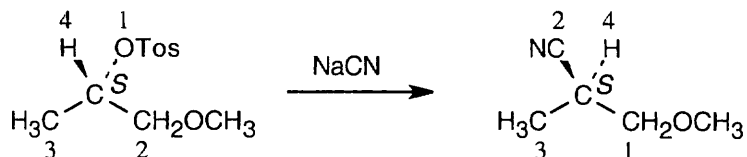
11.38 (*R*)-2-Bromooctane is a secondary bromoalkane, which undergoes S_N2 substitution. Since S_N2 reactions proceed with inversion of configuration, the configuration at the carbon chirality center is inverted. (This does not necessarily mean that all *R* isomers become *S* isomers after an S_N2 reaction. The *R,S* designation refers to the priorities of groups, which may change when the nucleophile is varied.)



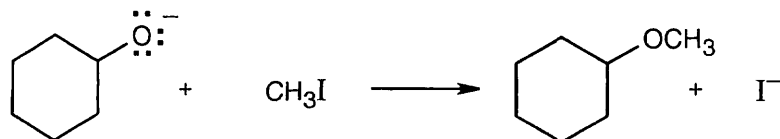
11.39 After 50% of the starting material has reacted, the reaction mixture consists of 50% (*R*)-2-bromooctane and 50% (*S*)-2-bromooctane. At this point, the *R* starting material is completely racemized.



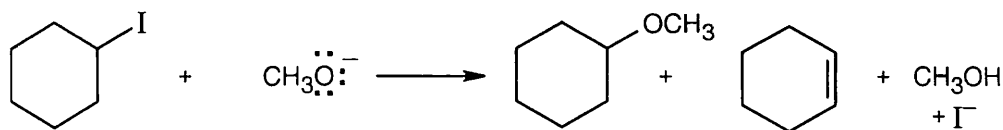
11.40 According to Cahn–Ingold–Prelog rules (Section 6.5), the nucleophile (CN^-) has a lower priority than the leaving group (OTos). Thus, even though the reaction proceeds with inversion of configuration, the priorities of the substituents also change, and the configuration remains *S*.



11.41

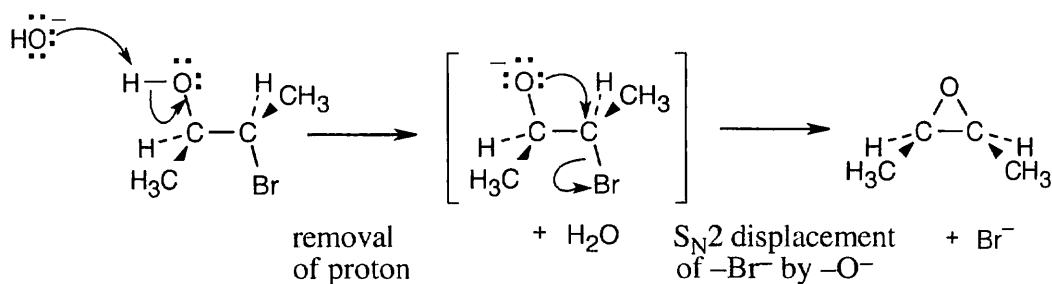
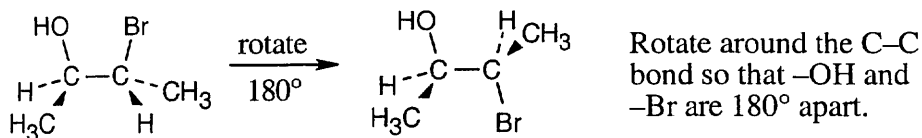


This is an excellent method of ether preparation because iodomethane is very reactive in $\text{S}_{\text{N}}2$ displacements.



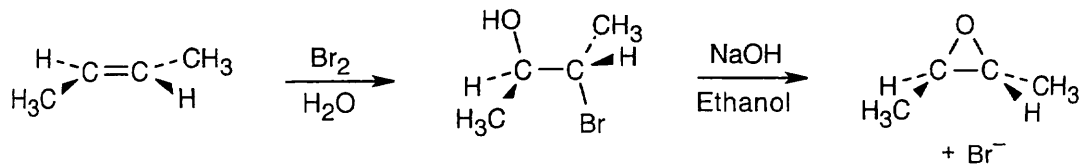
Reaction of a secondary haloalkane with a basic nucleophile yields both substitution and elimination products. This is a less satisfactory method of ether preparation.

11.42

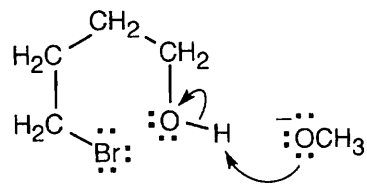


This reaction is an intramolecular $\text{S}_{\text{N}}2$ displacement.

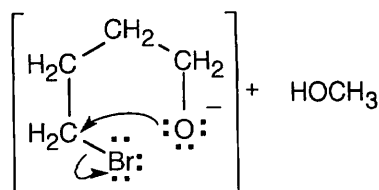
11.43



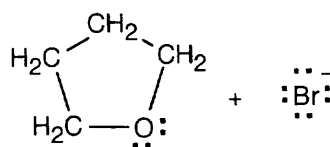
11.44



Methoxide removes a proton from the hydroxyl group of 4-bromo-1-butanol.



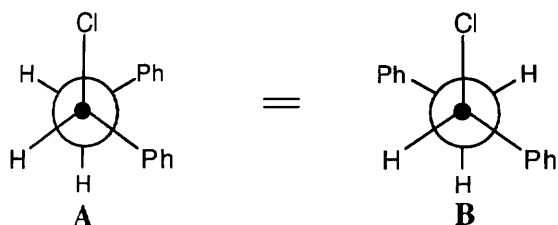
S_N2 displacement of Br^- by O^- yields the cyclic ether tetrahydrofuran.



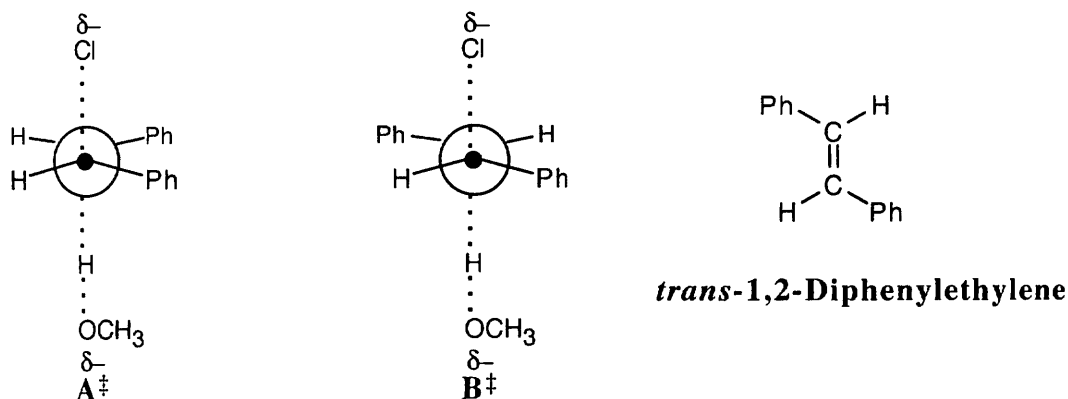
Tetrahydrofuran

- 11.45** The first step in an S_N1 displacement is dissociation of the substrate to form a planar, sp^2 -hybridized carbocation and a leaving group. The carbocation that would form from dissociation of this alkyl halide can't become planar because of the rigid structure of the ring skeleton. Because it's not possible to form the necessary carbocation, an S_N1 reaction can't occur. In addition, approach by a nucleophile from the back side of the alkyl halide is blocked by the rigid ring system, and S_N2 displacement can't take place.
- 11.46** In a molecule containing a double bond, all atoms bonded to the sp^2 carbons must lie in a common plane. For this compound, planar geometry at the "bridgehead" of the ring system is not possible because the rigid ring framework won't allow it. Thus, $E2$ elimination does not take place because the product containing a bridgehead double bond can't form.

11.47

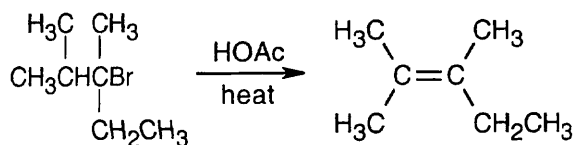


Both Newman projections place -H and -Cl in the correct anti periplanar geometry for E2 elimination.

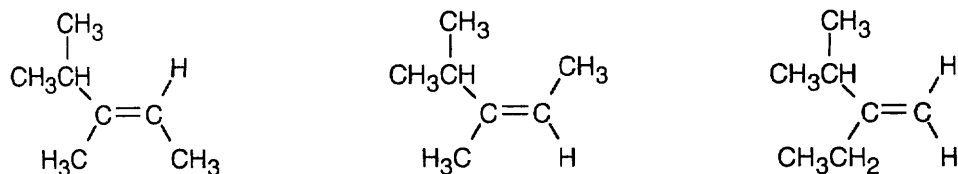


Either transition state \mathbf{A}^\ddagger or \mathbf{B}^\ddagger can form when 1-chloro-1,2-diphenylethane undergoes E2 elimination. Crowding of the two phenyl groups in \mathbf{A}^\ddagger makes this transition state (and the product resulting from it) of higher energy than transition state \mathbf{B}^\ddagger . Formation of the product from \mathbf{B}^\ddagger is therefore favored, and *trans*-1,2-diphenylethylene is the major product.

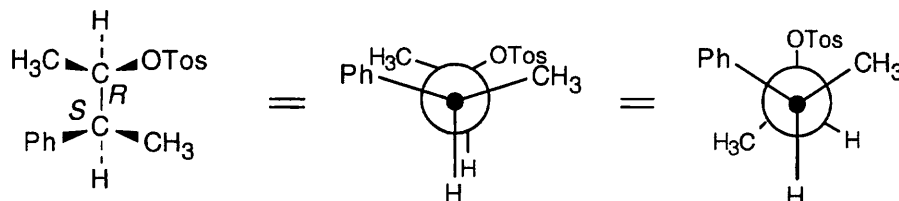
11.48



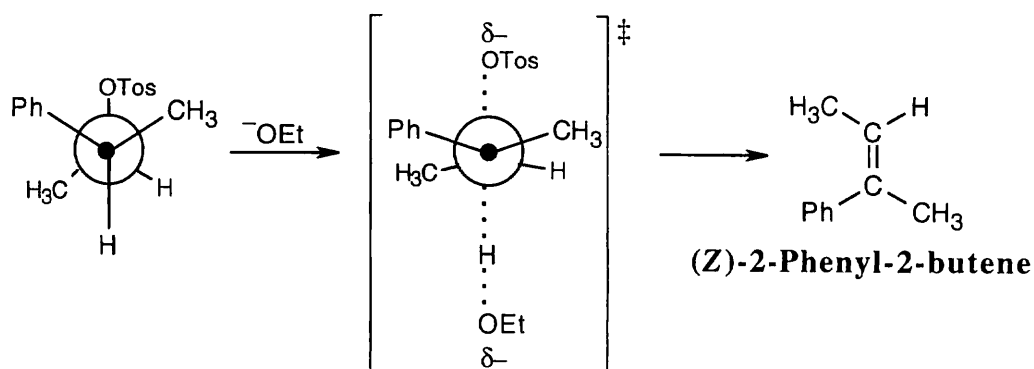
The alkene shown above has the most highly substituted double bond, and, according to Zaitsev's rule, is the major product. The following minor products may also form.



11.49

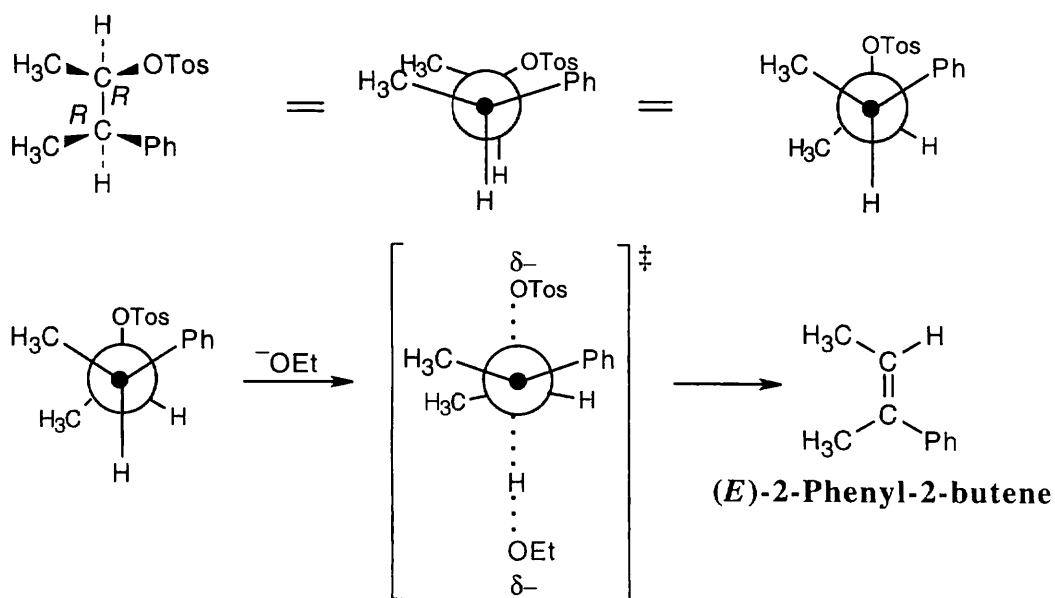


Draw a Newman projection of the tosylate of (2*R*,3*S*)-3-phenyl-2-butanol, and rotate the projection until the -OTos and the -H on the adjoining carbon atom are anti periplanar. Even though this conformation has several gauche interactions, it is the only conformation in which -OTos and -H are 180° apart.



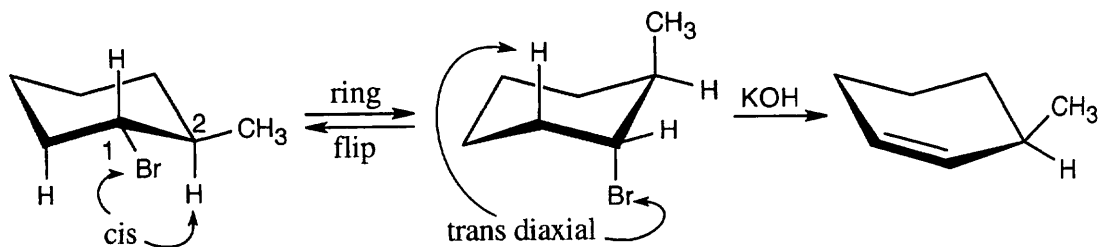
Elimination yields the *Z* isomer of 2-phenyl-2-butene.

11.50 Using the same argument used in the previous problem, you can show that elimination from the tosylate of (2*R*,3*R*)-3-phenyl-2-butanol gives the *E*-alkene.



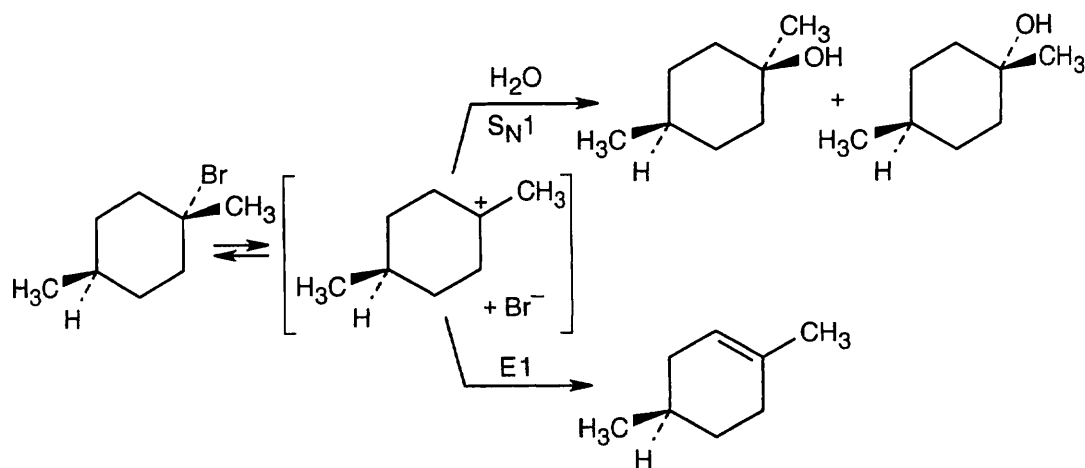
The (2*S*,3*S*) isomer also forms the *E* alkene; the (2*S*,3*R*) isomer yields the *Z* alkene.

11.51



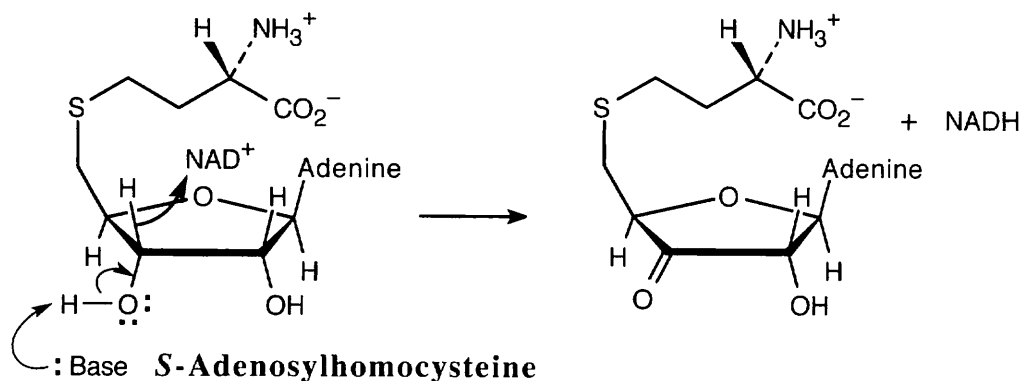
E2 reactions require that the two atoms to be eliminated have a periplanar relationship. Since it's impossible for bromine and the hydrogen at C2 to be periplanar, elimination occurs in the non-Zaitsev direction to yield 3-methylcyclohexene.

11.52

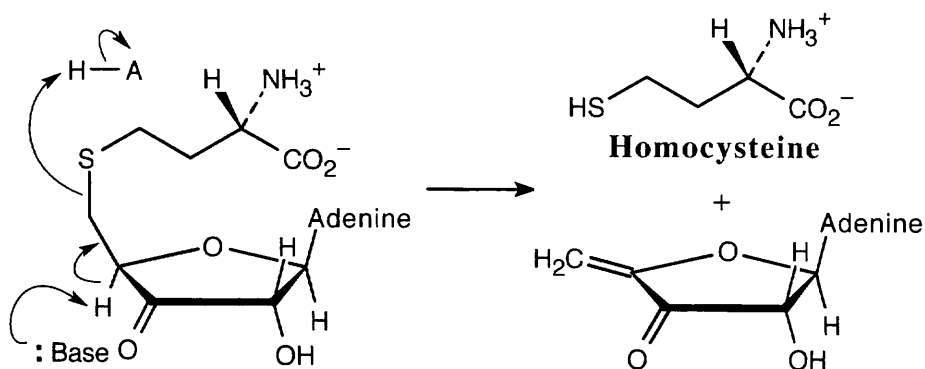


This tertiary bromoalkane reacts by S_N1 and E1 routes to yield alcohol and alkene products. The alcohol products are diastereomers.

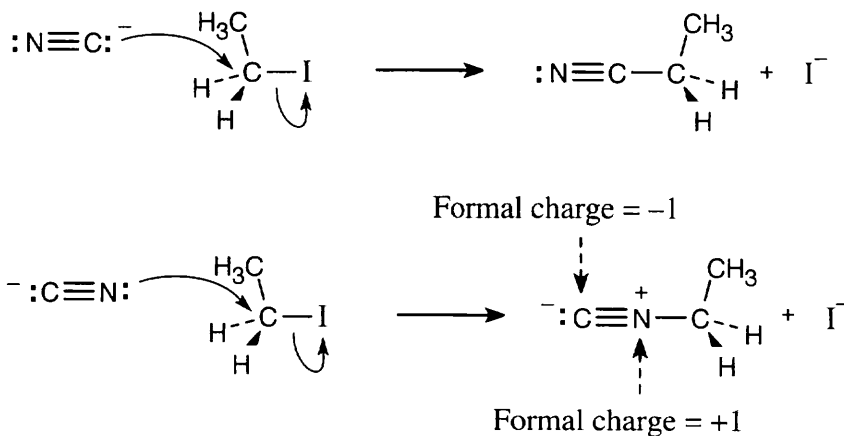
11.53 Step 1: NAD^+ oxidizes an alcohol to a ketone.



Step 2: Base brings about an E1cB elimination reaction that has homocysteine as the leaving group.

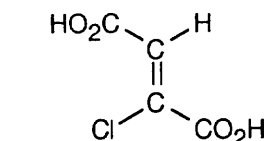
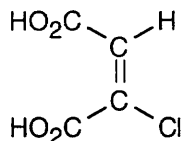


11.54



$\text{S}_{\text{N}}2$ attack by the lone pair electrons associated with carbon gives the nitrile product. Attack by the lone pair electrons associated with nitrogen yields the isonitrile product.

11.55

**(Z)-2-Chloro-2-butene-1,4-dioic acid****(E)-2-Chloro-2-butene-1,4-dioic acid**

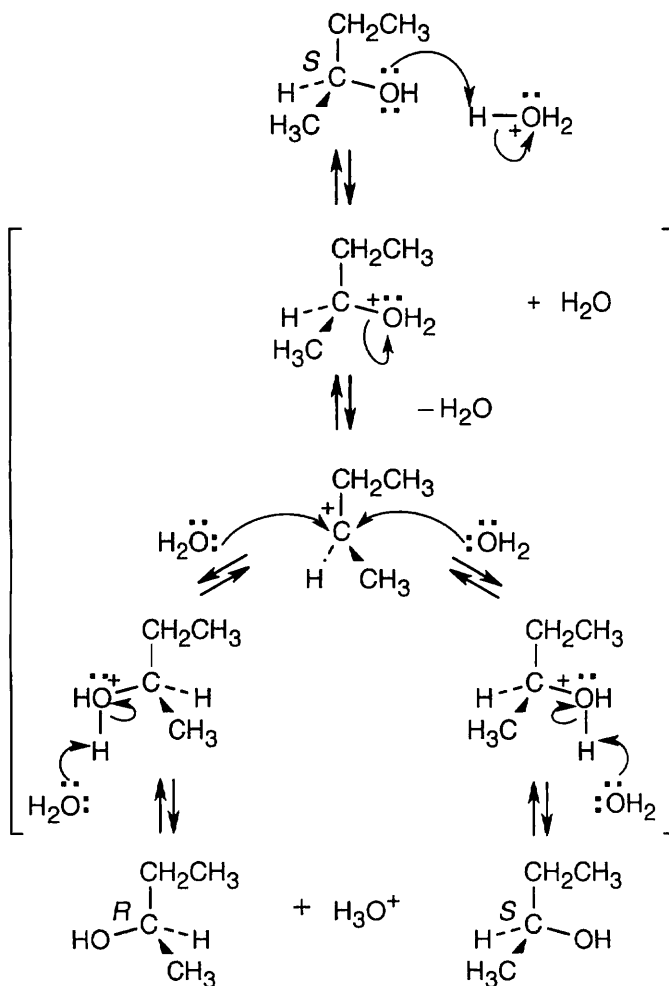
Hydrogen and chlorine are anti to each other in the *Z* isomer and are syn in the *E* isomer. Since the *Z* isomer reacts fifty times faster than the *E* isomer, elimination must proceed more favorably when the substituents to be eliminated are anti to one another. This is the same stereochemical result that occurs in E2 eliminations of alkyl halides.

- 11.56** Since 2-butanol is a secondary alcohol, substitution can occur by either an $\text{S}_{\text{N}}1$ or $\text{S}_{\text{N}}2$ route, depending on reaction conditions. Two factors favor an $\text{S}_{\text{N}}1$ mechanism in this case. (1) The reaction is run under acidic conditions in a polar, protic solvent. (2) Dilute acid converts a poor leaving group (^-OH) into a good leaving group (OH_2^+), which dissociates easily.

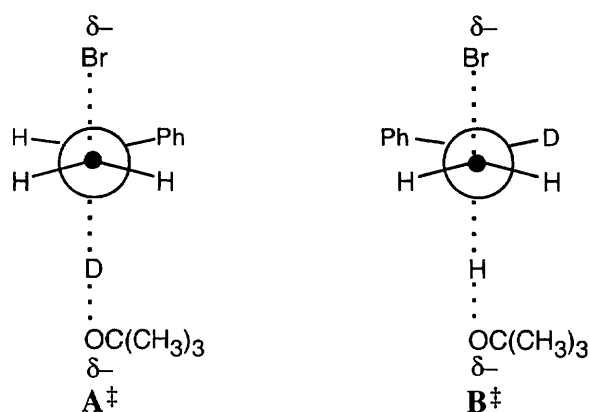
Protonation of the hydroxyl oxygen..

is followed by loss of water to form a planar carbocation.

Attack of water from either side of the planar carbocation yields racemic product.

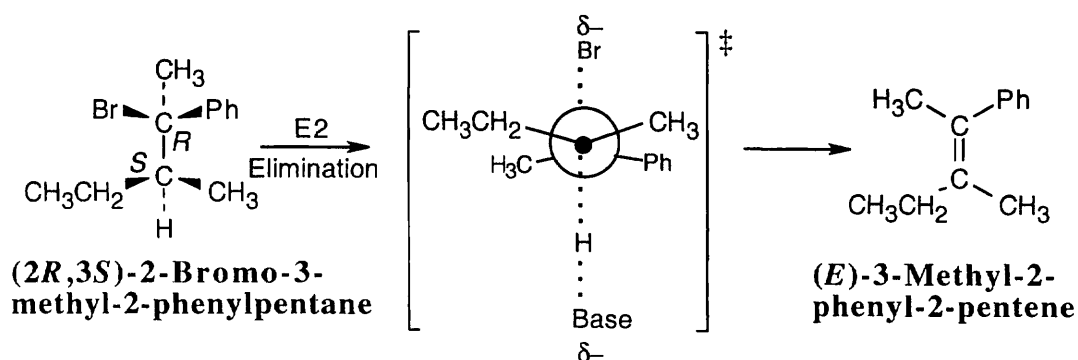


- 11.57** The chiral tertiary alcohol (*R*)-3-methyl-3-hexanol reacts with HBr by an S_N1 pathway. HBr protonates the hydroxyl group, which dissociates to yield a planar, achiral carbocation. Reaction with the nucleophilic bromide anion can occur from either side of the carbocation to produce (\pm)-3-bromo-3-methylhexane.
- 11.58** Since carbon-deuterium bonds are slightly stronger than carbon-hydrogen bonds, more energy is required to break a C–D bond than to break a C–H bond. In a reaction where either a carbon-deuterium or a carbon-hydrogen bond can be broken in the rate-limiting step, a higher percentage of C–H bond-breaking occurs because the energy of activation for C–H breakage is lower.



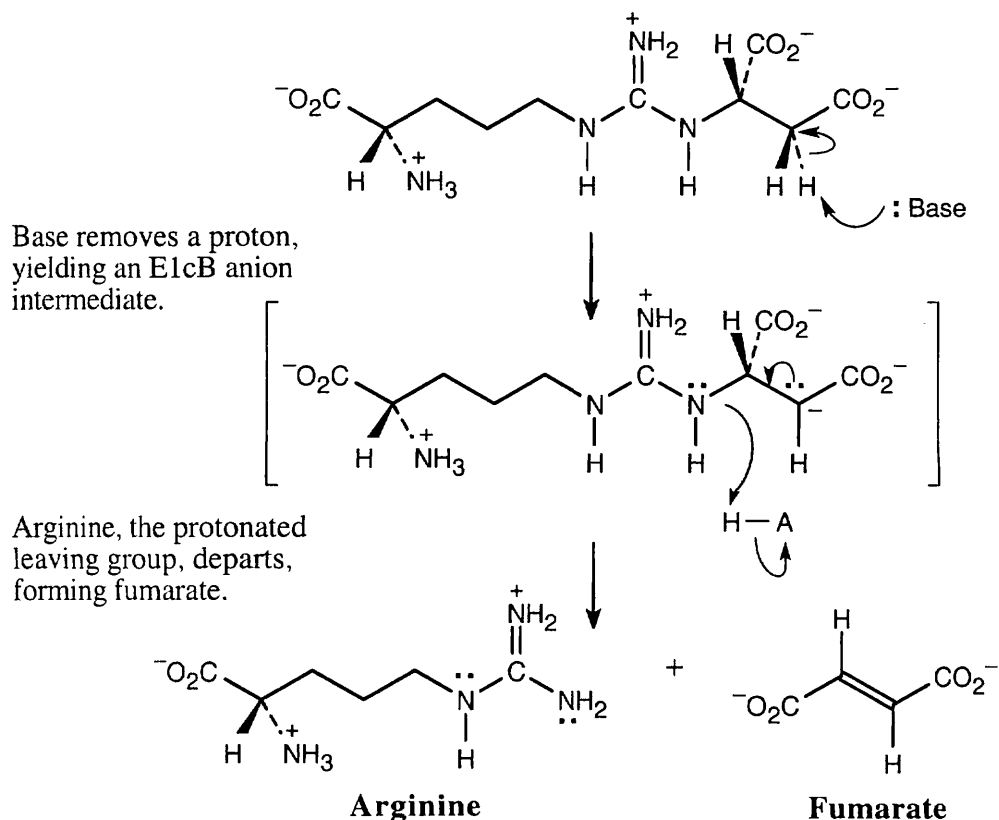
Transition state A^\ddagger is of higher energy than transition state B^\ddagger because more energy is required to break the C–D bond. The product that results from transition state B^\ddagger is thus formed in greater abundance.

11.59



The (2*S*,3*R*) isomer also yields *E* product.

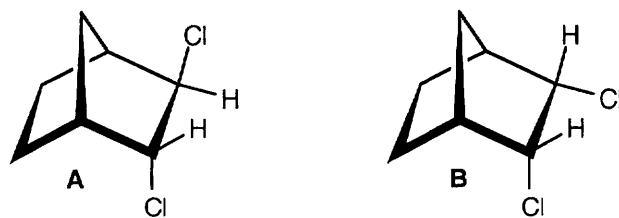
11.60



11.61 One of the steric requirements of E2 elimination is the need for periplanar geometry, which optimizes orbital overlap in the transition state leading to alkene product. Two types of periplanar arrangements of substituents are possible — syn and anti.

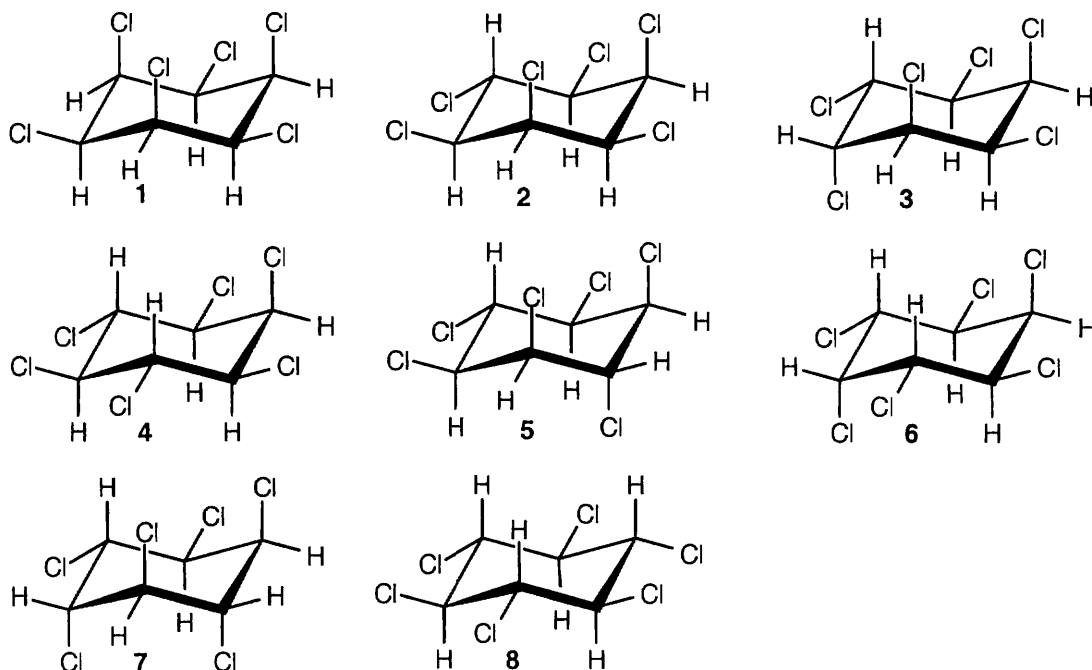
A model of the deuterated bromo compound shows that the deuterium, bromine, and the two carbon atoms that will constitute the double bond all lie in a plane. This arrangement of atoms leads to syn elimination. Even though anti elimination is usually preferred, it doesn't occur for this compound because the bromine, hydrogen, and two carbons can't achieve the necessary geometry.

11.62



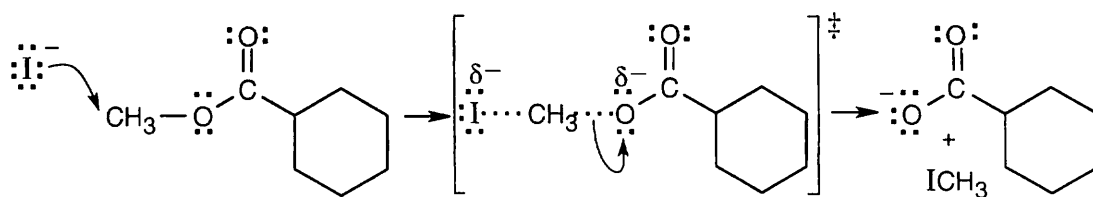
We concluded in Problem 11.61 that E2 elimination in compounds of this bicyclic structure occurs with syn periplanar geometry. In compound **A**, -H and -Cl can be eliminated via the syn-periplanar route. Since neither syn nor anti periplanar elimination is possible for **B**, elimination occurs by a slower, E1 route.

11.63



Diastereomer 8 reacts much more slowly than other isomers in an E2 reaction because no pair of hydrogen and chlorine atoms can adopt the anti periplanar orientation preferred for E2 elimination.

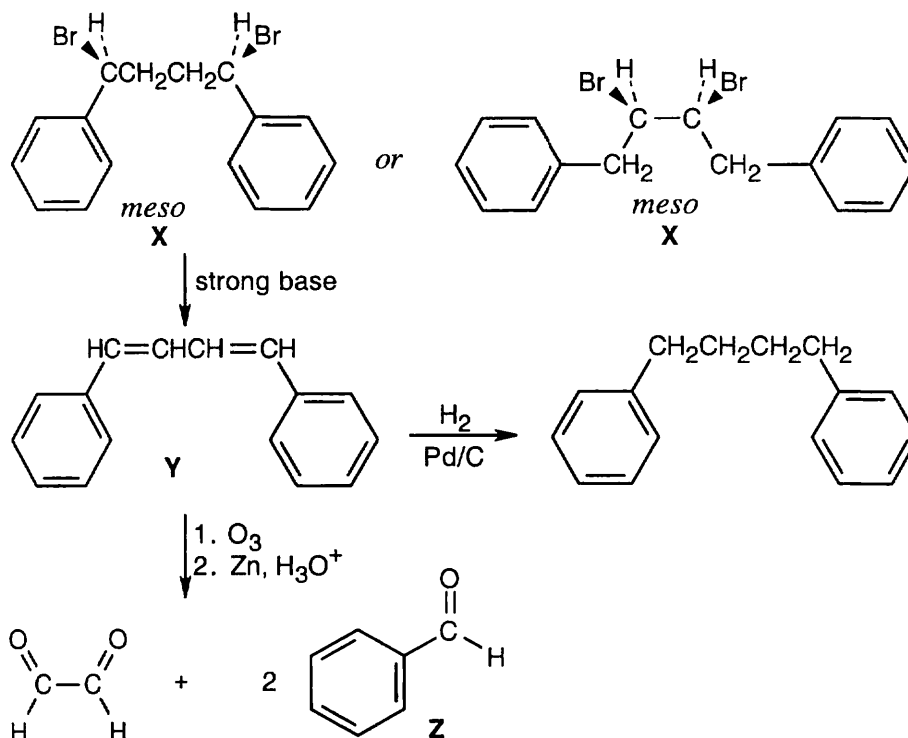
11.64 The two pieces of evidence indicate that the reaction proceeds by an S_N2 mechanism: S_N2 reactions proceed much faster in polar aprotic solvents such as DMF, and methyl esters react faster than ethyl esters. This reaction is an S_N2 displacement on a methyl ester by iodide ion.



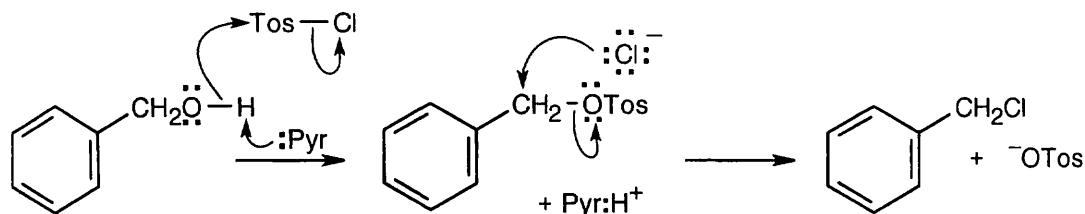
Other experiments can provide additional evidence for an S_N2 mechanism. We can determine if the reaction is second-order by varying the concentration of LiI . We can also vary the type of nucleophile to distinguish an S_N2 mechanism from an S_N1 mechanism, which does not depend on the identity of the nucleophile.

11.65 Because Cl^- is a relatively poor leaving group and acetate is a relatively poor nucleophile, a substitution reaction involving these two groups proceeds at a very slow rate. I^- , however, is both a good nucleophile and a good leaving group. 1-Chlorooctane thus reacts preferentially with iodide to form 1-iodooctane. Only a small amount of 1-iodooctane is formed (because of the low concentration of iodide ion), but 1-iodooctane is more reactive than 1-chlorooctane toward substitution by acetate. Reaction with acetate produces 1-octyl acetate and regenerates iodide ion. The whole process can now be repeated with another molecule of 1-chlorooctane. The net result is production of 1-octyl acetate, and no iodide is consumed.

11.66 Two optically inactive compounds are possible structures for compound **X**.

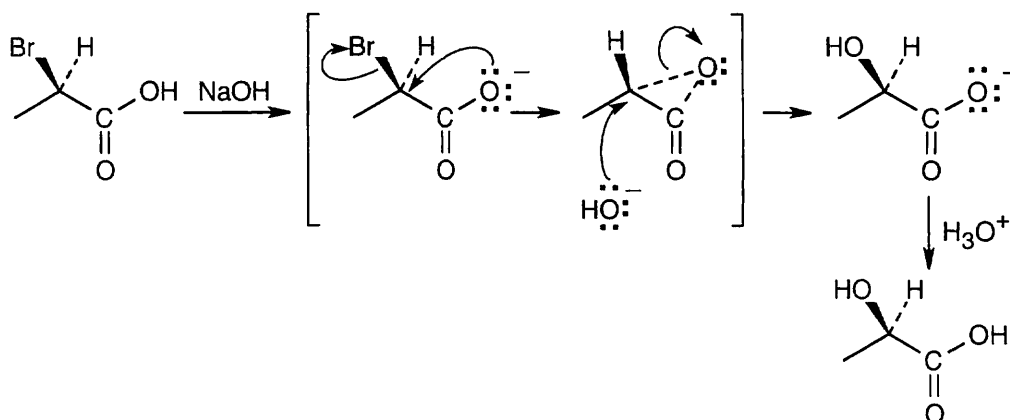


11.67



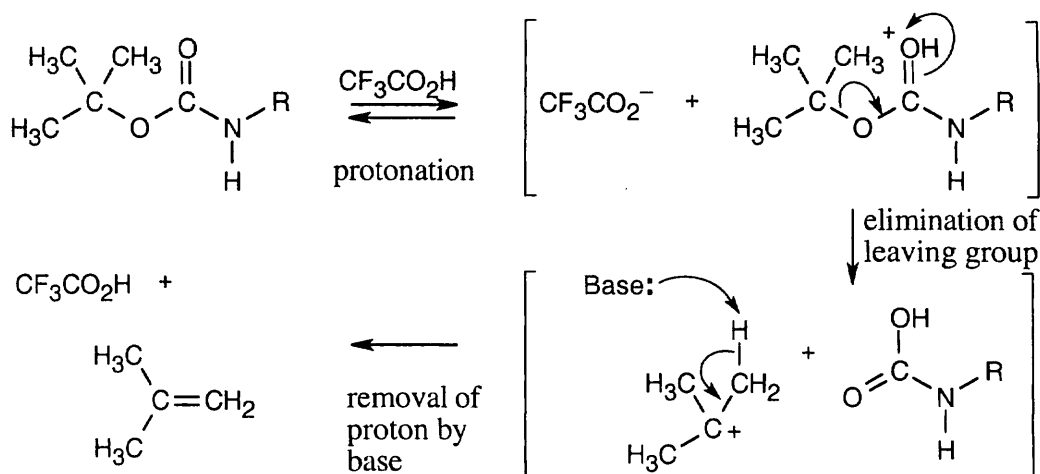
At lower temperatures, a tosylate is formed from the reaction of *p*-toluenesulfonyl chloride and an alcohol. The new bond is formed between the toluenesulfonyl group and the oxygen of the alcohol. At higher temperatures, the chloride anion can displace the $-\text{OTos}$ group, which is an excellent leaving group, to form an organochloride.

11.68



Two inversions of configuration equal a net retention of configuration.

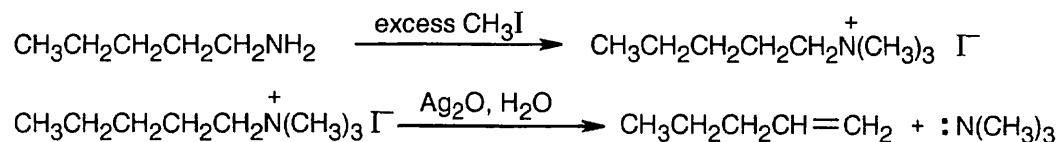
11.69



This reaction proceeds by an E1 mechanism.

11.70 Notice that the chiral methyl group has the (*R*) configuration in both *N*-methyltetrahydrofolate and in methionine. This fact suggests that methylation proceeds with two inversions of configuration which, in fact, has been shown to be the case.

11.71



The intermediate is a charged quaternary ammonium compound that results from $\text{S}_{\text{N}}2$ substitutions on three CH_3I molecules by the amine nitrogen. E2 elimination occurs because the neutral $\text{N}(\text{CH}_3)_3$ molecule is a good leaving group.

Review Unit 4: Stereochemistry; Alkyl Halides; Substitutions and Eliminations

Major Topics Covered (with vocabulary):

Handedness:

stereoisomer enantiomer chiral plane of symmetry achiral chirality center
plane-polarized light optical activity levorotatory dextrorotatory specific rotation

Stereoisomers and configuration:

configuration absolute configuration diastereomer meso compound racemate resolution
prochirality *re* face *si* face prochirality center *pro-R* *pro-S*

Stereochemistry of reactions.

Alkyl halides:

allylic position delocalization Grignard reagent Gilman reagent

Oxidation and reduction in organic chemistry:

Substitution reactions:

nucleophilic substitution reaction Walden inversion reaction rate kinetics second-order
reaction rate constant S_N2 reaction bimolecular nucleophilicity leaving group solvation
 S_N1 reaction first-order reaction rate-limiting step ion pair dielectric polarization

Elimination reactions:

Zaitsev's rule E2 reaction syn periplanar geometry anti periplanar geometry
deuterium isotope effect E1 reaction E1cB reaction

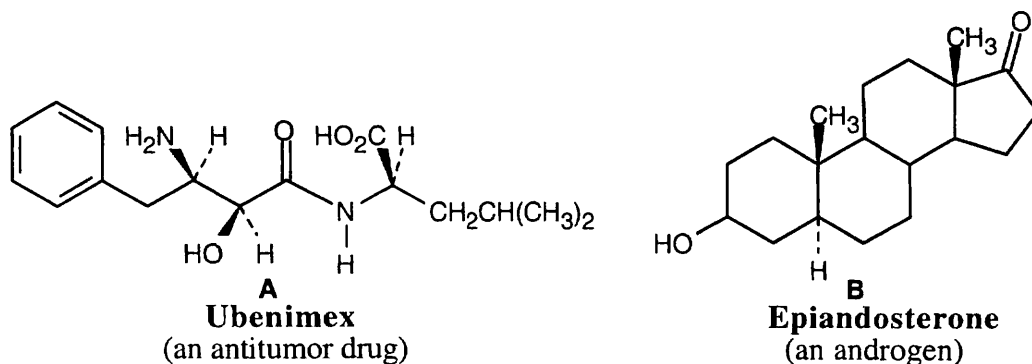
Types of Problems:

After studying these chapters, you should be able to:

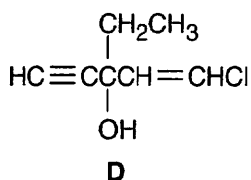
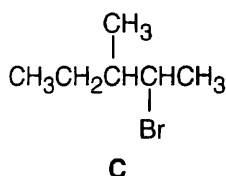
- Calculate the specific rotation of an optically active compound.
- Locate chirality centers, assign priorities to substituents, and assign *R,S* designations to chirality centers.
- Given a stereoisomer, draw its enantiomer and/or diastereomers.
- Locate the symmetry plane of a meso compound.
- Predict the stereochemistry of reaction products, using the concept of prochirality when appropriate.
- Draw, name, and synthesize alkyl halides.
- Understand the mechanism of radical halogenation and the stability order of radicals.
- Prepare Grignard reagents and dialkylcopper reagents and use them in synthesis.
- Predict the oxidation level of a compound.
- Formulate the mechanisms of S_N2 , S_N1 and elimination reactions.
- Predict the effect of substrate, nucleophile, leaving group and solvent on substitution and elimination reactions.
- Predict the products of substitution and elimination reactions.
- Classify substitution and elimination reactions by type.

Points to Remember:

- * A helpful strategy for assigning *R,S* designations: Using models, build two enantiomers by adding four groups to each of two tetrahedral carbons. Number the groups 1–4, to represent priorities of groups at a tetrahedral carbon, and assign a configuration to each carbon. Attach a label that indicates the configuration of each enantiomer. Keep these two enantiomers, and use them to check your answer every time that you need to assign *R,S* configurations to a chiral atom.
- * When assigning *pro-R* or *pro-S* designations to a hydrogen, mentally replace the hydrogen that points out of the plane of the page. The other hydrogen is then positioned for prochirality assignment without manipulating the molecule. If the designation is *R*, the replaced hydrogen is *pro-R*; if the designation is *S*, the replaced hydrogen is *pro-S*.
- * In naming alkyl halides by the IUPAC system, remember that a halogen is named as a substituent on an alkane. When numbering the alkyl halide, the halogens are numbered in the same way as alkyl groups and are cited alphabetically.
- * The definition of oxidation and reduction given in Chapter 10 expands the concept to reactions that you might not have considered to be oxidations or reductions. As you learn new reactions, try to classify them as oxidations, reductions or neither.
- * Predicting the outcome of substitutions and eliminations is only straightforward in certain cases. For primary halides, S_N2 and $E2$ reactions are predicted. For tertiary halides, S_N1 , $E2$ and $E1$ (to a certain extent) are the choices. The possibilities for secondary halides are more complicated. In addition, many reactions yield both substitution and elimination products, and both inversion and retention of configuration may occur in the same reaction.

Self-Test:

Assign *R,S* designations to the chiral carbons in **A**. Indicate the chirality centers in **B**. How many possible stereoisomers of **B** are possible?



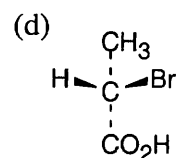
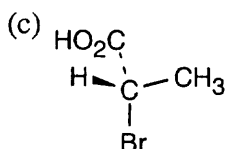
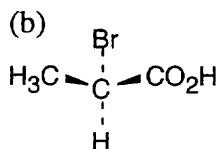
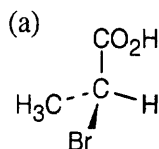
Ethchlorvynol
(a sedative)

Name **C**. Draw all stereoisomers of **C**, label them, and describe their relationship. Predict the products of reaction of **C** with: (a) NaOH; (b) Mg, then H₂O; (c) product of (b) + Br₂, *hν* (show the major product); (d) (CH₃CH₂)₂CuLi.

Draw the *R* enantiomer of **D**. Predict the products of reaction of **D** with: (a) HBr; (b) product of (a) + aqueous ethanol. Describe the reactivity of the -Cl atom in substitution and elimination reactions.

Multiple Choice:

1. A meso compound and a racemate are identical in all respects except:
(a) molecular formula (b) degree of rotation of plane-polarized light
(c) connectivity of atoms (d) physical properties
2. Which of the following projections represents an *R* enantiomer?



3. In the reaction of (2*R*,3*S*)-3-methyl-2-pentanol with tosyl chloride, what is the configuration of the product?
(a) a mixture of all four possible stereoisomers (b) (2*R*,3*S*) and (2*S*,3*S*) (c) (2*R*,3*S*)
(d) (2*S*,3*S*)
4. Monochlorination of 2,3-dimethylbutane yields what percent of 2-chloro-2,3-dimethylbutane?
(a) 16% (b) 35% (c) 45% (d) 55%
5. How many monobromination products can be formed by NBS bromination of 2-ethyl-1-pentene? Include double-bond isomers.
(a) 3 (b) 4 (c) 5 (d) 6
6. Which of the following reactions is an oxidation?
(a) hydroxylation (b) hydration (c) hydrogenation (d) addition of HBr

7. All of the following are true of S_N2 reactions except:
(a) The rate varies with the concentration of nucleophile (b) The rate varies with the type of nucleophile (c) The nucleophile is involved in the rate-determining step (d) The rate of the S_N2 reaction of a substrate and a nucleophile is the same as the rate of the E2 reaction of the same two compounds.
8. Which of the following is true of S_N1 reactions?
(a) The rate varies with the concentration of nucleophile (b) The rate varies with the type of nucleophile (c) The rate is increased by use of a polar solvent. (d) The nucleophile is involved in the rate-determining step.
9. Which base is best for converting 1-bromohexane to 1-hexene?
(a) $(CH_3)_3CO^-$ (b) ^-CN (c) ^-OH (d) $^-C\equiv CH$
10. Which of the following is both a good nucleophile and a good leaving group?
(a) ^-OH (b) ^-CN (c) ^-Cl (d) ^-I