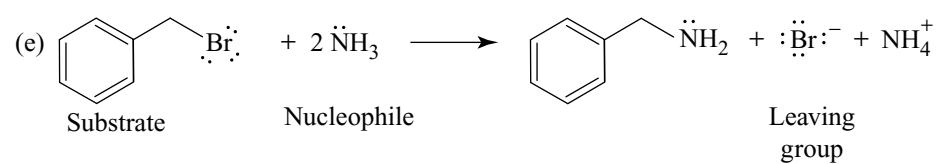
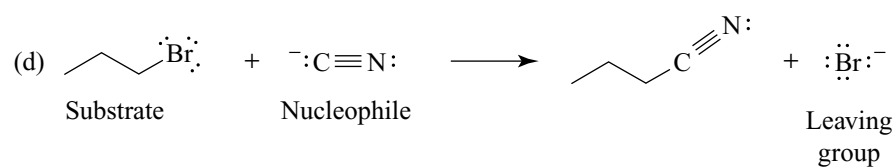
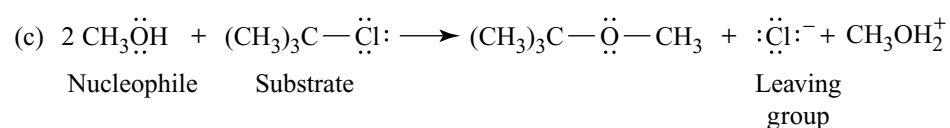
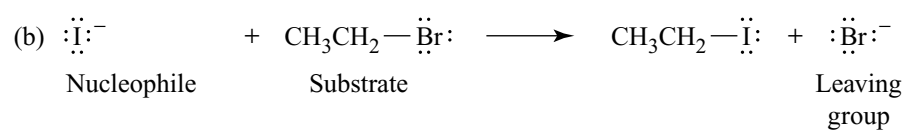
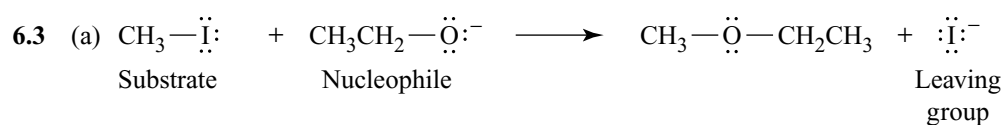


6 IONIC REACTIONS — NUCLEOPHILIC SUBSTITUTION AND ELIMINATION REACTIONS OF ALKYL HALIDES

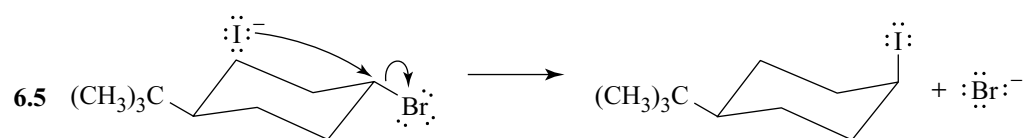
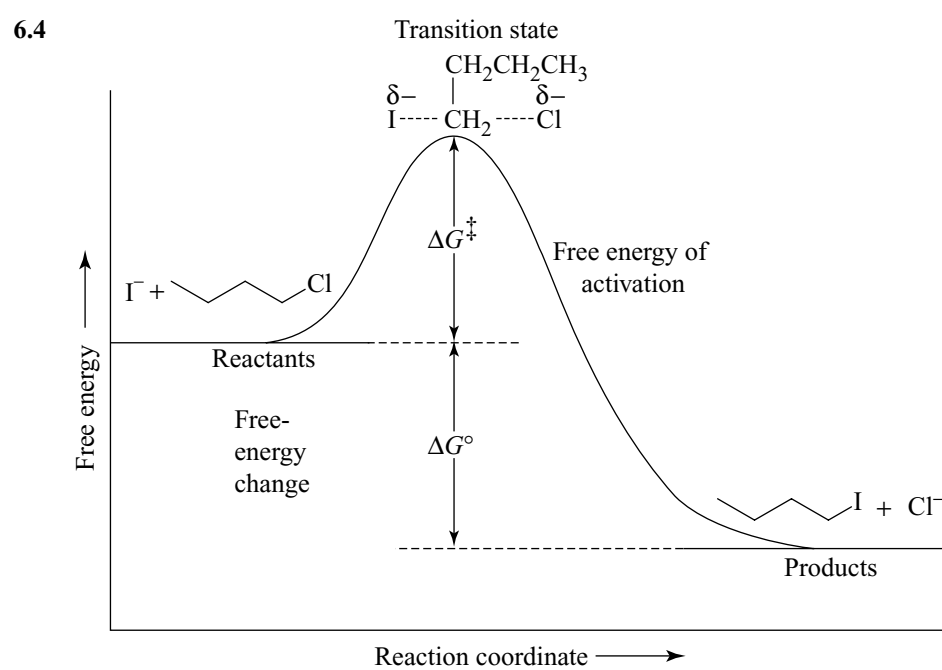
SOLUTIONS TO PROBLEMS

- 6.1 (a) *cis*-1-Bromo-2-methylcyclohexane
(b) *cis*-1-Bromo-3-methylcyclohexane
(c) 2,3,4-Trimethylheptane

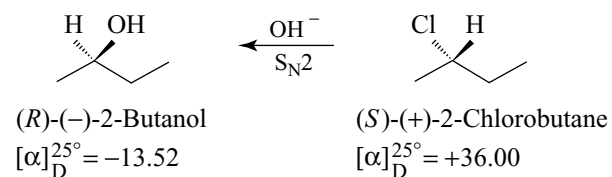
- 6.2 (a) 3° (b) vinylic (c) 2° (d) aryl (e) 1°



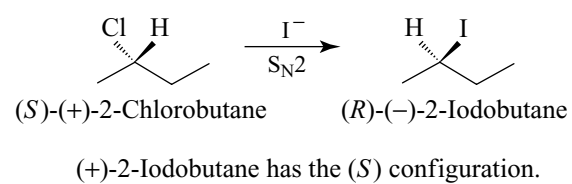
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- 6.6 (a) We know that when a secondary alkyl halide reacts with hydroxide ion by substitution, the reaction occurs with *inversion of configuration* because the reaction is $\text{S}_{\text{N}}2$. If we know that the configuration of (–)-2-butanol (from Section 5.8C) is that shown here, then we can conclude that (+)-2-chlorobutane has the opposite configuration.



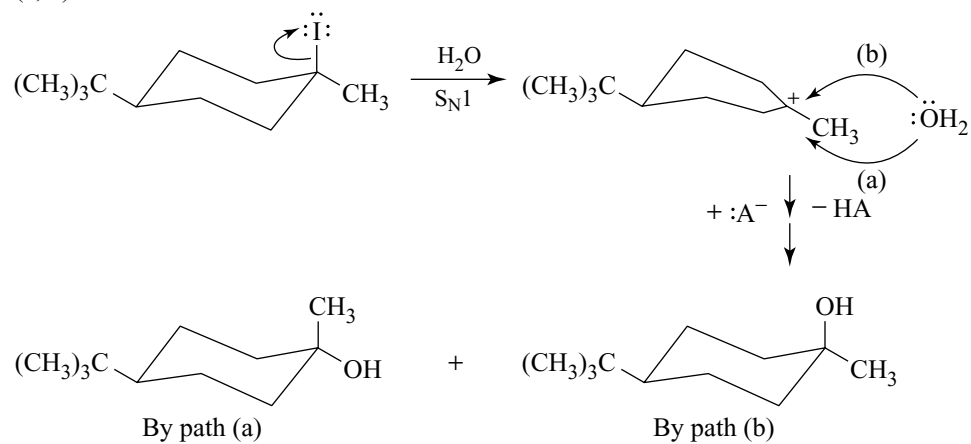
- (b) Again the reaction is $\text{S}_{\text{N}}2$. Because we now know the configuration of (+)-2-chlorobutane to be (*S*) [cf., part (a)], we can conclude that the configuration of (–)-2-iodobutane is (*R*).



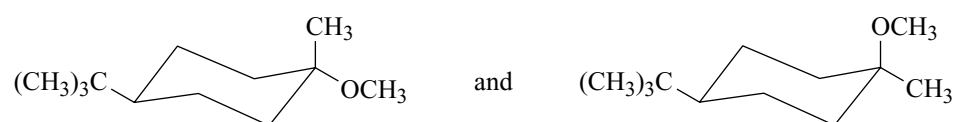
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6.7 (b) < (c) < (a) in order of increasing stability

6.8 (a, b)



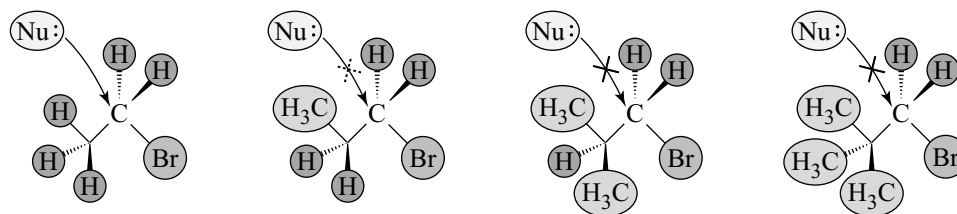
6.9



6.10 (c) is most likely to react by an S_N1 mechanism because it is a tertiary alkyl halide, whereas (a) is primary and (b) is secondary.

6.11 (a) Being primary halides, the reactions are most likely to be S_N2 , with the nucleophile in each instance being a molecule of the solvent (i.e., a molecule of ethanol).

(b) Steric hindrance is provided by the substituent or substituents on the carbon β to the carbon bearing the leaving group. With each addition of a methyl group at the β carbon (below), the number of pathways open to the attacking nucleophile becomes fewer.



6.12 $CN^- > CH_3O^- > CH_3CO_2^- > CH_3CO_2H > CH_3OH$
Order of decreasing nucleophilicity in methanol

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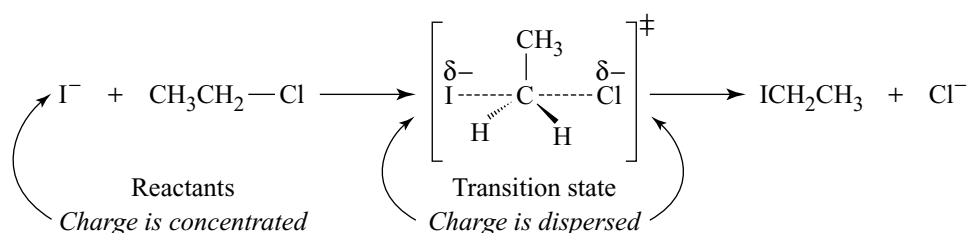
6.13 $\text{CH}_3\text{S}^- > \text{CH}_3\text{O}^- > \text{CH}_3\text{CO}_2^- > \text{CH}_3\text{SH} > \text{CH}_3\text{OH}$
 Order of decreasing nucleophilicity in methanol

6.14 Protic solvents are those that have an H bonded to an oxygen or nitrogen (or to another strongly electronegative atom). Therefore, the protic solvents are formic acid, HCOH ;
 formamide, HCNH_2 ; ammonia, NH_3 ; and ethylene glycol, $\text{HOCH}_2\text{CH}_2\text{OH}$.
Aprotic solvents lack an H bonded to a strongly electronegative element. Aprotic solvents in this list are acetone, CH_3CCH_3 ; acetonitrile, $\text{CH}_3\text{C}\equiv\text{N}$; sulfur dioxide, SO_2 ; and trimethylamine, $\text{N}(\text{CH}_3)_3$.

6.15 The reaction is an $\text{S}_{\text{N}}2$ reaction. In the polar aprotic solvent (DMF), the nucleophile (CN^-) will be relatively unencumbered by solvent molecules, and, therefore, it will be more reactive than in ethanol. As a result, the reaction will occur faster in *N,N*-dimethylformamide.

6.16 (a) CH_3O^-
 (b) H_2S
 (c) $(\text{CH}_3)_3\text{P}$

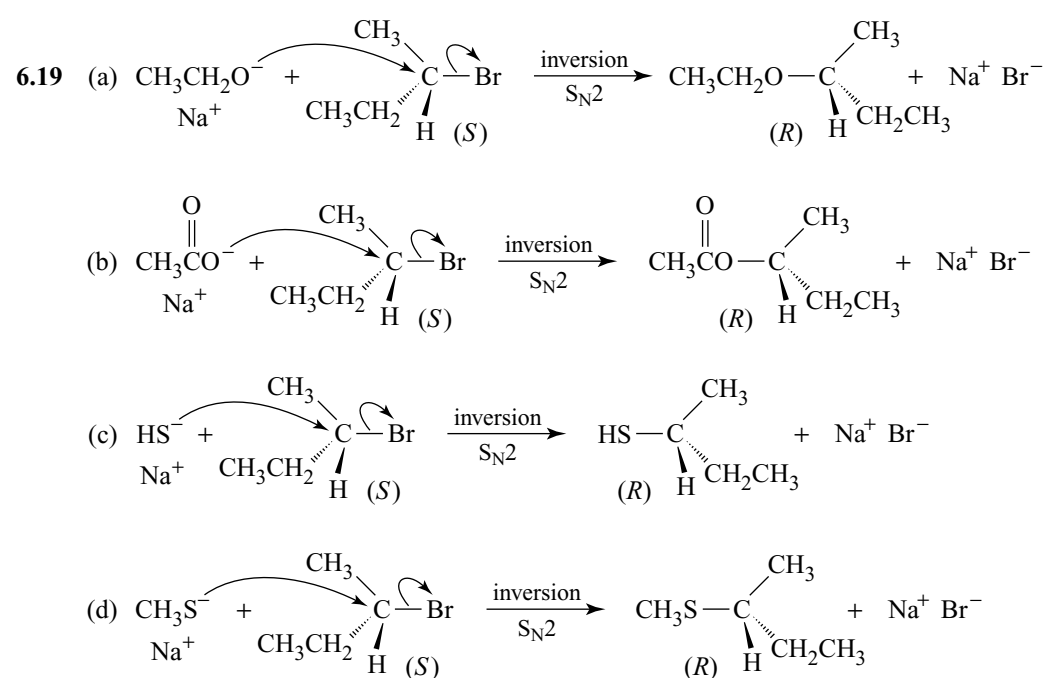
6.17 (a) Increasing the percentage of water in the mixture increases the polarity of the solvent. (Water is more polar than methanol.) Increasing the polarity of the solvent increases the rate of the solvolysis because separated charges develop in the transition state. The more polar the solvent, the more the transition state is stabilized (Section 6.13D).
 (b) In an $\text{S}_{\text{N}}2$ reaction of this type, the charge becomes dispersed in the transition state:



Increasing the polarity of the solvent increases the stabilization of the reactant I^- more than the stabilization of the transition state, and thereby increases the free energy of activation, thus decreasing the rate of reaction.

6.18 $\text{CH}_3\text{OSO}_2\text{CF}_3 > \text{CH}_3\text{I} > \text{CH}_3\text{Br} > \text{CH}_3\text{Cl} > \text{CH}_3\text{F} > {}^{14}\text{CH}_3\text{OH}$
 (Most reactive) (Least reactive)

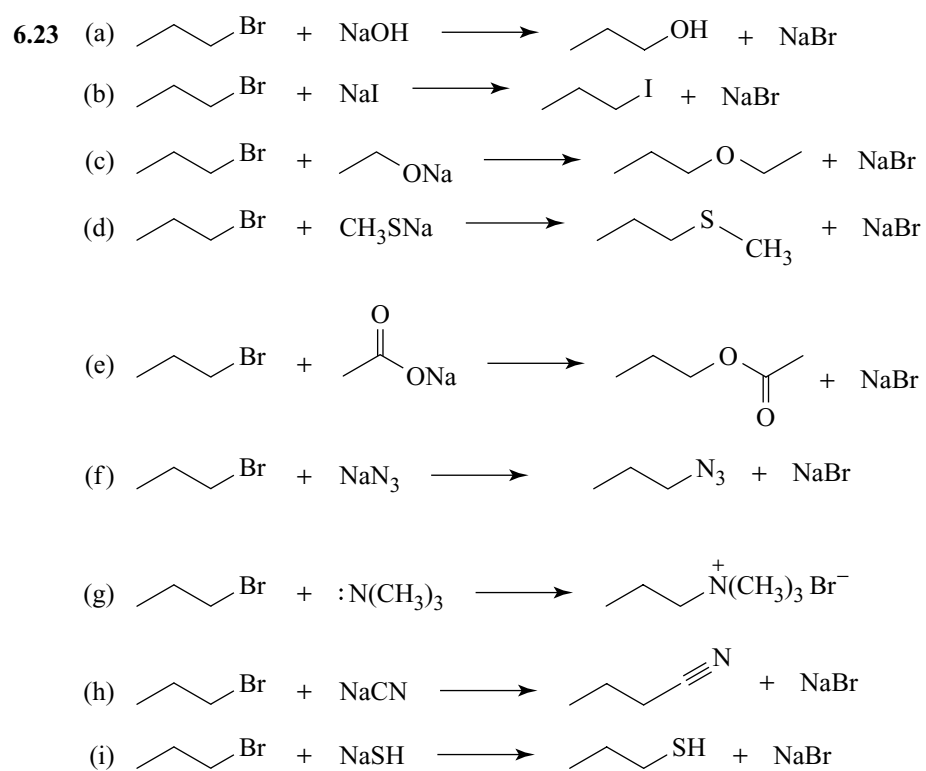
IONIC REACTIONS 89


Relative Rates of Nucleophilic Substitution

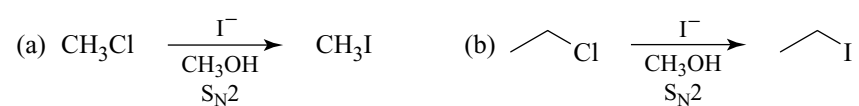
- 6.20 (a) 1-Bromopropane would react more rapidly because, being a primary halide, it is less hindered.
- (b) 1-Iodobutane, because iodide ion is a better leaving group than chloride ion.
- (c) 1-Chlorobutane, because the carbon bearing the leaving group is less hindered than in 1-chloro-2-methylpropane.
- (d) 1-Chloro-3-methylbutane, because the carbon bearing the leaving group is less hindered than in 1-chloro-2-methylbutane.
- (e) 1-Chlorohexane because it is a primary halide. Phenyl halides are unreactive in S_N2 reactions.
- 6.21 (a) Reaction (1) because ethoxide ion is a stronger nucleophile than ethanol.
- (b) Reaction (2) because the ethyl sulfide ion is a stronger nucleophile than the ethoxide ion in a protic solvent. (Because sulfur is larger than oxygen, the ethyl sulfide ion is less solvated and it is more polarizable.)
- (c) Reaction (2) because triphenylphosphine $[(C_6H_5)_3P]$ is a stronger nucleophile than triphenylamine. (Phosphorus atoms are larger than nitrogen atoms.)
- (d) Reaction (2) because in an S_N2 reaction the rate depends on the concentration of the substrate and the nucleophile. In reaction (2) the concentration of the nucleophile is twice that of the reaction (1).

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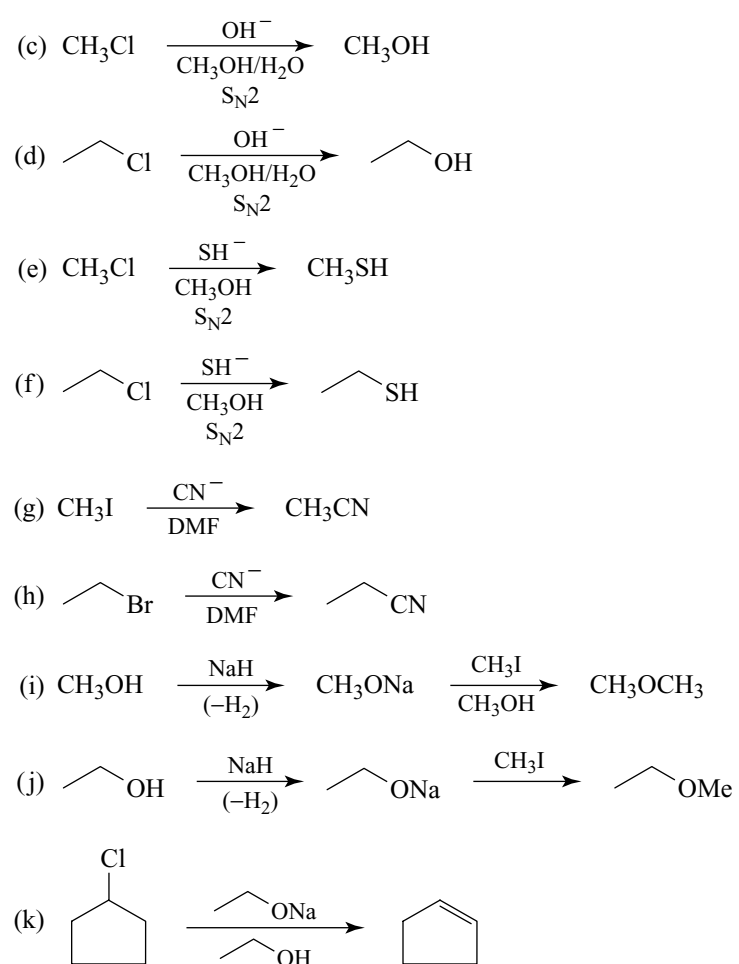
- 6.22** (a) Reaction (2) because bromide ion is a better leaving group than chloride ion.
- (b) Reaction (1) because water is a more polar solvent than methanol, and S_N1 reactions take place faster in more polar solvents.
- (c) Reaction (2) because the concentration of the substrate is twice that of reaction (1). The major reaction would be E2. (However, the problem asks us to consider that small portion of the overall reaction that proceeds by an S_N1 pathway.)
- (d) Considering only S_N1 reactions, as the problem specifies, both reactions would take place at the same rate because S_N1 reactions are independent of the concentration of the nucleophile. The predominant process in this pair of reactions would be E2, however.
- (e) Reaction (1) because the substrate is a tertiary halide. Phenyl halides are unreactive in S_N1 reactions.

Synthesis


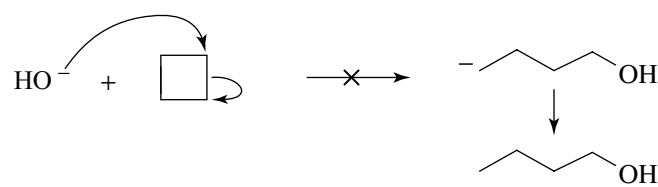
6.24 Possible methods are given here.



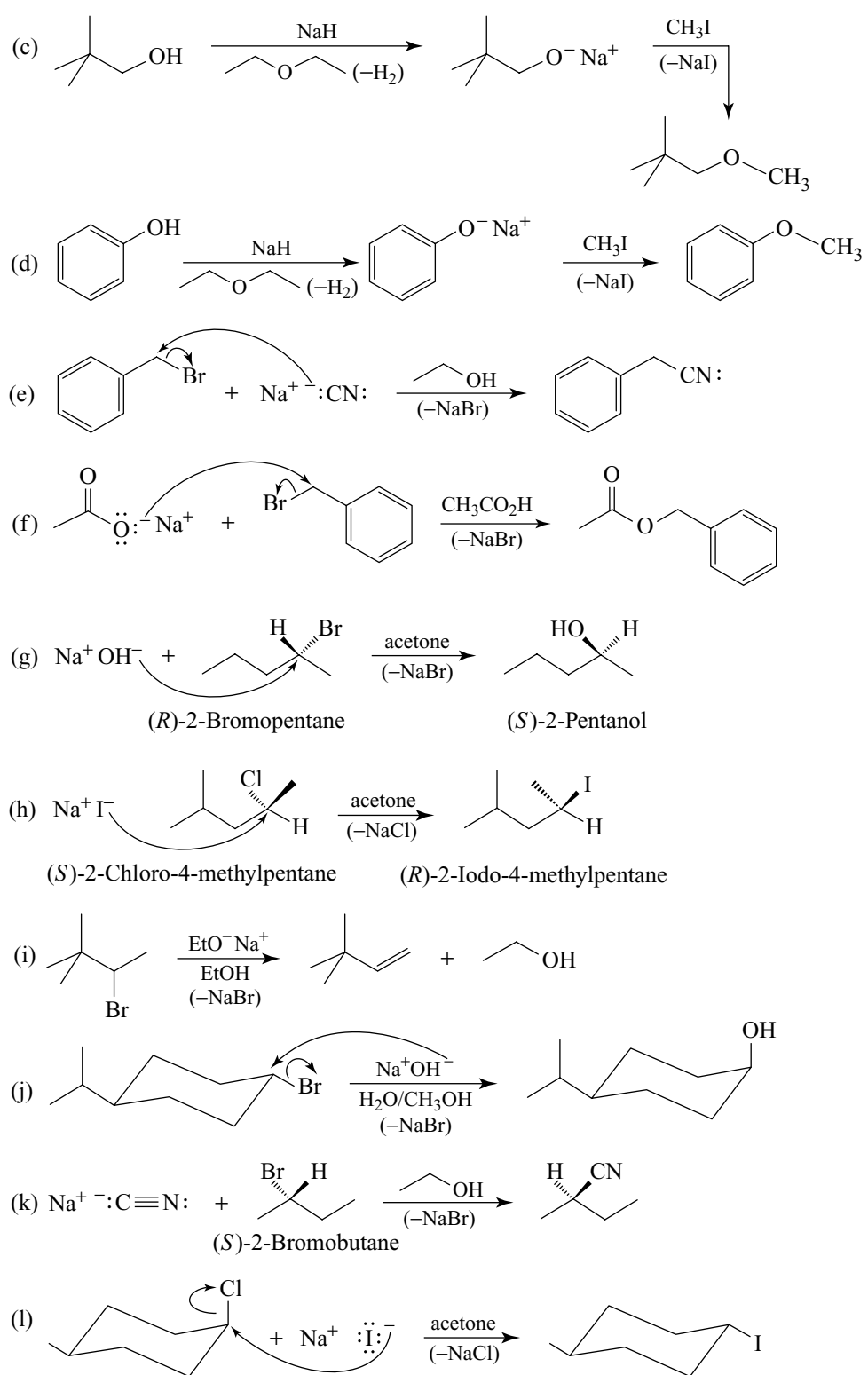
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- 6.25 (a) The reaction will not take place because the leaving group would have to be a methyl anion, a very powerful base, and a very poor leaving group.
- (b) The reaction will not take place because the leaving group would have to be a hydride ion, a very powerful base, and a very poor leaving group.
- (c) The reaction will not take place because the leaving group would have to be a carbanion, a very powerful base, and a very poor leaving group.

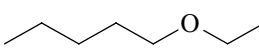
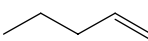


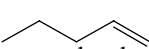
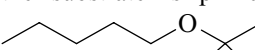
IONIC REACTIONS 93




94 IONIC REACTIONS

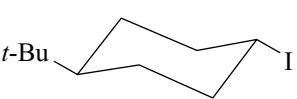
General S_N1, S_N2, and Elimination

6.29 (a) The major product would be  (by an S_N2 mechanism) because the substrate is primary and the nucleophile-base is not hindered. Some  would be produced by an E2 mechanism.

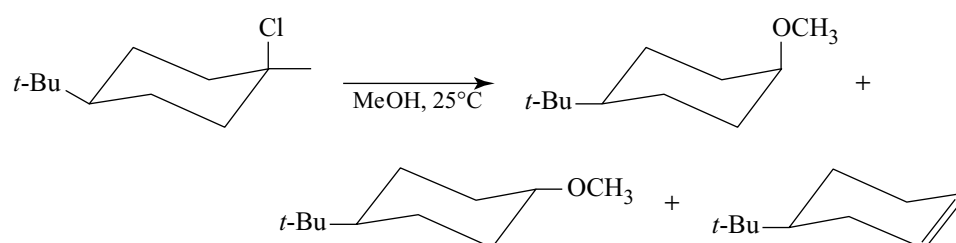
(b) The major product would be  (by an E2 mechanism), even though the substrate is primary, because the base is a hindered strong base. Some  would be produced by an S_N2 mechanism.

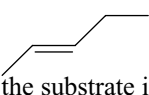
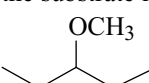
(c) For all practical purposes,  (by an E2 mechanism) would be the only product because the substrate is tertiary and the base is strong.

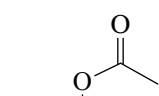
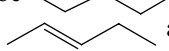
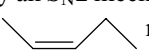
(d) Same answer as (c) above.

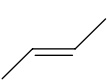
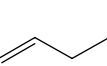
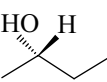
(e)  (formed by an S_N2 mechanism) would, for all practical purposes, be the only product. Iodide ion is a very weak base and a good nucleophile.

(f) Because the substrate is tertiary and the base weak, an S_N1 reaction (solvolysis) will occur, accompanied by elimination (E1). At 25°C, the S_N1 reaction would predominate.

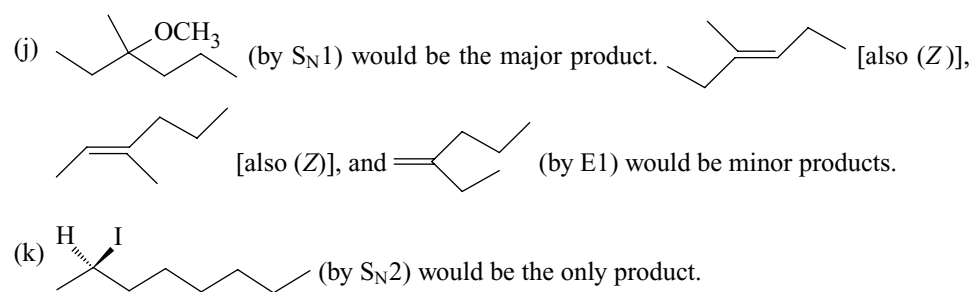


(g)  [also (Z)] (by an E2 mechanism) would be the major product because the substrate is secondary and the base/nucleophile is a strong base. Some of the ether  would be formed by an S_N2 pathway.

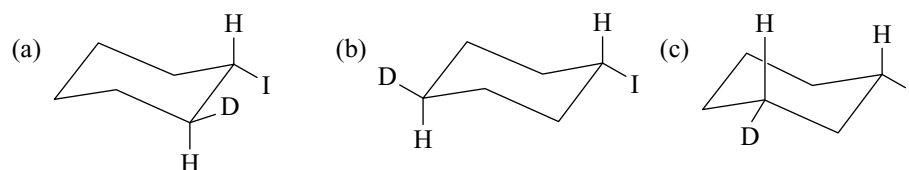
(h) The major product would be  (by an S_N2 mechanism) because the acetate ion is a weak base. Some  and  might be formed by an E2 pathway.

(i)  [also (Z)] and  (by E2) would be major products, and  [(S) isomer] (by S_N2) would be the minor products.

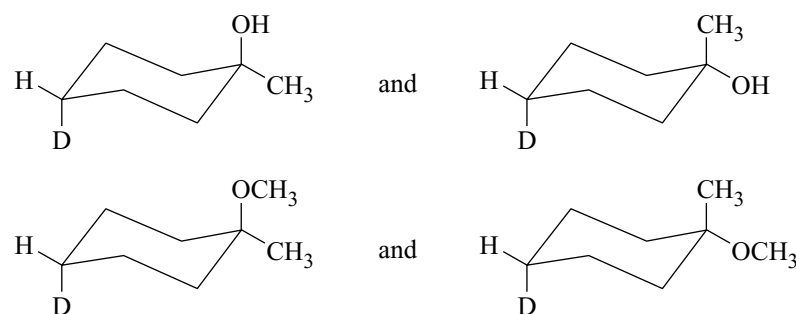
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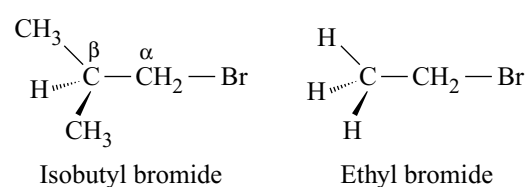
6.30 (a), (b), and (c) are all S_N2 reactions and, therefore, proceed with inversion of configuration. The products are



(d) is an S_N1 reaction. The carbocation that forms can react with either nucleophile (H_2O or CH_3OH) from either the top or bottom side of the molecule. Four substitution products (below) would be obtained. (Considerable elimination by an E1 path would also occur.)



6.31 Isobutyl bromide is more sterically hindered than ethyl bromide because of the methyl groups on the β carbon atom.



This steric hindrance causes isobutyl bromide to react more slowly in S_N2 reactions and to give relatively more elimination (by an E2 path) when a strong base is used.

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6.32 (a) S_N2 because the substrate is a 1° halide.

$$\begin{aligned} \text{(b) Rate} &= k [\text{CH}_3\text{CH}_2\text{Cl}][\text{I}^-] \\ &= 5 \times 10^{-5} \text{ L mol}^{-1}\text{s}^{-1} \times 0.1 \text{ mol L}^{-1} \times 0.1 \text{ mol L}^{-1} \\ \text{Rate} &= 5 \times 10^{-7} \text{ mol L}^{-1}\text{s}^{-1} \end{aligned}$$

$$\text{(c) } 1 \times 10^{-6} \text{ mol L}^{-1}\text{s}^{-1}$$

$$\text{(d) } 1 \times 10^{-6} \text{ mol L}^{-1}\text{s}^{-1}$$

$$\text{(e) } 2 \times 10^{-6} \text{ mol L}^{-1}\text{s}^{-1}$$

6.33 (a) CH_3NH^- because it is the stronger base.

(b) CH_3O^- because it is the stronger base.

(c) CH_3SH because sulfur atoms are larger and more polarizable than oxygen atoms.

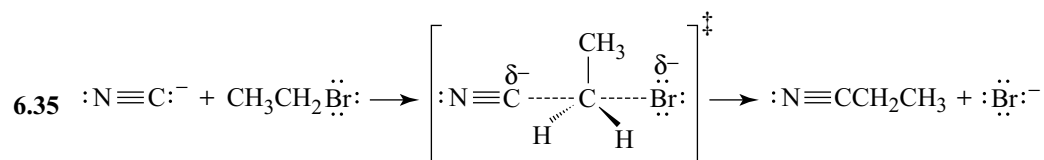
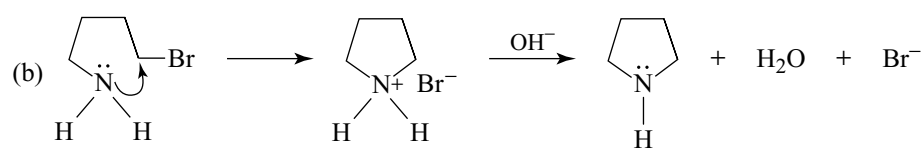
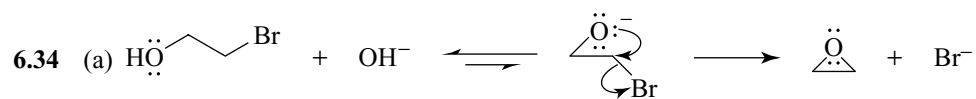
(d) $(\text{C}_6\text{H}_5)_3\text{P}$ because phosphorus atoms are larger and more polarizable than nitrogen atoms.

(e) H_2O because it is the stronger base.

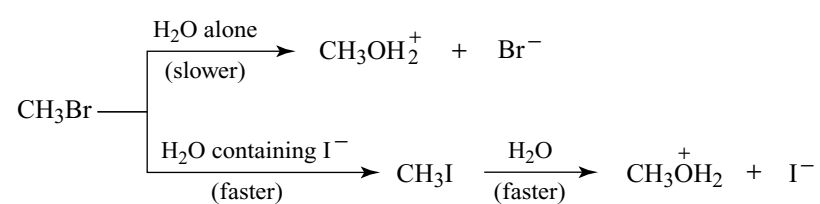
(f) NH_3 because it is the stronger base.

(g) HS^- because it is the stronger base.

(h) OH^- because it is the stronger base.

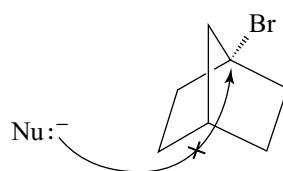


6.36 Iodide ion is a good nucleophile and a good leaving group; it can rapidly convert an alkyl chloride or alkyl bromide into an alkyl iodide, and the alkyl iodide can then react rapidly with another nucleophile. With methyl bromide in water, for example, the following reaction can take place:



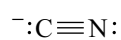
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- 6.37** *tert*-Butyl alcohol and *tert*-butyl methyl ether are formed via an S_N1 mechanism. The rate of the reaction is independent of the concentration of methoxide ion (from sodium methoxide). This, however, is only one reaction that causes *tert*-butyl bromide to disappear. A competing reaction that also causes *tert*-butyl bromide to disappear is an E2 reaction in which methoxide ion reacts with *tert*-butyl bromide. This reaction is dependent on the concentration of methoxide ion; therefore, increasing the methoxide ion concentration causes an increase in the rate of disappearance of *tert*-butyl bromide.
- 6.38** (a) You should use a strong base, such as RO^- , at a higher temperature to bring about an E2 reaction.
 (b) Here we want an S_N1 reaction. We use ethanol as the solvent *and as the nucleophile*, and we carry out the reaction at a low temperature so that elimination will be minimized.
- 6.39** 1-Bromobicyclo[2.2.1]heptane is unreactive in an S_N2 reaction because it is a tertiary halide and its ring structure makes the backside of the carbon bearing the leaving group completely inaccessible to attack by a nucleophile.

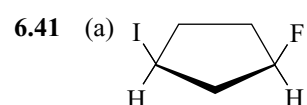
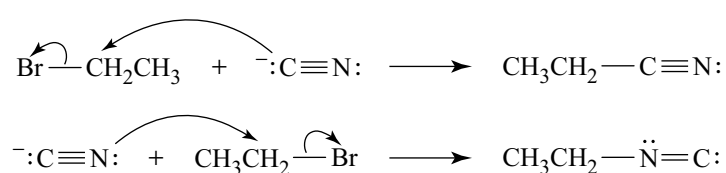


1-Bromobicyclo[2.2.1]heptane is unreactive in an S_N1 reaction because the ring structure makes it impossible for the carbocation that must be formed to assume the required trigonal planar geometry around the positively charged carbon. Any carbocation formed from 1-bromobicyclo[2.2.1]heptane would have a trigonal pyramidal arrangement of the $-CH_2-$ groups attached to the positively charged carbon (make a model). Such a structure does not allow stabilization of the carbocation by overlap of sp^3 orbitals from the alkyl groups (see Fig. 6.7).

- 6.40** The cyanide ion has two nucleophilic atoms; it is what is called an ambident nucleophile.

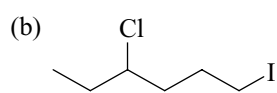


It can react with a substrate using either atom, although the carbon atom is more nucleophilic.

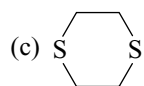


(Formation of this product depends on the fact that bromide ion is a much better leaving group than fluoride ion.)

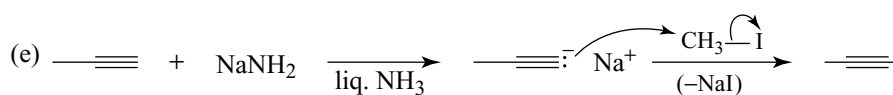
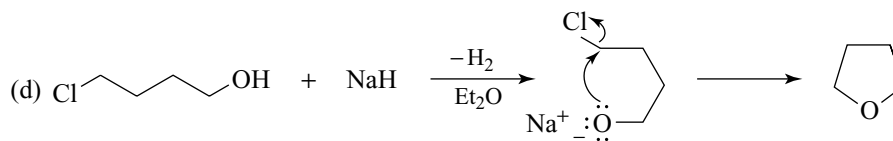
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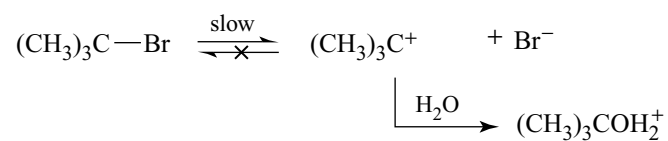
(Formation of this product depends on the greater reactivity of 1° substrates in S_N2 reactions.)



(Here two S_N2 reactions produce a cyclic molecule.)

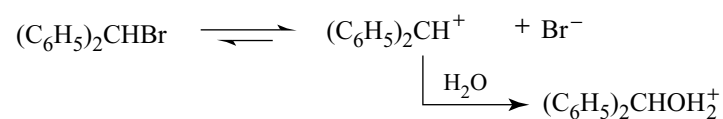


6.42 The rate-determining step in the S_N1 reaction of *tert*-butyl bromide is the following:



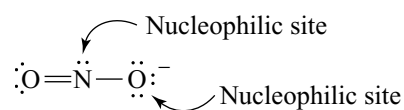
(CH₃)₃C⁺ is so unstable that it reacts almost immediately with one of the surrounding water molecules, and, for all practical purposes, no reverse reaction with Br⁻ takes place. Adding a common ion (Br⁻ from NaBr), therefore, has no effect on the rate.

Because the (C₆H₅)₂CH⁺ cation is more stable, a reversible first step occurs and adding a common ion (Br⁻) slows the overall reaction by increasing the rate at which (C₆H₅)₂CH⁺ is converted back to (C₆H₅)₂CHBr.



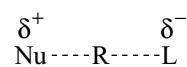
6.43 Two different mechanisms are involved. (CH₃)₃CBr reacts by an S_N1 mechanism, and apparently this reaction takes place faster. The other three alkyl halides react by an S_N2 mechanism, and their reactions are slower because the nucleophile (H₂O) is weak. The reaction rates of CH₃Br, CH₃CH₂Br, and (CH₃)₂CHBr are affected by the steric hindrance, and thus their order of reactivity is CH₃Br > CH₃CH₂Br > (CH₃)₂CHBr.

6.44 The nitrite ion is an *ambident nucleophile*; that is, it is an ion with two nucleophilic sites. The equivalent oxygen atoms and the nitrogen atom are nucleophilic.



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- 6.45 (a) The transition state has the form:

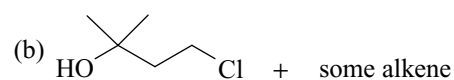
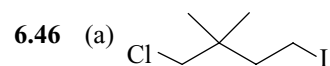


in which charges are developing. The more polar the solvent, the better it can solvate the transition state, thus lowering the free energy of activation and increasing the reaction rate.

- (b) The transition state has the form:



in which the charge is becoming dispersed. A polar solvent is less able to solvate this transition state than it is to solvate the reactant. The free energy of activation, therefore, will become somewhat larger as the solvent polarity increases, and the rate will be slower.



- 6.47 (a) In an
- S_N1
- reaction the carbocation intermediate reacts rapidly with any nucleophile it encounters in a Lewis acid-Lewis base reaction. In the case of the
- S_N2
- reaction, the leaving group departs only when "pushed out" by the attacking nucleophile and some nucleophiles are better than others.

- (b)
- CN^-
- is a much better nucleophile than ethanol and hence the nitrile is formed in the
- S_N2

reaction of Cl. In the case of Cl, the *tert*-butyl cation reacts chiefly with the nucleophile present in higher concentration, here the ethanol solvent.

Challenge Problems

- 6.48 (a) The entropy term is slightly favorable. (The enthalpy term is highly unfavorable.)

$$\begin{aligned} \Delta G^\circ &= \Delta H^\circ - T\Delta S^\circ \\ &= 26.6 \text{ kJ mol}^{-1} - (298)(0.00481 \text{ kJ mol}^{-1}) \\ &= 25.2 \text{ kJ mol}^{-1} \end{aligned}$$

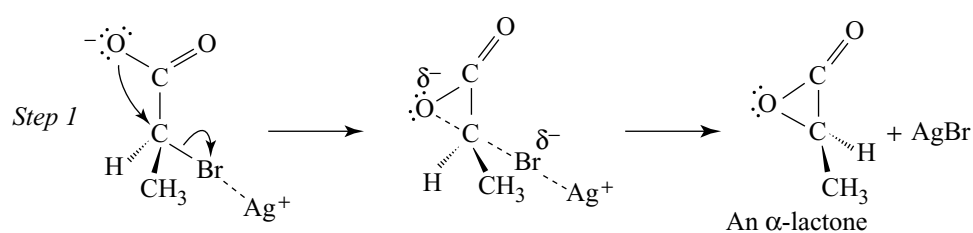
The hydrolysis process will not occur to any significant extent.

$$\begin{aligned} \text{(c)} \quad \log K_{eq} &= \frac{-\Delta G^\circ}{2.303RT} \\ &= \frac{-25.2 \text{ kJ mol}^{-1}}{(2.303)(0.008314 \text{ kJ mol}^{-1}\text{K}^{-1})(298 \text{ K})} \\ &= -4.4165 \\ K_{eq} &= 10^{-4.4165} = 3.85 \times 10^{-5} \end{aligned}$$

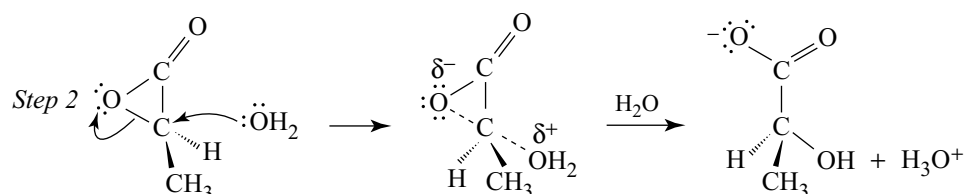
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(d) The equilibrium is very much more favorable in aqueous solution because solvation of the products (ethanol, hydronium ions, and chloride ions) takes place and thereby stabilizes them.

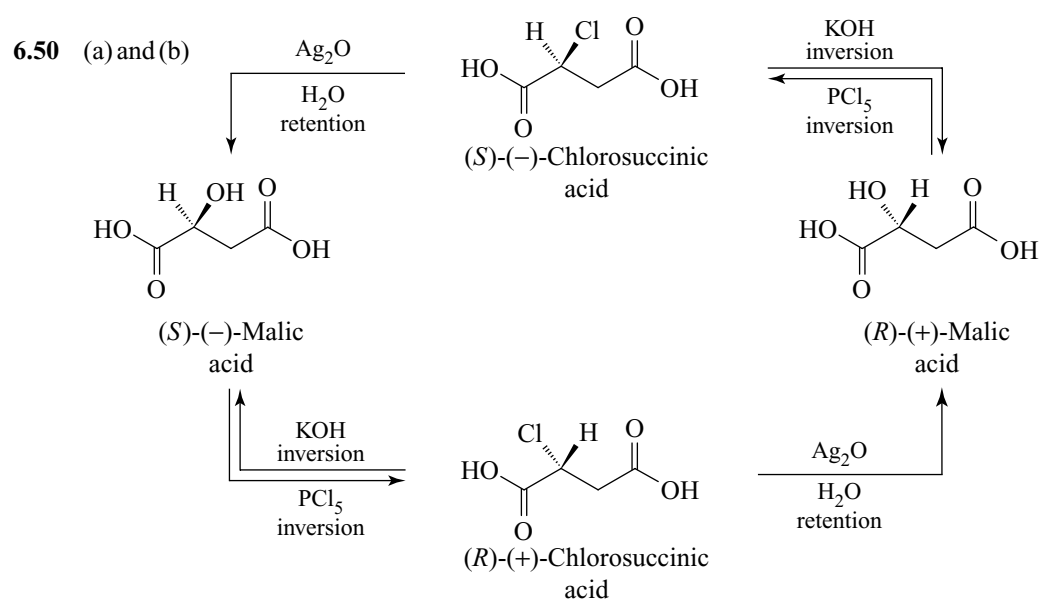
6.49 The mechanism for the reaction, in which a low concentration of OH^- is used in the presence of Ag_2O , involves the participation of the carboxylate group. In step 1 (see following reaction) an oxygen of the carboxylate group attacks the chirality center from the back side and displaces bromide ion. (Silver ion aids in this process in much the same way that protonation assists the ionization of an alcohol.) The configuration of the chirality center inverts in step 1, and a cyclic ester called an α -lactone forms.



The highly strained three-membered ring of the α -lactone opens when it is attacked by a water molecule in step 2. This step also takes place with an inversion of configuration.

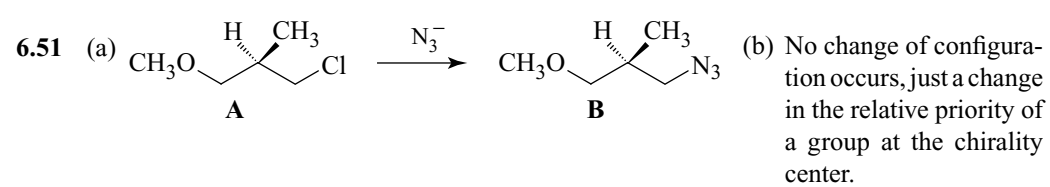
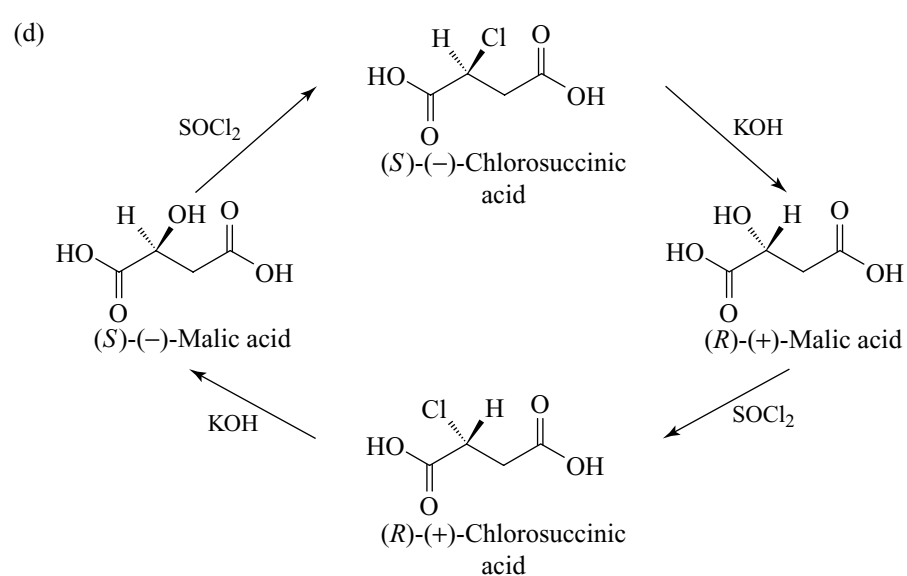


The net result of two inversions (in steps 1 and 2) is an overall *retention of configuration*.



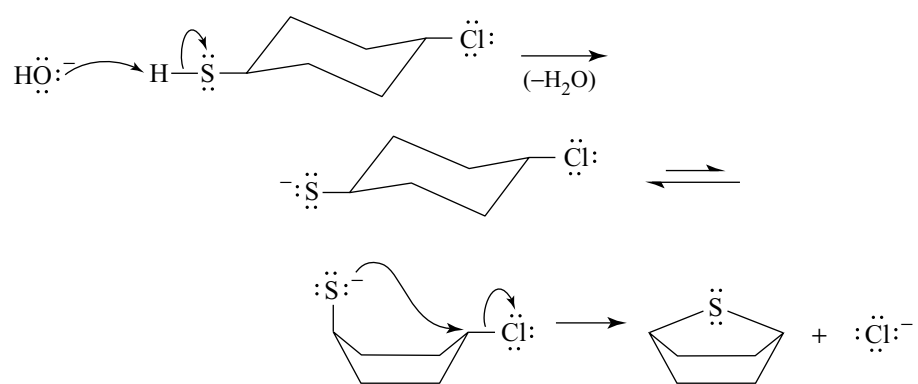
(c) The reaction takes place with retention of configuration.

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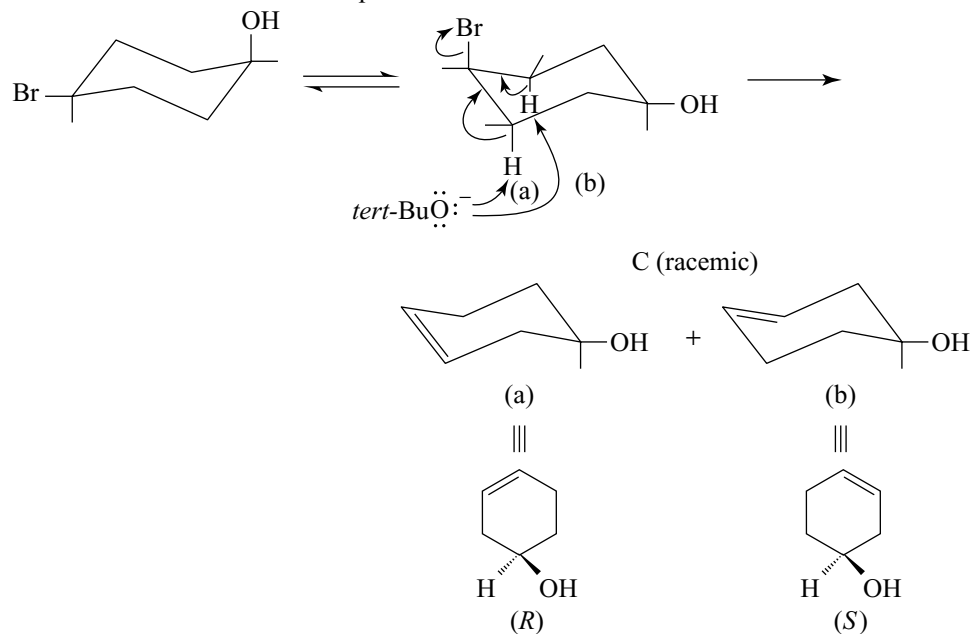
6.52 Comparison of the molecular formulas of starting material and product indicates a loss of HCl. The absence of IR bands in the $1620\text{--}1680\text{ cm}^{-1}$ region rules out the presence of the alkene function.

A nucleophilic substitution agrees with the evidence:

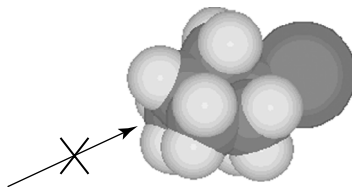


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- 6.53 The IR evidence indicates that C possesses both an alkene function and a hydroxyl group. An E2 reaction on this substrate produces enantiomeric unsaturated alcohols.

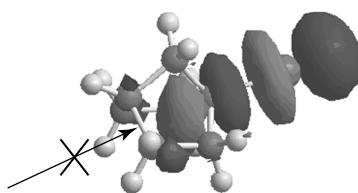


- 6.54 Regarding the S_N2 reaction, there is extreme steric hindrance for attack by the nucleophile from the back side with respect to the leaving group due to atoms on the other side of the rigid ring structure, as the following model shows.



For the S_N1 reaction, formation of a carbocation would require that the bridgehead carbon approach trigonal planar geometry, which would lead to a carbocation of extremely high energy due to the geometric constraints of the bicyclic ring.

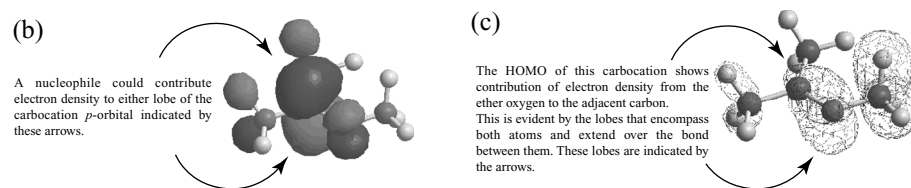
- 6.55 The lobe of the LUMO that would accept electron density from the nucleophile is buried within the bicyclic ring structure of 1-bromobicyclo[2.2.1]heptane (the large blue lobe), effectively making it inaccessible for approach by the nucleophile.



- 6.56 (a) The LUMO in an S_N1 reaction is the orbital that includes the vacant p orbital in our simplified molecular orbital diagrams of carbocations. (b) The large lobes above and below the trigonal planar carbon atom of the isopropyl group are the ones that would interact with a nucleophile. These are the lobes associated with stylized p orbitals we

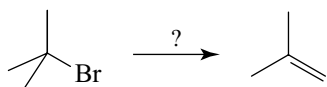
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draw in simplified diagrams of carbocations. (c) The HOMO for this carbocation shows the contribution of electron density from a nonbonding electron pair of the ether oxygen that is adjacent to the carbocation. This is evident by the lobes that extend over these two atoms and encompass the bond between them. In effect, this orbital model represents the resonance hybrid we can draw where a nonbonding electron pair from oxygen is shifted to the bonding region between the carbon and oxygen.



QUIZ

6.1 Which set of conditions would you use to obtain the best yield in the reaction shown?



(a) H₂O, heat

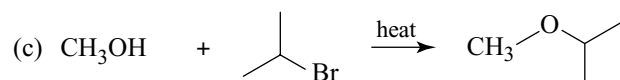
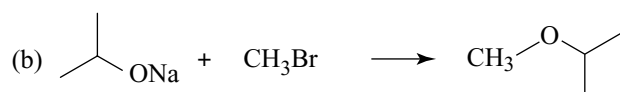
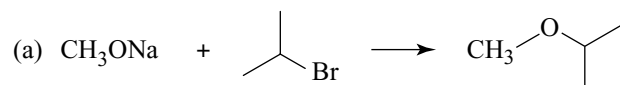
(b) CCONa, CCO, heat

(c) Heat alone

(d) H₂SO₄

(e) None of the above

6.2 Which of the following reactions would give the best yield?



6.3 A kinetic study yielded the following reaction rate data:

Experiment Number	Initial Concentrations		Initial Rate of Disappearance of R—Br and Formation of R—OH
	[OH ⁻]	[R—Br]	
1	0.50	0.50	1.00
2	0.50	0.25	0.50
3	0.25	0.25	0.25

Which of the following statements best describe this reaction?

(a) The reaction is second order.

(b) The reaction is first order.

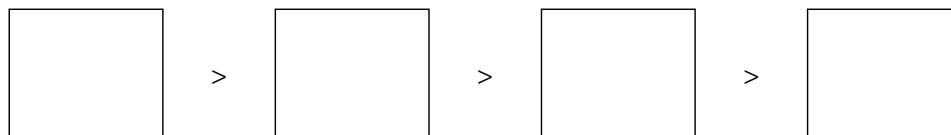
(c) The reaction is S_N1.

(d) Increasing the concentration of OH⁻ has no effect on the rate.

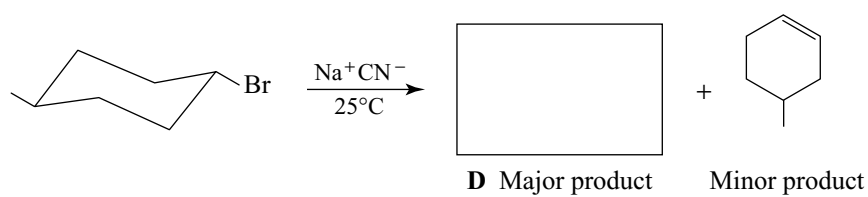
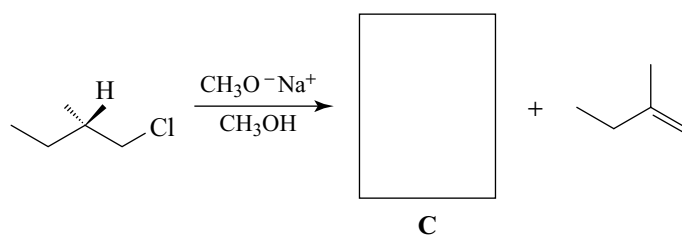
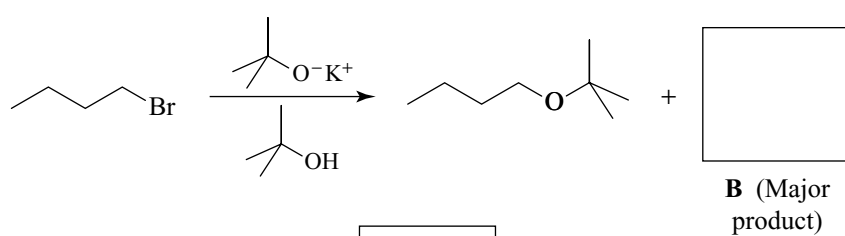
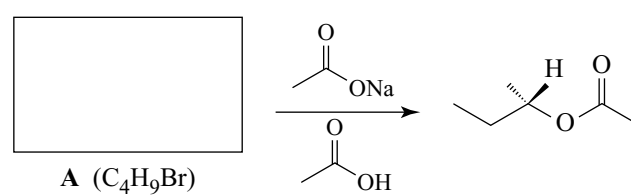
(e) More than one of the above.

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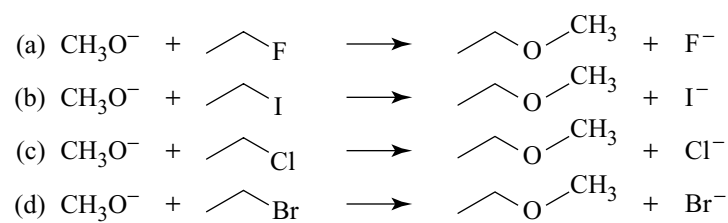
- 6.4 There are four compounds with the formula C_4H_9Br . List them in order of decreasing reactivity in an S_N2 reaction.



- 6.5 Supply the missing reactants, reagents, intermediates, or products.



- 6.6 Which S_N2 reaction will occur most rapidly. (Assume the concentrations and temperatures are all the same.)



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6.7 Provide three-dimensional structures for the missing boxed structures and formulas for missing reagents.

