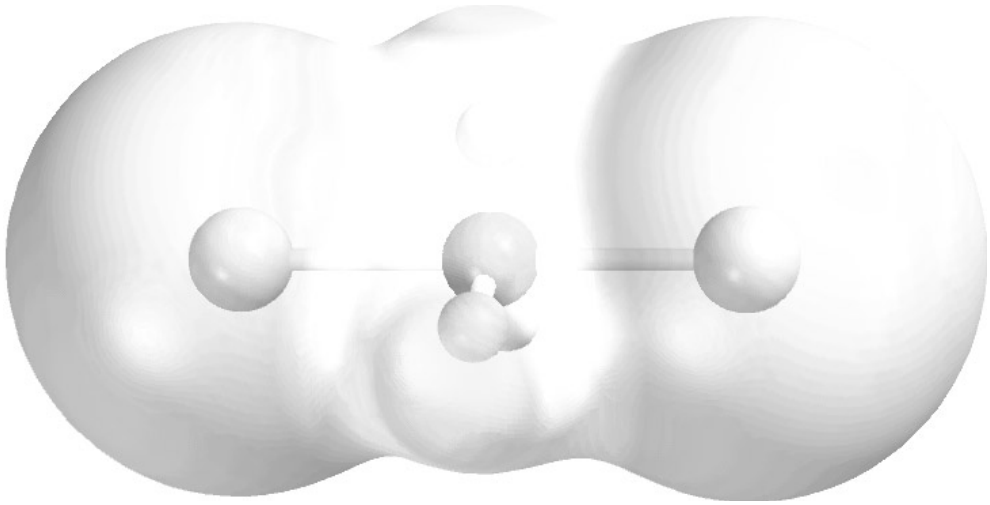


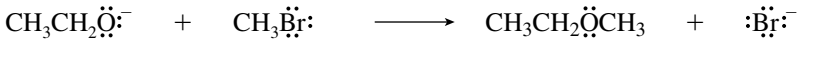
# CHAPTER 8

## NUCLEOPHILIC SUBSTITUTION

## SOLUTIONS TO TEXT PROBLEMS

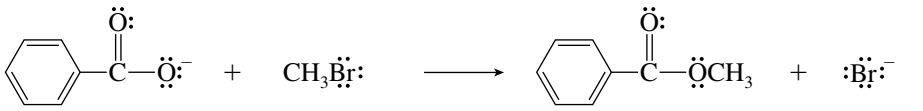
**8.1** Identify the nucleophilic anion in each reactant. The nucleophilic anion replaces bromine as a substituent on carbon.

(*b*) Potassium ethoxide serves as a source of the nucleophilic anion $CH_3CH_2O^-$.



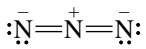
Ethoxide ion (nucleophile) | Methyl bromide | Ethyl methyl ether (product) | Bromide ion

(*c*)

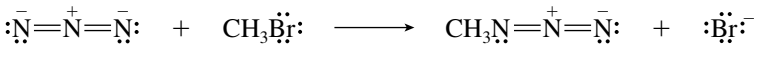


Benzoate ion | Methyl bromide | Methyl benzoate | Bromide ion

(*d*) Lithium azide is a source of the azide ion.



It reacts with methyl bromide to give methyl azide.

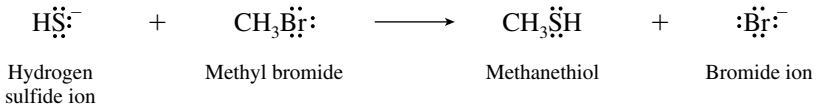


Azide ion (nucleophile) | Methyl bromide | Methyl azide (product) | Bromide ion

(*e*) The nucleophilic anion in KCN is cyanide ($:\bar{C}\equiv N:$). The carbon atom is negatively charged and is normally the site of nucleophilic reactivity.

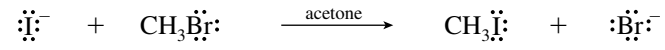
Cyanide ion (nucleophile) | Methyl bromide | Methyl cyanide (product) | Bromide ion

(*f*) The anion in sodium hydrogen sulfide (NaSH) is $^{-}:\ddot{S}H$ .



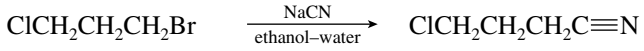

Hydrogen sulfide ion — Methyl bromide — Methanethiol — Bromide ion

(*g*) Sodium iodide is a source of the nucleophilic anion iodide ion, $:\ddot{I}:^{-}$ . The reaction of sodium iodide with alkyl bromides is usually carried out in acetone to precipitate the sodium bromide formed.




Iodide ion — Methyl bromide — Methyl iodide — Bromide ion

**8.2** Write out the structure of the starting material. Notice that it contains a primary bromide and a primary chloride. Bromide is a better leaving group than chloride and is the one that is displaced faster by the nucleophilic cyanide ion.




1-Bromo-3-chloropropane — 4-Chlorobutanenitrite

**8.3** No, the two-step sequence is not consistent with the observed behavior for the hydrolysis of methyl bromide. The rate-determining step in the two-step sequence shown is the first step, ionization of methyl bromide to give methyl cation.

**1.** $CH_3Br \xrightarrow{\text{slow}} CH_3^{+} + Br^{-}$

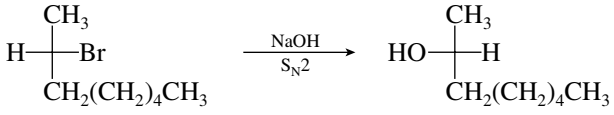
**2.** $CH_3^{+} + HO^{-} \xrightarrow{\text{fast}} CH_3OH$

In such a sequence the nucleophile would not participate in the reaction until after the rate-determining step is past, and the reaction rate would depend only on the concentration of methyl bromide and be independent of the concentration of hydroxide ion.

$$\text{Rate} = k[CH_3Br]$$

The predicted kinetic behavior is first order. Second order kinetic behavior is actually observed for methyl bromide hydrolysis, so the proposed mechanism cannot be correct.

**8.4** Inversion of configuration occurs at the stereogenic center. When shown in a Fischer projection, this corresponds to replacing the leaving group on the one side by the nucleophile on the opposite side.



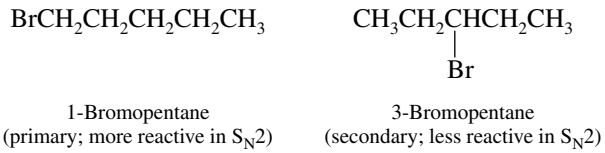

(*S*)-(+)-2-Bromooctane — (*R*)-(−)-2-Octanol

**8.5** The example given in the text illustrates inversion of configuration in the $S_N2$ hydrolysis of (*S*)-(+)-2-bromooctane, which yields (*R*)-(−)-2-octanol. The hydrolysis of (*R*)-(−)-2-bromooctane exactly mirrors that of its enantiomer and yields (*S*)-(+)-2-octanol.

Hydrolysis of racemic 2-bromooctane gives racemic 2-octanol. Remember, optically inactive reactants must yield optically inactive products.

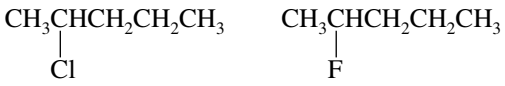
**8.6** Sodium iodide in acetone is a reagent that converts alkyl chlorides and bromides into alkyl iodides by an $S_N2$ mechanism. Pick the alkyl halide in each pair that is more reactive toward $S_N2$ displacement.

(*b*) The less crowded alkyl halide reacts faster in an $S_N2$ reaction. 1-Bromopentane is a primary alkyl halide and so is more reactive than 3-bromopentane, which is secondary.



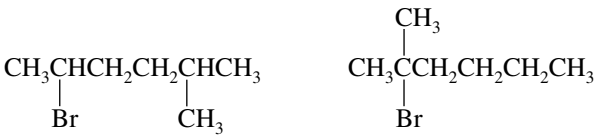

1-Bromopentane (primary; more reactive in $S_N2$) — 3-Bromopentane (secondary; less reactive in $S_N2$)

(*c*) Both halides are secondary, but fluoride is a poor leaving group in nucleophilic substitution reactions. Alkyl chlorides are more reactive than alkyl fluorides.




2-Chloropentane (more reactive) — 2-Fluoropentane (less reactive)

(*d*) A secondary alkyl bromide reacts faster under $S_N2$ conditions than a tertiary one.

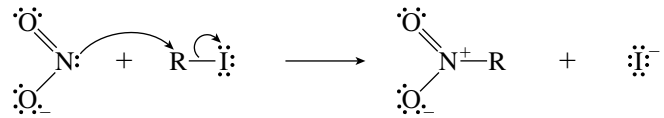



2-Bromo-5-methylhexane (secondary; more reactive in $S_N2$) — 2-Bromo-2-methylhexane (tertiary; less reactive in $S_N2$)

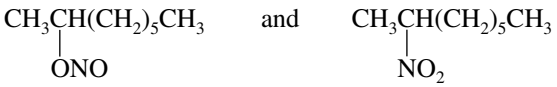
(*e*) The number of carbons does not matter as much as the degree of substitution at the reaction site. The primary alkyl bromide is more reactive than the secondary.


1-Bromodecane (primary; more reactive in $S_N2$) — 2-Bromopropane (secondary; less reactive in $S_N2$)

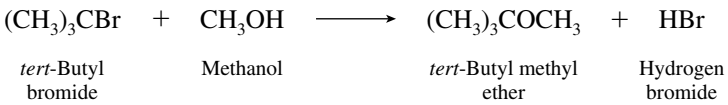
**8.7** Nitrite ion has two potentially nucleophilic sites, oxygen and nitrogen.

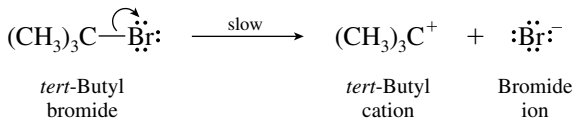

Thus, an alkyl iodide can yield either an alkyl nitrite or a nitroalkane depending on whether the oxygen or the nitrogen of nitrite ion attacks carbon. Both do, and the product from 2-iodooctane is a mixture of

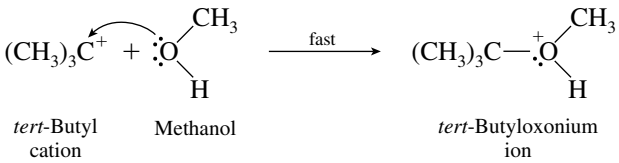


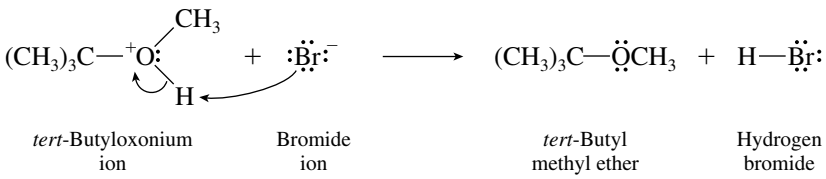
**8.8** Solvolysis of alkyl halides in alcohols yields ethers as the products of reaction.




The reaction proceeds by an $S_N1$ mechanism.




**8.9** The reactivity of an alkyl halide in an $S_N1$ reaction is dictated by the ease with which it ionizes to form a carbocation. Tertiary alkyl halides are the most reactive, methyl halides the least reactive.

(*b*) Cyclopentyl iodide ionizes to form a secondary carbocation, and the carbocation from 1-methylcyclopentyl iodide is tertiary. The tertiary halide is more reactive.


1-Methylcyclopentyl iodide (tertiary; more reactive in $S_N1$)

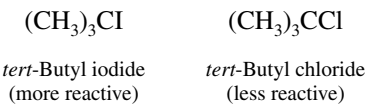
Cyclopentyl iodide (secondary; less reactive in $S_N1$)

(*c*) Cyclopentyl bromide ionizes to a secondary carbocation. 1-Bromo-2,2-dimethyl-propane is a primary alkyl halide and is therefore less reactive.


Cyclopentyl bromide (secondary; more reactive in $S_N1$)

1-Bromo-2,2-dimethylpropane (primary; less reactive in $S_N1$)

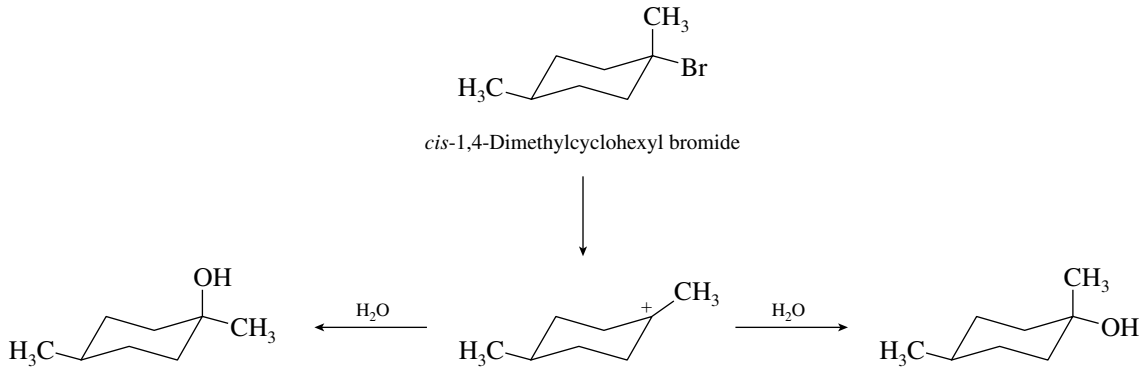
(*d*) Iodide is a better leaving group than chloride in both $S_N1$ and $S_N2$ reactions.




*tert*-Butyl iodide (more reactive)

*tert*-Butyl chloride (less reactive)

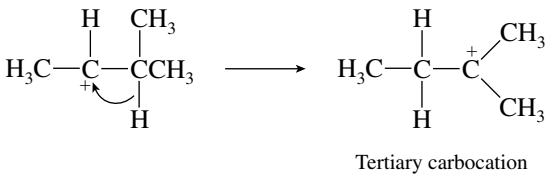
**8.10** The alkyl halide is tertiary and so undergoes hydrolysis by an $S_N1$ mechanism. The carbocation can be captured by water at either face. A mixture of the axial and the equatorial alcohols is formed.



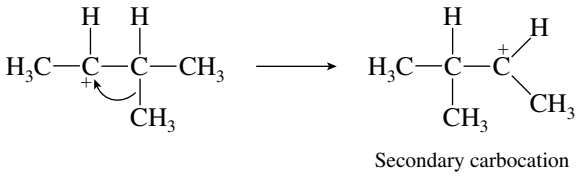

The same two substitution products are formed from *trans*-1,4-dimethylcyclohexyl bromide because it undergoes hydrolysis via the same carbocation intermediate.

**8.11** Write chemical equations illustrating each rearrangement process.

**Hydride shift:**

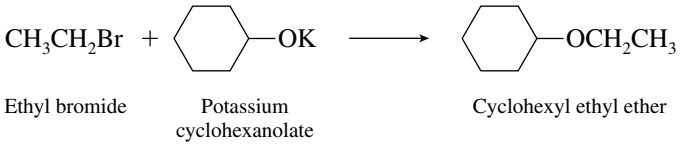



**Methyl shift:**

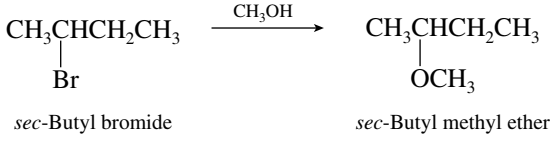



Rearrangement by a hydride shift is observed because it converts a secondary carbocation to a more stable tertiary one. A methyl shift gives a secondary carbocation—in this case the same carbocation as the one that existed prior to rearrangement.

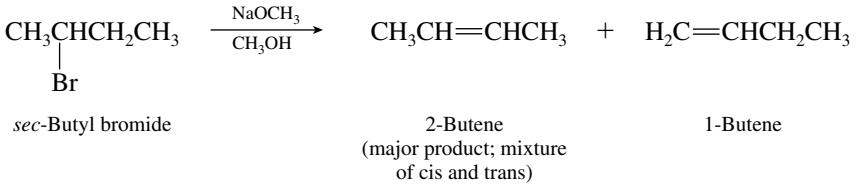
**8.12** (*b*) Ethyl bromide is a primary alkyl halide and reacts with the potassium salt of cyclohexanol by substitution.



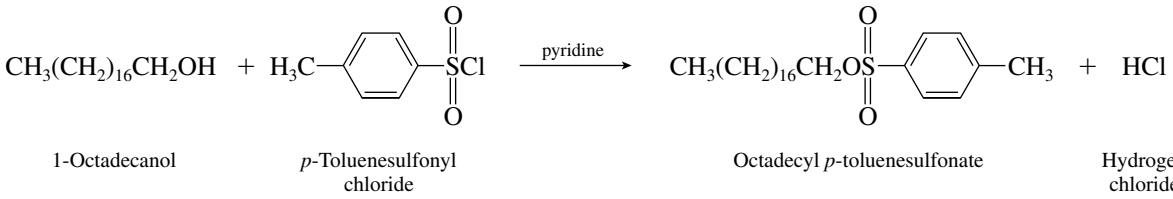

(*c*) No strong base is present in this reaction; the nucleophile is methanol itself, not methoxide. It reacts with *sec*-butyl bromide by substitution, not elimination.



(*d*) Secondary alkyl halides react with alkoxide bases by E2 elimination.



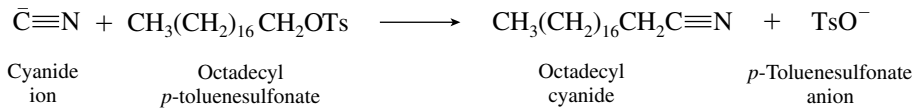

**8.13** Alkyl *p*-toluenesulfonates are prepared from alcohols and *p*-toluenesulfonyl chloride.



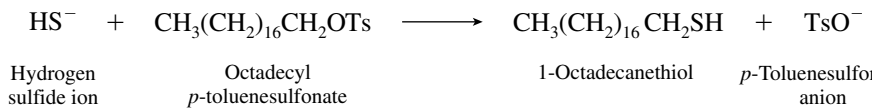

**8.14** As in part (*a*), identify the nucleophilic anion in each part. The nucleophile replaces the *p*-toluenesulfonate (tosylate) leaving group by an $S_N2$ process. The tosylate group is abbreviated as OTs.

(*b*)

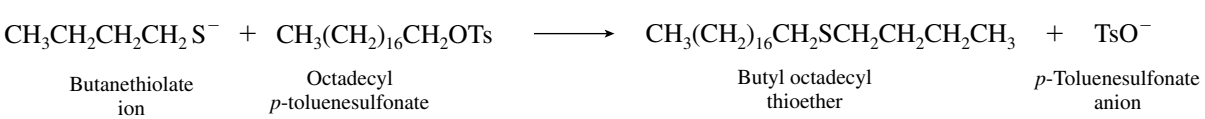

(*c*)



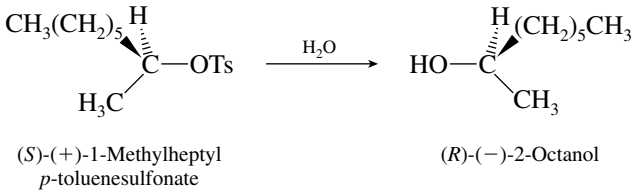

(*d*)




(*e*)

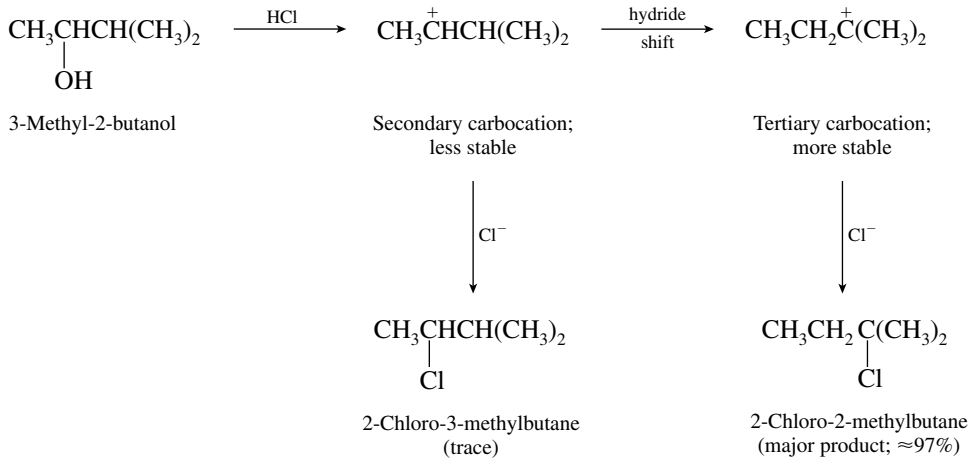



**8.15** The hydrolysis of (*S*)-(+)-1-methylheptyl *p*-toluenesulfonate proceeds with inversion of configuration, giving the *R* enantiomer of 2-octanol.




In Section 8.14 of the text we are told that optically pure (*S*)-(+)-1-methylheptyl *p*-toluenesulfonate is prepared from optically pure (*S*)-(+)-2-octanol having a specific rotation $[\alpha]_D^{25}$ +9.9°. The conversion of an alcohol to a *p*-toluenesulfonate proceeds with complete *retention* of configuration. Hydrolysis of this *p*-toluenesulfonate with *inversion* of configuration therefore yields optically pure (*R*)-(−)-2-octanol of $[\alpha]_D^{25}$ −9.9°.

**8.16** Protonation of 3-methyl-2-butanol and dissociation of the alkyloxonium ion gives a secondary carbocation. A hydride shift yields a tertiary, and thus more stable, carbocation. Capture of this carbocation by chloride ion gives the major product, 2-chloro-2-methylbutane.




**8.17** 1-Bromopropane is a primary alkyl halide, and so it will undergo predominantly $S_N2$ displacement regardless of the basicity of the nucleophile.

(*a*) $CH_3CH_2CH_2Br \xrightarrow[\text{acetone}]{NaI} CH_3CH_2CH_2I$

1-Bromopropane → 1-Iodopropane

(*b*) $CH_3CH_2CH_2Br \xrightarrow[\text{acetic acid}]{CH_3CONa} CH_3CH_2CH_2OCCH_3$ (O)

Propyl acetate

(*c*) $CH_3CH_2CH_2Br \xrightarrow[\text{ethanol}]{NaOCH_2CH_3} CH_3CH_2CH_2OCH_2CH_3$

Ethyl propyl ether

(*d*) $CH_3CH_2CH_2Br \xrightarrow[\text{DMSO}]{NaCN} CH_3CH_2CH_2CN$

Butanenitrite

(*e*) $CH_3CH_2CH_2Br \xrightarrow[\text{ethanol–water}]{NaN_3} CH_3CH_2CH_2N_3$

1-Azidopropane

(*f*) $CH_3CH_2CH_2Br \xrightarrow[\text{ethanol}]{NaSH} CH_3CH_2CH_2SH$

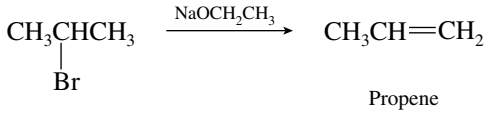
1-Propanethiol

(*g*) $CH_3CH_2CH_2Br \xrightarrow[\text{ethanol}]{NaSCH_3} CH_3CH_2CH_2SCH_3$

Methyl propyl sulfide

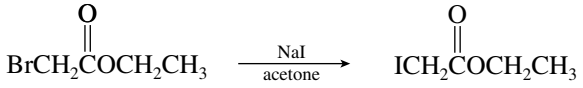
**8.18** Elimination is the major product when secondary halides react with anions as basic as or more basic than hydroxide ion. Alkoxide ions have a basicity comparable with hydroxide ion and react with

secondary halides to give predominantly elimination products. Thus ethoxide ion [part (*c*)] will react with 2-bromopropane to give mainly propene.



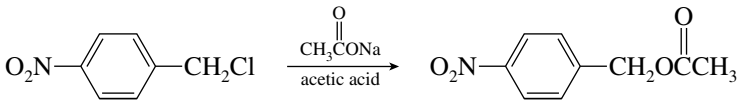

Propene

**8.19** (*a*) The substrate is a primary alkyl bromide and reacts with sodium iodide in acetone to give the corresponding iodide.



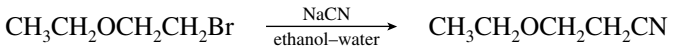

Ethyl bromoacetate — Ethyl iodoacetate (89%)

(*b*) Primary alkyl chlorides react with sodium acetate to yield the corresponding acetate esters.



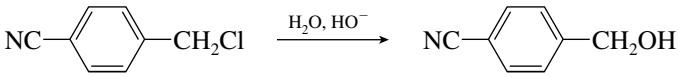

*p*-Nitrobenzyl chloride — *p*-Nitrobenzyl acetate (78–82%)

(*c*) The only leaving group in the substrate is bromide. Neither of the carbon–oxygen bonds is susceptible to cleavage by nucleophilic attack.



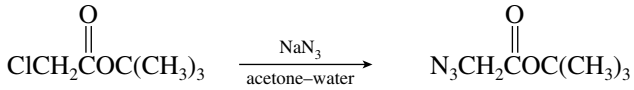

2-Bromoethyl ethyl ether — 2-Cyanoethyl ethyl ether (52–58%)

(*d*) Hydrolysis of the primary chloride yields the corresponding alcohol.



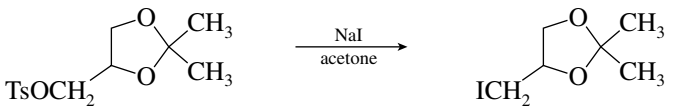

*p*-Cyanobenzyl chloride — *p*-Cyanobenzyl alcohol (85%)

(*e*) The substrate is a primary chloride.



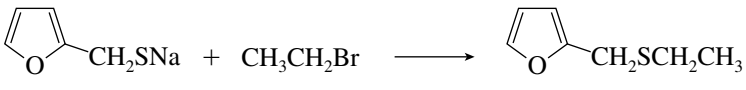

*tert*-Butyl chloroacetate — *tert*-Butyl azidoacetate (92%)

(*f*) Primary alkyl tosylates yield iodides on treatment with sodium iodide in acetone.



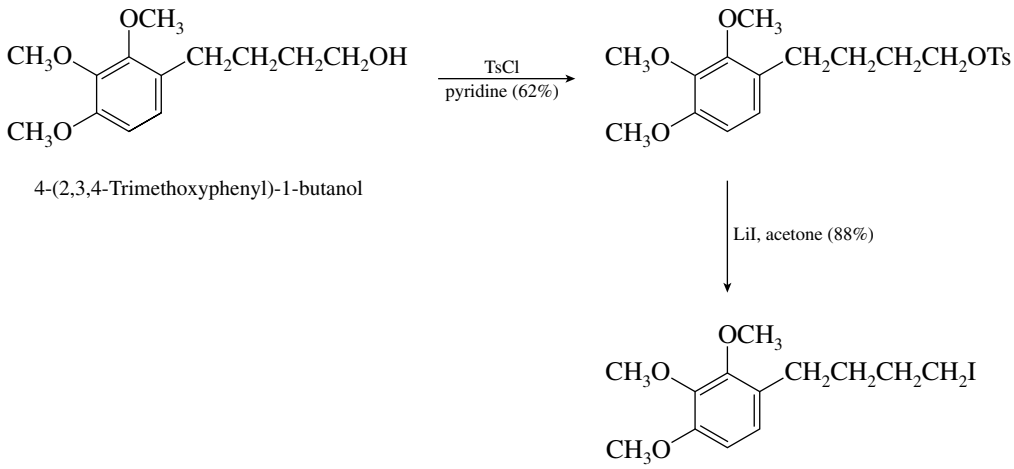

(2,2-Dimethyl-1,3-dioxolan-4-yl)-methyl *p*-toluenesulfonate — 2,2-Dimethyl-4-(iodomethyl)-1,3-dioxolane (60%)

(*g*) Sulfur displaces bromide from ethyl bromide.




Sodium (2-furyl)-methanethiolate — Ethyl bromide — Ethyl (2-furyl)methyl sulfide (80%)

(*h*) The first reaction is one in which a substituted alcohol is converted to a *p*-toluenesulfonate ester. This is followed by an $S_N2$ displacement with lithium iodide.

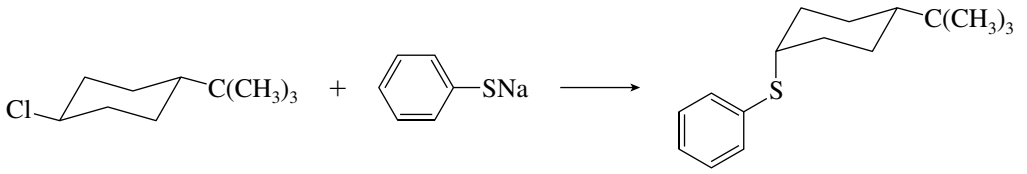



4-(2,3,4-Trimethoxyphenyl)-1-butanol

4-(2,3,4-Trimethoxyphenyl)-1-butyl iodide

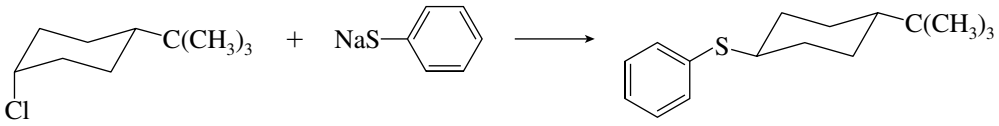
**8.20** The two products are diastereomers of each other. They are formed by bimolecular nucleophilic substitution ($S_N2$). In each case, a good nucleophile ($C_6H_5S^-$) displaces chloride from a secondary carbon with inversion of configuration.

(*a*) The trans chloride yields a cis substitution product.



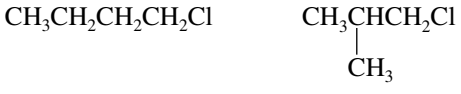

*trans*-4-*tert*-Butylcyclohexyl chloride | Sodium benzenethiolate | *cis*-4-*tert*-Butylcyclohexyl phenyl sulfide

(*b*) The cis chloride yields a trans substitution product.

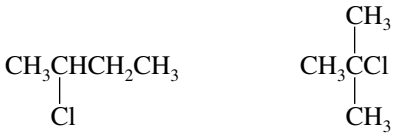



*cis*-4-*tert*-Butylcyclohexyl chloride | Sodium benzenethiolate | *trans*-4-*tert*-Butylcyclohexyl phenyl sulfide

**8.21** The isomers of $C_4H_9Cl$ are:




1-Chlorobutane (*n*-butyl chloride) | 1-Chloro-2-methylpropane (isobutyl chloride)

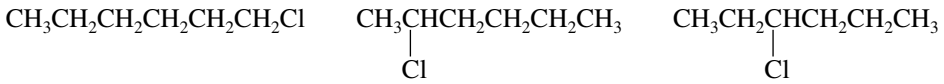



2-Chlorobutane (*sec*-butyl chloride) | 2-Chloro-2-methylpropane (*tert*-butyl chloride)

The reaction conditions (sodium iodide in acetone) are typical for an $S_N2$ process.

The order of $S_N2$ reactivity is primary > secondary > tertiary, and branching of the chain close to the site of substitution hinders reaction. The unbranched primary halide *n*-butyl chloride will be the most reactive and the tertiary halide *tert*-butyl chloride the least. The order of reactivity will therefore be: 1-chlorobutane > 1-chloro-2-methylpropane > 2-chlorobutane > 2-chloro-2-methylpropane.

**8.22** 1-Chlorohexane is a primary alkyl halide; 2-chlorohexane and 3-chlorohexane are secondary.



1-Chlorohexane (primary) | 2-Chlorohexane (secondary) | 3-Chlorohexane (secondary)

Primary and secondary alkyl halides react with potassium iodide in acetone by an $S_N2$ mechanism, and the rate depends on steric hindrance to attack on the alkyl halide by the nucleophile.

(*a*) Primary alkyl halides are more reactive than secondary alkyl halides in $S_N2$ reactions. 1-Chlorohexane is the most reactive isomer.

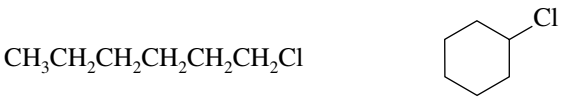
(*b*) Substituents at the carbon adjacent to the one that bears the leaving group slow down the rate of nucleophilic displacement. In 2-chlorohexane the group adjacent to the point of attack is $CH_3$. In 3-chlorohexane the group adjacent to the point of attack is $CH_2CH_3$. 2-Chlorohexane has been observed to be more reactive than 3-chlorohexane by a factor of 2.

**8.23** (*a*) Iodide is a better leaving group than bromide, and so 1-iodobutane should undergo $S_N2$ attack by cyanide faster than 1-bromobutane.

(*b*) The reaction conditions are typical for an $S_N2$ process. The methyl branch in 1-chloro-2-methylbutane sterically hinders attack at C-1. The unbranched isomer, 1-chloropentane, reacts faster.

1-Chloro-2-methylbutane is more sterically hindered, therefore less reactive. | 1-Chloropentane is less sterically hindered, therefore more reactive.

(*c*) Hexyl chloride is a primary alkyl halide, and cyclohexyl chloride is secondary. Azide ion is a good nucleophile, and so the $S_N2$ reactivity rules apply; primary is more reactive than secondary.



Hexyl chloride is primary, therefore more reactive in $S_N2$. | Cyclohexyl chloride is secondary, therefore less reactive in $S_N2$.

(*d*) 1-Bromo-2,2-dimethylpropane is too hindered to react with the weakly nucleophilic ethanol by an $S_N2$ reaction, and since it is a primary alkyl halide, it is less reactive in $S_N1$ reactions. *tert*-Butyl bromide will react with ethanol by an $S_N1$ mechanism at a reasonable rate owing to formation of a tertiary carbocation.

*tert*-Butyl bromide; more reactive in $S_N1$ solvolysis | 1-Bromo-2,2-dimethylpropane; relatively unreactive in nucleophilic substitution reactions

(*e*) Solvolysis of alkyl halides in aqueous formic acid is faster for those that form carbocations readily. The $S_N1$ reactivity order applies here: secondary > primary.

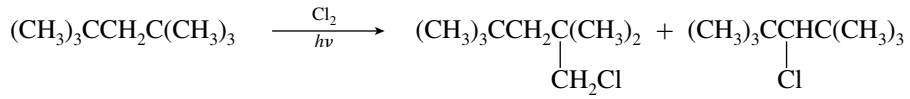
*sec*-Butyl bromide; secondary, therefore more reactive in $S_N1$

Isobutyl bromide; primary, therefore less reactive in $S_N1$

(*f*) 1-Chlorobutane is a primary alkyl halide and so should react by an $S_N2$ mechanism. Sodium methoxide is more basic than sodium acetate and is a better nucleophile. Reaction will occur faster with sodium methoxide than with sodium acetate.

(*g*) Azide ion is a very good nucleophile, whereas *p*-toluenesulfonate is a very good leaving group but a very poor nucleophile. In an $S_N2$ reaction with 1-chlorobutane, sodium azide will react faster than sodium *p*-toluenesulfonate.

**8.24** There are only two possible products from free-radical chlorination of the starting alkane:



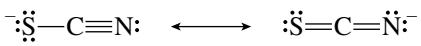
2,2,2,4,4-Tetramethylpentane

1-Chloro-2,2,4,4-tetramethylpentane (primary)

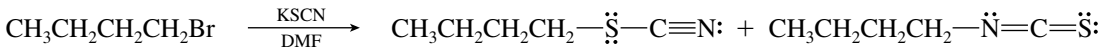
3-Chloro-2,2,4,4-tetramethylpentane (secondary)

As revealed by their structural formulas, one isomer is a primary alkyl chloride, the other is secondary. The problem states that the major product (compound A) undergoes $S_N1$ hydrolysis much more slowly than the minor product (compound B). Since secondary halides are much more reactive than primary halides under $S_N1$ conditions, the major (unreactive) product is the primary alkyl halide 1-chloro-2,2,4,4-tetramethylpentane (compound A) and the minor (reactive) product is the secondary alkyl halide 3-chloro-2,2,4,4-tetramethylpentane (compound B).

**8.25** (*a*) The two most stable Lewis structures (resonance forms) of thiocyanate are:



(*b*) The two Lewis structures indicate that the negative charge is shared by two atoms: S and N. Thus thiocyanate ion has two potentially nucleophilic sites, and the two possible products are



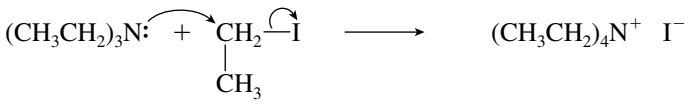
1-Bromobutane

Butyl thiocyanate

Butyl isothiocyanate

(*c*) Sulfur is more polarizable than nitrogen and is more nucleophilic. The major product is butyl thiocyanate and arises by attack of sulfur of thiocyanate on butyl bromide.

**8.26** Using the unshared electron pair on its nitrogen, triethylamine acts as a nucleophile in an $S_N2$ reaction toward ethyl iodide.



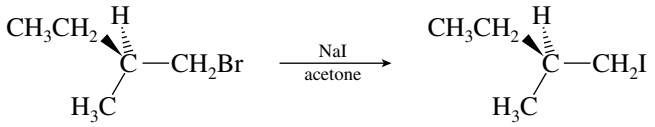
Triethylamine

Ethyl iodide

Tetraethylammonium iodide

The product of the reaction is a salt and has the structure shown. The properties given in the problem (soluble in polar solvents, high melting point) are typical of those of an ionic compound.

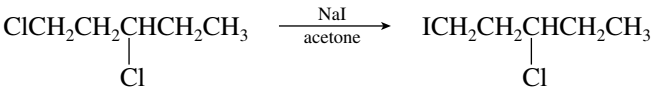
**8.27** This reaction has been reported in the chemical literature and proceeds as shown (91% yield):




(*S*)-1-Bromo-2-methylbutane (*S*)-1-Iodo-2-methylbutane

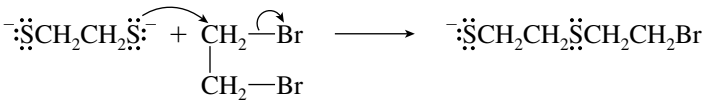
Notice that the configuration of the product is the *same* as the configuration of the reactant. This is because the stereogenic center is not involved in the reaction. When we say that $S_N2$ reactions proceed with inversion of configuration we refer only to the carbon at which substitution takes place, not a stereogenic center elsewhere in the molecule.

**8.28** (*a*) The starting material incorporates both a primary chloride and a secondary chloride. The nucleophile (iodide) attacks the less hindered primary position.

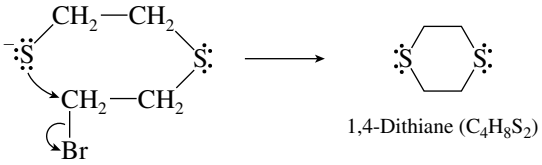



1,3-Dichloropentane 3-Chloro-1-iodopentane ($C_5H_{10}ClI$)

(*b*) Nucleophilic substitution of the first bromide by sulfur occurs in the usual way.

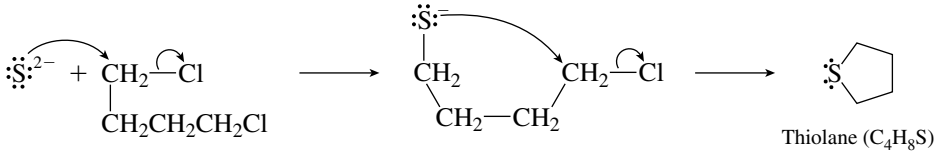



The product of this step cyclizes by way of an intramolecular nucleophilic substitution.




1,4-Dithiane ($C_4H_8S_2$)

(*c*) The nucleophile is a dianion ($S^{2-}$). Two nucleophilic substitution reactions take place; the second of the two leads to intramolecular cyclization.




Thiolane ($C_4H_8S$)

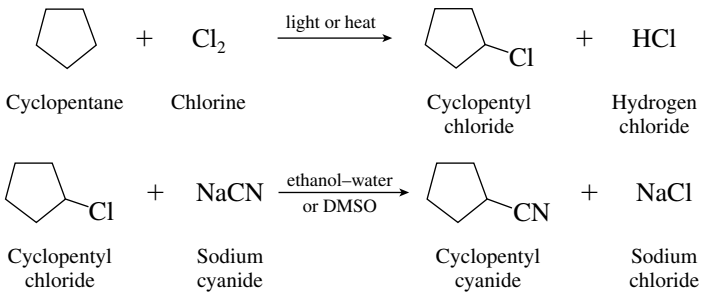
**8.29** (*a*) Methyl halides are unhindered and react rapidly by the $S_N2$ mechanism.
(*b*) Sodium ethoxide is a good nucleophile and will react with unhindered primary alkyl halides by the $S_N2$ mechanism.
(*c*) Cyclohexyl bromide is a secondary halide and will react with a strong base (sodium ethoxide) predominantly by the E2 mechanism.
(*d*) The tertiary halide *tert*-butyl bromide will undergo solvolysis by the $S_N1$ mechanism.
(*e*) The presence of the strong base sodium ethoxide will cause the E2 mechanism to predominate.
(*f*) Concerted reactions are those which occur in a single step. The bimolecular mechanisms $S_N2$ and E2 represent concerted processes.
(*g*) In a stereospecific reaction, stereoisomeric reactants yield products that are stereoisomers of each other. Reactions that occur by the $S_N2$ and E2 mechanisms are stereospecific.

(*h*) The unimolecular mechanisms $S_N1$ and E1 involve the formation of carbocation intermediates.

(*i*) Rearrangements are possible when carbocations are intermediates in a reaction. Thus reactions occurring by the $S_N1$ and E1 mechanisms are most likely to have a rearranged carbon skeleton.

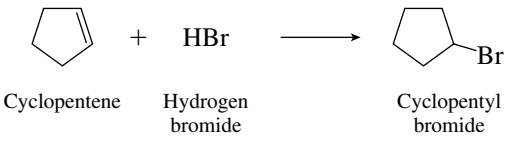
(*j*) Iodide is a better leaving group than bromide, and alkyl iodides will react faster than alkyl bromides by any of the four mechanisms $S_N1$, $S_N2$, E1, and E2.

**8.30** (*a*) Cyclopentyl cyanide can be prepared from a cyclopentyl halide by a nucleophilic substitution reaction. The first task, therefore, is to convert cyclopentane to a cyclopentyl halide.



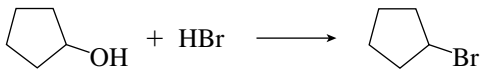

An analogous sequence involving cyclopentyl bromide could be used.

(*b*) Cyclopentene can serve as a precursor to a cyclopentyl halide.

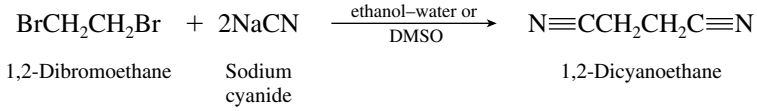



Once cyclopentyl bromide has been prepared, it is converted to cyclopentyl cyanide by nucleophilic substitution, as shown in part (*a*).

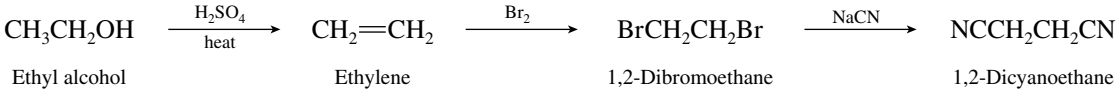
(*c*) Reaction of cyclopentanol with hydrogen bromide gives cyclopentyl bromide. Then cyclopentyl bromide can be converted to cyclopentyl cyanide, as shown in part (*a*).



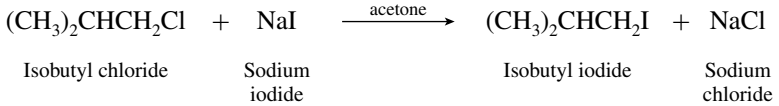

(*d*) Two cyano groups are required here, both of which must be introduced in nucleophilic substitution reactions. The substrate in the key reaction is $BrCH_2CH_2Br$.




1,2-Dibromoethane is prepared from ethylene. The overall synthesis from ethyl alcohol is therefore formulated as shown:




(*e*) In this synthesis a primary alkyl chloride must be converted to a primary alkyl iodide. This is precisely the kind of transformation for which sodium iodide in acetone is used.



(*f*) First convert *tert*-butyl chloride into an isobutyl halide.

$$(CH_3)_3CCl \xrightarrow{NaOCH_3} (CH_3)_2C{=}CH_2 \xrightarrow[\text{peroxides}]{HBr} (CH_3)_2CHCH_2Br$$

*tert*-Butyl chloride — 2-Methylpropene — Isobutyl bromide

Treating isobutyl bromide with sodium iodide in acetone converts it to isobutyl iodide.

$$(CH_3)_2CHCH_2Br \xrightarrow[\text{acetone}]{NaI} (CH_3)_2CHCH_2I$$

Isobutyl bromide — Isobutyl iodide

A second approach is by way of isobutyl alcohol.

$$(CH_3)_3CCl \xrightarrow{NaOCH_3} (CH_3)_2C{=}CH_2 \xrightarrow[2.\ H_2O_2,\ HO^-]{1.\ B_2H_6} (CH_3)_2CHCH_2OH$$

*tert*-Butyl chloride — 2-Methylpropene — Isobutyl alcohol

Isobutyl alcohol is then converted to its *p*-toluenesulfonate ester, which reacts with sodium iodide in acetone in a manner analogous to that of isobutyl bromide.

(*g*) First introduce a leaving group into the molecule by converting isopropyl alcohol to an isopropyl halide. Then convert the resulting isopropyl halide to isopropyl azide by a nucleophilic substitution reaction

$$CH_3CHCH_3 \;(OH) \xrightarrow{HBr} CH_3CHCH_3 \;(Br) \xrightarrow{NaN_3} CH_3CHCH_3 \;(N_3)$$

Isopropyl alcohol — Isopropyl bromide — Isopropyl azide

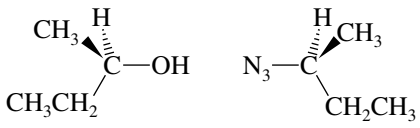
(*h*) In this synthesis 1-propanol must be first converted to an isopropyl halide.

$$CH_3CH_2CH_2OH \xrightarrow[\text{heat}]{H_2SO_4} CH_3CH{=}CH_2 \xrightarrow{HBr} CH_3CHCH_3 \;(Br)$$

1-Propanol — Propene — Isopropyl bromide

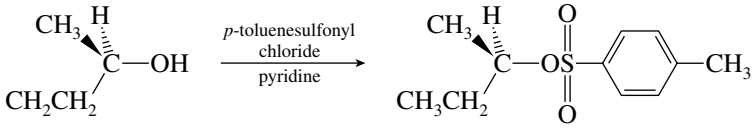
After an isopropyl halide has been obtained, it can be treated with sodium azide as in part (*g*).

(*i*) First write out the structure of the starting material and of the product so as to determine their relationship in three dimensions.



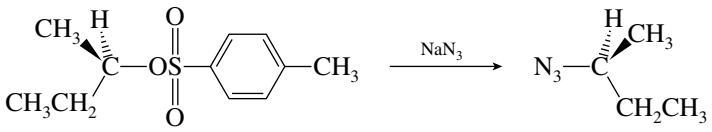

(*R*)-*sec*-Butyl alcohol — (*S*)-*sec*-Butyl azide

The hydroxyl group must be replaced by azide with inversion of configuration. First, however, a leaving group must be introduced, and it must be introduced in such a way that the configuration at the stereogenic center is not altered. The best way to do this is to convert (*R*)-*sec*-butyl alcohol to its corresponding *p*-toluenesulfonate ester.



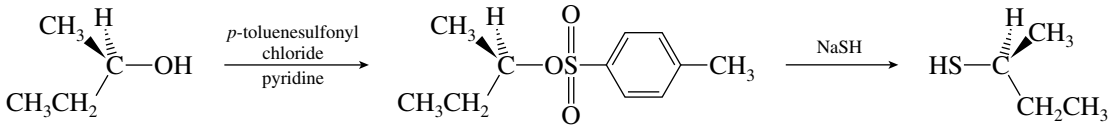

(*R*)-*sec*-Butyl alcohol — (*R*)-*sec*-Butyl *p*-toluenesulfonate

Next, convert the *p*-toluenesulfonate to the desired azide by an $S_N2$ reaction.




(*R*)-*sec*-Butyl *p*-toluenesulfonate (*S*)-*sec*-Butyl azide

(*j*) This problem is carried out in exactly the same way as the preceding one, except that the nucleophile in the second step is $HS^-$.




(*R*)-*sec*-Butyl alcohol (*R*)-*sec*-Butyl *p*-toluenesulfonate (*S*)-2-Butanethiol

**8.31** (*a*) The two possible combinations of alkyl bromide and alkoxide ion that might yield *tert*-butyl methyl ether are

**1.** $CH_3Br + (CH_3)_3CO^- \xrightarrow{\text{fast}} (CH_3)_3COCH_3$

Methyl bromide; *tert*-Butoxide ion; *tert*-Butyl methyl ether

**2.** $CH_3O^- + (CH_3)_3CBr \xrightarrow{\text{slow}} (CH_3)_3COCH_3$

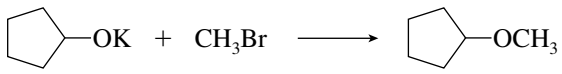
Methoxide ion; *tert*-Butyl bromide; *tert*-Butyl methyl ether

We choose the first approach because it is an $S_N2$ reaction on the unhindered substrate, methyl bromide. The second approach requires an $S_N2$ reaction on a hindered tertiary alkyl halide, a very poor choice. Indeed, we would expect that the reaction of methoxide ion with *tert*-butyl bromide could not give any ether at all but would proceed entirely by E2 elimination:

$$CH_3O^- + (CH_3)_3CBr \xrightarrow{\text{fast}} CH_3OH + CH_2{=}C(CH_3)_2$$

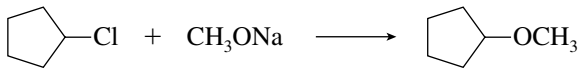
Methanol; 2-Methylpropene

(*b*) Again, the better alternative is to choose the less hindered alkyl halide to permit substitution to predominate over elimination.




Potassium cyclopentoxide; Methyl bromide; Cyclopentyl methyl ether

An attempt to prepare this compound by the reaction




Chlorocyclopentane; Sodium methoxide; Cyclopentyl methyl ether

gave cyclopentyl methyl ether in only 24% yield. Cyclopentene was isolated in 31% yield.

(*c*) A 2,2-dimethylpropyl halide is too sterically hindered to be a good candidate for this synthesis. The only practical method is

$$(CH_3)_3CCH_2OK + CH_3CH_2Br \longrightarrow (CH_3)_3CCH_2OCH_2CH_3$$

Potassium 2,2-dimethylpropoxide; Bromoethane; Ethyl 2,2-dimethylpropyl ether

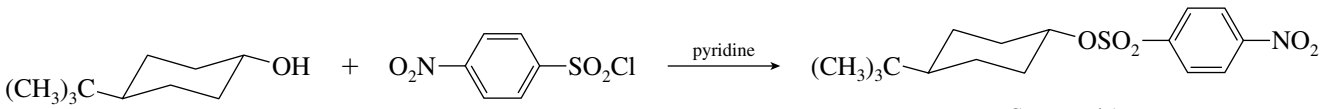
**8.32** (*a*) The problem states that the reaction type is nucleophilic substitution. Sodium acetylide is therefore the nucleophile and must be treated with an alkyl halide to give the desired product.

$$Na^+ :\bar{C}{\equiv}CH + CH_3CH_2Br \longrightarrow CH_3CH_2C{\equiv}CH + NaBr$$

Sodium acetylide — Ethyl bromide — 1-Butyne — Sodium bromide

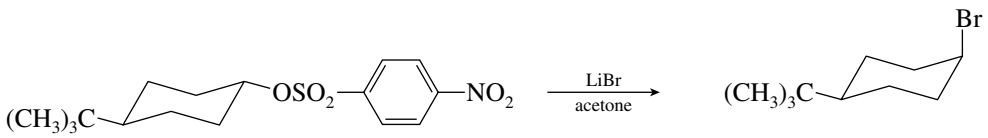
(*b*) The acidity data given in the problem for acetylene tell us that HC≡CH is a very weak acid ($K_a = 10^{-26}$), so that sodium acetylide must be a very strong base—stronger than hydroxide ion. *Elimination* by the E2 mechanism rather than $S_N2$ substitution is therefore expected to be the principal (probably the exclusive) reaction observed with secondary and tertiary alkyl halides. The substitution reaction will work well with primary alkyl halides but will likely fail for secondary and tertiary ones. Alkynes such as $(CH_3)_2CHC{\equiv}CH$ and $(CH_3)_3CC{\equiv}CH$ could not be prepared by this method.

**8.33** The compound that reacts with *trans*-4-*tert*-butylcyclohexanol is a sulfonyl chloride and converts the alcohol to the corresponding sulfonate.



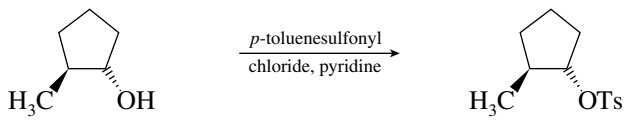

Compound A

Reaction of compound A with lithium bromide in acetone effects displacement of the sulfonate leaving group by bromide with inversion of configuration.



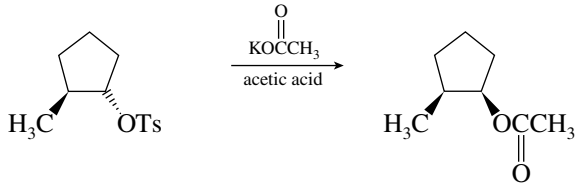

Compound A — *cis*-1-Bromo-4-*tert*-butylcyclohexane
Compound B

**8.34** (*a*) To convert *trans*-2-methylcyclopentanol to *cis*-2-methylcyclopentyl acetate the hydroxyl group must be replaced by acetate with inversion of configuration. Hydroxide is a poor leaving group and so must first be converted to a good leaving group. The best choice is *p*-toluenesulfonate, because this can be prepared by a reaction that alters none of the bonds to the stereogenic center.



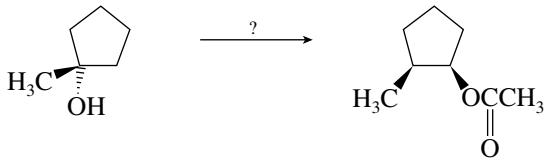

*trans*-2-Methylcyclopentanol — *trans*-2-Methylcyclopentyl *p*-toluenesulfonate

Treatment of the *p*-toluenesulfonate with potassium acetate in acetic acid will proceed with inversion of configuration to give the desired product.



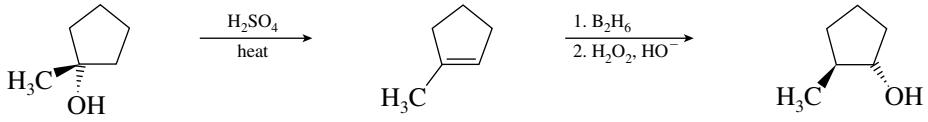

*trans*-2-Methylcyclopentyl *p*-toluenesulfonate — *cis*-2-Methylcyclopentyl acetate

(*b*) To decide on the best sequence of reactions, we must begin by writing structural formulas to determine what kinds of transformations are required.




1-Methylcyclopentanol *cis*-2-Methylcyclopentyl acetate

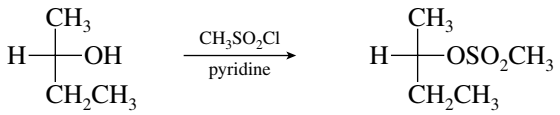
We already know from part (*a*) how to convert *trans*-2-methylcyclopentanol to *cis*-2-methylcyclopentyl acetate. So all that is really necessary is to design a synthesis of *trans*-2-methylcyclopentanol. Therefore,




1-Methylcyclopentanol 1-Methylcyclopentene *trans*-2-Methylcyclopentanol

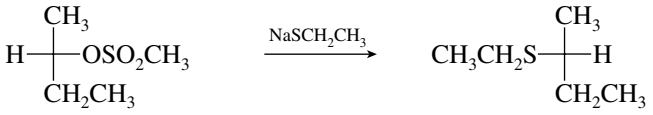
Hydroboration–oxidation converts 1-methylcyclopentene to the desired alcohol by anti-Markovnikov syn hydration of the double bond. The resulting alcohol is then converted to its *p*-toluenesulfonate ester and treated with acetate ion as in part (*a*) to give *cis*-2-methylcyclopentyl acetate.

**8.35** (*a*) The reaction of an alcohol with a sulfonyl chloride gives a sulfonate ester. The oxygen of the alcohol remains in place and is the atom to which the sulfonyl group becomes attached.



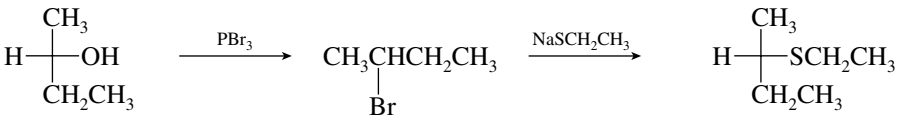

(*S*)-(+)-2-Butanol (*S*)-*sec*-Butyl methanesulfonate

(*b*) Sulfonate is similar to iodide in its leaving-group behavior. The product in part (*a*) is attacked by $NaSCH_2CH_3$ in an $S_N2$ reaction. Inversion of configuration occurs at the stereogenic center.



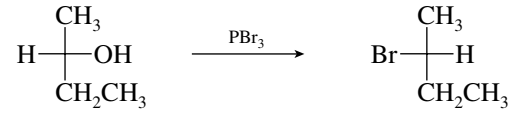

(*S*)-*sec*-Butyl methanesulfonate (*R*)-(−)-*sec*-Butyl ethyl sulfide

(*c*) In this part of the problem we deduce the stereochemical outcome of the reaction of 2-butanol with $PBr_3$. We know the absolute configuration of (+)-2-butanol (*S*) from the statement of the problem and the configuration of (−)-*sec*-butyl ethyl sulfide (*R*) from part (*b*). We are told that the sulfide formed from (+)-2-butanol via the bromide has a positive rotation. It must therefore have the opposite configuration of the product in part (*b*).




(*S*)-(+)-2-Butanol 2-Bromobutane (*S*)-(+)-*sec*-Butyl ethyl sulfide

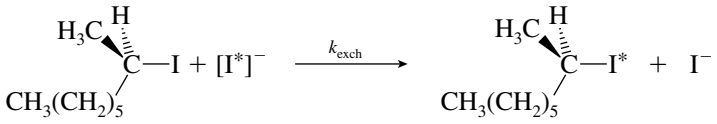
Since the reaction of the bromide with $NaSCH_2CH_3$ proceeds with inversion of configuration at the stereogenic center, and since the final product has the same configuration as the starting alcohol, the conversion of the alcohol to the bromide must proceed with inversion of configuration.




(*S*)-(+)-2-Butanol (*R*)-(−)-2-Bromobutane

(*d*) The conversion of 2-butanol to *sec*-butyl methanesulfonate does not involve any of the bonds to the stereogenic center, and so it must proceed with 100% retention of configuration. Assuming that the reaction of the methanesulfonate with $NaSCH_2CH_3$ proceeds with 100% inversion of configuration, we conclude that the maximum rotation of *sec*-butyl ethyl sulfide is the value given in the statement of part (*b*), that is, ±25°. Since the sulfide produced in part (*c*) has a rotation of +23°, it is 92% optically pure. It is reasonable to assume that the loss of optical purity occurred in the conversion of the alcohol to the bromide, rather than in the reaction of the bromide with $NaSCH_2CH_3$. If the bromide is 92% optically pure and has a rotation of −38°, optically pure 2-bromobutane therefore has a rotation of 38/0.92, or ±41°.

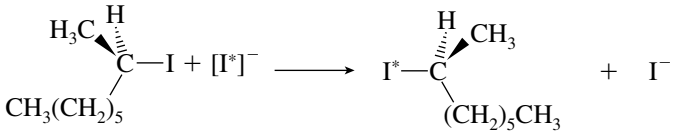
**8.36** (*a*) If each act of exchange (substitution) occurred with retention of configuration, there would be no observable racemization; $k_{rac} = 0$.




(*R*)-(−)-2-Iodooctane (*indicates radioactive label) [(*R*)-(−)-2-Iodooctane]*

Therefore $k_{rac}/k_{exch} = 0$.

(*b*) If each act of exchange proceeds with inversion of configuration, (*R*)-(−)-2-iodooctane will be transformed to radioactively labeled (*S*)-(+)-2-iodooctane.




(*R*)-(−)-2-Iodooctane [(*S*)-(+)-2-Iodooctane]*

Starting with 100 molecules of (*R*)-(−)-2-iodooctane, the compound will be completely racemized when 50 molecules have become radioactive. Therefore,

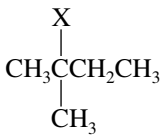
$$\frac{k_{rac}}{k_{exch}} = 2$$

(*c*) If radioactivity is incorporated in a stereorandom fashion, then 2-iodooctane will be 50% racemized when 50% of it has reacted. Therefore,

$$\frac{k_{rac}}{k_{exch}} = 1$$

In fact, Hughes found that the rate of racemization was twice the rate of incorporation of radioactive iodide. This experiment provided strong evidence for the belief that bimolecular nucleophilic substitution proceeds stereospecifically with inversion of configuration.

**8.37** (*a*) Tertiary alkyl halides undergo nucleophilic substitution only by way of carbocations: $S_N1$ is the most likely mechanism for solvolysis of the 2-halo-2-methylbutanes.

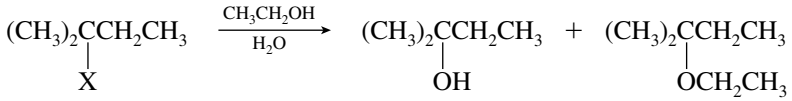


2-Halo-2-methylbutanes are tertiary alkyl halides.

(*b*) Tertiary alkyl halides can undergo either E1 or E2 elimination. Since no alkoxide base is present, solvolytic elimination most likely occurs by an E1 mechanism.

(*c*, *d*) Iodides react faster than bromides in substitution and elimination reactions irrespective of whether the mechanism is E1, E2, $S_N1$, or $S_N2$.

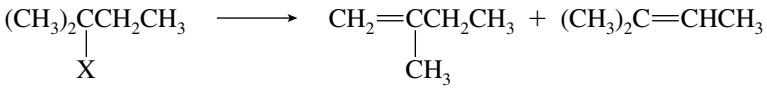
(*e*) Solvolysis in aqueous ethanol can give rise to an alcohol or an ether as product, depending on whether the carbocation is captured by water or ethanol.



2-Methyl-2-butanol

Ethyl 1,1-dimethylpropyl ether

(*f*) Elimination can yield either of two isomeric alkenes.



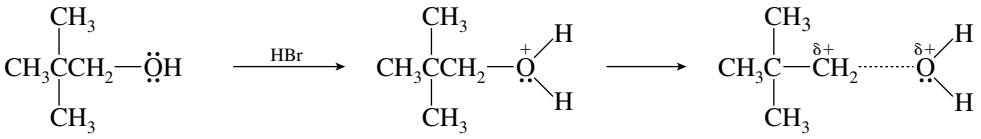
2-Methyl-1-butene

2-Methyl-2-butene

Zaitsev's rule predicts that 2-methyl-2-butene should be the major alkene.

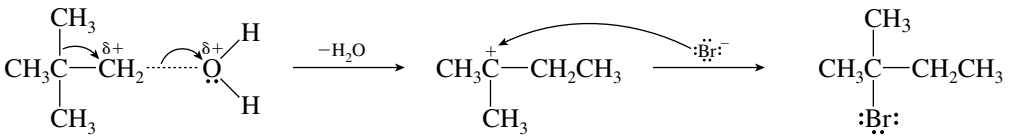
(*g*) The product distribution is determined by what happens to the carbocation intermediate. If the carbocation is free of its leaving group, its fate will be the same no matter whether the leaving group is bromide or iodide.

**8.38** Both aspects of this reaction—its slow rate and the formation of a rearranged product—have their origin in the positive character developed at a primary carbon. The alcohol is protonated and the carbon–oxygen bond of the resulting alkyloxonium ion begins to break:



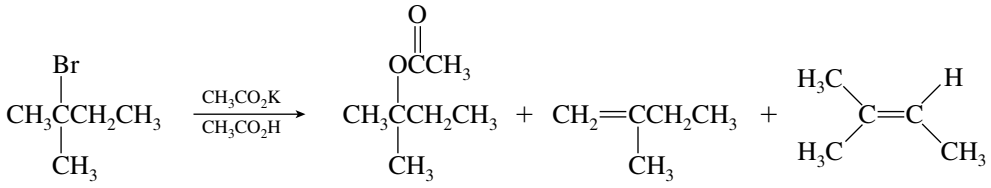
2,2-Dimethyl-1-propanol

As positive character develops at the primary carbon, a methyl group migrates. Rearrangement gives a tertiary carbocation, which is captured by bromide to give the product.



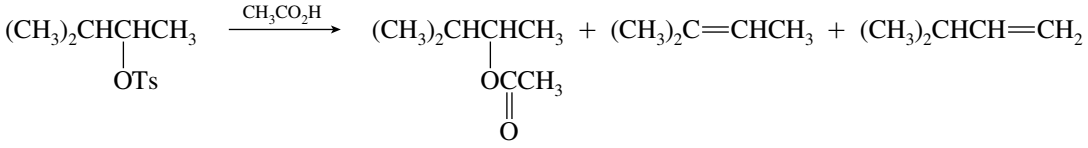
2-Bromo-2-methylbutane

**8.39** The substrate is a tertiary alkyl bromide and can undergo $S_N1$ substitution and E1 elimination under these reaction conditions. Elimination in either of two directions to give regioisomeric alkenes can also occur.



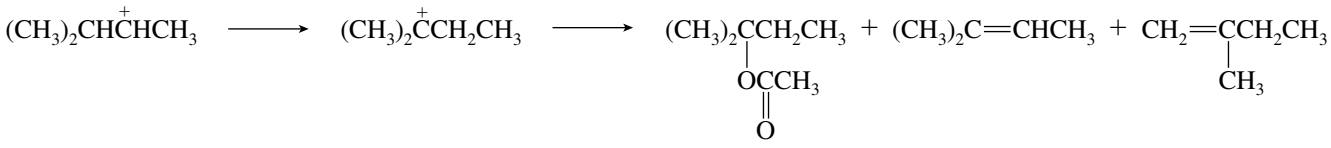

2-Bromo-2-methylbutane | 1,1-Dimethylpropyl acetate | 2-Methyl-1-butene | 2-Methyl-2-butene

**8.40** Solvolysis of 1,2-dimethylpropyl *p*-toluenesulfonate in acetic acid is expected to give one substitution product and two alkenes.



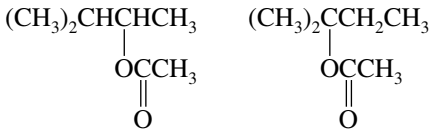

1,2-Dimethylpropyl *p*-toluenesulfonate | 1,2-Dimethylpropyl acetate | 2-Methyl-2-butene | 3-Methyl-1-butene

Since five products are formed, we are led to consider the possibility of carbocation rearrangements in $S_N1$ and E1 solvolysis.



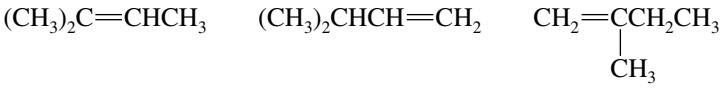

1,2-Dimethylpropyl cation (secondary) | 1,1-Dimethylpropyl cation (tertiary) | 1,1-Dimethylpropyl acetate | 2-Methyl-2-butene | 2-Methyl-1-butene

Since 2-methyl-2-butene is a product common to both carbocation intermediates, a total of five different products are accounted for. There are two substitution products:



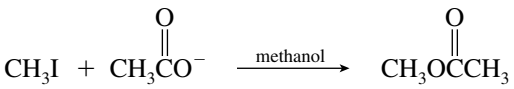

1,2-Dimethylpropyl acetate | 1,1-Dimethylpropyl acetate

and three elimination products:



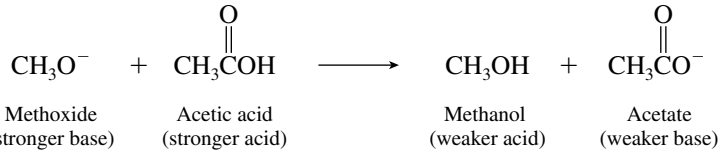

2-Methyl-2-butene | 3-Methyl-1-butene | 2-Methyl-1-butene

**8.41** Solution A contains both acetate ion and methanol as nucleophiles. Acetate is more nucleophilic than methanol, and so the major observed reaction is:



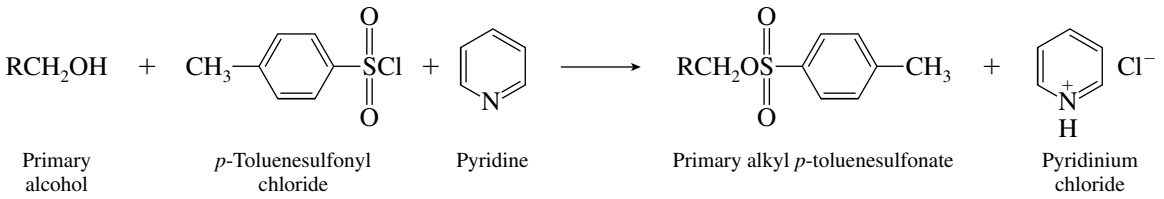

Methyl iodide | Acetate | Methyl acetate

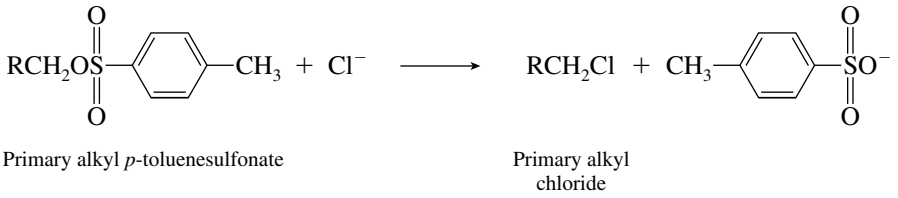
Solution B prepared by adding potassium methoxide to acetic acid rapidly undergoes an acid–base reaction:




Thus the major base present is not methoxide but acetate. Methyl iodide therefore reacts with acetate anion in solution B to give methyl acetate.

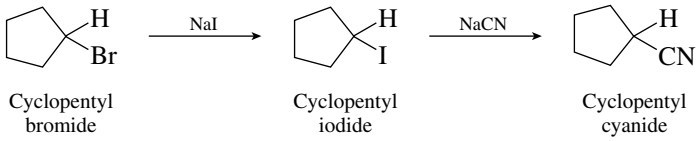
**8.42** Alkyl chlorides arise by the reaction sequence:




The reaction proceeds to form the alkyl *p*-toluenesulfonate as expected, but the chloride anion formed in this step subsequently acts as a nucleophile and displaces *p*-toluenesulfonate from $RCH_2OTs$.

**8.43** Iodide ion is both a better nucleophile than cyanide and a better leaving group than bromide. The two reactions shown are therefore faster than the reaction of cyclopentyl bromide with sodium cyanide alone.



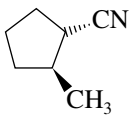

**8.44–8.47** Solutions to molecular modeling exercises are not provided in this *Study Guide and Solutions Manual.* You should use *Learning By Modeling* for these exercises.

## SELF-TEST

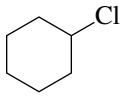
### PART A

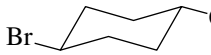
**A-1.** Write the correct structure of the reactant or product omitted from each of the following. Clearly indicate stereochemistry where it is important.

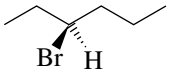
(*a*) $CH_3CH_2CH_2CH_2Br \xrightarrow[CH_3CH_2OH]{CH_3CH_2ONa}$ ?

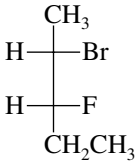
(*b*) ? $\xrightarrow{NaCN}$ 

(*c*) 1-Chloro-3-methylbutane + sodium iodide $\xrightarrow{\text{acetone}}$ ?

(*d*)  $\xrightarrow[CH_3OH]{CH_3ONa}$ ? (major)

(*e*)  + $NaN_3$ $\longrightarrow$ ?

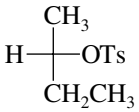
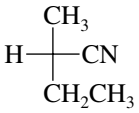
(*f*)  + $NaSCH_3$ $\longrightarrow$ ?

(g)  $\xrightarrow{\text{NaSH}}$ ?

**A-2.** Choose the best pair of reactants to form the following product by an $S_N2$ reaction:

$$(CH_3)_2CHOCH_2CH_2CH_3$$

**A-3.** Outline the chemical steps necessary to convert:

(*a*)  to 

(*b*) (*S*)-2-Pentanol to (*R*)-$CH_3\overset{\displaystyle SCH_3}{\overset{|}{C}}HCH_2CH_2CH_3$

**A-4.** Hydrolysis of 3-chloro-2,2-dimethylbutane yields 2,3-dimethyl-2-butanol as the major product. Explain this observation, using structural formulas to outline the mechanism of the reaction.

**A-5.** Identify the class of reaction (e.g., E2), and write the kinetic and chemical equations for:
(*a*) The solvolysis of *tert*-butyl bromide in methanol
(*b*) The reaction of chlorocyclohexane with sodium azide ($NaN_3$).

**A-6.** (*a*) Provide a brief explanation why the halogen exchange reaction shown is an acceptable synthetic method:

$$CH_3\overset{\displaystyle Br}{\overset{|}{C}}HCH_3 + NaI \xrightarrow{\text{acetone}} CH_3\overset{\displaystyle I}{\overset{|}{C}}HCH_3 + NaBr$$

(*b*) Briefly explain why the reaction of 1-bromobutane with sodium azide occurs faster in dimethyl sulfoxide [$(CH_3)_2S{=}O$] than in water.

**A-7.** Write chemical structures for compounds A through D in the following sequence of reactions. Compounds A and C are alcohols.

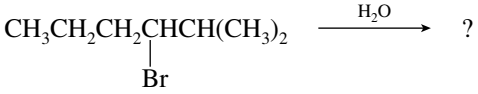
$$A \xrightarrow{NaNH_2} B$$

$$C \xrightarrow{HBr,\ heat} D$$

$$B + D \longrightarrow CH_3CH_2O\text{—}\langle\text{cyclohexane}\rangle$$

**A-8.** Write a mechanism describing the solvolysis ($S_N1$) of 1-bromo-1-methylcyclohexane in ethanol.

**A-9.** Solvolysis of the compound shown occurs with carbocation rearrangement and yields an alcohol as the major product. Write the structure of this product, and give a mechanism to explain its formation.



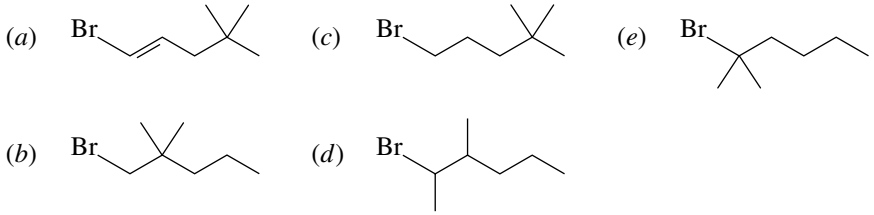
## PART B

**B-1.** The bimolecular substitution reaction

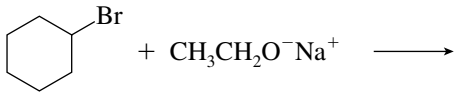
is represented by the kinetic equation:

(*a*) Rate = $k[CH_3Br]^2$
(*b*) Rate = $k[CH_3Br][OH^-]$
(*c*) Rate = $k[CH_3Br] + k[OH^-]$
(*d*) Rate = $k/[CH_3Br][OH^-]$

**B-2.** Which compound undergoes nucleophilic substitution with NaCN at the fastest rate?



**B-3.** For the reaction



the major product is formed by

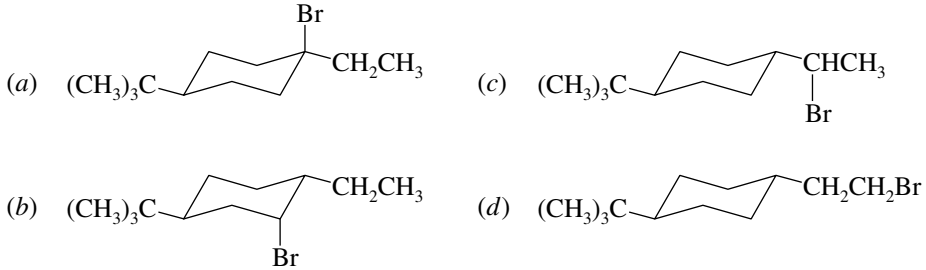
(*a*) An $S_N1$ reaction
(*b*) An $S_N2$ reaction
(*c*) An E1 reaction
(*d*) An E2 reaction

**B-4.** Which of the following statements pertaining to an $S_N2$ reaction are true?

1. The rate of reaction is independent of the concentration of the nucleophile.
2. The nucleophile attacks carbon on the side of the molecule opposite the group being displaced.
3. The reaction proceeds with simultaneous bond formation and bond rupture.
4. Partial racemization of an optically active substrate results.

(*a*) 1, 4 (*b*) 1, 3, 4 (*c*) 2, 3 (*d*) All

**B-5.** Which one of the following alkyl halides would be expected to give the *highest* substitution-to-elimination ratio (most substitution, least elimination) on treatment with sodium ethoxide in ethanol?

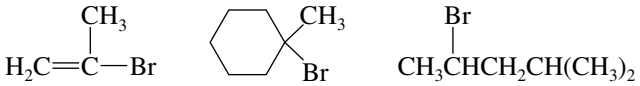


**B-6.** Which of the following phrases are *not* correctly associated with an $S_N1$ reaction?

1. Rearrangement is possible.
2. Rate is affected by solvent polarity.
3. The strength of the nucleophile is important in determining rate.
4. The reactivity series is tertiary > secondary > primary.
5. Proceeds with complete inversion of configuration.

(*a*) 3, 5 (*b*) 5 only (*c*) 2, 3, 5 (*d*) 3 only

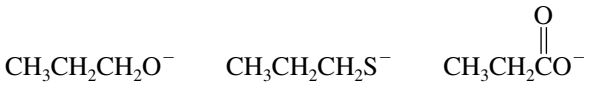
**B-7.** Rank the following in order of decreasing rate of solvolysis with aqueous ethanol (fastest → slowest):



1 2 3

(*a*) 2 > 1 > 3 (*b*) 1 > 2 > 3 (*c*) 2 > 3 > 1 (*d*) 1 > 3 > 2

**B-8.** Rank the following species in order of decreasing nucleophilicity in a polar protic solvent (most → least nucleophilic):



1 2 3

(*a*) 3 > 1 > 2 (*b*) 2 > 3 > 1 (*c*) 1 > 3 > 2 (*d*) 2 > 1 > 3

**B-9.** From each of the following pairs select the compound that will react faster with sodium iodide in acetone.

2-Chloropropane (1) or 2-bromopropane (2)

1-Bromobutane (3) or 2-bromobutane (4)

(*a*) 1, 3 (*b*) 1, 4 (*c*) 2, 3 (*d*) 2, 4

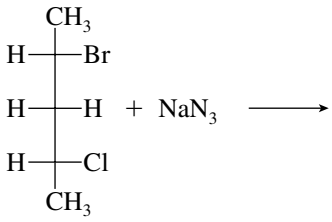
**B-10.** Select the reagent that will yield the greater amount of substitution on reaction with 1-bromobutane.

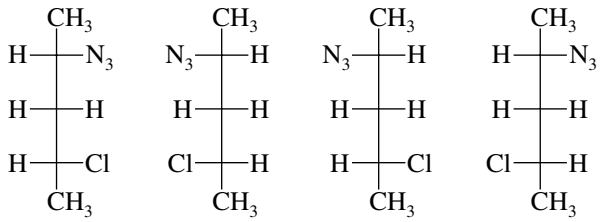
(*a*) $CH_3CH_2OK$ in dimethyl sulfoxide (DMSO)
(*b*) $(CH_3)_3COK$ in dimethyl sulfoxide (DMSO)
(*c*) Both (*a*) and (*b*) will give comparable amounts of substitution.
(*d*) Neither (*a*) nor (*b*) will give any appreciable amount of substitution.

**B-11.** The reaction of (*R*)-1-chloro-3-methylpentane with sodium iodide in acetone will yield 1-iodo-3-methylpentane that is

(*a*) *R* (*c*) A mixture of *R* and *S* (*e*) None of these
(*b*) *S* (*d*) Meso

**B-12.** What is the principal product of the following reaction?



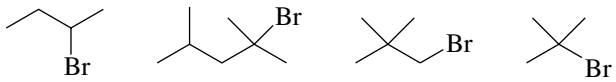


(*a*) (*b*) (*c*) (*d*)

**B-13.** Which of the following statements is true?

(*a*) $CH_3CH_2S^-$ is both a stronger base and more nucleophilic than $CH_3CH_2O^-$.
(*b*) $CH_3CH_2S^-$ is a stronger base but is less nucleophilic than $CH_3CH_2O^-$.
(*c*) $CH_3CH_2S^-$ is a weaker base but is more nucleophilic than $CH_3CH_2O^-$.
(*d*) $CH_3CH_2S^-$ is both a weaker base and less nucleophilic than $CH_3CH_2O^-$.

**B-14.** Which of the following alkyl halides would be most likely to give a rearranged product under $S_N1$ conditions?



(*a*) (*b*) (*c*) (*d*)

(*e*) None of these. Rearrangements only occur under $S_N2$ conditions.