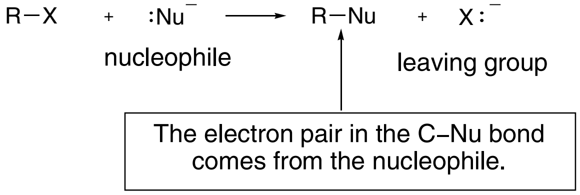
Chapter 7: Alkyl Halides and Nucleophilic Substitution

♦ General facts about alkyl halides

- Alkyl halides contain a halogen atom X bonded to an sp^3 hybridized carbon (7.1).
- Alkyl halides are named as halo alkanes, with the halogen as a substituent (7.2).
- Alkyl halides have a polar C–X bond, so they exhibit dipole–dipole interactions but are incapable of intermolecular hydrogen bonding (7.3).
- The polar C–X bond containing an electrophilic carbon makes alkyl halides reactive towards nucleophiles and bases (7.5).

♦ The central theme (7.6)

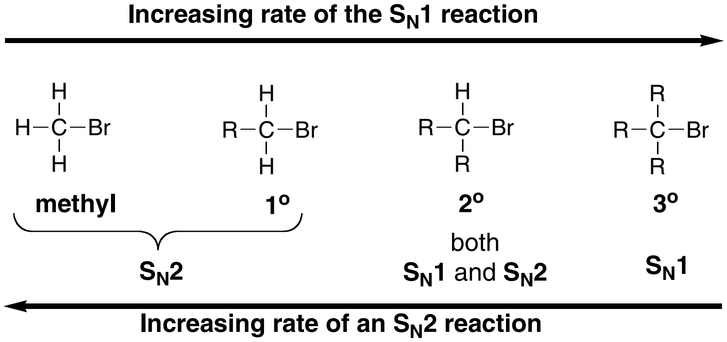
- Nucleophilic substitution is one of the two main reactions of alkyl halides. A nucleophile replaces a leaving group on an sp^3 hybridized carbon.



- One σ bond is broken and one σ bond is formed.
- There are two possible mechanisms: S_N1 and S_N2.

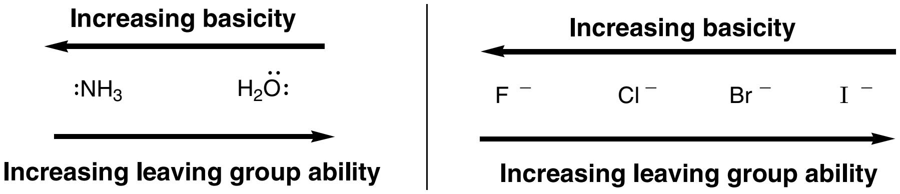
♦ S_N1 and S_N2 mechanisms compared

	S_N2 mechanism	**S_N1 mechanism**
[1] Mechanism	• One step (7.11B)	• Two steps (7.13B)
[2] Alkyl halide	• Order of reactivity: $CH_3X > RCH_2X > R_2CHX > R_3CX$ (7.11D)	• Order of reactivity: $R_3CX > R_2CHX > RCH_2X > CH_3X$ (7.13D)
[3] Rate equation	• rate = $k[RX][:Nu^-]$ • second-order kinetics (7.11A)	• rate = $k[RX]$ • first-order kinetics (7.13A)
[4] Stereochemistry	• backside attack of the nucleophile (7.11C) • inversion of configuration at a stereogenic center	• trigonal planar carbocation intermediate (7.13C) • racemization at a stereogenic center
[5] Nucleophile	• favored by stronger nucleophiles (7.17B)	• favored by weaker nucleophiles (7.17B)
[6] Leaving group	• better leaving group → faster reaction (7.17C)	• better leaving group → faster reaction (7.17C)
[7] Solvent	• favored by polar aprotic solvents (7.17D)	• favored by polar protic solvents (7.17D)

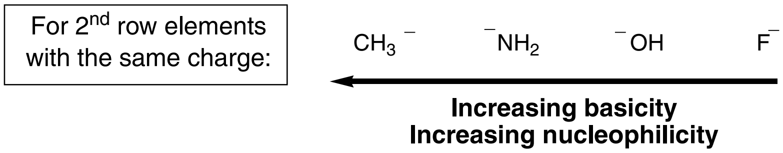


♦ Important trends

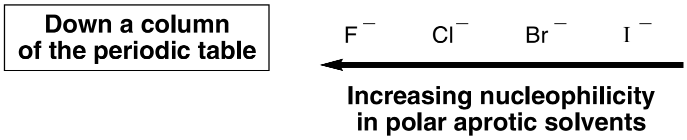
- The best leaving group is the weakest base. Leaving group ability increases across a row and down a column of the periodic table (7.7).



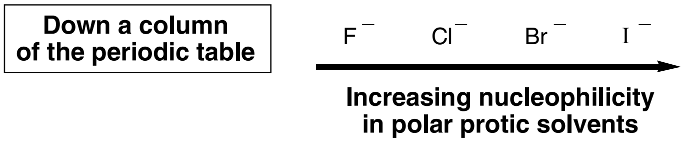
- Nucleophilicity decreases across a row of the periodic table (7.8A).



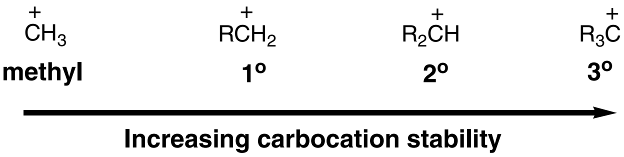
- Nucleophilicity decreases down a column of the periodic table in polar aprotic solvents (7.8C).



- Nucleophilicity increases down a column of the periodic table in polar protic solvents (7.8C).



- The stability of a carbocation increases as the number of R groups bonded to the positively charged carbon increases (7.14).



◆ Important principles

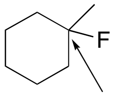
Principle	Example
• Electron-donating groups (such as R groups) stabilize a positive charge (7.14A).	• 3^o Carbocations (R_3C^+) are more stable than 2^o carbocations (R_2CH^+), which are more stable than 1^o carbocations (RCH_2^+).
• Steric hindrance decreases nucleophilicity but not basicity (7.8B).	• $(CH_3)_3CO^-$ is a stronger base but a weaker nucleophile than $CH_3CH_2O^-$.
• Hammond postulate: In an endothermic reaction, the more stable product is formed faster. In an exothermic reaction, this fact is not necessarily true (7.15).	• S_N1 reactions are faster when more stable (more substituted) carbocations are formed, because the rate-determining step is endothermic.
• Planar, *sp*^{2} hybridized atoms react with reagents from both sides of the plane (7.13C).	• A trigonal planar carbocation reacts with nucleophiles from both sides of the plane.

7.1 Classify the alkyl halide as 1°, 2°, or 3° **by counting the number of carbons bonded directly to the carbon bonded to the halogen.**

C bonded to 1 C
1° alkyl halide

a. $CH_3CH_2CH_2CH_2CH_2-Br$

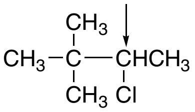
b.



C bonded to 3 C's
3° alkyl halide

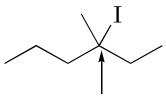
C bonded to 2 C's
2° alkyl halide

c.



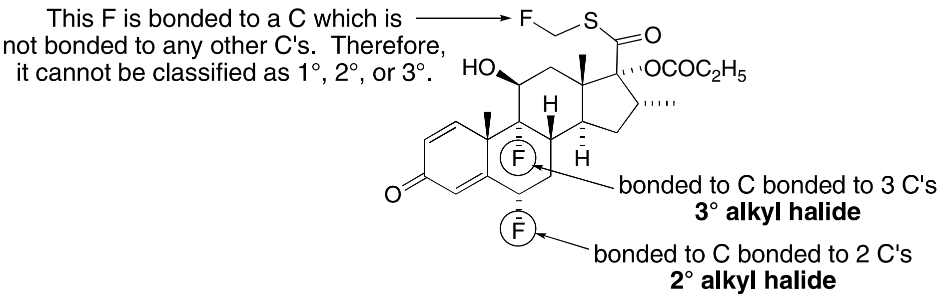
$$CH_3-\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}-\underset{\displaystyle Cl}{C}HCH_3$$

d.



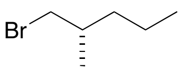
C bonded to 3 C's
3° alkyl halide

7.2 Use the directions from Answer 7.1.



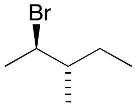
7.3 Draw a compound of molecular formula $C_6H_{13}Br$ to fit each description.

a.



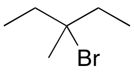
1° alkyl halide
one stereogenic center

b.



2° alkyl halide
two stereogenic centers

c.

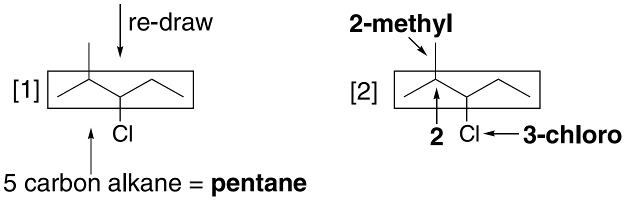


3° alkyl halide
no stereogenic centers

7.4 To name a compound with the IUPAC system:

[1] **Name the parent** chain by finding the longest carbon chain.
[2] **Number the chain** so the first substituent gets the lower number. Then **name and number all substituents**, giving like substituents a prefix (di, tri, etc.). **To name the halogen substituent, change the *-ine* ending to *-o*.**
[3] **Combine all parts**, alphabetizing substituents, and ignoring all prefixes except iso.

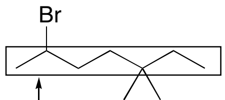
a. $(CH_3)_2CHCH(Cl)CH_2CH_3$



[3] **3-chloro-2-methylpentane**

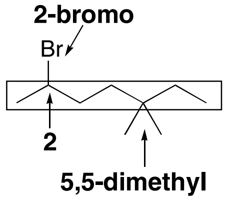
b.

[1]



7 carbon alkane = **heptane**

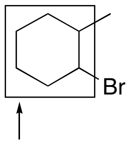
[2]



[3] **2-bromo-5,5-dimethylheptane**

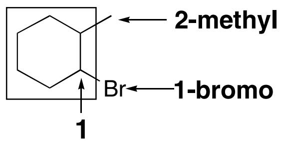
c.

[1]



6 carbon cycloalkane =
cyclohexane

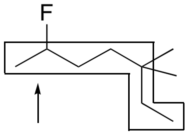
[2]



[3] **1-bromo-2-methylcyclohexane**

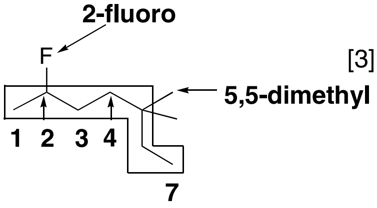
d.

[1]



7 carbon alkane = **heptane**

[2]



[3] **2-fluoro-5,5-dimethylheptane**

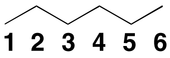
7.5 To work backwards from a name to a structure:

[1] Find the parent name and draw that number of carbons. Use the suffix to identify the functional group **(-ane = alkane).**

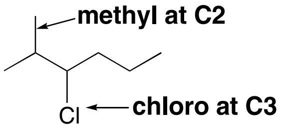
[2] Arbitrarily number the carbons in the chain. Add the substituents to the appropriate carbon.

a. 3-chloro-2-methyl**hexane**

[1] 6 carbon alkane

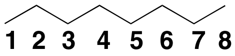


[2]

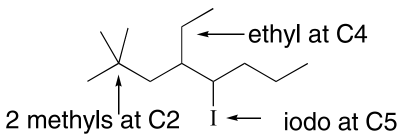


b. 4-ethyl-5-iodo-2,2-dimethyl**octane**

[1] 8 carbon alkane

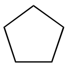


[2]

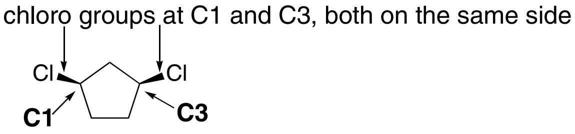


c. *cis*-1,3-dichloro**cyclopentane**

[1] 5 carbon cycloalkane

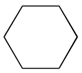


[2]

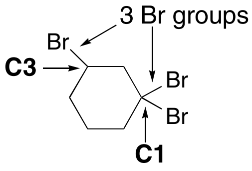


d. 1,1,3-tribromo**cyclohexane**

[1] 6 carbon cycloalkane



[2]



e. **propyl** chloride

[1] 3 carbon alkyl group

$CH_3CH_2CH_2—$

[2] **chloride on end**

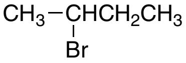
$CH_3CH_2CH_2-Cl$

f. ***sec*-butyl** bromide

[1] 4 carbon alkyl group

$CH_3-\underset{|}{C}HCH_2CH_3$

[2] **bromide**



$CH_3-\underset{\underset{Br}{|}}{C}HCH_2CH_3$

7.6 Boiling points of alkyl halides increase as the size (and polarizability) of X increases. Remember: **stronger intermolecular forces = higher boiling point.**

a. $CH_3CH_2CH_2F$
smallest halogen
least polarizable
lowest boiling point

$CH_3CH_3CH_2Cl$
middle size halogen
intermediate
boiling point

$CH_3CH_2CH_2I$
largest halogen
most polarizable
highest boiling point

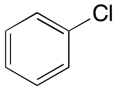
b. $CH_3(CH_2)_4CH_3$
weakest forces
nonpolar
lowest boiling point

$CH_3(CH_2)_5Br$
VDW, DD forces
intermediate
boiling point

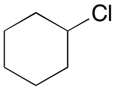
$CH_3(CH_2)_5OH$
OH is capable of hydrogen bonding.
strongest forces
highest boiling point

7.7 a. Because an *sp*^{2} hybridized C has a higher percent *s*-character than an *sp*^{3} hybridized C, it holds electron density closer to C. This pulls a little more electron density towards C, away from Cl, and thus a C*sp*^{2}–Cl bond is less polar than a C*sp*^{3}–Cl bond.

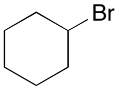
b.



lowest boiling point



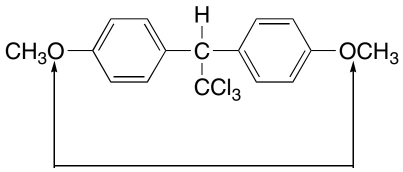
sp^3 C–Cl bond
intermediate
boiling point



larger halogen, *sp*^{3} C–Br bond
highest boiling point

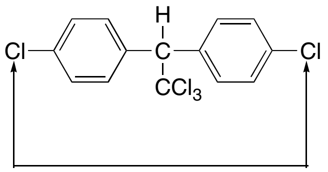
7.8 Since more polar molecules are more water soluble, look for polarity differences between methoxychlor and DDT.

methoxychlor



2 methoxy groups
more polar
The O atoms can hydrogen bond to H_2O.
more biodegradable

DDT



2 chloro groups
less polar
readily soluble in an organic medium

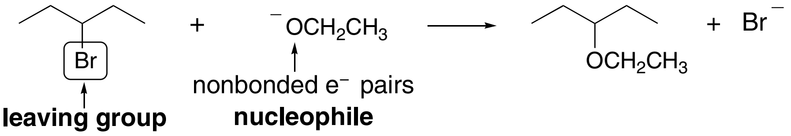
7.9 To draw the products of a nucleophilic substitution reaction:

[1] **Find the *sp*^{3} hybridized electrophilic carbon** with a leaving group.

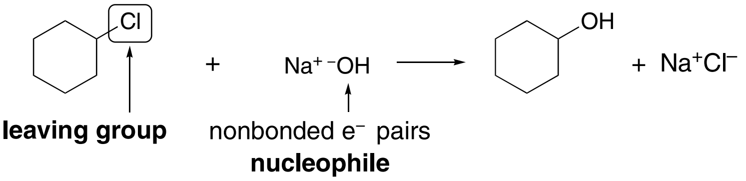
[2] **Find the nucleophile** with lone pairs or electrons in π bonds.

[3] **Substitute the nucleophile for the leaving group** on the electrophilic carbon.

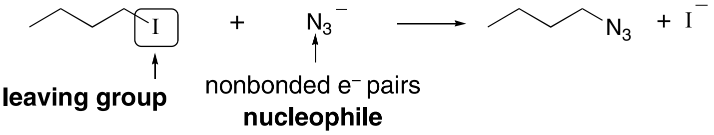
a.



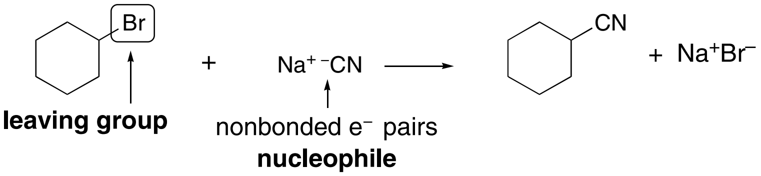
b.



c.

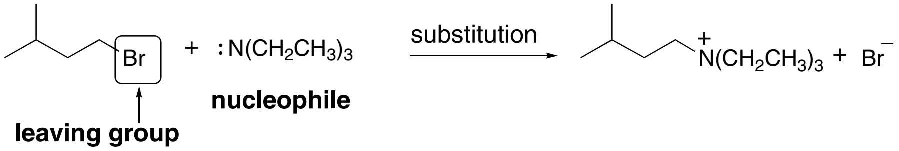


d.

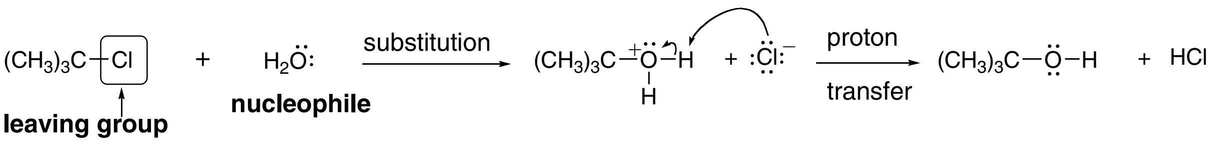


7.10 Use the steps from Answer 7.9 and then draw the proton transfer reaction.

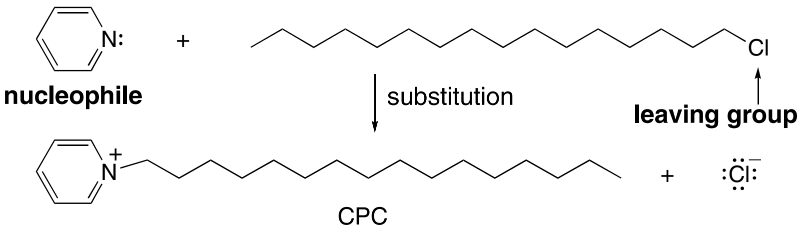
a.



b.



7.11 Draw the structure of CPC using the steps from Answer 7.9.



7.12 Compare the leaving groups based on these trends:

- Better leaving groups are weaker bases.
- A neutral leaving group is always better than its conjugate base.

a. Cl^-, $\underset{\uparrow}{I^-}$

farther down a column
of the periodic table
less basic
better leaving group

b. $\underset{\uparrow}{NH_3}$, NH_2^-

neutral compound
less basic
better leaving group

c. H_2O, $\underset{\uparrow}{H_2S}$

farther down a column
of the periodic table
less basic
better leaving group

7.13 Good leaving groups include Cl^-, Br^-, I^-, H_2O.

a. $CH_3CH_2CH_2-\boxed{Br}$

Br^- is a **good leaving group.**

b. $CH_3CH_2CH_2OH$

No good leaving group.
^-OH is too strong a base.

c. $CH_3CH_2CH_2-\boxed{\overset{+}{O}H_2}$

H_2O is a **good leaving group.**

d. CH_3CH_3

No good leaving group.
H^- is too strong a base.

7.14 To decide whether the equilibrium favors the starting material or the products, **compare the nucleophile and the leaving group.** The reaction proceeds towards the weaker base.

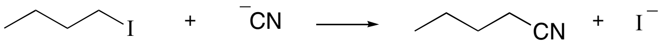
a. $CH_3CH_2-NH_2 \quad + \quad Br^- \longrightarrow CH_3CH_2-Br \quad + \quad ^-NH_2$

Br^-: **nucleophile**
better leaving group
weaker base
pK_a (HBr) = –9

$^-NH_2$: **leaving group**
pK_a (NH_3) = 38

Reaction favors starting material.

b.



^-CN: **nucleophile**
pK_a (HCN) = 9.1

I^-: **leaving group**
better leaving group
weaker base
pK_a (HI) = –10

Reaction favors product.

7.15 It is not possible to convert $CH_3CH_2CH_2OH$ to $CH_3CH_2CH_2Cl$ by nucleophilic substitution with NaCl because ^-OH is a stronger base and poorer leaving group than Cl^-. The equilibrium favors the reactants, not the products.

$$CH_3CH_2CH_2OH \quad + \quad \underset{\substack{\uparrow \\ \text{weaker base}}}{Na^+\,Cl^-} \quad \not\longrightarrow \quad CH_3CH_2CH_2Cl \quad + \quad \underset{\substack{\uparrow \\ \text{stronger base}}}{Na^+\ ^-OH}$$

7.16 Use these three rules to find the stronger nucleophile in each pair:

[1] Comparing two nucleophiles having the ***same attacking atom***, **the stronger base is a stronger nucleophile**.

[2] **Negatively charged nucleophiles** are always **stronger than their conjugate acids**.

[3] **Across a row of the periodic table**, **nucleophilicity decreases** when comparing species of similar charge.

a. NH_3, NH_2^-

A negatively charged nucleophile is stronger than its conjugate acid.
stronger nucleophile

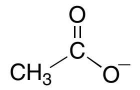
b. CH_3^-, HO^-

Across a row of the periodic table, nucleophilicity decreases with species of the same charge.
stronger nucleophile

c. CH_3NH_2, CH_3OH

Across a row of the periodic table, nucleophilicity decreases with species of the same charge.
stronger nucleophile

d.



$CH_3CH_2O^-$

same attacking atom (O)
stronger base
stronger nucleophile

7.17 ***Polar protic solvents*** **are capable of H-bonding**, and therefore must contain a **H bonded to an electronegative O or N**. ***Polar aprotic solvents*** **are incapable of H-bonding**, and therefore do not contain any O–H or N–H bonds.

a. $HOCH_2CH_2OH$

contains 2 O–H bonds
polar protic

b. $CH_3CH_2OCH_2CH_3$

no O–H bonds
polar aprotic

c. $CH_3COOCH_2CH_3$

no O–H bonds
polar aprotic

7.18 • In ***polar protic solvents*****, the trend in nucleophilicity is opposite to the trend in basicity** down a column of the periodic table so that nucleophilicity increases.

• In ***polar aprotic solvents*****, the trend is identical to basicity** so that nucleophilicity decreases down a column.

a. Br^- and Cl^- in polar protic solvent

farther down the column
more nucleophilic
in protic solvent

b. ^-OH and Cl^- in polar aprotic solvent

farther up the column
and to the left in the row
more basic
more nucleophilic

In polar aprotic solvents:
nucleophilicity increases ←

O F
Cl

↑ nucleophilicity increases

c. HS^- and F^- in polar protic solvent

farther down the column
and left in the row
more nucleophilic
in protic solvent

In polar protic solvents:
nucleophilicity increases ←

O F
S

↓ nucleophilicity increases

7.19 The stronger base is the stronger nucleophile except in polar protic solvents when nucleophilicity increases down a column. For other rules, see Answers 7.16 and 7.18.

a.	H_2O	^-OH	$^-NH_2$
	no charge **weakest nucleophile**	negatively charged **intermediate nucleophile**	negatively charged farther left in periodic table **strongest nucleophile**
b.	Br^-	F^-	^-OH
	Basicity decreases down a column in polar aprotic solvents. **weakest nucleophile**	Basicity decreases across a row. **intermediate nucleophile**	**strongest nucleophile**
c.	H_2O	CH_3COO^-	^-OH
	weakest nucleophile	weaker base than ^-OH **intermediate nucleophile**	**strongest nucleophile**

7.20 To determine what nucleophile is needed to carry out each reaction, look at the product to see what has replaced the leaving group.

a. $(CH_3)_2CHCH_2CH_2{-}Br \longrightarrow (CH_3)_2CHCH_2CH_2{-}SH$
SH replaces Br.
HS^- is needed.

b. $(CH_3)_2CHCH_2CH_2{-}Br \longrightarrow (CH_3)_2CHCH_2CH_2{-}OCH_2CH_3$
OCH_2CH_3 replaces Br.
$CH_3CH_2O^-$ is needed.

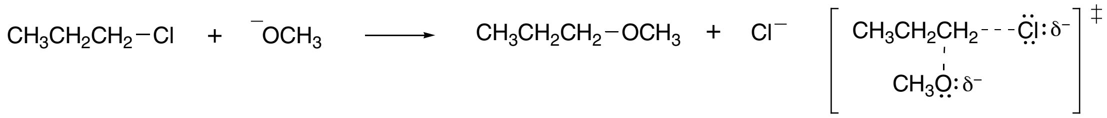
c. $(CH_3)_2CHCH_2CH_2{-}Br \longrightarrow (CH_3)_2CHCH_2CH_2{-}OCOCH_3$
$OCOCH_3$ replaces Br.
CH_3COO^- is needed.

d. $(CH_3)_2CHCH_2CH_2{-}Br \longrightarrow (CH_3)_2CHCH_2CH_2{-}C{\equiv}CH$
$C{\equiv}CH$ replaces Br.
$HC{\equiv}C^-$ is needed.

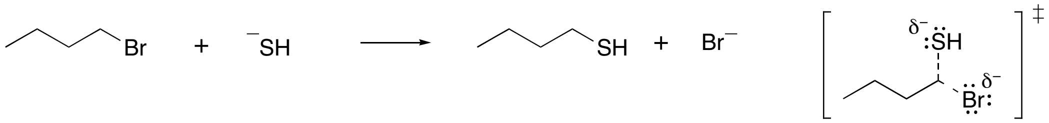
7.21 The general rate equation for an S_N2 reaction is rate = $k[RX][:Nu^-]$.

a. $[RX]$ is tripled, and $[:Nu^-]$ stays the same: **rate triples.**
b. Both $[RX]$ and $[:Nu^-]$ are tripled: **rate increases by a factor of 9 (3 × 3 = 9).**
c. $[RX]$ is halved, and $[:Nu^-]$ stays the same: **rate halved.**
d. $[RX]$ is halved, and $[:Nu^-]$ is doubled: **rate stays the same (1/2 × 2 = 1).**

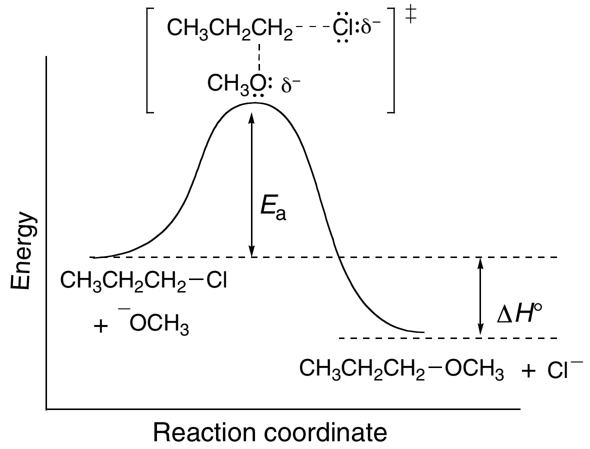
7.22 The transition state in an S_N2 reaction has **dashed bonds to both the leaving group and the nucleophile**, and must contain partial charges.

a.


$CH_3CH_2CH_2{-}Cl + {}^-OCH_3 \longrightarrow CH_3CH_2CH_2{-}OCH_3 + Cl^-$

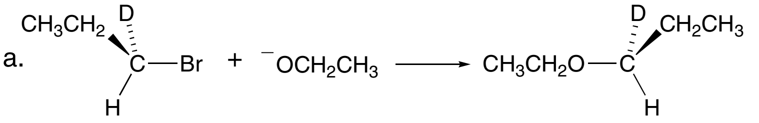
b.


7.23 All S_N2 reactions have one step.

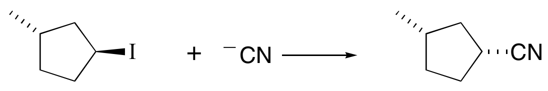


7.24 To draw the products of S_N2 reactions, **replace the leaving group by the nucleophile, and then draw the stereochemistry with *inversion* at the stereogenic center**.

a.



b.



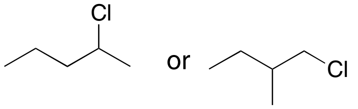
7.25 *Increasing* the number of R groups *increases* crowding of the transition state and *decreases* the rate of an S_N2 reaction.

a. CH_3CH_2-Cl or CH_3-Cl

1° alkyl halide

methyl halide **faster reaction**

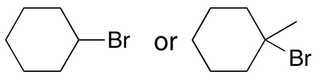
b.



2° alkyl halide

1° alkyl halide **faster reaction**

c.

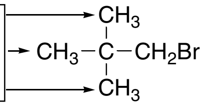


2° alkyl halide **faster reaction**

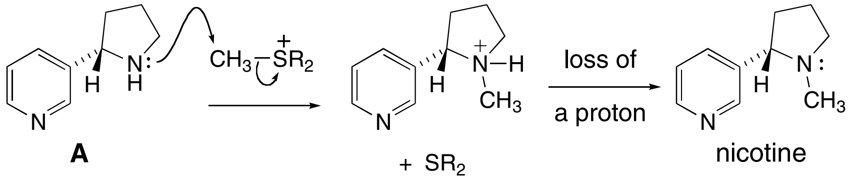
3° alkyl halide

7.26

These three methyl groups make the alkyl halide sterically hindered.
This slows the rate of an S_N2 reaction even though it is a 1° alkyl halide.



7.27



7.28 In a first-order reaction, **the rate changes with any change in [RX]**. The rate is independent of any change in [nucleophile].

a. [RX] is tripled, and [:Nu⁻] stays the same: **rate triples.**

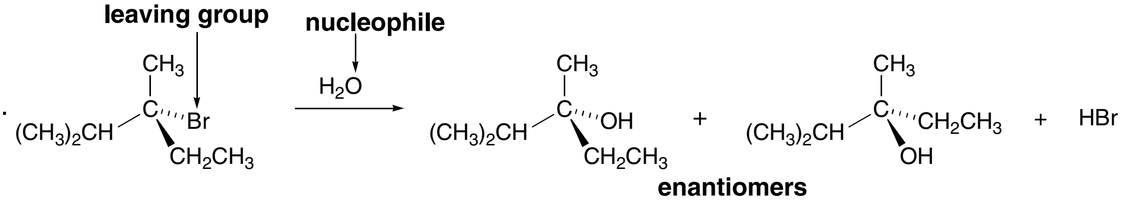
b. Both [RX] and [:Nu⁻] are tripled: **rate triples.**

c. [RX] is halved, and [:Nu⁻] stays the same: **rate halved.**

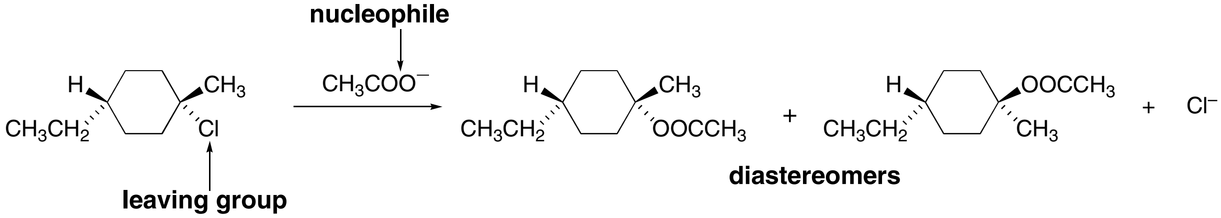
d. [RX] is halved, and [:Nu⁻] is doubled: **rate halved.**

7.29 In S_N1 reactions, racemization always occurs at a stereogenic center. Draw two products, with the two possible configurations at the stereogenic center.

a.

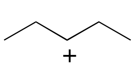


b.



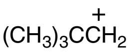
7.30 Carbocations are classified by the number of R groups bonded to the carbon: 0 R groups = methyl, 1 R group = 1°, 2 R groups = 2°, and 3 R groups = 3°.

a.



2 R groups
2° carbocation

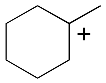
b.



$(CH_3)_3C\overset{+}{C}H_2$

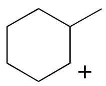
1 R group
1° carbocation

c.



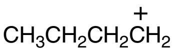
3 R groups
3° carbocation

d.



2 R groups
2° carbocation

7.31 For carbocations: Increasing number of R groups = Increasing stability.

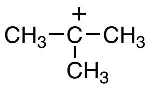


$CH_3CH_2CH_2\overset{+}{C}H_2$

1° carbocation
least stable

$CH_3\overset{+}{C}HCH_2CH_3$

2° carbocation
intermediate stability

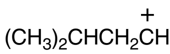


$CH_3-\underset{CH_3}{\overset{+}{C}}-CH_3$

3° carbocation
most stable

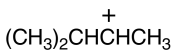
7.32 For carbocations: Increasing number of R groups = Increasing stability.

a.



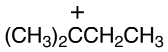
$(CH_3)_2CHCH_2\overset{+}{C}H_2$

1° carbocation
least stable



$(CH_3)_2CH\overset{+}{C}HCH_3$

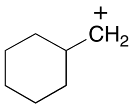
2° carbocation
intermediate stability



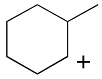
$(CH_3)_2\overset{+}{C}CH_2CH_3$

3° carbocation
most stable

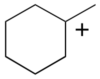
b.



1° carbocation
least stable



2° carbocation
intermediate stability



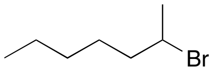
3° carbocation
most stable

7.33 The rate of an S_N1 reaction increases with increasing alkyl substitution.

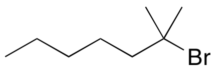
a. $(CH_3)_3CBr$ or $(CH_3)_3CCH_2Br$

3° alkyl halide
faster S_N1 reaction

1° alkyl halide
slower S_N1 reaction

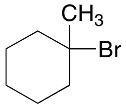
b.


or

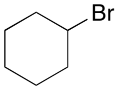


2° alkyl halide
slower S_N1 reaction

3° alkyl halide
faster S_N1 reaction

c.


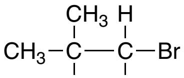
or



3° alkyl halide
faster S_N1 reaction

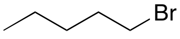
2° alkyl halide
slower S_N1 reaction

7.34 • For **methyl and 1° alkyl halides**, only S_N2 will occur.
• For **2° alkyl halides**, S_N1 and S_N2 will occur.
• For **3° alkyl halides**, only S_N1 will occur.

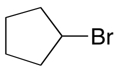
a.


$$CH_3-\underset{CH_3}{\overset{CH_3}{C}}-\underset{CH_3}{\overset{H}{C}}-Br$$

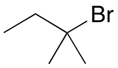
2° alkyl halide
S_N1 and S_N2

b.


1° alkyl halide
S_N2

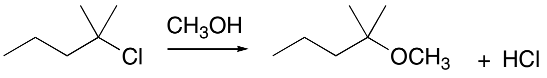
c.


2° alkyl halide
S_N1 and S_N2

d.


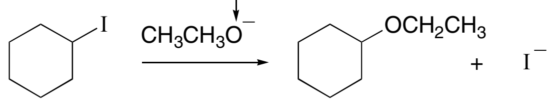
3° alkyl halide
S_N1

7.35 • Draw the product of nucleophilic substitution for each reaction.
• For **methyl and 1° alkyl halides**, only S_N2 will occur.
• For **2° alkyl halides**, S_N1 and S_N2 will occur and other factors determine which mechanism operates.
• For **3° alkyl halides**, only S_N1 will occur.

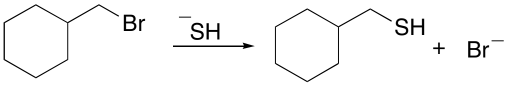
a.


3° alkyl halide
only S_N1

Strong nucleophile
favors S_N2.

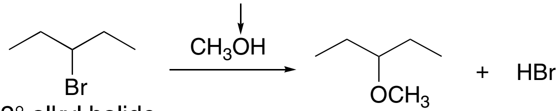
c.


2° alkyl halide
Both S_N1 and S_N2 are possible.

b.


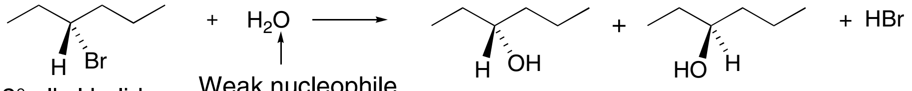
1° alkyl halide
only S_N2

Weak nucleophile
favors S_N1.

d.


2° alkyl halide
Both S_N1 and S_N2 are possible.

7.36 First decide whether the reaction will proceed via an S_N1 or S_N2 mechanism. Then draw the products with stereochemistry.

a.


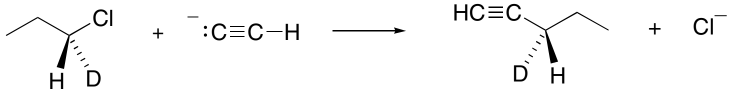
2° alkyl halide
S_N1 and S_N2

Weak nucleophile
favors S_N1.

enantiomers

S_N1 = racemization at the stereogenic C

b.



1° alkyl halide

S_N2 only

S_N2 = inversion at the stereogenic C

7.37 Compounds with better leaving groups react faster. Weaker bases are better leaving groups.

a. $CH_3CH_2CH_2Cl$ or $CH_3CH_2CH_2I$

$\uparrow$ weaker base

better leaving group

b. $(CH_3)_3CBr$ or $(CH_3)_3CI$

$\uparrow$ weaker base

better leaving group

c. $(CH_3)_3C{-}OH$ or $(CH_3)_3C{-}\boxed{\overset{+}{O}H_2}$

$\uparrow$ weaker base

better leaving group

d. $CH_3CH_2CH_2OH$ or $CH_3CH_2CH_2{-}\boxed{OCOCH_3}$

$\uparrow$ weaker base

better leaving group

7.38
- **Polar protic solvents** favor the S_N1 mechanism by solvating the intermediate carbocation and halide.
- **Polar aprotic solvents** favor the S_N2 mechanism by making the nucleophile stronger.

a. CH_3CH_2OH	b. CH_3CN	c. CH_3COOH	d. $CH_3CH_2OCH_2CH_3$
polar protic solvent	polar aprotic solvent	polar protic solvent	polar aprotic solvent
contains an O–H bond	no O–H or N–H bond	contains an O–H bond	no O–H or N–H bond
favors S_N1	**favors S_N2**	**favors S_N1**	**favors S_N2**

7.39 Compare the solvents in the reactions below. **For the solvent to increase the reaction rate of an S_N1 reaction, the solvent must be *polar protic.***

a. $(CH_3)_3CBr + H_2O \xrightarrow[\text{or } (CH_3)_2C=O]{H_2O} (CH_3)_3COH + HBr$

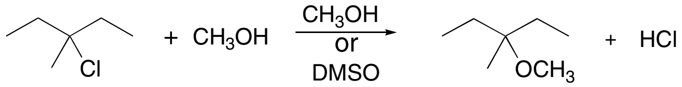
3° RX – S_N1 reaction

H_2O

Polar protic solvent

increases the rate of an S_N1 reaction.

b.



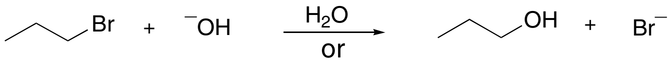
3° RX – S_N1 reaction

CH_3OH

Polar protic solvent

increases the rate of an S_N1 reaction.

c.



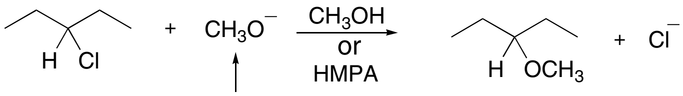
1° RX – S_N2 reaction

DMF $[HCON(CH_3)_2]$

Polar aprotic solvent

increases the rate of an S_N2 reaction.

d.



2° RX strong nucleophile

S_N2 reaction

HMPA $[(CH_3)_2N]_3P=O$

Polar aprotic solvent

increases the rate of an S_N2 reaction.

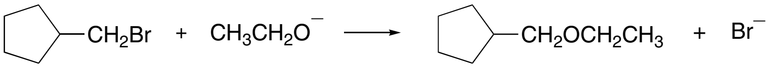
7.40 To predict whether the reaction follows an S_N1 or S_N2 mechanism:

[1] **Classify RX as a methyl, 1°, 2°, or 3° halide**. (Methyl, 1° = S_N2; 3° = S_N1; 2° = either.)

[2] **Classify the nucleophile as strong or weak**. (Strong favors S_N2; weak favors S_N1.)

[3] **Classify the solvent as polar protic or polar aprotic**. (Polar protic favors S_N1; polar aprotic favors S_N2.)

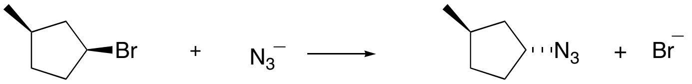
a.



1° alkyl halide
S_N2

S_N2 reaction

b.

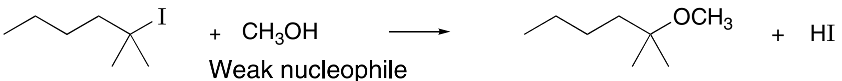


2° alkyl halide
S_N1 or S_N2

Strong nucleophile
favors S_N2.

S_N2 reaction = ***inversion*** at the stereogenic center
The leaving group was "up."
The nucleophile attacks from below.

c.

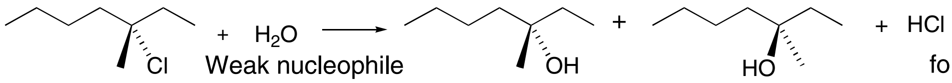


3° alkyl halide
S_N1

Weak nucleophile
favors S_N1.

S_N1 reaction

d.



3° alkyl halide
S_N1

Weak nucleophile
favors S_N1.

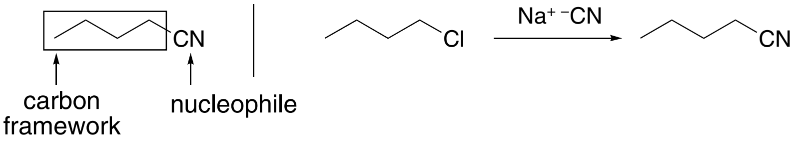
S_N1 reaction
forms **two enantiomers.**

7.41 Vinyl carbocations are even less stable than 1° carbocations.

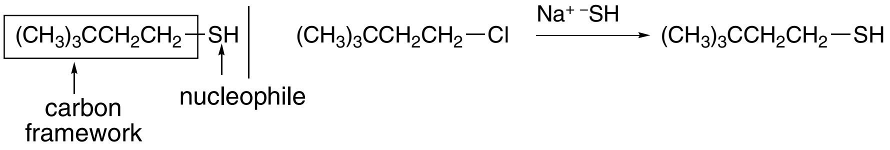
$CH_3CH_2CH_2CH_2CH{=}\overset{+}{C}H$	$CH_3CH_2CH_2CH_2CH_2\overset{+}{C}H_2$	$CH_3CH_2CH_2CH_2\overset{+}{C}HCH_3$
vinyl carbocation **least stable**	1° carbocation **intermediate stability**	2° carbocation **most stable**

7.42

a.

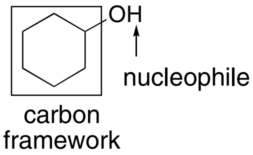


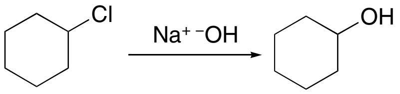
b.



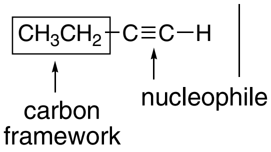
$(CH_3)_3CCH_2CH_2{-}Cl \xrightarrow{Na^+\,^-SH} (CH_3)_3CCH_2CH_2{-}SH$

c.



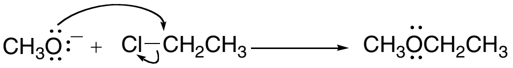


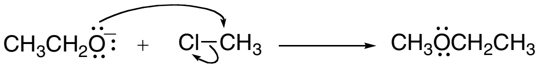
d.



$CH_3CH_2{-}Cl \xrightarrow{Na^{+}\,{}^{-}C{\equiv}CH} CH_3CH_2{-}C{\equiv}C{-}H$

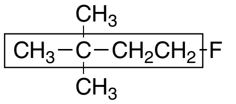
7.43





7.44 Use the directions from Answer 7.4 to name the compounds.

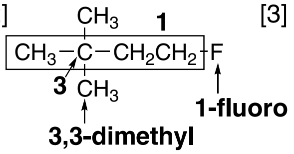
a. [1]



$CH_3{-}C(CH_3)_2{-}CH_2CH_2{-}F$

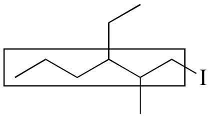
4 carbon alkane = **butane**

[2]



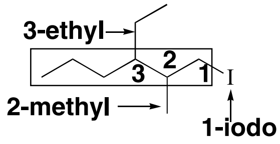
[3] **1-fluoro-3,3-dimethylbutane**

b.[1]



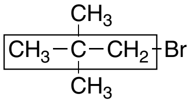
6 carbon alkane = **hexane**

[2]



[3] **3-ethyl-1-iodo-2-methylhexane**

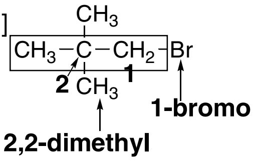
c.[1] $(CH_3)_3CCH_2Br$



$CH_3{-}C(CH_3)_2{-}CH_2{-}Br$

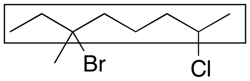
3 carbon alkane = **propane**

[2]



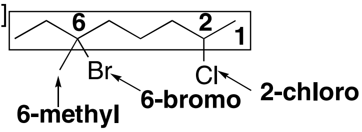
[3] **1-bromo-2,2-dimethylpropane**

d.[1]



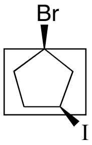
8 carbon alkane = **octane**

[2]



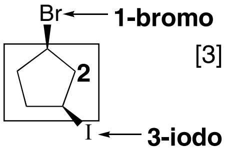
[3] **6-bromo-2-chloro-6-methyloctane**

e.[1]



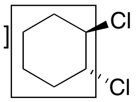
5 carbon cycloalkane = **cyclopentane**

[2]



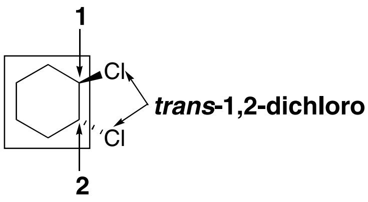
[3] ***cis*-1-bromo-3-iodocyclopentane**

f. [1]



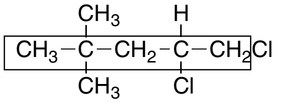
6 carbon cycloalkane = **cyclohexane**

[2]



[3] ***trans*-1,2-dichlorocyclohexane**

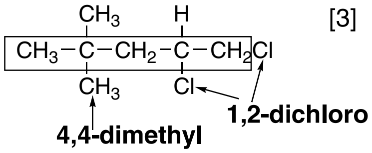
g.[1] $(CH_3)_3CCH_2CH(Cl)CH_2Cl$



$CH_3-\overset{CH_3}{\underset{CH_3}{C}}-CH_2-\overset{H}{\underset{Cl}{C}}-CH_2Cl$

5 carbon alkane = **pentane**

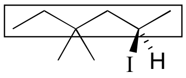
[2]



$CH_3-\overset{CH_3}{\underset{CH_3}{C}}-CH_2-\overset{H}{\underset{Cl}{C}}-CH_2Cl$

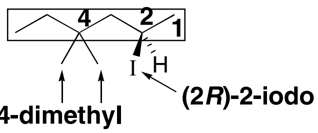
[3] **1,2-dichloro-4,4-dimethylpentane**

h.[1]

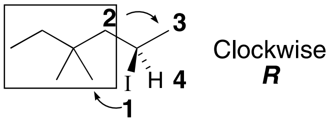


6 carbon alkane = **hexane**
(Indicate the *R*/*S*
designation also)

[2]

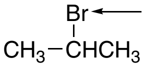


[3] **(2*R*)-2-iodo-4,4-dimethylhexane**



7.45 To work backwards to a structure, use the directions in Answer 7.5.

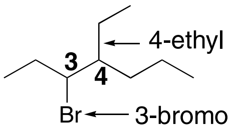
a. **isopropyl** bromide



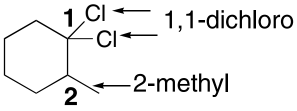
$CH_3-\overset{Br}{C}HCH_3$

Bromine on middle C makes it an isopropyl group.

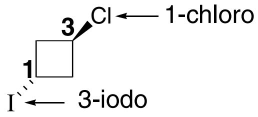
b. 3-bromo-4-ethyl**heptane**



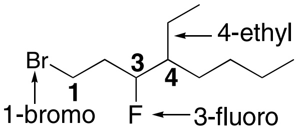
c. 1,1-dichloro-2-methyl**cyclohexane**



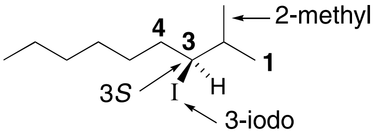
d. *trans*-1-chloro-3-iodo**cyclobutane**



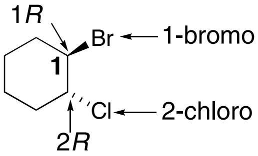
e. 1-bromo-4-ethyl-3-fluoro**octane**



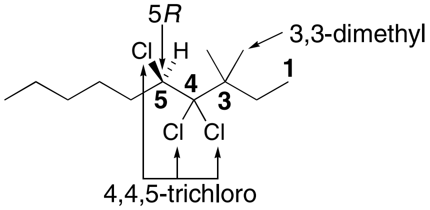
f. (3*S*)-3-iodo-2-methyl**nonane**



g. (1*R*,2*R*)-*trans*-1-bromo-2-chloro**cyclohexane**

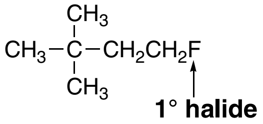


h. (5*R*)-4,4,5-trichloro-3,3-dimethyl**decane**



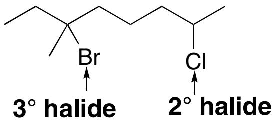
7.46

a.

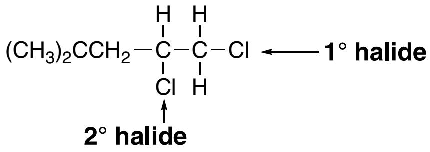


$$CH_3-\overset{CH_3}{\underset{CH_3}{C}}-CH_2CH_2F$$

d.

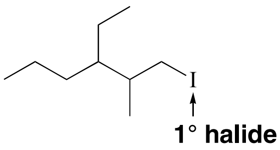


g.

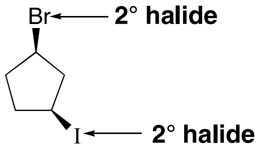


$$(CH_3)_2CCH_2-\overset{H}{\underset{Cl}{C}}-\overset{H}{\underset{H}{C}}-Cl$$

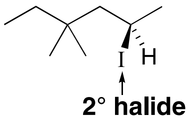
b.



e.



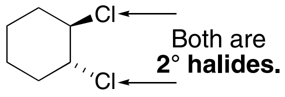
h.



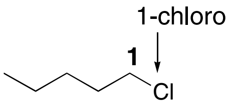
c. $(CH_3)_3CCH_2Br$

1° halide

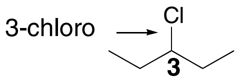
f.



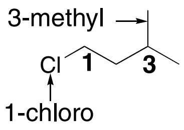
7.47



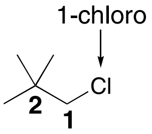
1-chloropentane



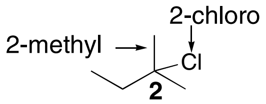
3-chloropentane



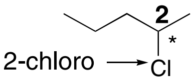
1-chloro-3-methylbutane



1-chloro-2,2-dimethylpropane

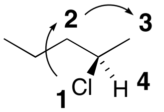


2-chloro-2-methylbutane

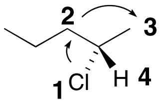


2-chloropentane
[* denotes stereogenic center]

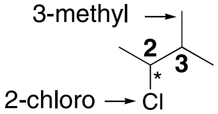
Two stereoisomers



Clockwise
"4" in *back* =
R

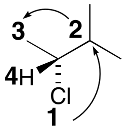


Clockwise
"4" in *front* =
S

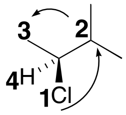


2-chloro-3-methylbutane
[* denotes stereogenic center]

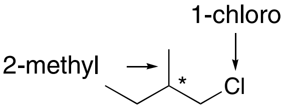
Two stereoisomers



Counterclockwise
"4" in *front* =
R

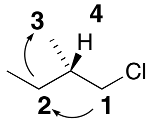


Counterclockwise
"4" in *back* =
S

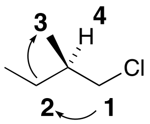


1-chloro-2-methylbutane
[* denotes stereogenic center]

Two stereoisomers

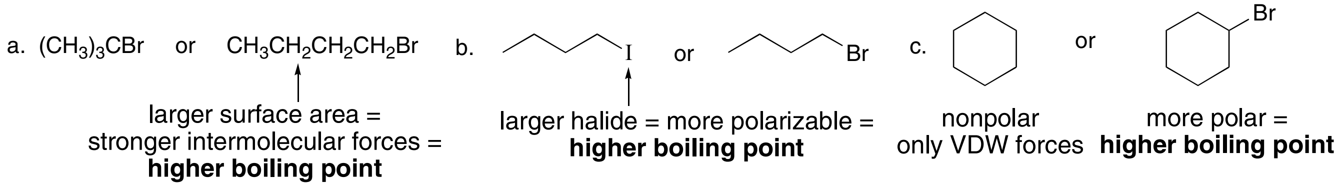


Clockwise
"4" in *front* =
S



Clockwise
"4" in *back* =
R

7.48 Use the directions from Answer 7.6.



7.49

a. $CH_3CH_2CH_2CH_2{-}Br + {}^{-}OH \longrightarrow CH_3CH_2CH_2CH_2OH + Br^{-}$

b. $CH_3CH_2CH_2CH_2{-}Br + {}^{-}SH \longrightarrow CH_3CH_2CH_2CH_2SH + Br^{-}$

c. $CH_3CH_2CH_2CH_2{-}Br + {}^{-}CN \longrightarrow CH_3CH_2CH_2CH_2CN + Br^{-}$

d. $CH_3CH_2CH_2CH_2{-}Br + {}^{-}OCH(CH_3)_2 \longrightarrow CH_3CH_2CH_2CH_2OCH(CH_3)_2 + Br^{-}$

e. $CH_3CH_2CH_2CH_2{-}Br + {}^{-}C{\equiv}CH \longrightarrow CH_3CH_2CH_2CH_2C{\equiv}CH + Br^{-}$

f. $CH_3CH_2CH_2CH_2{-}Br + H_2\ddot{O}\!: \longrightarrow CH_3CH_2CH_2CH_2\overset{+}{\underset{\cdot\cdot}{O}}H_2 + Br^{-} \longrightarrow CH_3CH_2CH_2CH_2OH + HBr$

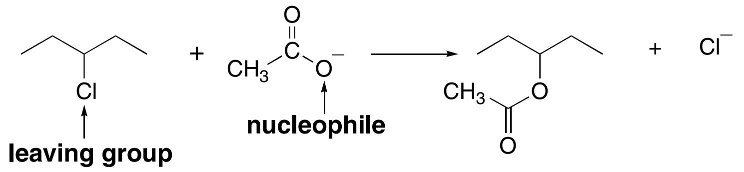
g. $CH_3CH_2CH_2CH_2{-}Br + \ddot{N}H_3 \longrightarrow CH_3CH_2CH_2CH_2\overset{+}{N}H_3 + Br^{-} \longrightarrow CH_3CH_2CH_2CH_2NH_2 + HBr$

h. $CH_3CH_2CH_2CH_2{-}Br + Na^{+}\,I^{-} \longrightarrow CH_3CH_2CH_2CH_2I + Na^{+}\,Br^{-}$

i. $CH_3CH_2CH_2CH_2{-}Br + Na^{+}\,N_3^{-} \longrightarrow CH_3CH_2CH_2CH_2N_3 + Na^{+}\,Br^{-}$

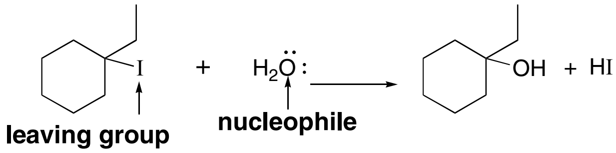
7.50 Use the steps from Answer 7.9 and then draw the proton transfer reaction, when necessary.

a.

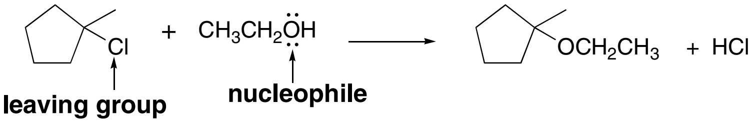


b.

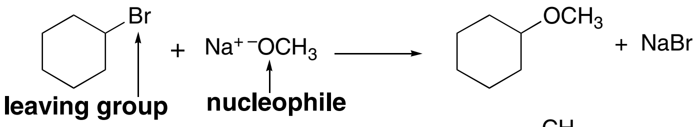
c.



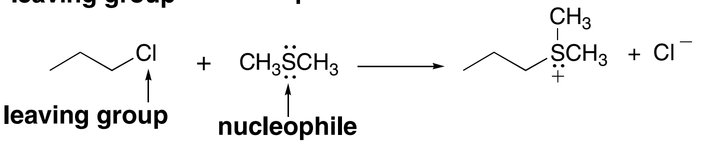
d.



e.

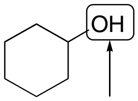


f.



7.51 A good leaving group is a weak base.

a.

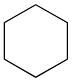


bad leaving group
^-OH is a strong base.

b. $CH_3CH_2CH_2CH_2\boxed{Cl}$

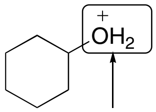
Cl^- good leaving group
weak base

c.



This has only C–C
and C–H bonds.
No good leaving group.

d.



good leaving group
H_2O is a weak base.

e. $CH_3CH_2\boxed{NH_2}$

bad leaving group
$^-NH_2$ is a strong base.

f. $CH_3CH_2CH_2\boxed{I}$

I^- good leaving group
weak base

7.52 Use the rules from Answer 7.12.

a. increasing leaving group ability: $^-NH_2 < {}^-OH < F^-$

$^-NH_2$: most basic **worst leaving group**
F^-: least basic **best leaving group**

b. increasing leaving group ability: $^-NH_2 < {}^-OH < H_2O$

$^-NH_2$: most basic **worst leaving group**
H_2O: least basic **best leaving group**

c. increasing leaving group ability: $Cl^- < Br^- < I^-$

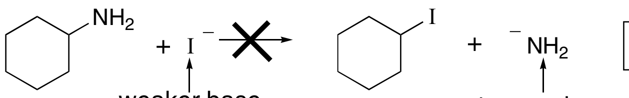
Cl^-: most basic **worst leaving group**
I^-: least basic **best leaving group**

d. increasing leaving group ability: $NH_3 < H_2O < H_2S$

NH_3: most basic **worst leaving group**
H_2S: least basic **best leaving group**

7.53 Compare the nucleophile and the leaving group in each reaction. The reaction will occur if it proceeds towards the weaker base. Remember that the stronger the acid (lower pK_a), the weaker the conjugate base.

a.



weaker base
pK_a (HI) = –10

stronger base
pK_a (NH_3) = 38

Reaction will not occur.

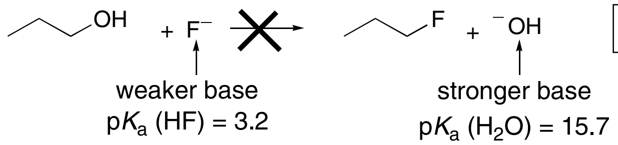
b. $CH_3CH_2I + CH_3O^- \longrightarrow CH_3CH_2OCH_3 + I^-$

stronger base
pK_a (CH_3OH) = 15.5

weaker base
pK_a (HI) = –10

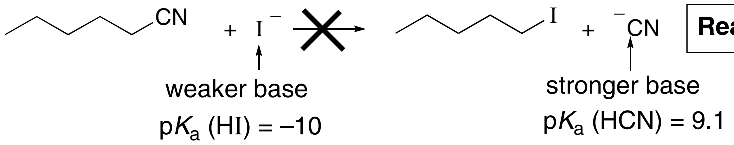
Reaction will occur.

c.



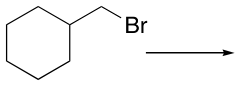
Reaction will not occur.

d.



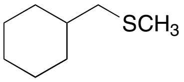
Reaction will not occur.

7.54



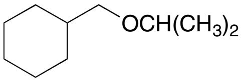
A

a.



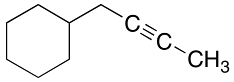
SCH_3 replaces Br.
$^-SCH_3$ is needed.

b.



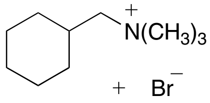
$OCH(CH_3)_2$ replaces Br.
$^-OCH(CH_3)_2$ needed.

c.



$C{\equiv}CCH_3$ replaces Br.
$^-C{\equiv}CCH_3$ is needed.

d.



$N(CH_3)_3$ replaces Br.
$N(CH_3)_3$ is needed.

7.55 Use the directions in Answer 7.16.

a. Across a row of the periodic table nucleophilicity decreases.

$^-OH < {}^-NH_2 < CH_3^-$

b. • In a **polar protic solvent** (CH_3OH), nucleophilicity *increases down a column* of the periodic table, so: ^-SH is more nucleophilic than ^-OH.
- *Negatively charged species* are more nucleophilic than neutral species so ^-OH is more nucleophilic than H_2O.

$H_2O < {}^-OH < {}^-SH$

c. • In a **polar protic solvent** (CH_3OH), nucleophilicity *increases down a column* of the periodic table, so: $CH_3CH_2S^-$ is more nucleophilic than $CH_3CH_2O^-$.
- For two species with the same attacking atom, the more basic is the more nucleophilic so $CH_3CH_2O^-$ is more nucleophilic than CH_3COO^-.

$CH_3COO^- < CH_3CH_2O^- < CH_3CH_2S^-$

d. Compare the nucleophilicity of N, S, and O. In a polar aprotic solvent (acetone), nucleophilicity parallels basicity.

$CH_3SH < CH_3OH < CH_3NH_2$

e. In a **polar aprotic solvent** (acetone), nucleophilicity parallels basicity. Across a row and down a column of the periodic table nucleophilicity decreases.

$Cl^- < F^- < {}^-OH$

f. Nucleophilicity decreases across a row so ^-SH is more nucleophilic than Cl^-. In a **polar protic solvent** (CH_3OH), nucleophilicity increases down a column so Cl^- is more nucleophilic than F^-.

$F^- < Cl^- < {}^-SH$

7.56 ***Polar protic solvents* are capable of hydrogen bonding**, and therefore must contain a H bonded to an electronegative O or N. ***Polar aprotic solvents* are incapable of hydrogen bonding**, and therefore do not contain any O–H or N–H bonds.

a. $(CH_3)_2CHOH$
contains O–H bond
protic

b. CH_3NO_2
no O–H or N–H bond
aprotic

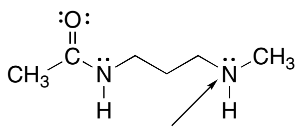
c. CH_2Cl_2
no O–H or N–H bond
aprotic

d. NH_3
contains N–H bond
protic

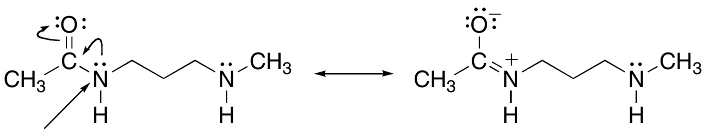
e. $N(CH_3)_3$
no O–H or N–H bond
aprotic

f. $HCONH_2$
contains an N–H bond
protic

7.57



The amine N is more nucleophilic since the electron pair is localized on the N.

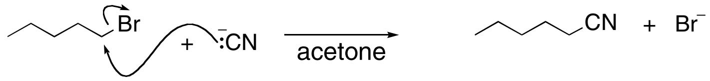


The amide N is less nucleophilic since the electron pair is delocalized by resonance.

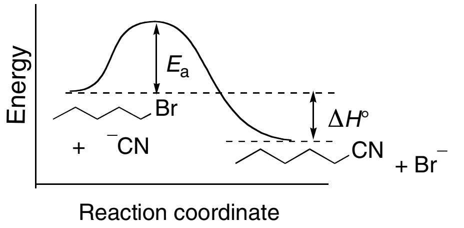
7.58

1° alkyl halide
S_N2 reaction

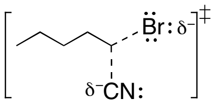
a. Mechanism:



b. Energy diagram:



c. Transition state:

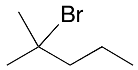


d. Rate equation**:** one step reaction with both nucleophile and alkyl halide in the only step:
rate = k[R–Br][$^-$CN]

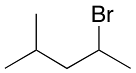
e. [1] The leaving group is changed from Br^- to I^-:
Leaving group becomes less basic → a better leaving group → faster reaction.
[2] The solvent is changed from acetone to CH_3CH_2OH:
Solvent changed to polar protic → decreases reaction rate.
[3] The alkyl halide is changed from $CH_3(CH_2)_4Br$ to $CH_3CH_2CH_2CH(Br)CH_3$:
Changed from 1° to 2° alkyl halide → the alkyl halide gets more crowded and the reaction rate decreases.
[4] The concentration of $^-$CN is increased by a factor of 5.
Reaction rate will increase by a factor of 5.
[5] The concentration of both the alkyl halide and $^-$CN are increased by a factor of 5:
Reaction rate will increase by a factor of 25 (5 x 5 = 25).

7.59 Use the directions for Answer 7.25.

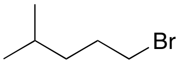
a.



3° alkyl halide
least reactive

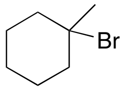


2° alkyl halide
intermediate reactivity

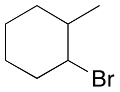


1° alkyl halide
most reactive

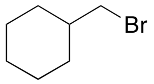
b.



3° alkyl halide
least reactive

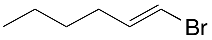


2° alkyl halide
intermediate reactivity

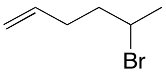


1° alkyl halide
most reactive

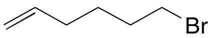
c.



vinyl halide
least reactive



2° alkyl halide
intermediate reactivity



1° alkyl halide
most reactive

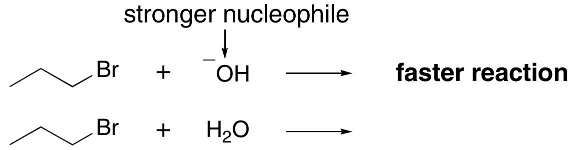
7.60

better leaving group

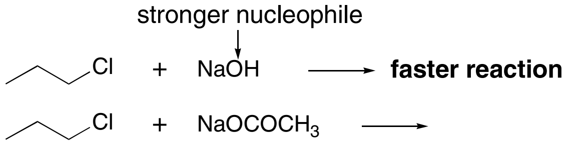
a. $CH_3CH_2Br \quad + \quad {}^{-}OH \longrightarrow$ **faster reaction**

$CH_3CH_2Cl \quad + \quad {}^{-}OH \longrightarrow$

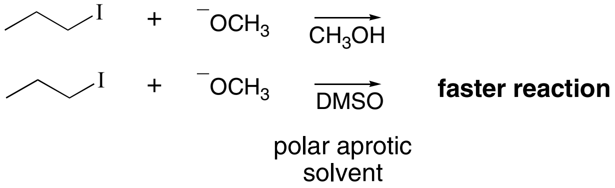
b.



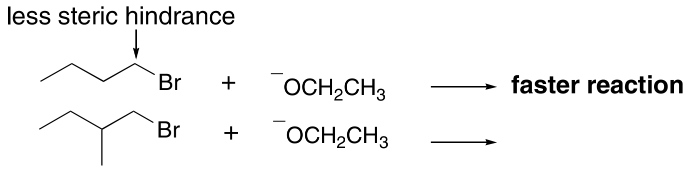
c.



d.

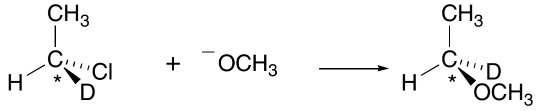


e.



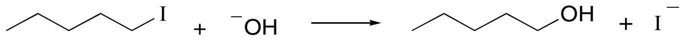
7.61 All S_N2 reactions proceed with backside attack of the nucleophile. When nucleophilic attack occurs at a stereogenic center, inversion of configuration occurs.

a.

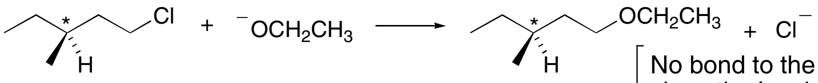


inversion of configuration

b.

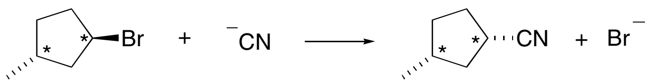


c.



No bond to the stereogenic center is broken, since the leaving group is not bonded to the stereogenic center.

d.

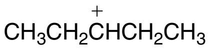


inversion of configuration

[* denotes a stereogenic center]

7.62 Follow the definitions from Answer 7.30.

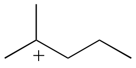
a.



$CH_3CH_2\overset{+}{C}HCH_2CH_3$

2° carbocation

b.



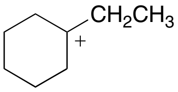
3° carbocation

c.

$(CH_3)_2CHCH_2\overset{+}{C}H_2$

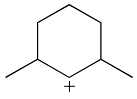
1° carbocation

d.



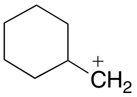
3° carbocation

e.



2° carbocation

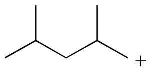
f.



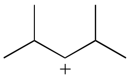
1° carbocation

7.63 For carbocations: **Increasing number of R groups = Increasing stability**.

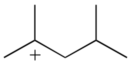
a.



1° carbocation
least stable

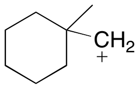


2° carbocation
intermediate stablity

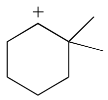


3° carbocation
most stable

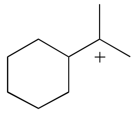
b.



1° carbocation
least stable

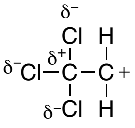


2° carbocation
intermediate stablity

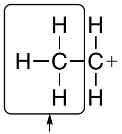


3° carbocation
most stable

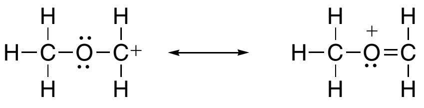
7.64



3 Cl groups –
electron-*withdrawing*
destabilizing
least stable



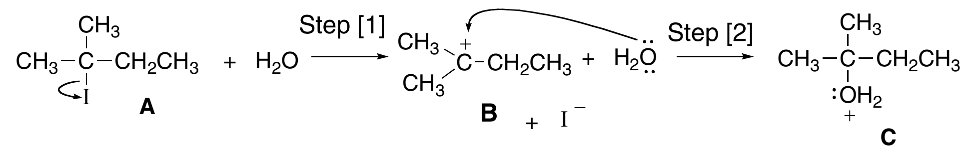
methyl group
without added Cl's
more stable



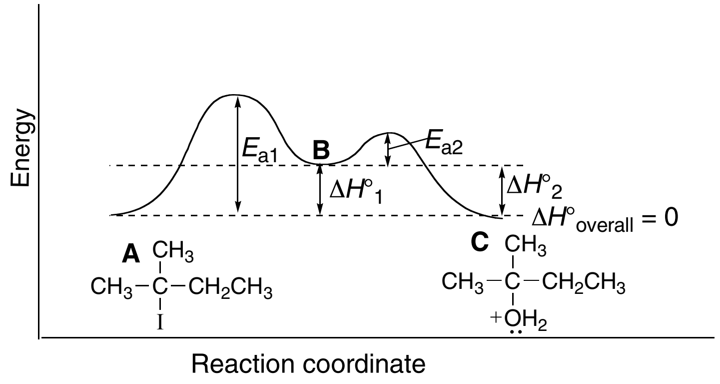
resonance stabilized
most stable

7.65

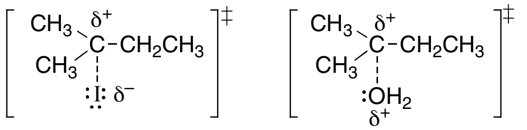
a. Mechanism:
S_N1 only



b. Energy diagram:



c. Transition states:

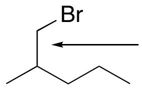


d. rate equation: **rate = $k[(CH_3)_2CICH_2CH_3]$**

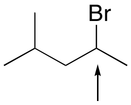
e. [1] Leaving group changed from I^- to Cl^-: **rate decreases** since I^- is a better leaving group.
[2] Solvent changed from H_2O (polar protic) to DMF (polar aprotic):
rate decreases since polar protic solvent favors S_N1.
[3] Alkyl halide changed from 3° to 2°: **rate decreases** since 2° carbocations are less stable.
[4] $[H_2O]$ increased by factor of five: **no change in rate** since H_2O is not in rate equation.
[5] [R–X] and $[H_2O]$ increased by factor of five: **rate increases** by a factor of five. (Only the concentration of R–X affects the rate.)

7.66 The rate of an S_N1 reaction increases with increasing alkyl substitution.

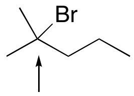
a.



1° alkyl halide
least reactive

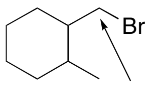


2° alkyl halide
intermediate reactivity

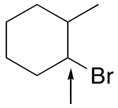


3° alkyl halide
most reactive

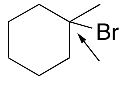
b.



1° alkyl halide
least reactive

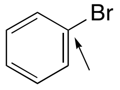


2° alkyl halide
intermediate reactivity

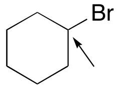


3° alkyl halide
most reactive

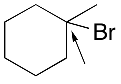
c.



aryl halide
least reactive

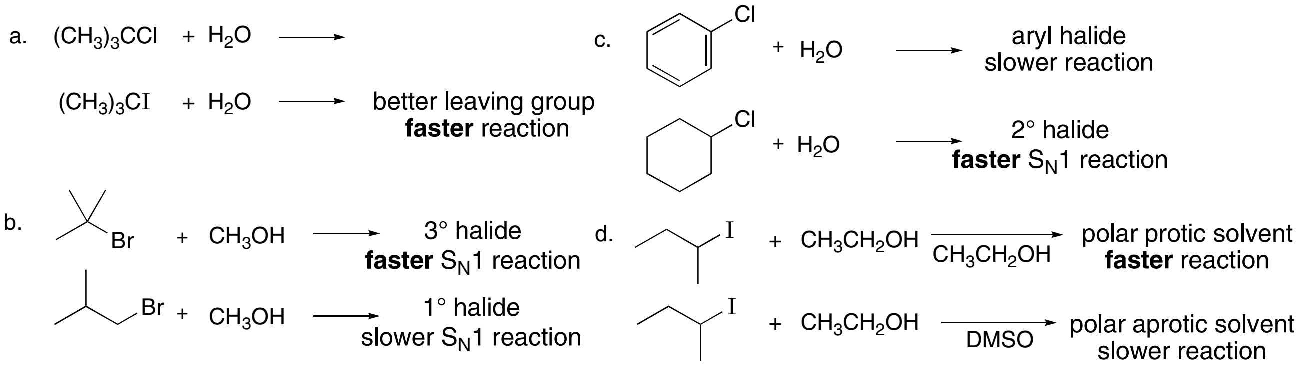


2° alkyl halide
intermediate reactivity

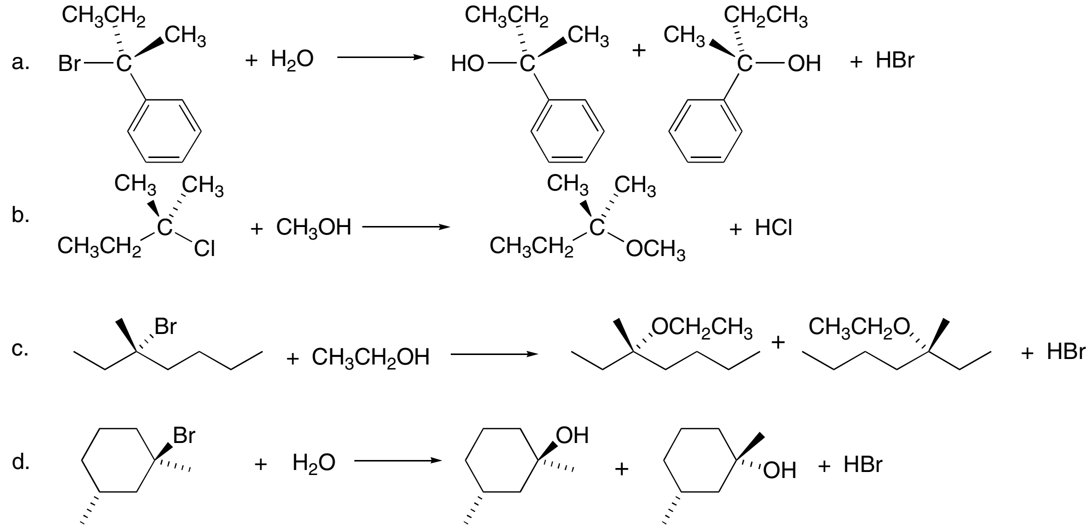


3° alkyl halide
most reactive

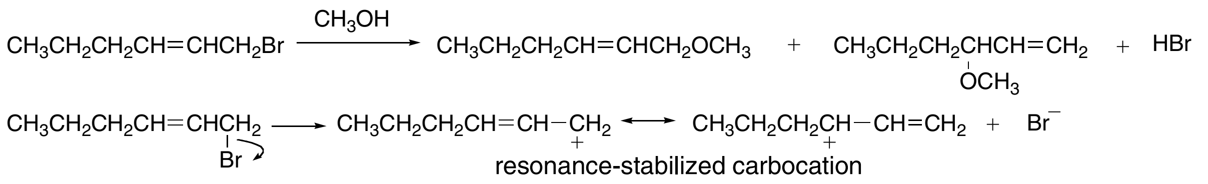
7.67 The rate of an S_N1 reaction increases with increasing alkyl substitution, polar protic solvents, and better leaving groups.



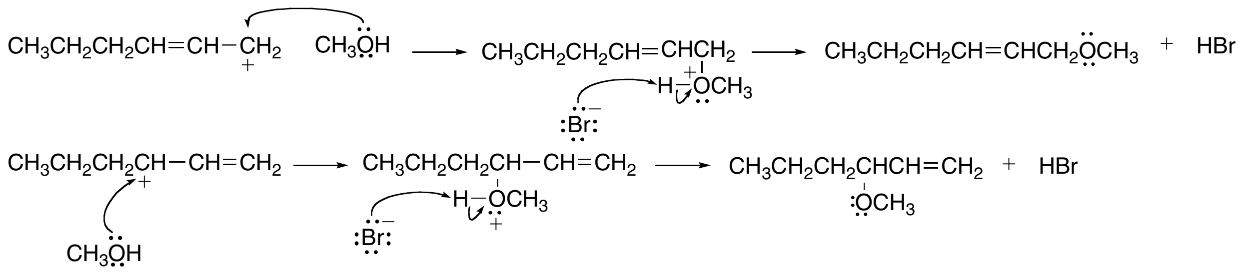
7.68



7.69 The 1° alkyl halide is also allylic, so it forms a resonance-stabilized carbocation. Increasing the stability of the carbocation by resonance, increases the rate of the S_N1 reaction.

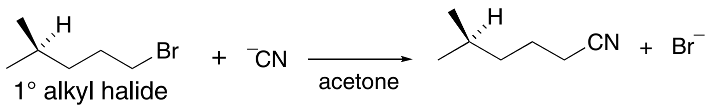


Use each resonance structure individually to continue the mechanism:



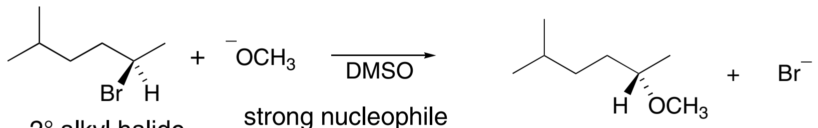
7.70

a.



1° alkyl halide
S_N2 only

b.

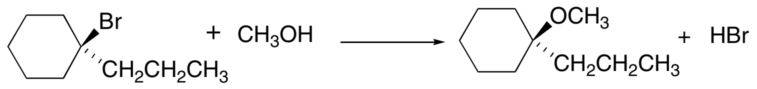


2° alkyl halide
S_N1 and S_N2

strong nucleophile
polar aprotic solvent
Both favor S_N2.

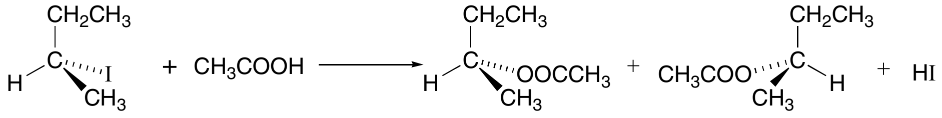
reaction at a stereogenic center
inversion of configuration

c.



3° alkyl halide
S_N1 only

d.



2° alkyl halide
S_N1 and S_N2

Weak nucleophile
favors S_N1.

reaction at a stereogenic center
racemization of product

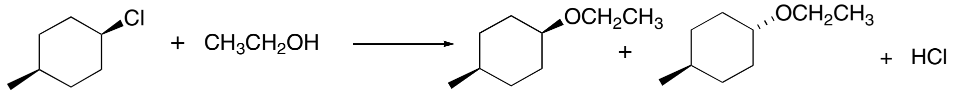
e.

2° alkyl halide
S_N1 and S_N2

strong nucleophile
polar aprotic solvent
Both favor S_N2.

reaction at a stereogenic center
inversion of configuration

f.



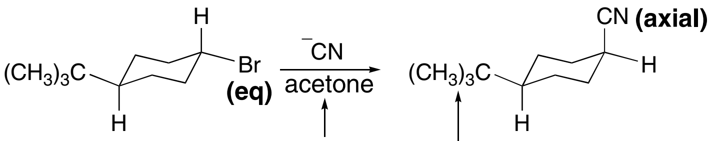
2° alkyl halide
S_N1 and S_N2

Weak nucleophile
favors S_N1.

two products – **diastereomers**
Nucleophile attacks
from above and below.

7.71

a.

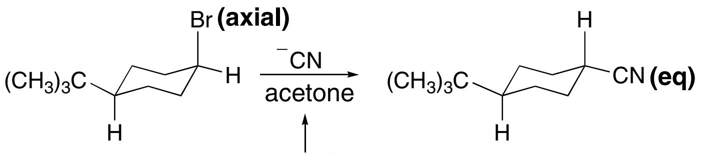


inversion (equatorial to axial)

polar aprotic solvent
S_N2 reaction

Large *tert*-butyl group in
more roomy equatorial
position.

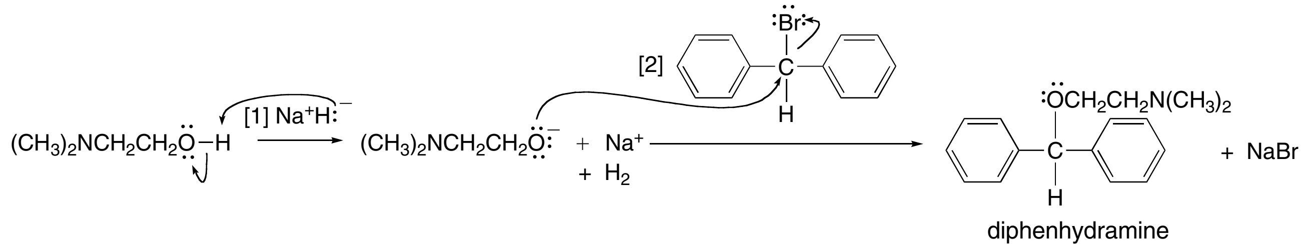
b.



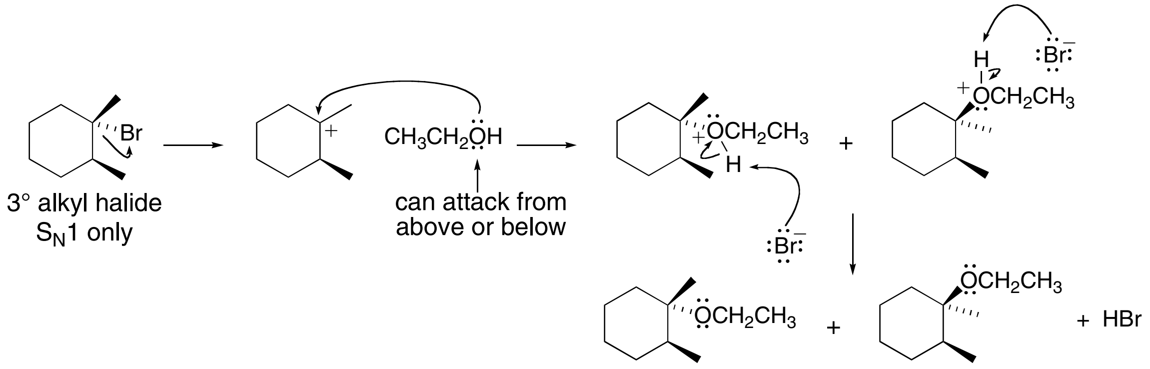
inversion (axial to equatorial)

polar aprotic solvent
S_N2 reaction

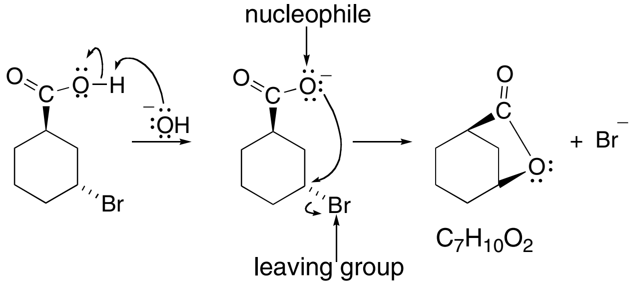
7.72



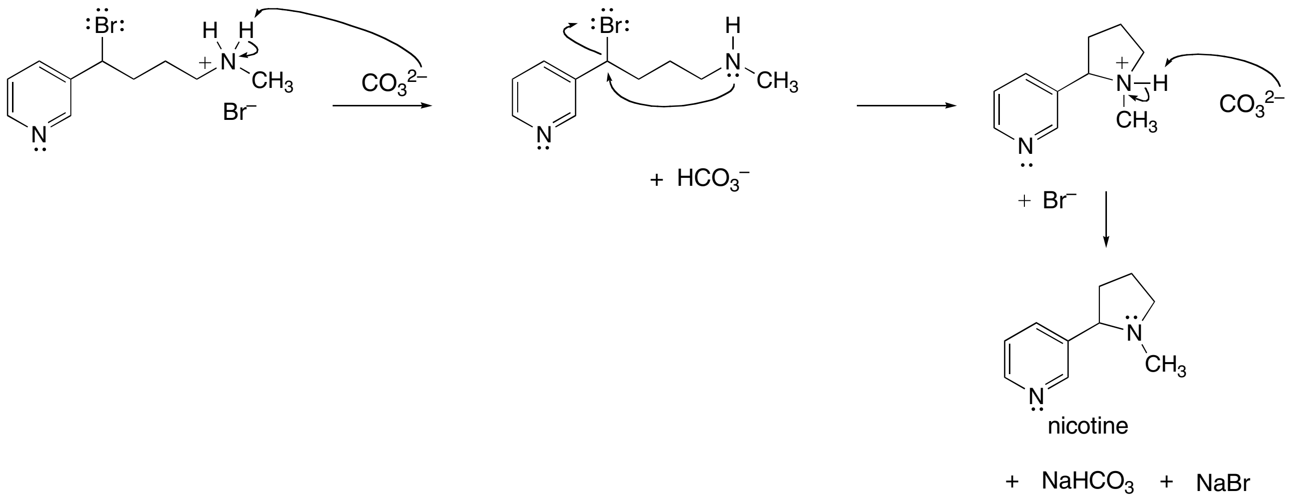
7.73 First decide whether the reaction will proceed via an S_N1 or S_N2 mechanism (Answer 7.40), and then draw the mechanism.



7.74



7.75



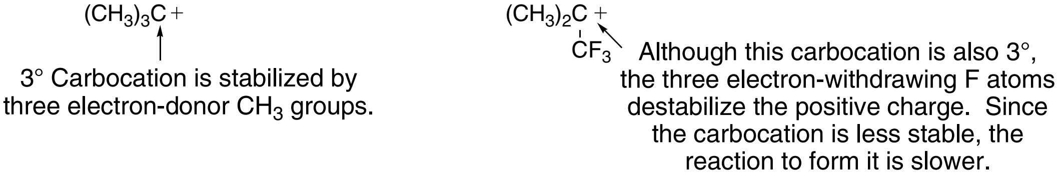
7.76

a. Hexane is nonpolar and therefore few nucleophiles will dissolve in it.

b. $(CH_3)_3CO^-$ is a stronger base than $CH_3CH_2O^-$:

The three electron-donating CH_3 groups add electron density to the negative charge of the conjugate base, destabilizing it and making it a stronger base.

c. By the Hammond postulate, the S_N1 reaction is faster with RX that form more stable carbocations.

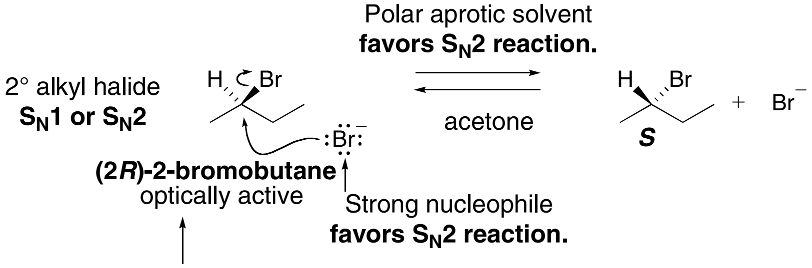


3° Carbocation is stabilized by three electron-donor CH_3 groups.

Although this carbocation is also 3°, the three electron-withdrawing F atoms destabilize the positive charge. Since the carbocation is less stable, the reaction to form it is slower.

d. The identity of the nucleophile does not affect the rate of S_N1 reactions since the nucleophile does not appear in the rate-determining step.

e.



Polar aprotic solvent **favors S_N2 reaction.**

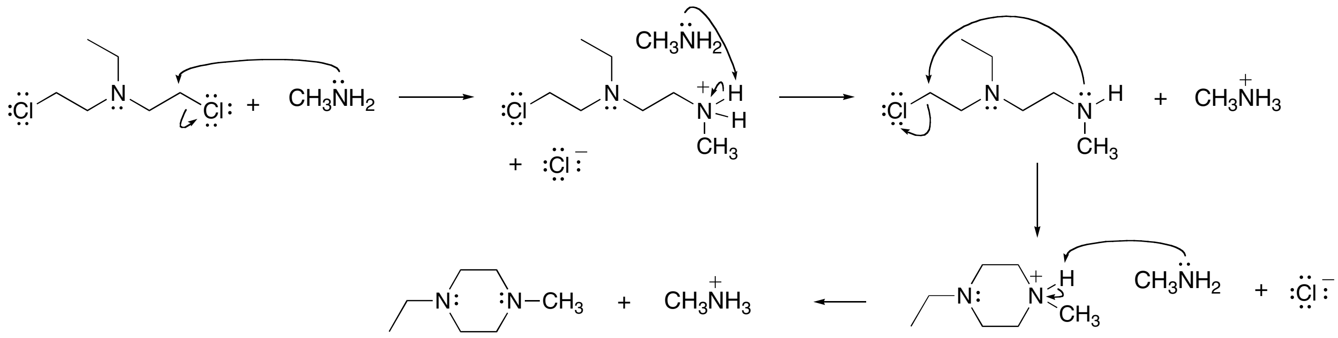
2° alkyl halide **S_N1 or S_N2**

(2*R*)-2-bromobutane optically active

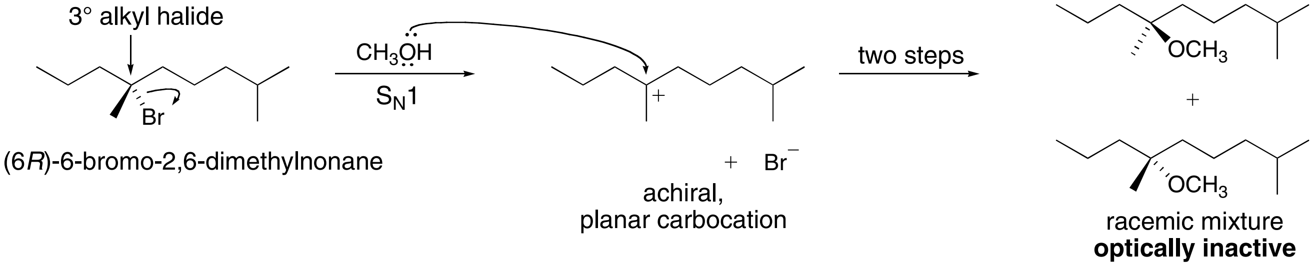
Strong nucleophile **favors S_N2 reaction.**

This compound reacts with Br⁻ until a 50:50 mixture results, making the mixture optically inactive. Then either compound can react with Br⁻ and the mixture remains optically inactive.

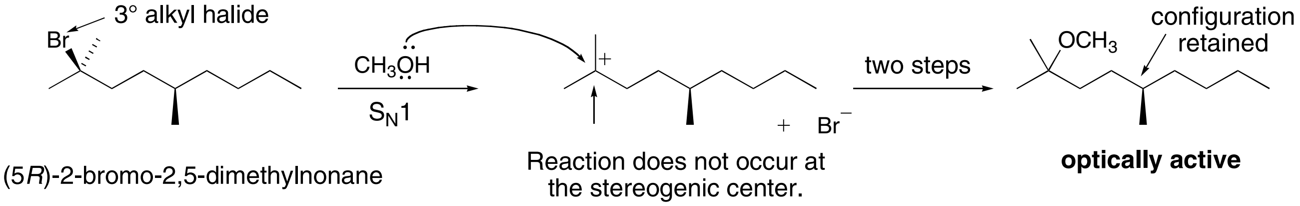
7.77



7.78 In the first reaction, substitution occurs at the stereogenic center. Since an achiral, planar carbocation is formed, the nucleophile can attack from either side, thus generating a racemic mixture.

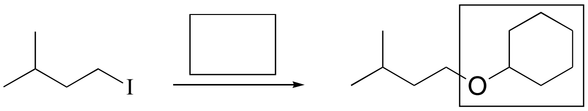


In the second reaction, the starting material contains a stereogenic center, but the nucleophile does not attack at that carbon. Since a bond to the stereogenic center is not broken, the configuration is retained and a chiral product is formed.

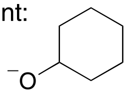


7.79

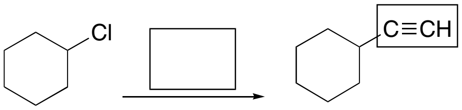
a.



The nucleophile has replaced the leaving group.
Missing reagent:

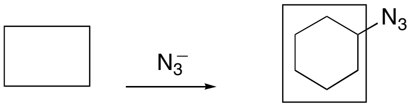


b.

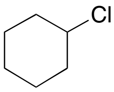


The nucleophile has replaced the leaving group.
Missing reagent: $^{-}C\equiv CH$

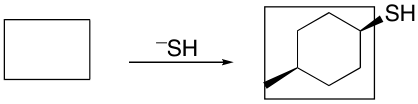
c.



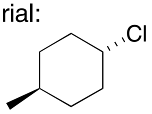
The nucleophile has replaced the halide.
Starting material:



d.



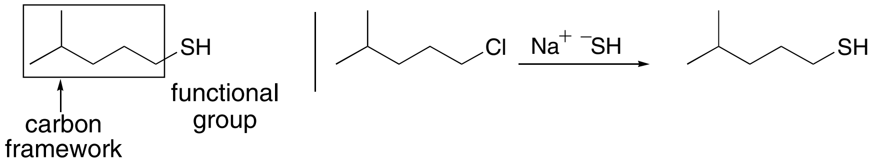
The nucleophile has replaced the halide.
Starting material:



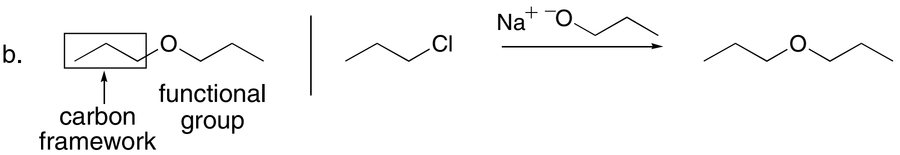
The leaving group must have the opposite orientation to the position of the nucleophile in the product.

7.80 To devise a synthesis, look for the carbon framework and the functional group in the product. **The carbon framework is from the alkyl halide and the functional group is from the nucleophile.**

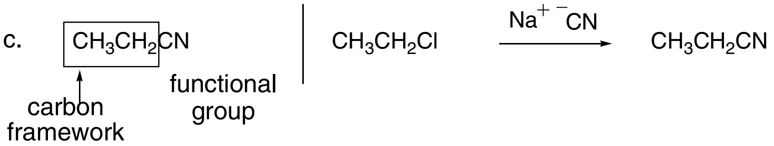
a.



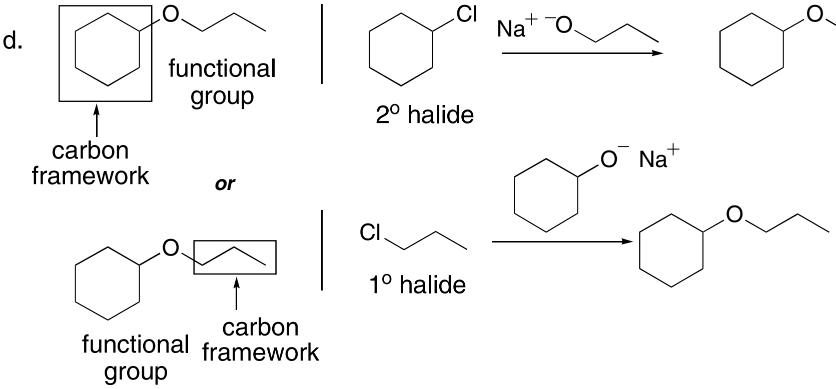
b.



c.

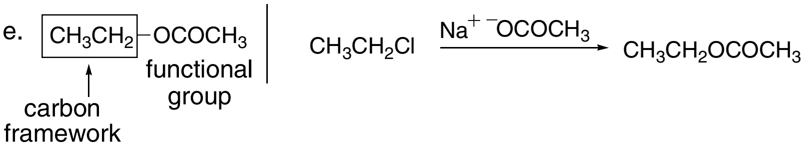


d.



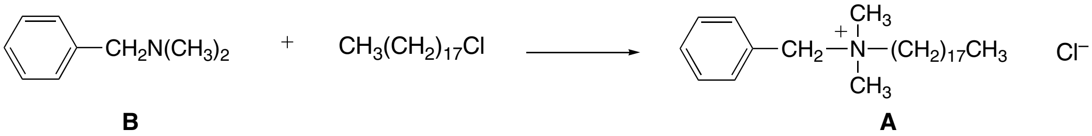
This path is preferred.
The strong nucleophile favors an S_N2 reaction so an unhindered 1° alkyl halide reacts faster.

e.

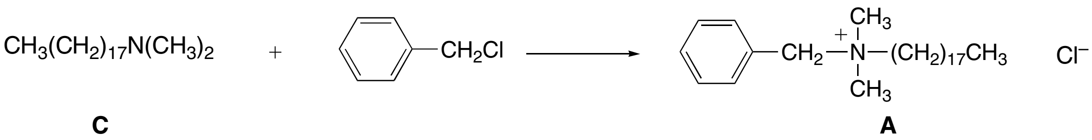


7.81 Work backwards to determine the alkyl chloride needed to prepare benzalkonium chloride **A**.

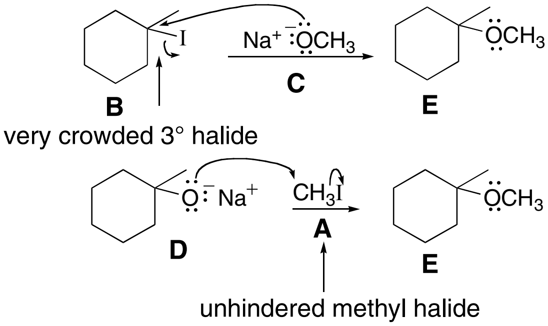
a.



b.

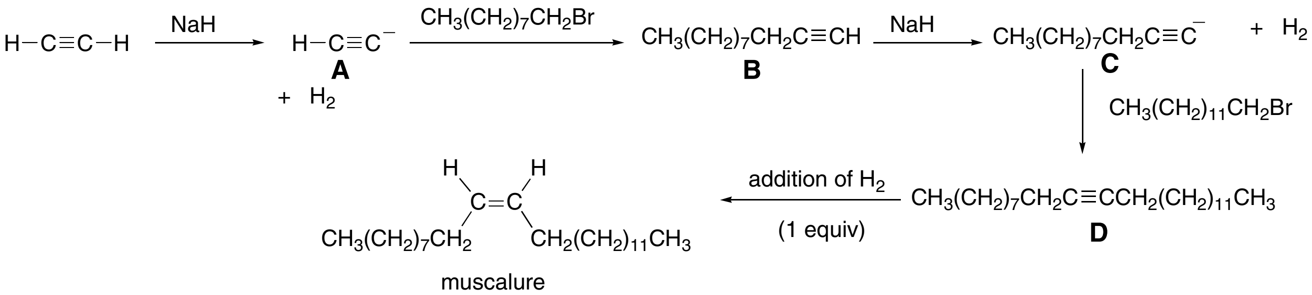


7.82



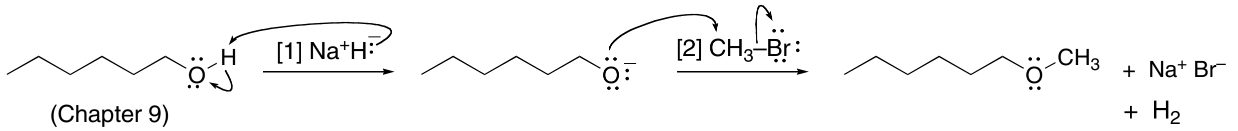
preferred method
The strong nucleophile favors S_N2 reaction so the alkyl halide should be unhindered for a faster reaction.

7.83

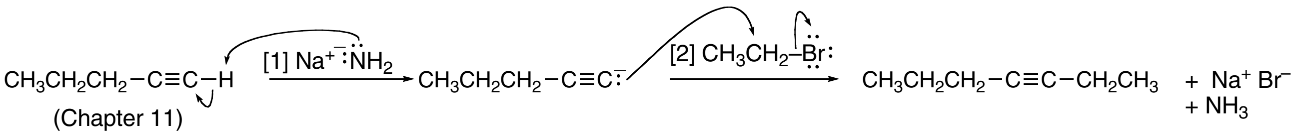


7.84

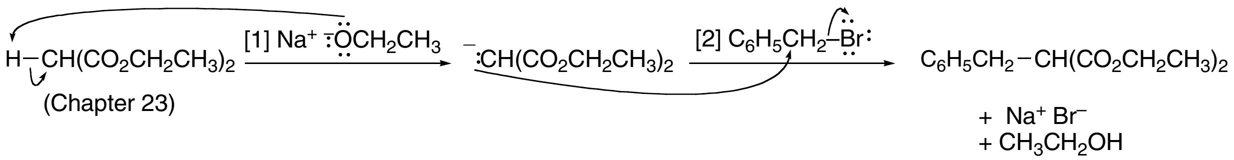
a.



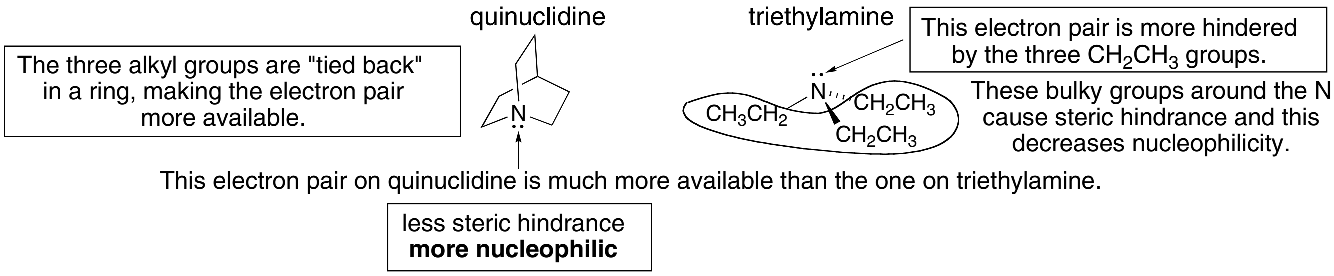
b.



c.



7.85



The three alkyl groups are "tied back" in a ring, making the electron pair more available.

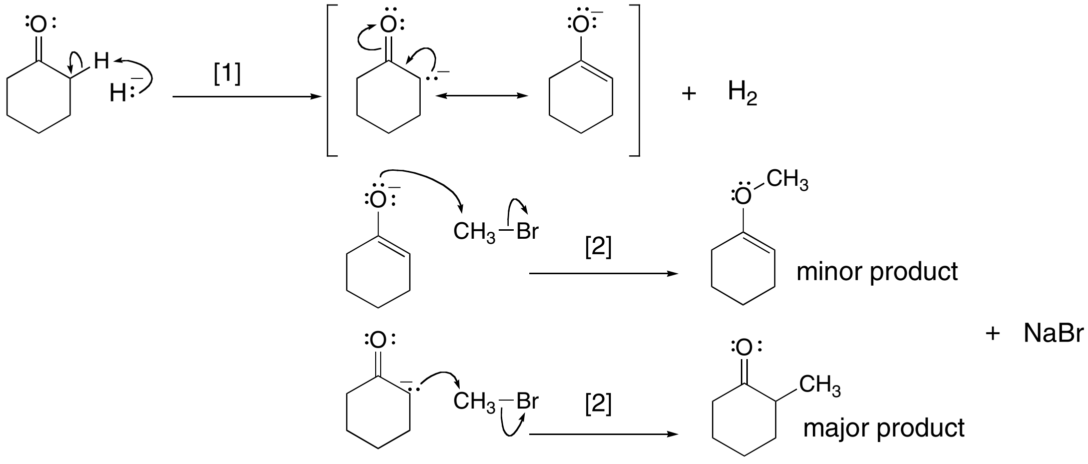
This electron pair is more hindered by the three CH_2CH_3 groups.

These bulky groups around the N cause steric hindrance and this decreases nucleophilicity.

This electron pair on quinuclidine is much more available than the one on triethylamine.

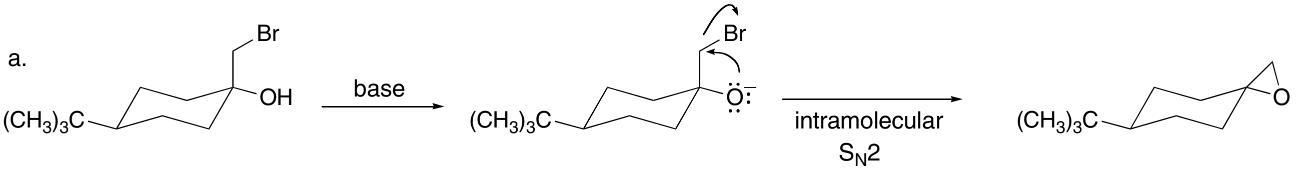
less steric hindrance
more nucleophilic

7.86

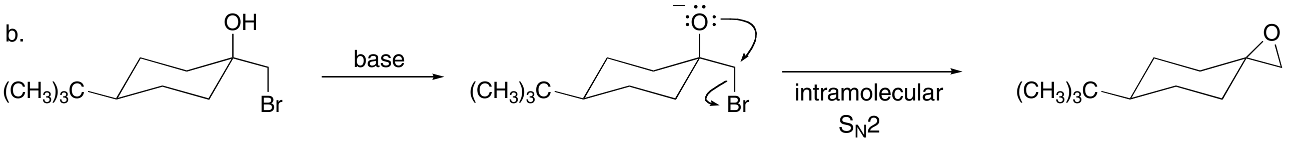


7.87

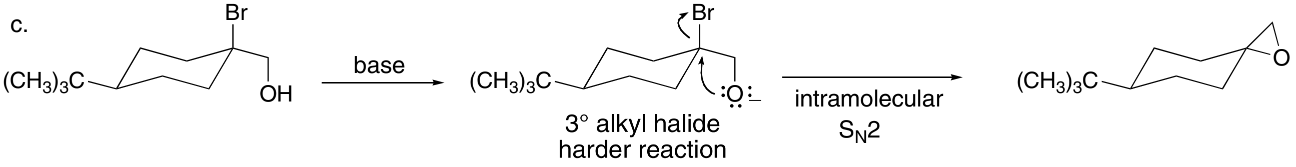
a.



b.

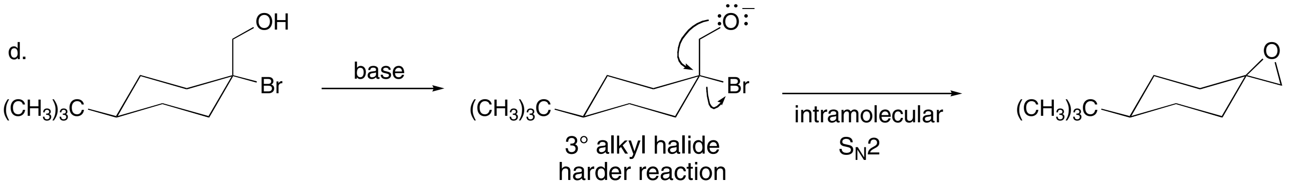


c.



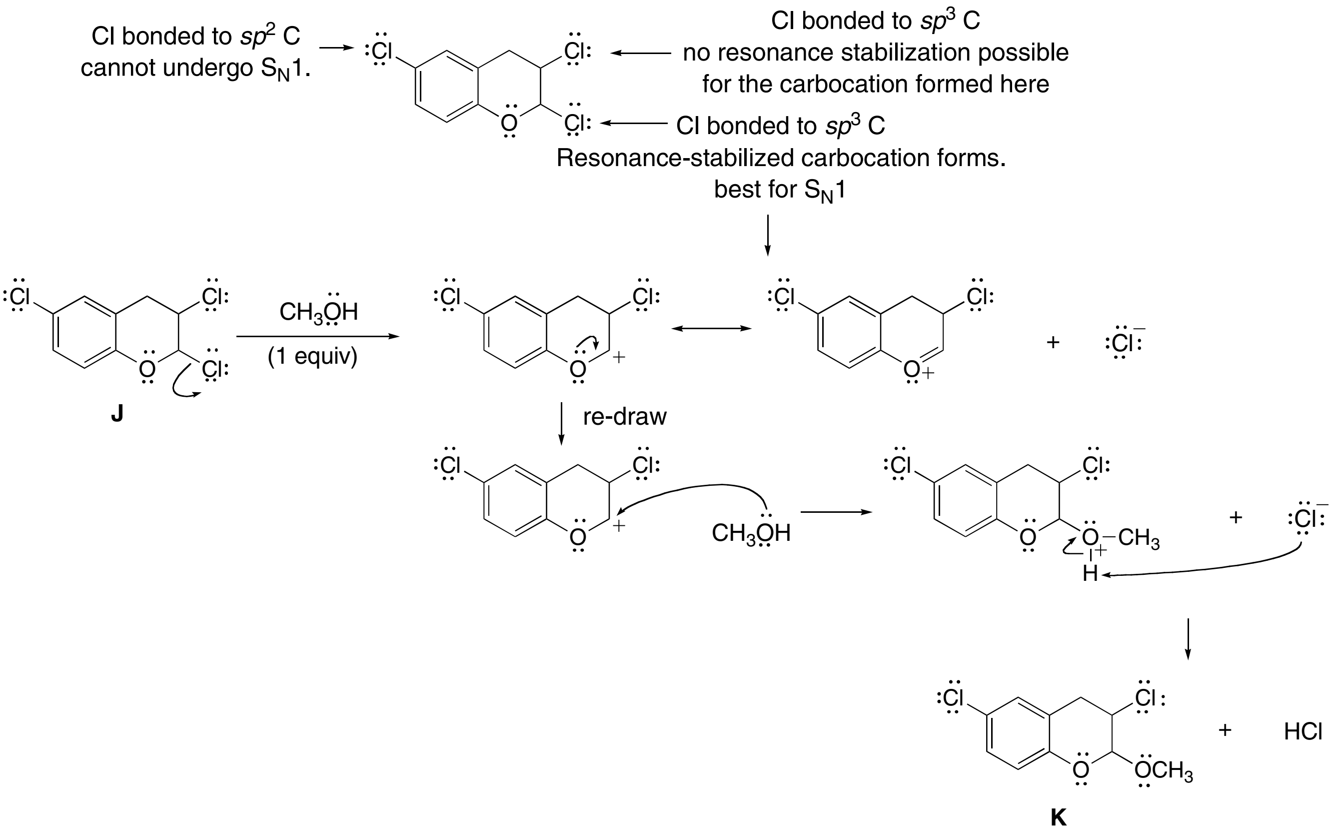
3° alkyl halide
harder reaction

d.



3° alkyl halide
harder reaction

7.88



Cl bonded to sp^2 C cannot undergo S_N1.

Cl bonded to sp^3 C
no resonance stabilization possible
for the carbocation formed here

Cl bonded to sp^3 C
Resonance-stabilized carbocation forms.
best for S_N1