PART 3

Substitution and Elimination reactions

Chapter 8. Substitution reactions of RX
9. Elimination reactions of RX
10. Substit'n/Elimin'n of other comp'ds
11. Organometallic comp'ds
12. Radical reactions

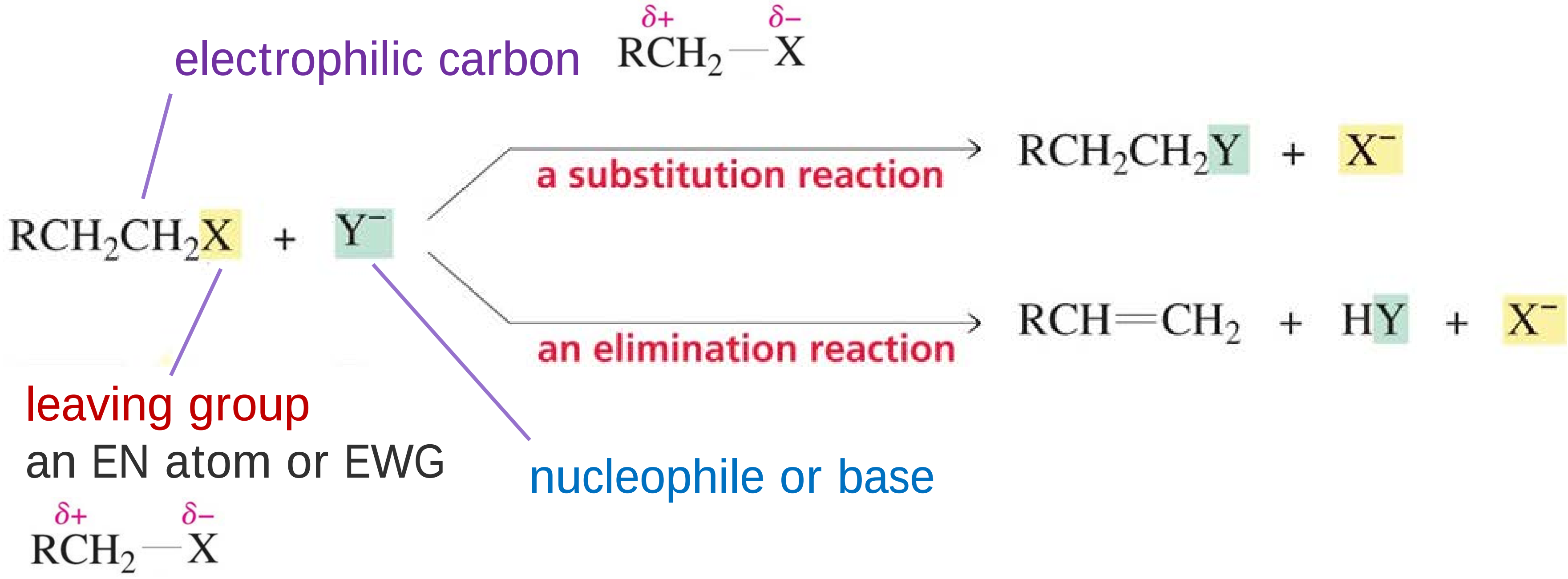
Chapter 8

Substitution reactions

S_N2 reactions

S_N1 reactions

Substitution and/or elimination rxns



electrophilic carbon

$\overset{\delta+}{RCH_2}-\overset{\delta-}{X}$

$$RCH_2CH_2X + Y^- \xrightarrow{\text{a substitution reaction}} RCH_2CH_2Y + X^-$$

$$RCH_2CH_2X + Y^- \xrightarrow{\text{an elimination reaction}} RCH{=}CH_2 + HY + X^-$$

leaving group

an EN atom or EWG

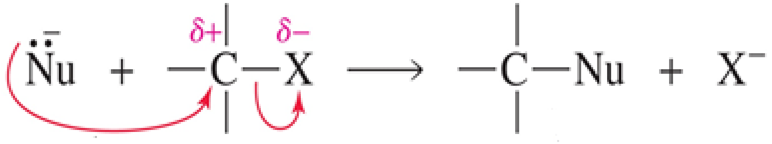
$\overset{\delta+}{RCH_2}-\overset{\delta-}{X}$

nucleophile or base

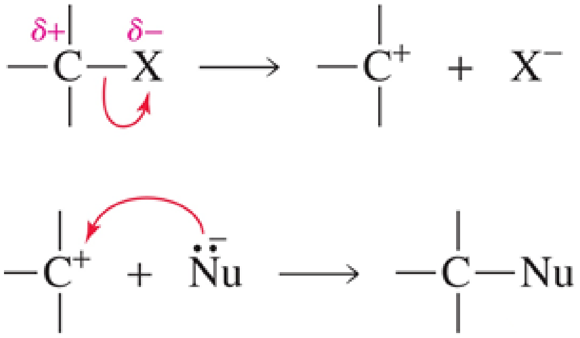
- S_N1, S_N2, E1 and/or E2 mechanism, depending on
  - the nature of e-philic C, LG, Nu: (B:)
  - solvent polarity

Substitution reactions

- nucleophilic substitution [S_N]
- 2 mechanisms
  - S_N2

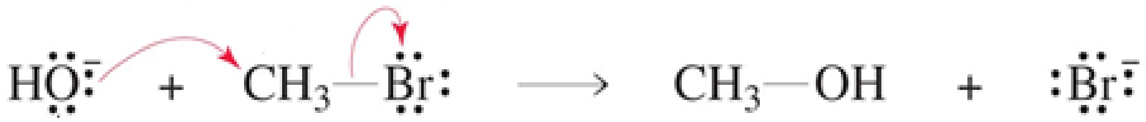


    - rate = k [Nu:] [R-X] ~ 2nd-order ~ bimolecular
    - 1-step ~ concerted ~ 1 TS
  - S_N1

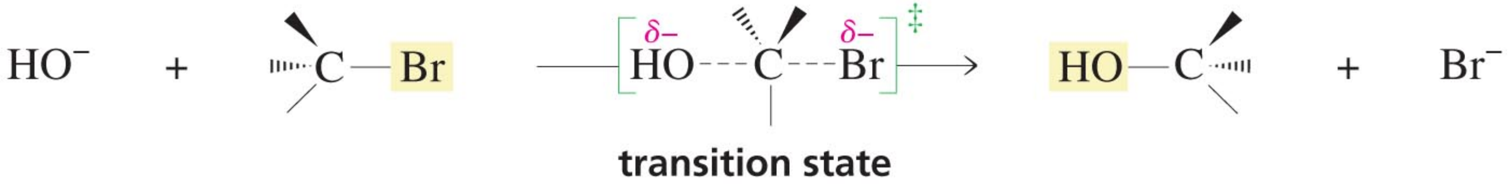


    - rate = k [R-X] ~ 1st-order ~ unimolecular (in RDS)
    - 2-step ~ 1 interm and 2 TS

S_N2: mechanism and stereochemistry

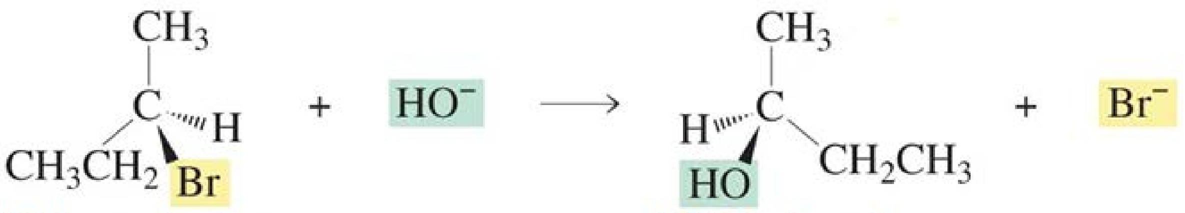


- back-side attack



trigonal bipyramid w/ sp^2 C

- inversion of configuration



(*R*)-2-bromobutane

(*S*)-2-butanol

S_N2: steric effect

- # of alkyl groups

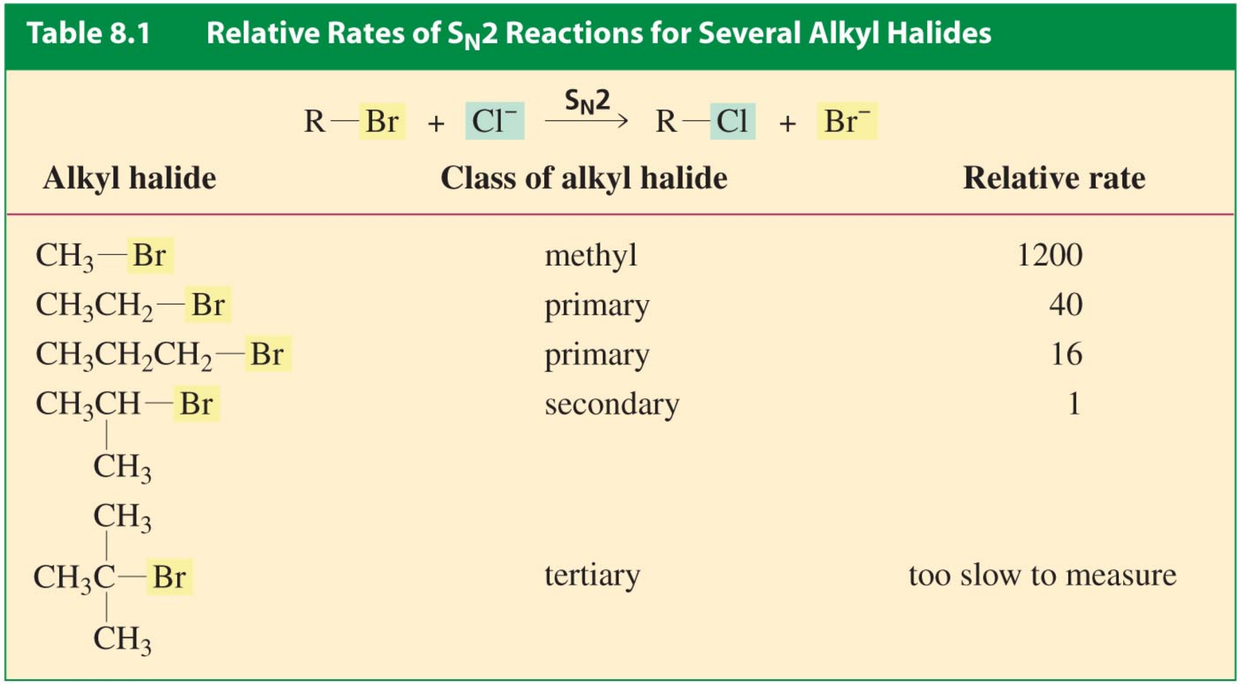
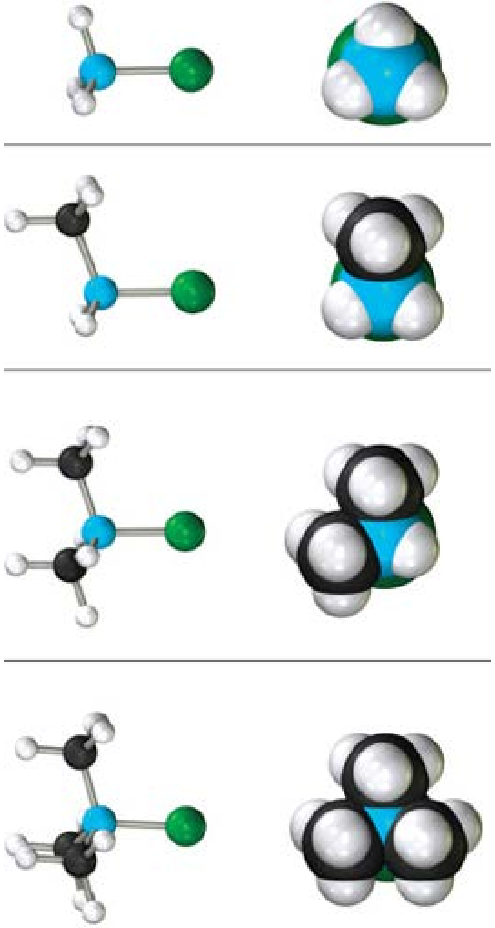


Table 8.1 **Relative Rates of S_N2 Reactions for Several Alkyl Halides**

$$R-Br + Cl^- \xrightarrow{S_N2} R-Cl + Br^-$$

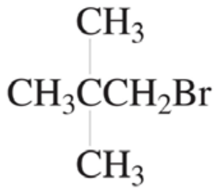
Alkyl halide	Class of alkyl halide	Relative rate
CH_3-Br	methyl	1200
CH_3CH_2-Br	primary	40
$CH_3CH_2CH_2-Br$	primary	16
$CH_3\underset{CH_3}{\underset{\mid}{CH}}-Br$	secondary	1
$CH_3\overset{CH_3}{\overset{\mid}{\underset{CH_3}{\underset{\mid}{C}}}}-Br$	tertiary	too slow to measure



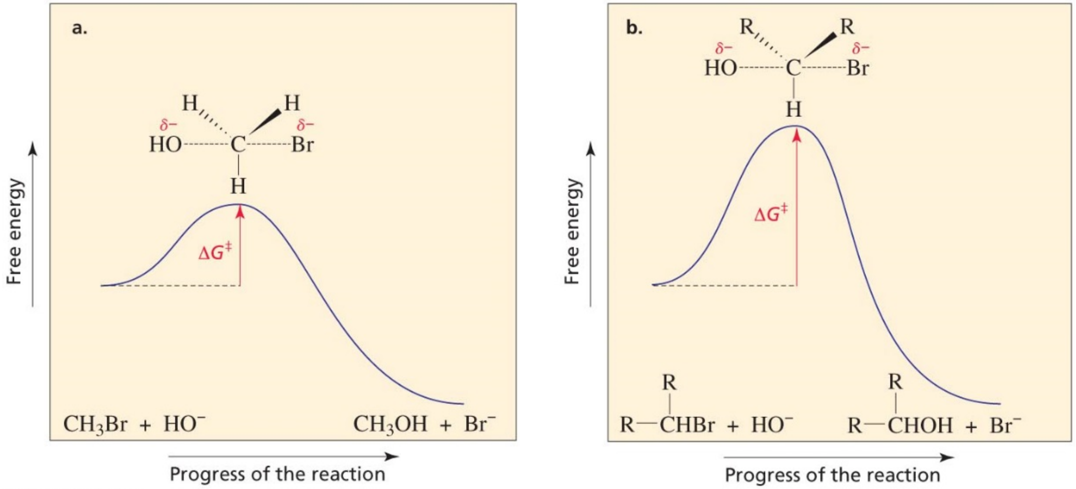
relative reactivities of alkyl halides in an S_N2 reaction

most reactive > methyl halide > 1° alkyl halide > 2° alkyl halide > ~~3° alkyl halide~~ < too unreactive to undergo an S_N2 reaction

- size of substituent

$CH_3CH_2—Br$	primary	40
$CH_3CH_2CH_2—Br$	primary	16
 $(CH_3)_3CCH_2Br$	primary	10^{-6}

- steric hindrance and activation energy



S_N2: effect of leaving group

- Weaker base is better leaving group.

	relative rates of reaction
$HO^- + RCH_2I \longrightarrow RCH_2OH + I^-$	30,000
$HO^- + RCH_2Br \longrightarrow RCH_2OH + Br^-$	10,000
$HO^- + RCH_2Cl \longrightarrow RCH_2OH + Cl^-$	200
$HO^- + RCH_2F \longrightarrow RCH_2OH + F^-$	1

  - strong acid ~ weak conj base ~ good leaving group

relative reactivities of alkyl halides in an S_N2 reaction

most reactive → $RI > RBr > RCl > RF$ ← too unreactive to undergo an S_N2 reaction

  - EN of I = 2.5 ~ RI not polar, but reactive ~ polarizability

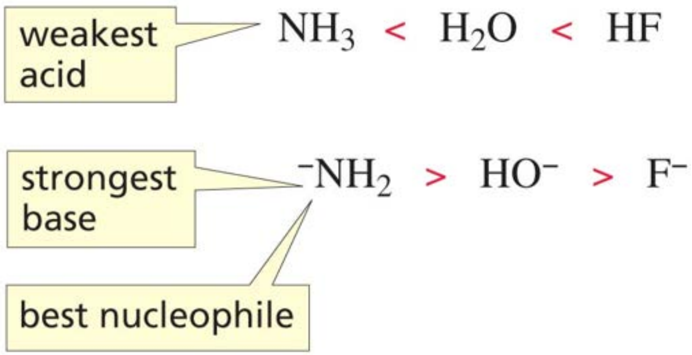
S_N2: effect of Nu: (1) - basicity

- basicity ~ ability to accept [share a lone pair with] proton
- nucleophilicity ~ ability to attack [give e to] e-philic C
- The two are not always parallel.

Stronger base is better nucleophile.

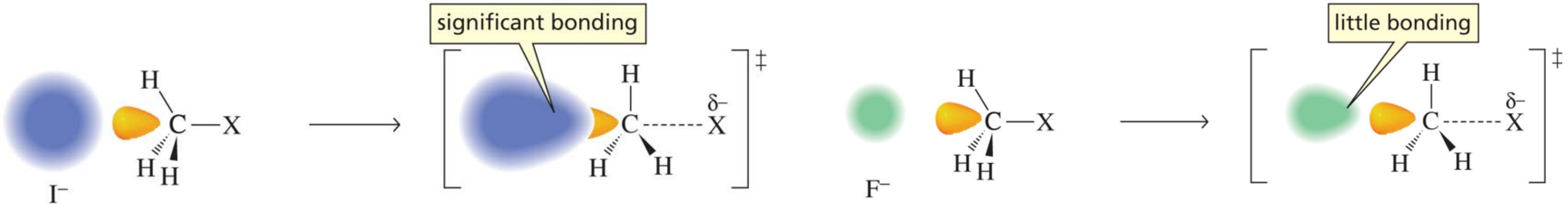
- charged vs neutral
  - Actually, (very strong) conj base of weak acid.

stronger base, better nucleophile		**weaker base, poorer nucleophile**
HO^-	>	H_2O
CH_3O^-	>	CH_3OH
$^-NH_2$	>	NH_3
$CH_3CH_2NH^-$	>	$CH_3CH_2NH_2$



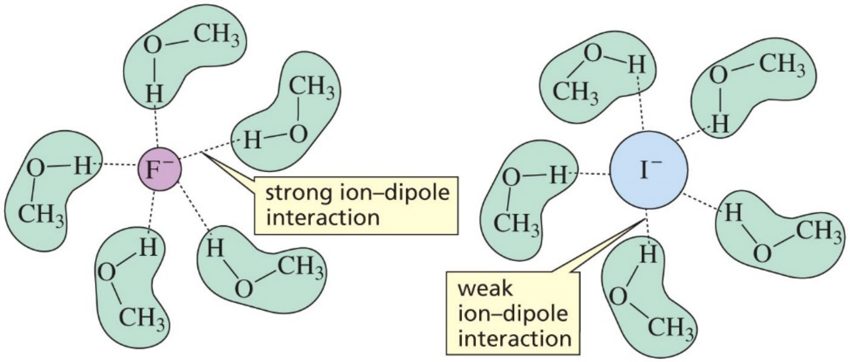
S_N2: effect of Nu: (2) - size and solvent

- size and solvent effect
  - larger Nu → better polarizable → better overlap with C



  - larger Nu: → weaker B: → less solvated by protic solvent
    - protic solvent ~ donates H ~ contains H bonded to O or N
      - eg H_2O, ROH, RCOOH, RNH_2

~ poor Nu:'s, used in S_N1



weaker B: → weaker interaction to solvent → better access to e-philic C

- Larger Nu: is better Nu: in protic polar solvent.
  - basicity and nucleophilicity antiparallel

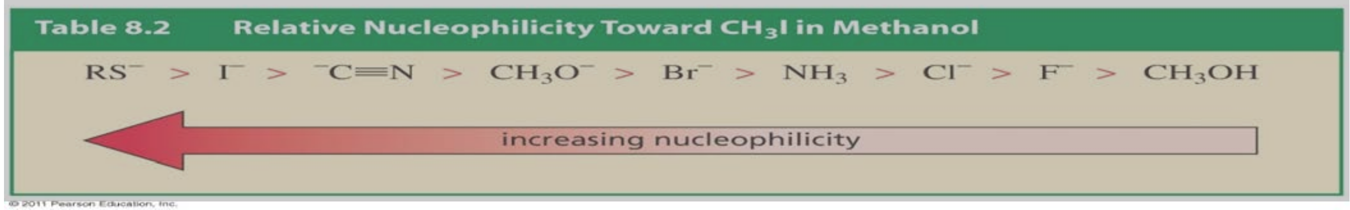
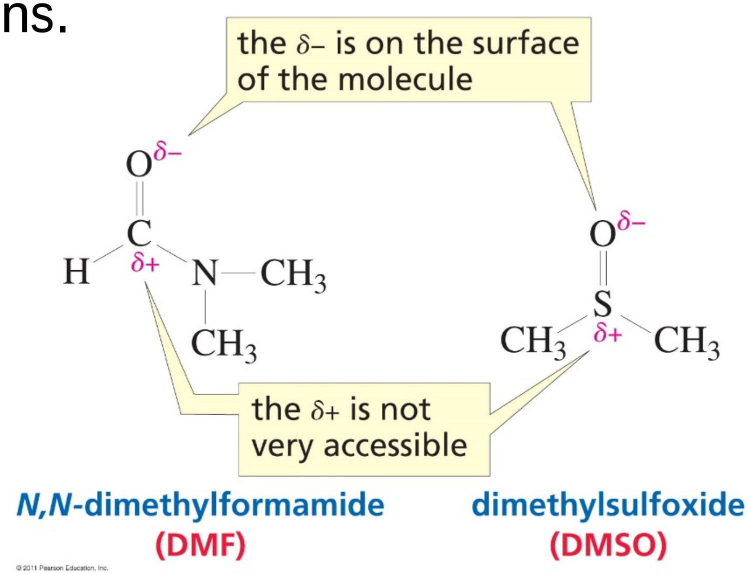


Table 8.2 **Relative Nucleophilicity Toward CH_3I in Methanol**

$RS^- > I^- > {}^-C{\equiv}N > CH_3O^- > Br^- > NH_3 > Cl^- > F^- > CH_3OH$

increasing nucleophilicity

- In aprotic solvents, stronger B: is better Nu:.
  - Nonpolar solvents do not dissolve ions.
  - Aprotic polar solvents do not strongly interact with anions.
    - eg DMF, DMSO ~ solvents for S_N2

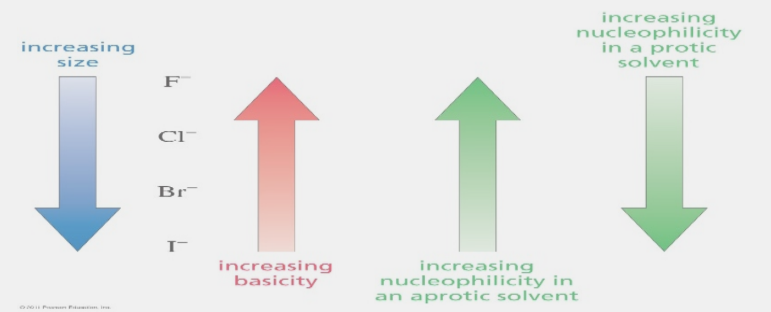


the δ– is on the surface of the molecule

the δ+ is not very accessible

***N,N*-dimethylformamide (DMF)**

dimethylsulfoxide (DMSO)

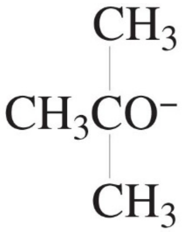


S_N2: effect of Nu: (3) - steric

- bulky Nu: → sterically-hindered → lower nucleophilicity

$CH_3CH_2O^-$

ethoxide ion
better nucleophile



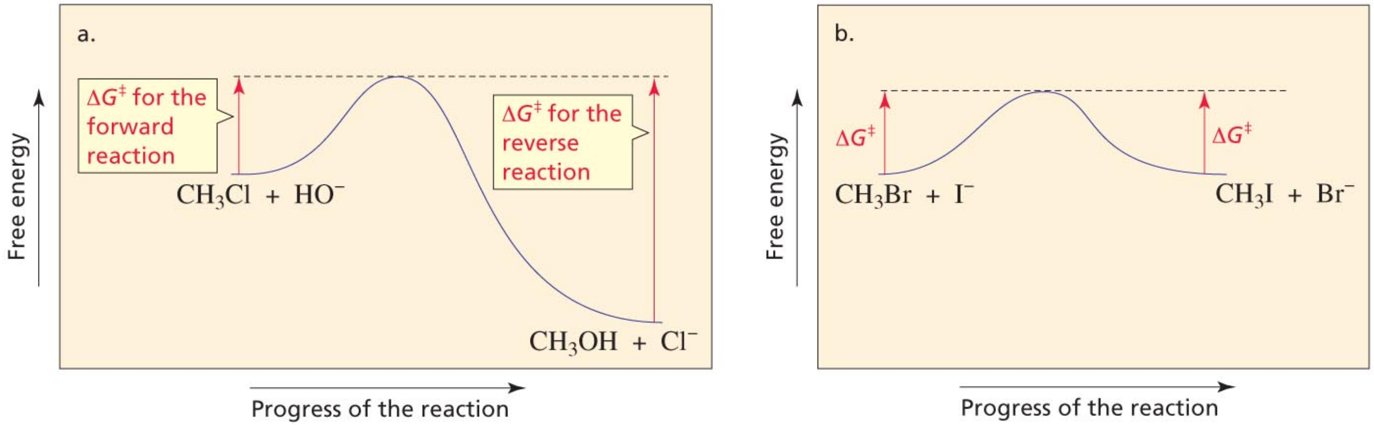
$$CH_3\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}O^-$$

***tert*-butoxide ion**
stronger base

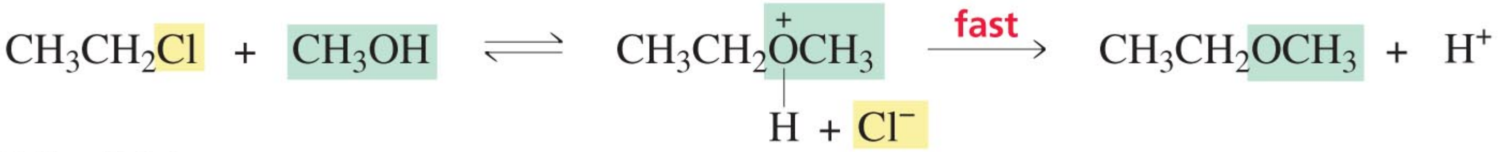
  - B: attacks H (from surface); Nu: attacks C (from back)
  - *t*-Bu-O^-
    - strong B: with poor nucleophilicity
    - sometimes useful

S_N2: reversibility

- reversible when $\Delta G^\ddagger$(forward) ≈ $\Delta G^\ddagger$(reverse)
  - when ΔG or $\Delta\Delta G^\ddagger$ is not large
  - when with similar basicity



- reversible to irreversible, when Le Chatelier



$$CH_3CH_2Cl + CH_3OH \rightleftharpoons CH_3CH_2\overset{+}{\underset{|\atop H}{O}}CH_3 + Cl^- \xrightarrow{\text{fast}} CH_3CH_2OCH_3 + H^+$$

$$CH_3CH_2Cl + HO^- \longrightarrow CH_3CH_2OH + Cl^-$$

an alcohol

H_2O vs HCl

$$CH_3CH_2Br + HS^- \longrightarrow CH_3CH_2SH + Br^-$$

a thiol

$$CH_3CH_2I + RO^- \longrightarrow CH_3CH_2OR + I^-$$

an ether

$$CH_3CH_2Br + RS^- \longrightarrow CH_3CH_2SR + Br^-$$

a thioether

$$CH_3CH_2Cl + {}^-NH_2 \longrightarrow CH_3CH_2NH_2 + Cl^-$$

a primary amine

$$CH_3CH_2Br + {}^-C{\equiv}CR \longrightarrow CH_3CH_2C{\equiv}CR + Br^-$$

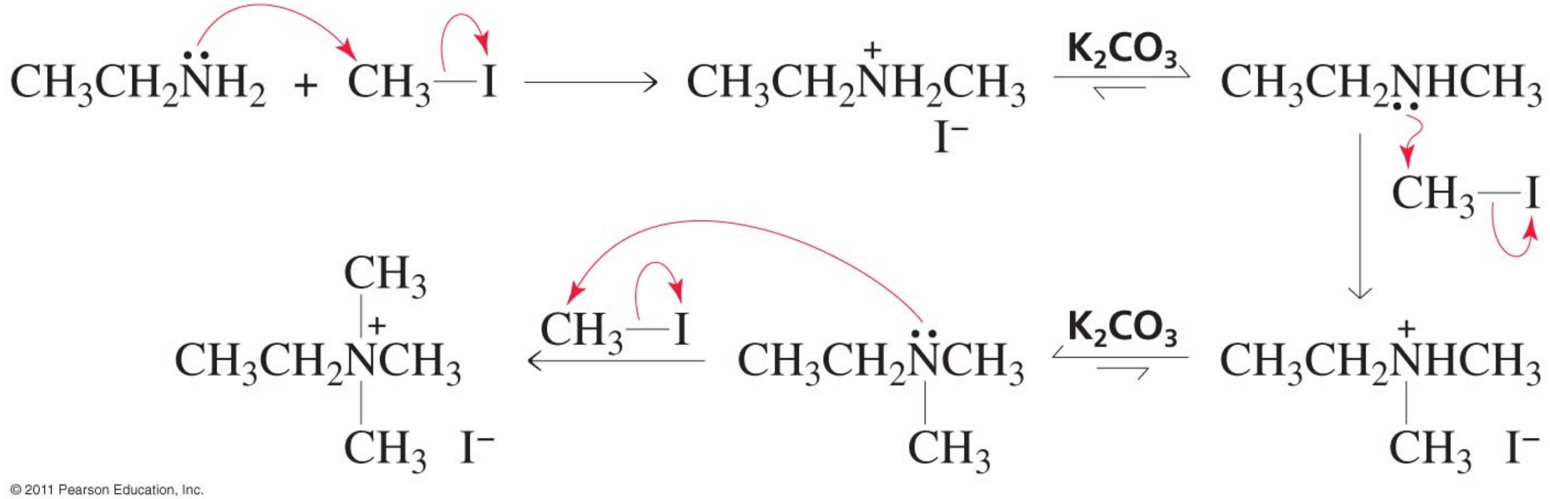
an alkyne

$$CH_3CH_2I + {}^-C{\equiv}N \longrightarrow CH_3CH_2C{\equiv}N + I^-$$

a nitrile

- Check the direction and reversibility (with Table 8.3 p345).

Prob 13 p346 good Nu: amine and good leaving iodide



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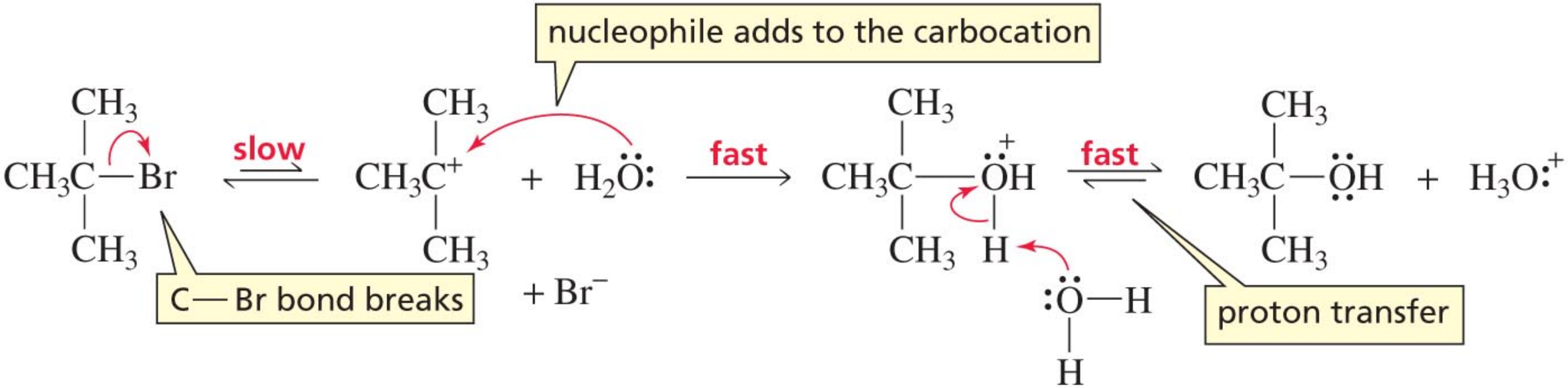
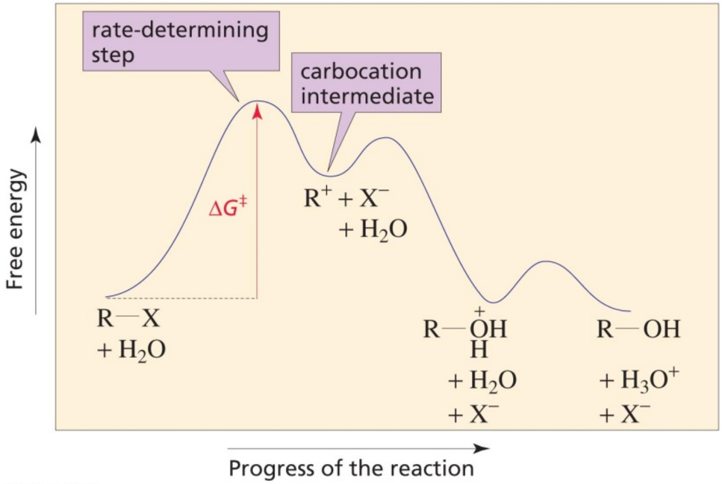
- exhaustive methylation
- Actually, method for amine preparation
  - 1° → 2° → 3° → 4°

S_N1: unimolecular nucleophilic substit'n

- 2-step rxn with 1st RDS
  - rate = k [R-X] ~ 1st-order ~ unimolecular



  - C^+ intermediate



S_N1: reactivity

- reactivity ← stability of C^+ intermediate
  - 3° > 2° alkyl halide
  - no S_N1 for 1° and methyl

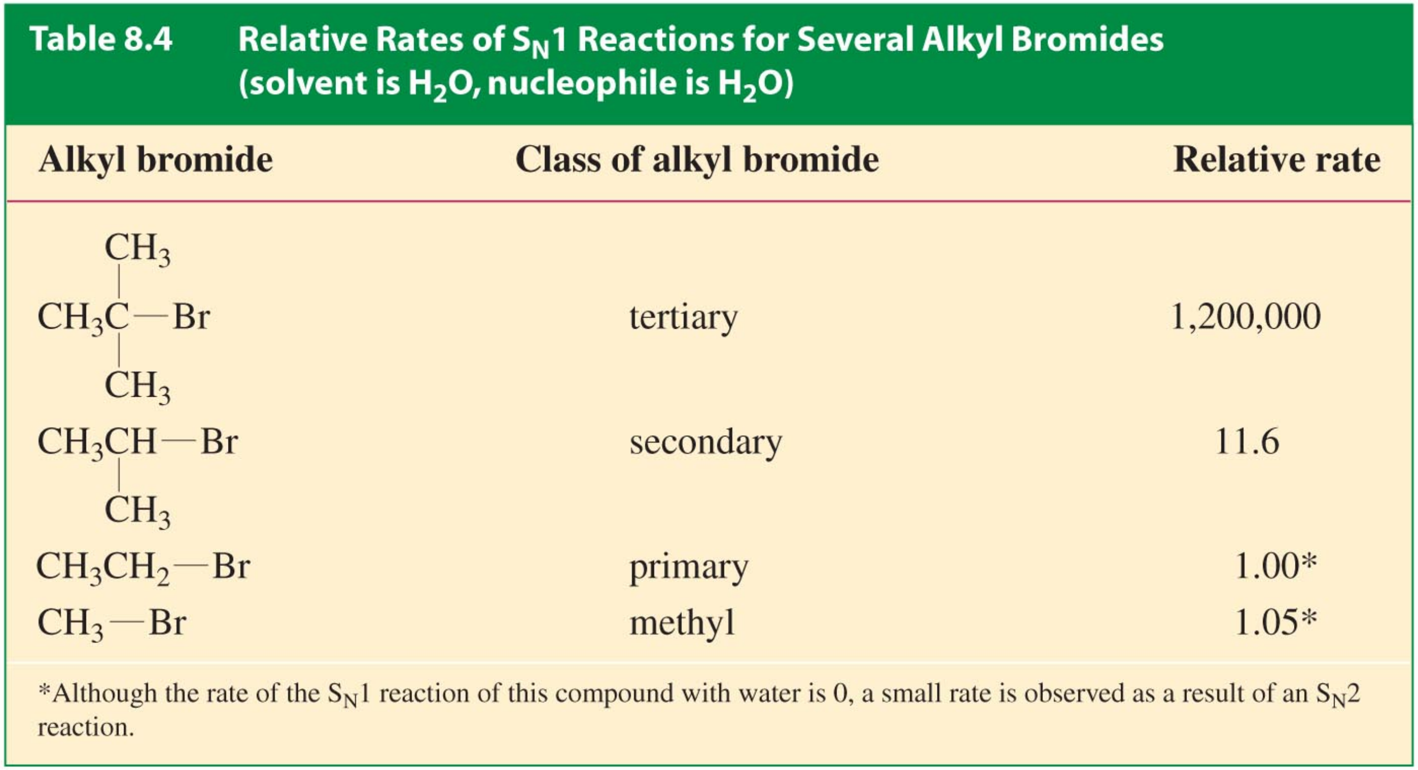


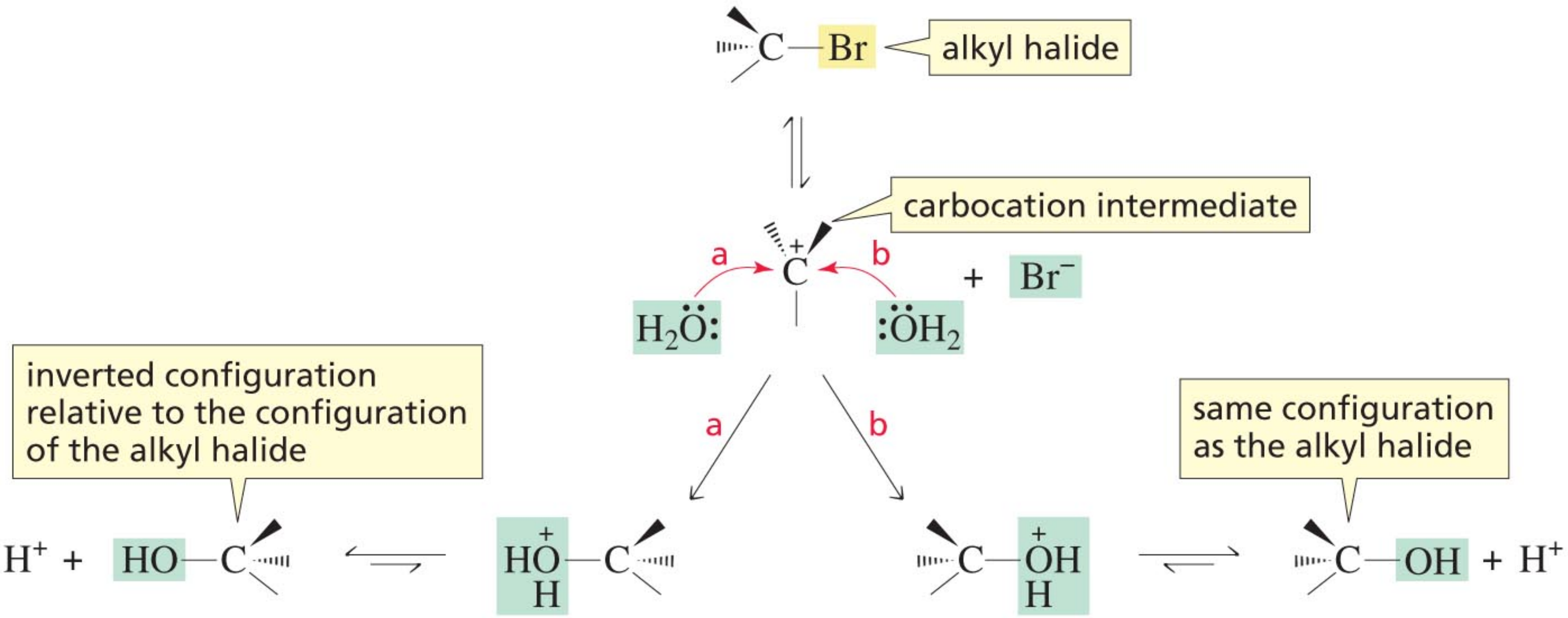
Table 8.4 **Relative Rates of S_N1 Reactions for Several Alkyl Bromides (solvent is H_2O, nucleophile is H_2O)**

Alkyl bromide	Class of alkyl bromide	Relative rate
$CH_3\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}-Br$	tertiary	1,200,000
$CH_3\underset{\displaystyle CH_3}{CH}-Br$	secondary	11.6
CH_3CH_2-Br	primary	1.00*
CH_3-Br	methyl	1.05*

*Although the rate of the S_N1 reaction of this compound with water is 0, a small rate is observed as a result of an S_N2 reaction.

S_N1: stereochemistry

- addition of Nu: on sp^2 C of intermediate → racemic

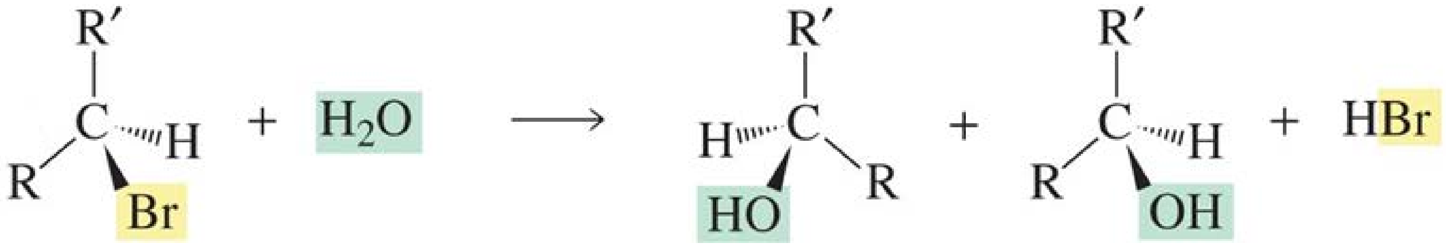


alkyl halide

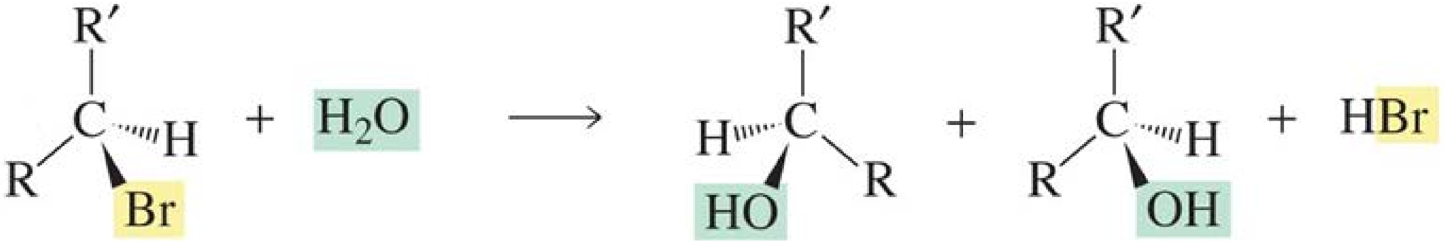
carbocation intermediate

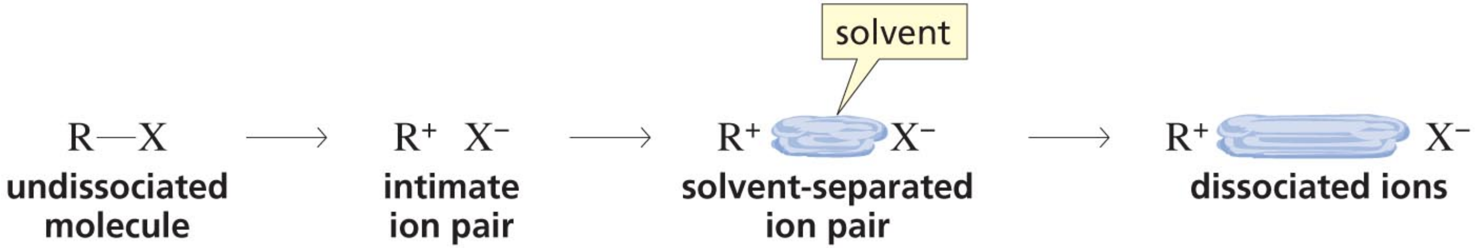
inverted configuration relative to the configuration of the alkyl halide

same configuration as the alkyl halide



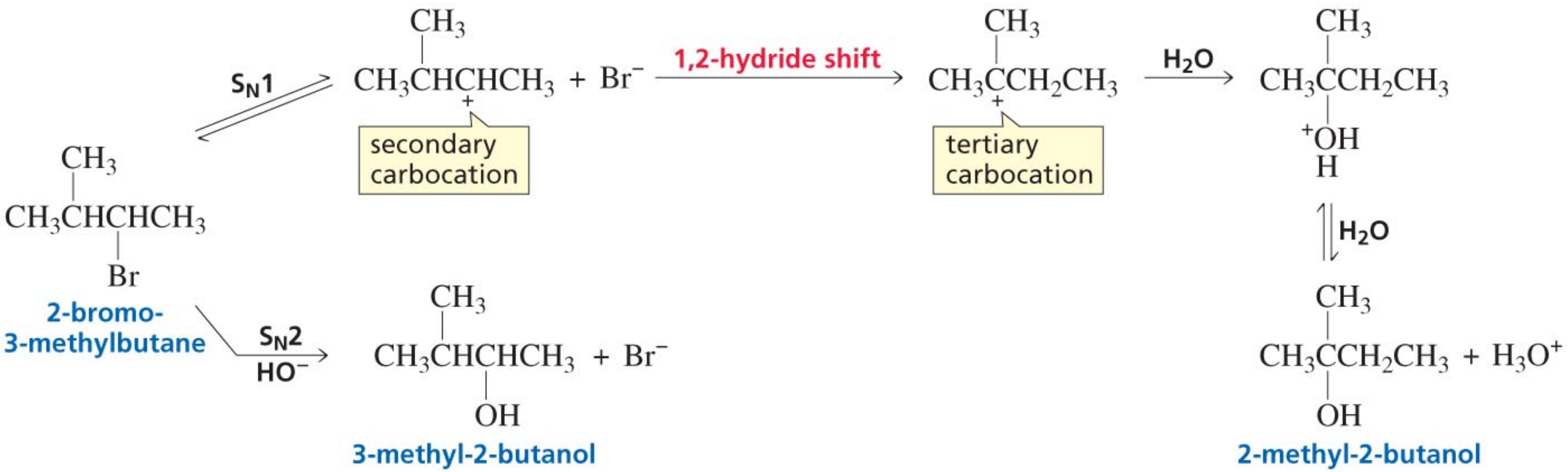
- stereochemistry affected by solvent polarity
  - high portion of inverted product in nonpolar solvent
  - typically 50 – 70%





S_N1: C^+ rearrangement

- in S_N1, not in S_N2



S_N1: factors

- effect of leaving group
  - the same as in S_N2

relative reactivities of alkyl halides in an S_N1 reaction

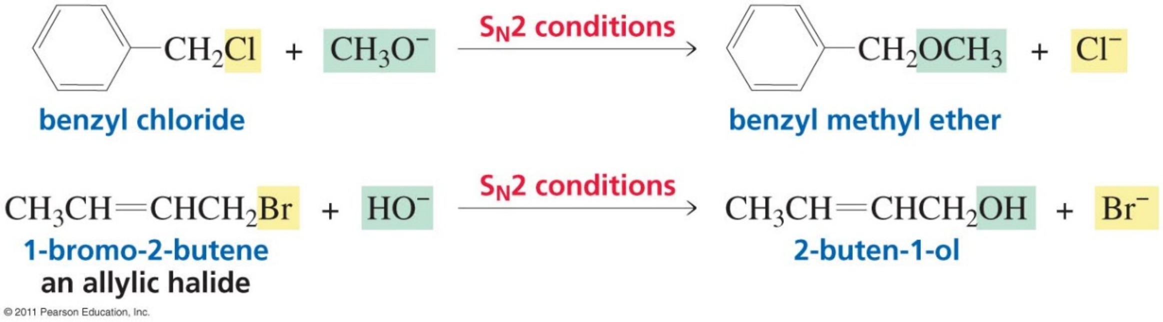
most reactive RI > RBr > RCl > RF least reactive

- effect of Nu:
  - no effect ~ not participate in RDS

- Typically, Nu: in S_N1 is also the solvent.
  - ‘solvolysis’ in general
  - hydrolysis, alcoholysis

Allylic and benzylic halides

- in S_N2
  - resonance-stabilized TS



S_N2 conditions

$$\text{CH}_3\text{CH}{=}\text{CHCH}_2\text{Br} + \text{HO}^- \xrightarrow{S_N2\text{ conditions}} \text{CH}_3\text{CH}{=}\text{CHCH}_2\text{OH} + \text{Br}^-$$

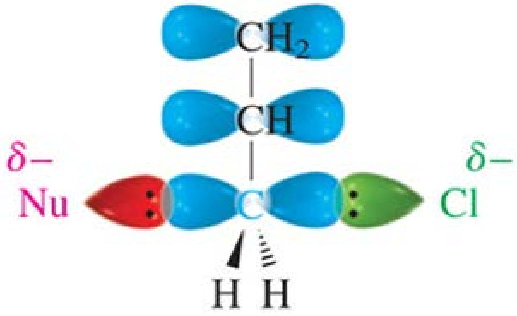
benzyl chloride

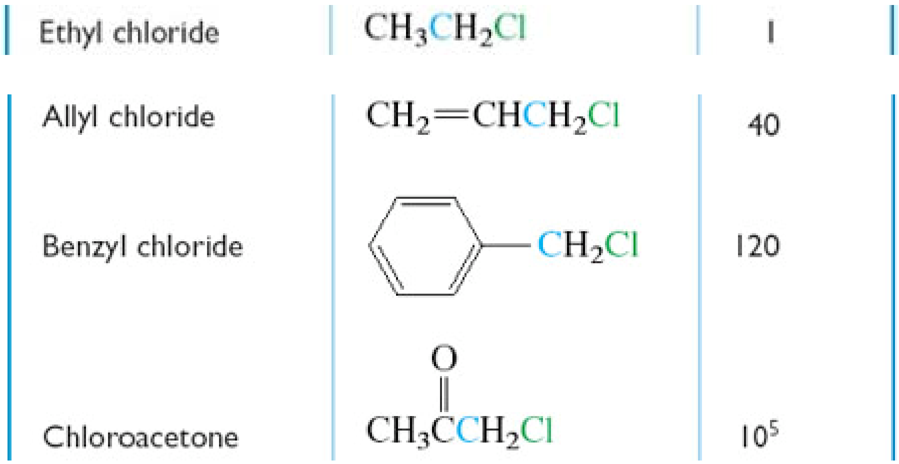
benzyl methyl ether

1-bromo-2-butene

an allylic halide

2-buten-1-ol

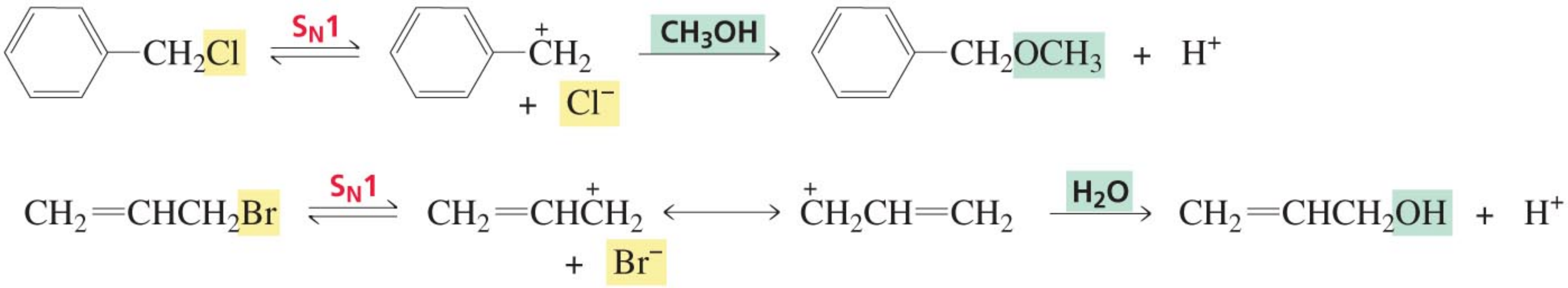




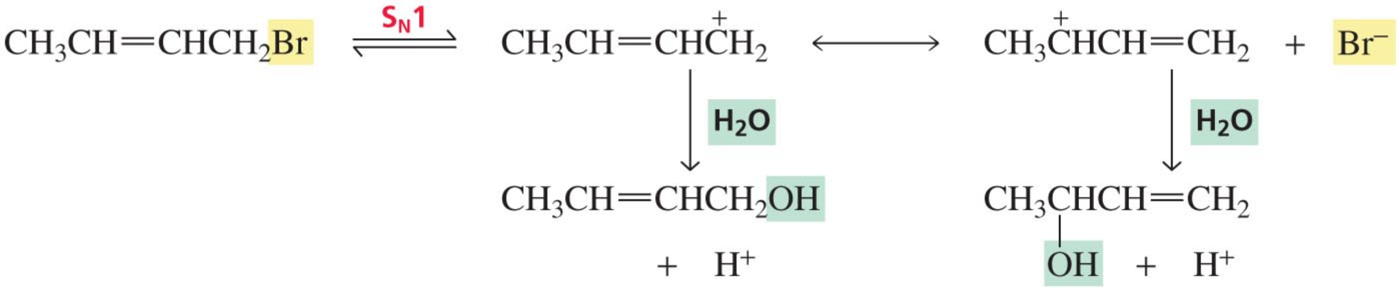
Ethyl chloride	CH_3CH_2Cl	1
Allyl chloride	$CH_2{=}CHCH_2Cl$	40
Benzyl chloride	CH_2Cl	120
Chloroacetone	$CH_3\overset{O}{\overset{\Vert}{C}}CH_2Cl$	10^5

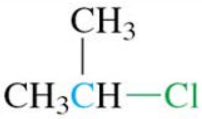
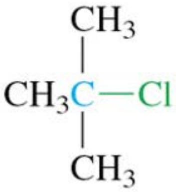
  - 1° and 2°, not 3°

- in S_N1
  - resonance-stabilized C^+
  - 3° and 2°, 1° also

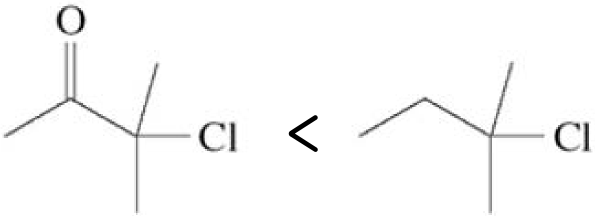


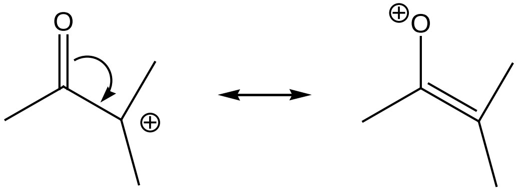
  - may give more than 1 product



Name	Structure	Relative Rate
Isopropyl chloride	 $CH_3CH(CH_3){-}Cl$	1
tert-Butyl chloride	 $CH_3C(CH_3)_2{-}Cl$	1 × 10^5
Allyl chloride	$CH_2{=}CHCH_2{-}Cl$	3
Benzyl chloride	$PhCH_2{-}Cl$	30
Diphenylmethyl chloride	$Ph_2CH{-}Cl$	1 × 10^4
Triphenylmethyl chloride	$Ph_3C{-}Cl$	1 × 10^9

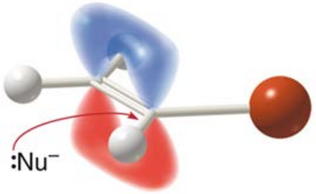
- resonance-stabilizing carbonyl?

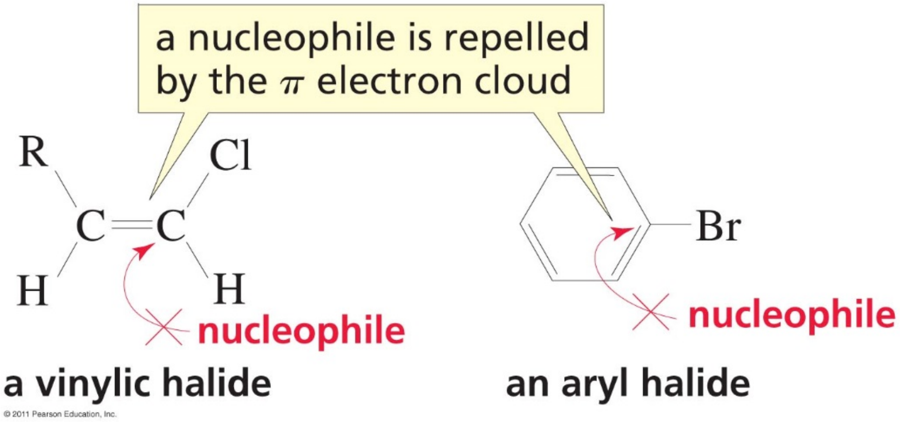




Vinyl and aryl halides

- in S_N2
    - TS sterically hindered
    - no S_N2 reaction





a vinylic halide

an aryl halide

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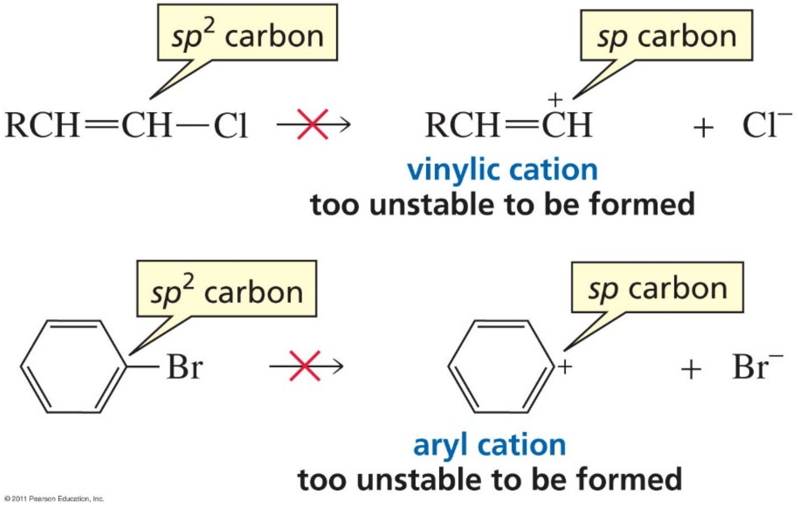
- in S_N1
    - negligible S_N1 reaction

1. unstable sp C^+
2. strong sp^2 C – X bond



vinylic cation

too unstable to be formed

aryl cation

too unstable to be formed

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Competition btwn S_N2 and S_N1

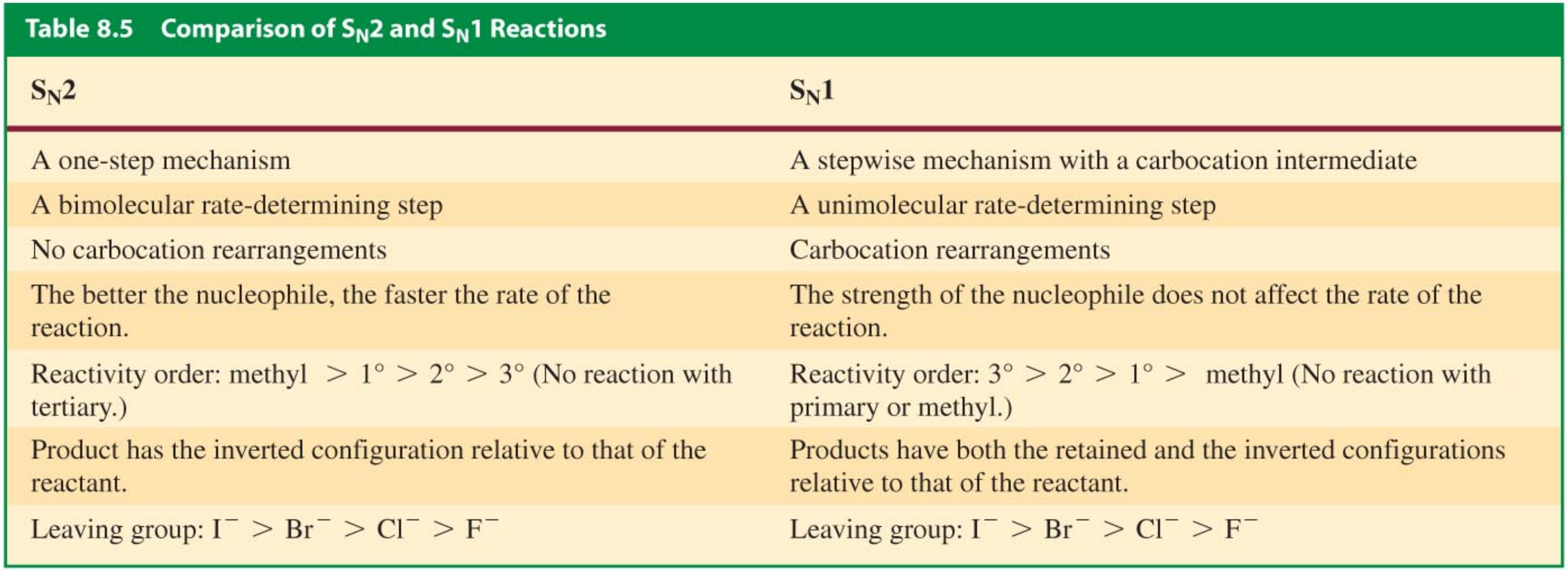


Table 8.5 Comparison of S_N2 and S_N1 Reactions

S_N2	S_N1
A one-step mechanism	A stepwise mechanism with a carbocation intermediate
A bimolecular rate-determining step	A unimolecular rate-determining step
No carbocation rearrangements	Carbocation rearrangements
The better the nucleophile, the faster the rate of the reaction.	The strength of the nucleophile does not affect the rate of the reaction.
Reactivity order: methyl > 1° > 2° > 3° (No reaction with tertiary.)	Reactivity order: 3° > 2° > 1° > methyl (No reaction with primary or methyl.)
Product has the inverted configuration relative to that of the reactant.	Products have both the retained and the inverted configurations relative to that of the reactant.
Leaving group: $I^- > Br^- > Cl^- > F^-$	Leaving group: $I^- > Br^- > Cl^- > F^-$

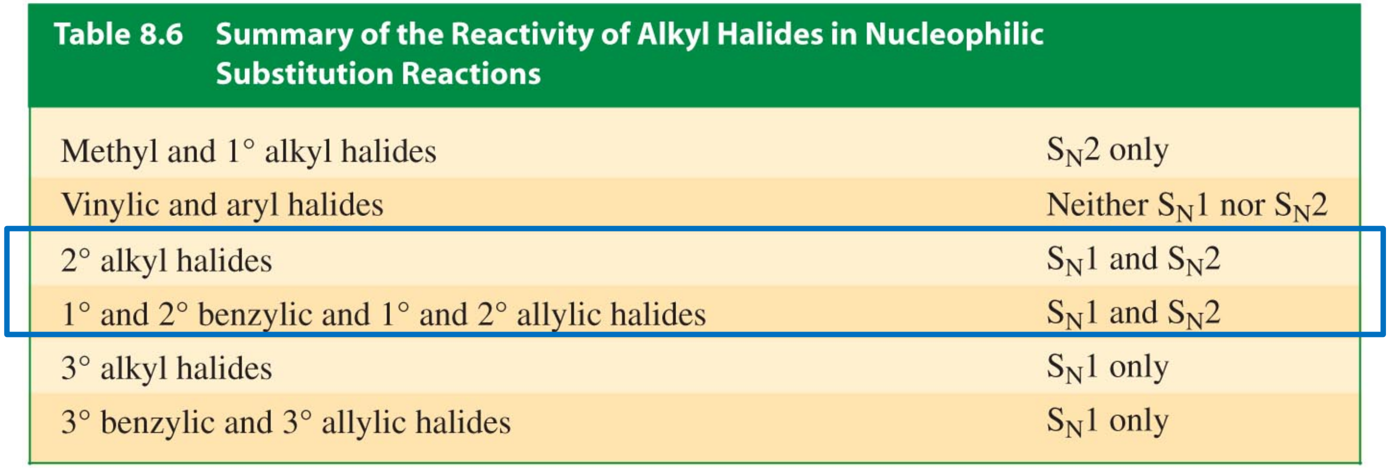


Table 8.6 Summary of the Reactivity of Alkyl Halides in Nucleophilic Substitution Reactions

Methyl and 1° alkyl halides	S_N2 only
Vinylic and aryl halides	Neither S_N1 nor S_N2
2° alkyl halides	S_N1 and S_N2
1° and 2° benzylic and 1° and 2° allylic halides	S_N1 and S_N2
3° alkyl halides	S_N1 only
3° benzylic and 3° allylic halides	S_N1 only

Competition: effect of Nu:

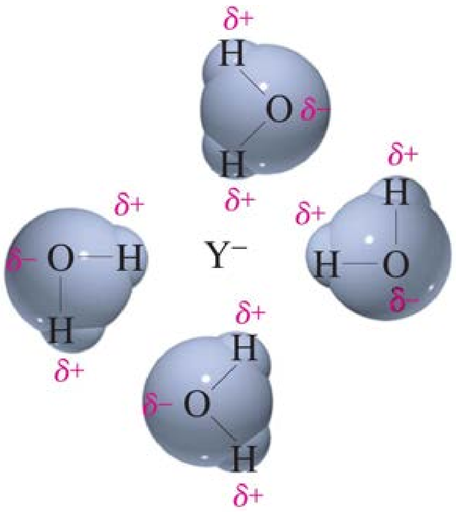
- rate of 2°, (1°/2°) allylic, or benzylic halide

$$\textbf{rate} = k_2[\textbf{alkyl halide}][\textbf{nucleophile}] + k_1[\textbf{alkyl halide}]$$

  - as reactivity and concentration of Nu: up, more S_N2
  - absence of good Nu: → S_N1
- high conc’n of good Nu: → S_N2
  poor Nu: [absence of good Nu:] → S_N1
  - good Nu: ~ ^-OH, ^-OR
    poor Nu: ~ H_2O, ROH
- Usually, S_N2 more desirable over S_N1
  - gives single product
  - no racemization, no C^+ rearrangement, no resonance interm

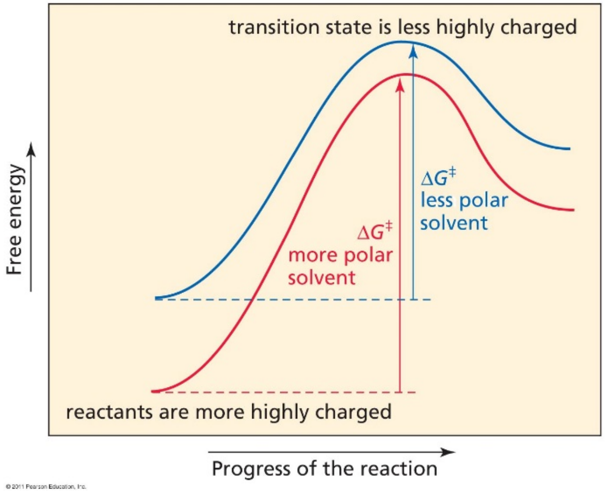
Solvent in organic reactions

- homogenize and control heat of the rxn
  - must not react with the reactants, interm’s, and products
  - (must) dissolve the reactants, interm’s, and/or products
  - must be chosen considering polarity.
- polar vs non-polar solvent
  - water-like [hydrophilic] vs oil-like [hydrophobic]
  - favorable vs not-favorable interaction with ion
  - high vs low ε   Table 8.7 p361
- protic (polar) vs aprotic (polar) solvent
  - giving vs not-giving H
  - containing H bonded to O or N vs not



Effect of solvent in S_N1 and S_N2

- relative charge in reactant(s) vs in TS
  - When reactant(s) is more highly charged than TS is,
    - a polar solvent stabilizes [solvates] reactant(s) more than it solvates TS,
    - and raises $\Delta G^{‡}$.
    - As ε up, rate down.
  - When reactant(s) is less highly charged than TS is,
    - a polar solvent stabilizes TS more than it solvates reactants, and enhance $\Delta G^{‡}$.
    - As ε ↑, rate ↑.



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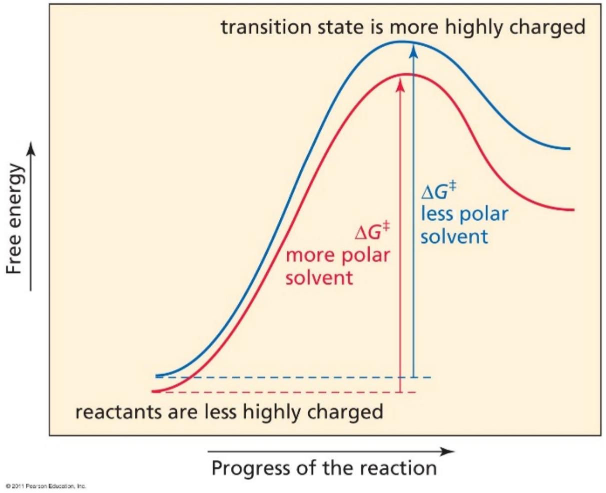

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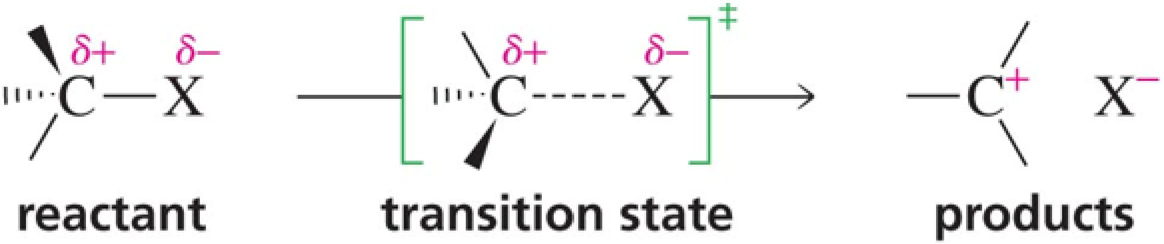
- in S_N1



  - reactants [RX] neutral; TS more highly charged (close to C^+)
  - S_N1 faster in polar solvent
  - If with charged reactant(s), slower in polar solvent.
    - full vs dispersed charge

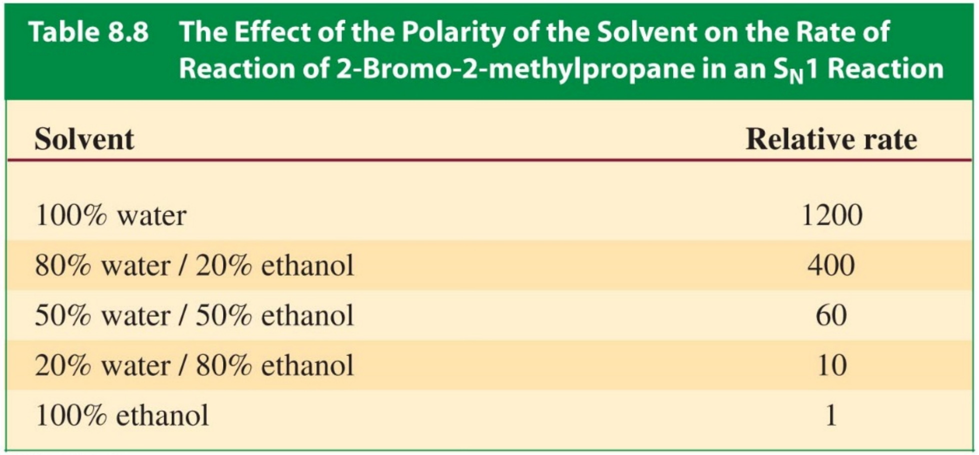
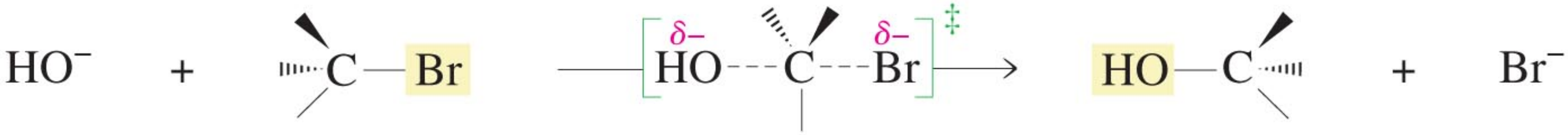


Table 8.8 The Effect of the Polarity of the Solvent on the Rate of Reaction of 2-Bromo-2-methylpropane in an S_N1 Reaction

Solvent	Relative rate
100% water	1200
80% water / 20% ethanol	400
50% water / 50% ethanol	60
20% water / 80% ethanol	10
100% ethanol	1

Actually, ion-dipole interaction energy provides much of the R-X dissociation energy.

- in S_N2



transition state

  - reactant [$^-$OH] charged; TS less [dispersed] charged
  - S_N2 slower in polar solvent
  - If with neutral reactant(s), faster in polar solvent.
    - neutral vs partially charged
- Typically, S_N2 in aprotic polar solvent
  - best to use non-polar solvent, but ions not soluble
  - aprotic polar [DMF, DMSO] better than protic polar

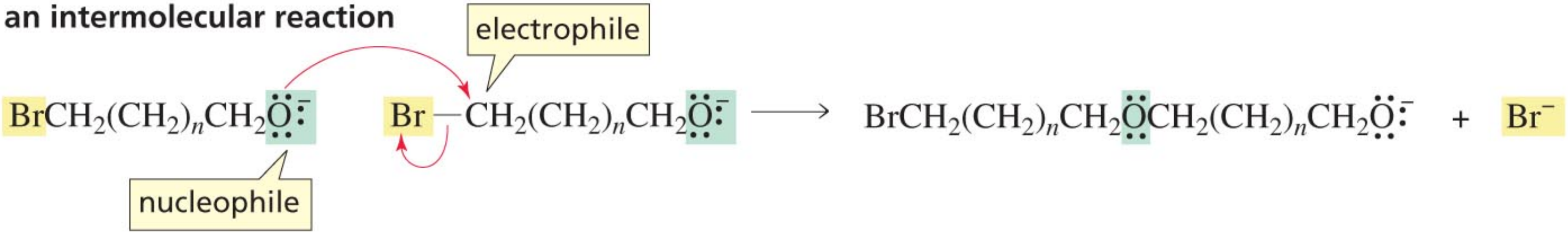
S_N2 is favored by good Nu: in aprotic polar solvent.

S_N1 is favored by poor Nu: in protic polar solvent.

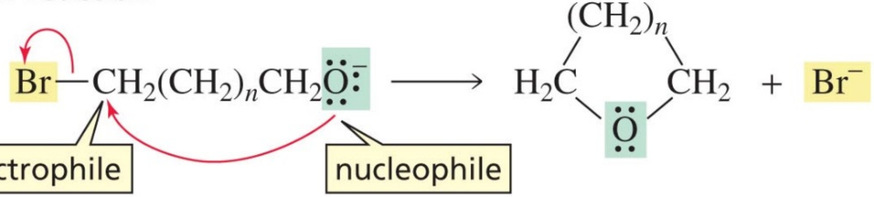
Inter- vs intramolecular S_N

- bifunctional molecules
  - can undergo inter- or intra-molecular substitution reaction

an intermolecular reaction

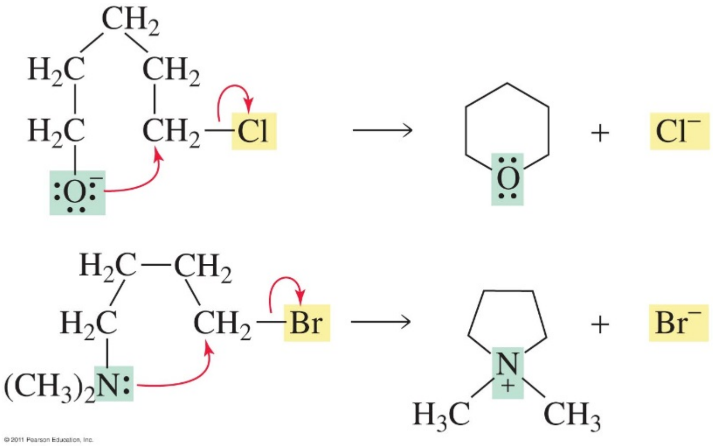


an intramolecular reaction



  - depending on
    - concentration ~ high conc’n favors intermolecular reaction
    - size of the ring ~ effect of ring strain and tethering

- (intramolecular) cyclization substitution rxn
  - 5- or 6-membered rings are easily formed
    - tethering and low ring strain



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  - 3- > 4-
    - tethering effect > ring strain effect

  - 7- or higher-membered rings are hardly formed
    - One end hard to find the other

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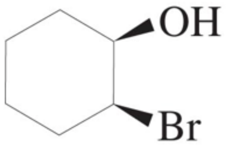

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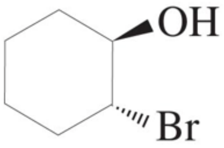
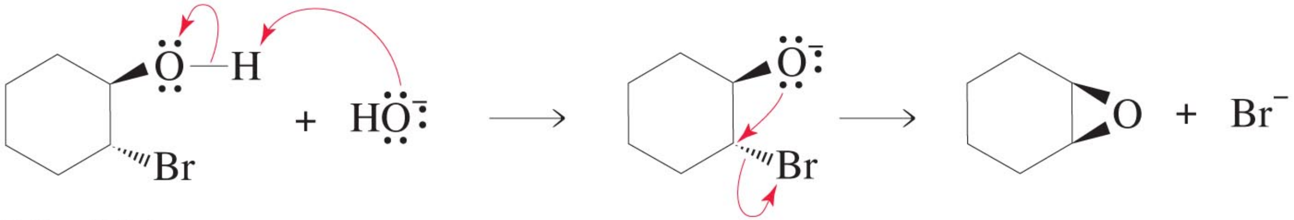
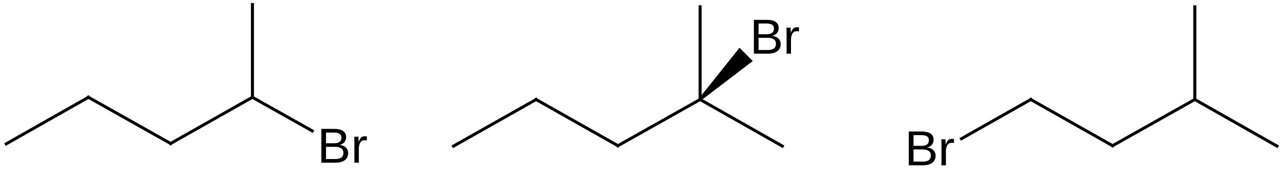
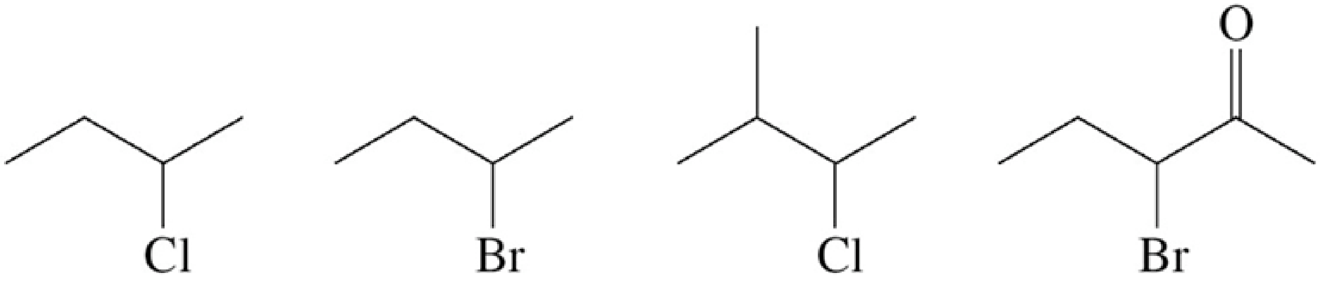




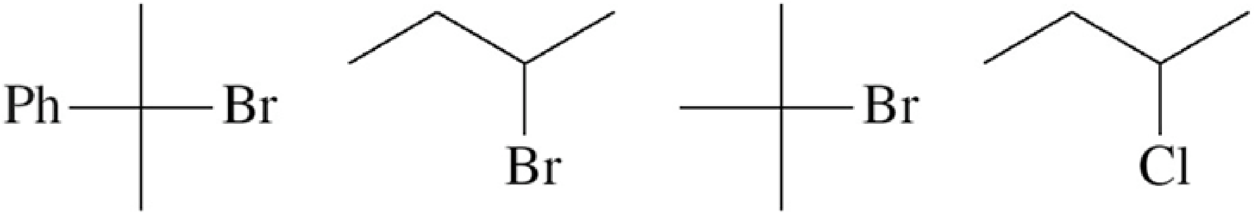
- S_N1 or S_N2?



- rate of S_N2? RO^-/DMSO

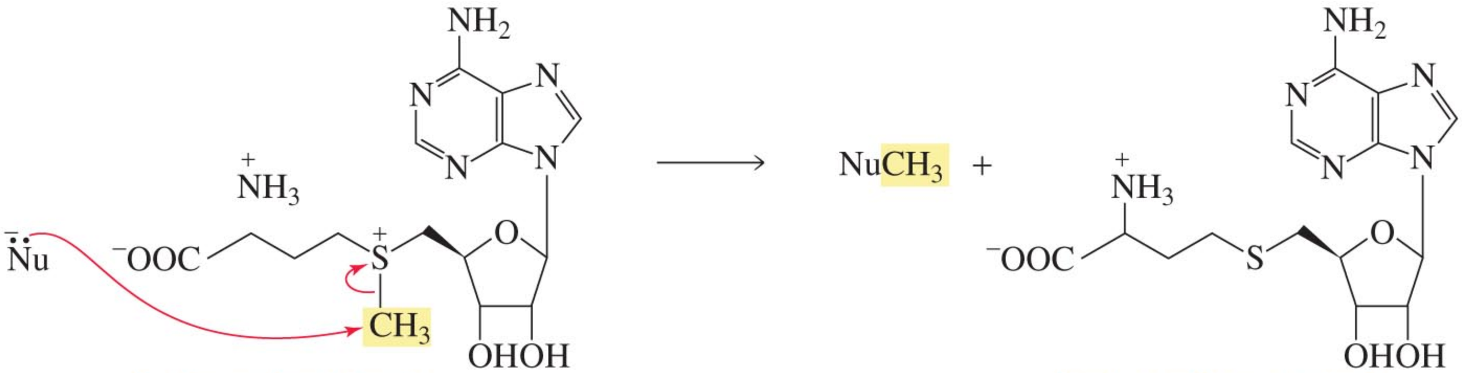


- rate of S_N1? ROH



Biological methylating agent

- CH_3I is a good methylating agent
  - better than CH_3Br or CH_3Cl
  - insoluble in water ~ cannot be used in biological system
  - use SAM instead ← SAH is a good leaving group



S-adenosylmethionine
SAM
AdoMet

S-adenosylhomocysteine
SAH