Lecture 18
Organic Chemistry 1

Professor Duncan Wardrop

March 9, 2010

Nucleophilicity

nucleophilicity: measures the strength of the nucleophile ; more nucleophilic = faster SN2 reaction

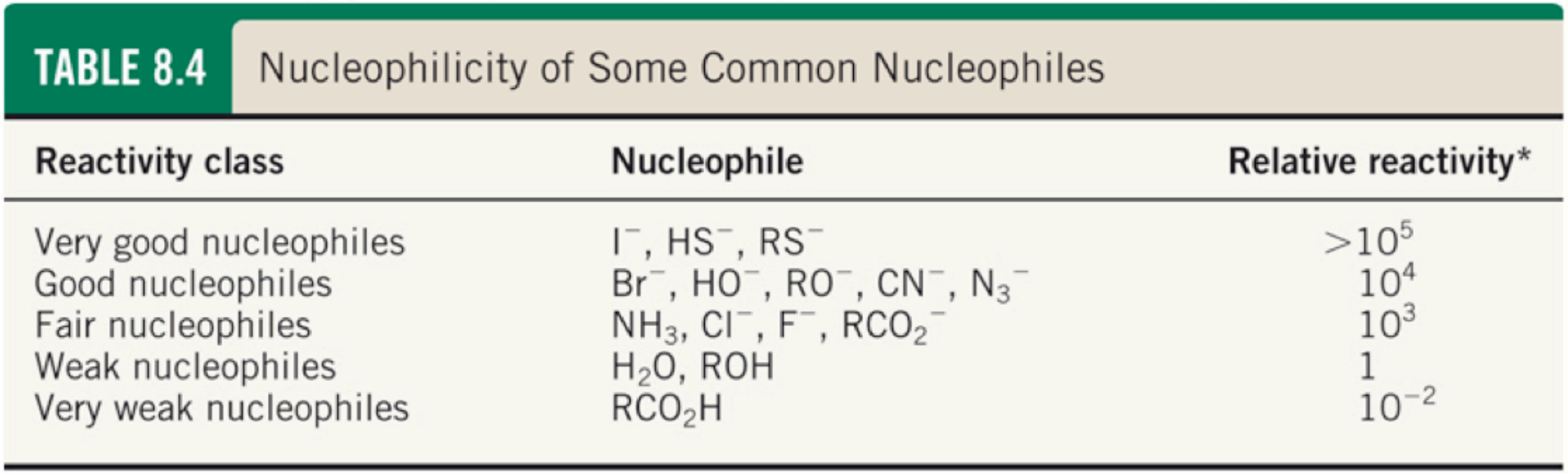
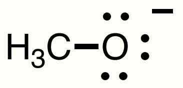


TABLE 8.4 Nucleophilicity of Some Common Nucleophiles

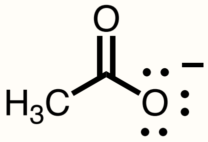
Reactivity class	Nucleophile	Relative reactivity*
Very good nucleophiles	I^-, HS^-, RS^-	$>10^5$
Good nucleophiles	Br^-, HO^-, RO^-, CN^-, N_3^-	10^4
Fair nucleophiles	NH_3, Cl^-, F^-, RCO_2^-	10^3
Weak nucleophiles	H_2O, ROH	1
Very weak nucleophiles	RCO_2H	10^{-2}

1. for identical atoms, more basic = more nucleophilic



CH_3OH
(conjugate acid)
pKa = 15.2

is more nucleophilic than
(stronger base = stronger nuc)



CH_3CO_2H
(conjugate acid)
pKa = 4.7

Nucleophilicity

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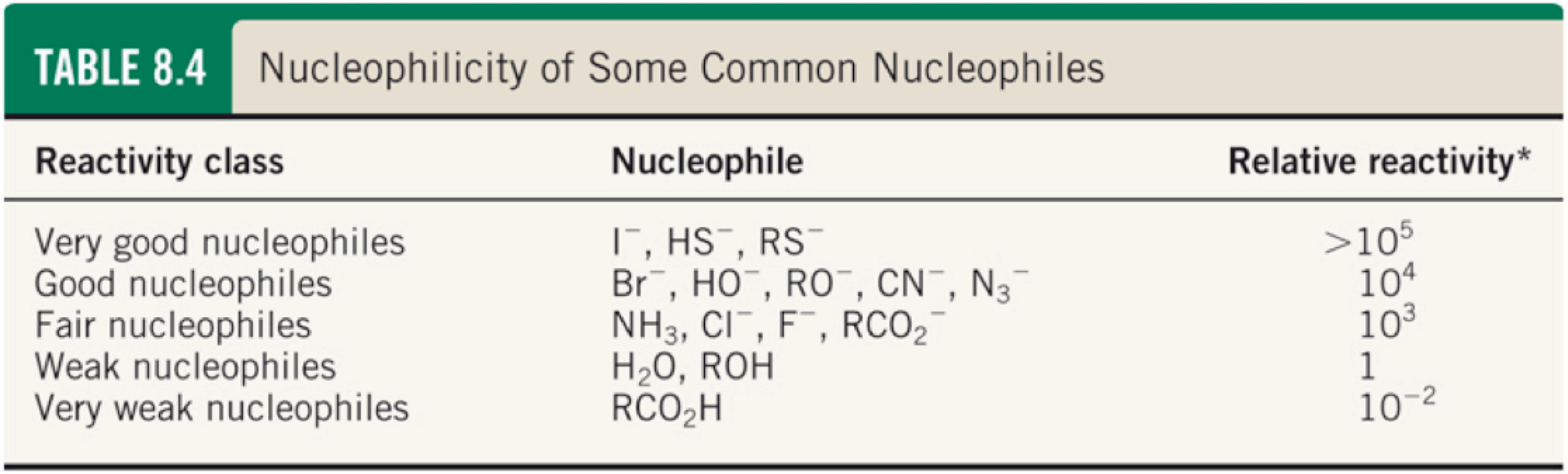

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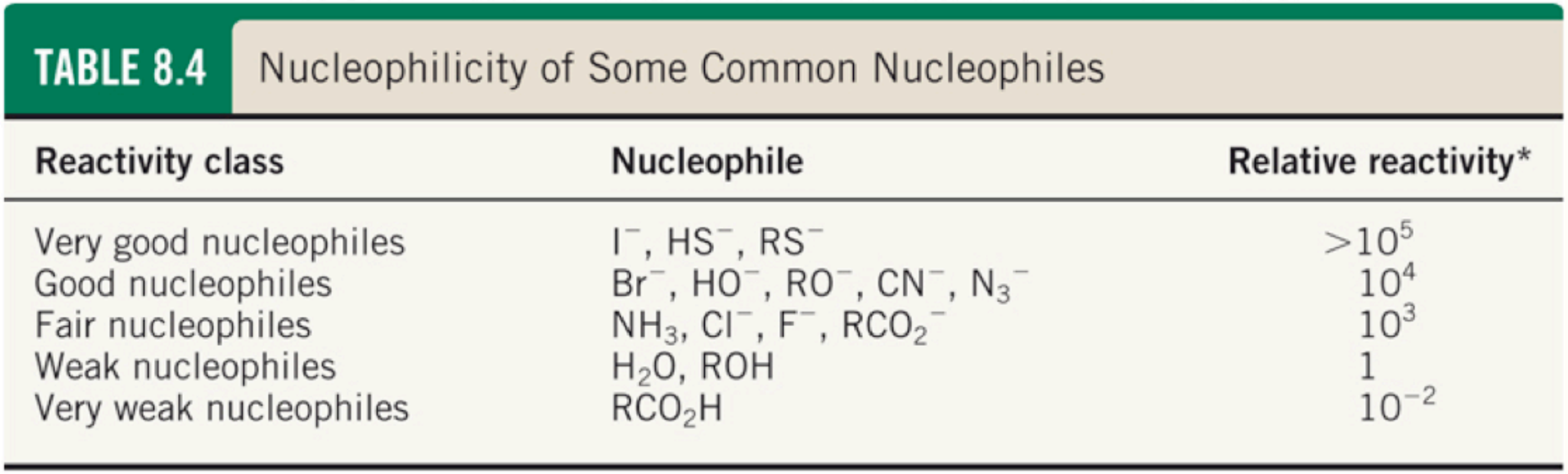
2. For atoms in the same row and with same charge, nucleophilicity decreases left to right

$H_3C-\ddot{N}H_2$	is more nucleophilic than (stronger base = stronger nuc)	$H_3C-\ddot{\underset{\cdot\cdot}{O}}H$
$CH_3NH_3^+$ (conjugate acid) pKa = 10.7		$CH_3OH_2^+$ (conjugate acid) pKa = -2

Nucleophilicity

nucleophilicity: measures the strength of the nucleophile ; more nucleophilic = faster SN2 reaction



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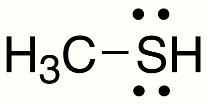
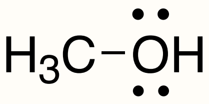
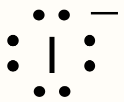
3. Nucleophilicity does not follow basicity down a column; nucleophilicity increase down a column

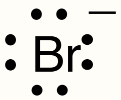

H_3C-SH

is more nucleophilic than

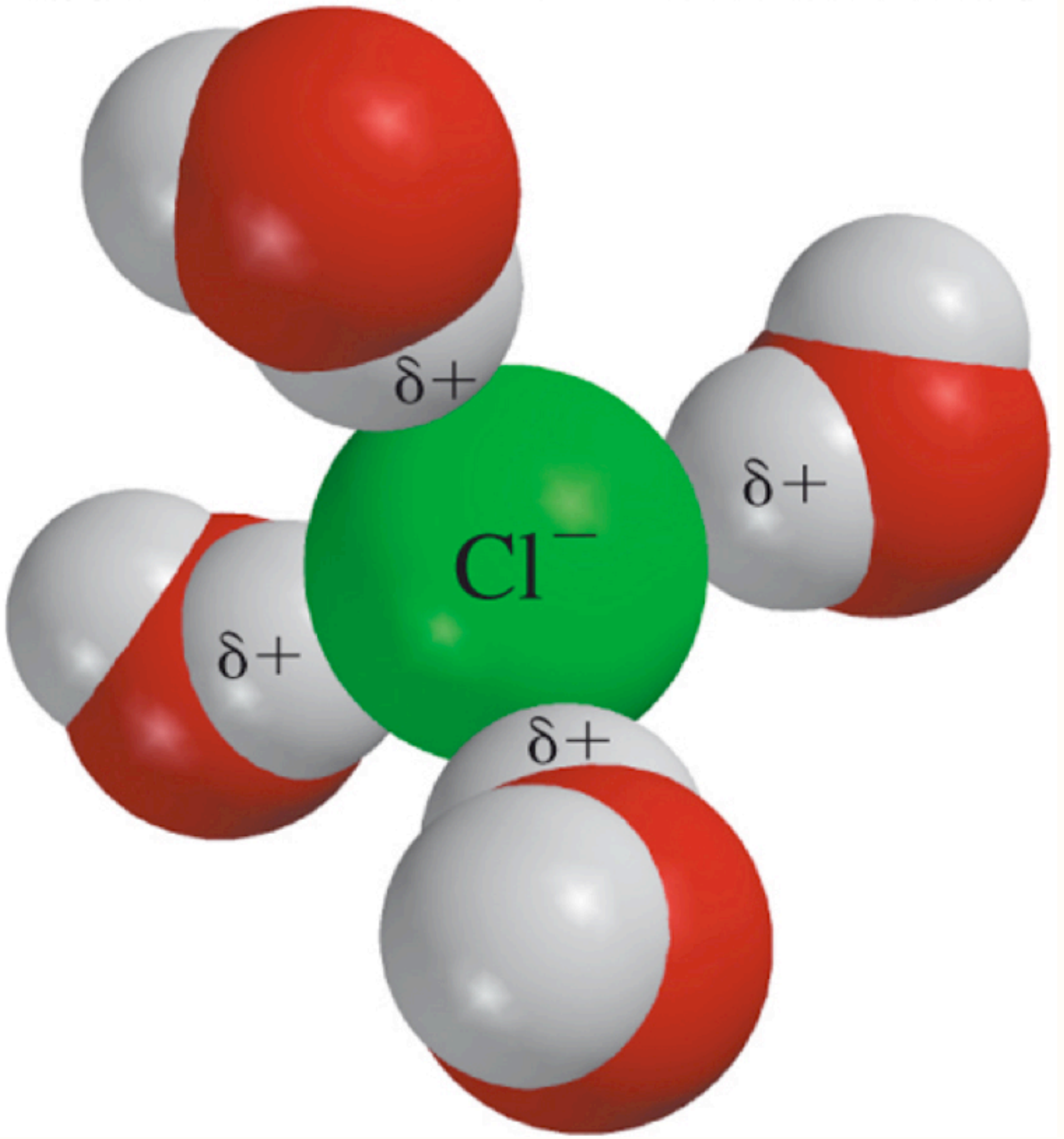

H_3C-OH


I^-

is more nucleophilic than


Br^-

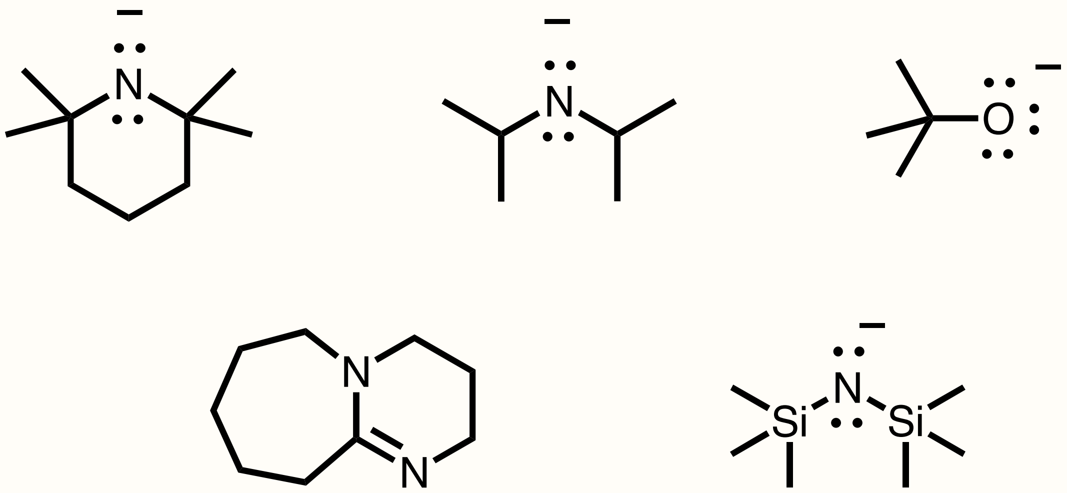
Explanation for Halide Nucleophilicity



- small anions =
- high charge to size ratio =
- ion-dipole forces between halide and solvent strongest for F^- and weakest for I^- =
- F– more solvated
- more difficult for F– to shed solvent molecules to react with electrophile =
- weaker nucleophile

Self-Test Question

All of the molecules/anions below are strong bases. However, each is non-nucleophilic; they do not participate in S_N2 reactions. Why?



sterically hindered = non-nucleophilic

- [✓ A.] large van der Waals radius
- B. unstable; decompose rapidly
- C. each atom already satisfies octet rule; can't form more bonds
- D. nucleophiles must be neutral
- E. too highly solvated

Chapter 8

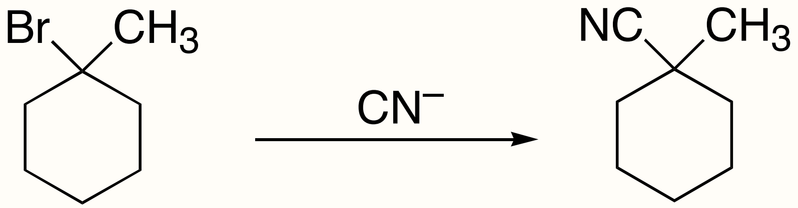
S_N1 Mechanism of Nucleophilic Substitution

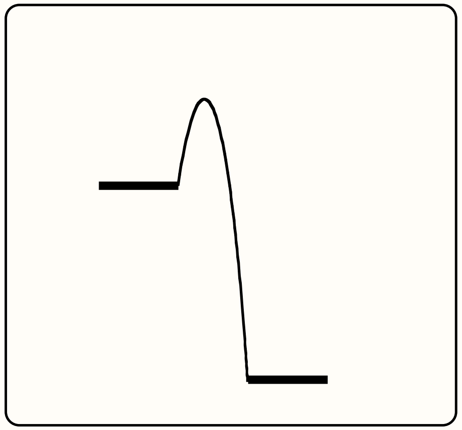
Sections 8.8 - 8.13

Self-Test Question

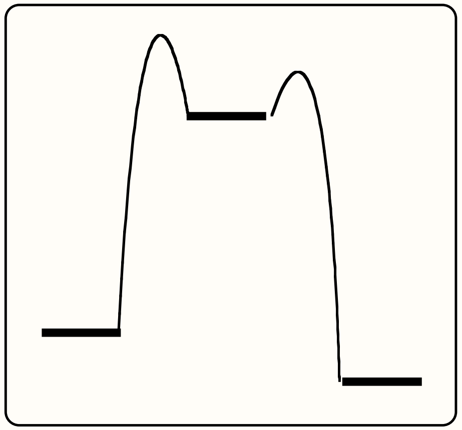
Which potential energy diagram best describes the substitution reaction of 1-bromo-1-methylcyclohexane with a cyanide nucleophile.

Hint: 3º alkyl halides do not proceed through an S_N2 mechanism.

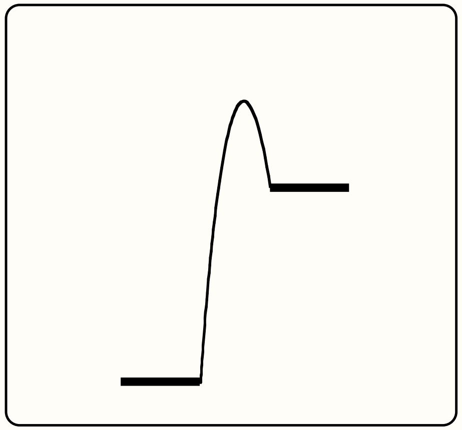




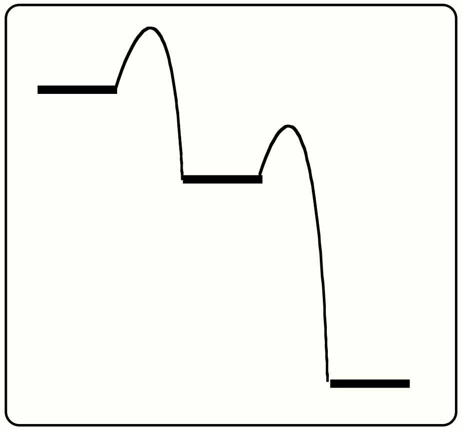
A



[✓ B]

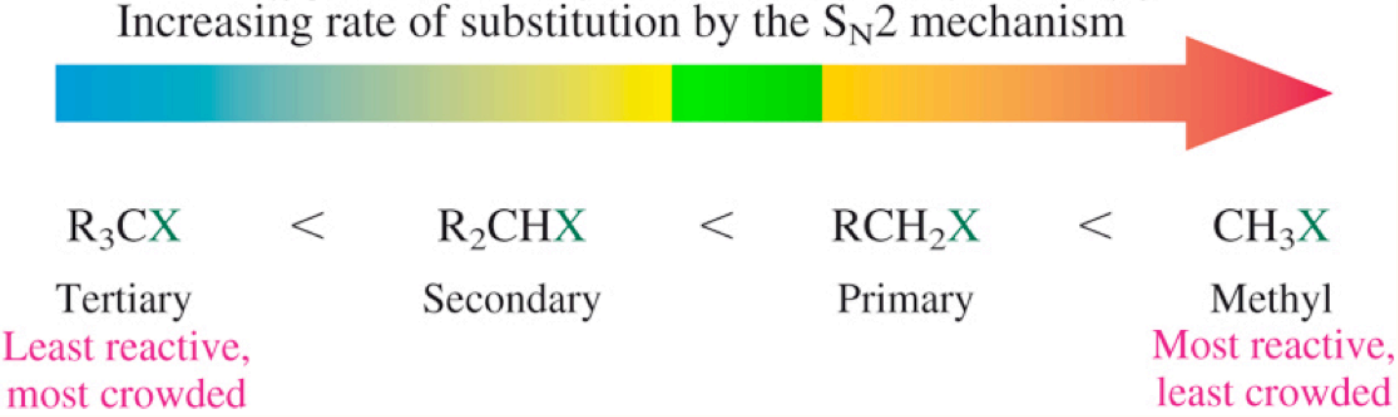


C



D

Tertiary Alkyl Halides Do Not Proceed Through an S_N2 Mechanism



Increasing rate of substitution by the S_N2 mechanism

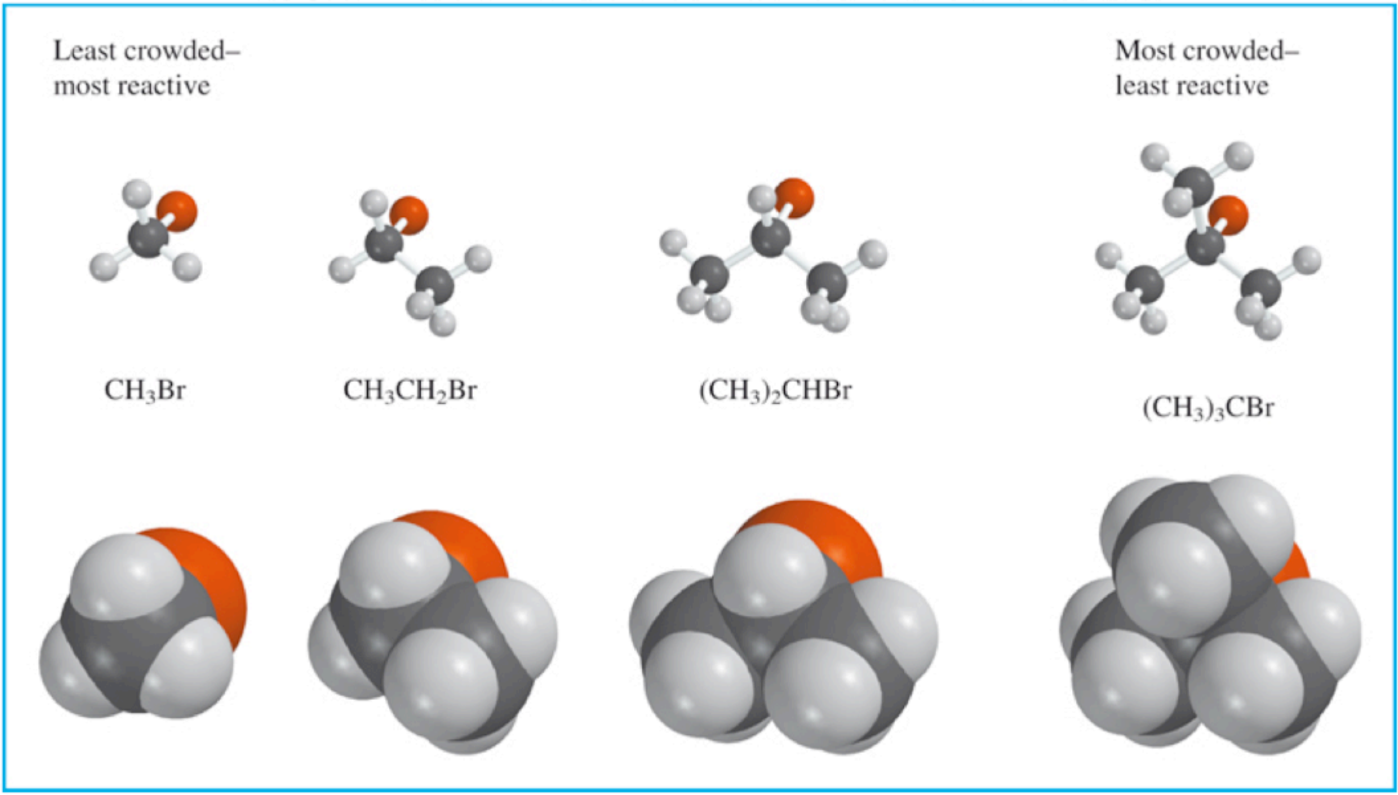
R_3CX < R_2CHX < RCH_2X < CH_3X

Tertiary — Least reactive, most crowded

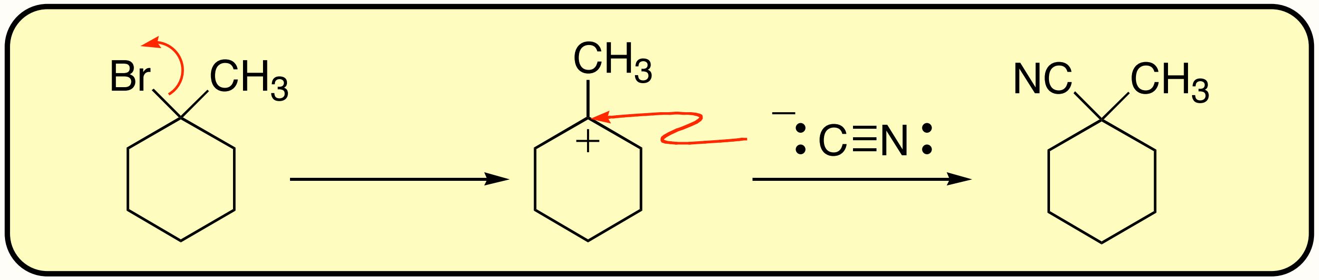
Secondary

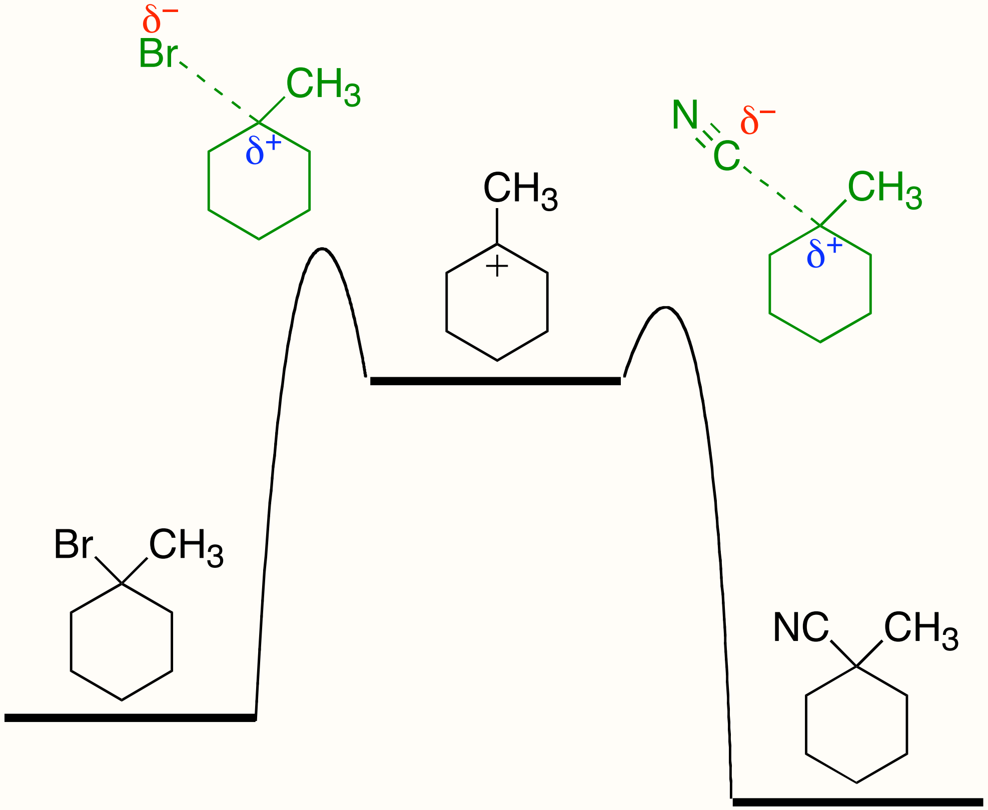
Primary

Methyl — Most reactive, least crowded



S_N1 Mechanism

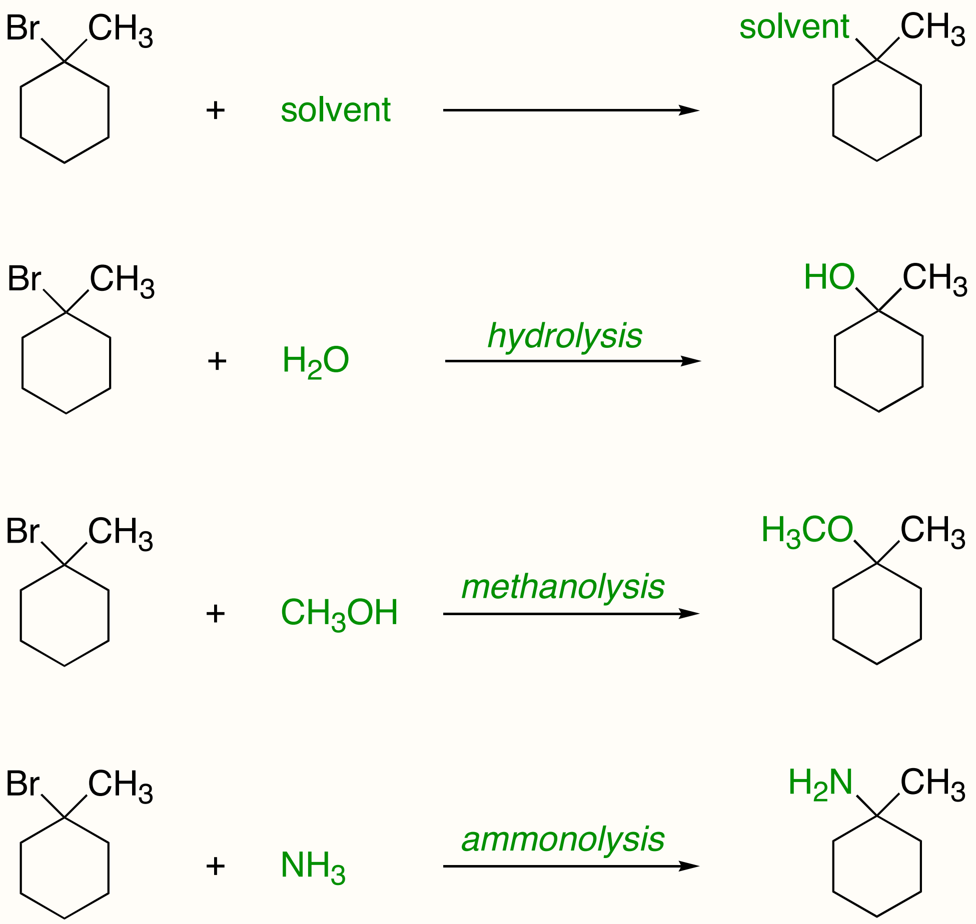




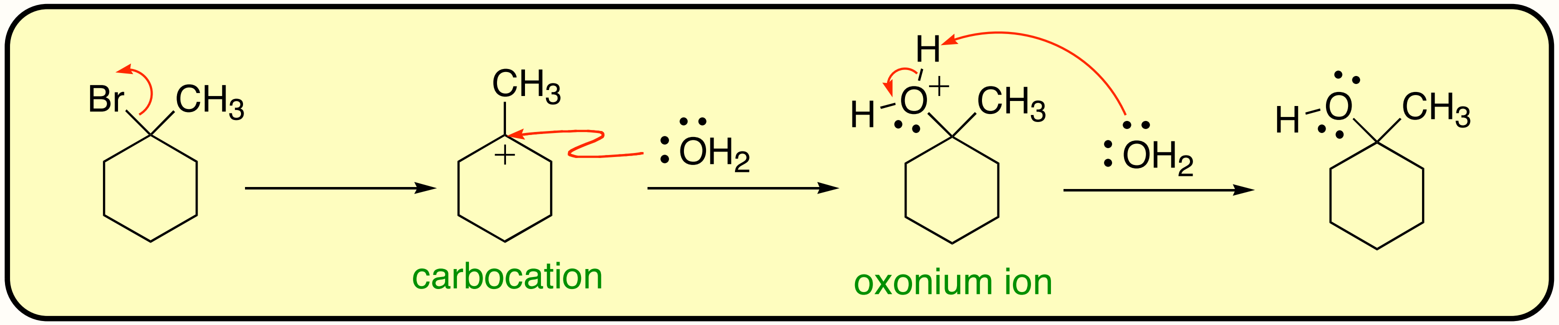
- C-LG bond breaks first; rate determining step (RDS)
- form carbocation intermediate
- nucleophile adds rapidly to carbocation
- rate = *k*[alkyl halide]
- unimolecular

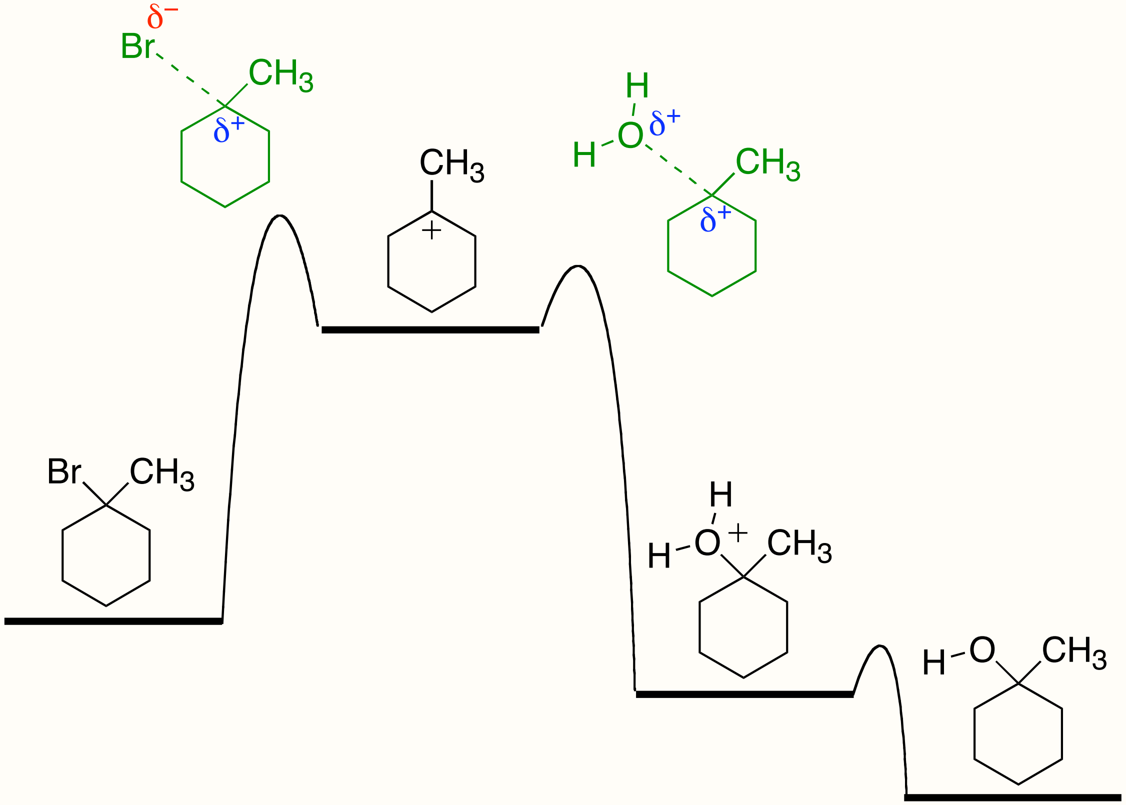
S_N1 Mechanism: Solvolysis

When the nucleophile undergoing either S_N1 or S_N2 is a molecule of the solvent, the process is called solvolysis



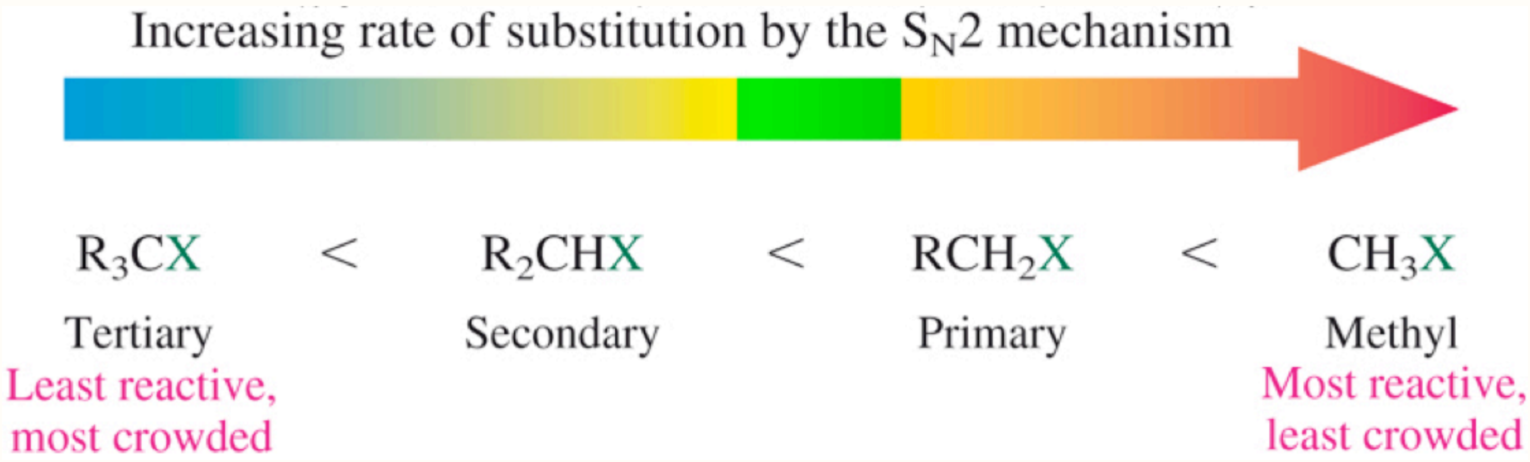
S_N1 Mechanism: Solvolysis





- solvent acts as nucleophile (neutral)
- same mechanism
- extra deprotonation step at the end (fast)
- any Bronsted base in solution can perform the deprotonation (here = H_2O or Br^-)

Rate of S_N1 vs. S_N2



Increasing rate of substitution by the S_N2 mechanism

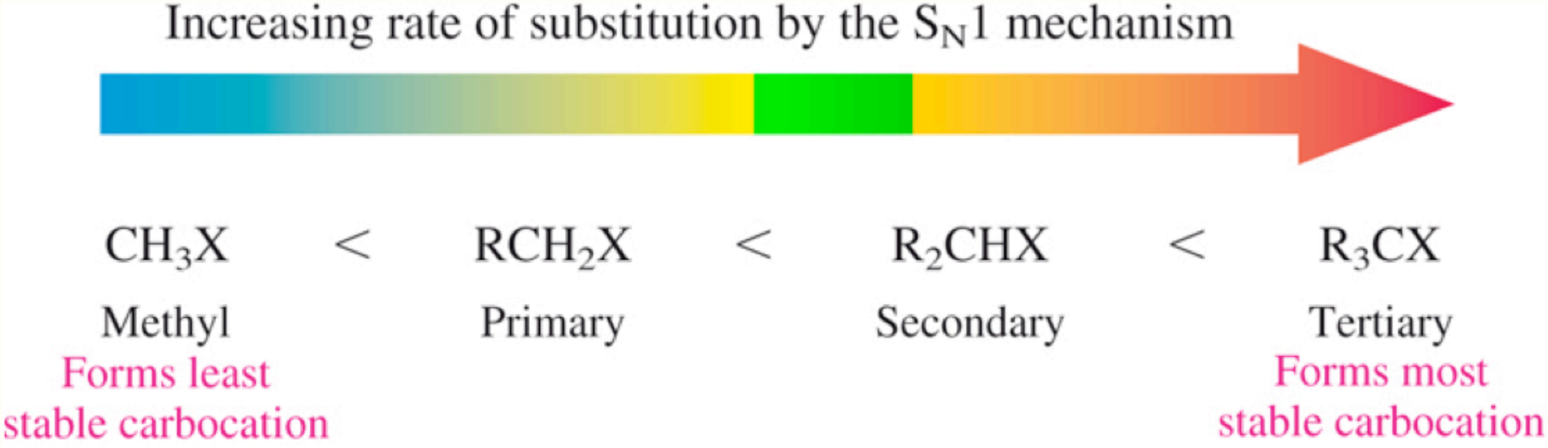
R_3CX < R_2CHX < RCH_2X < CH_3X

Tertiary — Least reactive, most crowded

Secondary

Primary

Methyl — Most reactive, least crowded



Increasing rate of substitution by the S_N1 mechanism

CH_3X < RCH_2X < R_2CHX < R_3CX

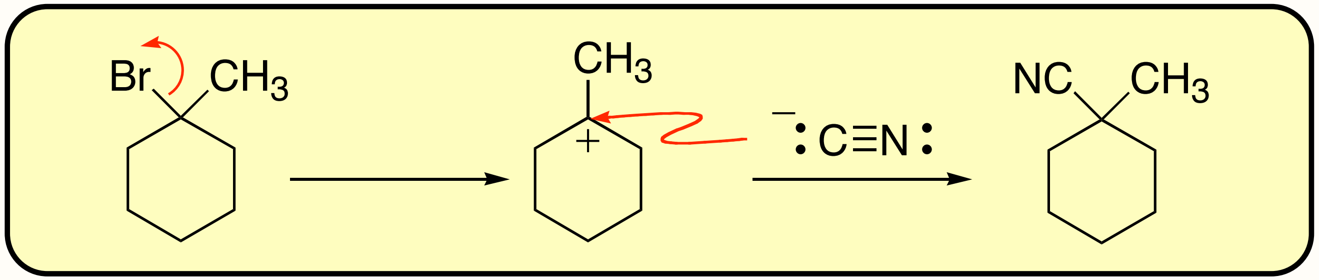
Methyl — Forms least stable carbocation

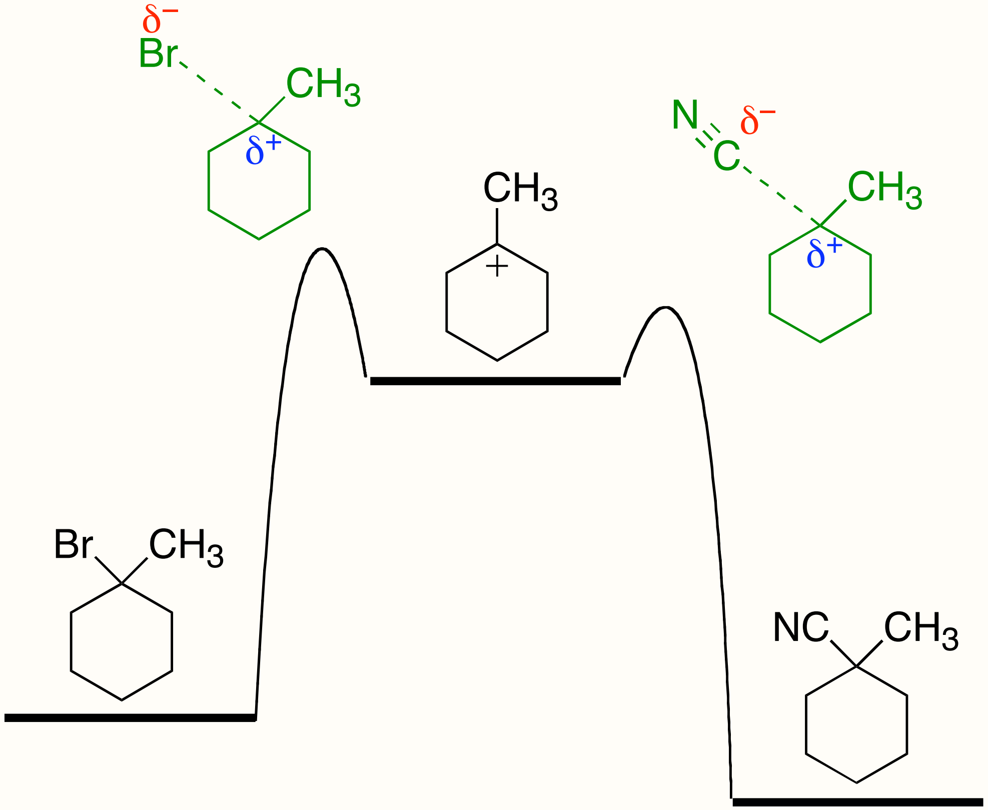
Primary

Secondary

Tertiary — Forms most stable carbocation

S_N1 Mechanism

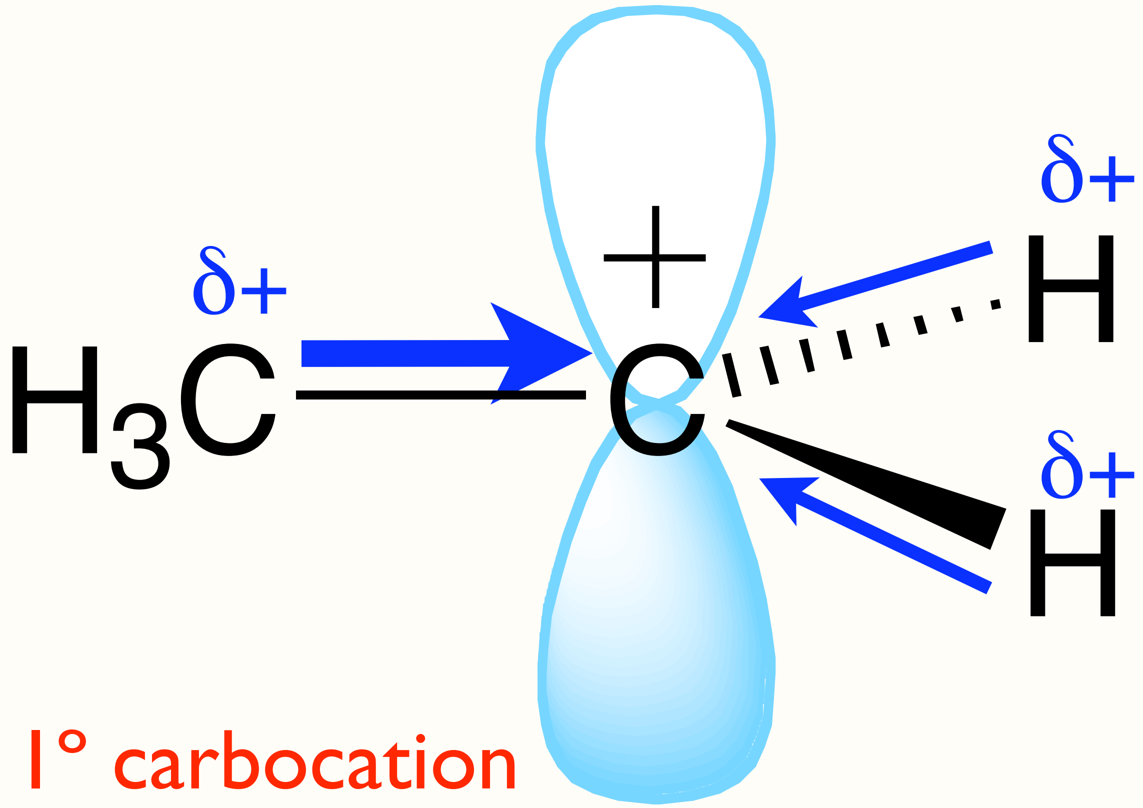




- Hammond Postulate: late transition state (TS) = TS is similar in structure to carbocation intermediate =
- what stabilizes carbocation will also stabilize the TS
- lower energy TS = faster reaction
- What lowers the energy of carbocations and thus the TS?

Review: Carbocation Stability

1. Inductive Effect
2. Hyperconjugation
3. Resonance



1° carbocation

- electron donation through σ-bonds toward carbocation delocalizes charge (spreads out)
- C-C σ-bonds are more polarizable, therefore donate more electron density through σ-bonds
- more C-C σ-bonds = more stable carbocation

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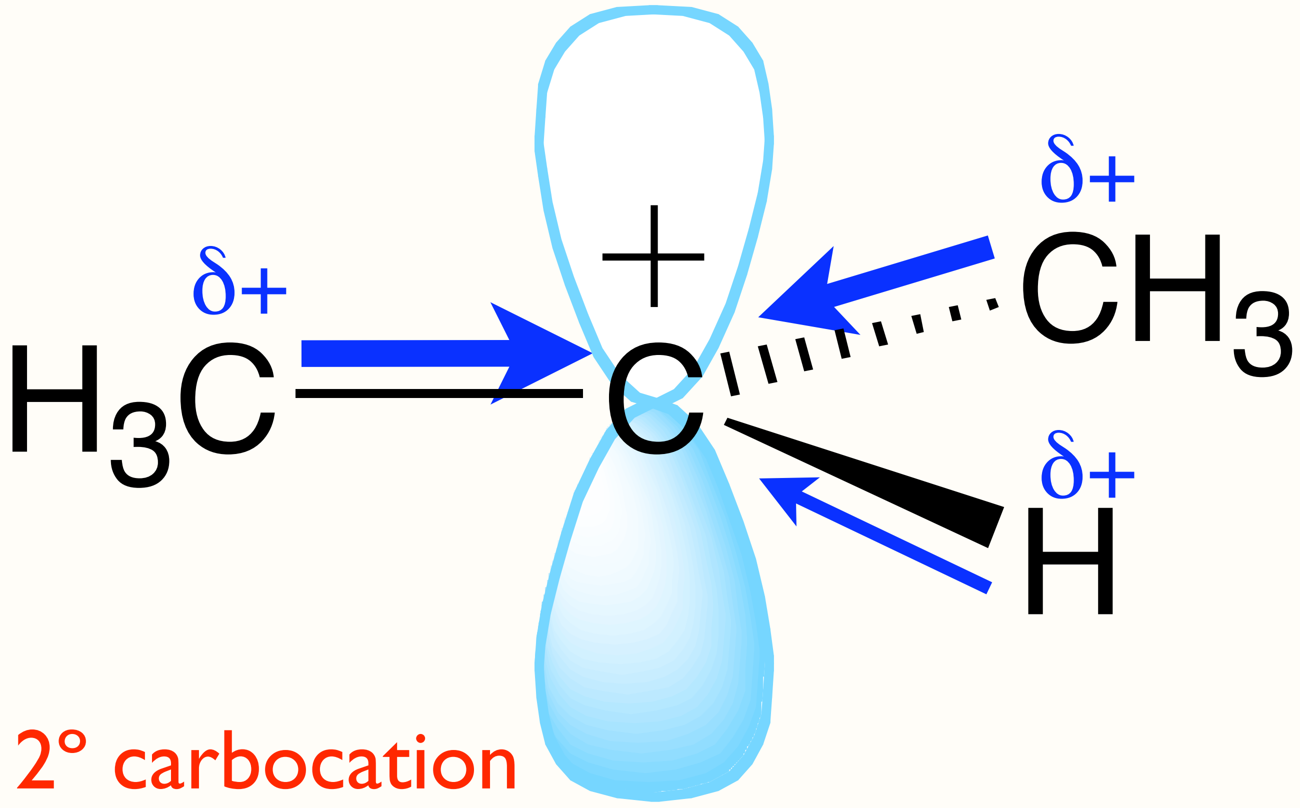

2° carbocation

- electron donation through σ-bonds toward carbocation delocalizes charge (spreads out)
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Review: Carbocation Stability

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2. Hyperconjugation
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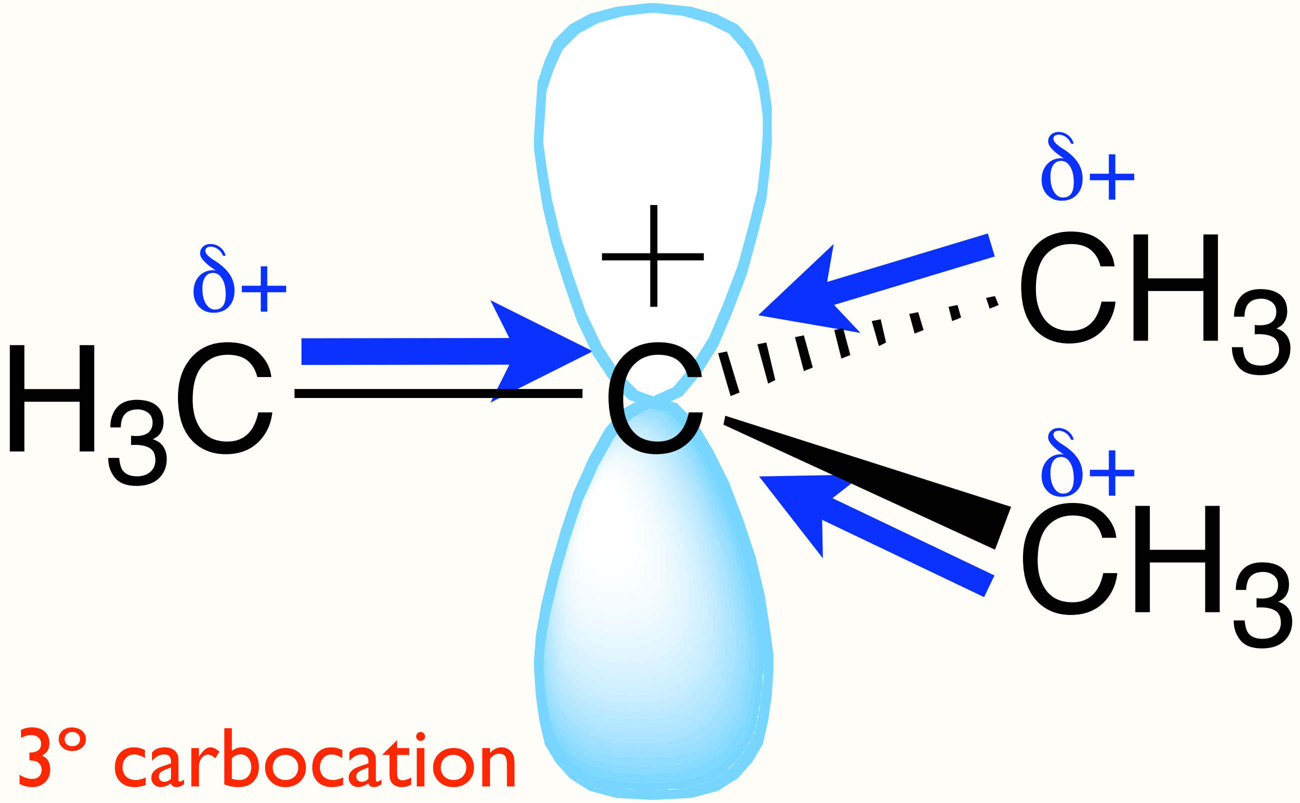

3° carbocation

- electron donation through σ-bonds toward carbocation delocalizes charge (spreads out)
- C-C σ-bonds are more polarizable, therefore donate more electron density through σ-bonds
- more C-C σ-bonds = more stable carbocation

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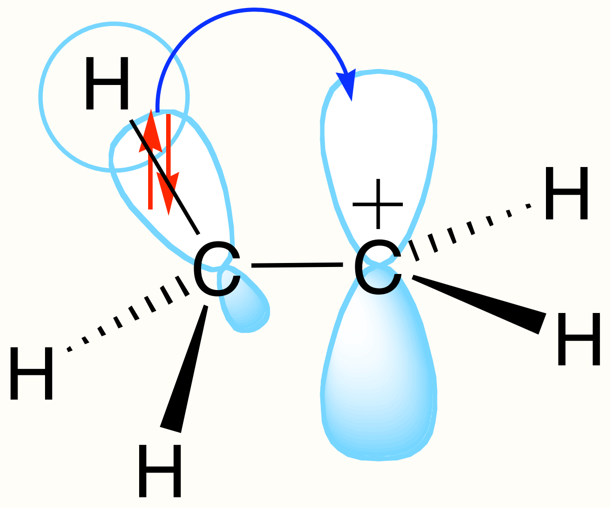

1° carbocation

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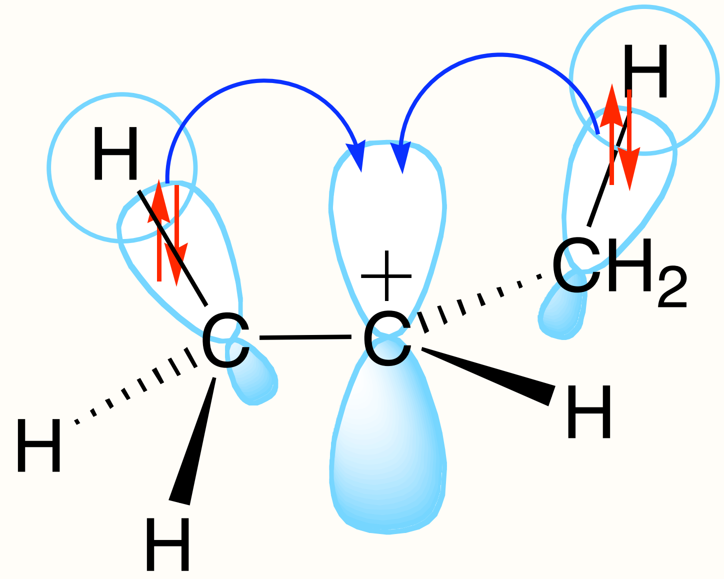

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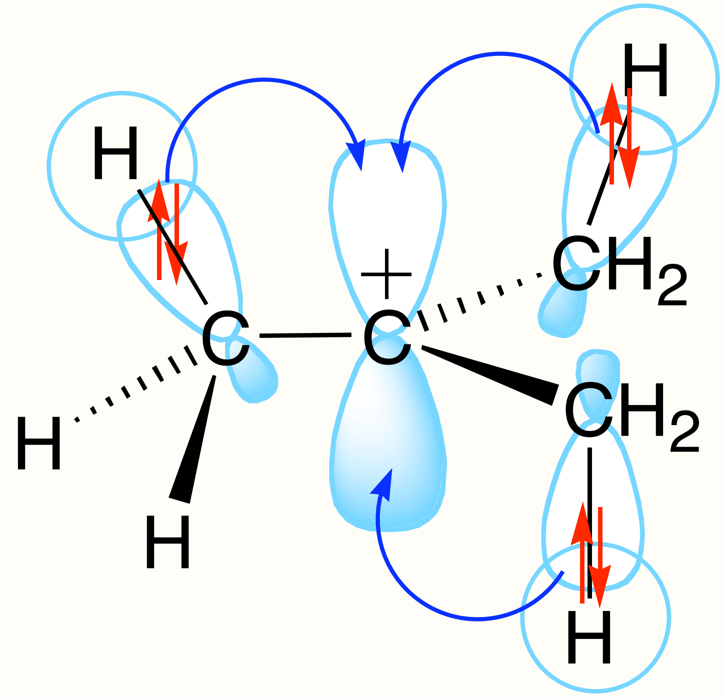

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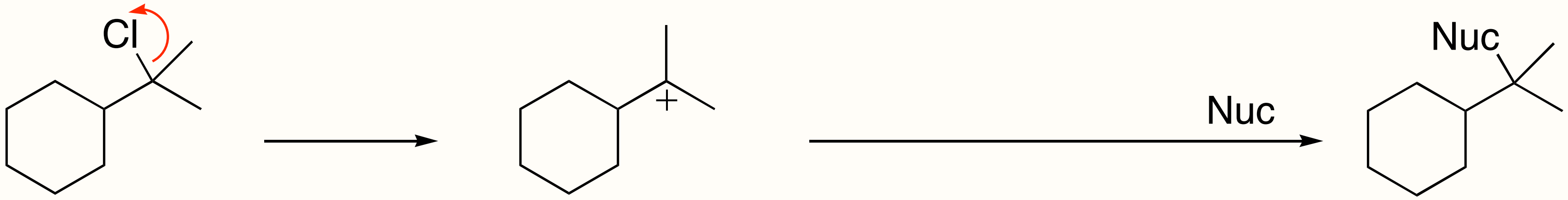
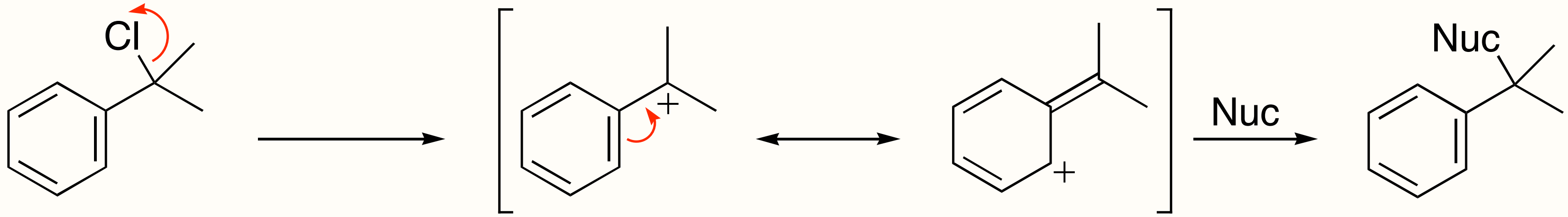
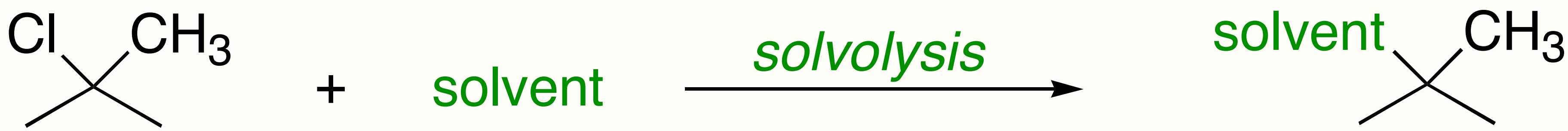


no resonance = less stable (higher energy) = slower



resonance = more stable (lower energy) = faster

Carbocation Stability: Solvent Effect



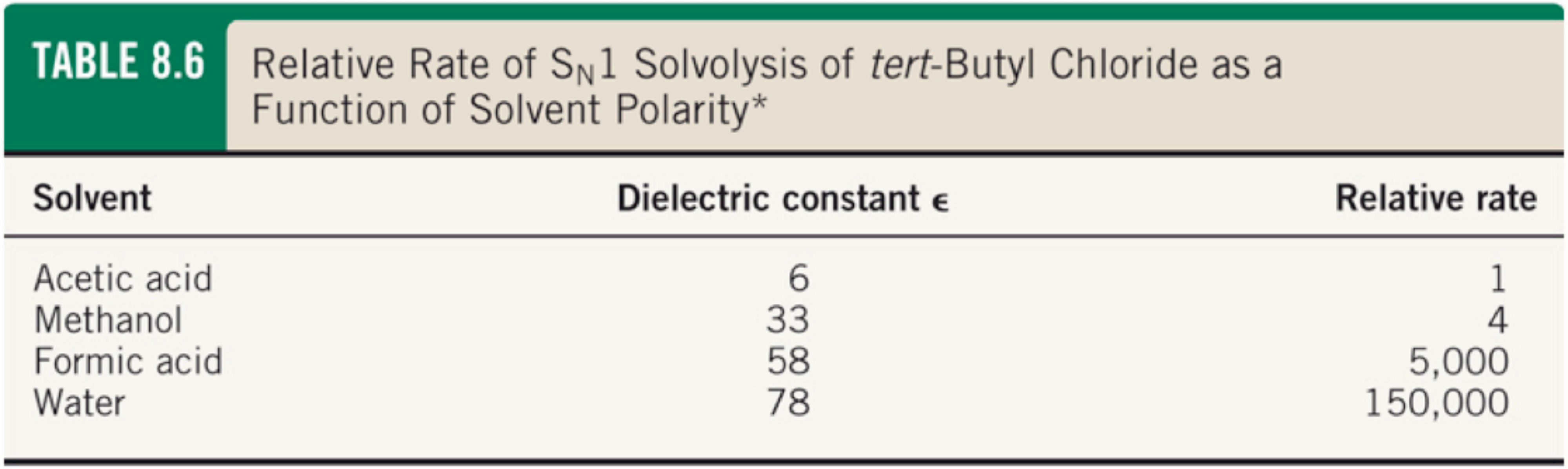


TABLE 8.6 Relative Rate of S_N1 Solvolysis of *tert*-Butyl Chloride as a Function of Solvent Polarity*

Solvent	**Dielectric constant ϵ**	**Relative rate**
Acetic acid	6	1
Methanol	33	4
Formic acid	58	5,000
Water	78	150,000

- dielectric constant (ε) = a crude measure of a solvent's polarity
- more polar solvent = more stable carbocation = faster reaction (krel)
- polar stabilizes polar

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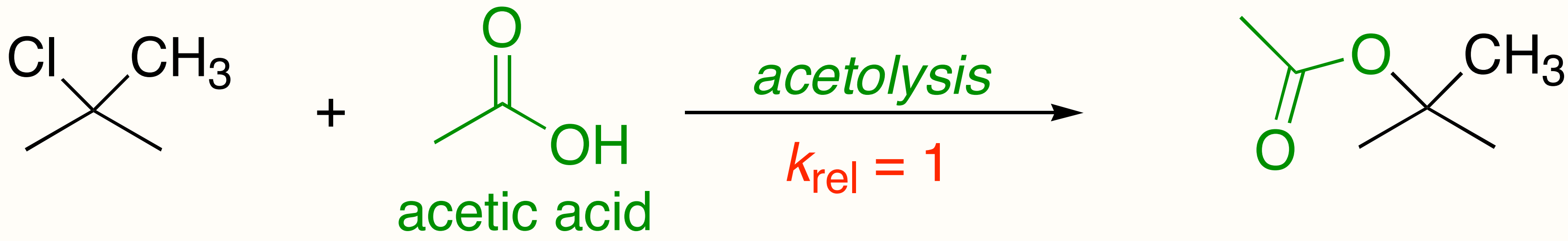

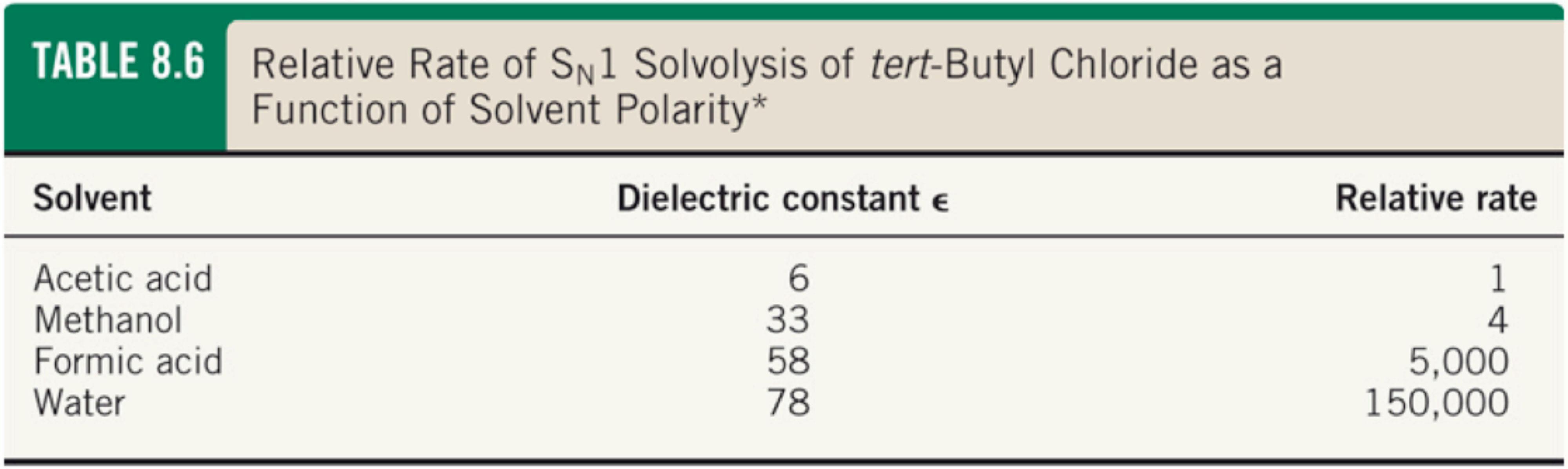

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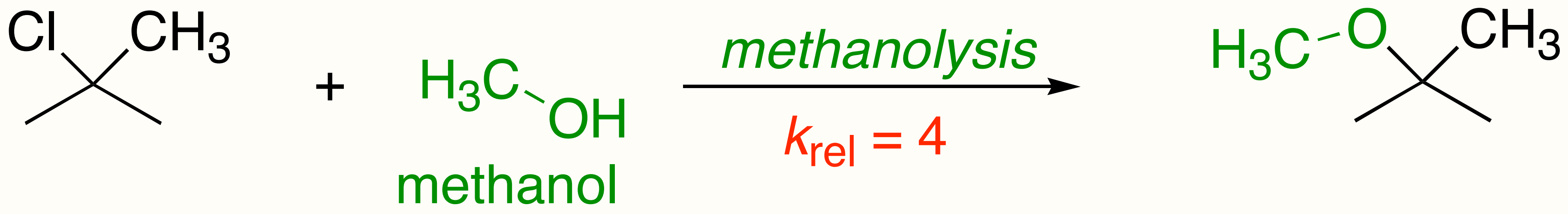

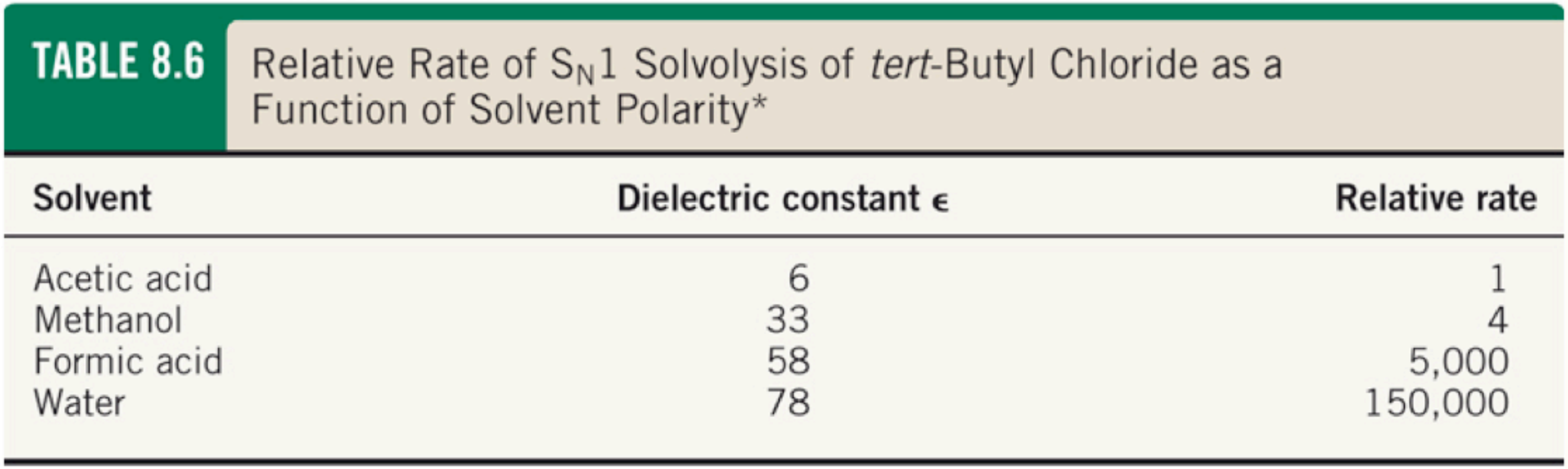

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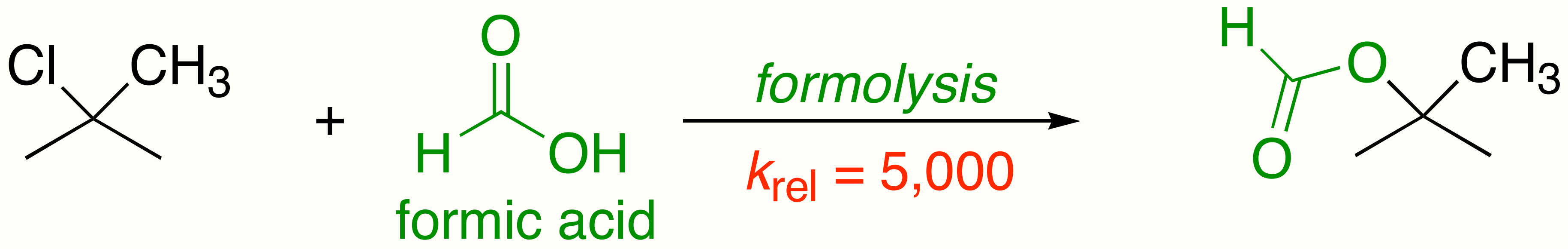

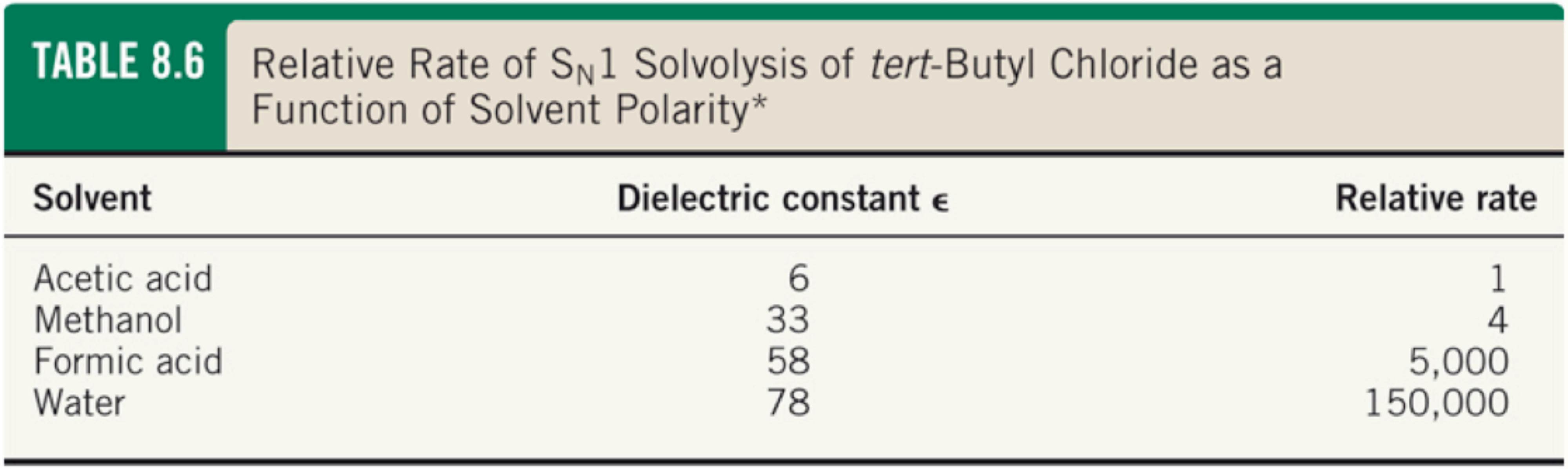

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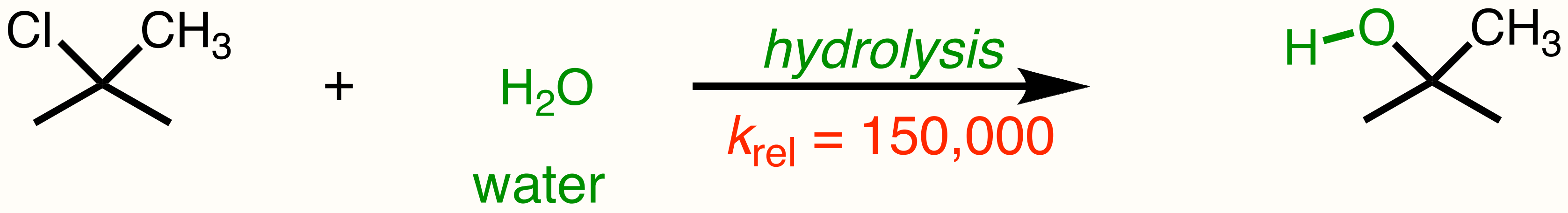

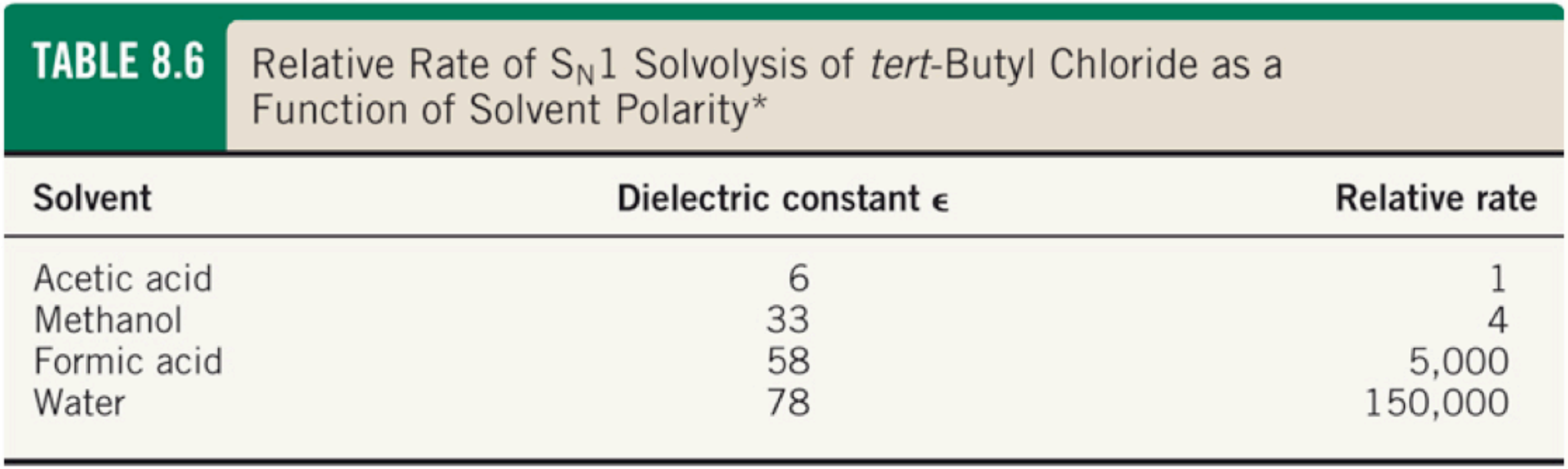

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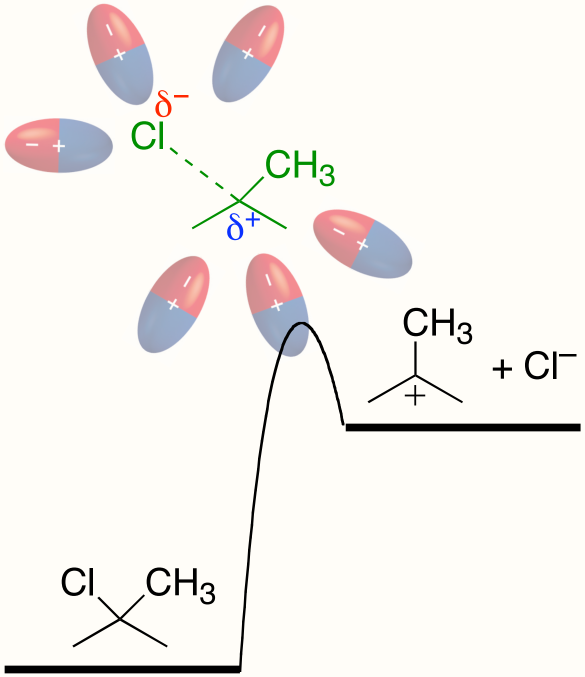
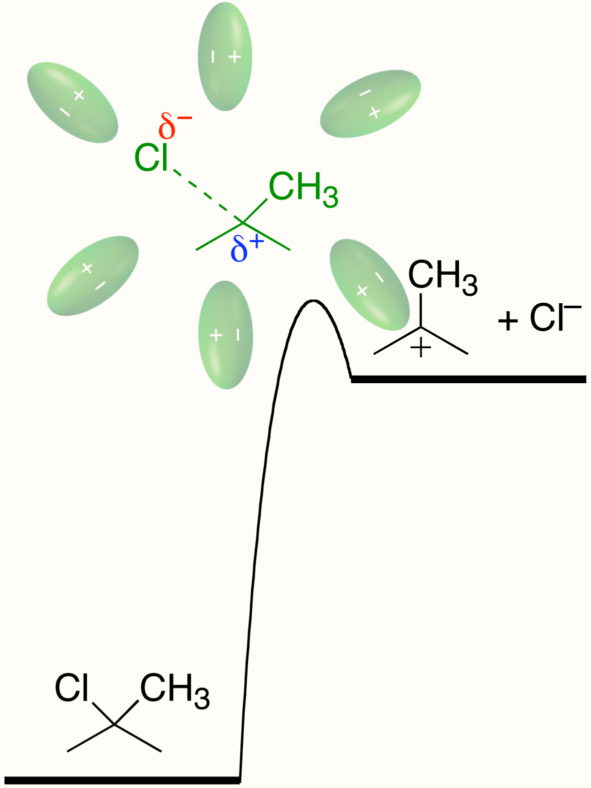
Solvent Effect on Carbocation Stability





- polar solvent reduce charge in TS through dipole-dipole interactions
- less TS charge = lower energy
- lower energy TS = faster S_N1
- little effect on alkyl halide reactant

- non-polar solvent does not have strong VW interactions
- more TS charge = higher energy
- higher energy TS = faster S_N1
- little effect on alkyl halide reactant

Solvent Effects on S_N2 Reactions?

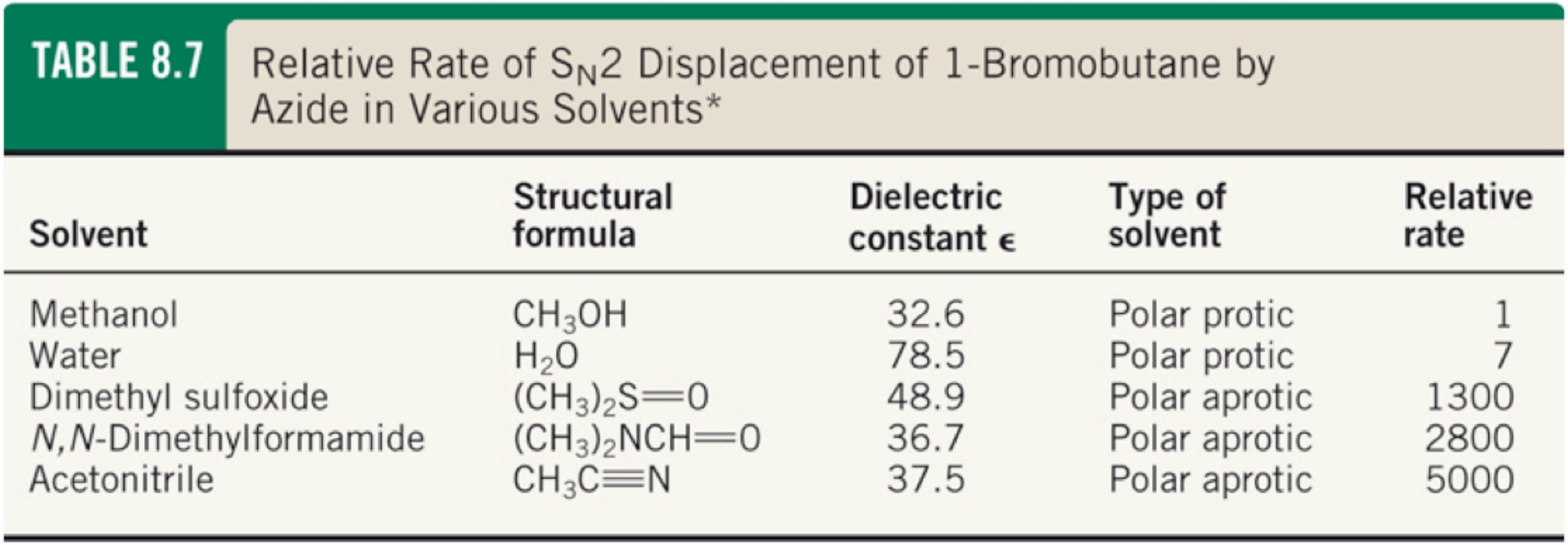


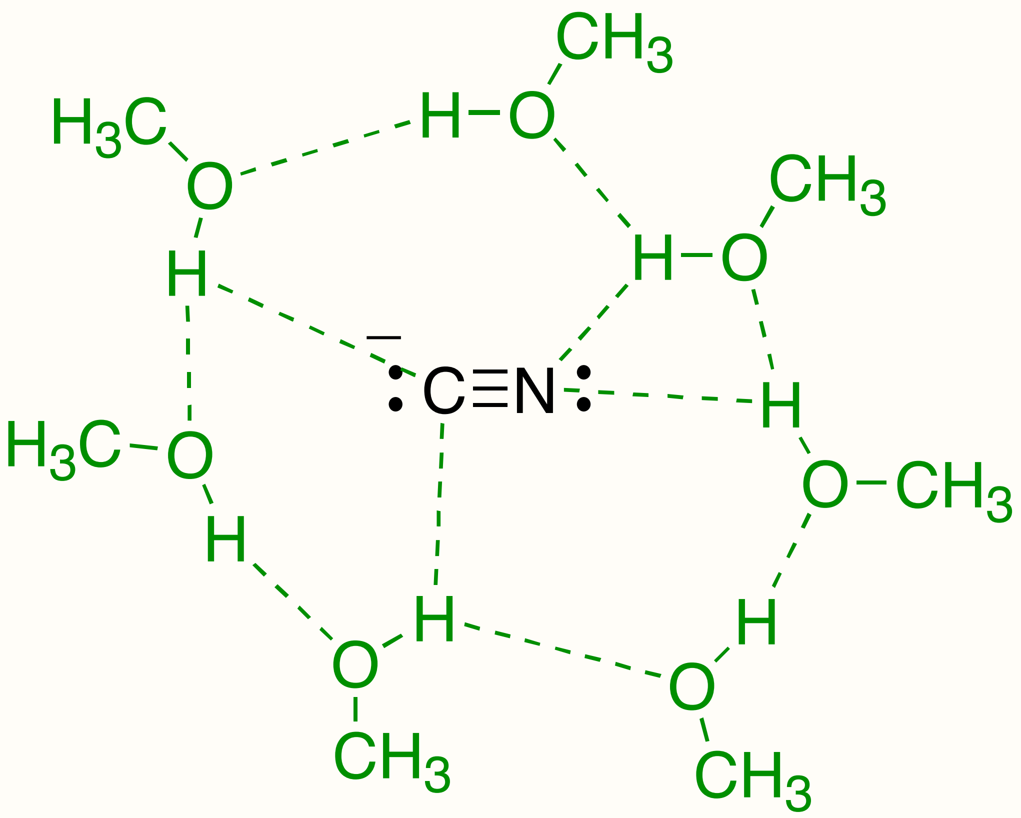
TABLE 8.7 Relative Rate of S_N2 Displacement of 1-Bromobutane by Azide in Various Solvents*

Solvent	Structural formula	Dielectric constant ϵ	Type of solvent	Relative rate
Methanol	CH_3OH	32.6	Polar protic	1
Water	H_2O	78.5	Polar protic	7
Dimethyl sulfoxide	$(CH_3)_2S{=}O$	48.9	Polar aprotic	1300
N,N-Dimethylformamide	$(CH_3)_2NCH{=}O$	36.7	Polar aprotic	2800
Acetonitrile	$CH_3C{\equiv}N$	37.5	Polar aprotic	5000

- protic: contains an acidic hydrogen capable of H-bonding (OH, NH, SH)
- no trend between dielectric constant and rate for S_N2 reactions
- fastest S_N2 reactions in polar aprotic (no acidic hydrogen)

Solvent Effects on S_N2 Reactions

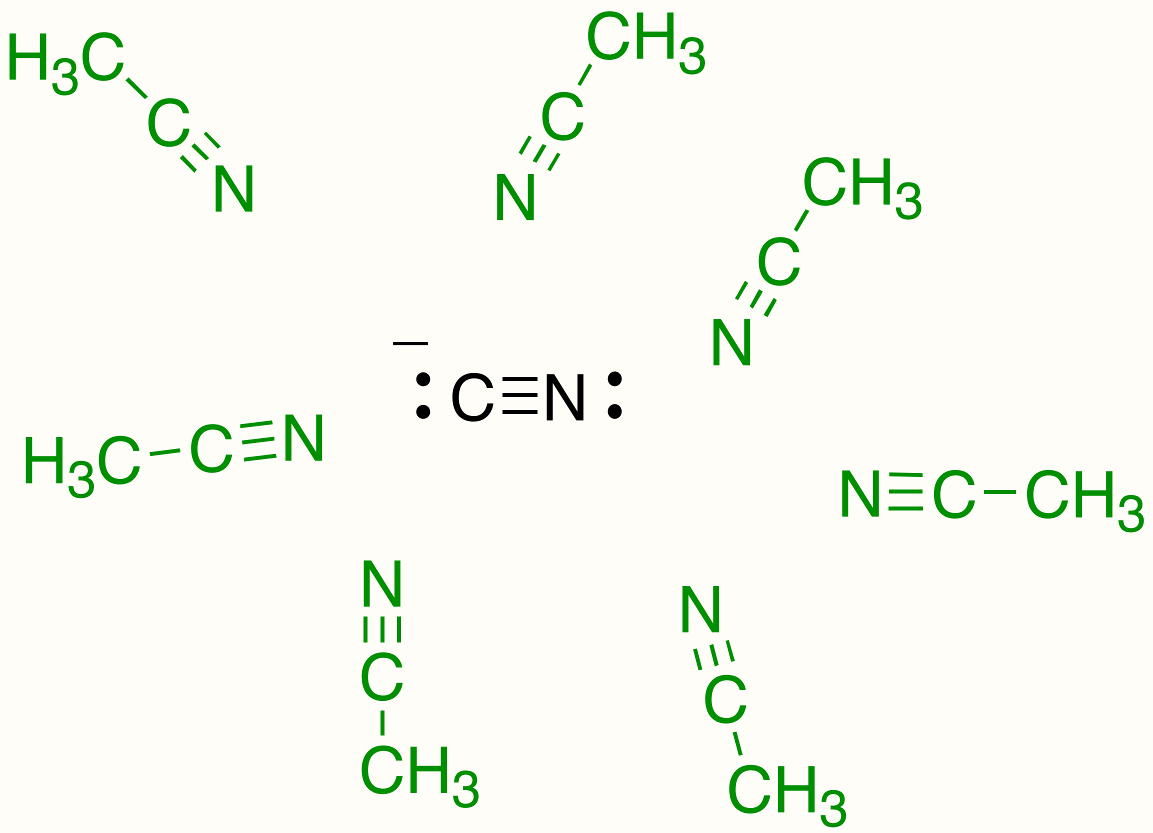
polar protic solvents = more solvation of nucleophile, especially through hydrogen bonding



- protic solvent = capable of hydrogen bonding
- more hydrogen bonding = more solvation of nucleophile
- form a solvation <u>shell</u> around nucleophile
- more solvated = decreased nucleophilicity
- slower S_N2 reaction

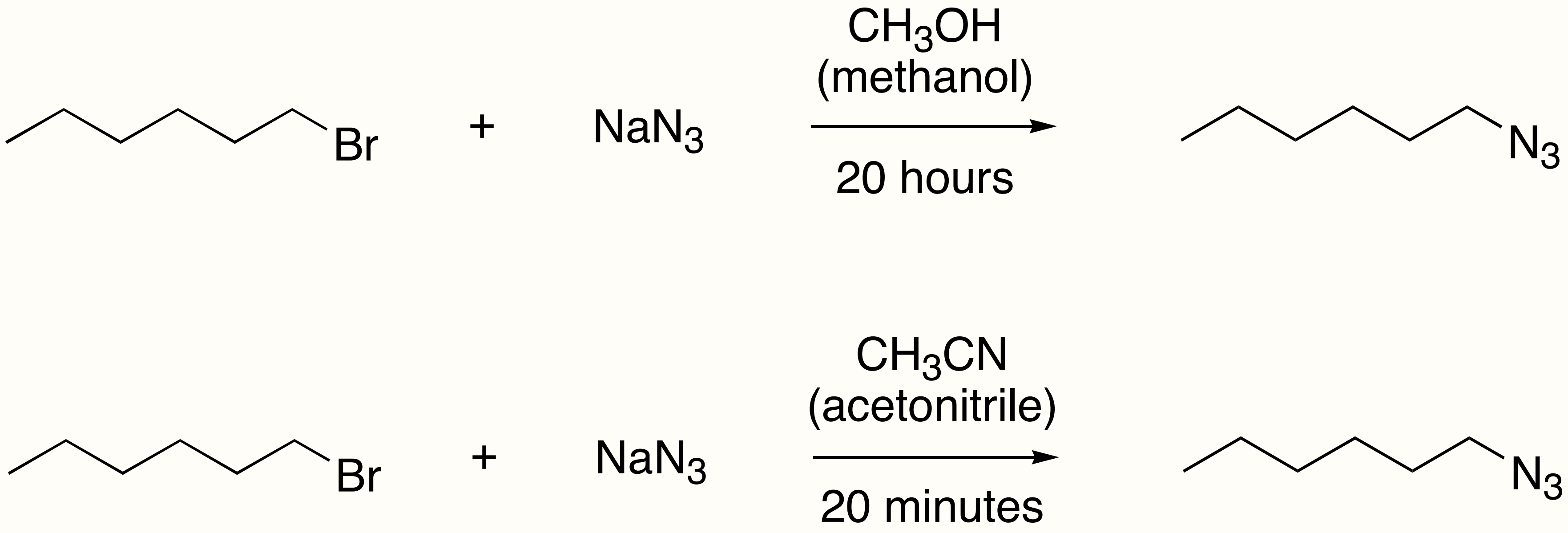
Solvent Effects on S_N2 Reactions

polar aprotic solvents = less solvation of nucleophile = more nucleophilic = faster S_N2



- aprotic solvent = not capable of hydrogen bonding
- less solvation than protic
- nucleophile is “freer”
- less solvated = increased nucleophilicity
- faster S_N2 reaction

Solvent Effects on S_N2 Reactions

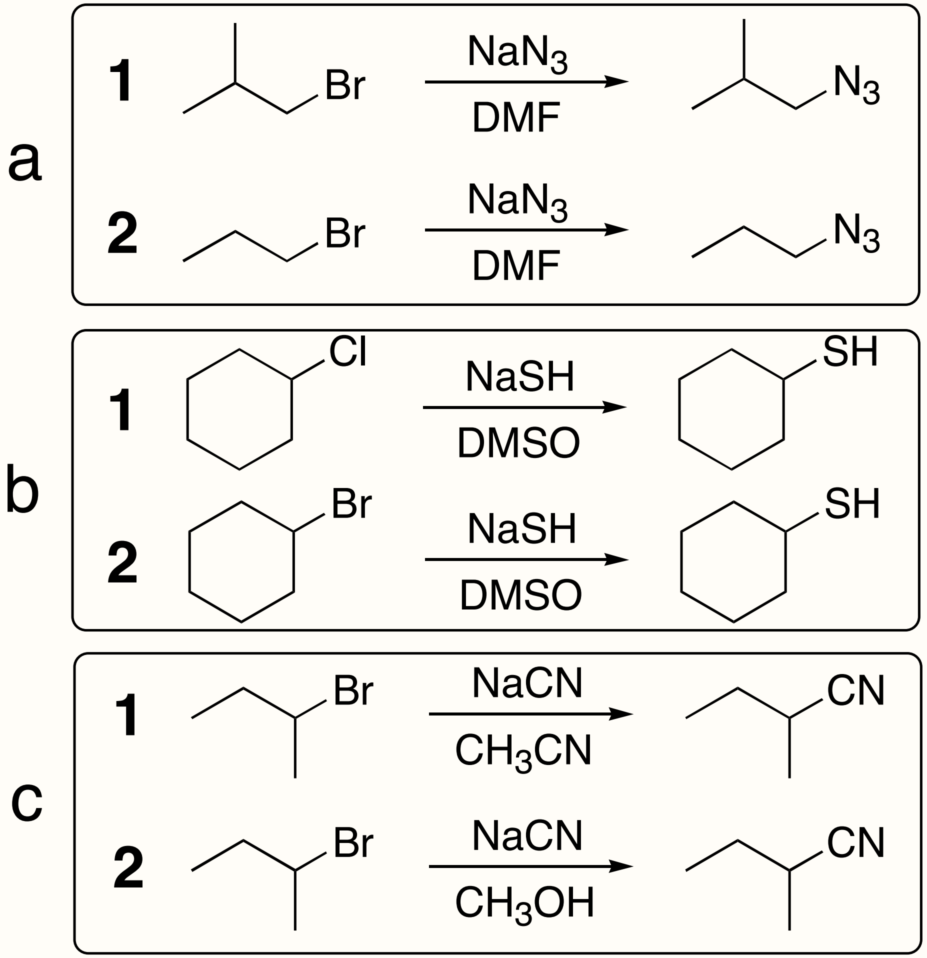


Br + NaN_3 $\xrightarrow[\text{20 hours}]{CH_3OH \text{ (methanol)}}$ N_3

Br + NaN_3 $\xrightarrow[\text{20 minutes}]{CH_3CN \text{ (acetonitrile)}}$ N_3

Self-Test Question

Determine the fastest reaction in each pair and list them in order of a,b,c.



A. 1,1,1

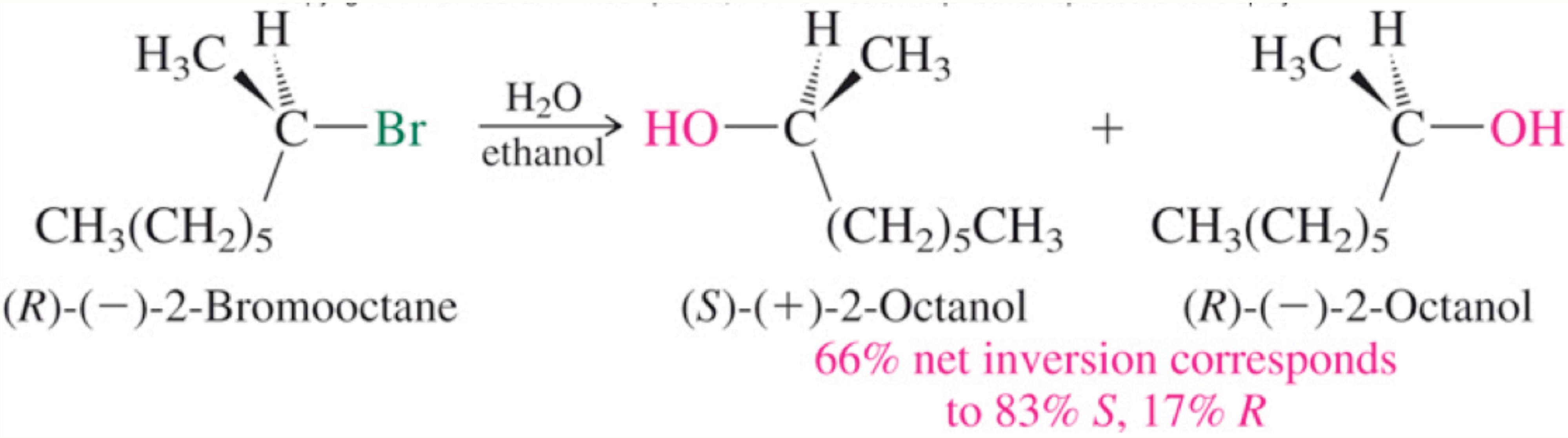
[✓ B.] 2,2,1

C. 1,2,2

D. 2,1,1

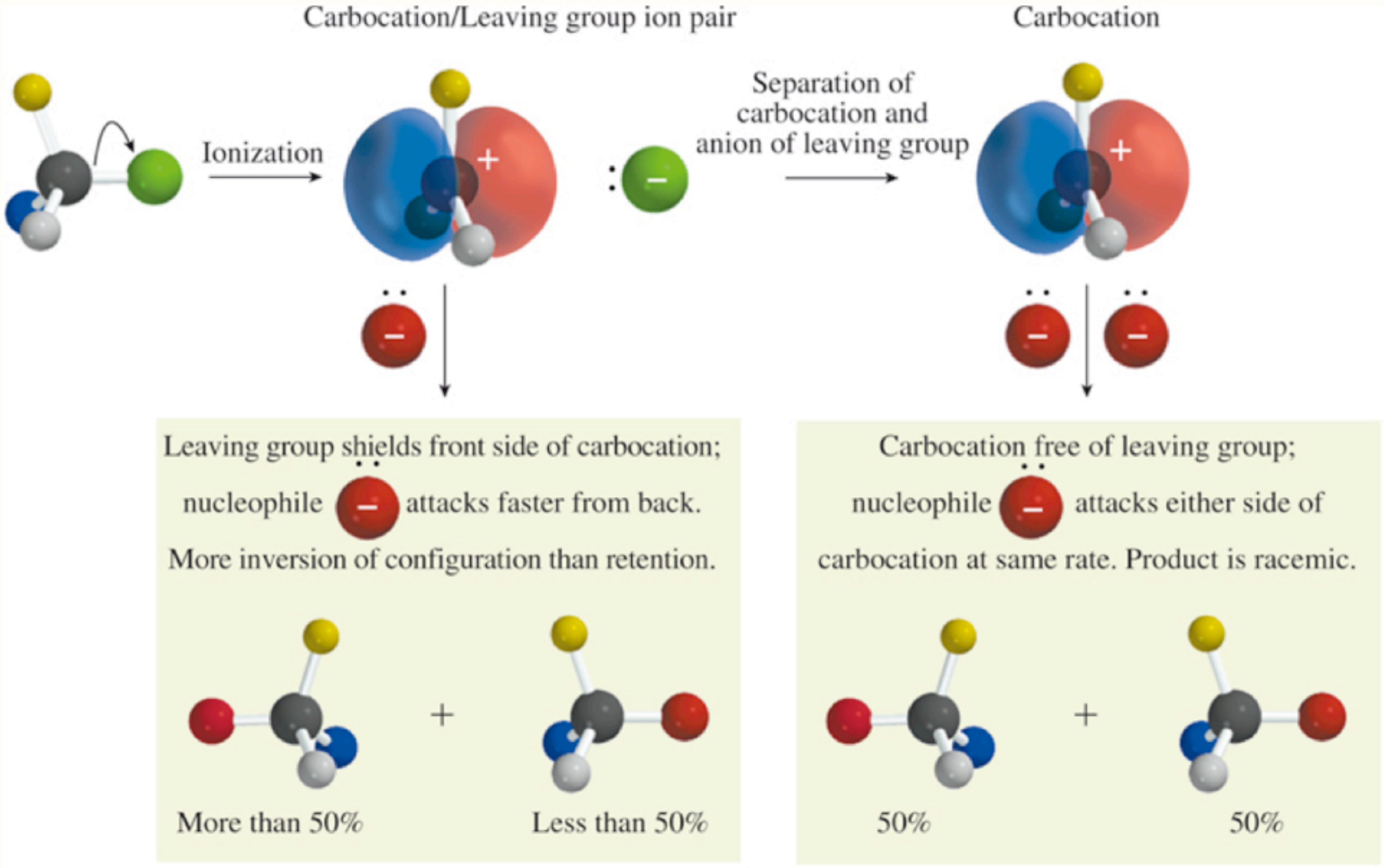
E. 2,1,2

Stereochemistry of S_N1 Reactions



- generally, S_N1 reactions are <u>not</u> stereospecific
- nucleophiles can add to both sides of a carbocation intermediate
- results in inversion of configuration and retention of configuration
- racemization: conversion of optically active starting material to a racemic mixture (1:1 of enantiomers)
- Why is racemization not <u>complete</u> in above example?

Stereochemistry of S_N1 Reactions

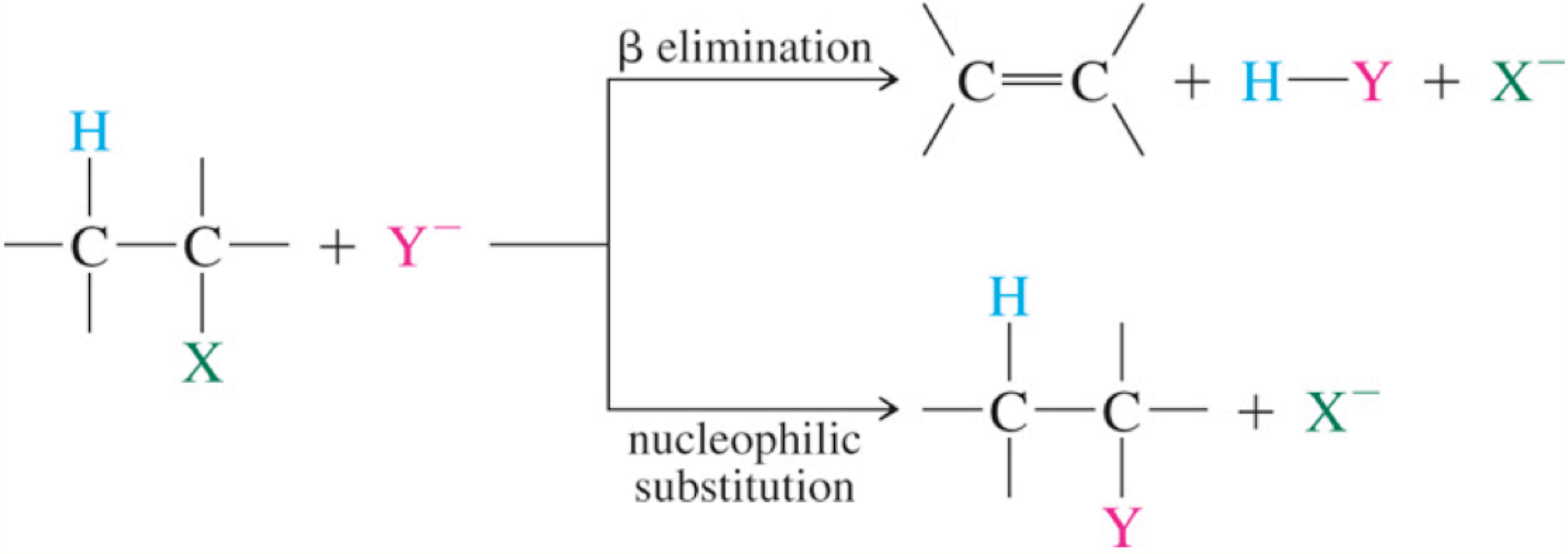


Leaving group shields front side of carbocation; nucleophile ⊖ attacks faster from back. More inversion of configuration than retention.

Carbocation free of leaving group; nucleophile ⊖ attacks either side of carbocation at same rate. Product is racemic.

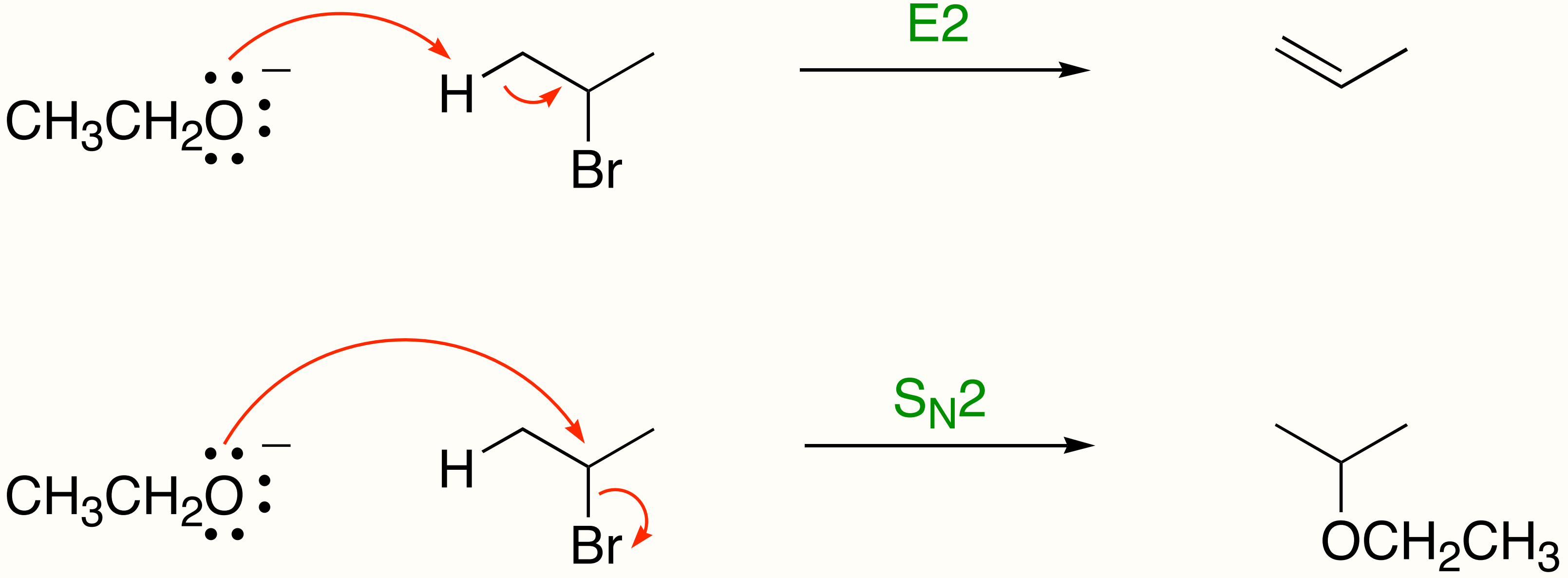
Elimination-Substitution Competition

When the nucleophile is anionic,
elimination competes with substitution



Elimination-Substitution Competition

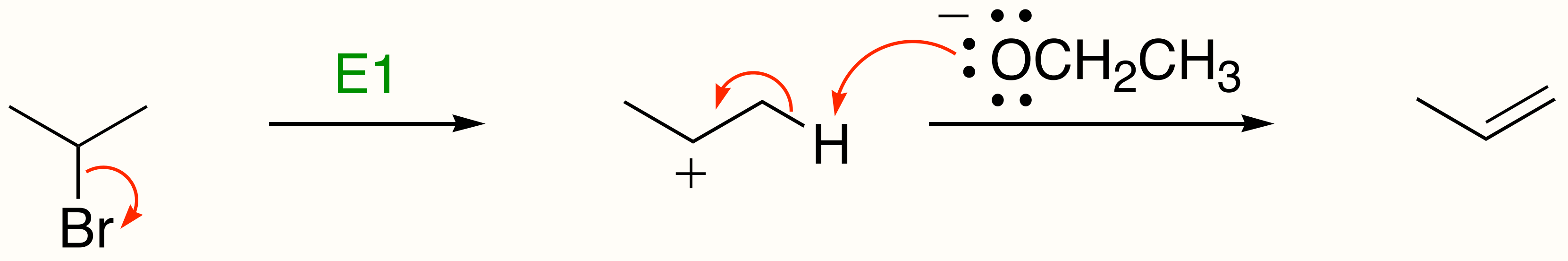
When the nucleophile is anionic, elimination competes with substitution

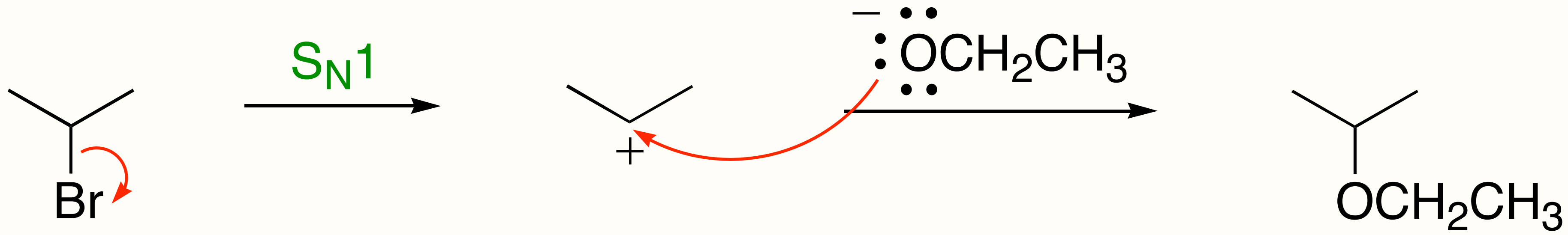


Anion must be more basic than hydroxide (pKa of conjugate acid > 15.7) for E1 or E2 to be a competing mechanism

Elimination-Substitution Competition

When the nucleophile is anionic, elimination competes with substitution

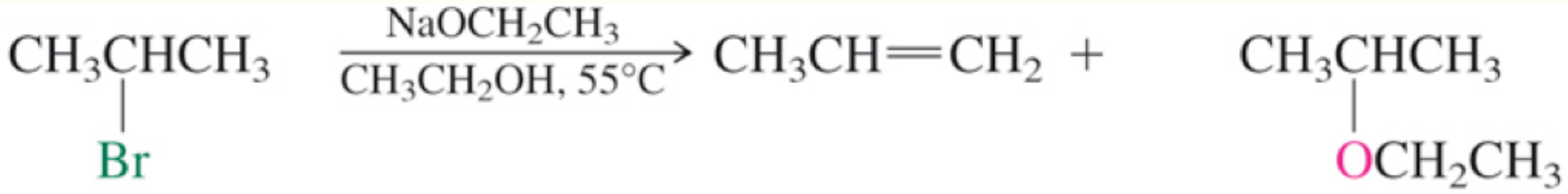




Anion must be more basic than hydroxide (pKa of conjugate acid > 15.7) for E1 or E2 to be a competing mechanism

Conditions Favoring Substitution

1. Low steric hinderance:
    a. small nucleophiles
    b. least substituted alkyl halide possible
2. Neutral nucleophiles (like solvolysis)
3. Or anionic nucleophiles less basic than OH^-



$$\underset{\displaystyle Br}{CH_3\underset{|}{C}HCH_3} \xrightarrow[CH_3CH_2OH,\ 55^\circ C]{NaOCH_2CH_3} CH_3CH{=}CH_2 + \underset{\displaystyle OCH_2CH_3}{CH_3\underset{|}{C}HCH_3}$$

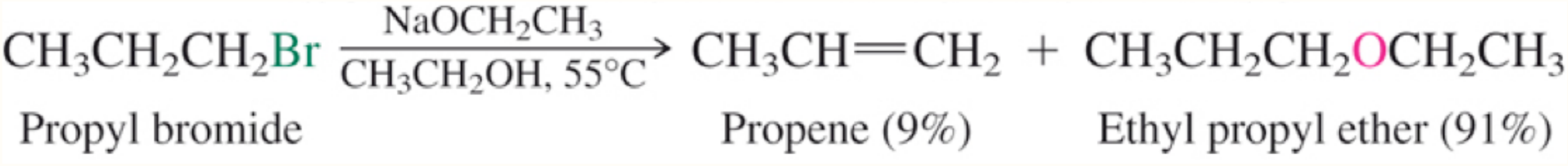
Isopropyl bromide

Propene (87%)

Ethyl isopropyl ether (13%)

Conditions Favoring Substitution

1. Low steric hinderance:
    - a. small nucleophiles
    - b. least substituted alkyl halide possible
2. Neutral nucleophiles (like solvolysis)
3. Or anionic nucleophiles less basic than OH^-

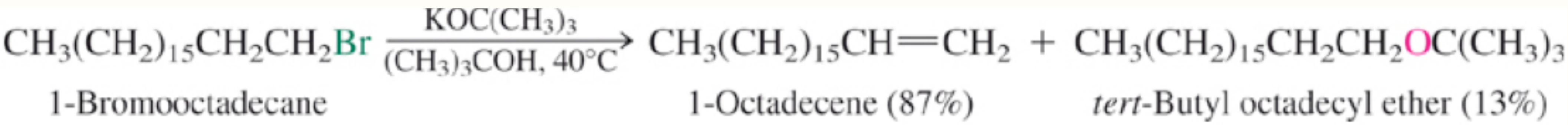


$$CH_3CH_2CH_2Br \xrightarrow[CH_3CH_2OH,\ 55°C]{NaOCH_2CH_3} CH_3CH{=}CH_2 + CH_3CH_2CH_2OCH_2CH_3$$

Propyl bromide — Propene (9%) — Ethyl propyl ether (91%)

Conditions Favoring Substitution

1. Low steric hinderance:
    a. small nucleophiles
    b. least substituted alkyl halide possible
2. Neutral nucleophiles (like solvolysis)
3. Or anionic nucleophiles less basic than OH^-



$$CH_3(CH_2)_{15}CH_2CH_2Br \xrightarrow[(CH_3)_3COH,\ 40°C]{KOC(CH_3)_3} CH_3(CH_2)_{15}CH{=}CH_2 + CH_3(CH_2)_{15}CH_2CH_2OC(CH_3)_3$$

1-Bromooctadecane

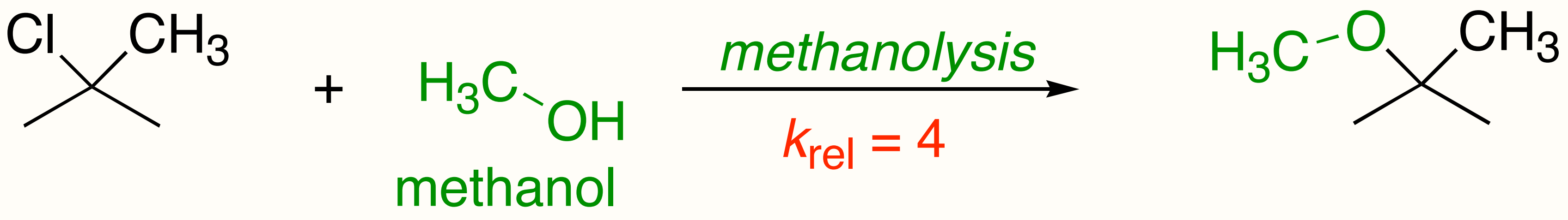
1-Octadecene (87%)

tert-Butyl octadecyl ether (13%)

$KOC(CH_3)_3$ is so large that it prefers E_2 even when the alkyl halide is primary

Conditions Favoring Substitution

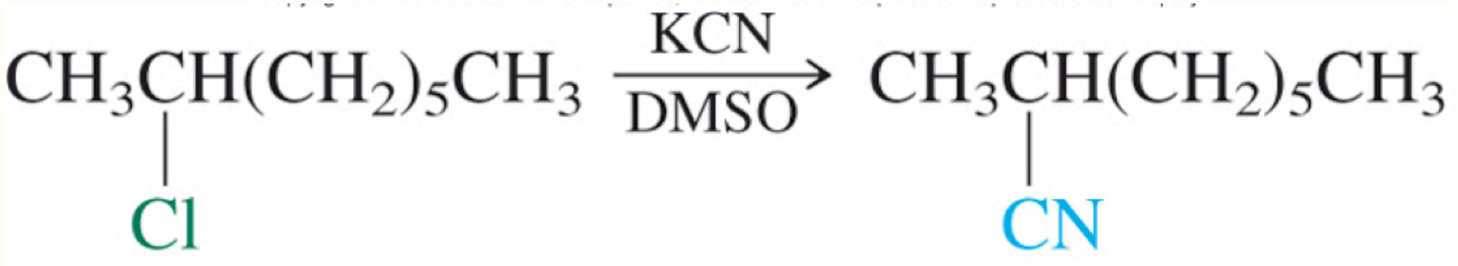
1. Low steric hinderance:
    a. small nucleophiles
    b. least substituted alkyl halide possible
2. Neutral nucleophiles (like solvolysis)
3. Or anionic nucleophiles less basic than OH^-



Neutral nucleophiles are not basic enough to deprotonate a β-hydrogen in an E2 mechanism; they also undergo addition to carbocations faster than deprotonation in an E1 mechanism

Conditions Favoring Substitution

1. Low steric hinderance:
   - a. small nucleophiles
   - b. least substituted alkyl halide possible
2. Neutral nucleophiles (like solvolysis)
3. Or anionic nucleophiles less basic than OH^-



$$\underset{\displaystyle Cl}{CH_3CH}(CH_2)_5CH_3 \xrightarrow[\text{DMSO}]{\text{KCN}} \underset{\displaystyle CN}{CH_3CH}(CH_2)_5CH_3$$

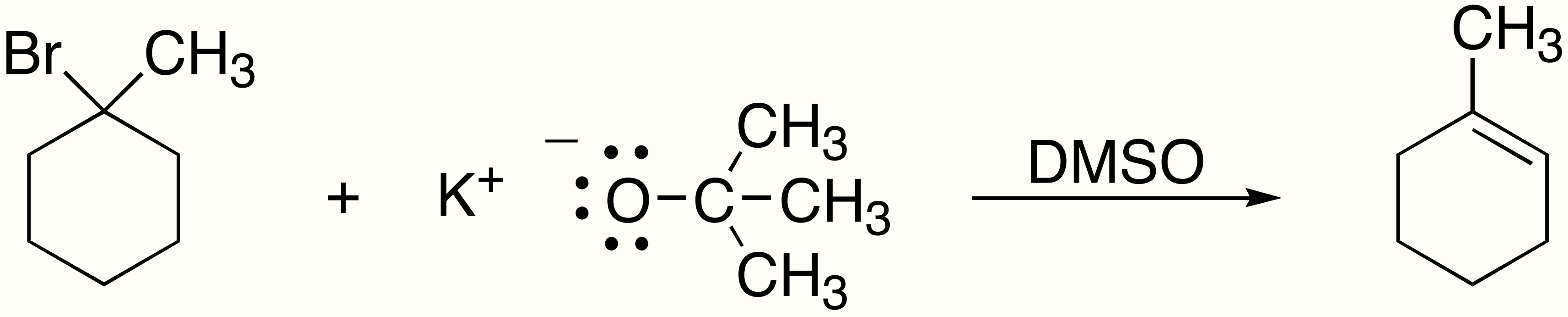
2-Chlorooctane 2-Cyanooctane (70%)

pK_a (H_2O) = 15.7 pK_a (HCN) = 9.1

stonger acid = weaker conjugate base

Conditions Favoring Elimination

1. Large steric interactions:
   - a. large nucleophiles
   - b. most substituted alkyl halide possible
2. Anionic nucleophiles more basic than OH^-

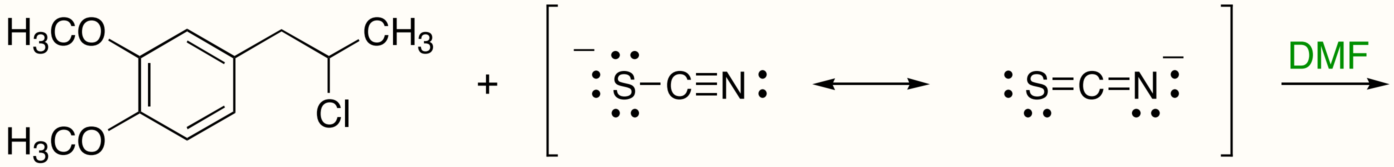


pK_a (H_2O) = 15.7 pK_a (*tert*-butanol) = 18

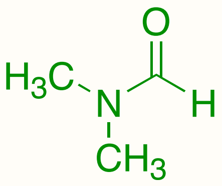
stonger acid = weaker conjugate base

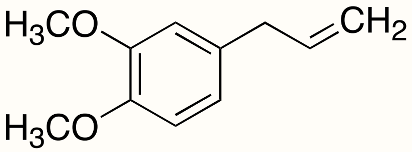
Self-Test Question

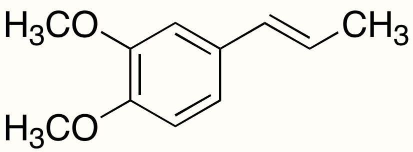
What is the *major* product of the reaction below?

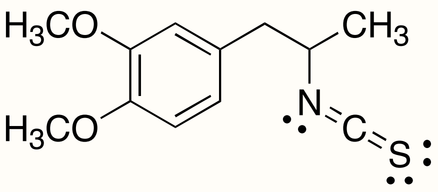


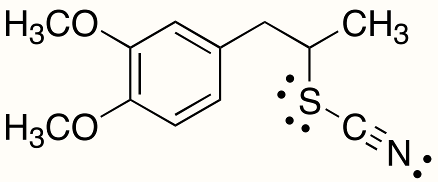
DMF = *N,N*-dimethylformamide
(common polar aprotic solvent)



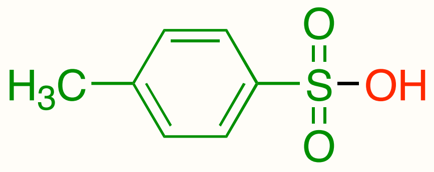
A


B


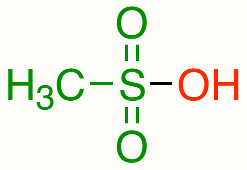
C


[✓ D]


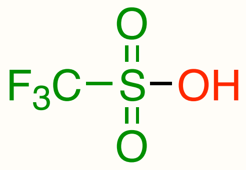
Sulfonic Acids & Sulfonyl Chlorides



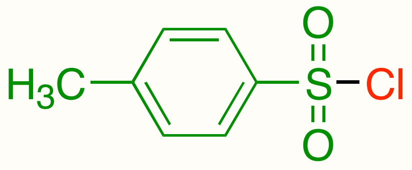
p-toluenesulfonic acid
TsOH


$H_3C-\overset{O}{\underset{O}{S}}-OH$

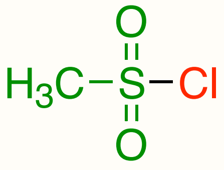
methanesulfonic acid
MsOH


$F_3C-\overset{O}{\underset{O}{S}}-OH$

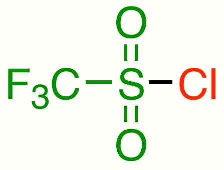
trifluoromethanesulfonic acid
TfOH



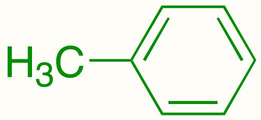
p-toluenesulfonyl chloride
TsCl


$H_3C-\overset{O}{\underset{O}{S}}-Cl$

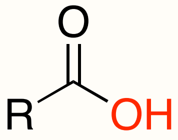
methanesulfonyl chloride
MsCl


$F_3C-\overset{O}{\underset{O}{S}}-Cl$

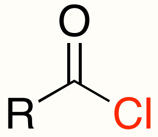
trifluoromethanesulfonyl chloride
TfCl



toluene

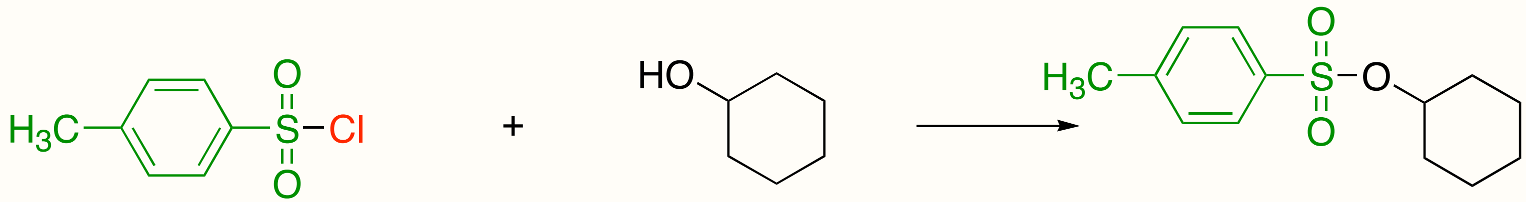


carboxylic acid

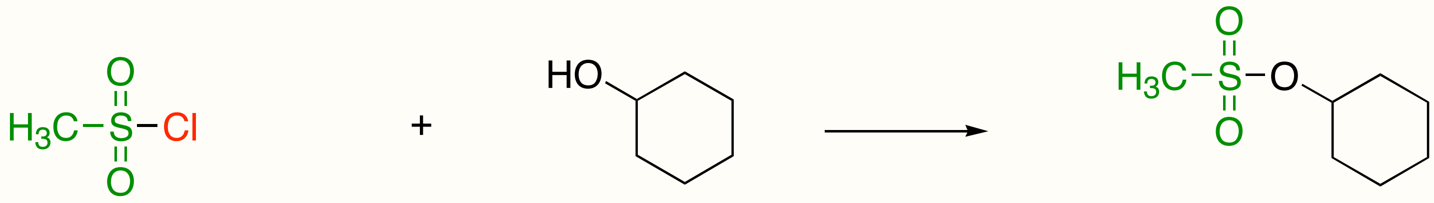


acid chloride

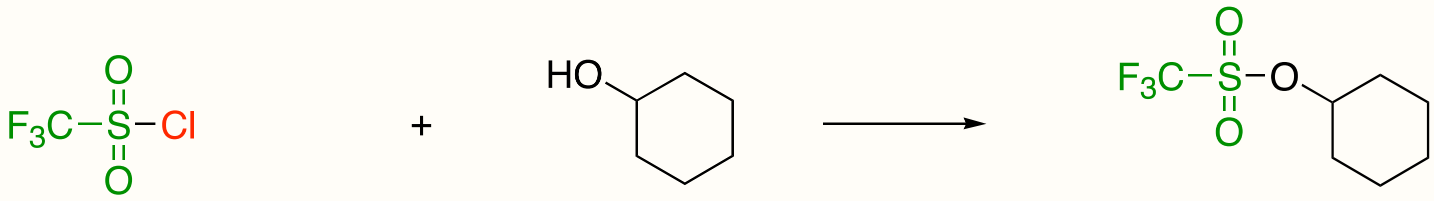
Alkyl Sulfonates



p-toluenesulfonyl chloride
TsCl



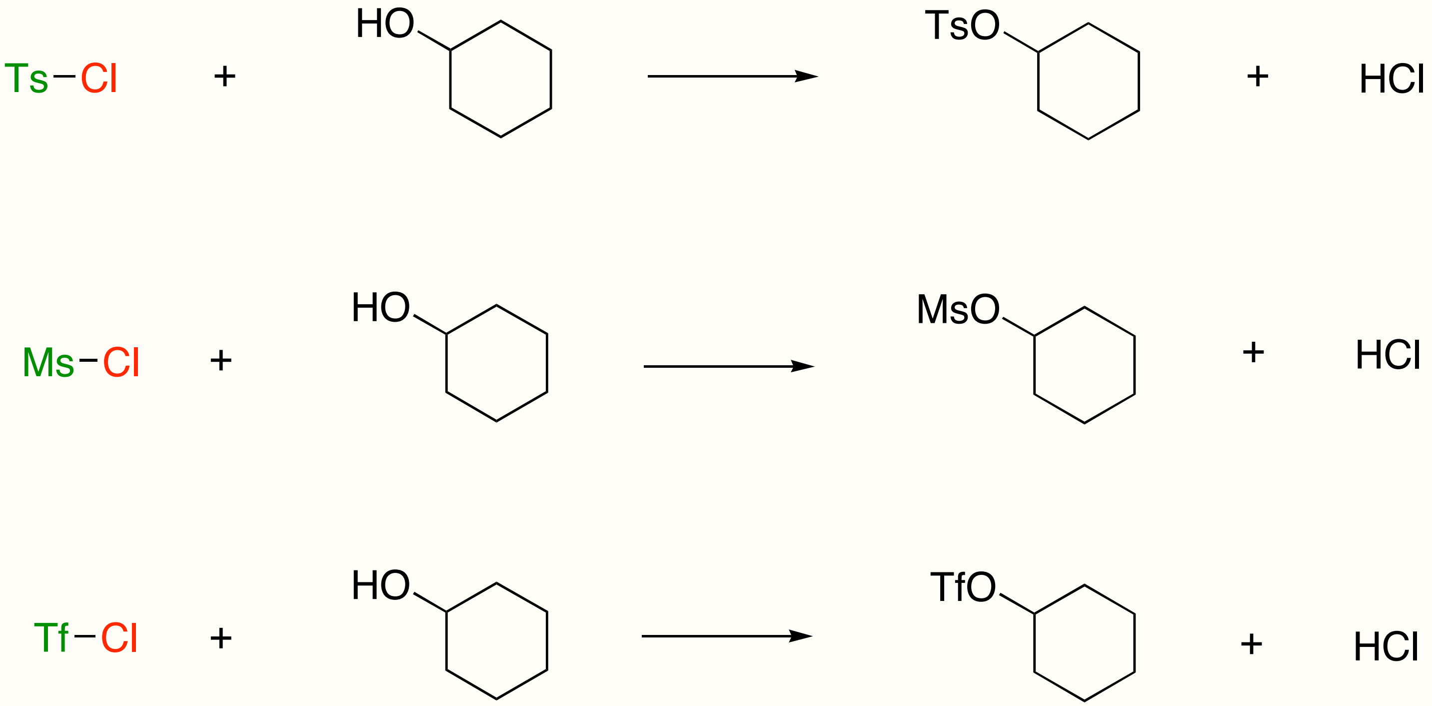
methanesulfonyl chloride
MsCl



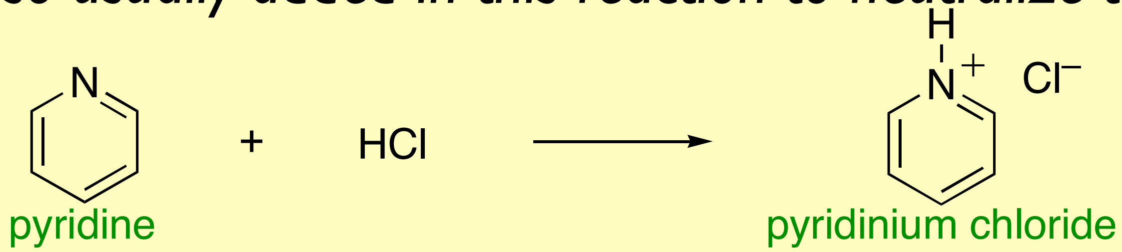
trifluoromethanesulfonyl chloride
TfCl

You will learn the mechanism for this process in Chapter 20; Don't worry about it for now.

Alkyl Sulfonates

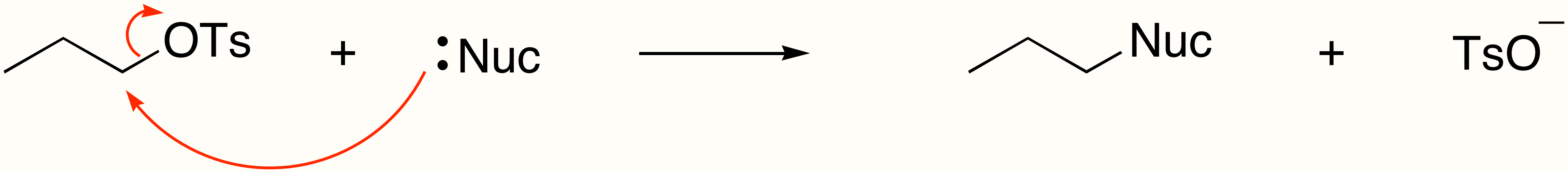


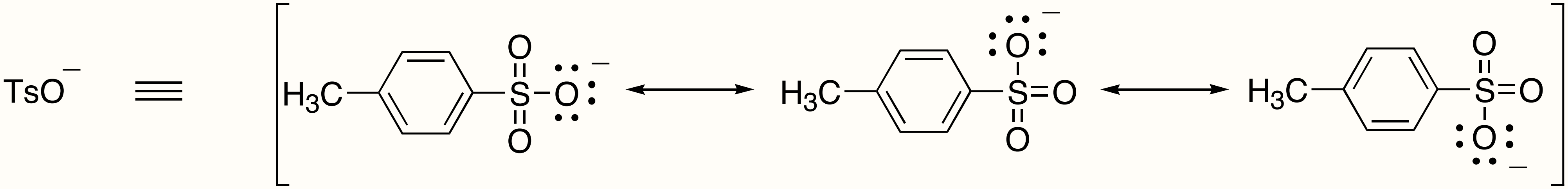
Pyridine (Py) is also usually added in this reaction to neutralize the HCl produced



You should memorize the abbreviations for these three groups.

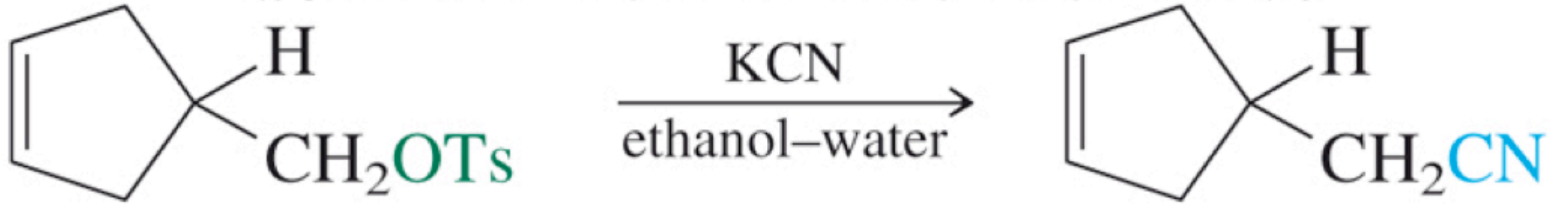
Alkyl Sulfonates Are Electrophiles





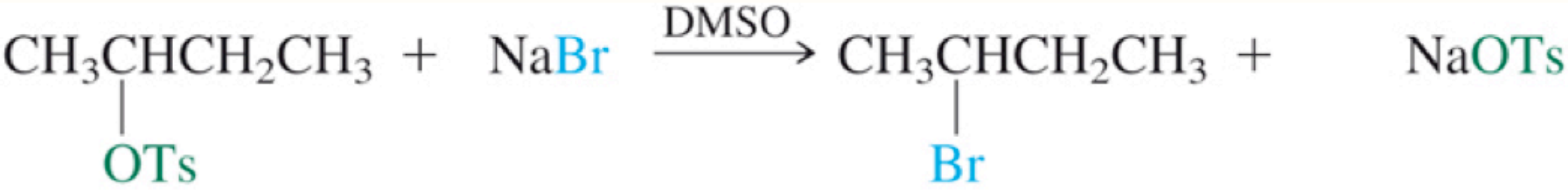
- sulfonates (TsO^-, MsO^-, TfO^-) are highly stabilized by resonance =
- very weak conjugate bases =
- very good leaving group

Alkyl Sulfonates Are Electrophiles



(3-Cyclopentenyl)methyl *p*-toluenesulfonate

4-(Cyanomethyl)cyclopentene (86%)



$$CH_3\underset{\displaystyle OTs}{\underset{|}{C}}HCH_2CH_3 + NaBr \xrightarrow{DMSO} CH_3\underset{\displaystyle Br}{\underset{|}{C}}HCH_2CH_3 + NaOTs$$

sec-Butyl *p*-toluenesulfonate

Sodium bromide

sec-Butyl bromide (82%)

Sodium *p*-toluenesulfonate

TsO, MsO & TfO are Excellent Leaving Groups

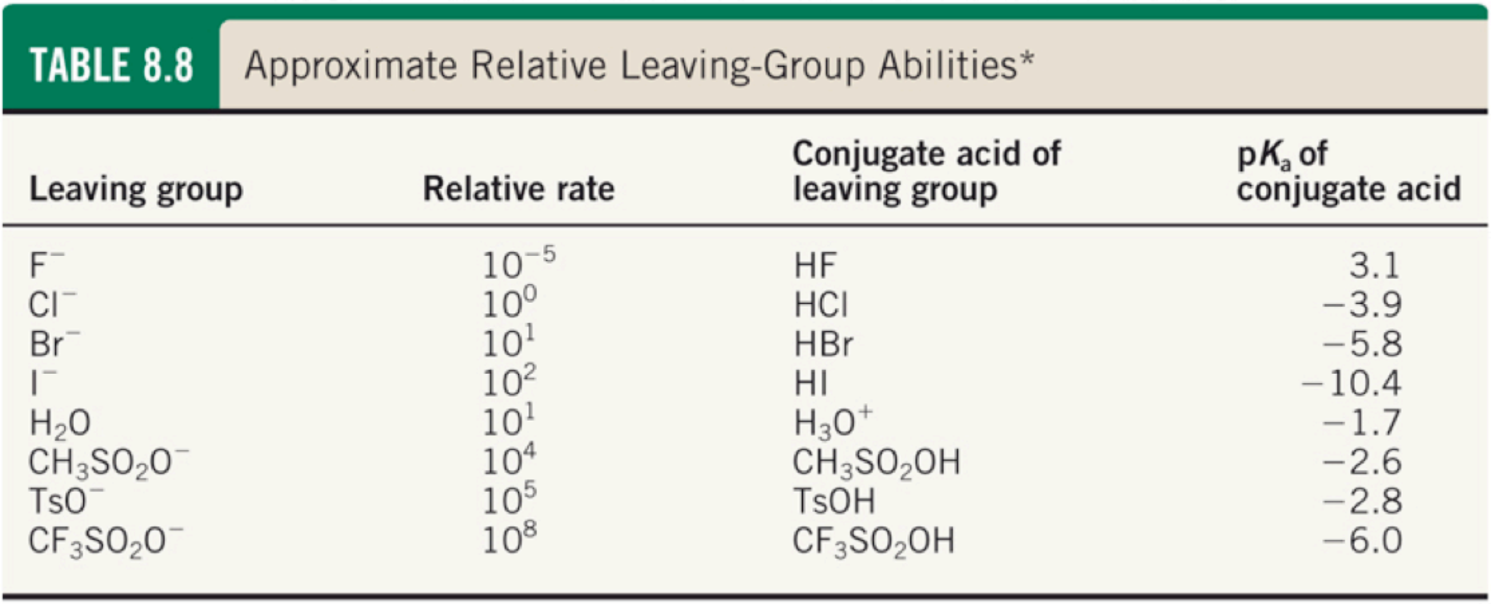
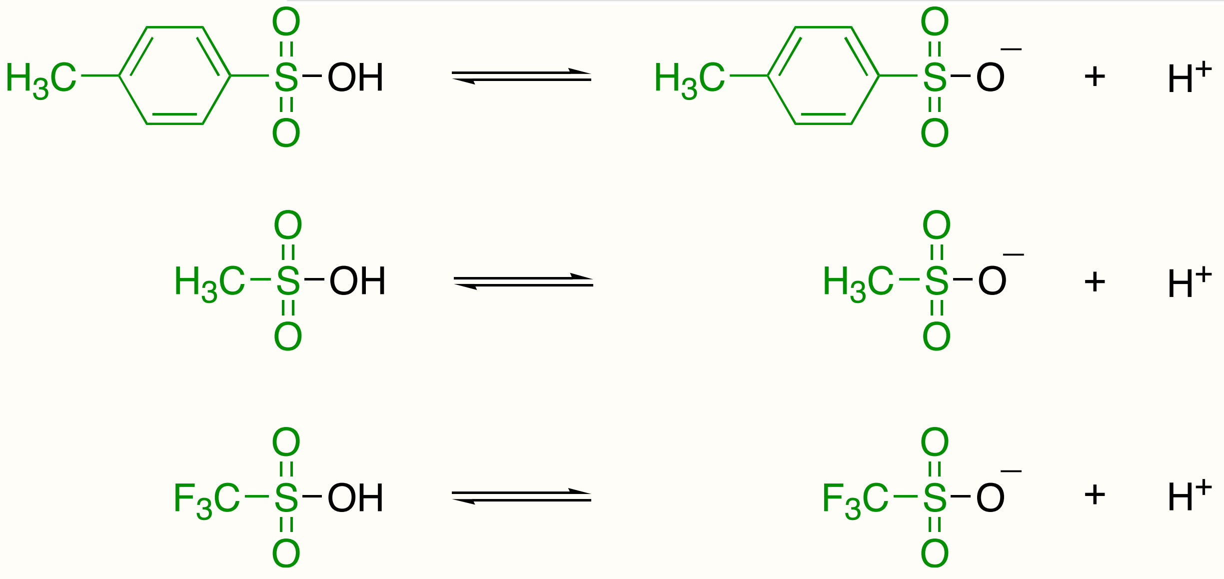


TABLE 8.8 Approximate Relative Leaving-Group Abilities*

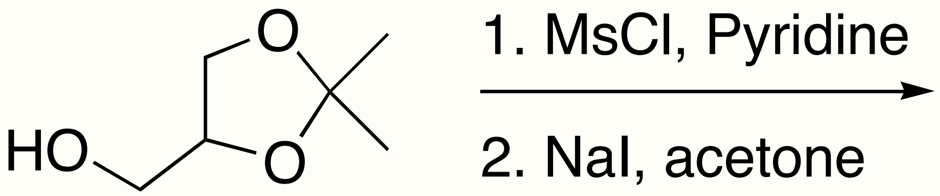
Leaving group	Relative rate	Conjugate acid of leaving group	pK_a of conjugate acid
F^-	10^{-5}	HF	3.1
Cl^-	10^{0}	HCl	−3.9
Br^-	10^{1}	HBr	−5.8
I^-	10^{2}	HI	−10.4
H_2O	10^{1}	H_3O^+	−1.7
$CH_3SO_2O^-$	10^{4}	CH_3SO_2OH	−2.6
TsO^-	10^{5}	TsOH	−2.8
$CF_3SO_2O^-$	10^{8}	CF_3SO_2OH	−6.0



- sulfonic acids are very strong acids =
- conjugate bases very stable (weak):
- conjugate bases stabilized by resonance and inductive effects =
- that makes sulfonates (conjugate bases) very good leaving groups

Self-Test Question

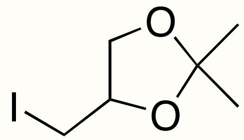
Predict the *major* organic product of the reaction below.



1. MsCl, Pyridine

2. NaI, acetone

[✓ A]



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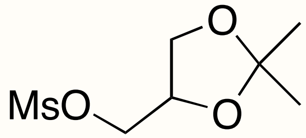
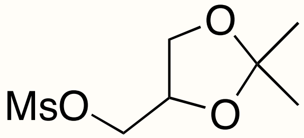


C



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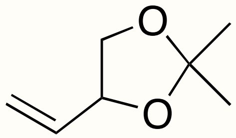
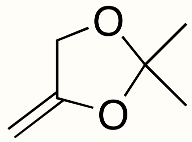


E



Next Lecture. . .

Chapter 9: Sections 9.1-9.6

Quiz Next Week. . .

Chapter 8