Alkyl Halides: Substitution Reactions - Chapter 7, part 1 (Klein 4th ed.)

Chapter Outline

I. Intro to RX (7.1, 7.2)
II. Substitution Reactions
  A) S_N2 Mechanism (7.3)
  B) S_N1 Mechanism (7.8)
  C) Leaving Groups, LG (7.1, 7.10)
  D) Nucleophiles, Nu: (6.6, 7.4)
  E) S_N2 vs. S_N1
III. Competing Reactions
  A) Carbocation Rearrangements (6.11)
  B) Elimination Rxns (7.5-7.9) continued in Ch. 7 Part 2
IV. Synthesis Strategies (7.11)
V. Solvent Effects (7.12)

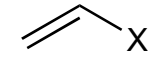
I. Introduction to Alkyl Halides, RX (7.1, 7.2)

Types of Halides, X = Cl, Br, I *(F = N/R in Ch. 7 - no substitution or elimination rxns with fluoride)*

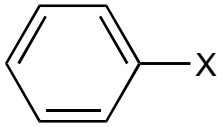
R—X

alkyl halide

- can be 1º, 2º, 3º, allylic, benzylic
- RBr, RCl can be prepared by free-radical halogenation (Chapter 10)

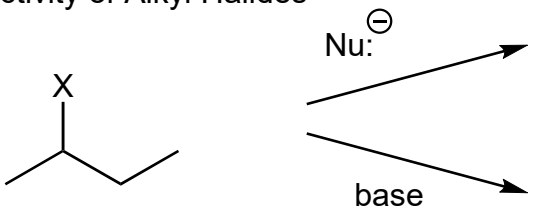


vinyl halide
(on pi bond)



aryl halide
(on benzene ring)

Reactivity of Alkyl Halides



Substitution (Ch. 7 Part 1)
(replace X with Nu:)
(Nu: = nucleophile)

Elimination (Ch. 7 Part 2)
(– HX)
(forms an alkene)

II. Substitution Reactions

Example: $H-O^{\ominus}$ + CH_3-Cl ⇌ $H-O-CH_3$ + $Cl^{\ominus}$

Nu: E^+ product LG

Nucleophile (Nu:)
- electron-rich (lone pair or pi bond), often has negative charge
- seeks electron-deficient species

Electrophile (E^+)
- electron-poor (δ+ or +)
- seeks electron-rich species

Why are Cl^-, Br^- and I^- good LGs?

Leaving Group (LG)
- group leaves and takes 2 electrons with it
- stable groups (weak bases) make good LG's (e.g., X^-, halide)

General Reaction: $Nu:^{\ominus}$ + R—LG ⇌ Nu—R + $LG^{\ominus}$

General Reaction: $Nu:^{\ominus} + R{-}LG \rightleftharpoons Nu{-}R^{+} \quad LG^{\ominus}$

What are the possible mechanisms for this substitution reaction?

A) simultaneous (concerted) B) stepwise (LG leaves first)

this is called the S_N2 mechanism (7.3)

this is called the S_N1 mechanism (7.9, 7.12)

II. A) S_N2 - Substitution Nucleophilic Bimolecular (7.3)

Example: $CH_3O^{\ominus} + CH_3CH_2{-}I: \longrightarrow$

Mechanism: one step, backside attack

S_N2 Kinetics Rate = $k\,[CH_3O^-]\,[CH_3CH_2I]$

- rate is dependant on **both** Nu: and E+
- bimolecular reaction
- **sterics** affect the rate of S_N2

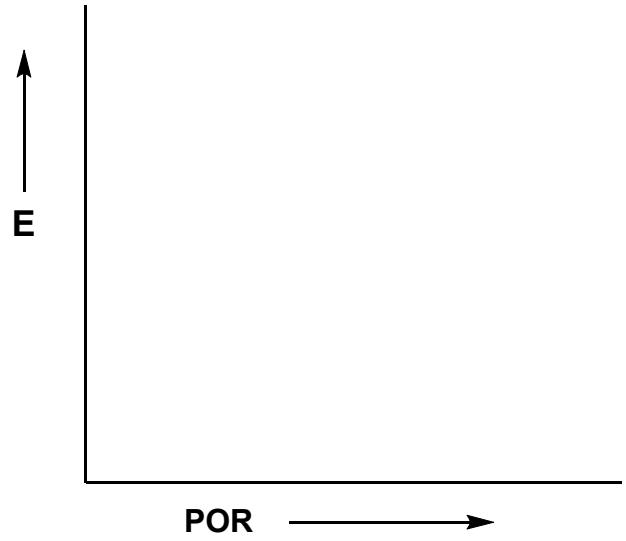
$R{-}Br + {}^{\ominus}CN \longrightarrow R{-}CN + Br^{\ominus}$

consider *tert*-butyl bromide:

R group	abbrev.	carbon type	relative rate
$CH_3{-}$			
$CH_3CH_2{-}$			
$(CH_3)_2CH{-}$			
$(CH_3)_3C{-}$			
$(CH_3)_3CCH_2{-}$			

Rate of S_N2 (by type of RX):

S_N2 Energy vs. Progress of Reaction Diagram



If LG carbon is too sterically hindered (e.g., 3º), then:

S_N2 Transition State Structure

Transition State (TS)
(high energy, partial bonds/charges)

What is the hybridization of the carbon in the transition state? sp^4?!

Note: the presence of a neighboring (conjugated) p orbital would be good for the S_N2 mechanism because TS would be stabilized e.g., allylic LG (next to a pi bond)

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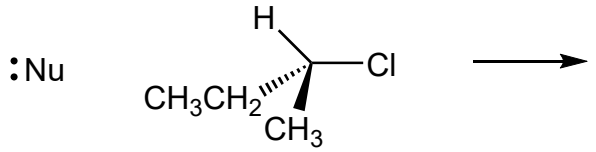
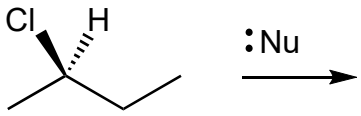
Stereochemistry of the S_N2 Mechanism

backside attack ⟶ inversion of stereochemistry



typical line drawing point of view:



LG is a wedge

- like a flipped umbrella
- can only be observed at a chiral center
- S_N2 usually changes configuration (*R* to *S* or *S* to *R*), because usually the LG and the Nu: are both #1 priority group

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S_N2 Summary

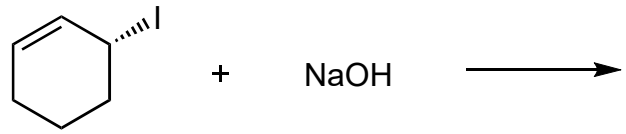
- one-step mechanism
- inversion of stereochemistry
- requires: 1) unhindered LG (on tetrahedral sp^3 carbon)
  2) good Nu: (negative charge or NH_3)

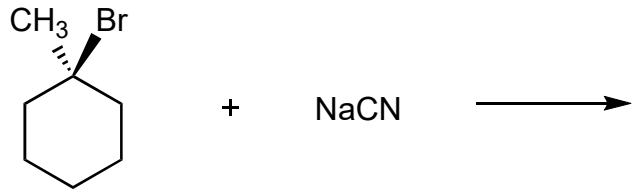
Rate (by RX type)

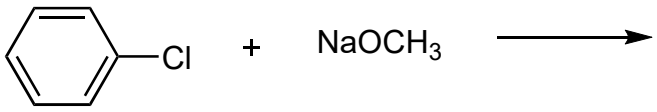
methyl > 1º > 2º >> 3º

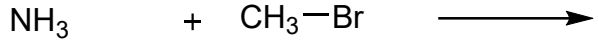
Predict the Major Product(s) (S_N2)

Include stereochemistry, where appropriate. Write N.R. if no reaction is expected.









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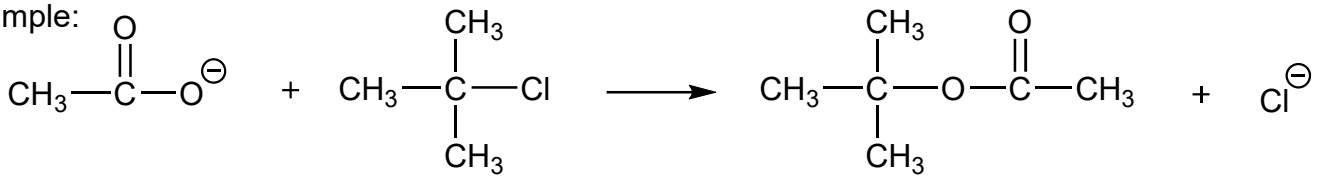
II. B) S_N1 - Substitution Nucleophilic Unimolecular (7.8)

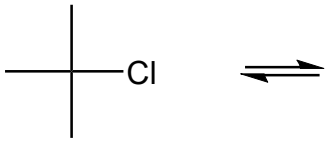
Example:



Could this be an S_N2 mechanism?
Still a **substitution**, but a different mechanism (stepwise).

S_N1 Mechanism: two key steps (but usually three total steps)

Step 1
Loss of the leaving group



Step 2
Addition of nucleophile

S_N1 Kinetics Rate = k [*t*-BuCl]

- rate-determining step involves E^+ only (unimolecular reaction)

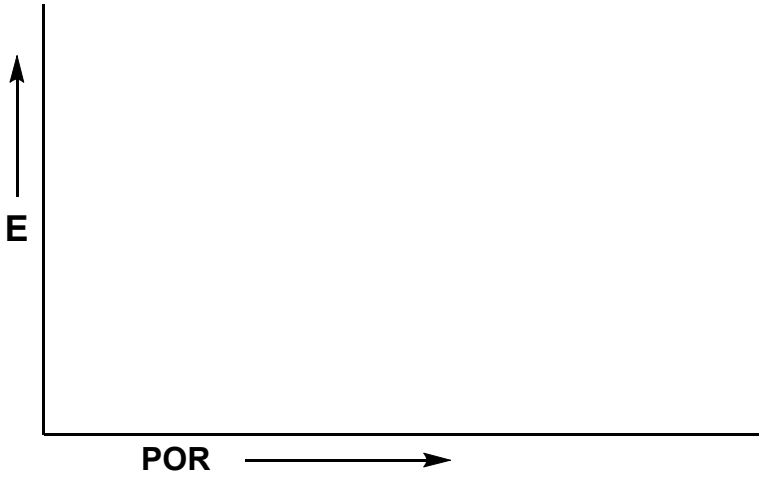
- rate is independent of [Nu:]

- a **more stable carbocation** will be formed faster

Rate of S_N1 (by type of RX):

S_N1 Energy vs. Progress of Reaction Diagram

Structure of first Transition State, TS-1



Structure of TS-2?

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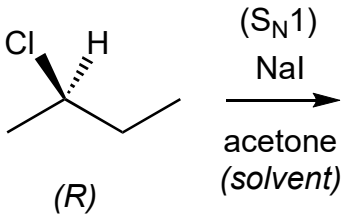
Stereochemistry of the S_N1 Mechanism

carbocation intermediate ⟶ racemization

S_N1 results in **racemization** (loss of stereochemistry) due to the achiral carbocation intermediate.



S_N1 Summary

Rate (by RX type)

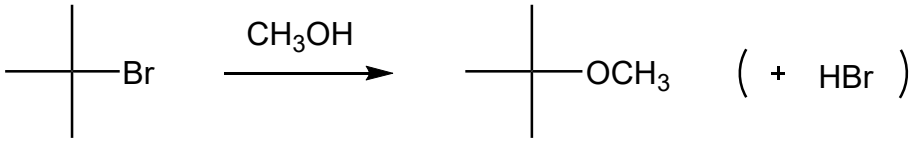
benzyl/allyl/3º > 2º >> 1º, methyl

- stepwise mechanism via carbocation
- more stable carbocation =
- racemization occurs
- requires: 1) stable carbocation (not 1º or methyl)
  2) weak Nu: (usually the solvent, H_2O or ROH, is the nucleophile = "solvolysis")

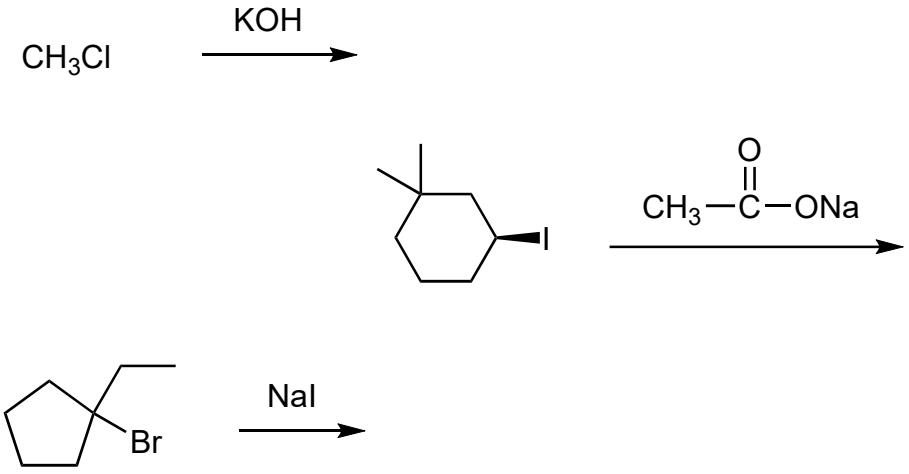
Solvolysis: S_N1 Mechanism is three steps

- Nu: is H_2O or ROH
- final deprotonation step required

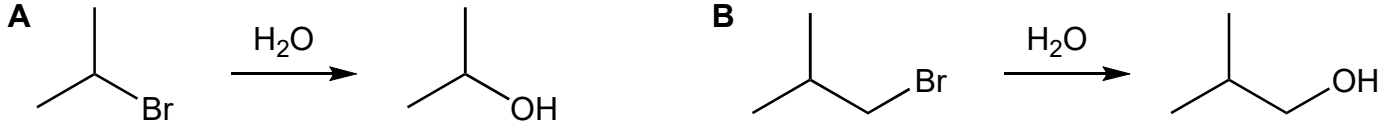
Example:



Predict the Major Product(s) (S_N2 or S_N1 mechanism? See 7.9)
Include stereochemistry, where appropriate. Write N.R. if no reaction is expected.



Which would be the faster reaction (A or B)? Explain. (Consider first: S_N2 or S_N1 mechanism?)



II. C) Leaving Groups (7.1, 7.10)

- weak bases make good leaving groups
- more stable = less reactive, weaker base
- typical leaving group? halide (X^-)
  (all have strong conj. acids: HCl, HBr, HI)

Leaving groups

$F^{\ominus}$ $Cl^{\ominus}$ < $Br^{\ominus}$ < $I^{\ominus}$

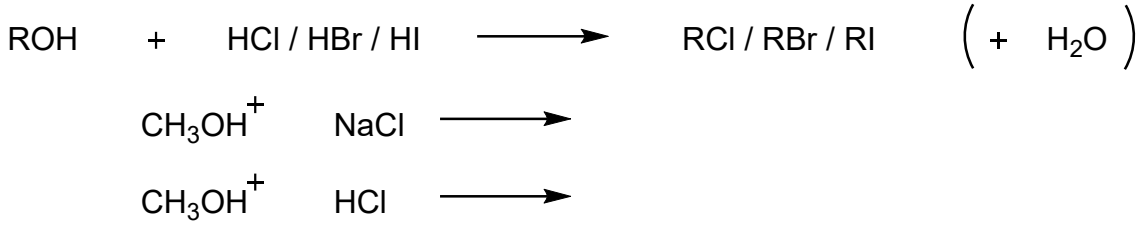
Is the Forward or Reverse reaction favored?

Best substitution reaction has best LG leaving (gives more stable products so $\Delta H < 0$ and $\Delta G < 0$)

$$CH_3OH + NaCl \rightleftharpoons CH_3Cl + NaOH$$

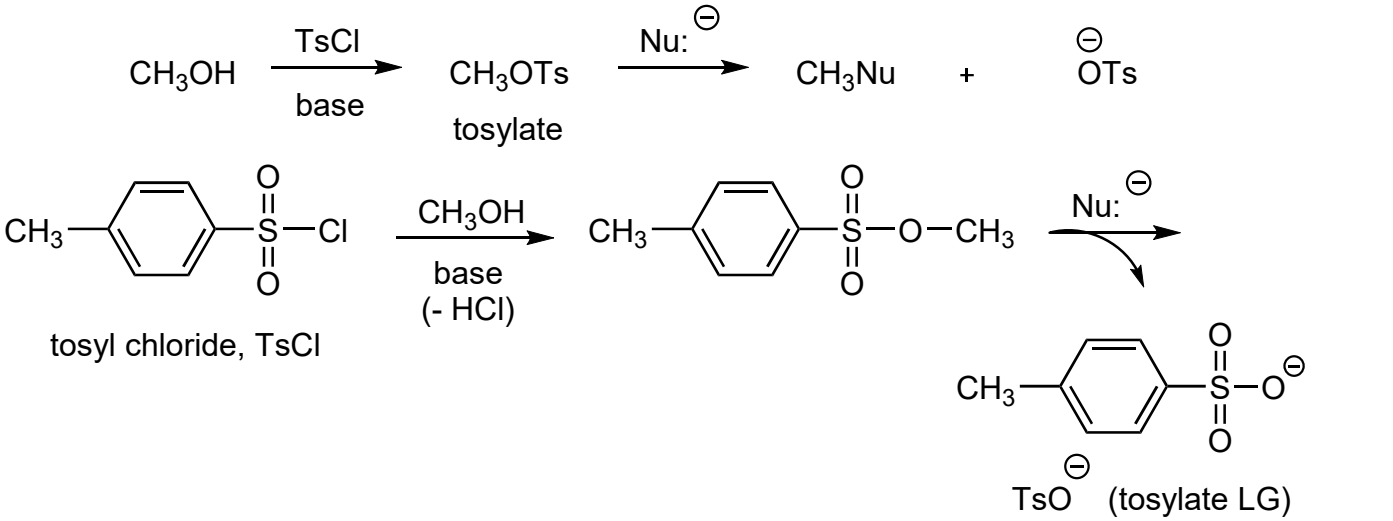
Hydroxide, HO^-, is a poor leaving group BUT we can make it better. There are two methods.

1. Add a strong acid (acid protonates the alcohol to make a great LG, H_2O)



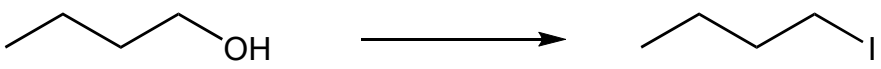
mechanism:

2. Make a tosylate LG



why is this more stable than HO^-?

Synthesis/"Transform" Problem (7.11) - Provide the reagents needed to transform the given starting material into the desired product. More than one step may be required.



II. D) Nucleophilicity (Nucleophile strength) (7.4)

1. More electron-rich, better Nu:

$CH_3\overset{\oplus}{O}H_2$ CH_3OH $CH_3O^{\ominus}$

2. Periodic Trends: across row: ⟶ decreasing nucleophilicity

NH_3 H_2O

down a family: ↓ generally increasing nucleophilicity (BUT this trend depends on solvent!)

$I^{\ominus}$ $Cl^{\ominus}$

Good Nucleophiles (Nu:)

$HO^{\ominus}$ $RO^{\ominus}$ $HS^{\ominus}$ $RS^{\ominus}$ $^{\ominus}CN$ $N_3^{\ominus}$ $I^{\ominus}$ $Br^{\ominus}$

NH_3 NH_2R R_3P

Weak Nucleophiles (Nu:)

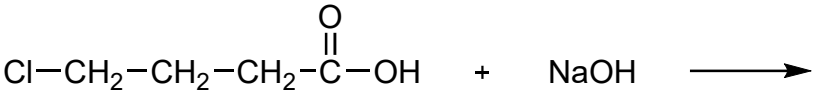
H_2O ROH

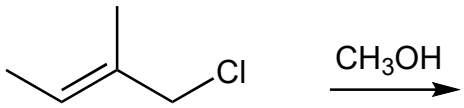
Summary of Substitution Reactions

Alkyl Group	S_N1	S_N2
3° (tertiary)	common	rare (N/R)
2° (secondary)	sometimes	sometimes
1° (primary)	rare (N/R)	common
CH_3 (methyl)	never (N/R)	common
allyl/benzyl	common	common (if not 3°)

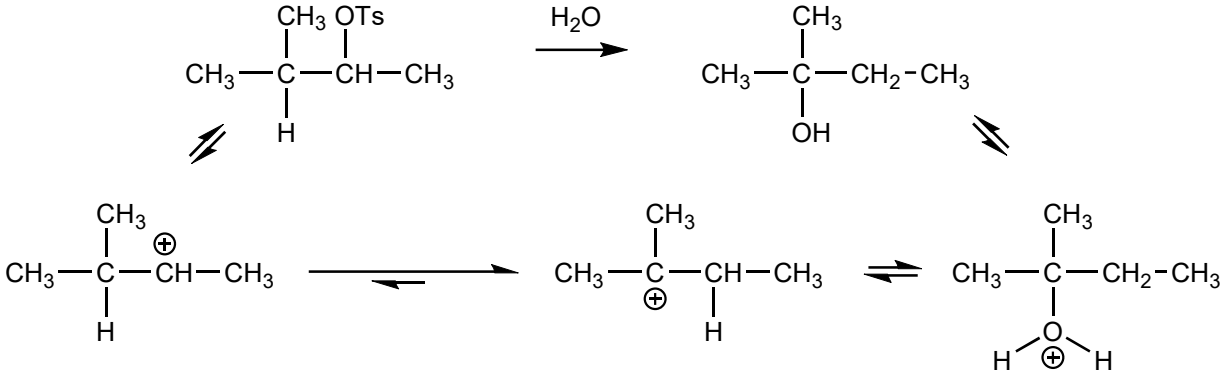
S_N2 requires **strong Nu:** and **minimal steric hindrance**
S_N1 requires a **stable carbocation** and typically involves a **weak Nu:**

See page 6-7 for examples, and S_N2/S_N1 Predict the Product homework for practice problems.
After attempting the homework, let's look more closely at the following problems:

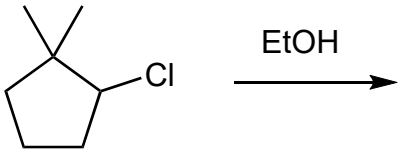




III. A) Competing Reactions: Carbocation Rearrangements (6.11)



Alkyl groups can also shift



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IV. Solvent Effects (7.12)

Both S_N1 and S_N2 reactions need **POLAR** solvents to stabilize charges in the mechanism.

Protic

- has an OH group
- extremely polar
- strongly stabilizes charges

Aprotic

- has no OH group

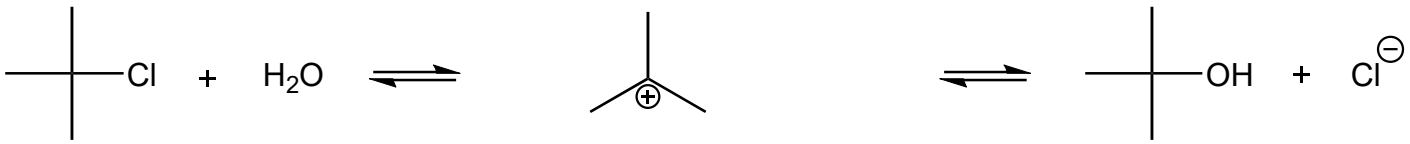
Solvent Effects on Reaction Rates

if you INCREASE solvent polarity, then S_N1 is _____ and S_N2 is _____

→ e.g. using a protic solvent instead of an aprotic solvent

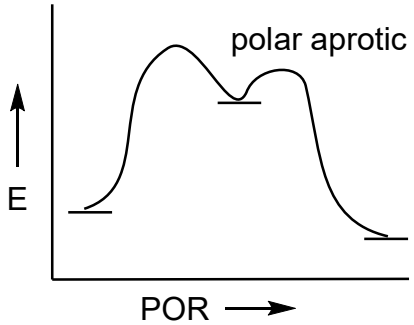
→ e.g. going from an 80:20, EtOH:H_2O solvent to 50:50

Why is a more polar solvent GOOD for an S_N1 mechanism? (speeds it up)



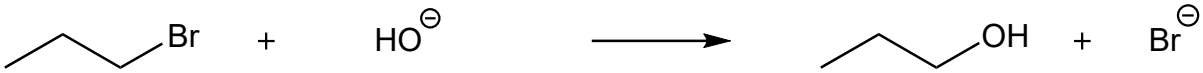
- carbocation will be better stabilized by more polar solvent
- C+ intermediate and transition state are more stable/lower E

- E_a (lower height of hill), rate of reaction



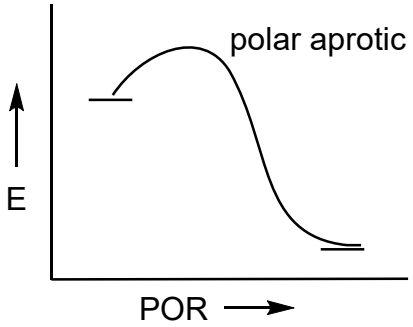
- S_N1 is FASTER in a more polar solvent

Why is a more polar solvent BAD for an S_N2 mechanism? (slows it down)



- nucleophile will be better stabilized by more polar solvent
- Nu: is more stable, less reactive

- E_a (increased height of hill), rate of reaction



- S_N2 is SLOWER in a more polar solvent

All Substitution and Elimination reactions need Electrophiles with good leaving groups (LG), such as Cl^-, Br^-, I^-, and TsO^-. Substitution reactions need Nucleophiles (S_N2 needs a good Nu:; S_N1 needs a weak Nu:) and Elimination reactions need Bases (E2 needs strong base; E1 needs weak base).

Poor Leaving Groups (LG)

$H_2N^{\ominus}$ $RO^{\ominus}$ $HO^{\ominus}$ $^{\ominus}CN$ $N_3^{\ominus}$ $F^{\ominus}$

Good Nucleophiles (Nu:)

$HO^{\ominus}$ $RO^{\ominus}$ $HS^{\ominus}$ $RS^{\ominus}$
$^{\ominus}CN$ $N_3^{\ominus}$ $I^{\ominus}$ $Br^{\ominus}$

$:NH_3$ $:NH_2R$ $R_3P:$

Weak Nucleophiles (Nu:)

H_2O ROH (these are also weak bases)

Strong Bases (B:)

$H_2N^{\ominus}$ $RO^{\ominus}$ $HO^{\ominus}$ (needed for E2)

Synthetic Utility of the S_N2: