CHEM 221 section 52

LECTURE #11 Thurs., March 20, 2008

ASSIGNED READINGS:

TODAY'S CLASS:

Ch.8 (all) Nucleophilic substitution reactions
S_N2 (from last day's notes)
S_N1
Competition between both mechanisms
→ trying to control what happens…

NEXT CLASS: lab exam (1st 40 min of class)
finish Ch.8, start Ch.9

The nucleophile affects an S_N2 reaction

"Nucleophilicity" = a measure of how readily a compound (a Nu) is able to attack an e-deficient atom (δ^+ C…)

- measured by a rate constant (k) ⇨ it is a kinetic parameter
- **Can the Nu get where it is going?**

RELATED TO, BUT NOT SAME AS…

"Basicity" = a measure of how well a compound (a base) shares its lone pair with a proton (H^+)

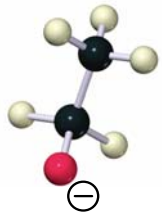
- measured via conjugate acid's dissociation constant (K_a) ⇨ a thermodynamic parameter
- **How inherently e-rich (Lewis basic) is it?**

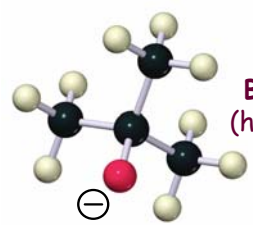
Nucleophilicity is decreased by steric hindrance

- Bulky Nu's have trouble accessing the back-side of Td C's:

EtO^- Basicity?
pK_a EtOH = 16

Small strong base
(low steric demand)
⇨ **Good Nu**





$^tBuO^-$ basicity?
pK_a t-BuOH = 18

Bulky strong base
(high steric demand)
⇨ **Poor Nu**

Steric effects influence nucleophilicity, but not basicity

- Acting as a base involves attacking Hs
- Hs are on the periphery of molecules, not buried like δ^+ Cs…
- **If want to deprotonate, but not substitute: use a bulky base!**

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Getting a feeling for nucleophilicity: how to compare?

For Nu's of SIMILAR STERIC DEMAND:

1. Same attacking atom:
2. Attacking atoms in same row (similar size)

} **STRONGER BASE ⇨ BETTER Nu**

3. Attacking atoms in different rows (different size)

} **MORE POLARIZABLE ⇨ BETTER Nu**

Remembering basicity & polarizability…
For each pair: which is the better Nu?

OH^- & H_2O

CH_3O^- & CH_3OH

$CH_3CH_2NH^-$ & $CH_3CH_2NH_2$

Conj. base always better B & Nu than conj.acid…
i.e., for same atom type, anion better Nu…

F^- & NH_2^-

F^- & I^-

CH_3O^- & $CH_3CH_2NH^-$

CH_3OH & CH_3SH

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Nucleophilicity trends: Same ideas, different wording

1. A species with a negative charge is a stronger nucleophile than a similar neutral species. In particular, a base is a stronger nucleophile than its conjugate acid.

   $OH^- > H_2O$ $SH^- > H_2S$ $NH_2^- > NH_3$

2. Nucleophilicity decreases from left to right in the periodic table (based on attacking atom), following the increase in electronegativity from left to right. The more electronegative elements have more tightly held nonbonding electrons (lone pairs) that are less reactive towards forming new bonds.

   $OH^- > F^-$ $NH_3 > H_2O$ $(CH_3CH_2)_3P > (CH_3CH_2)_2S$

3. Nucleophilicity increases down the periodic table, following the increase in size and polarizability.

   $I^- > Br^- > Cl^- > F^-$ $^-SeH > ^-SH > ^-OH$ $(CH_3CH_2)_3P > (CH_3CH_2)_3N$

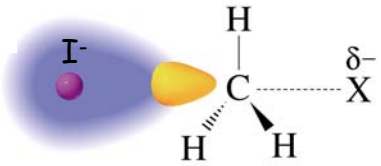
From Wade LJ, Organic Chemistry, 5th Ed.

Why does the POLARIZABILITY of Nu's attacking atom matter?

The S_N2 transition state:

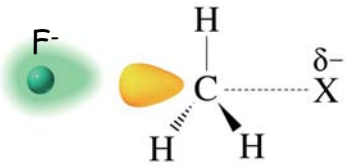
IODIDE = "soft"
highly polarizable
better Nu

better overlap with C
at farther distance away!



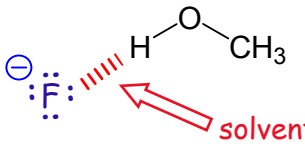
FLUORIDE = "hard"
not very polarizable
poorer Nu

less overlap with C
until very very close!



Interaction between the Nu & the solvent accentuates this…
(Actually, in gas phase, polarizability doesn't matter at all…only basicity does.)

Solvent effects: strong bases less Nu-ic in protic solvents



solvents with OH or NH groups
= **hydrogen-bond donors**

solvent forms H-bonds with Nu's lone pairs…
(or, could be strong ion-dipole interactions)

Nu's lone pairs "screened" ⇨ attack δ^+ C's less

- harder bases = H-bond acceptors ⇨ highly screened ⇨ less Nu-ic
- softer bases interact less with H's ⇨ less screened ⇨ more Nu-ic

Table 8.2 Relative Nucleophilicity Toward CH_3I in Methanol

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

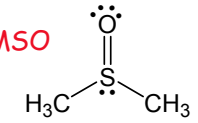
increasing nucleophilicity **in protic solvent**

CRUCIAL: always choose a solvent that your Nu CANNOT **deprotonate**!
(You must compare pK_as…) Otherwise, no Nu will remain to do desired rxn!

NUCLEOPHILE STRENGTH IN HYDROXYLIC (PROTIC) SOLVENTS (SUCH AS WATER & ALCOHOLS)		
STRONG nucleophiles	**MODERATE nucleophiles**	**WEAK nucleophiles**
$(CH_3CH_2)_3P$:	:Br:$^-$	:F:$^-$
:S-H$^-$	$:NH_3$	H-O-H
:C≡N:$^-$	CH_3-S-CH_3	CH_3-O-H
$(CH_3CH_2)_2$NH	:Cl:$^-$	
:O-H$^-$	O CH_3C-O:$^-$	REMEMBER: Nu concentration is also important… if lots is present, rxn WILL occur!
:O-CH_3^-		

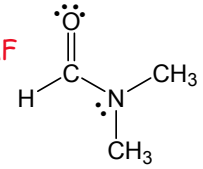
Solvent effects: usefulness of polar "aprotic" solvents

DMSO



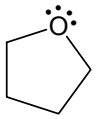
dimethylsulfoxide

DMF



dimethylformamide

THF



tetrahydrofuran

Aprotic polar solvents (not H-bond donors)

Aprotic polar solvents: facilitate rxn of ionic compounds M^+ Nu^-

1. Won't screen your Nu^-
   - no H-bond accepting groups in solvent molecules
2. Pull cations away from Nu^-
   - δ^- O, N atoms interact well with M^+
   - δ^- C, S atoms harder to access
   - makes Nu^- more naked & reactive to δ^+ Cs in your desired target (electrophile…)

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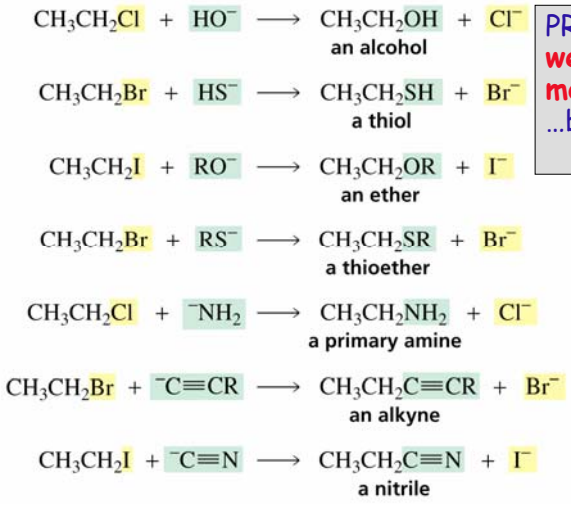
8.4 S_N2 reactions are equilibria (reversible rxns!)
Which direction dominates?



PREDICTING DIRECTION:
weaker base gets displaced more often…
…because is better able to carry its charge/lone-pair

THIS IS USEFUL:
- use substitution rxns to prepare interesting compounds from alkyl halides!
- since an eqm rxn, can drive rxn in 1 direction by removing product…

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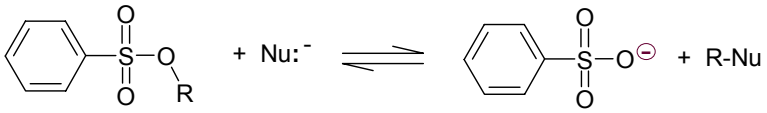
Not only alkyl halides: All of this applies to compounds containing other leaving groups

Compare pK_as of conjugate acids of common leaving groups
⇨ **convenient for predicting rxn's preferred direction**
⇨ **AND NOTE: not all leaving groups are ANIONS**

See Table 8.3

- protonated alcohols: H_2O can leave
- protonated ethers: ROH can leave
- protonated amines: NH_3 can leave



Tosylate "OTs" fantastic leaving group
HOTs pK_a ~ -0.6 (very strong conj. acid)

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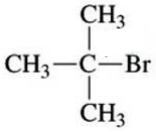
What if we have a 3° alkyl halide & a weak Nu



(so, no measurable S_N2 rxn)

BUT…

we are willing to wait around for a while…

8.5 The mechanism of an S_N1 reaction

Carbocation ⇨ open shell ⇨ HIGHLY electrophilic !

⇐ RATE-LIMITING STEP
- stable molecule falls apart!
- rxn shows 1st order kinetics
- rate = k [alkyl halide]

← *Deprotonation by H_2O (If in neutral solution, ROH will be mostly in its neutral form)*

"SUBSTITUTION NUCLEOPHILIC UNIMOLECULAR" = "S_N1"

└ RLS involves only 1 molecule

1st step (SLOW): LG leaves (heterolytic C-X bond cleavage)

2nd step (FAST): Nu attacks carbocation intermediate

& Possibly more steps: often see H^+ transfer to/from solvent

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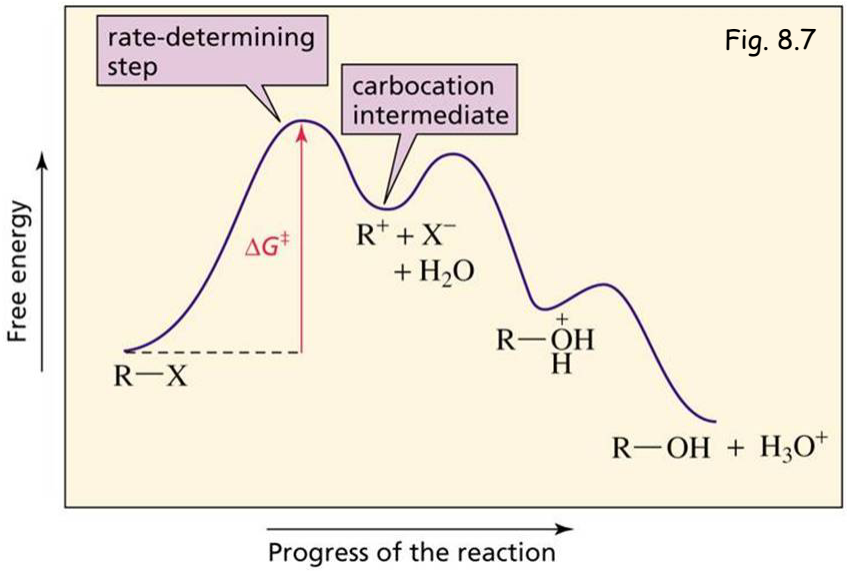
Reaction Coordinate Diagram for an S_N1 Reaction



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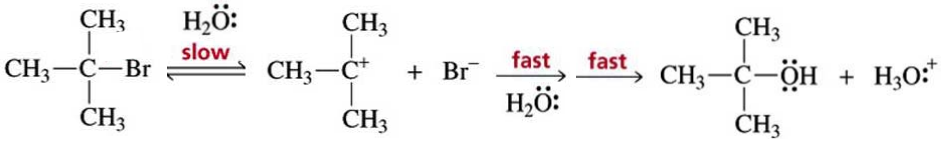
EXPERIMENTAL EVIDENCE: is it S_N1 substitution?

Condensed mechanism: STEP-WISE RXN *(but: must know FULL mechanism…)*

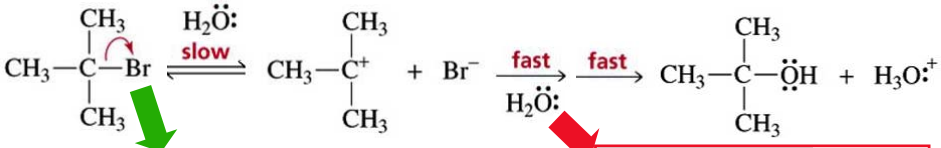


1. **1st order kinetics:** rate of rxn depends on [alkyl halide] only
   Not [Nu]: Nu not involved in RLS…
   & NOTE: even weak Nu can react with C+
   e.g., solvent (leads to "solvolysis")

2. **Structural effects: faster with bulky RX or good LG**
   a) Rxn rate ↑ if steric bulk ↑ *(more stable C+ form faster)*
   b) Rxn rate ↑ if leaving group is better *(more stable X^-…)*

3. **Racemization:** configuration of substituted C gets scrambled if δ^+ C is asymmetric ⇨ rxn not stereospecific
   planar C+ int. can be attacked from either face…

8.6 Factors affecting S_N1 rxns: LG & Nu



Leaving Group
- Better LG (= weaker base)
  ⇨ faster C-X cleavage (RLS)
  ⇨ faster S_N1 rxn !
  (but is always quite slow)

Nucleophile
- not involved in RLS
  ⇨ [Nu] & strength have NO EFFECT

Remember: WEAKER BASES = BETTER LGs
- more stable ⇨ more likely to stay OFF if they do leave…

Rank reactivity via S_N1
highest → lowest: R-Br R-F R-OH $R-OH_2$ $R-CH_3$

Steric effects: bulkier R-X ⇨ ↑ rate of S_N1 rxn (s.t. faster than S_N2…)

most reactive via S_N1 > 3° alkyl halide > 2° alkyl halide > 1° alkyl halide < least reactive via S_N1

opposite trend compared to S_N2 rxns!

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
$(CH_3)_3C-Br$	tertiary	1,200,000
$(CH_3)_2CH-Br$	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.

So: what causes this?

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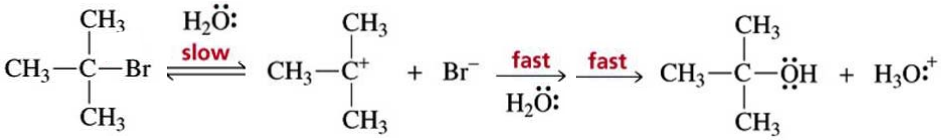
EXPERIMENTAL EVIDENCE: is it S_N1 substitution?

Condensed mechanism: STEP-WISE RXN (but: must know FULL mechanism…)



1. **1st order kinetics:** rate of rxn depends on [alkyl halide] only
   Not [Nu]: Nu not involved in RLS…

2. **Promoted by bulk:** rxn rate ↑ if steric bulk of alkyl halide ↑
   easier to form ‡ leading to more stable C+…

3. **Racemization:** configuration of substituted C gets scrambled if δ^+ C is asymmetric ⇨ rxn not stereospecific
   planar C+ int. can be attacked from either face…

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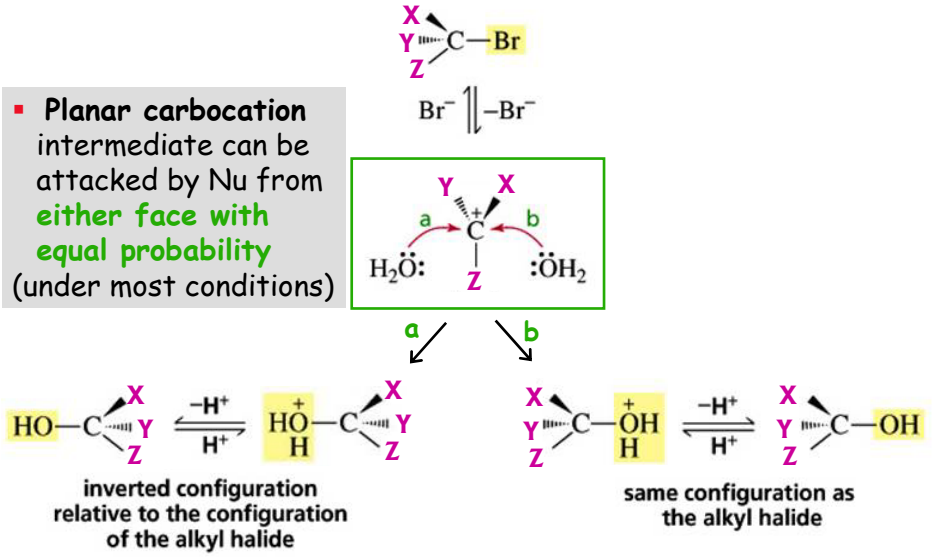
8.7 Stereochemistry of S_N1 reactions



- **Planar carbocation** intermediate can be attacked by Nu from **either face with equal probability** (under most conditions)

⇨ if substituting at a chiral C: RACEMIC PRODUCT
two stereoisomeric products form in equal quantities

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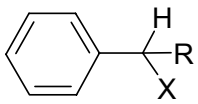
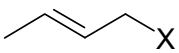
8.8 S_N rxns of benzylic, allylic, vinylic & aryl halides

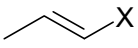
Benzylic: on C 1 bond away from phenyl ring



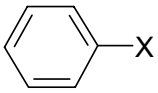
Allylic: on C 1 bond away from C=C



Vinylic: on C within a C=C group



Aryl: on C within a phenyl ring



S_N2:

S_N1:

Which can undergo substitution reactions? & which type?

- Consider:
  - a) S_N2: steric hindrance blocking Nu access
    electrostatic repulsion of Nu by π-electrons
  - b) S_N1: stability of carbocation intermediate

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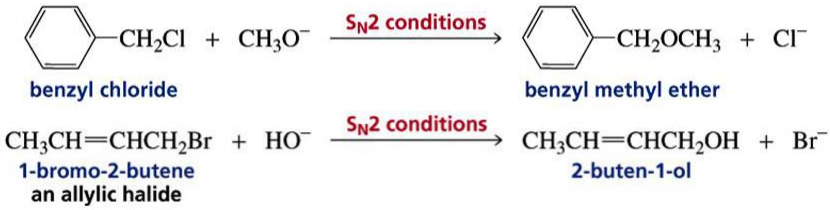
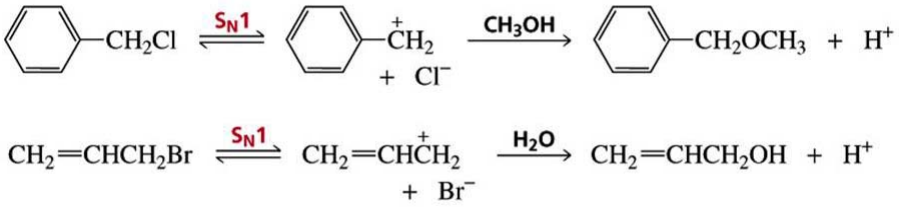
Benzylic & allylic halides: CAN do substitution reactions

☑ S_N2 reactions: readily accessible for both benzylic & allylic X's except if tertiary (too sterically hindered)



☑ S_N1 reactions: readily accessible for both benzylic & allylic X's → carbocation intermediate is resonance-stabilized !



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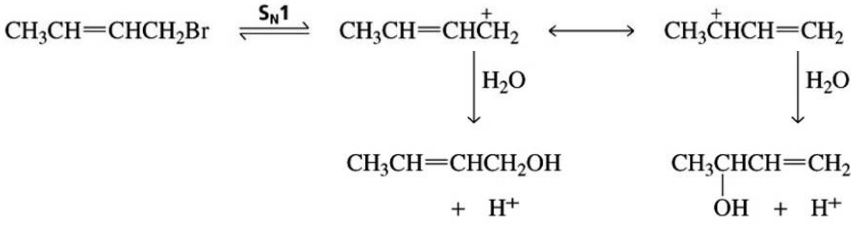
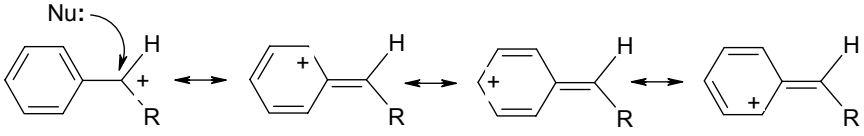
NOTE: > 1 product may result from S_N1 rxn of allylic halide

- two C+ carbons evident when draw resonance structures:



Multiple products do <u>not</u> occur for benzylic halides

- attacking within the benzene ring would break ring's "aromaticity" (e⁻s in cyclic array of overlapping p-orbitals gives extra stability)
- thus: resonance stabilizes the carbocation, but attack by Nu is still regioselective for the benzylic site



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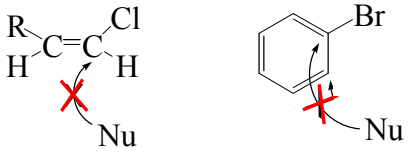
Vinyl & aryl halides: CANNOT do substitution reactions

☒ S_N2 reactions: Nu electrostatically repelled by π-electron cloud during approach to back-side of sp^2-carbon

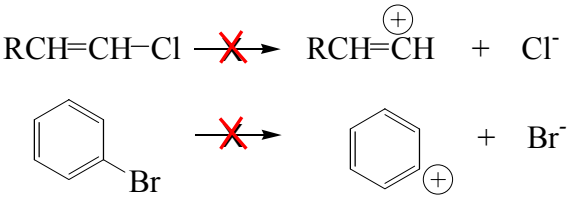


☒ S_N1 reactions: carbocation intermediate is HIGHLY unstable

⇨ C+ would rehybridize to become sp-hybridized

⇨ sp-C's have stronger pull on e⁻s ∴ less stable with + charge

Another view: sp^2-C—X bond stronger than sp^3-C—X bonds
…so, harder to break in the first place!



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8.9 Competition between S_N2 & S_N1 rxns

Table 8.5
Table 8.6

S_N2: predictable regio. & stereo.	S_N1: less control of regio./stereo.
A one-step mechanism	A stepwise mechanism that forms a carbocation intermediate
A bimolecular rate-determining step	A unimolecular rate-determining step
No carbocation rearrangements	Carbocation rearrangements ←
Product has inverted configuration relative to the reactant	Products have both retained and inverted configurations relative to the reactant
Reactivity order: methyl > 1° > 2° > 3°	Reactivity order: 3° > 2° > 1° > methyl

S_N2 only — doesn't occur — S_N1 only — doesn't occur

BOTH rxn mechanisms can (& do) occur for some R-Xs:

- 2° alkyl halides
- 1° & 2° benzylic halides
- 1° & 2° allylic halides

So how do we:
predict which is more likely?
control which one will dominate?

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Careful selection of rxn conditions:
helps control which mechanism will dominate

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Which substitution mechanism will dominate?

8.10 The role of solvent in S_N2 & S_N1 rxns

What to worry about with solvents:

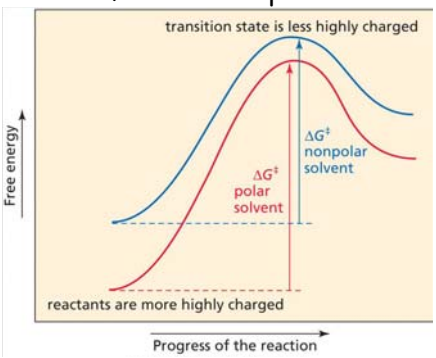
- Remember to check your Nu's basicity (pK_a of conj.acid)
  ⇨ don't want it to deprotonate your solvent
- So: consider the following properties of your solvent:
  - pK_a (to avoid deprotonating)
  - protic *vs.* aprotic (to avoid Nu screening)
  - polarity (to stabilize RLS's ‡)

1. Consider ‡ of desired mechanism's RLS

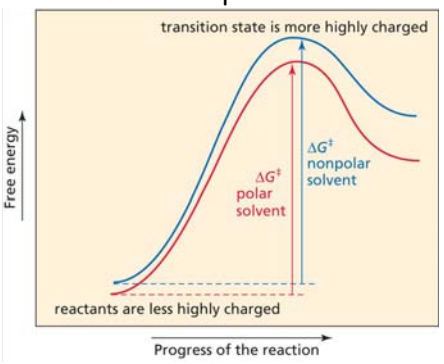
- Is the transition state (‡) charged or neutral?
- Is it more charged or less charged than the reactants?
- …choose a solvent that will encourage the ‡ to form

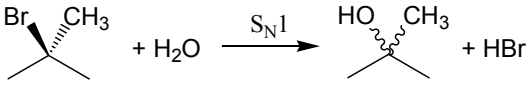
Choose solvent that stabilizes the ‡ of desired rxn

If ‡ is less highly charged
⇨ rxn faster in nonpolar solvent



If ‡ is more highly charged
⇨ rxn faster in polar solvent





What can you say about the ‡ of this rxn's RLS ?

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Table 8.8

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

Choosing a suitable solvent

- **Polarity?** check ε
- **Inertness?** check pK_a

Solvent	Structure	Abbreviation	Dielectric constant
PROTIC SOLVENTS: pK_a < 18 ⇨ be careful with bases			
Water	H_2O	—	79
Formic acid	HCOOH	—	59
Methanol	CH_3OH	MeOH	33
Ethanol	CH_3CH_2OH	EtOH	25
tert-Butyl alcohol	$(CH_3)_3COH$	*tert*-BuOH	11
Acetic acid	CH_3COOH	HOAc	6
APROTIC SOLVENTS: fine for use with strong bases			
→ Dimethyl sulfoxide	$(CH_3)_2SO$	DMSO	47
Acetonitrile	CH_3CN	MeCN	38
→ Dimethylformamide	$(CH_3)_2NCHO$	DMF	37
Acetone	$(CH_3)_2CO$	Me_2CO	21
Dichloromethane	CH_2Cl_2	—	9.1
→ Tetrahydrofuran		THF	7.6
Ethyl acetate	$CH_3COOCH_2CH_3$	EtOAc	6
Diethyl ether	$CH_3CH_2OCH_2CH_3$	Et_2O	4.3
Benzene		—	2.3
Hexane	$CH_3(CH_2)_4CH_3$	—	1.9

Table 8.7

Summary: controlling S_N2 / S_N1 competition

More examples

8.11 Intermolecular *vs.* intramolecular rxns

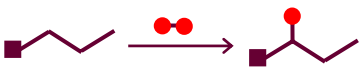
Between 2 molecules
- normal situation…
- rxn faster if ↑ [Nu] or [E^+]
- due to ↑ collision frequency

Nu & δ^+ C (E^+) in same molecule
- rxn more probable at low [molecule] = *high dilution*
- Nu end of molecule most likely to collide with its own δ^+ "tail" …not another molecule's

So… where are we now?

BASIC TYPES OF ORGANIC REACTIONS *(…more in Organic II)*

Ch.11 ✓ **1. Radical halogenation:** adds a functional group to alkanes *(unreactive!)*



Ch.8 **2. Substitution:** change to a different functional group

Ch.9 **3. Elimination:** create a π-bond

Ch.4 ✓ **4. Addition:** use π-bond to add a new functional group

ASSIGNED READINGS

BEFORE NEXT LECTURE:

Read: rest of Ch.8

Practice: writing mechanisms of S_N2 & S_N1
predicting products of S_N2 & S_N1
predicting which mechanism is more likely

Study: for lab exam, 1st 40 min of next class