

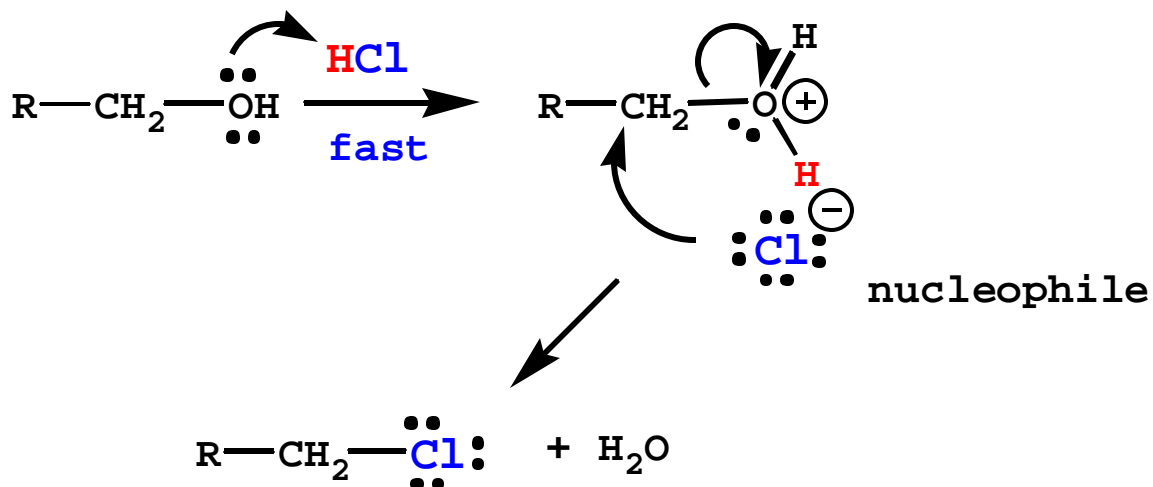
Chapter 11 - Alkyl Halide Reactions. Nucleophilic Substitution and Elimination Reactions*

Useful links:

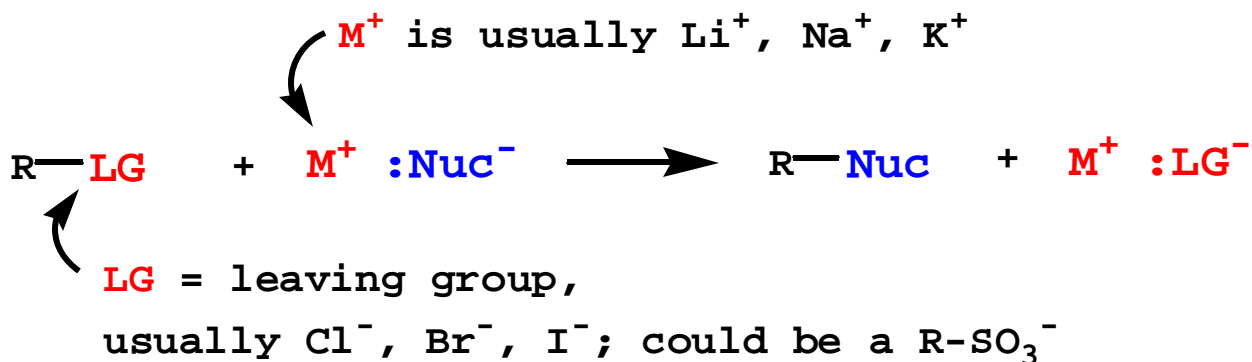
<http://radical.chem.pitt.edu/teaching/Handouts/Chapter6b>

<http://chemweb.stanford.edu/winter2000/chem33/Review/review3/Jake2.pdf>

Previous example of a **substitution** reaction...



General example...



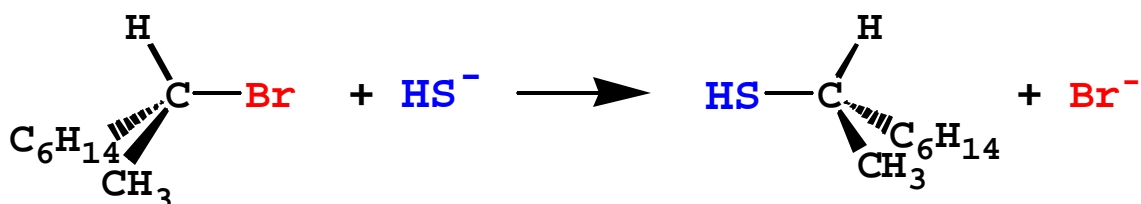
$\text{Nuc}^- = (\text{R})\text{HO}^-, (\text{R})\text{HS}^-, \text{RCO}_2^-, \text{NC}^-$ (cyanide), N_3^- (azide), $\text{X}^-, \text{NO}_3^-$

$\text{Nuc} = \text{H}_2\text{O}, \text{ROH}, \text{NH}_3, \text{HCO}_2\text{H}$ (formic acid)

Relative reactivities with $\text{CH}_3\text{-I}$...

Nucleophile	Relative Reactivity
CH_3OH	1
CH_3CO_2^-	$2 * 10^4$
Cl^-	$2.5 * 10^4$
NH_3	$3.2 * 10^5$
CH_3O^-	$2 * 10^6$
I^-	$2.7 * 10^7$
CH_3S^-	10^9

***S_N2 - substitution nucleophilic bimolecular...**



(R)-2-bromooctane

$[\alpha] = -34.6^\circ$

(S)-2-octanethiol

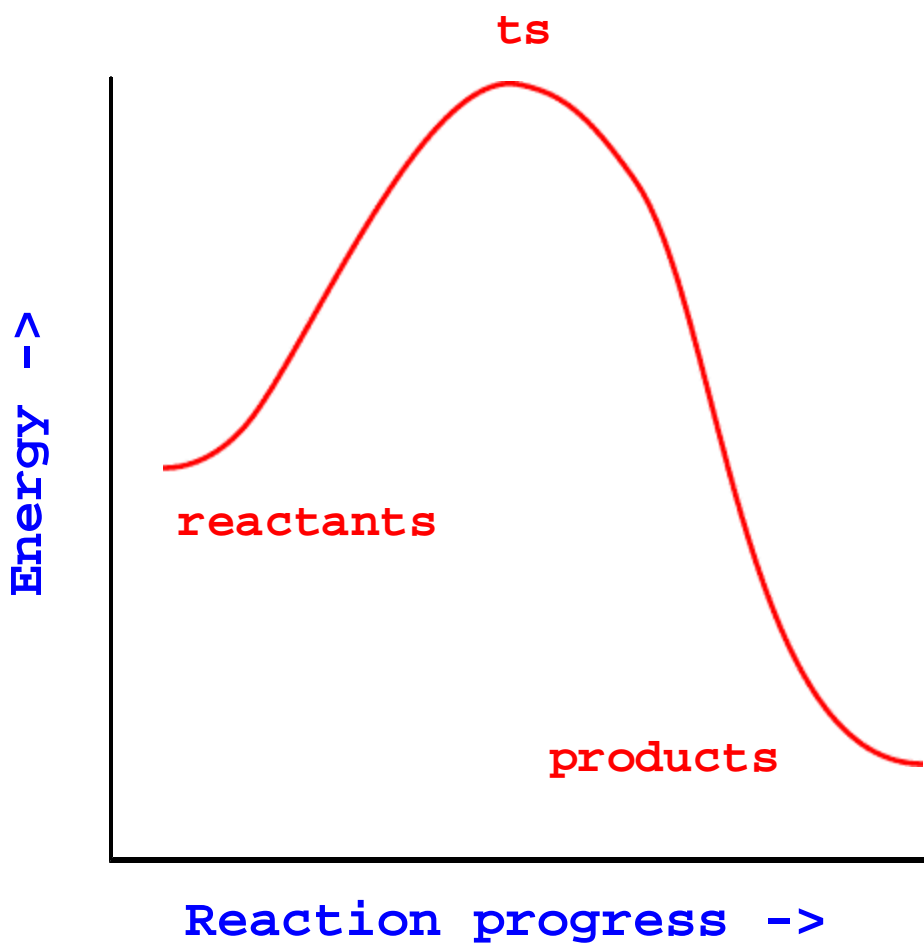
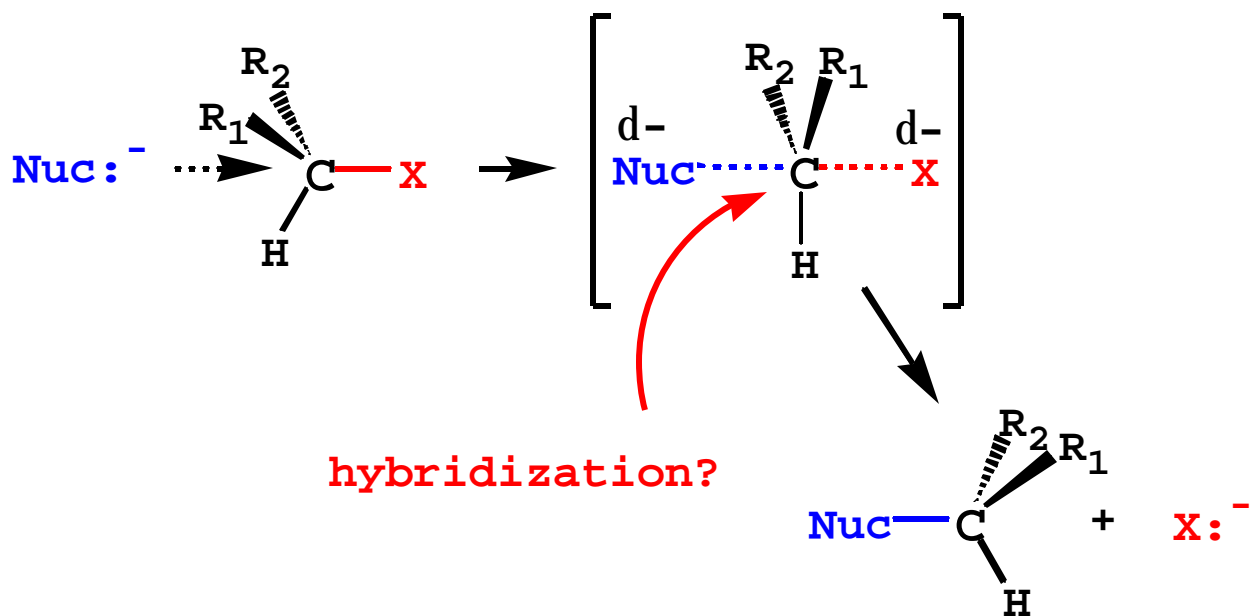
$[\alpha] = +36.4^\circ$

Characteristics...

(1) inversion of configuration (Walden inversion)

(2) 2nd order kinetics, rate = $k[\text{RX}][\text{Nuc}]$

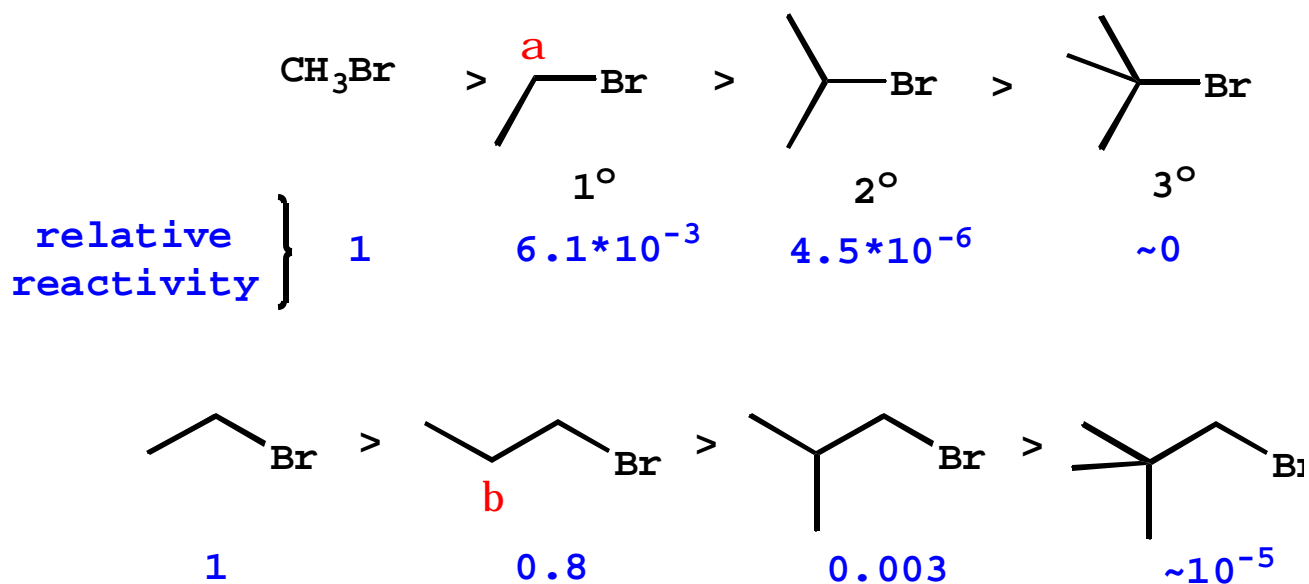
(3) mechanism and E profile

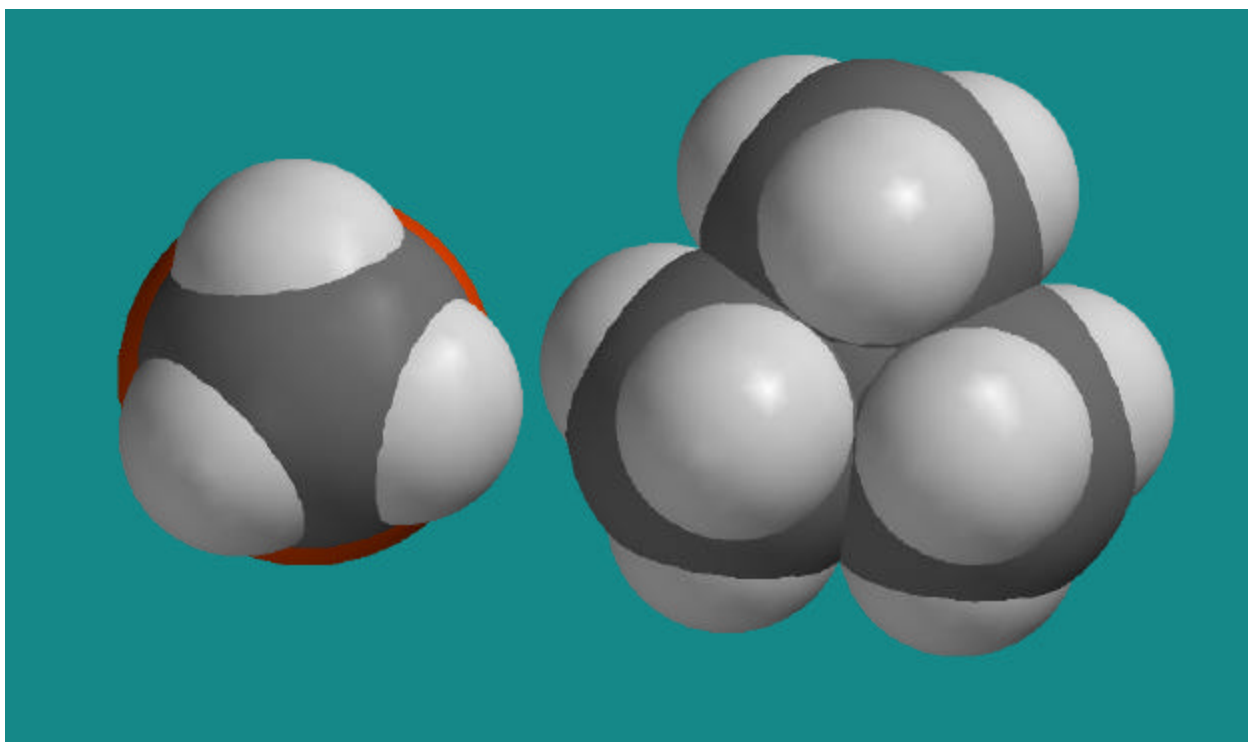


(4) R-X reactivity controlled by steric effects



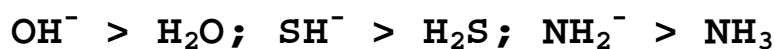
R-Br reactivity decreases with branching at a and b C's





(5) Nucleophilicity

(a) stronger nucleophiles have - charges;
base > conjugate acid

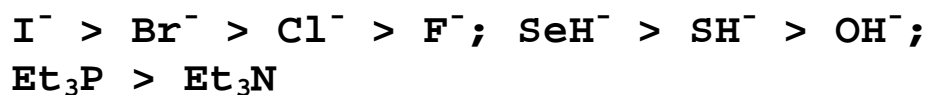


(b) nucleophilicity increases from right
to left in PT;
decrease follows increase in
electronegativity = more tightly held
non-bonding e's



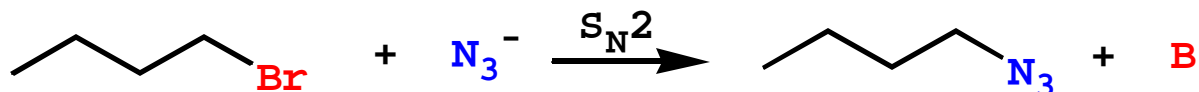
(c) nucleophilicity increases down a
column in PT;

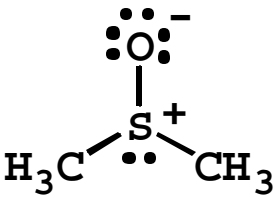
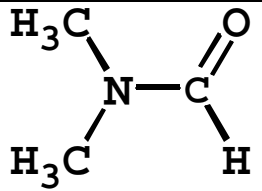
trend follows an increase in size and polarizability



(6) Solvent effects

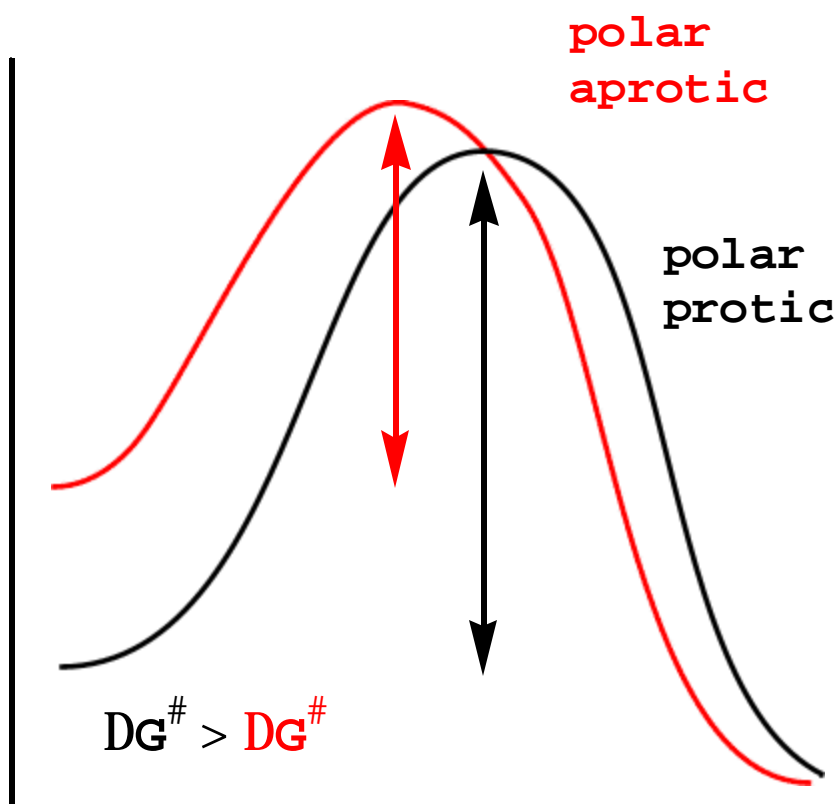
Polar protic solvents H-bond to - charged nucleophiles and decrease the reactivity of the nucleophile. Polar aprotic solvents are the best.



Solvent	Dielectric Constant (e)	Type of solvent	Relative rate
CH ₃ OH	32.6	Polar Protic	1
H ₂ O	78.5	Polar Protic	7
 DMSO; dimethylsulfoxide	48.9	Polar Aprotic	1300
 DMF; N,N-dimethylformamide	36.7	Polar Aprotic	2800

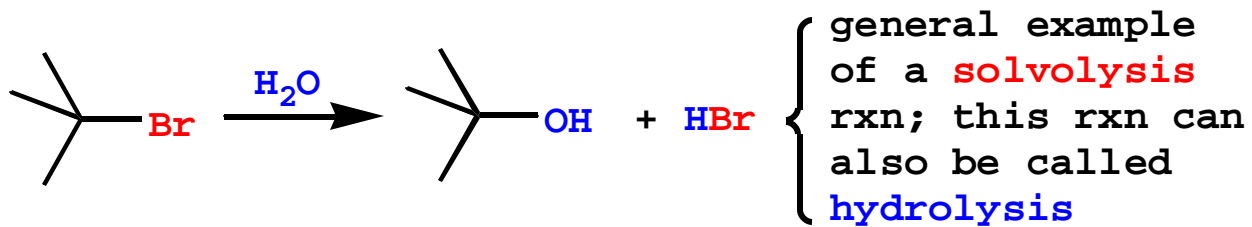
$\text{H}_3\text{C}-\text{C}\equiv\text{N}$ acetonitrile	37.5	Polar Aprotic	5000
$\begin{array}{c} (\text{CH}_3)_2\text{N} \\ (\text{CH}_3)_2\text{N} \diagdown \\ \text{P}=\text{O} \\ (\text{CH}_3)_2\text{N} \diagup \end{array}$ HMPA	30	Polar Aprotic	200,000

Energy profiles...



*S_N1 - Substitution nucleophilic unimolecular...

Example...

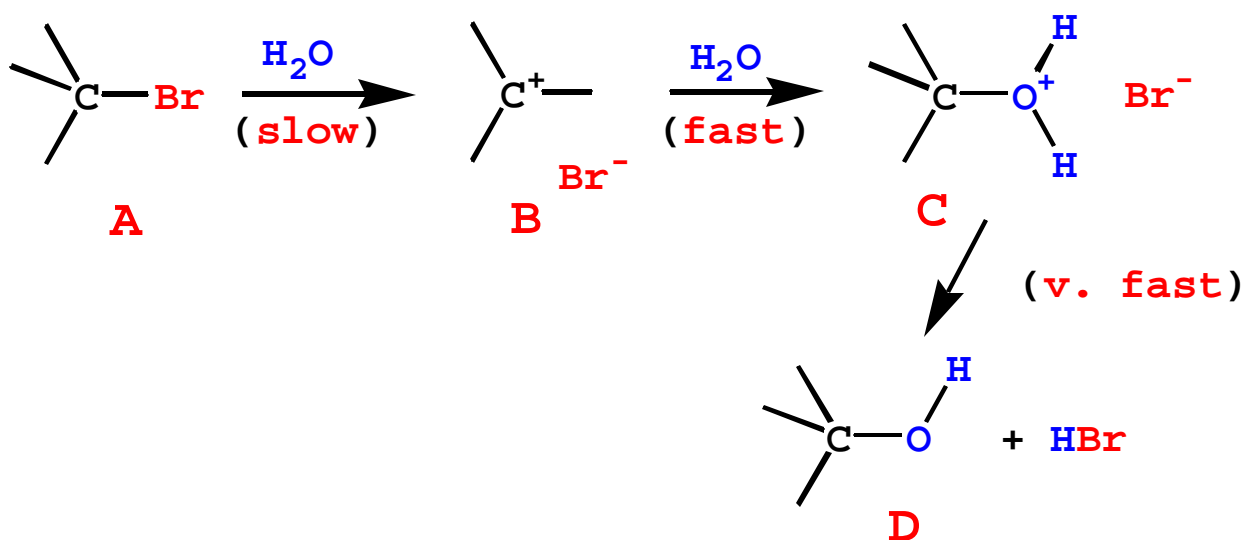


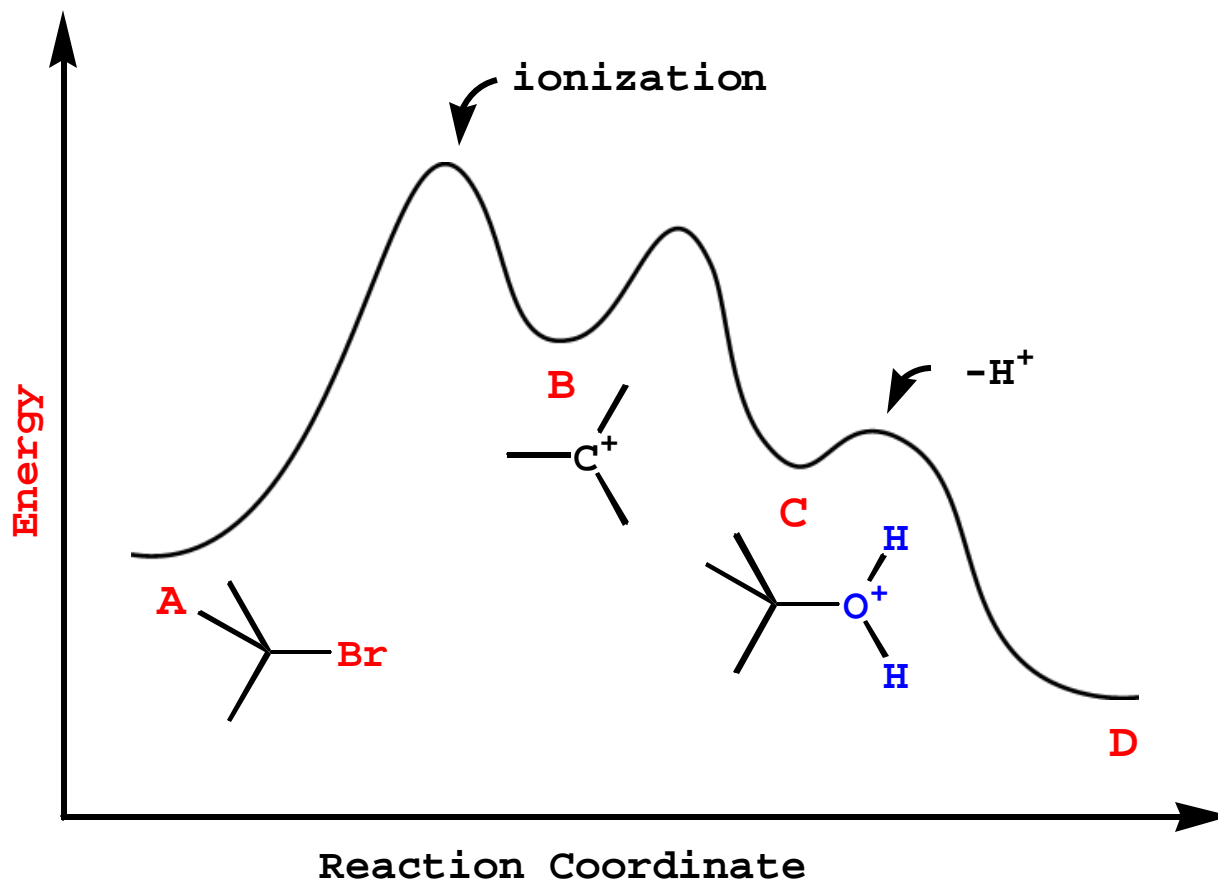
solvolysis = solvent is also a reactant

Characteristics...

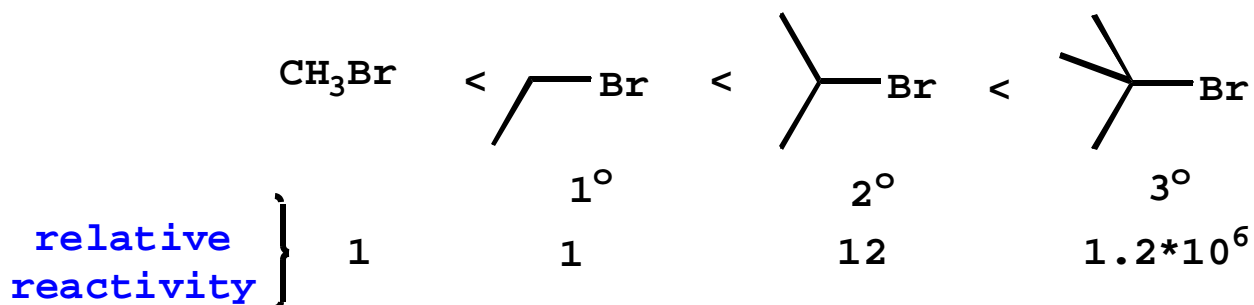
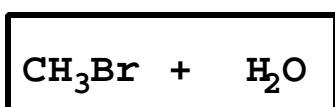
(1) 1st order, rate = $k[\text{R-X}]$

(2) mechanism and E profile

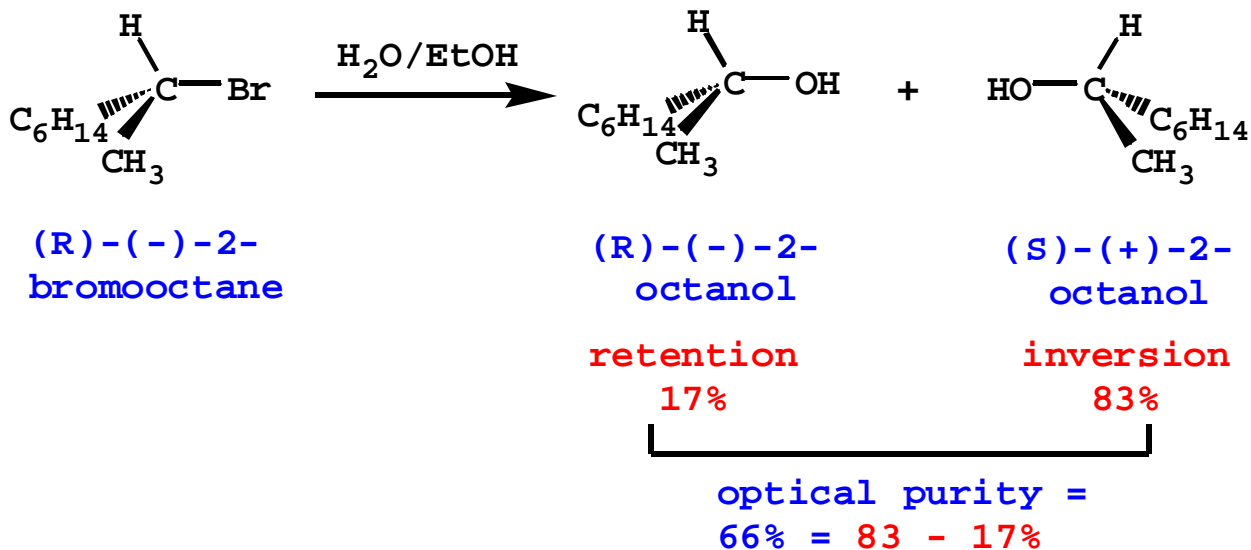




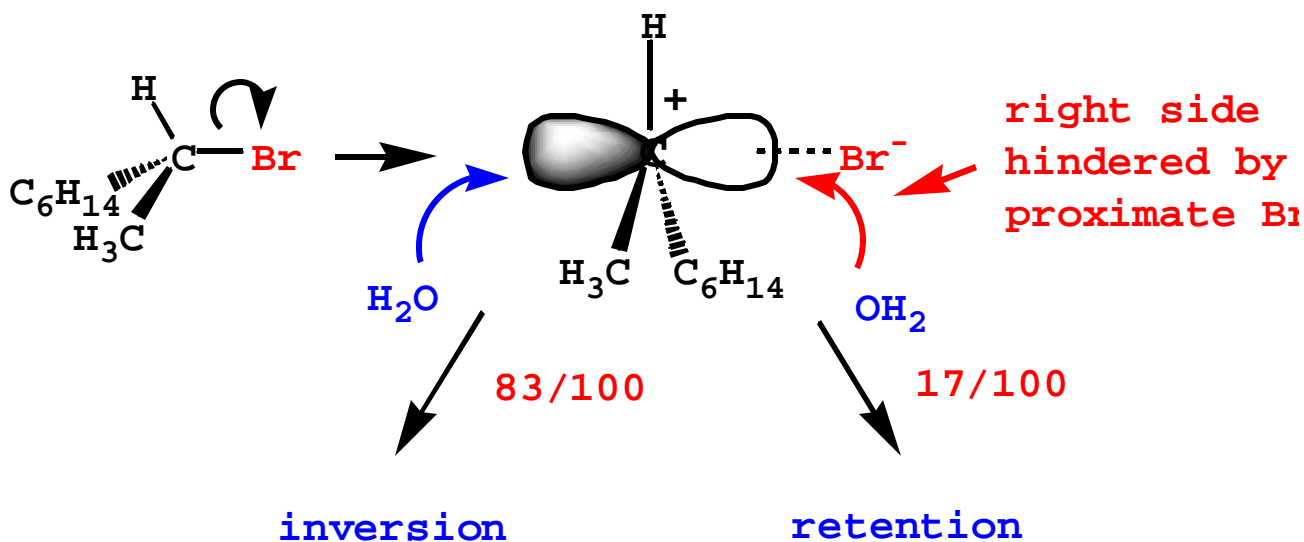
(3) R-X reactivity ~ carbocation stability



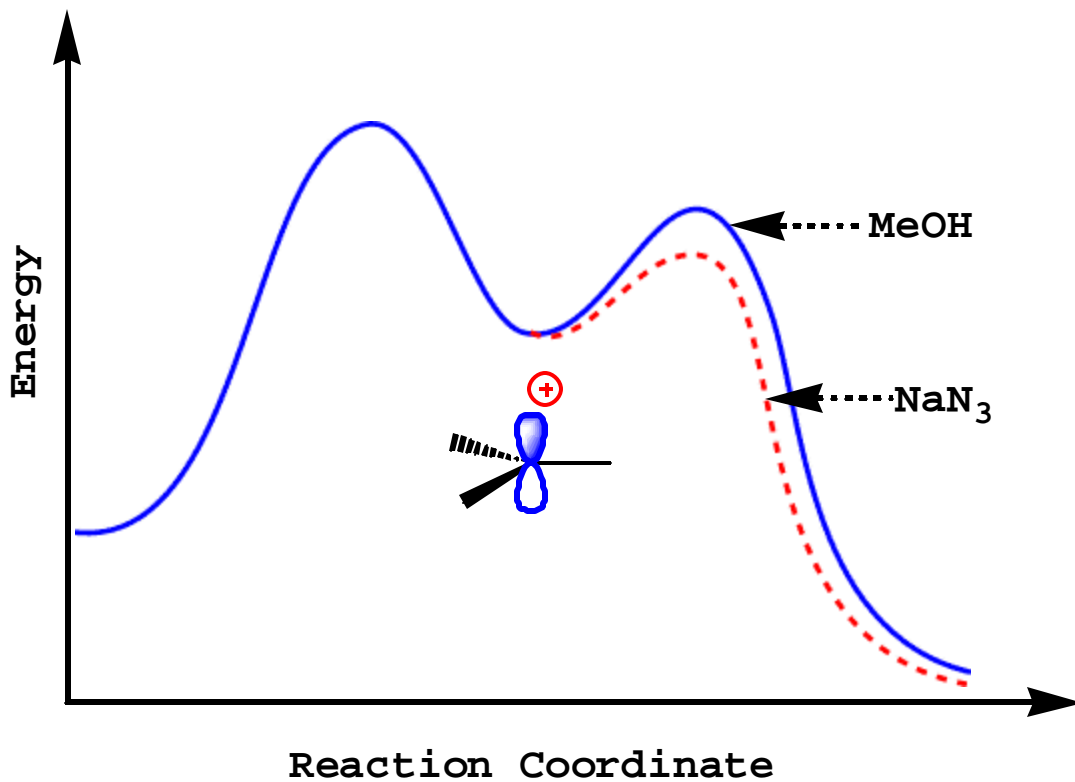
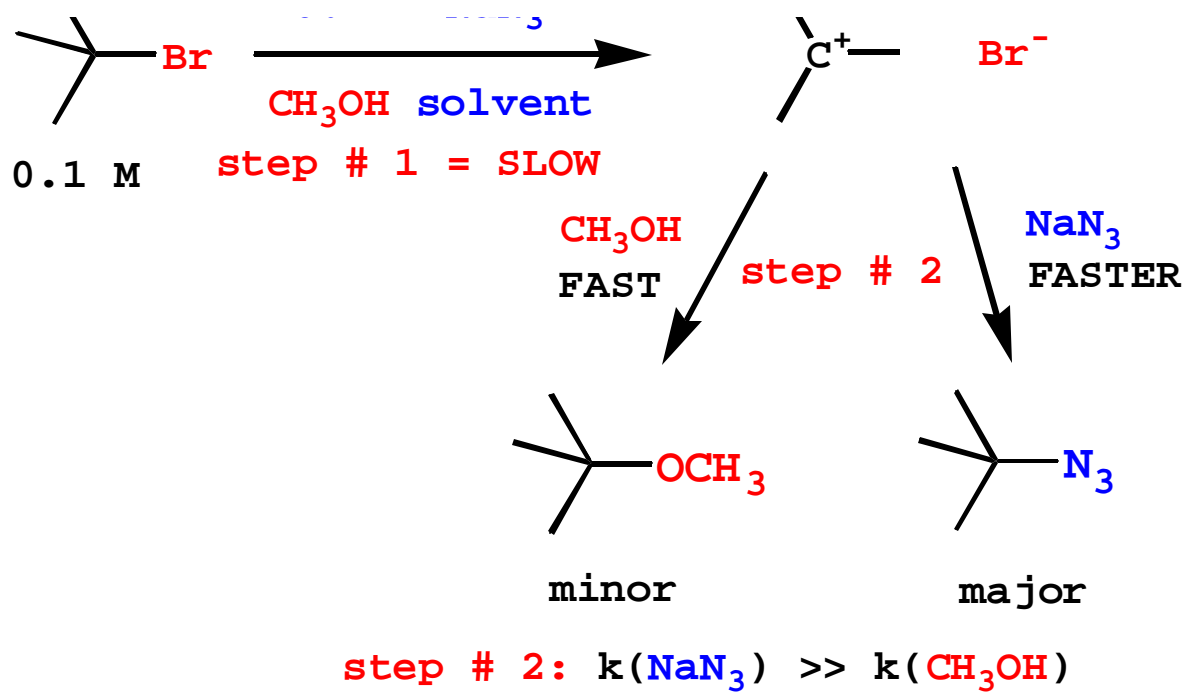
(4) Stereochemistry (partial racemization)



Leaving group (Br^-) partially protects one side from the nucleophile leading to more retention product than inversion product



(5) Nucleophilicity - rate determining step is formation of the carbocation; rate of decrease in $[\text{R-X}]$ is independent of $[\text{nuc}]$ and its nucleophilicity

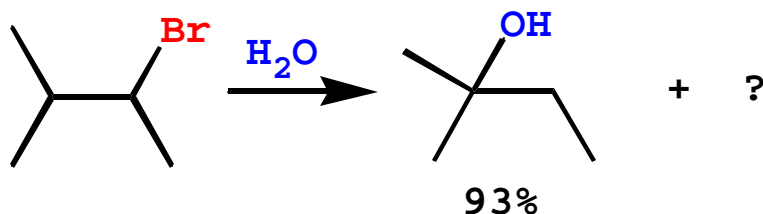


(6) Solvent effects - rate increases with carbocation stability a e

solvent	e	reaction rate
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AcOH	6	1
CH ₃ OH	33	4
HCO ₂ H	58	5000
H ₂ O	78	150,000

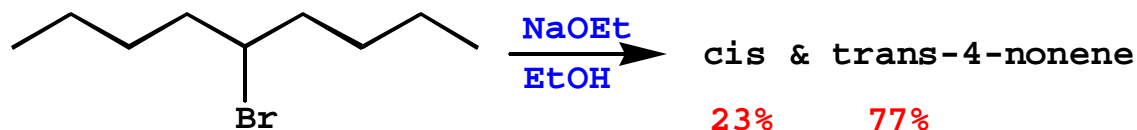
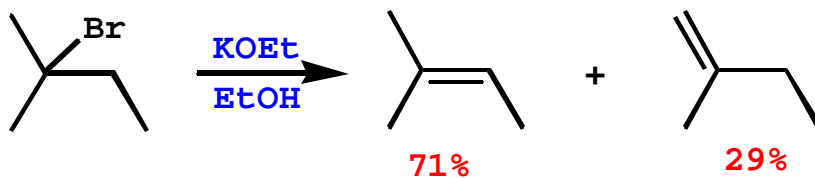
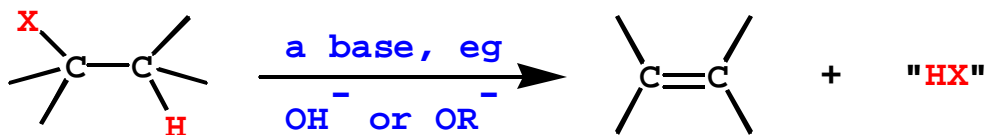
(7) Possible rearrangements -



***E2 - elimination bimolecular...**

(reaction is both regiospecific & stereospecific)

Examples...



5-bromononane

Zaitsev's (Saytzeff's) rule: In the elimination of HX from an alkyl halide, most highly substituted alkene predominates

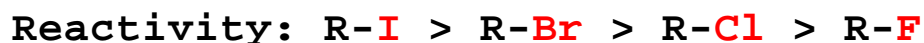
Kinetics and mechanism...

Useful links:

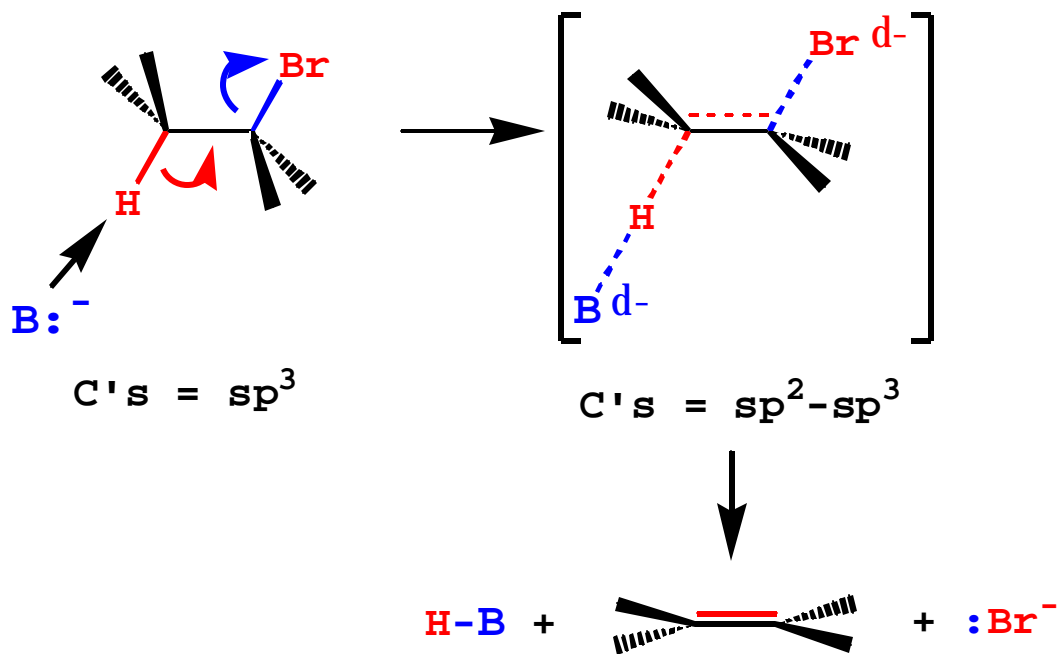
http://www.columbia.edu/itc/chemistry/chem-c3045/organic/text_chapters/ch5.html

http://www.ndsu.nodak.edu/instruct/grcook/chem341_98/lectures/lecture33.shtml

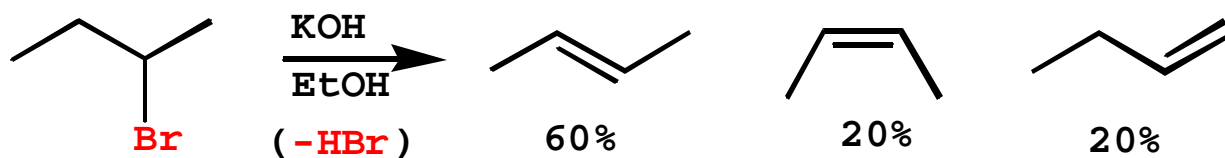
$$\text{Rate} = k[\text{R-X}][\text{base}]$$

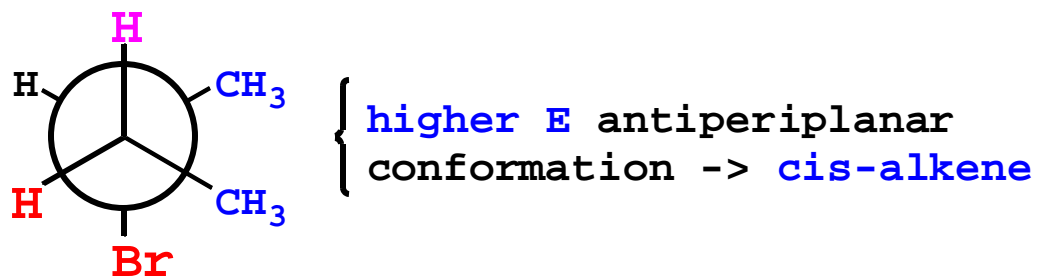
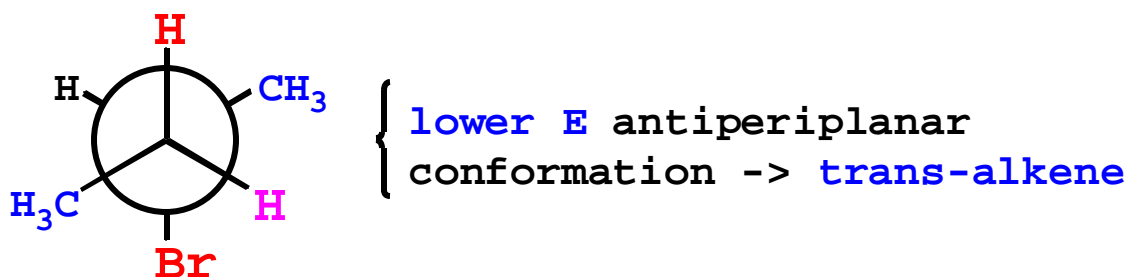


H and Br are antiperiplanar



Example/question: Rationalize the relative amounts of alkene products in the following reaction. Why more *trans* than *cis*?

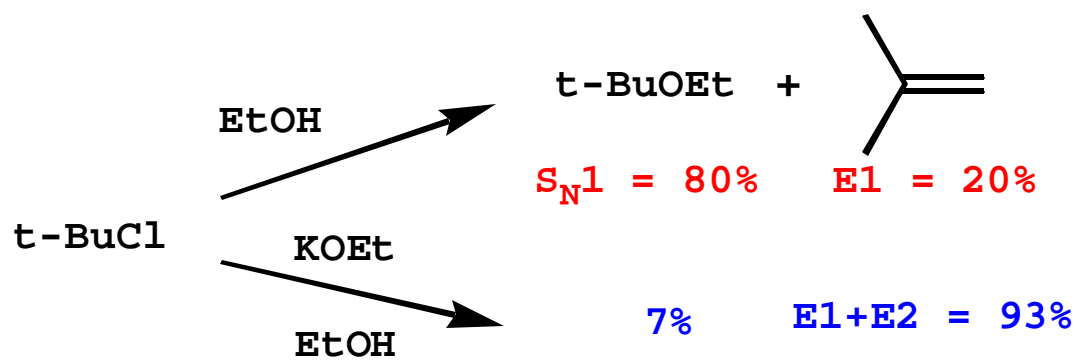
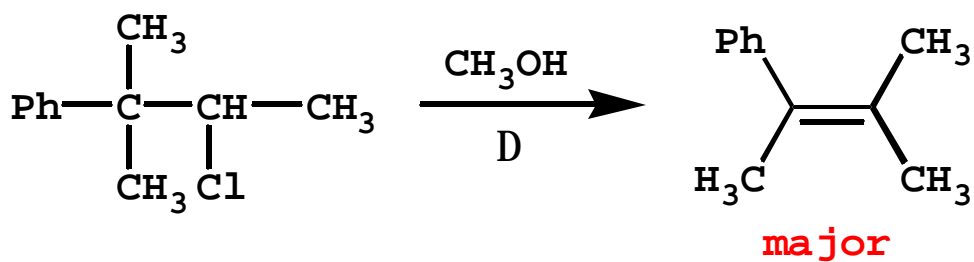
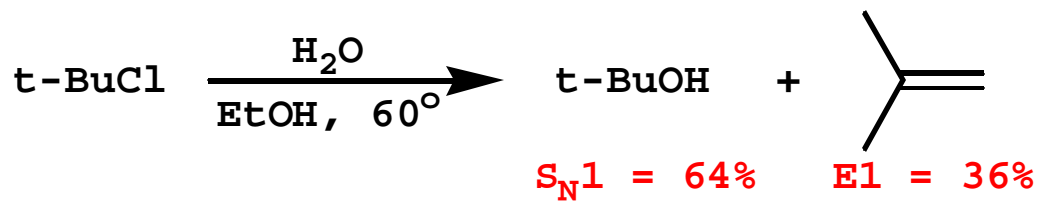




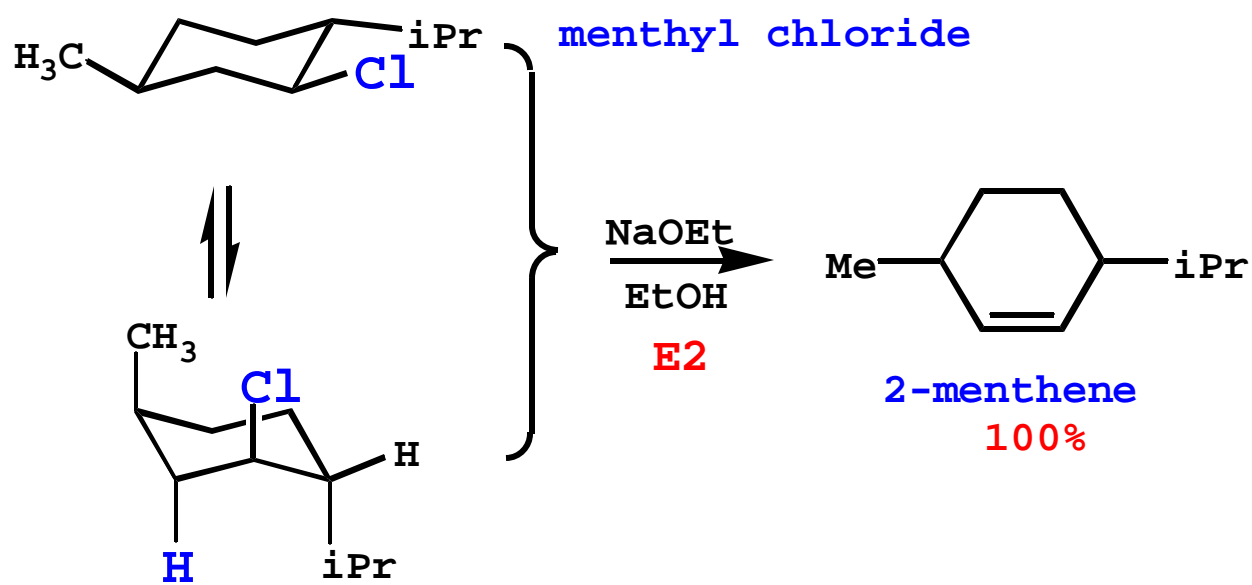
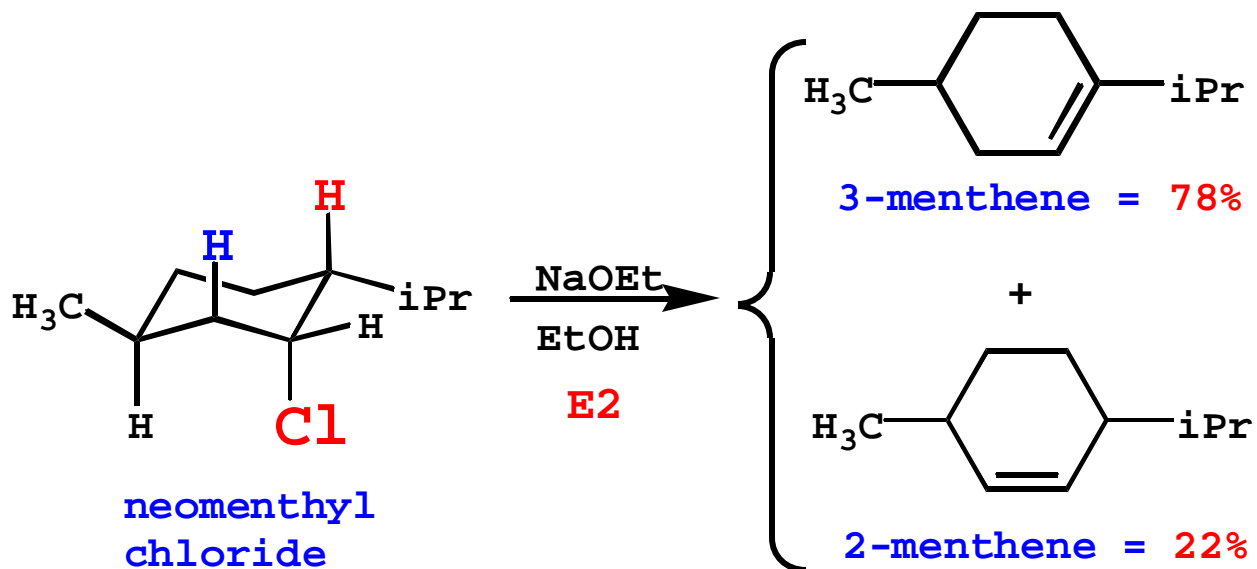
***E1 - elimination unimolecular...**

(for 2° and 3° R-X; like S_N1 -> has a carbocation intermediate)

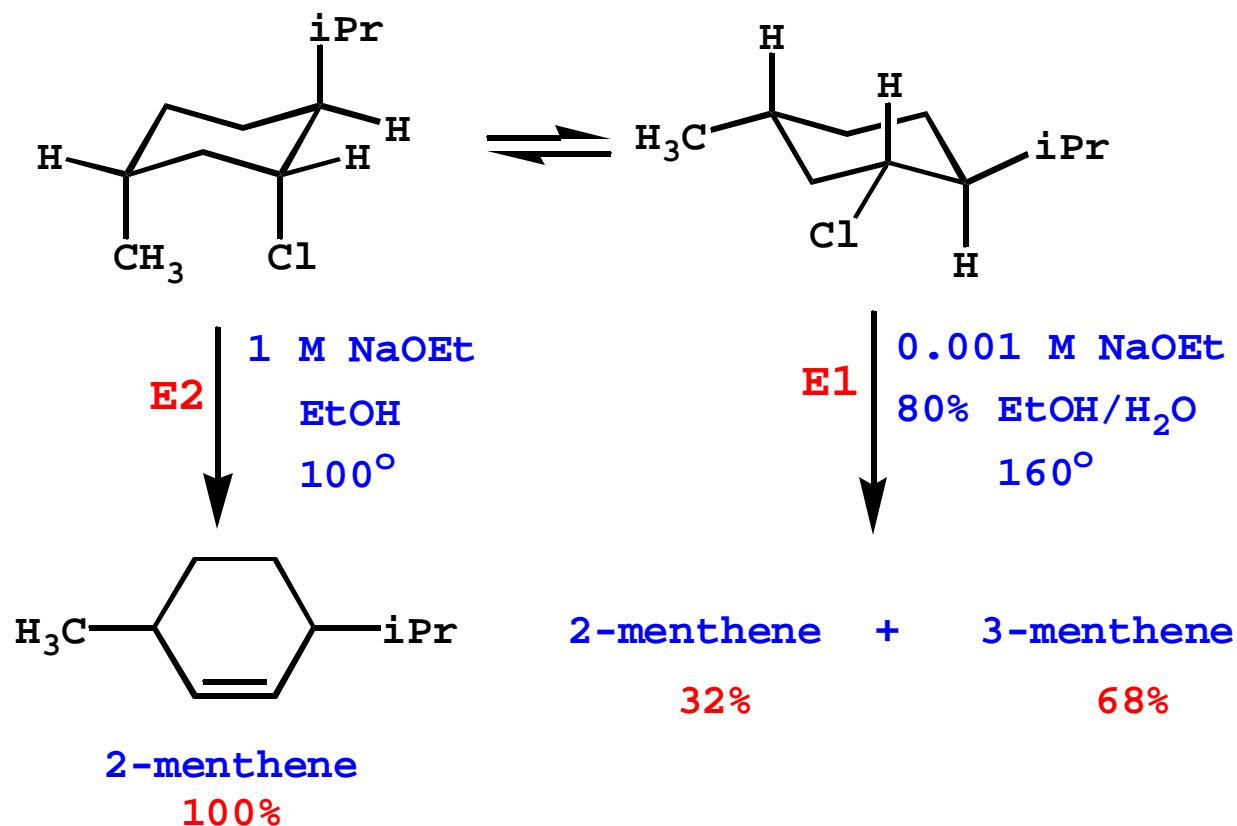
$$\text{rate} = k[\text{R-X}]$$



***Elimination reactions and cyclohexane conformations...**

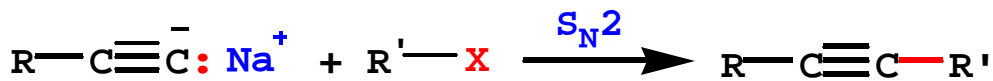
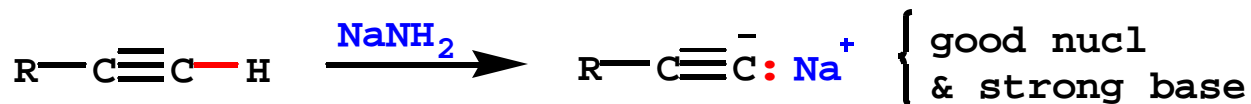


What a difference conditions can make...



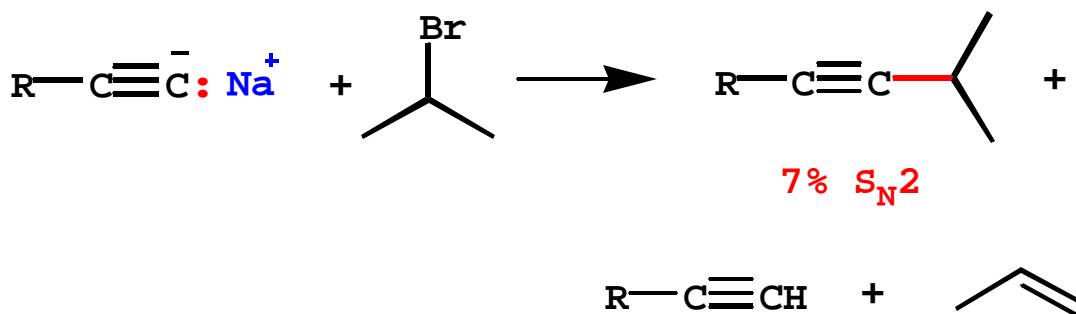
Take-home question: In an E2 reaction, the most stable stereoisomer of 1,2,3,4,5,6-hexachlorocyclohexane reacts ~7000 slower than any other stereoisomer. Why?

***Syntheses with substitution reactions**

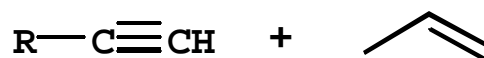


best if R' = CH₃ or 1°

X = Br, I, OTs



7% S_N2



93% E2



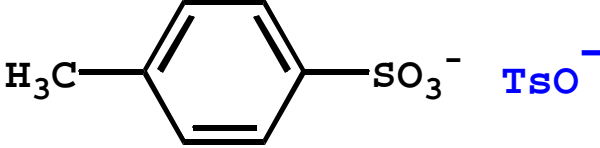
3° R = S_N1

1° R = S_N2

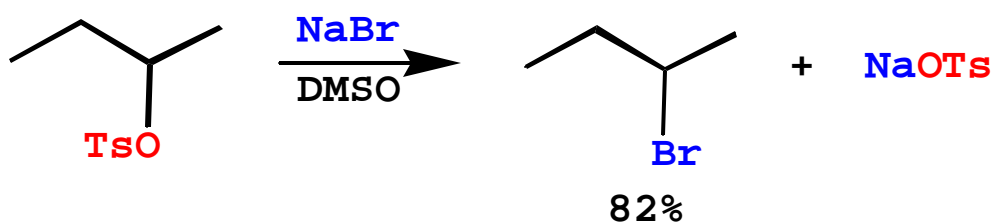
*Sulfonate leaving groups

In S reactions, leaving group abilities can be ~ correlated by basicities of LG's (eg LG⁻).

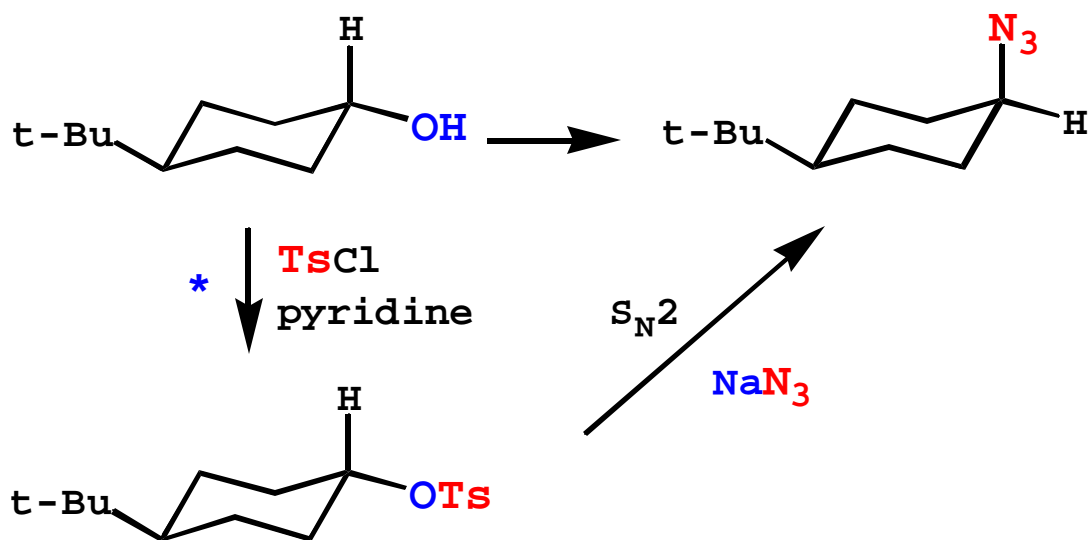
leaving group	pKa of conj. acid	relative rate
F ₃ C—SO ₃ ⁻ Tfo ⁻	-6	10 ⁸

	-2.8	10 ⁵
I ⁻	-10	100
Br ⁻	-9	10
H ₂ O	-1.7	10
Cl ⁻	-7	1
F ⁻	3.5	10 ⁻⁵

An example...

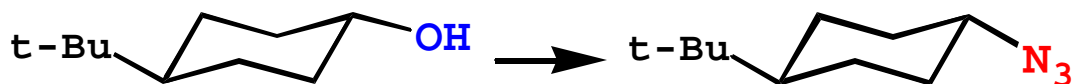


How could the following be done?



<http://www.chem.umd.edu/courses/chem233/ReactionMechanisms/clSOCl2.gif>

And this one?

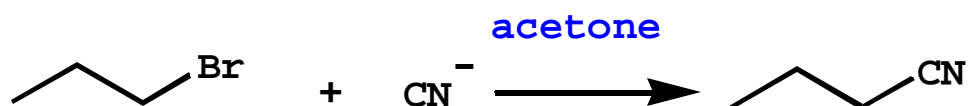


Summary of R_X and S vs E reactivities ->

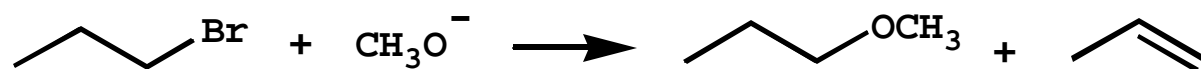
[http://www.chem.umd.edu/courses/chem233/Handouts
&Topics/substn_table.html](http://www.chem.umd.edu/courses/chem233/Handouts&Topics/substn_table.html)

Some specific examples...

(a) 1° R-X --> no S_N1

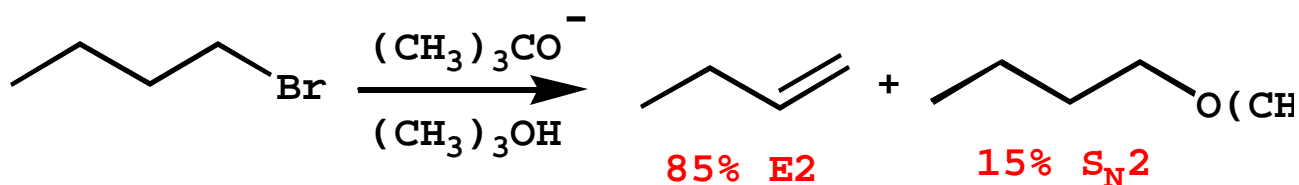


CN⁻ = good nucleophile & moderate base; only S_N2



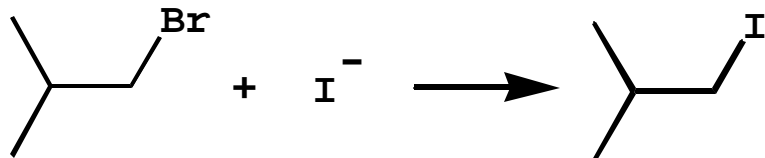
CH₃O⁻ = strong base & good nucleophile;

some E occurs at expense of S

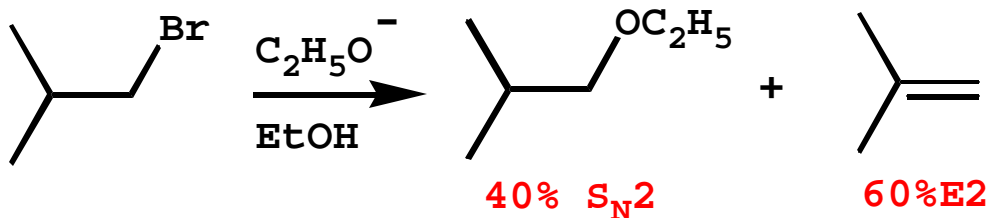


t-BuO⁻ is a strong hindered base;

S_N2 is hindered; rxn primarily E2

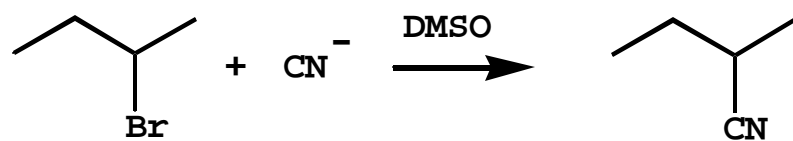
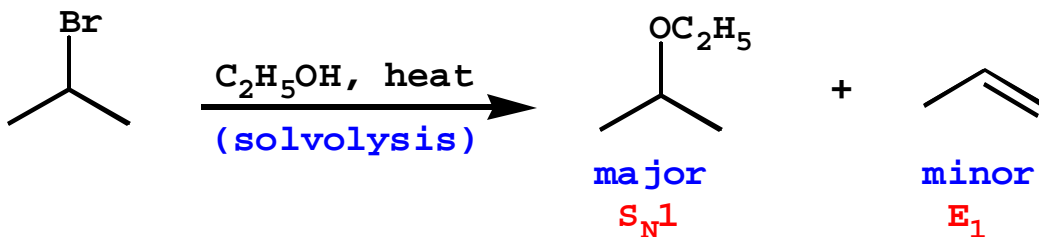


pure S_N2 ; I^- is good nucl & weak base

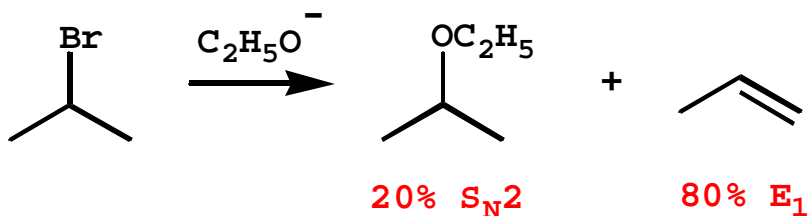


with branched 1° RX & strong base,
S is hindered & E favored

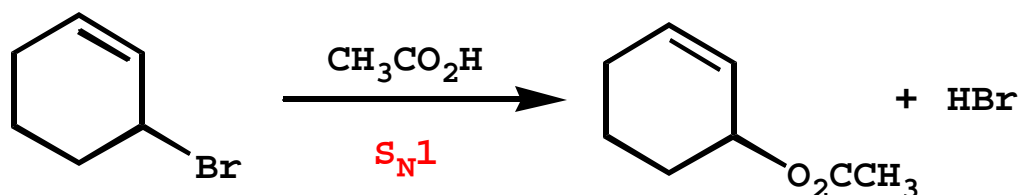
(b) 2° RX $\rightarrow S_N1$ & S_N2 & $E2$; $E1$ is minor



CN^- is a good nucleophile, not a strong base;
DMSO is a good solvent for S_N2

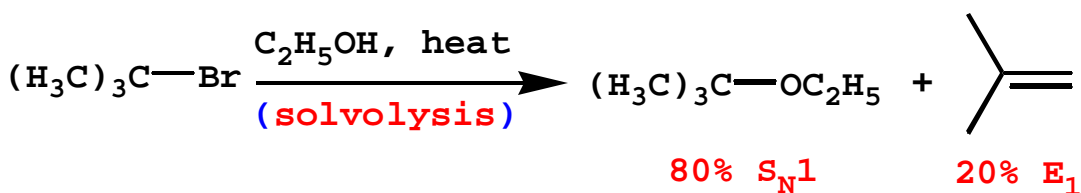


$C_2H_5O^-$ is a strong base

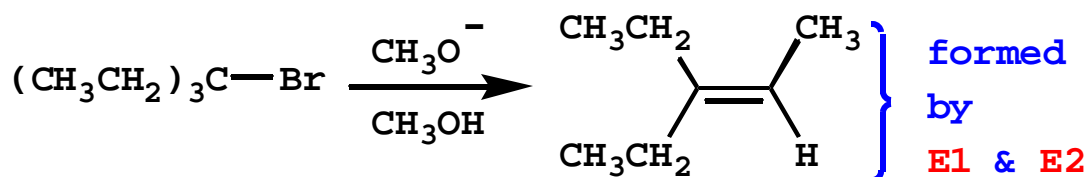


solvolysis (acetolysis) reaction;
 AcOH = poor nucleophile & good ionization solvent;
 key carbocation intermediate is the resonance
 stabilized **allylic cation**

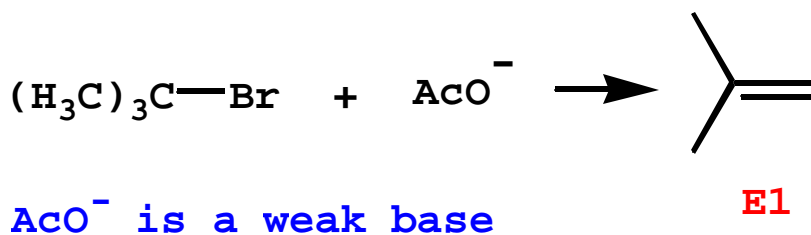
(c) 3° RX \rightarrow no S_N2



$\text{C}_2\text{H}_5\text{OH}$ is a weak base



S is hindered; with strong base both E_1 and E_2 occur



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