Today

Sections 9.3 & 9.4
Factors that affect S_N2 and S_N1

Section 9.5
Competition between S_N1 and S_N2

Next Class

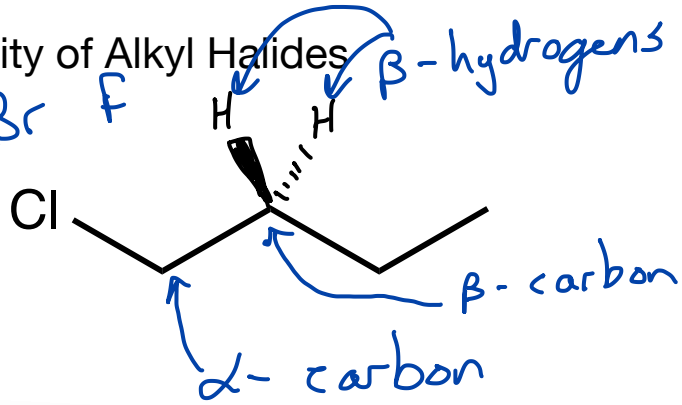
Final on Dec. 14 from 12:20 to 2:20

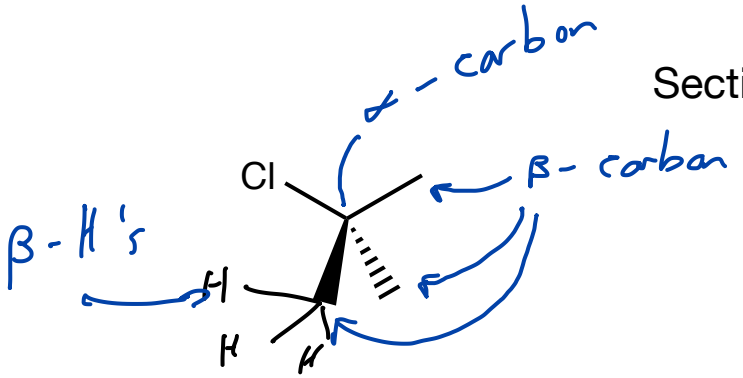
Rework test 3 (provide answers for any questions for which you did not receive full credit) and turn in the assignment at the final.

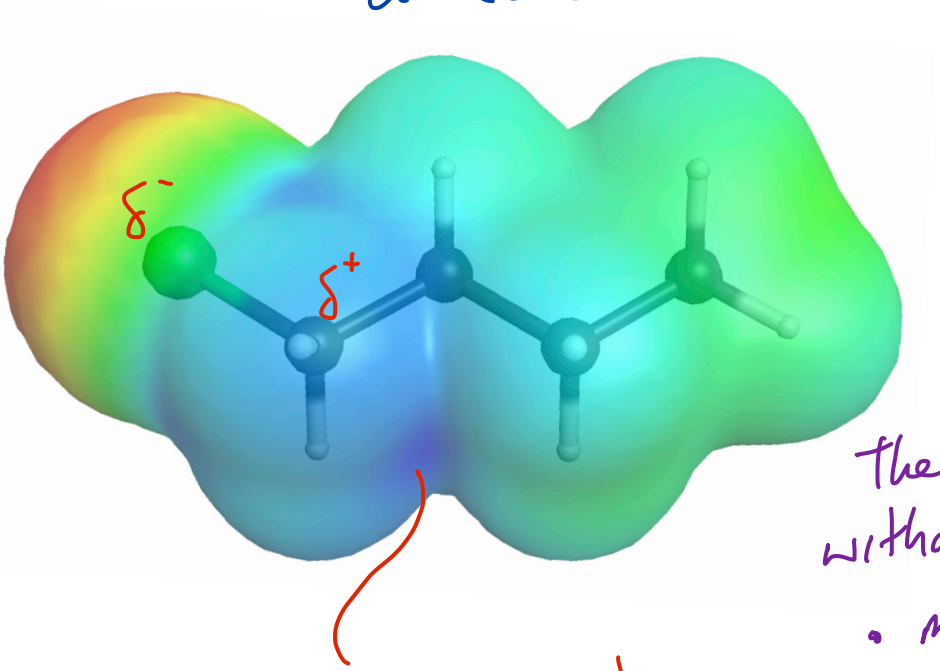
Remember to bring modeling kits at the final to hand them in.

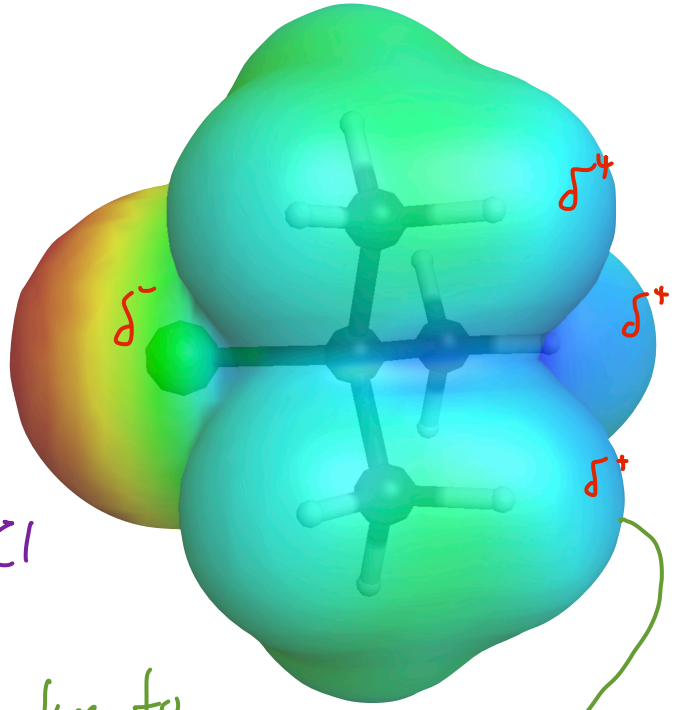
Review Session: Wilson 130 on Dec. 13 from 7:30 to 9:00.

I Br F









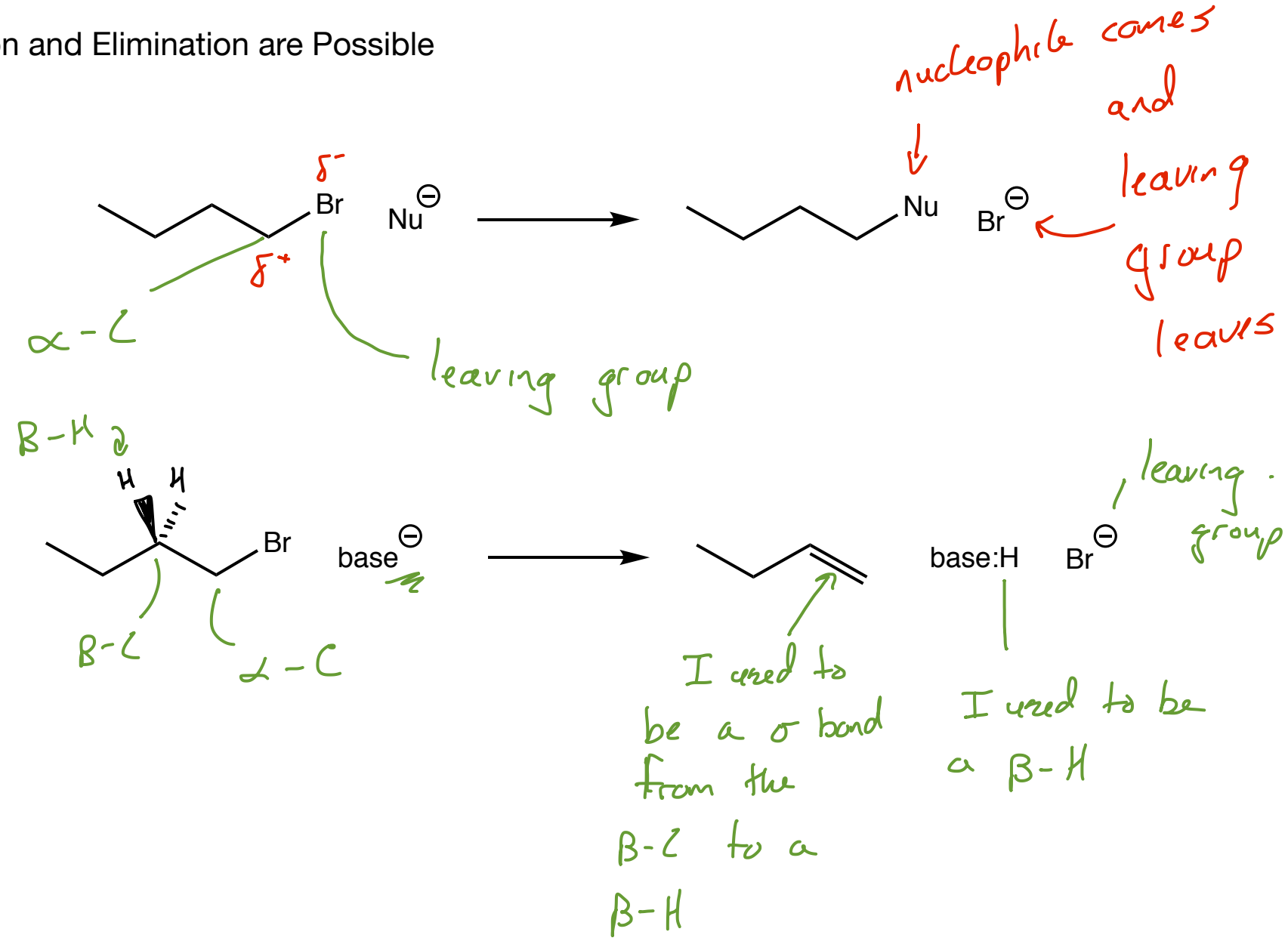
e⁻ deficient area δ⁺

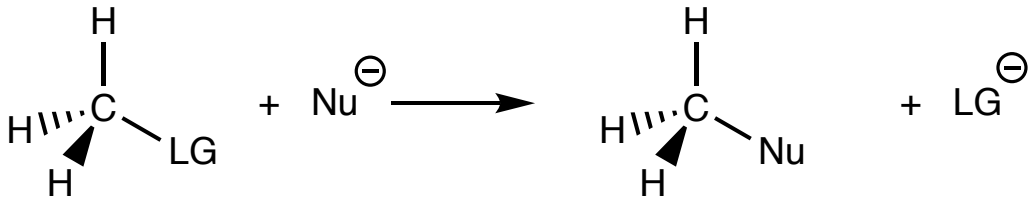
this will be attractive to e⁻ rich atoms and molecules ... nucleophiles

the e⁻ withdrawing Cl
- makes the α-C δ⁺ - attractive to nucleophiles
- makes the β-H δ⁺ makes them attractive to e⁻ rich atoms or molecules

the H's are more positive than H's in an unsubstituted alkane

Substitution and Elimination are Possible

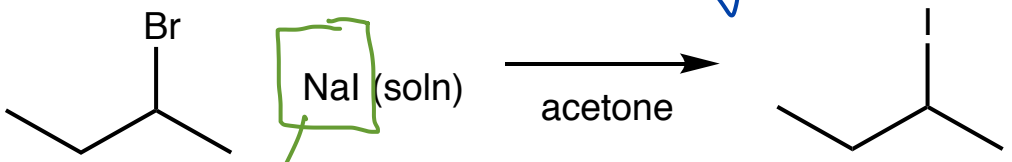




no valence electrons to act as a nucleophile.

$Na^{\oplus} I^{\ominus}$

In organic it is safe to assume that Na, K, Li behave like Na^+, Li^+, & K^+ when they a part of a compound

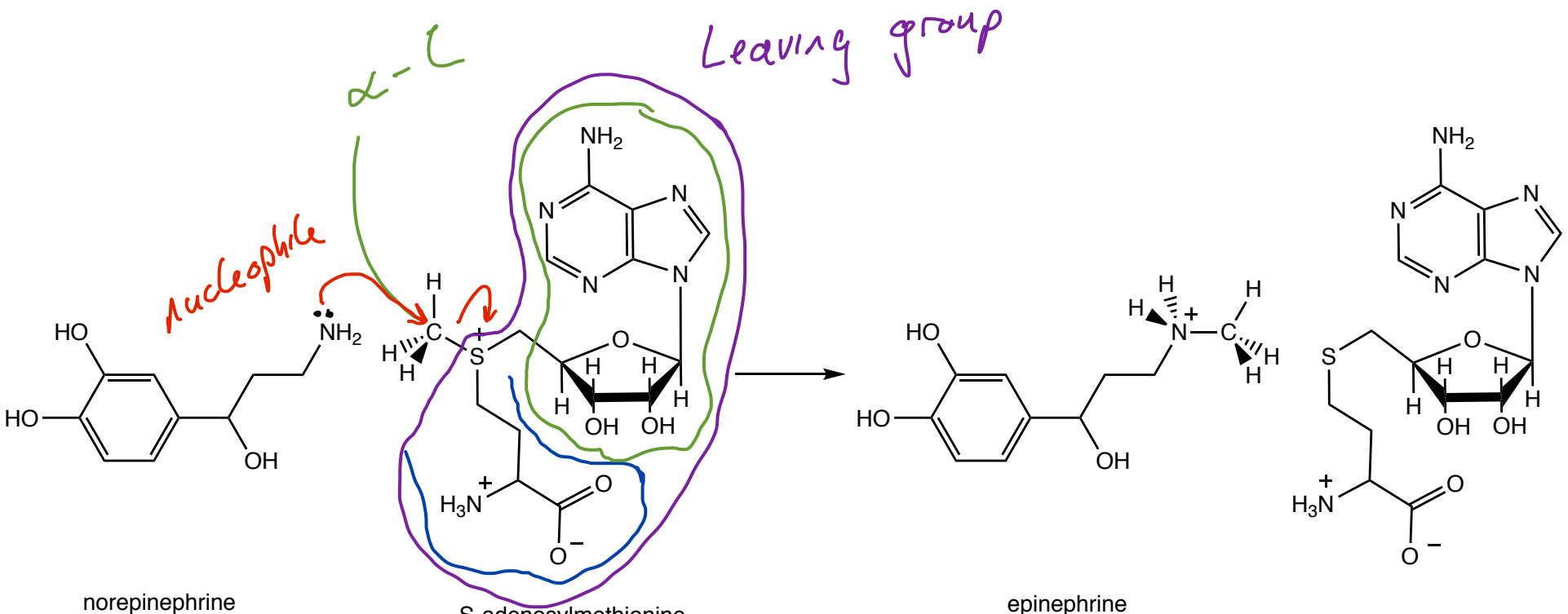


Na^+, Li^+, K^+

NaCl

Na^+ Cl^-

Nucleophilic Substitution Reactions in Biology



Nucleophilic Substitution Reactions in Biology

The lysozyme mechanism sorted — after 50 years

Anthony J Kirby

Unambiguous evidence for a glycosyl-enzyme intermediate on the lysozyme reaction pathway has recently been reported, finally settling what kind of mechanism this textbook enzyme uses.

The publication in 1965[1] of the hen egg white lysozyme crystal structure — the first such structure of any enzyme — was a major landmark, offering the prospect of detailed explanations of enzyme mechanisms at the molecular level. Such mechanisms involve some of the most subtle relationships between structure and function in all of biology, as enzymes have to recognize and thus stabilize transition states, which probably exist for only femtoseconds. Because the structure of lysozyme was a first, and because of the coherent messages the structure seemed to provide, lysozyme has been a textbook example of enzyme mechanism ever since. Now, in a recent issue of *Nature*, Vocadlo *et al.*[2] report new evidence about the mechanism of lysozyme, information that has been sought after for almost 50 years.

Lysozyme is the most prominent member of the very large class of glycosidases or glycohydrolases, enzymes that catalyze the transfer of a glycosyl group to water. *In vivo* lysozyme catalyzes the hydrolysis of a polysaccharide component of the cell wall of Gram-positive bacteria. To do this it accelerates enormously the extraordi-

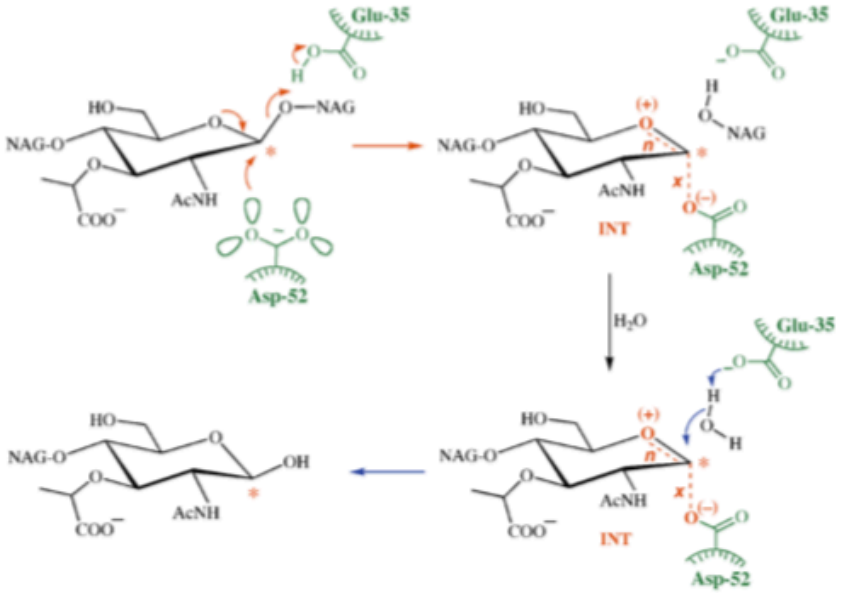


Fig. 1 The reaction catalyzed by lysozyme. The substrate is bound so that the leaving group oxygen, the 4-OH group of an N-acetylglucosamine (NAG) residue, is protonated as it leaves by the COOH group of Glu 35. Groups on the enzyme are colored green, electron movements and the key developing bonds and charges in red. Only one of the dashed *exo* and *endo* (*x* and *n*) bonds of the intermediate (INT) is actually present: which one defines the mechanism. Thus *n* is missing in mechanism (i), *x* in mechanism (ii).

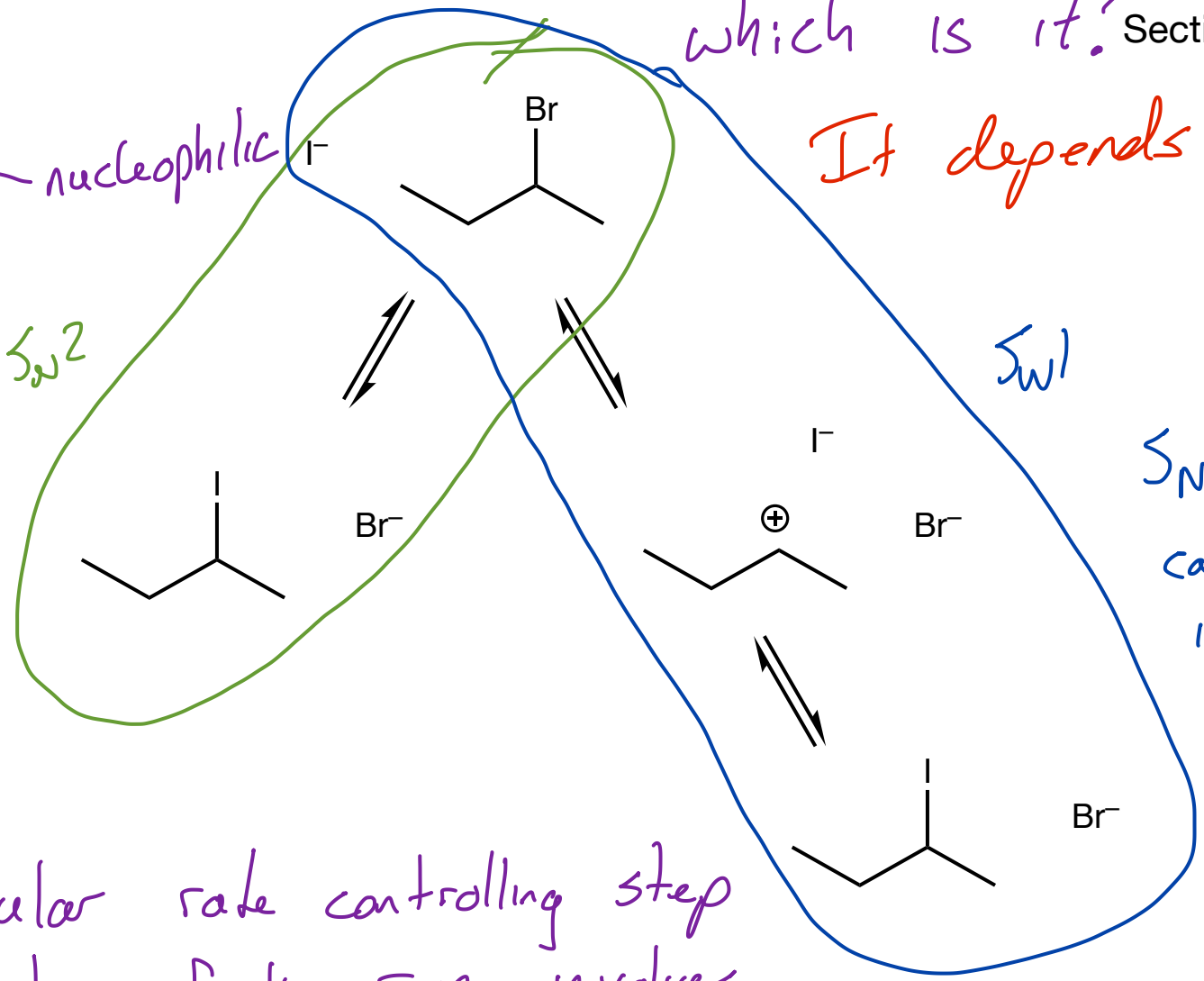
Nature structural biology (2001), v8(9), p73

substitution

nucleophilic

which is it?

It depends

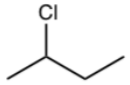
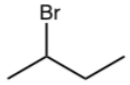
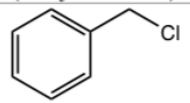
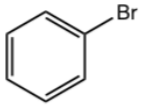


2 - bimolecular rate controlling step
slow step of the rxn involves
2 molecules/objects colliding

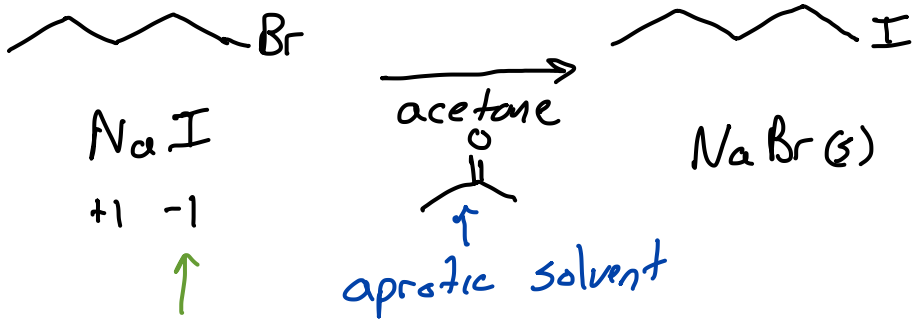
1 - unimolecular rate controlling step involves 1 molecule
wait for 1 molecule to do its thing

* aprotic – not able to act as an H-bond donor

Nucleophilic Substitution: The reactivity of halogenated hydrocarbons Lab

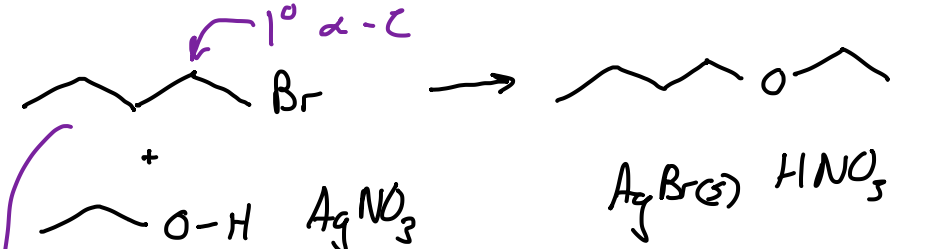
Compound	Acetone-NaI Reaction		Ethanol-$AgNO_3$ Reaction	
	Cold	Hot	Cold	Hot
 1-chlorobutane		cloudy		slow slightly cloudy S_N2
 1-bromobutane	precip		slow slightly cloudy S_N2	
 2-chlorobutane				cloudy slow S_N2
 2-bromobutane		precip	slow cloudy S_N2	
 2-chloro-2-methylpropane (*t*-butylchloride)			good rxn precip	
 1-chloro-2-butene (crotyl chloride)	precip		good rxn precip	
 benzylchloride (α-chlorotoluene)	precip		good rxn precip	
 bromobenzene				

S_N2 mechanism encouraged



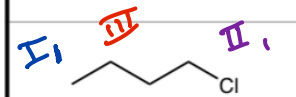
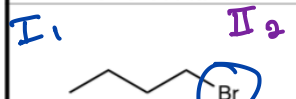
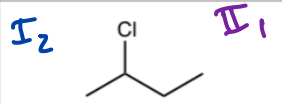
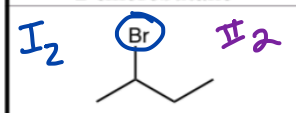
e⁻ rich nucleophile, very good Nu

S_N1 mechanism encouraged



so so nucleophile + protic solvent

Did this sluggish rxn that made the test tube slightly cloudy go via an S_N1 mechanism? No!
No 1° Ct... this is a sluggish S_N2

Compound	Acetone-NaI Reaction		Ethanol-$AgNO_3$ Reaction	
	Cold	Hot	Cold	Hot
 1-chlorobutane		cloudy		slow slightly cloudy S_N2
 1-bromobutane	precip		slow slightly cloudy S_N2	
 2-chlorobutane				cloudy slow S_N2
 2-bromobutane		precip	slow cloudy S_N2	
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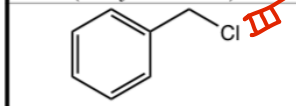
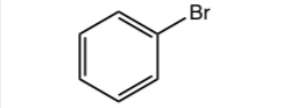
 benzylchloride (α-chlorotoluene)	precip		good rxn precip	
 bromobenzene				

I

Which is a better leaving group, Cl^- or Br^-? Provide three pieces of evidence to support your response.

Keep everything the same & compare Br to Cl

Br^- better

II

Which is a better substrate for an S_N2 reaction, a 1° or 2° alkyl halide? Provide evidence for your response.

1° α-C > 2° α-C

Are 3° substrates suitable substrates for an S_N2 reaction? Provide evidence for your answer.

No, X^{Cl} didn't react

Rank 1°, 2°, and 3° alkyl halides by their ability to react under conditions that favor S_N1 reactions. Provide evidence for your ranking.

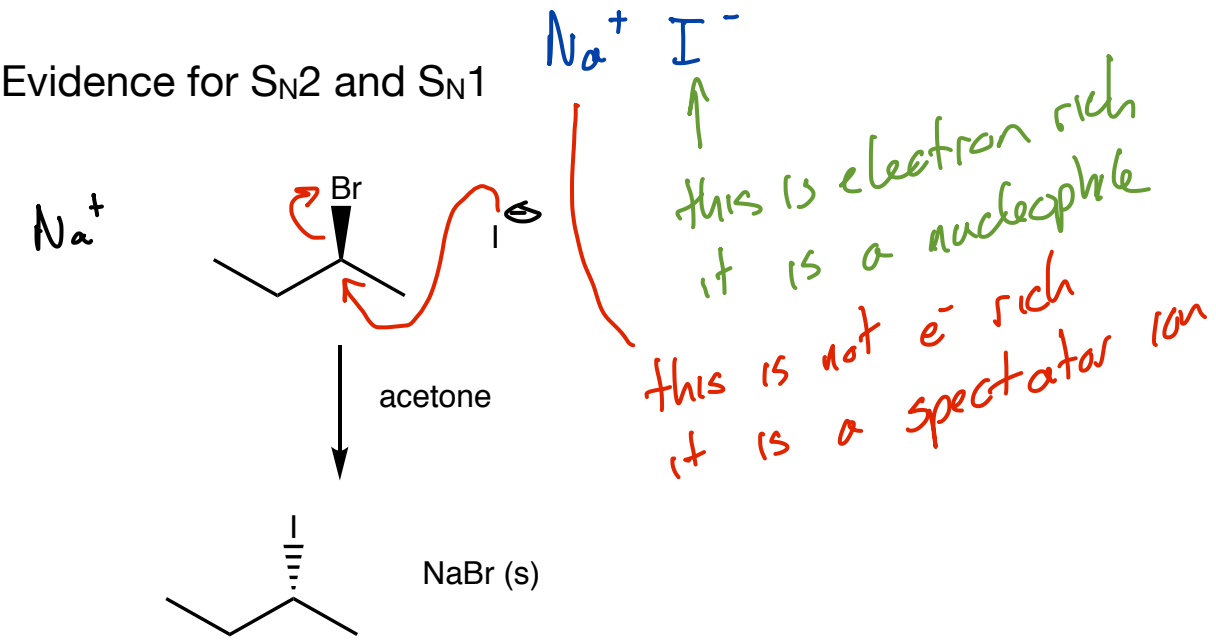
3° > 2° > 1°

↑ C^+ is more stable

Are any 1° chlorohyrdrocarbons used in this experiment reactive toward S_N1 reactions? Explain why these 1° chlorohydrocarbons behave differently than 1-chlorobutane.

III

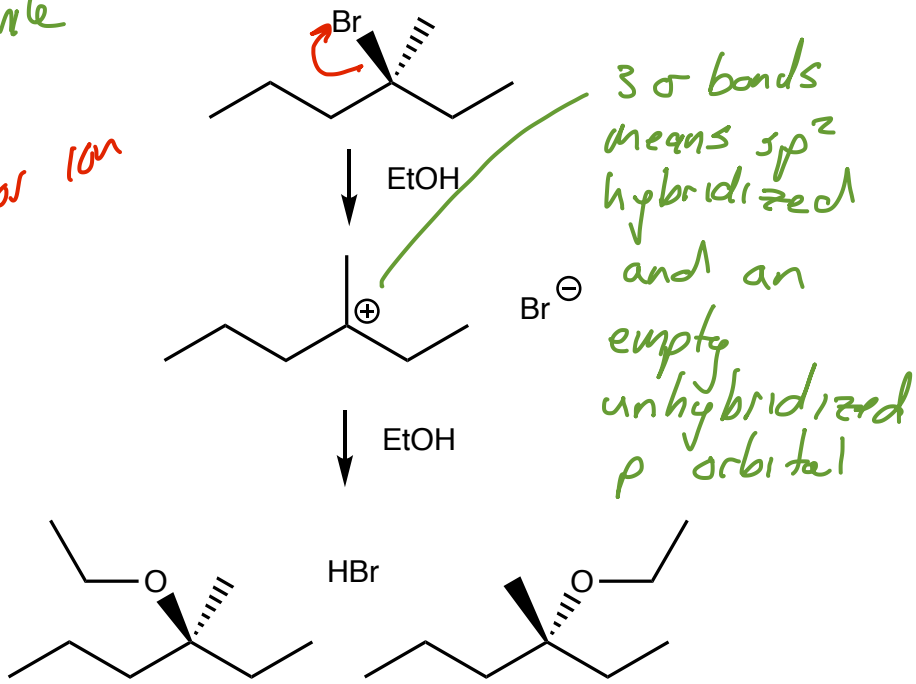
yes the 1° C-Cl bonds are very reactive. The π bond adjacent to the LG is important



except, the Br is blocking the front face...

The I^- would be repelled by the Br atom so the I^- cannot come in from the front.

Nu must come in from behind the LG... inversion of the configuration

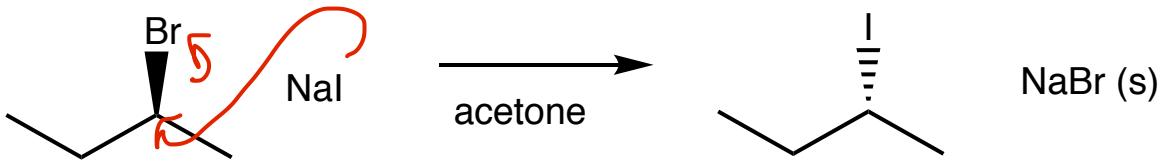


Since the empty p orbital exists in front of the screen and behind the screen, the Nu can attack from either face.

Both configurations are produced

racemization - creating both R & S

α-C is CH_3, 1°, 2° (alkyl compounds)

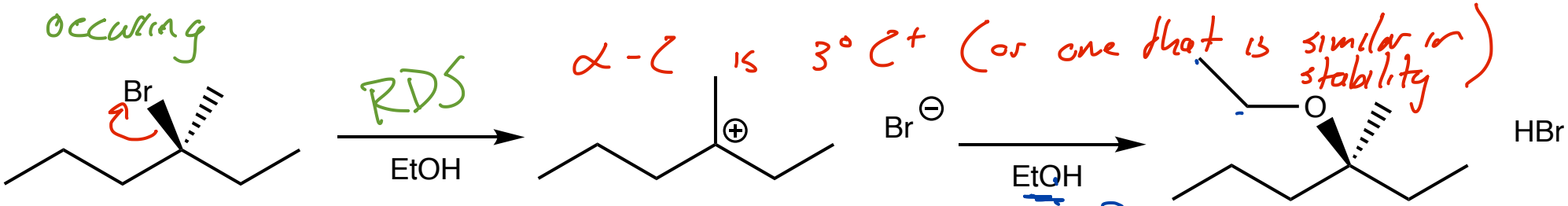


mechanism predicts bimolecular rate law

rate = k [$CH_3CH_2CH_2CH_2Br$][I^-]

collision of two molecules means both appear in the RDS because increasing the concentration of either one increases the chance of a collision, which increases the chance of the rxn occurring

α-C is 3° C^+ (or one that is similar in stability)

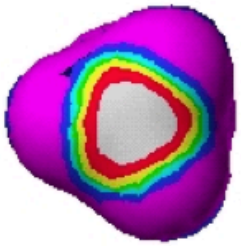


Et = CH_2CH_3

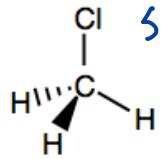
rate = -k [$CH_3CH_2CH_2C(CH_3)BrCH_3$]

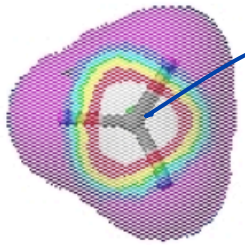
mechanism predicts that the concentration of the nucleophile will have no affect on the rate of the rxn

regardless of Nu concentration the rxn must wait for C^+ to form, so increasing conc of Nu does not change rate

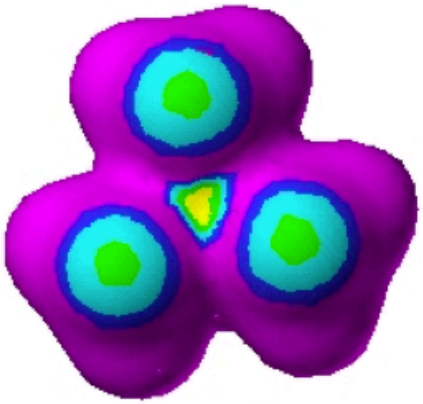


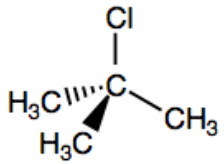
good S_N2 substrate



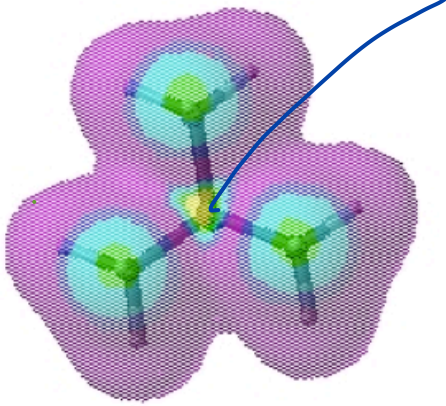


nothing in the way of the nucleophile getting to the backside of the α-C





3° α-C can't do S_N2 chemistry



lots of organic shrubbery in the way sterically hindered access to α-C

access to the backside of the α-C is key

methyl > 1° > 2° ~~3°~~ . less shrubbery adjacent to α-C is better too

less crowded

better

more crowded

worse

LG = Cl^- rxns were sluggish or didn't go

LG = Br^- rxns went much more quickly

$CH_3\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{—}LG + Nu^- \rightleftharpoons CH_3\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{—}Nu + LG^-$

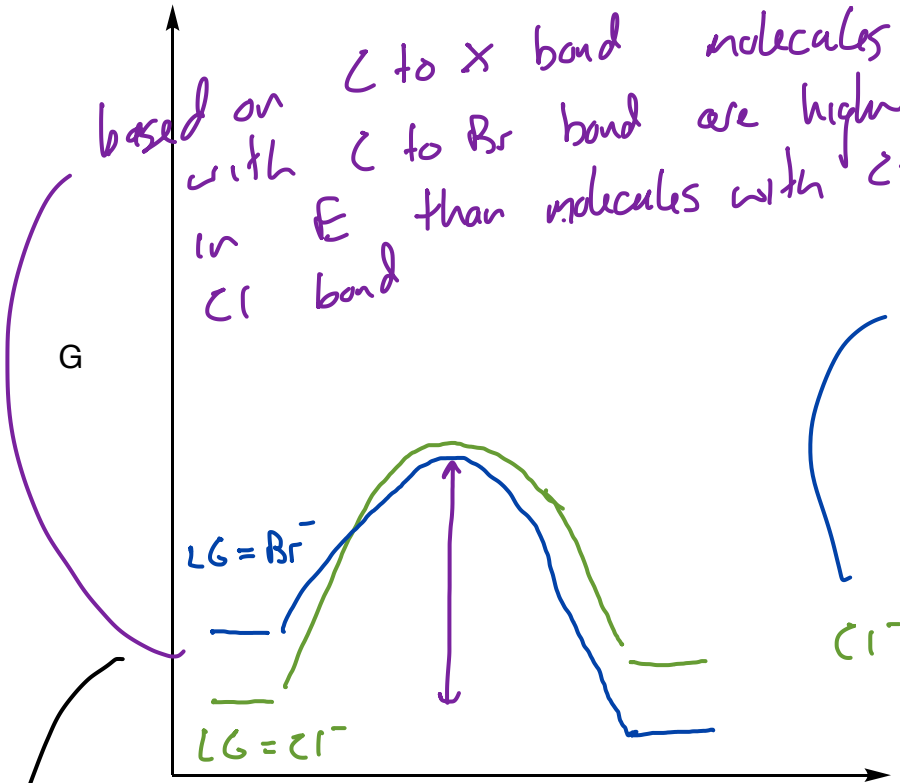
Which is higher in E, Br^- or Cl^-? Cl^-

$K \times 10^9$

$HBr \rightarrow H^+ + Br^-$

$HCl \rightarrow H^+ + Cl^-$

$K \approx 10^6$



based on C to X bond molecules with C to Br bond are higher in E than molecules with C to Cl bond

The relative energies were based on the strength of the C-X bond since everything else is the same

the less basic the LG is the easier it is to form... leave.

Cl^- is higher in E than Br^-

extremely weak bases are good leaving groups

Relative reaction rates from Bruice $I^- : Br^- : Cl^- : F^-$ 30,000 : 10,000 : 200 : 1

not a good LG at all and not usually used

rate = k [$CH_3CH_2CH_2CH_2Br$][Nu^-]

As nucleophile quality increases the rate should increase too, because there will be more successful collisions. So the rate constant would increase.

But what makes something a good nucleophile?

electrophiles love e^-'s because they don't have any, or have few (δ^+)

nucleophiles need to be electron rich ... like bases but the job of the Nu is to react with C not H^+.

$CH_3-Br + I^- \rightleftharpoons CH_3-I + Br^-$

and the equilibrium will favor the formation of the weaker base

Conjugate Acid	pK_a	Nucleophile
HI	–10	I^-
HBr	–9	Br^-
HCl	–7	Cl^-
$CH_3OH_2^+$	–2.5	CH_3OH
H_3O^+	–1.7	HOH
HF	3.2	F^-
H_2S	7.0	HS^-
$HC\equiv N$	9.1	$C\equiv N^-$
NH_4^+	9.4	NH_3
CH_3CH_2SH	10.5	$CH_3CH_2S^-$
CH_3OH	15.5	CH_3O^-
HOH	15.7	HO^-
HCCH	25	HCC^-

weaker nucleophiles better leaving groups

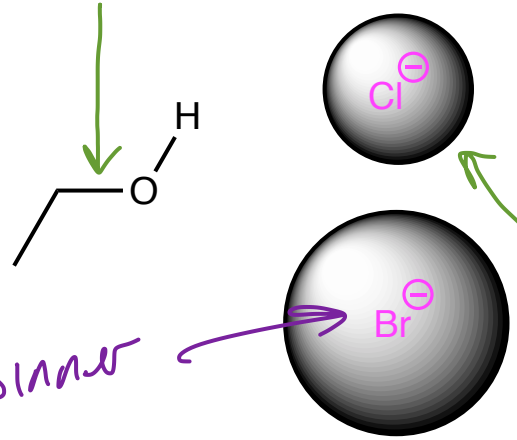
what do I buy if I want $CH_3O^\ominus$? CH_3ONa, CH_3OK

not leaving groups better nucleophiles more e^- rich

In lab we used Le Châtlier's Principle

$CH_3-Br + NaI \xrightarrow{\text{acetone}} CH_3-I + NaBr(s)$

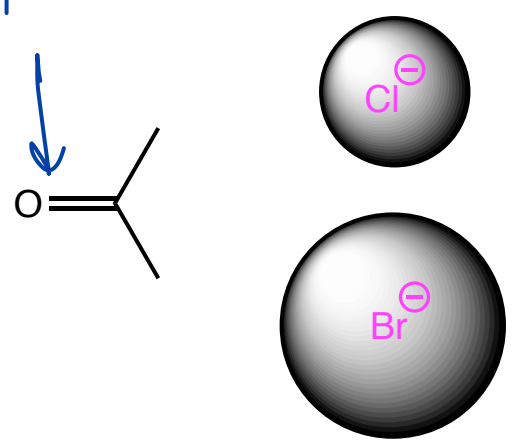
H-bond donor solvents interact more strongly with smaller nucleophiles.



winner

These smaller nucleophiles would be distracted by the solvent and not react as well with C

not an H bond donor no H-bonding distraction so smaller atom with more concentrated e⁻'s is the winner



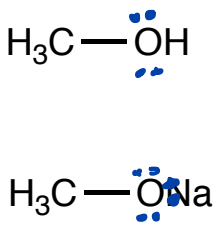
Cl^- is more basic than Br^-.

Cl^- is more e^- rich than Br^-.

Which is the better nucleophile?

It depends on the solvent.

in protic solvents bigger Nu's are better

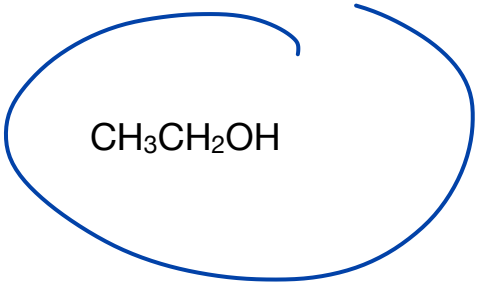


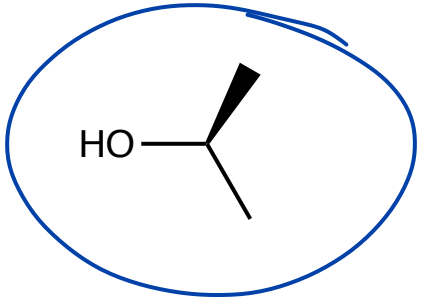
if atoms are the same size, the solvent wont matter, and the more e^- rich one will be the better Nu.

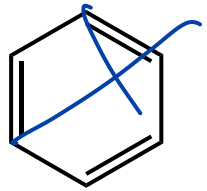
The CH_3ONa is the better nucleophile

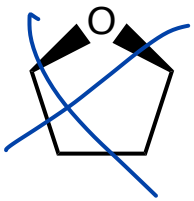
Protic or Aprotic

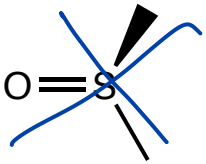
H-bond donor solvent = protic solvent

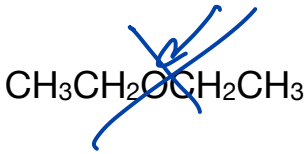


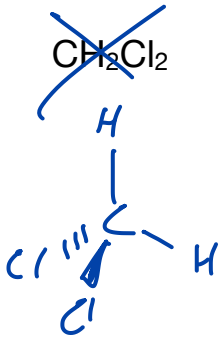


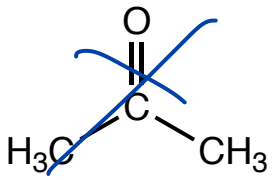












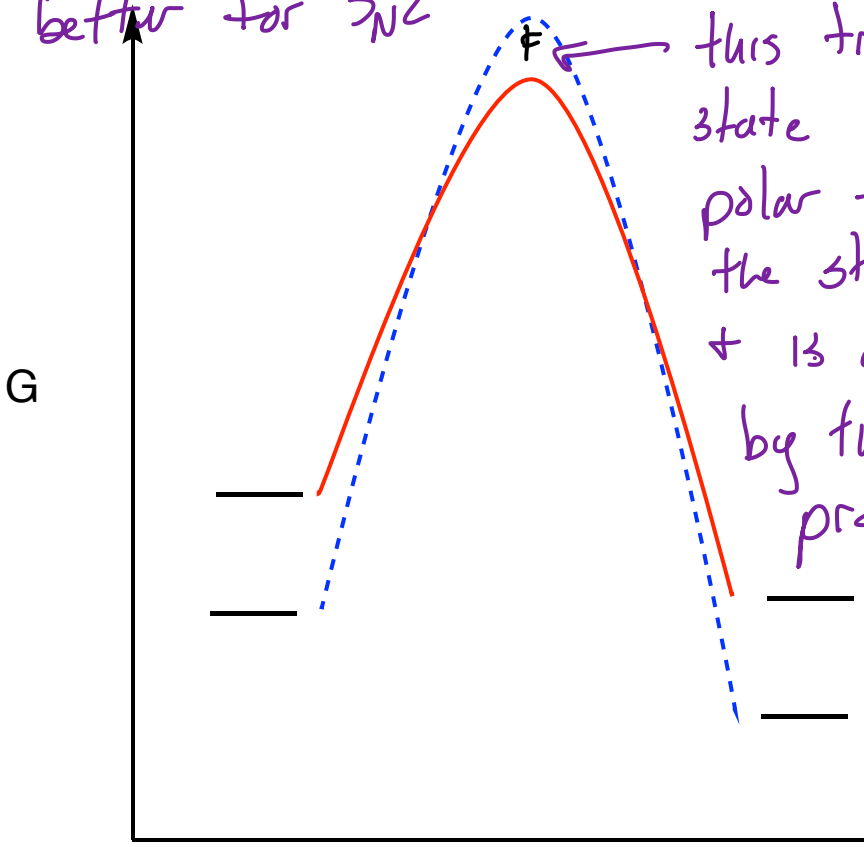
Factors affecting S_N2 (solvent)

polar

protic solvent

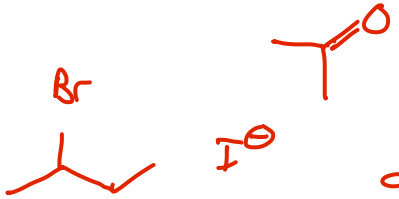
aprotic solvent

aprotic solvents are better for S_N2

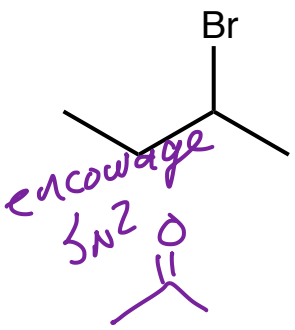


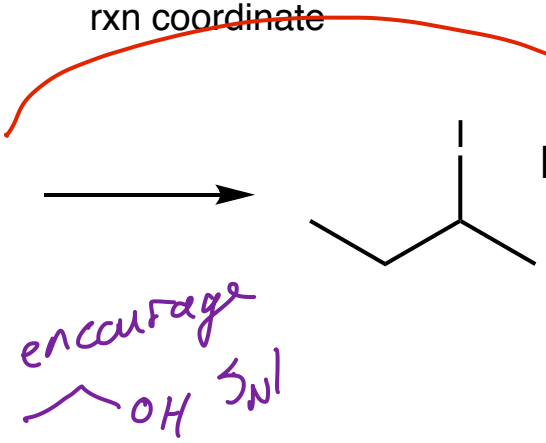
this transition state is less polar than the starting materials + is destabilized by the more polar protic solvent

H bond donor can stabilize polar molecules better

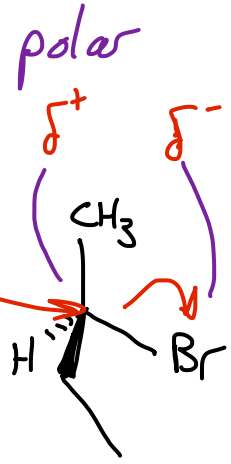


no H-bond donor ability so molecules are slightly higher in E

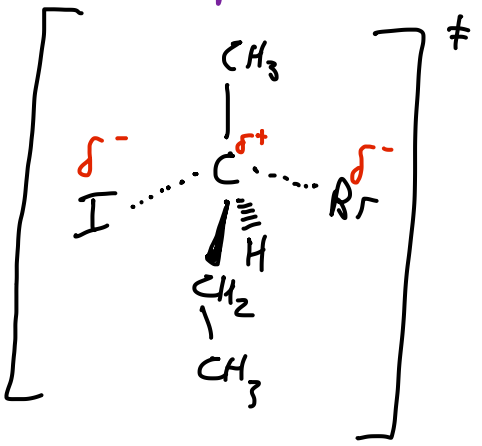




polar

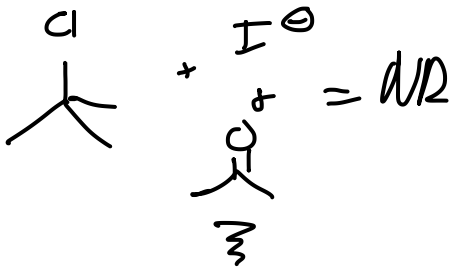


less polar

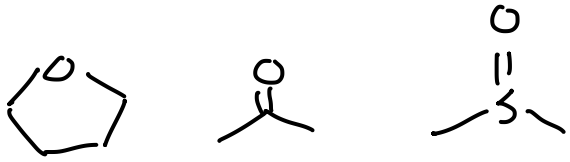


Low degree of substitution on α-C

$Br-CH_3$ > 1° α-C > 2° α-C ~~3° α-C~~



Aprotic Solvents



encourage S_N2 chemistry by discouraging carbocation formation

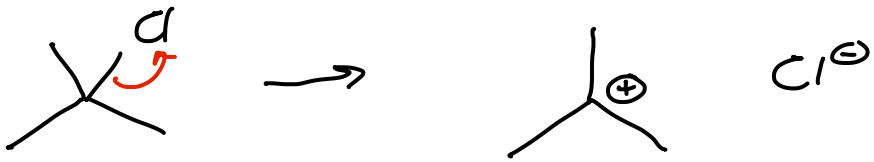
Good Leaving Group

good leaving groups are extremely weak bases

Good Nucleophiles

good nucleophiles encourage S_N2 chemistry by have more successful collisions

e^- rich atoms... more basic molecules make better nucleophiles



carbocation stability is the most important thing

~~CH_3~~ < ~~1° α-C~~ < ~~2° α-C~~ < 3° α-C

too unstable to form under typical laboratory conditions

can form under typical lab conditions when strong electrophiles are added to alkenes, but nucleophilic substitution doesn't use these strong acids to force formation of $C^{\oplus}$

✓ reasonably stable C^+ so 3° α-C's can react via S_N1

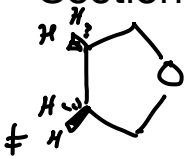
resonance stabilized C^+ intermeadiates are possible, and they will react via S_N1.

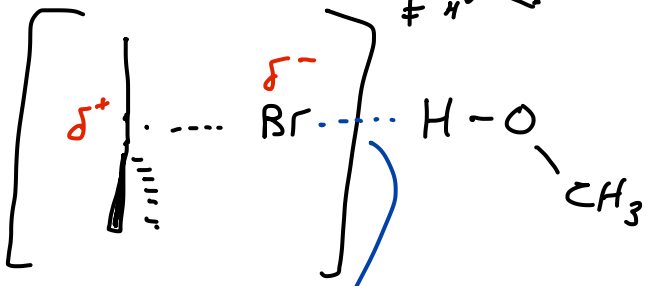
Factors Affecting S_N1 - solvent

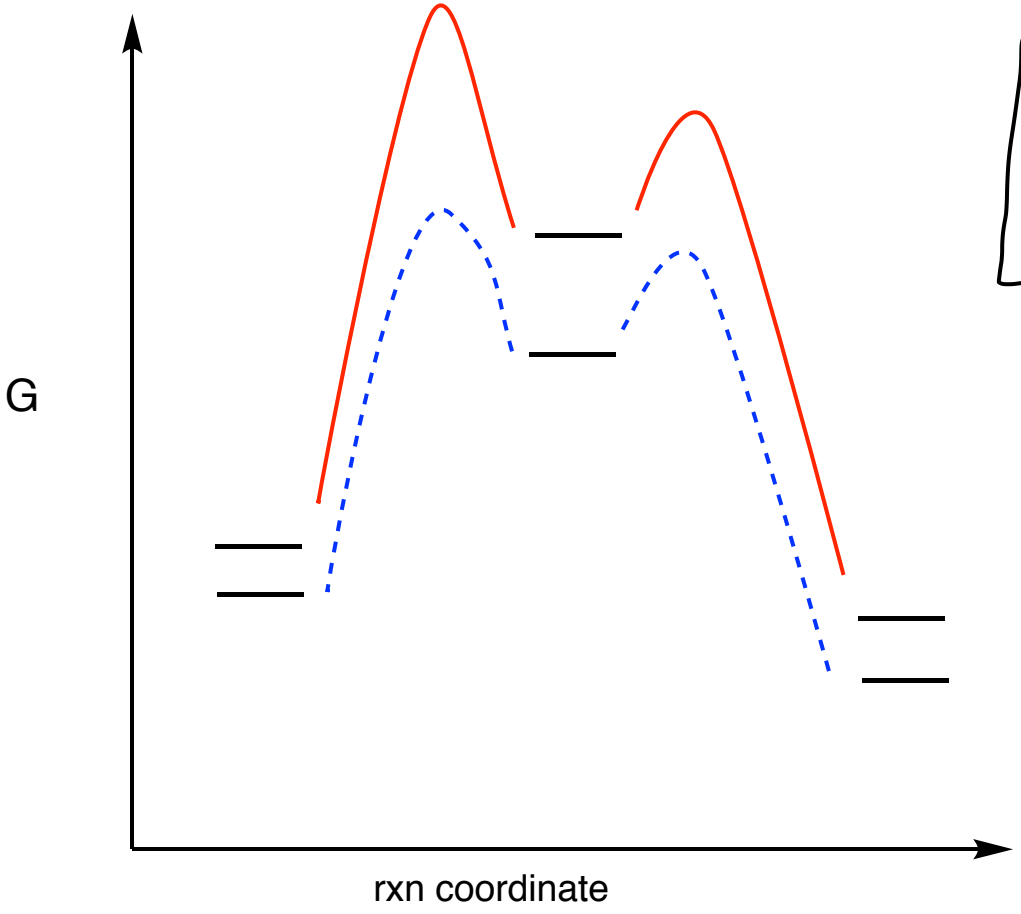
— aprotic

--- protic

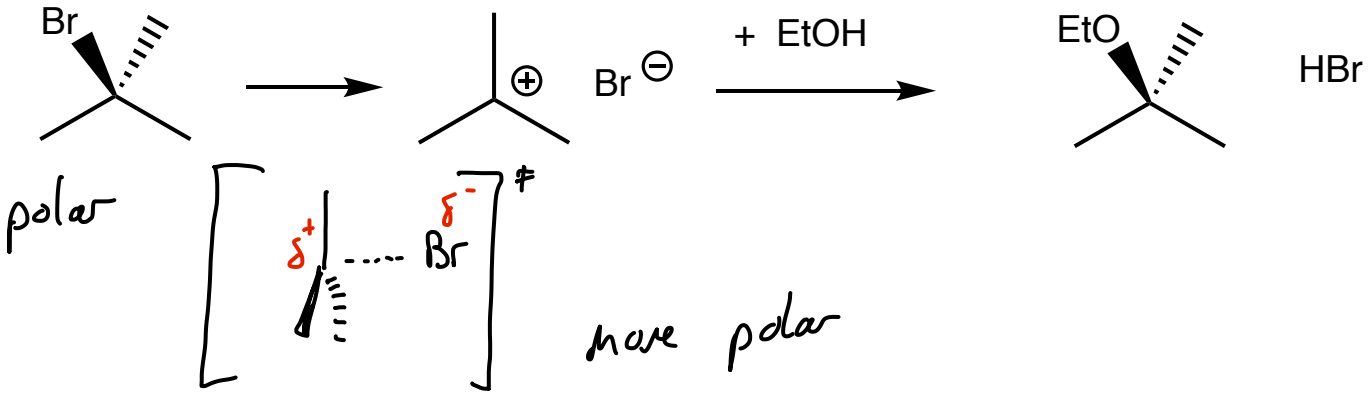
H_2O , CH_3OH

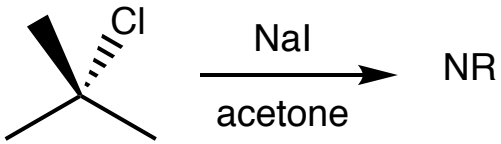




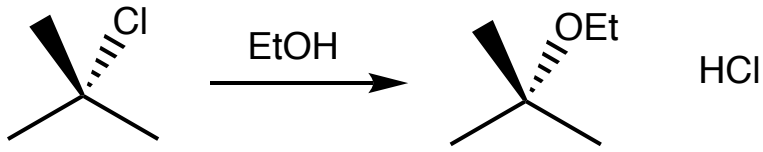


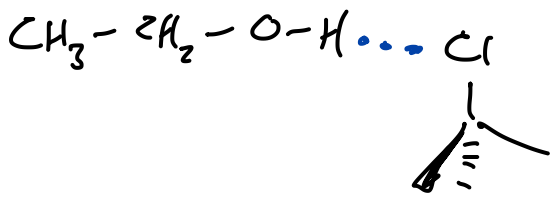
H- bond like interaction between leaving group and solvent encourages LG to leave.





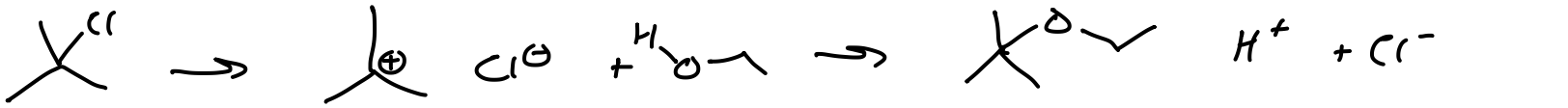
This polar aprotic solvent is not able to stabilized the Cl^- well enough to get it to leave





H-bonding solvent was able to stabilize $Cl^\ominus$ & encourage $C^\oplus$ formation

What role does the nucleophile play in encouraging an S_N1 reaction? There is no role



Good nucleophiles don't help S_N1 reactions go because they are not part of the rate determining step.

S_N1 reactions are often done with weak nucleophiles.

LG is very important... it has to leave! so, yes having a good LG is important.

High degree of substitution on α-C to promote C^+ stability

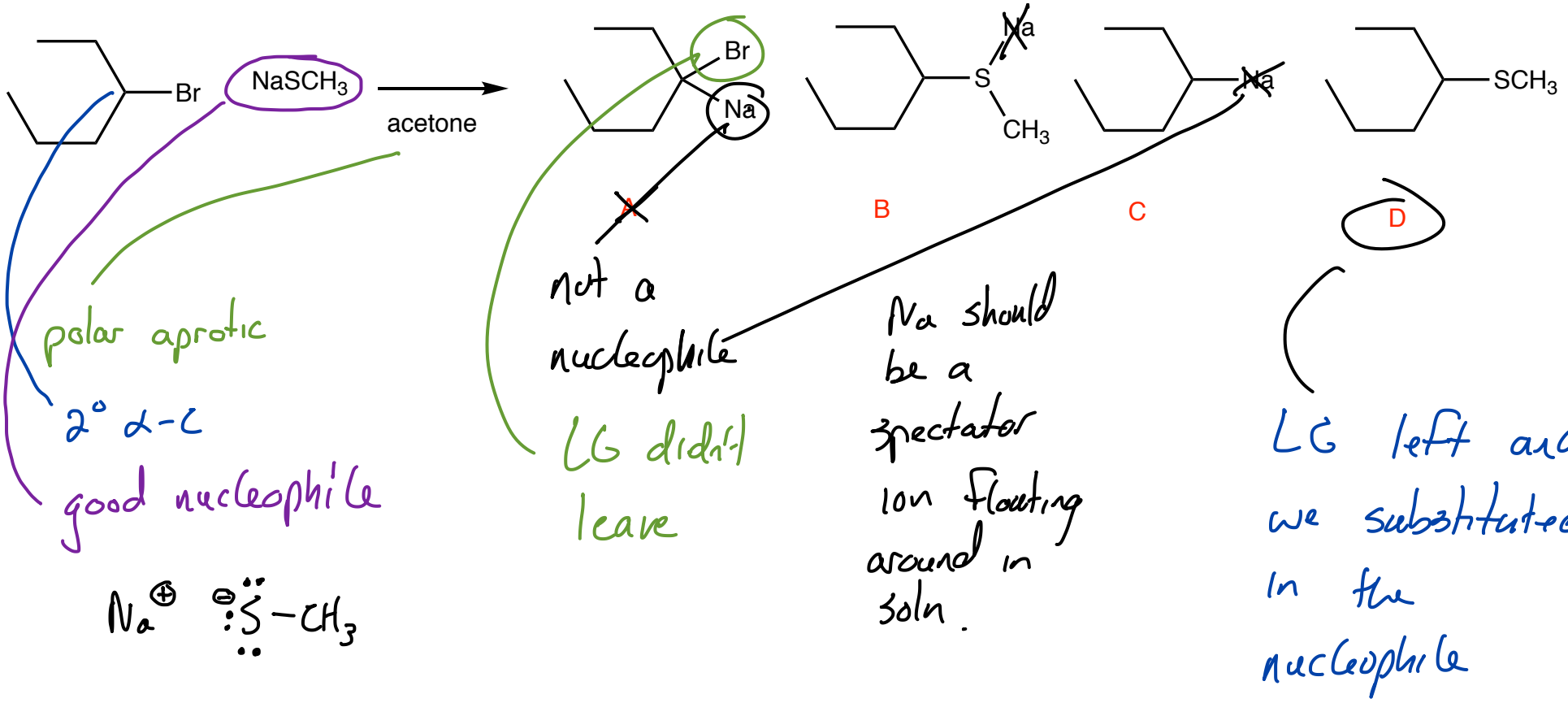
Protic Solvents

Good Leaving Group

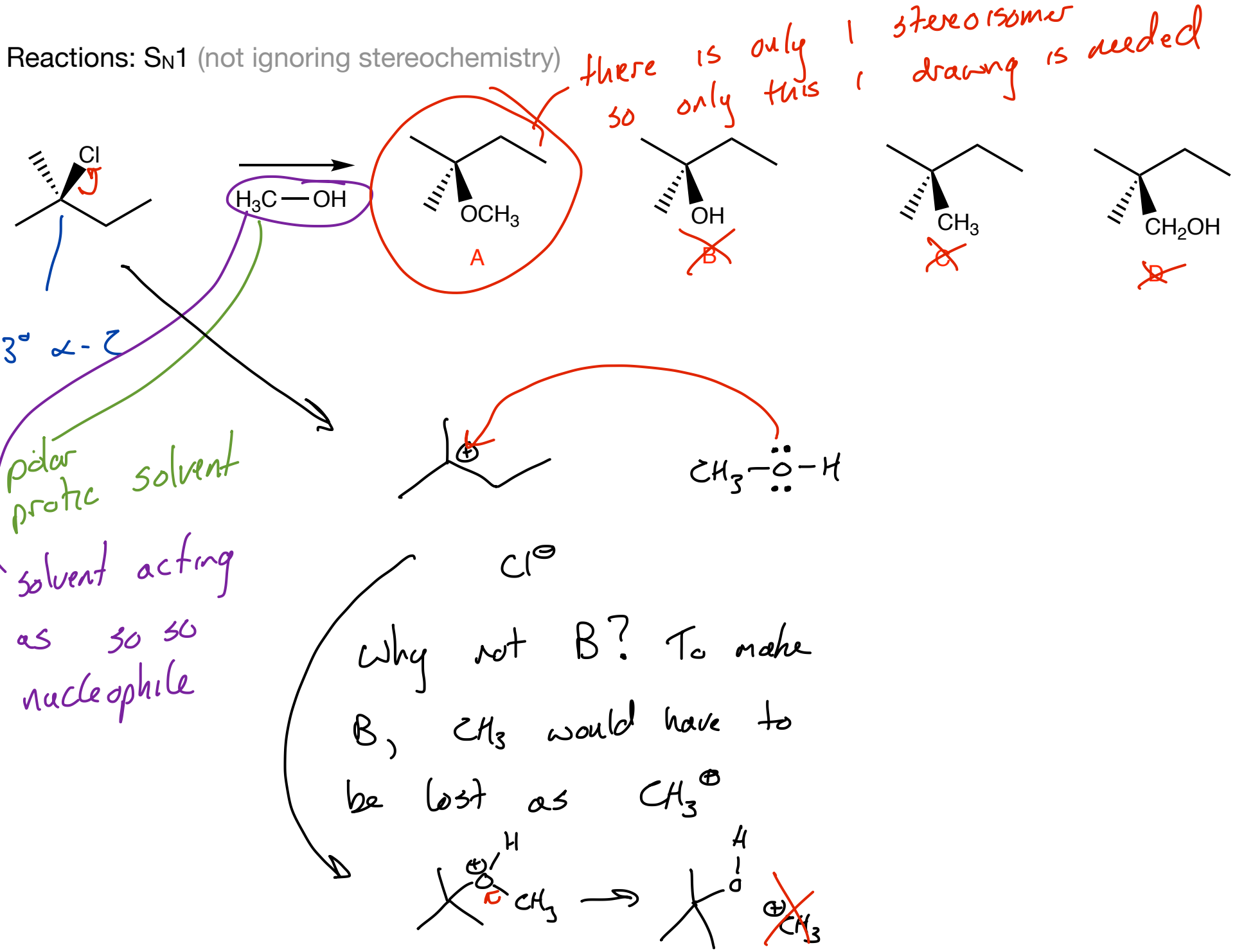
Poor Nucleophiles

Competition	
S_N2	S_N1
Two molecules collide in a 1 step mechanism	Dissociation of **one molecule** controls the rate of a two step reaction
bimolecular rate determining step	unimolecular rate determining step
stereochemistry is inverted	stereochemistry is a mixture of inverted and retained (not inverted)
methyl, 1°, 2°	only 3° alkyl substrates
better the nucleophile the faster the reaction	the nucleophile is not involved in the rate determining step
good nucleophile	So so nucleophile
polar aprotic solvent	polar protic solvent

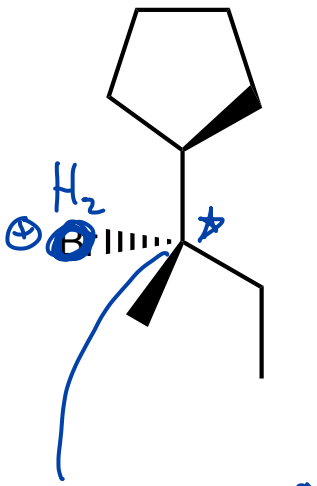
Reactions: S_N2 (ignoring stereochemistry)



Reactions: S_N1 (not ignoring stereochemistry)

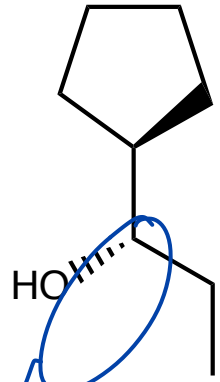


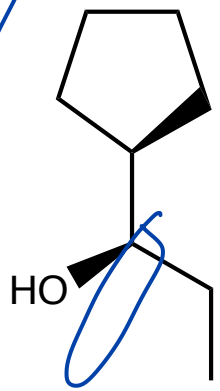
Reactions: S_N1 (not ignoring stereochemistry)



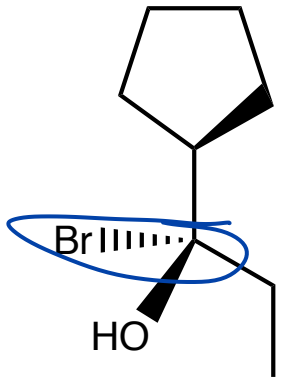
α-C is 3°

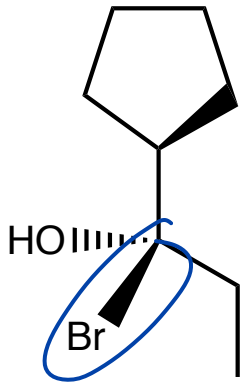
H_2O





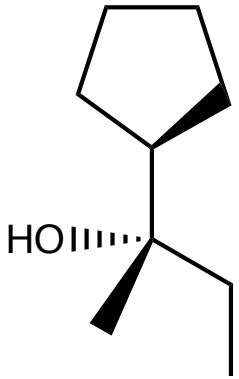
lost a CH_3

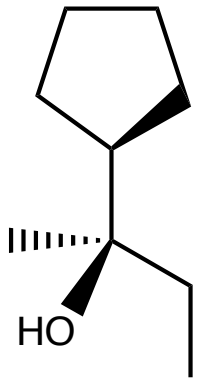




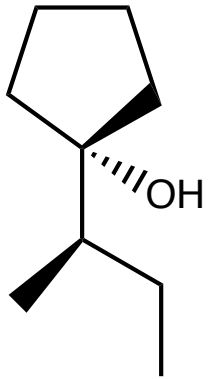
lost a CH_3 leaving group hasn't left!

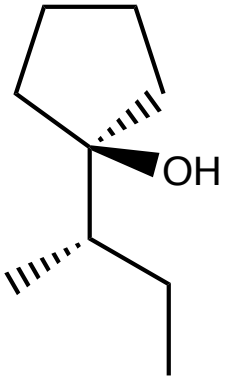
planar C^+ allows





Nu to attack from the front & the back





3° C^+ will not rearrange to another 3° C^+

~~S_N2~~

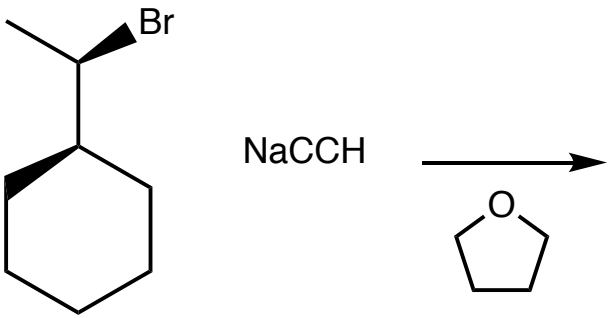
~~A~~

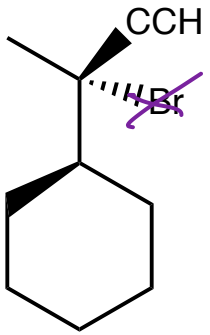
~~B~~

C ✓

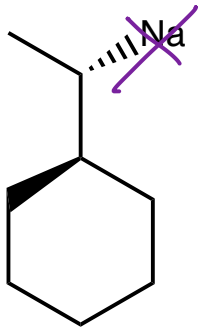
~~D~~

Reactions: S_N2 (not ignoring stereochemistry)

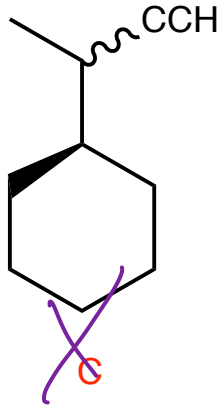




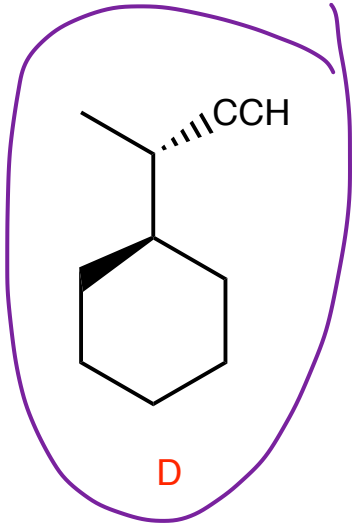
A



B



C



D

Na^+ $^{\ominus}CCH$

$^{\ominus}C\equiv C-H$

(

very good nucleophile

LG still attached

In S_N2 the nucleophile comes in opposite the LG on the α-C