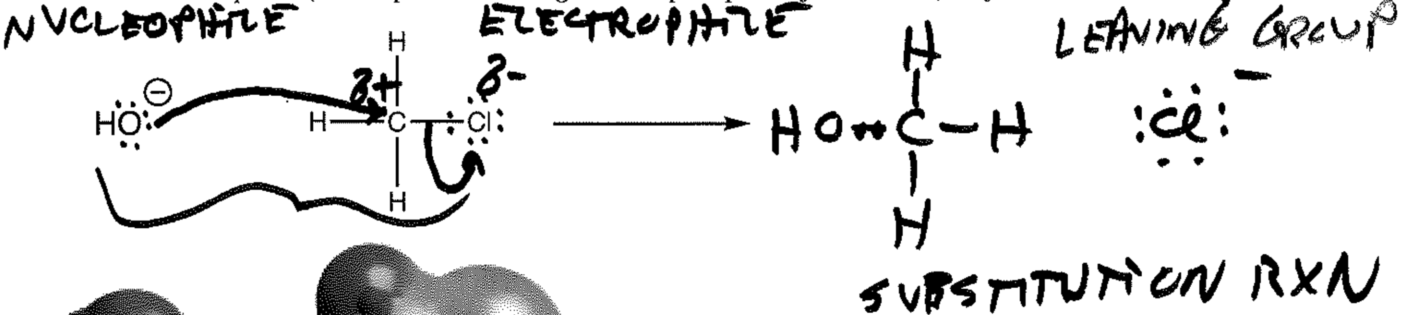
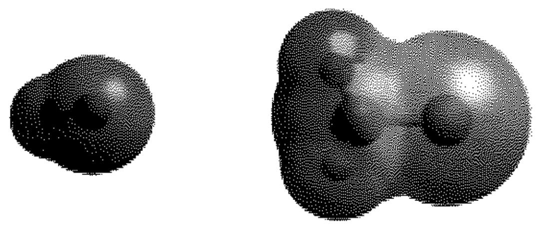
Chapter 7: Introduction to Substitution Reactions

[Sections: 6.11; 7.1-7.9]

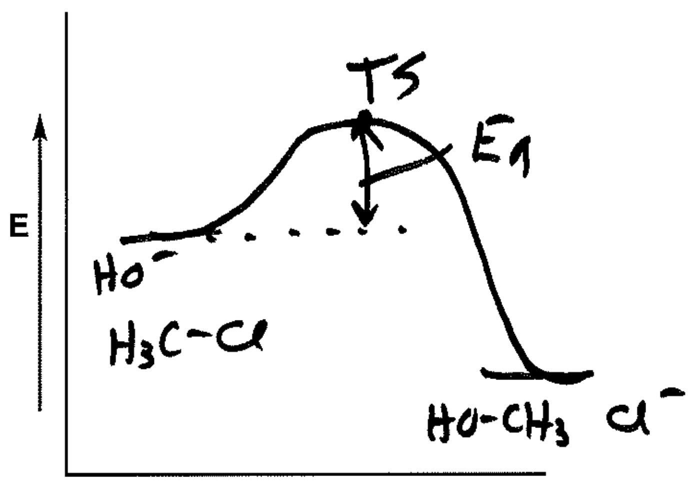
Nucleophilic Substitution Reactions

• *reactions of a nucleophile (a compound able to donate a pair of electrons [usually a lone pair]) with an electrophile (a compound willing to accept a pair of electrons) to form a substituted product*

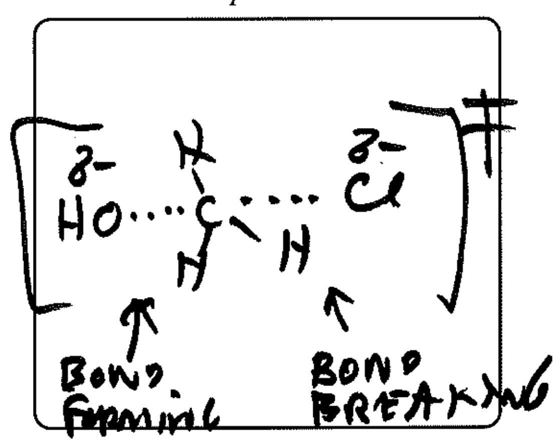




· BONDS BREAKING: C–Cl
· BONDS MAKING: C–OH



TS structure prediction:



• *identify starting materials and products*
• *exothermic or endothermic?* EXO
• *multistep or concerted?* CONCERTED RXN = SINGLE STEP W/ ALL BOND BREAKING & MAKING OCCURRING SIMULTANEOUSLY
• *RDS = unimolecular or bimolecular?*

rate law:

• *dependent upon concentrations of compounds during (and prior to) the RDS*

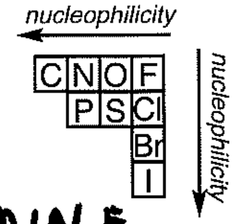
RATE CONSTANT

rate = $k\,[HO^-][CH_3Cl]$

order of rate law: SECOND ORDER = BIMOLECULAR

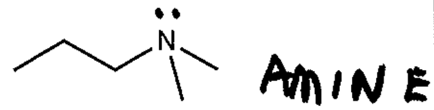
reaction name: SECOND ORDER NUCLEOPHILIC SUBSTITUTION

S_N2

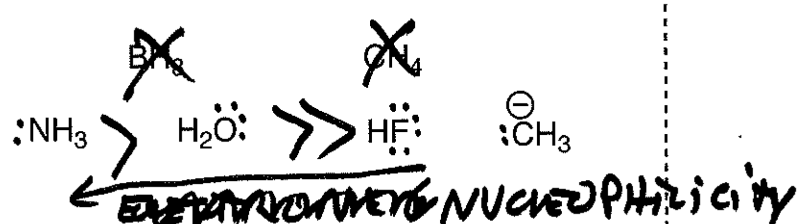


A. The Nucleophile

- *nucleophile = nucleus (positive charge) loving species*
- *any compound able to donate a pair of electrons, typically a lone pair of electrons*
- *nucleophiles = electron rich species*
- *while the molecule is considered to be the "nucleophile", the property is due to particular atoms within the molecule*

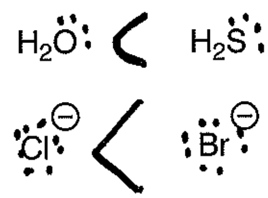


i. atoms in the same row



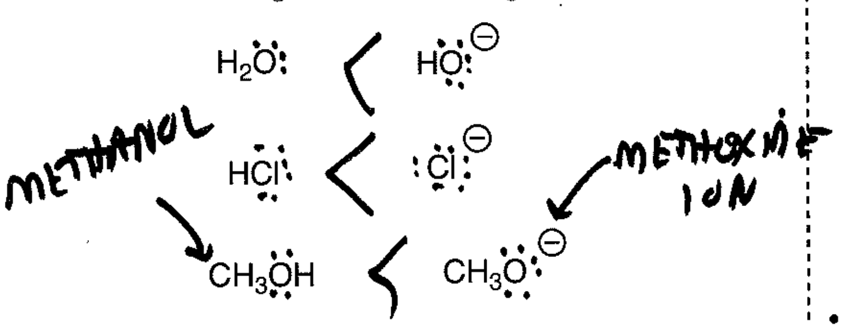
- *lower electronegativity = greater nucleophilicity since atoms with lower electronegativity more readily donate electron density*

ii. atoms in the same column



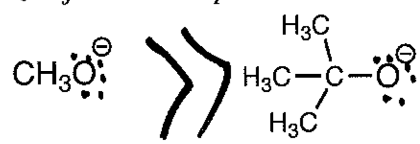
- *lower electronegativity*
- *larger atoms are more "polarizable" = able to donate their electron density more readily*

iv. charged versus uncharged



- *generally, charged atoms are more nucleophilic than uncharged atoms due to increased electron density*

v. size of the nucleophile

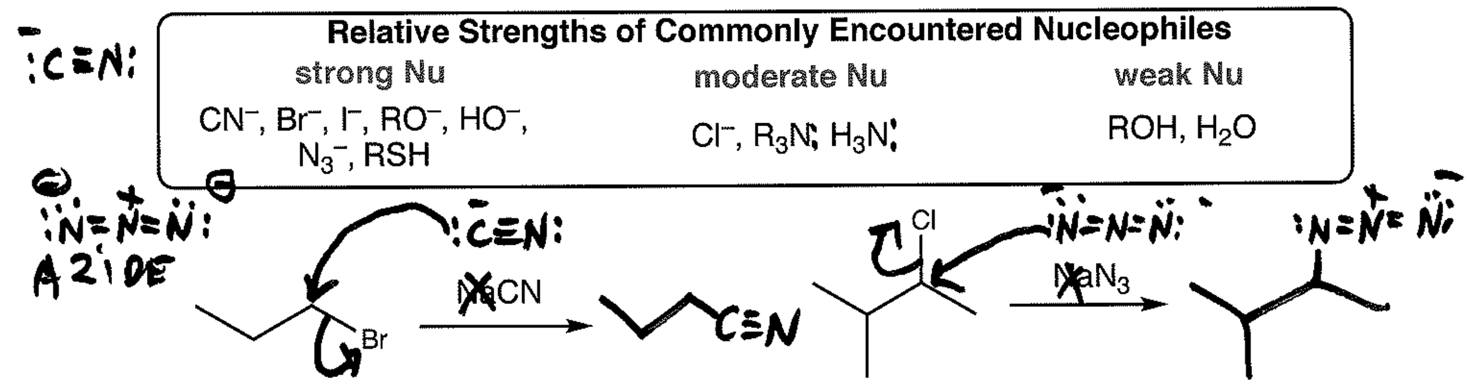


methoxide   *tert*-butoxide

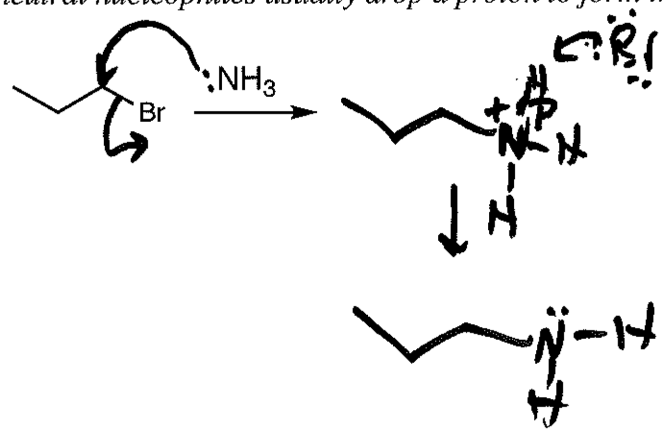
- *generally, small and linear nucleophiles are strongest since they are able to more easily attack the electrophilic atom to which they are forming a bond*

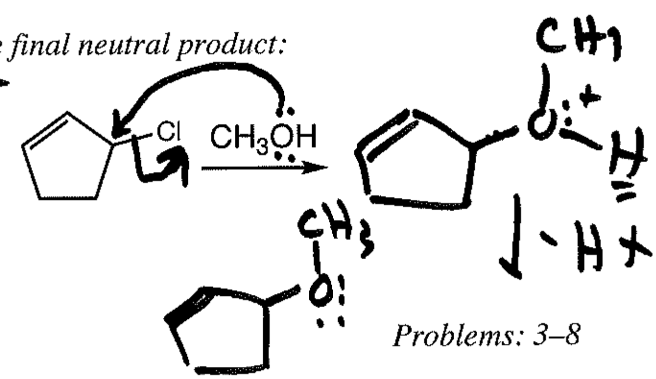
Relative Strengths of Commonly Encountered Nucleophiles

strong Nu	moderate Nu	weak Nu
CN^-, Br^-, I^-, RO^-, HO^-, N_3^-, RSH	Cl^-, R_3N:, H_3N:	ROH, H_2O



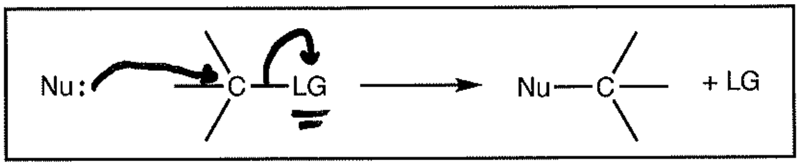
- *neutral nucleophiles usually drop a proton to form the final neutral product:*





Problems: 3–8

The S_N2 Reaction: bimolecular nucleophilic substitution

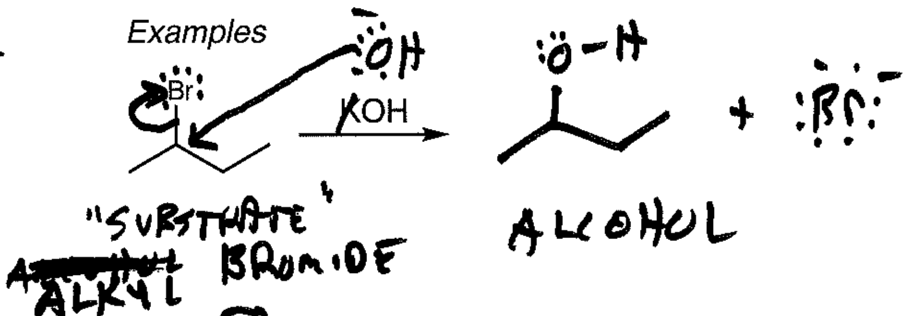


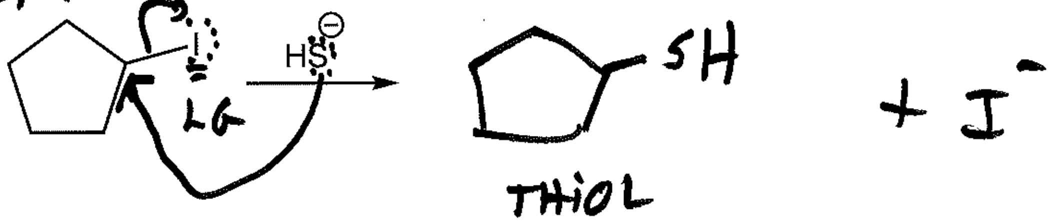
Plan of Attack *for an S_N2 problem:*

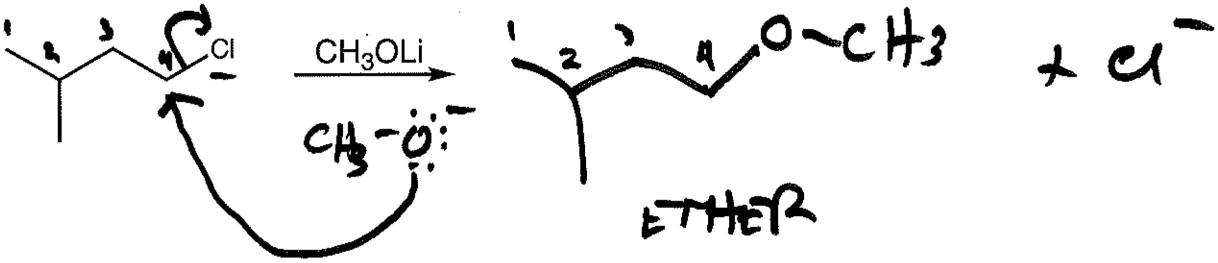
1. Identify LG
2. Identify Nu:
3. Nu: attacks carbon bearing LG

K+
Na+
Li+

Examples







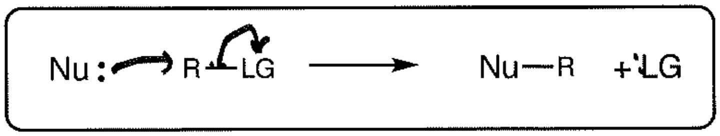
- *If we know a reaction is an S_N2 reaction, both the chemical process and the chemical steps are clearly defined:*
- *For an S_N2 reaction a nucleophile MUST attack the carbon of a compound bearing a leaving group, with formation of a new bond from the carbon to the nucleophile, bond rupture of the bond between the carbon and the leaving group, and all bond making and bond breaking occur simultaneously (i.e., in a concerted fashion)*
- *Not all S_N2 reactions occur at the same rate, nor does a reaction take place via an SN2 mechanism even though all of the "components" of a reaction are present*
- *We need to consider the impact of all three contributing components: What makes a good nucleophile versus a poor nucleophile? What makes a good leaving group versus a poor leaving group? Does it make a difference what sort of carbon the leaving group is attached to?*

We could potentially speed up the rate of an S_N2 reaction by altering each component:

nucleophile *leaving group* *type of carbon*

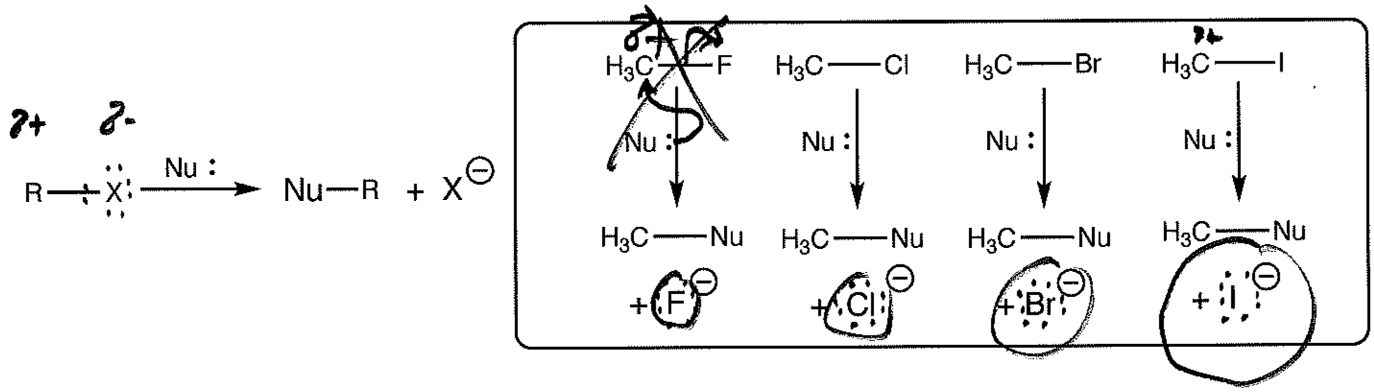
Problems: 1,2

B. The Leaving Group

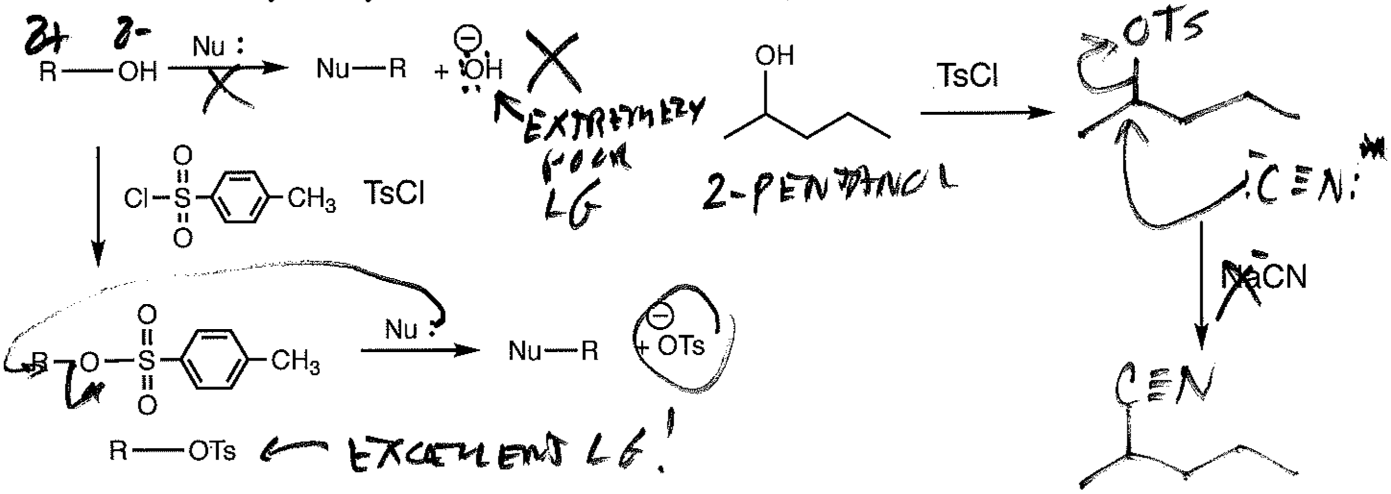


R—X a halide leaving group

R—OTs a tosylate leaving group

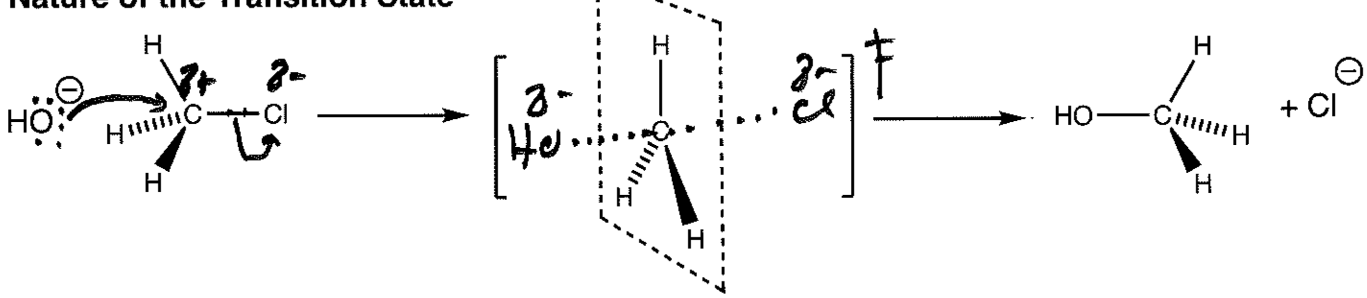


• relative reactivity of alkyl halides is: RI > RBr > RCl (RF = unreactive)

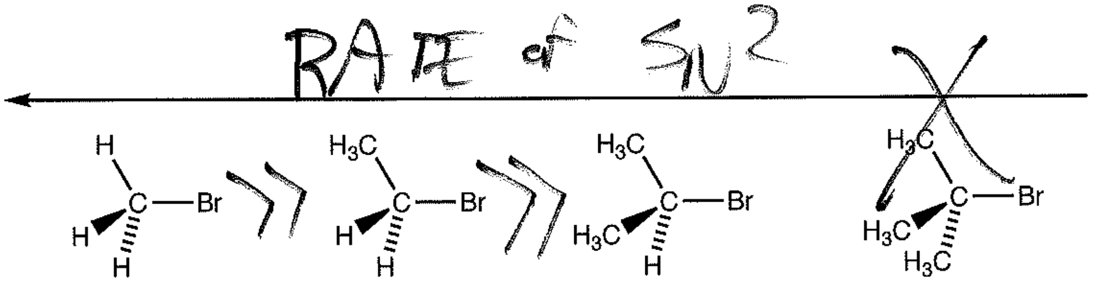


• *tosylates are EXCELLENT leaving groups (similar to I⁻)*
• *the S_N2 reaction is generally performed on alkyl halides and alkyl sulfonates*

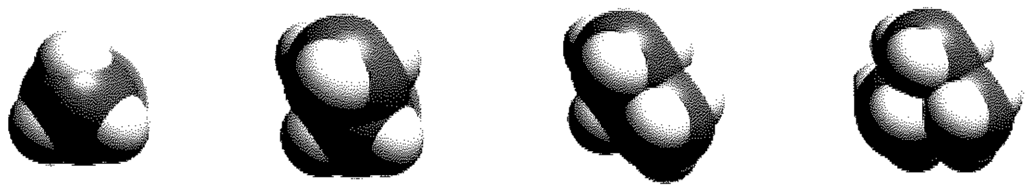
Nature of the Transition State



• *reaction occurs via "backside attack"*
• *this mode of attack avoids steric interactions of the nucleophile with the large halogen atom*
• *it also avoids an electron-rich nucleophile interacting with a negatively charged leaving group*
• *the result is an "inversion of configuration" of the carbon bearing the leaving group (X or OTs)*

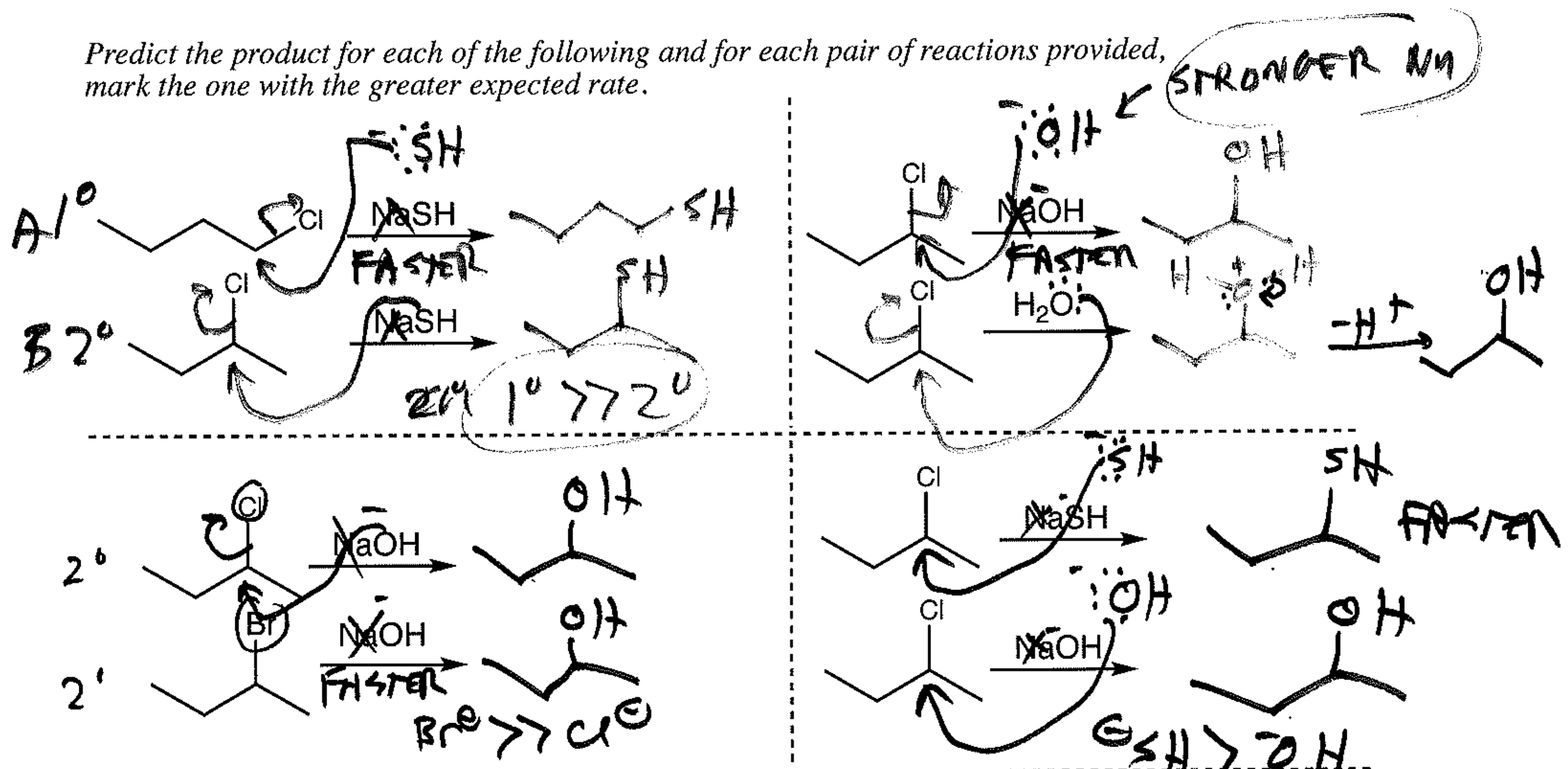


methyl substrate *1° substrate* *2° substrate* *3° substrate*

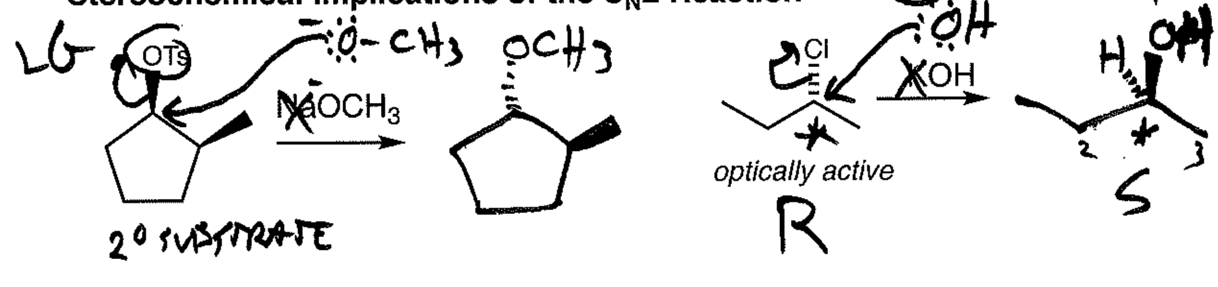


- *increasing steric bulk at the electrophilic carbon makes it more difficult for the nucleophile to approach*
- *relative reactivity of substrates: methyl > 1° >> 2°* ***(3° substrates are unreactive towards S_N2)***

Predict the product for each of the following and for each pair of reactions provided, mark the one with the greater expected rate.



Stereochemical Implications of the S_N2 Reaction



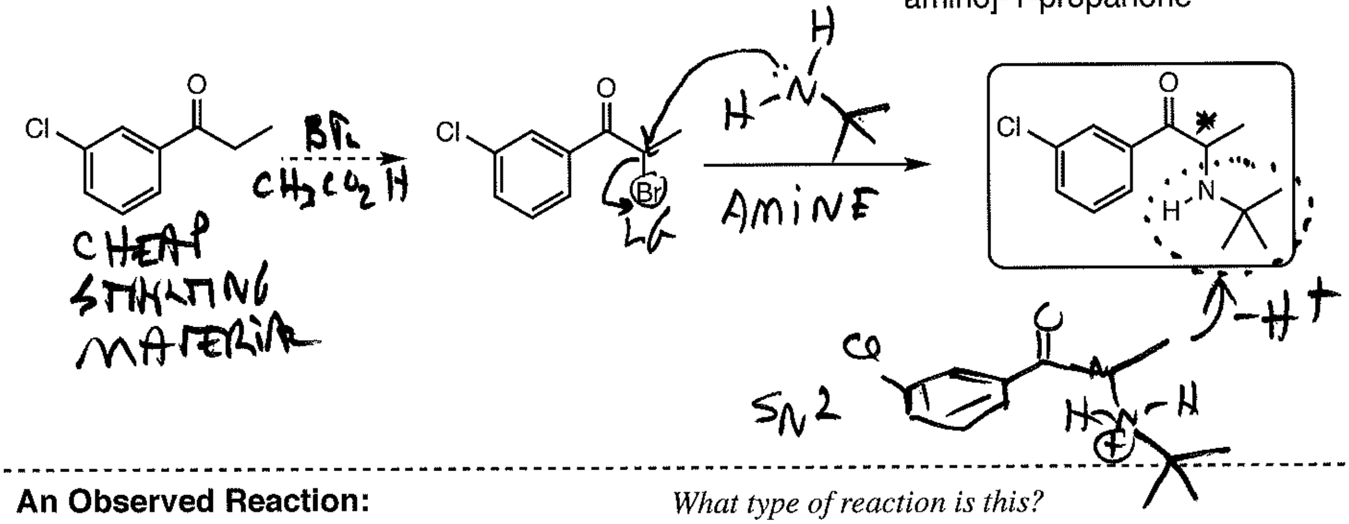
- *because the S_N2 reaction occurs via a concerted "backside" attack mechanism where bond making and bond breaking occur simultaneously, the product is the result of inverted configuration*
- *this is referred to as a "stereospecific" reaction*
- *optically active starting materials lead to optically active products*

Problems: 9–15

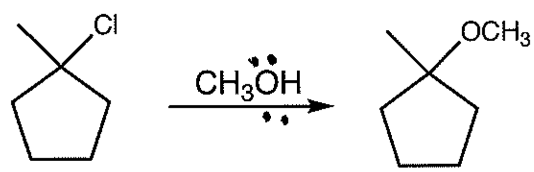
- *the S_N2 reaction is one of the most powerful methods for the synthesis of useful organic compounds*
- *the concerted nature of bond formation, coupled with the backside attack of the nucleophile, means it is possible to synthesize a single stereoisomer of a compound from a reaction in which more than one could potentially result: a stereospecific reaction*

Wellbutrin™: an antidepressant

(±)-1-(3-chlorophenyl)-2-[(1,1-dimethylethyl)-amino]-1-propanone



An Observed Reaction:



What type of reaction is this?

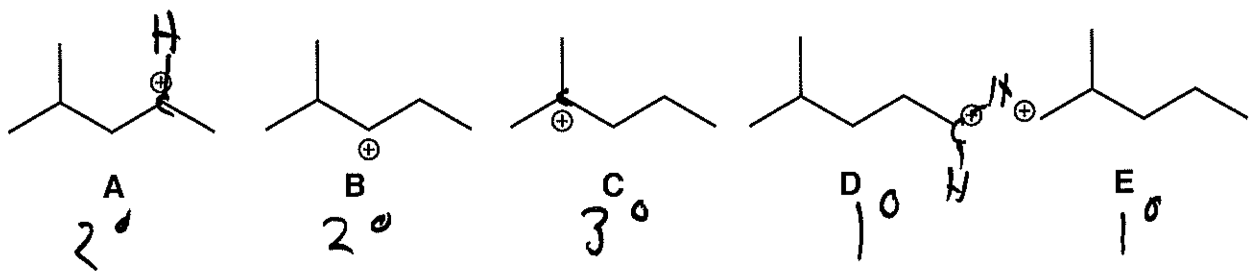
SUBSTITUTION

Why is this reaction unusual?

3° SUBSTRATE
POOR Nu
OK LG

) NOT AN S_N2 REACTION

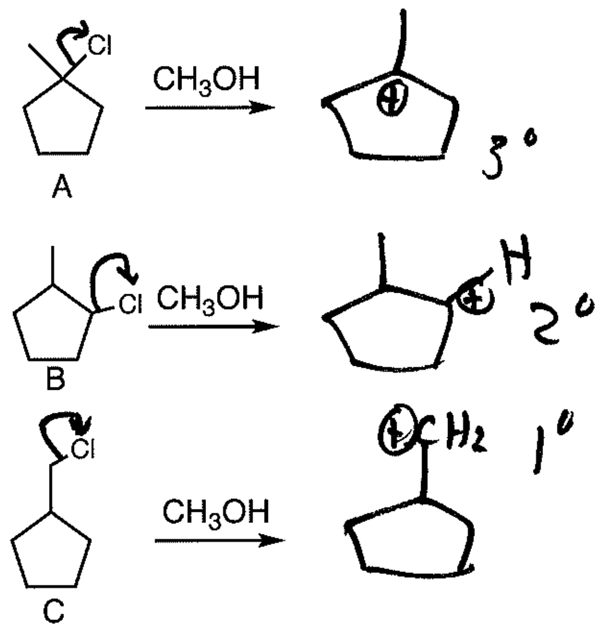
Rank the following carbocations in order of their expected stabilities (most >>> least):



C >> A, B >> D, E

STABILITY

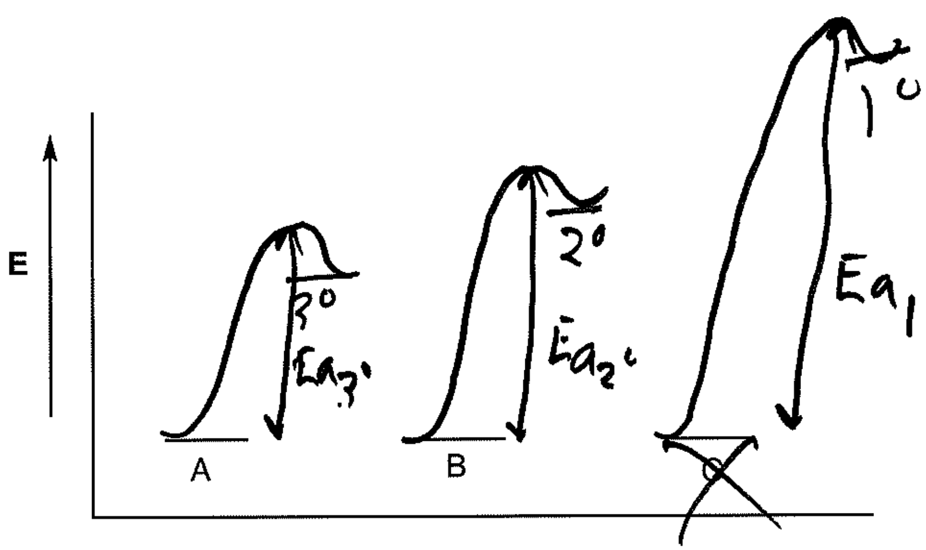
• *stability of carbocations correlates with their relative rate of formation i.e, 3° > 2° >>> 1°*



S_N1

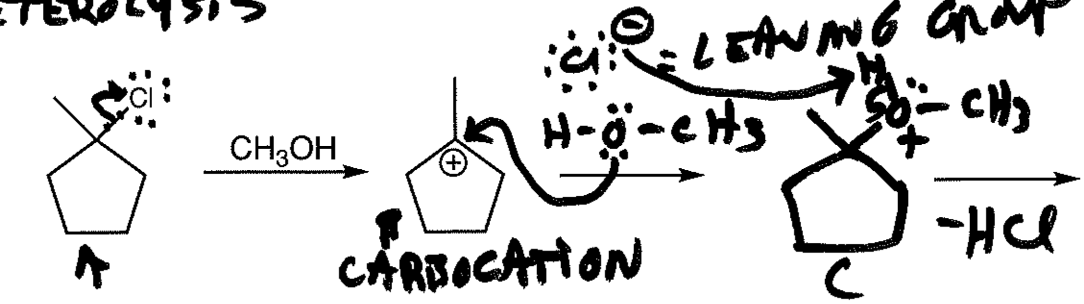
3° >> 2° 1°, CH_3 X

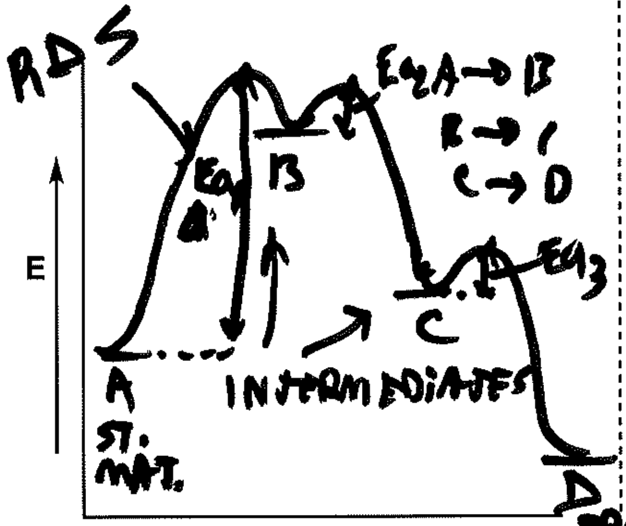
RATE



• *the S_N1 substitution mechanism is favored by 3° and 2° substrates and does NOT occur with 1° or methyl substrates (these must take place via the S_N2 mechanism)*

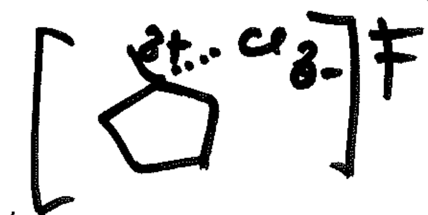
HETEROLYSIS





- identify starting materials and products
- exothermic or endothermic?
- multistep or concerted?
- RDS = unimolecular or bimolecular?

TS structure prediction: RDS C-Cl is BREAKING



rate law:

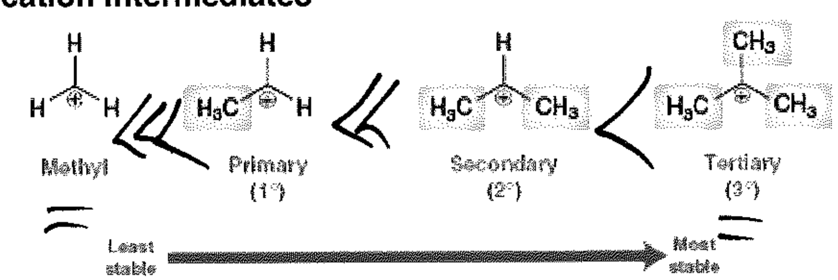
- *dependent upon concentrations of compounds during (and prior to) the RDS*

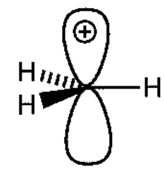
rate = k [R-LG]

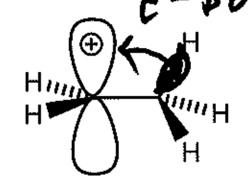
k = RATE CONSTANT

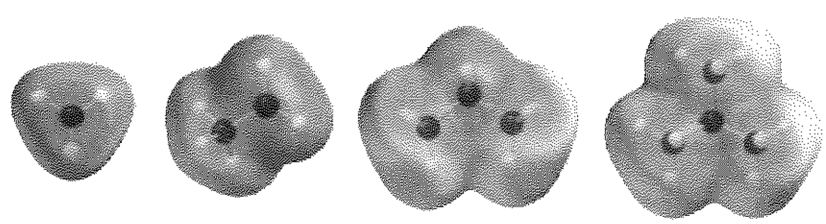
reaction name: S_N1

Carbocation Intermediates





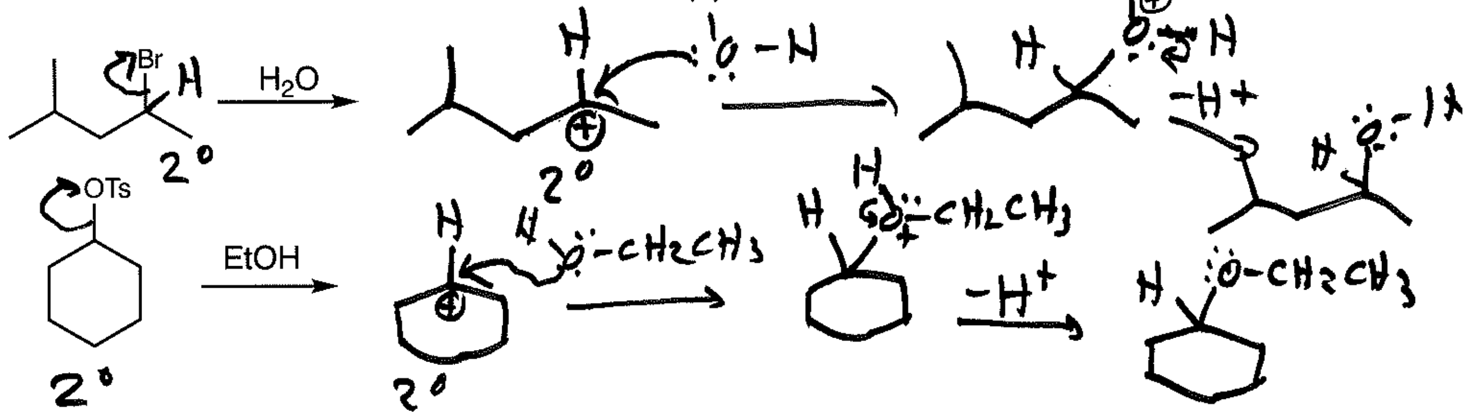




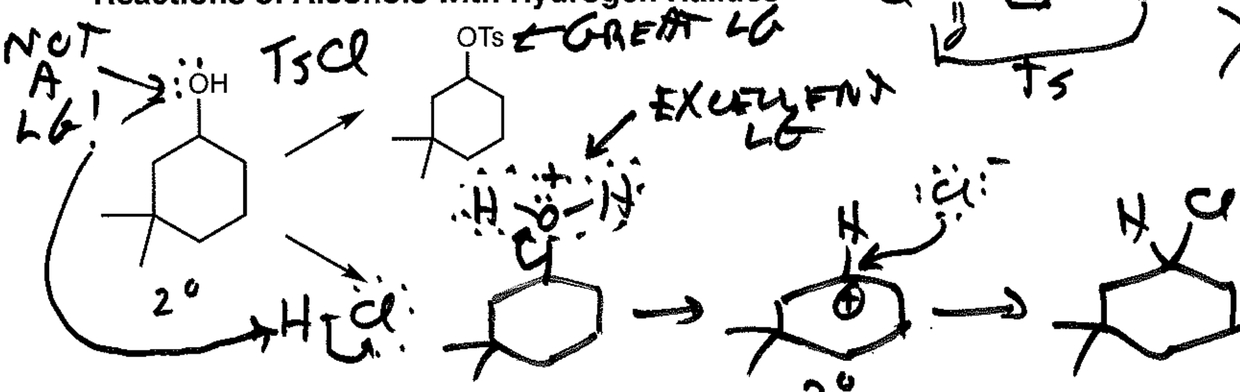
- *carbocations are species with a positive charge on a carbon atom*
- *the positive charge is localized in the empty, unhybridized P-orbital*
- *carbocations are highly electrophilic*
- *the positive charge can be stabilized by interaction with neighboring bonds (hyperconjugation); this helps delocalize the positive charge*
- *thus, the general order of stability of carbocations is:*
  3° > 2° >>> 1° >>> methyl
- ***for our purposes, the methyl and 1° carbocations are too unstable and will never be formed under ordinary S_N1 circumstances***

- *the nature of the nucleophile is fairly irrelevant since it is not involved in the reaction until after the RDS has taken place. Remember rate = k[RX]*
- *the S_N1 reaction may be performed on alkyl halides and alkyl sulfonates*
- *relative reactivity of alkyl halides is:* RI > RBr > RCl (RF = unreactive)

Predict the product of the following S_N1 reactions:

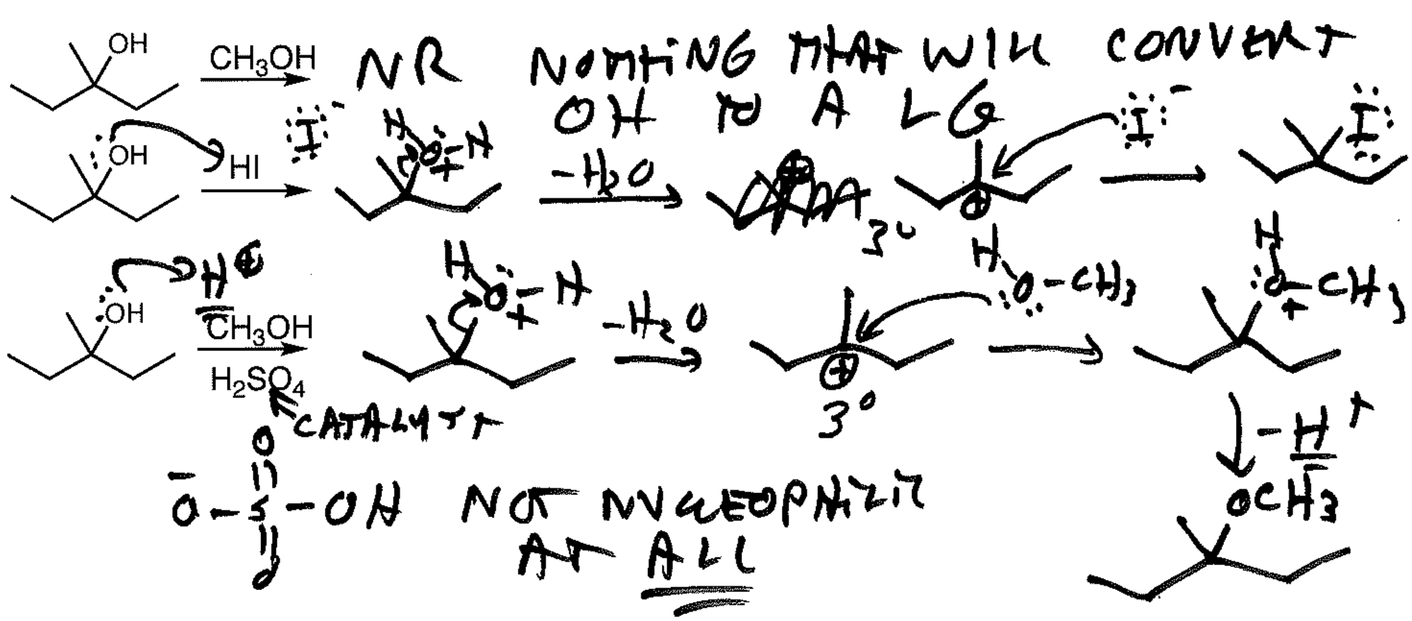


Reactions of Alcohols with Hydrogen Halides



	pK_a
HF	2
HCl	-3
HBr	-4
HI	-5

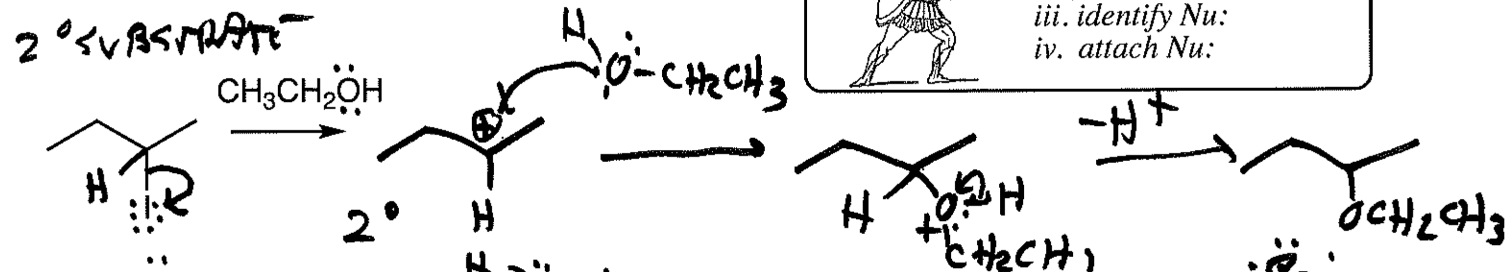
- *alcohols react with HX via an S_N1 reaction to afford alkyl halides*
- *the strong HX acids protonate the OH group of the alcohol to convert it to a good leaving group (H_2O)*
- *remember that alkyl halides (RX) and alkyl sulfonates (ROTs) do NOT require a strong acid to be present since they already contain a great leaving group*

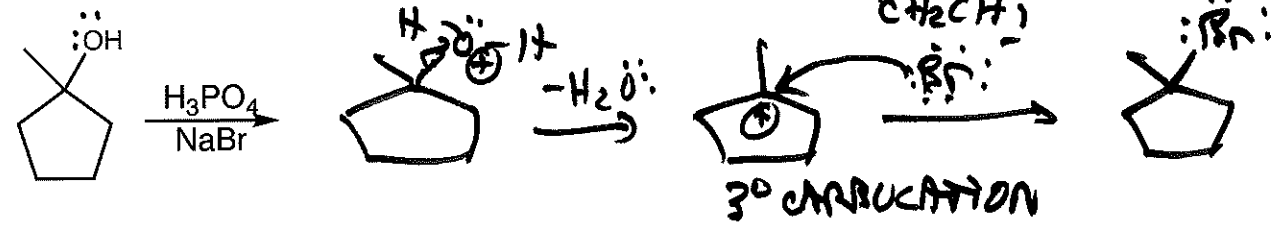


Predict the product of the following S_N1 reactions:

Plan of Attack *for an S_N1 problem:*

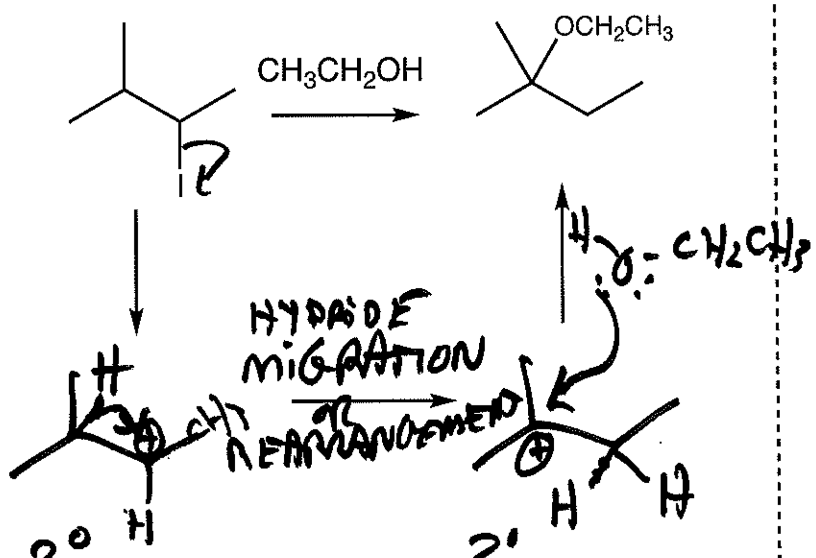
i. identify leaving group
ii. form carbocation
iii. identify Nu:
iv. attach Nu:

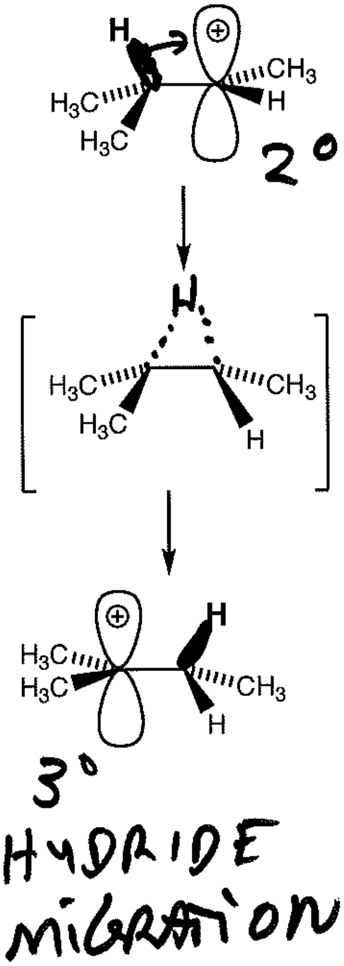


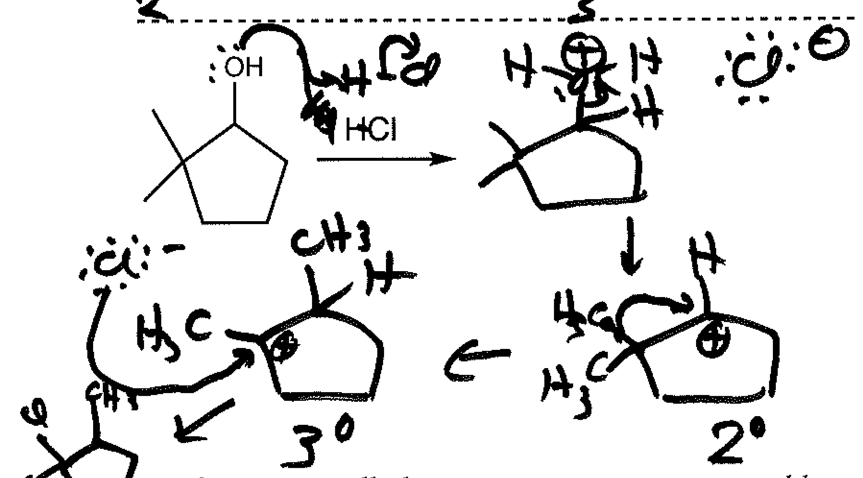


Carbocation Rearrangements

Observed:







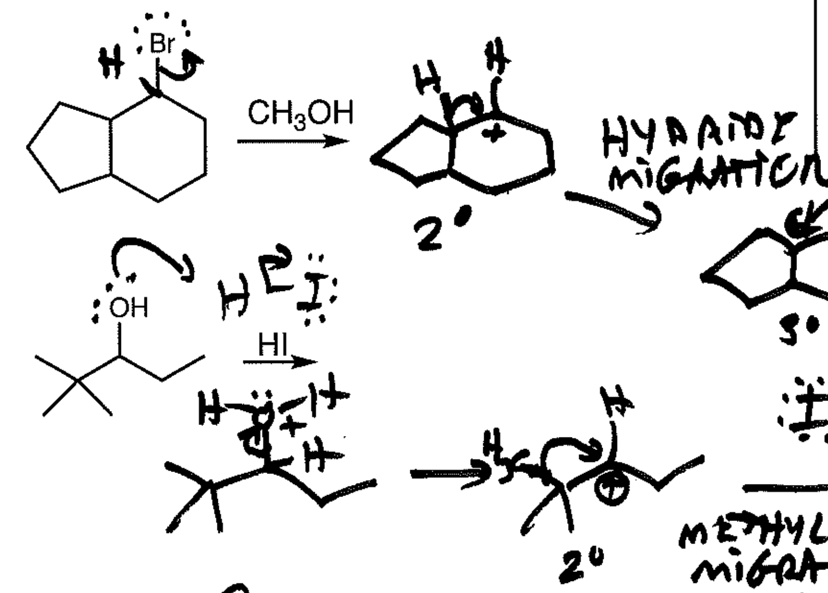
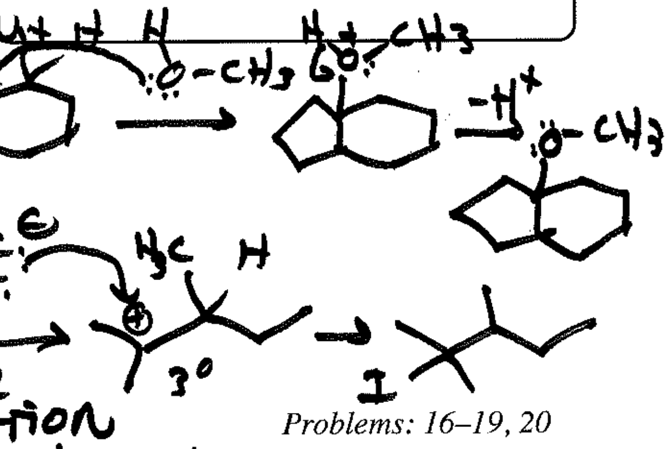
- carbocations will always rearrange to a more stable carbocation when possible
- the rearrangement is called a "hydride migration" if it is a hydrogen atom (and its electrons) that moves
- the rearrangement is called an "alkyl migration" if it is a methyl or other alkyl group that moves
- carbocations will not rearrange to carbocations of the same or lesser stability (i.e., a 2° will not rearrange to another 2° or to a 1°)

Predict the product of the following S_N1 reactions:

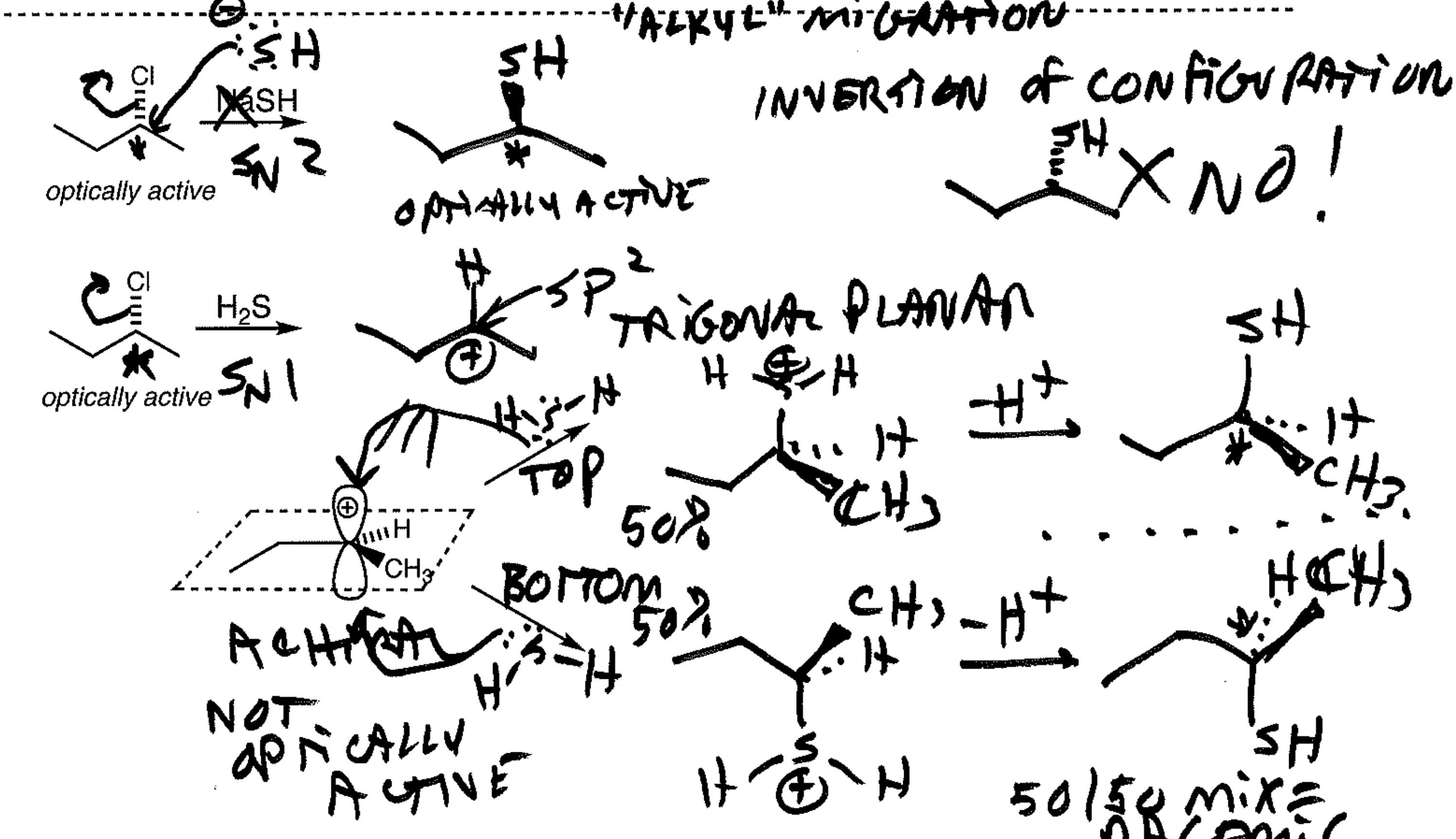
UPDATED

Plan of Attack *for an S_N1 problem:*

i. identify leaving group
ii. form carbocation
iii. identify Nu:
iv. rearrange if favorable
v. attach Nu:

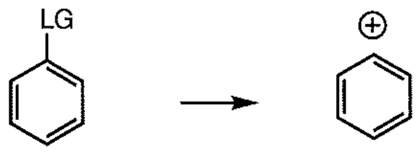



Problems: 16–19, 20

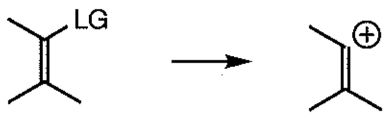


• *unlike the S_N2 reaction where optical activity in the starting materials can be retained in the product, S_N1 reactions lead to loss of optical activity*
• *optical activity can be transferred, but it cannot be created*
• *therefore, if optical activity is lost during a reaction, it cannot be regained!*
• *since carbocation intermediates (formed during the S_N1 reaction but NOT the S_N2) are planar, they cannot be optically active, and optical activity is lost during the reaction*
• *a 50/50 mixture of enantiomers is formed: i.e, a racemic mixture, and the process is known as "racemization"*

The Special Cases of Benzylic and Allylic Substrates

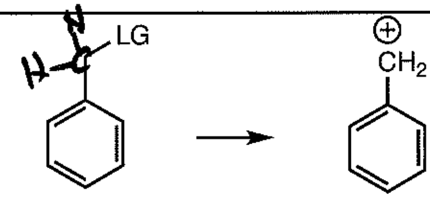


phenyl substrate **phenyl carbocation**

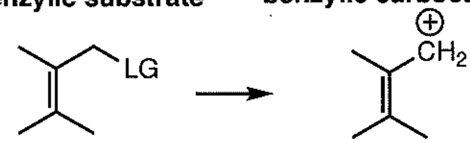


vinyl substrate **vinyl carbocation**

- *NEITHER of these substrates are reactive either by the S_N1 reaction OR the S_N2 reaction!*
- *the S_N2 reaction is prohibited since the nucleophile cannot correctly approach from the back side*
- *the S_N1 reaction is prohibited since the carbocation intermediates that would be formed are extremely unstable!*



benzylic substrate **benzylic carbocation**



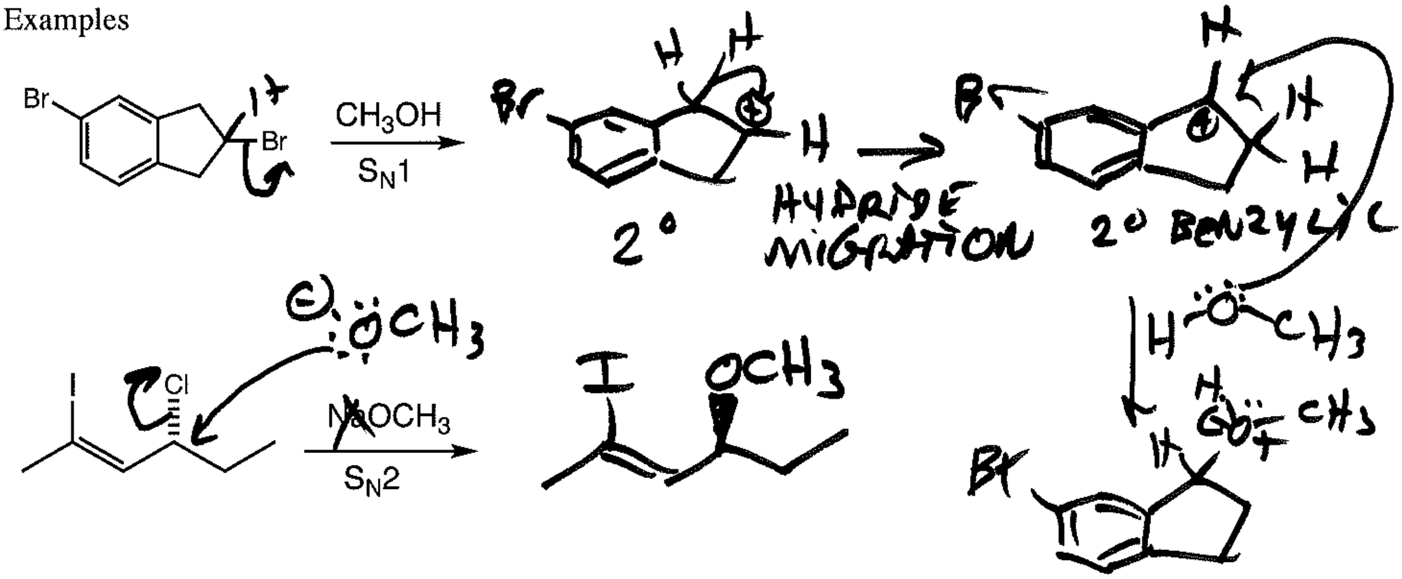
allylic substrate **allylic carbocation**

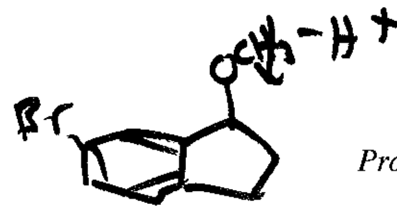
- *These substrates are very reactive by both the S_N1 AND S_N2 mechanism*
- *S_N2 reaction is enhanced for 1° and 2° benzylic and allylic subtrates since the planar nature of the benzene ring and the C=C bond decrease steric hindrance for nucleophilic attack (NOTE: reaction on 3° substrates is STILL forbidden)*
- *S_N1 reactivity is enhanced since the resulting carbocations are very stable due to resonance interactions*

updated carbocation stability

allylic, benzylic > 3° > 2° > 1° >>>>> phenyl, vinyl

Examples





Problems: 18

S_N2 vs S_N1. When Do They Compete?

RATE of S_N2 ←

	methyl	1°	2°	3°
SN_2	✓	✓	✓	X
substrate				
SN_1	X	X	✓	✓

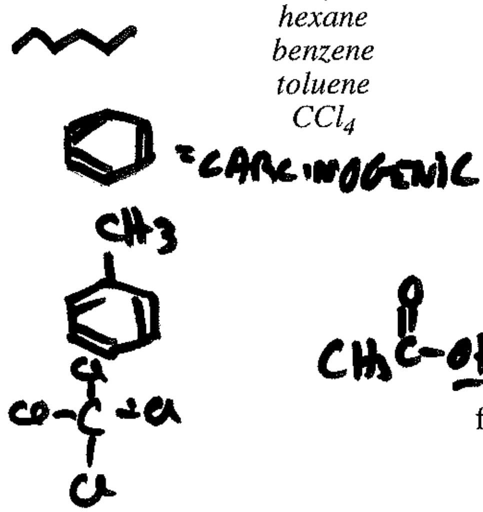
→ RATE of S_N1

• *methyl and 1° substates necessarily proceed via the S_N2 process since the carbocations required for the S_N1 process are of too high inenergy*
• *3° substrates necessarily proceed via the S_N1 process since they are too sterically hindered to proceed via the S_N2 process*
• *2° substrates may proceed via EITHER the S_N1 or the S_N2 process since they are not too sterically bulky for the S_N2 process, nor is the 2° carbocation too unstable for the S_N1 process*

Reaction Solvents → BRINGS REACTANTS INTO THE SAME PHASE

polarity?

- nonpolar: *hexane, benzene, toluene, CCl_4*
- polar
  - *hydrogen bonding?*
    - polar protic = H-BONDING: *H_2O, methanol, ethanol, acetic acid* — favors: S_N1
    - polar aprotic: *acetone, DMSO, ether, THF, CH_2Cl_2* — S_N2



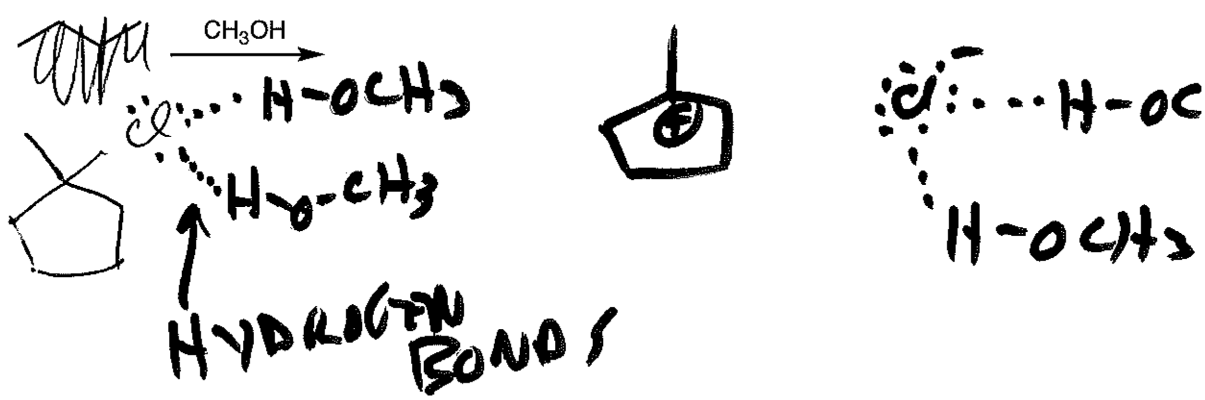
$CH_3C(=O)$-OH

CH_3-OH
CH_3CH_2-OH

DIMETHYL SULFOXIDE

CH_2Cl_2
DICHLOROMETHANE
METHYLENE CHLORIDE

How polar protic solvents favor S_N1 reactions



• *polar protic solvents act by hydrogen bonding to the leaving group and "tugging" it off*
•*generally, the solvent also acts as the nucleophile in the process: "solvolysis" process*

Predict whether the following reactions will proceed via S_N2 or S_N1 mechanism. Draw the product.

- *methyl and 1° substrates MUST occur via S_N2*
- *3° substrates MUST occur via S_N1*
- *S_N2 reactions on 2° substrates are favored by strong nucleophiles and polar aprotic solvents*
- *S_N1 reactions on 2° substrates are favored by weak nucleophiles (i.e., solvolysis reactions) and polar protic solvents*