LEC (21) CHEM 30A Mar 4th

- NUCLEOPHILIC SUBSTITUTION

(1) NUCLEOPHILE
(2) LEAVING GROUP
(3) SOLVENT

MIDTERM LOW 4 MEAN 39 HIGH 77
READ 8.1–8.10 PROBLEMS 8.14–8.35

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(1) NUCLEOPHILE

Trends:

(i) Same nucleophilic atom (parallels basicity)

$HO^{\ominus}$ > $CH_3C(=O)-O^{\ominus}$ > $H_2\ddot{O}$ X

16 5 -2 pKa of H–X

consider CHARGE | RESONANCE

(ii) nucleophiles in same row (parallels basicity)

$CH_3^{\ominus}$ > $NH_2^{\ominus}$ > $HO^{\ominus}$ > $F^{\ominus}$

need to consider ELECTRONEGATIVITY

(iii) nucleophiles in the same group (complicated)

In general, NUCLEOPHILICITY increases down a group

$HS^{\ominus} > HO^{\ominus}$ $\quad I^{\ominus} > Br^{\ominus} > Cl^{\ominus} > F^{\ominus}$

opposite to basicity – WHY?

– MANY FACTORS

a) ENERGY LEVELS

Higher energy of lone pair electrons as you go down the group ⇒ better overlap w/ σ^*

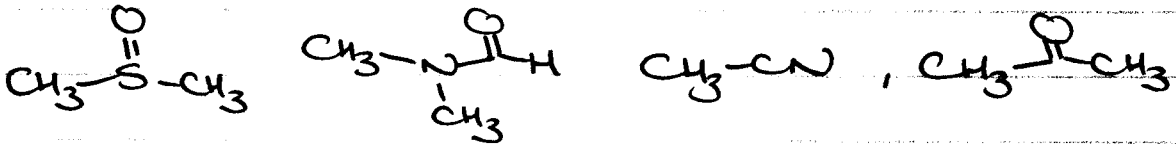
b) POLARISABILITY

Larger atoms, more diffuse electron clouds ⇒ greater POLARISABILITY → bonds can begin to form at greater interatomic distances.

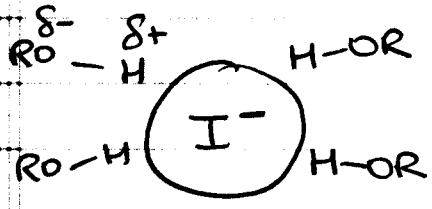
c) SOLVENT (v. large effect)

– POLAR PROTIC (H_2O, CH_3OH, CH_3CH_2OH)

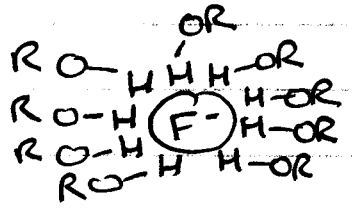
– POLAR APROTIC (DMSO, DMF, MeCN, Acetone)



POLAR PROTIC SOLVENTS $\quad I^- > Br^- > Cl^- > F^-$



LOW CHARGE DENSITY
(weak solvent cage)



HIGH CHARGE DENSITY
(strong solvent cage)

HYDROGEN BONDING – noncovalent interaction

$X-\overset{\delta-}{H}\overset{\delta+}{\cdots\cdots}\ Y^{\ominus}$

So, smaller NUCLEOPHILE = higher charge density => less nucleophilic

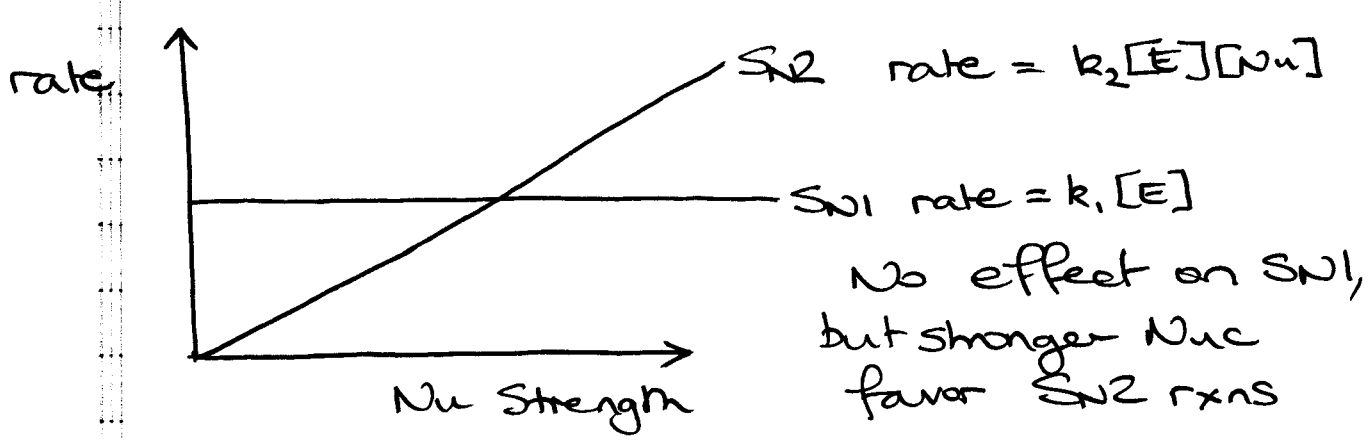
BUT IN POLAR APROTIC SOLVENTS
anions are only weakly solvated

TREND is REVERSED – correlates w/ BASICITY

consider: $Nu^{\ominus}_{s} \curvearrowright CH_3-I \longrightarrow Nu-CH_3 + I^{\ominus}$

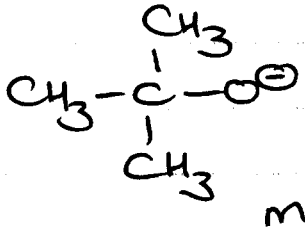
Nu	pka	MeOH (Time to complete RXN)	DMF (Time to complete RXN)	
I^-	-10	17min	8.7s	overall message
Br^-	-8	12h	8.7s	→
Cl^-	-6	13d	1.4s	POLAR APROTIC SOLVENTS ARE GOOD
F^-	3	>2yrs	<1.2s	

DMF/MeOH → equivalent polarities



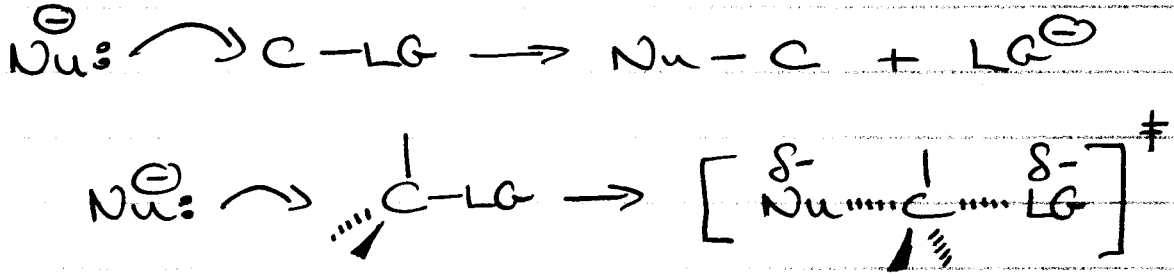
d) SIZE
consider:

$CH_3-O^{\ominus}$
methoxide
pKa 15.5



t-butoxide
pKa ~18
MORE BASIC but much LESS nucleophilic (STERICS)

(2) LEAVING GROUP



(also, IN SN1, form $LG^{\ominus}$ in RDS)

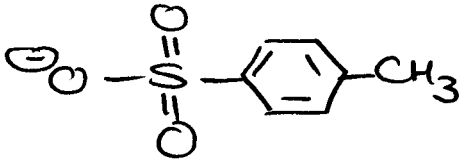
BETTER CHARGE STABILIZATION → BETTER LG
↳ reduces energy of TS, hence faster reaction

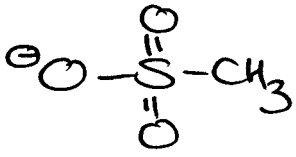
So, more ACIDIC H-LG, more stable $LG^{\ominus}$

GOOD / BAD LEAVING GROUPS
– relative reactivity

$NH_2^{\ominus}$	$OH^{\ominus}$	$OR^{\ominus}$	$F^{\ominus}$	$Cl^{\ominus}$	$Br^{\ominus}$	$I^{\ominus}$
$<<1$			1	200	10000	30000

- other good LG

tosylate  ~60,000

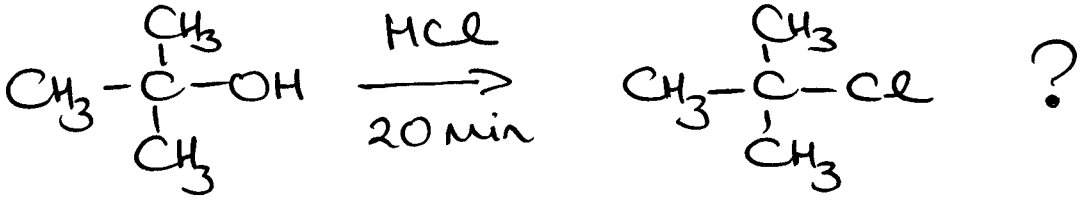
mesylate 

So, R-F, R-OH, R-OR', R-NH$_2$

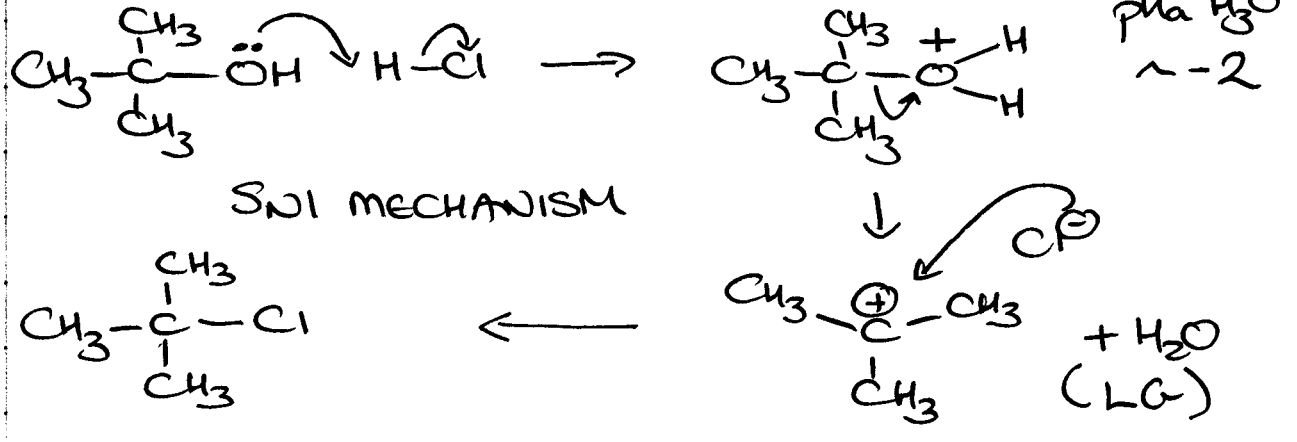
DO NOT UNDERGO SN2 reactions

DOES NOT HAPPEN

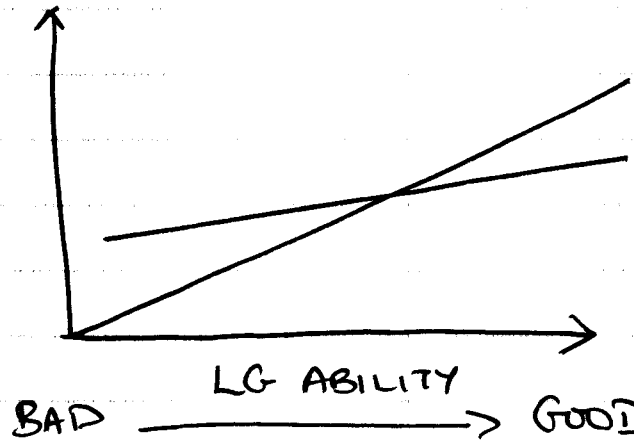
BUT



- converted OH into a better LG



SN1 vs SN2



SN1 rxn much more sensitive to LG ABILITY

RDS

$R\text{-}\overset{\curvearrowright}{LG} \rightarrow R^+ + LG^\ominus$

In SN2 reaction, as long as $LG^\ominus$ is more stable than $Nu^\ominus$, reaction can proceed

But on LG ABILITY alone, not possible to figure out SN1 vs SN2

(3) SOLVENT

SN2 RXNS → POLAR APROTIC SOLVENTS

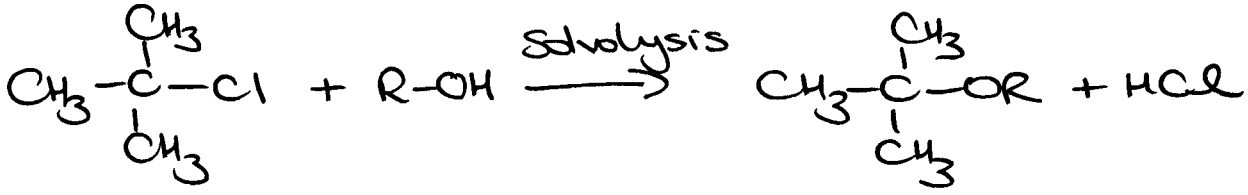
↳ solvate cations well, but not ANIONS

e.g. $NaBr \xrightarrow{\text{solvent}} Na^+ + Br^-$ (each ion surrounded by solvent molecules)

SN1 reaction $R\text{-}\overset{\curvearrowright}{LG} \rightarrow R^\oplus + LG^\ominus$

creation & separation of charge

⇒ more polar the solvent, the better



Water	/ Ethanol	Relative rate
100	0	100,000
80	20	14,000
40	60	100
0	100	1

So

S_N2 reactions

DISFAVORED IN PROTIC SOLVENTS

(ground state energy lowered by SOLVATION)

S_N1 reactions

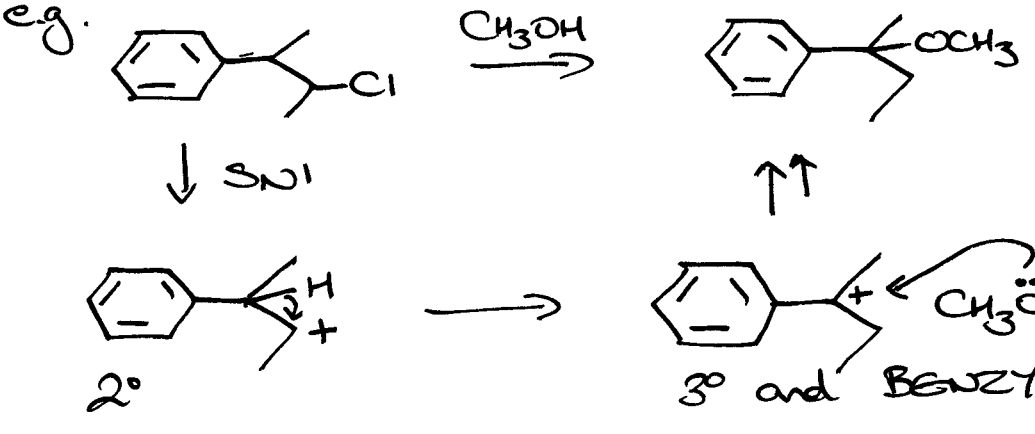
FAVORED IN PROTIC SOLVENTS

(transition state energy lowered by SOLVATION)

Note about S_N1

- goes through C^+, so be on the lookout for skeletal rearrangement

e.g.



SUMMARY

Electrophile	SN2	SN1
Me / 1°	✓	✗
2°	FAVORED GOOD NUCLEOPHILES POLAR APROTIC SOLVENTS	FAVORED POLAR NUCLEOPHILES POLAR PROTIC SOLVENTS
3°	✗	✓

also helped by really GOOD LG

- it gets COMPLICATED

⇒ COMPETING ELIMINATION REACTIONS