

- NUCLEOPHILIC SUBSTITUTION

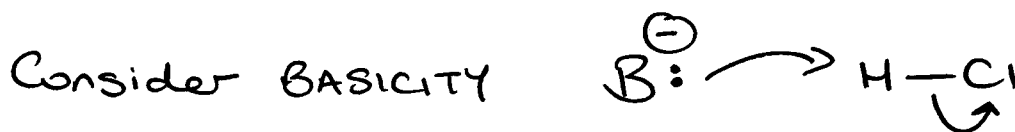
- ① NUCLEOPHILE
- ② LEAVING GROUP
- ③ SOLVENT

MIDTERM ② ROOM ASSIGNMENTS

READ 8.1 - 8.10
 PROBLEMS 8.14 - 8.35

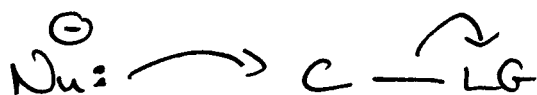
THURSDAY -
 CARI'S OFFICE
 HOURS
 CANCELLED

① THE NUCLEOPHILE



measure of how strong the affinity
 a base has for a proton

NUCLEOPHILICITY is similar



- affinity for a CARBON atom
- KINETIC rather than a THERMODYNAMIC effect

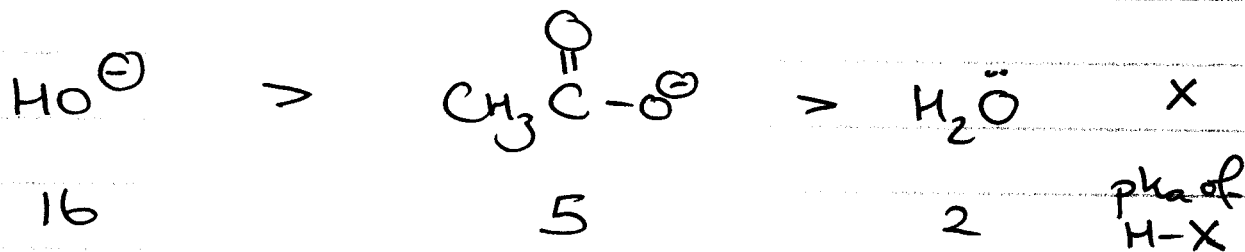
②

- IMPRECISE QUANTITY

For any given species, can vary depending on SOLVENT / ELECTROPHILE

Some general trends:

(i) same nucleophilic atom
(parallels basicity)



need to consider RESONANCE / CHARGE

(ii) nucleophiles in the same row
(parallels basicity)

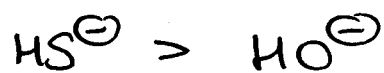


need to consider ELECTRONEGATIVITY

(iii) nucleophiles in the same group

in general NUCLEOPHILICITY increases going down a group

3



opposite to basicity - WHY?

- MANY FACTORS

a) ENERGY LEVELS

As you go down the periodic table, lone pair electrons in valence shell are in higher energy orbitals \rightarrow better overlap with O^*

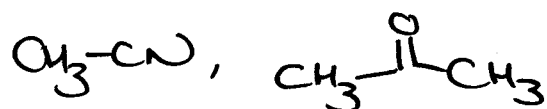
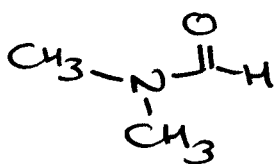
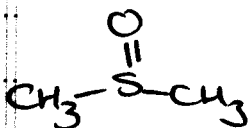
b) POLARISABILITY

Larger atoms \rightarrow more diffuse electron clouds (greater POLARISABILITY) - bonds can begin to form at greater INTER-ATOMIC DISTANCES

c) SOLVENT (very dramatic effect)

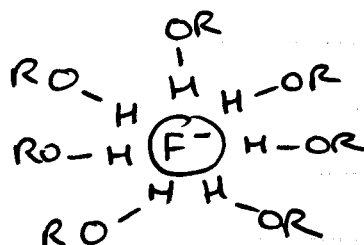
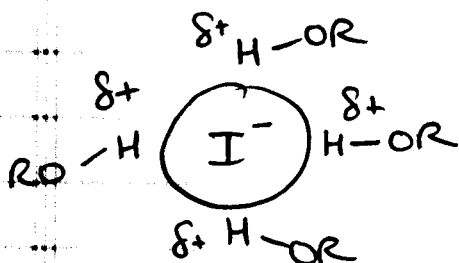
- POLAR PROTIC (H_2O , CH_3OH , $\text{CH}_3\text{CH}_2\text{OH}$)

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



4

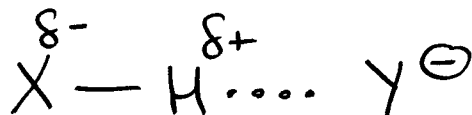
- In POLAR PROTIC SOLVENTS



LOW CHARGE DENSITY
- weak solvent cage

HIGH CHARGE DENSITY
- strong solvent cage

HYDROGEN BONDING - noncovalent interaction



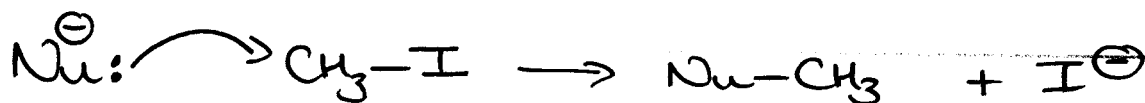
So, smaller nucleophile \rightarrow more solvated
 \Rightarrow LESS NUCLEOPHILIC

BUT IN POLAR APROTIC SOLVENTS

- anions are only weakly solvated,

TREND REVERSED - correlates w/ BASICITY

consider



5

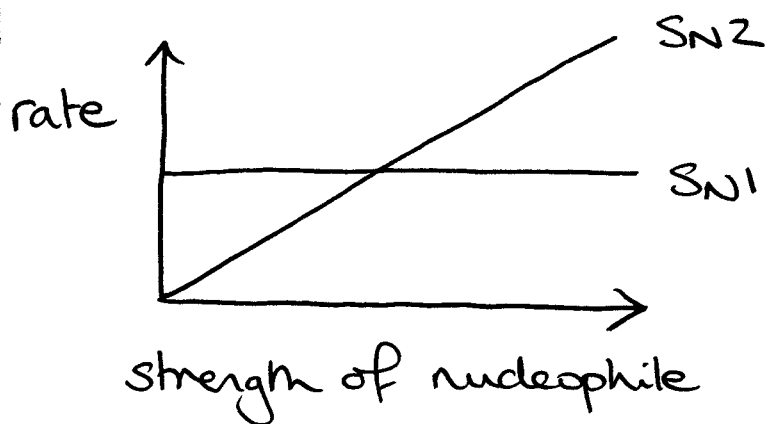
Nuc	pKa	PROTIC MeOH (time to complete reaction)	APROTIC DMF
I ⁻	-10	17 min	8.7 s
Br ⁻	-8	12 h	8.7 s
Cl ⁻	-6	13 d	1.4 s
F ⁻	3	> 2 yrs	< 1.2 s

DMF / MeOH ~ equal polarities

Overall Polar aprotic solvents are the best in S_N2 reactions

(more on solvent effects later)

S_N1 vs S_N2



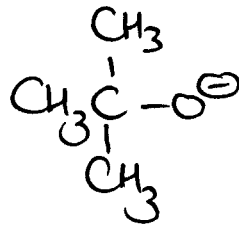
Nu strength has no effect on S_N1, but in S_N2, the stronger the Nu, the faster the rate, so **STRONG NUCLEOPHILES** favor S_N2 reactions

6

d) size

... consider

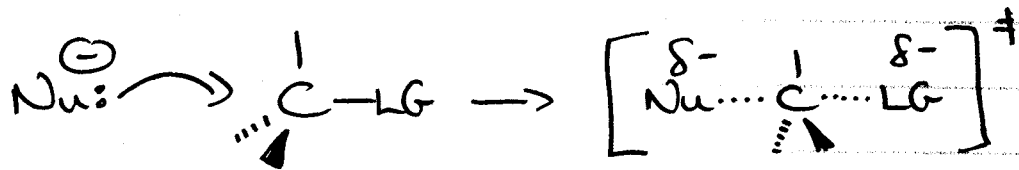
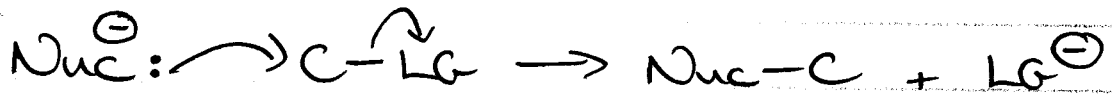
... $\text{CH}_3\text{O}^\ominus$
... methoxide
... pK_a 15.5



t-butoxide
 $\text{pK}_a \sim 18$

MORE BASIC, but
much less nucleophilic
(STERICS)

② LEAVING GROUP



(also in $\text{S}_{\text{N}}1$, form LG^\ominus in RDS)

BETTER CHARGE STABILIZATION \rightarrow

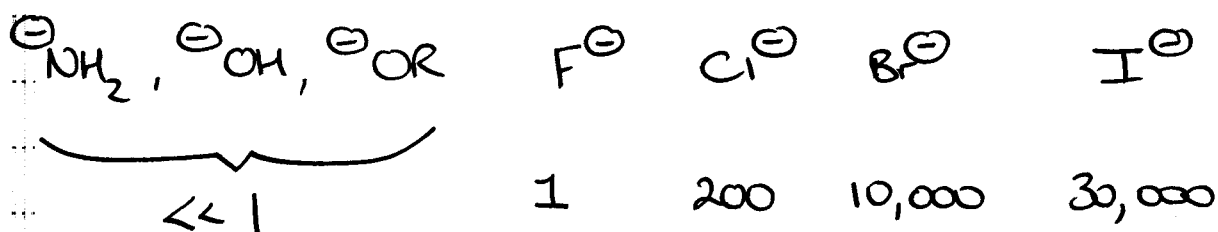
BETTER LEAVING GROUP

... reduces energy of transition state, faster reaction

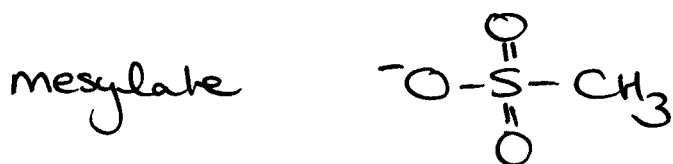
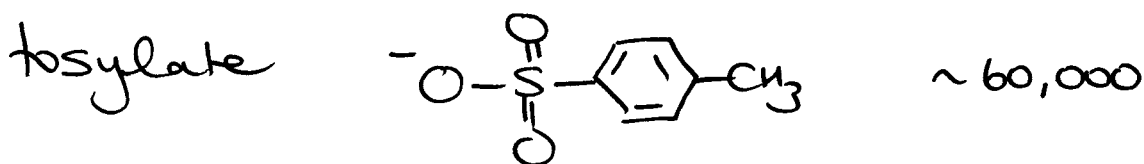
... So, more ACIDIC H-LG, more stable LG^\ominus

... GOOD LEAVING GROUPS / BAD LEAVING GROUPS

relative reactivity

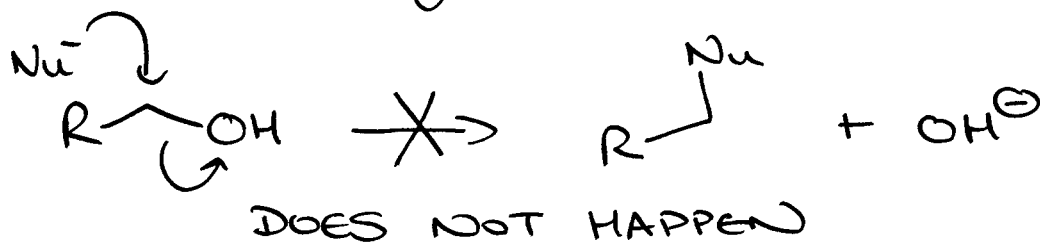


other good leaving groups

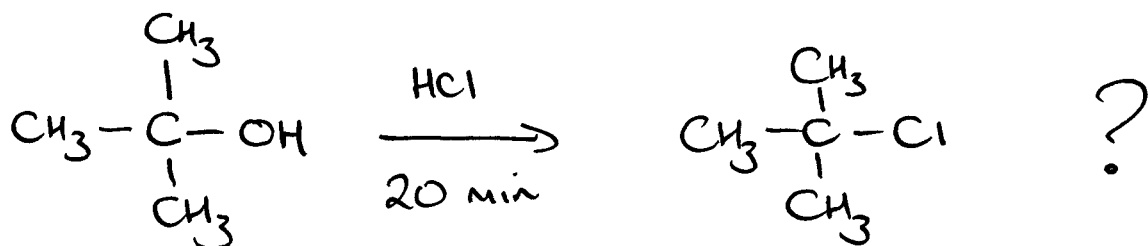


so, $\text{R-F}, \text{R-OH}, \text{R-OR}', \text{R-NH}_2$

- do not undergo $\text{S}_\text{N}2$ reactions



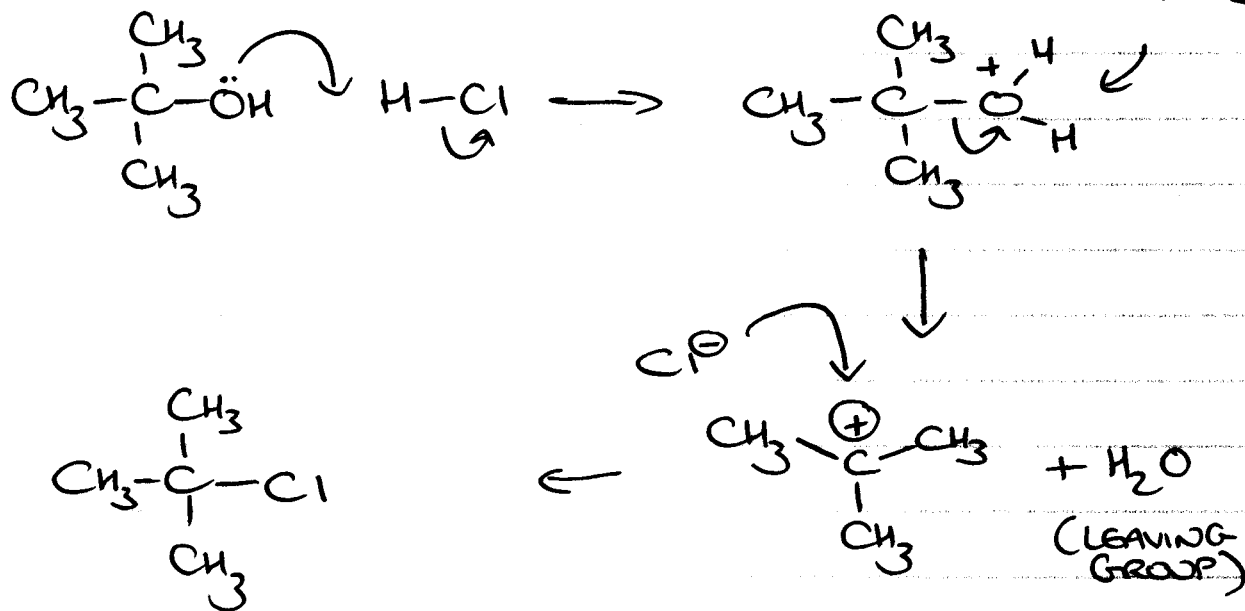
BUT



(8)

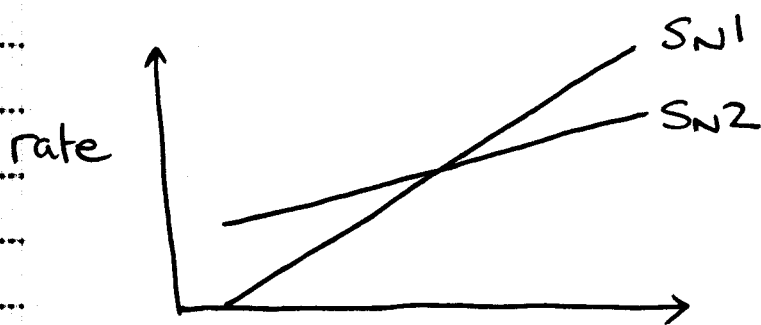
- converted OH into a better LG

$pK_a H_3O^+ \approx -2$



(SN1 mechanism)

SN1 vs SN2



BAD \rightarrow LG ABILITY \rightarrow V. GOOD

SN1 reaction is MUCH MORE SENSITIVE to the leaving group ability, as RDS involves



9

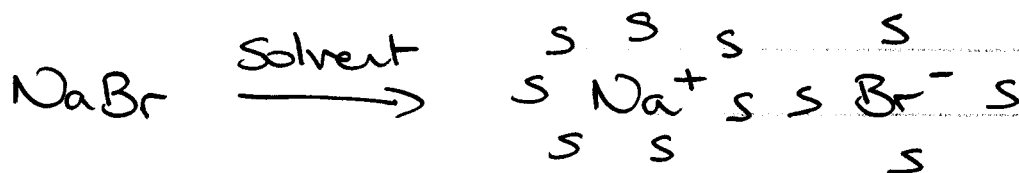
In S_N2 reaction \rightarrow as long as
 LG^\ominus more stable than Nu^\ominus ,
reaction can proceed

BUT deciding on LG ability alone, not
easy to figure out S_N1 vs S_N2

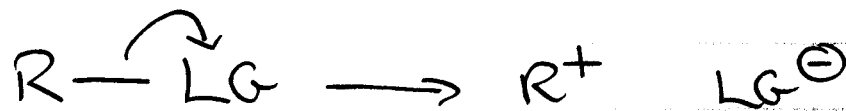
③ SOLVENT

S_N2 reactions POLAR APROTIC solvents
 \downarrow
solvate CATIONS well,
but not ANIONS

e.g.



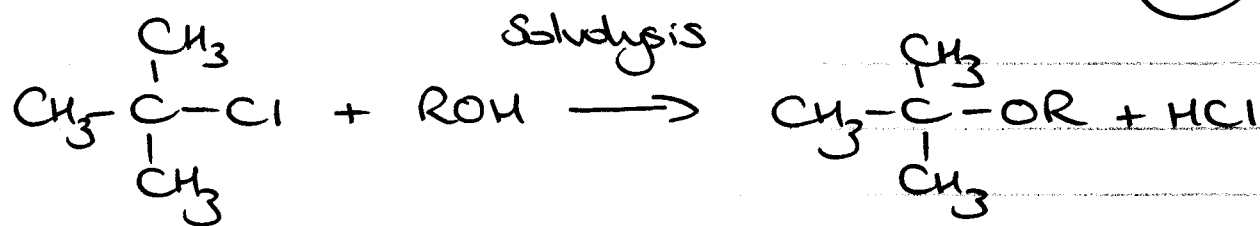
S_N1 reaction



creation and separation of charge

\Rightarrow more polar the solvent, the better

(10)



Water / Ethanol

100	0
80	20
40	60
0	100

relative rate

100,000
14,000
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

