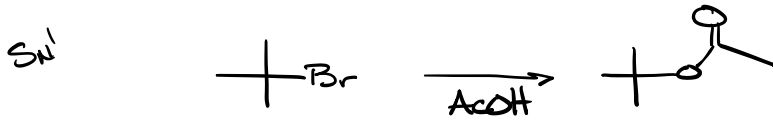
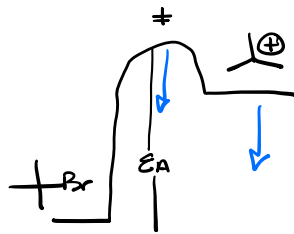


Solvent Affects cont...

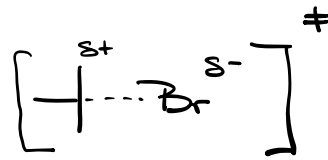
Unimolecular (S_N^1 / E_1)



ϵ	Solvent	⁶ AcOH	³³ MeOH	⁵⁸ Formic Acid	⁷⁸ H ₂ O
$\frac{k}{k_{AcOH}}$		1	4	5,000	150,000



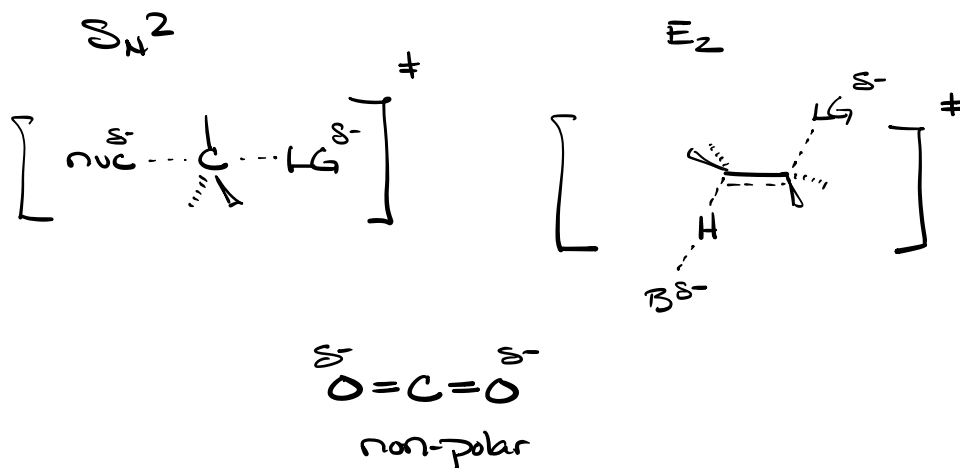
Decrease in energy of \ddagger reduces E_A and Speed reaction UP



Transition state polar highly affected by solvent

Higher dielectric constant solvents (High ϵ), will strongly solvate and stabilize transition state

What about bimolecular S_N2 & $E2$?



S_N2 & $E2$ Similarly non-polar

Bimolecular non-polar \neq not strongly affected by solvent.

Non-polar solvents will make $S_N2/E2$ faster,
but a polar solvent will not shut them down.

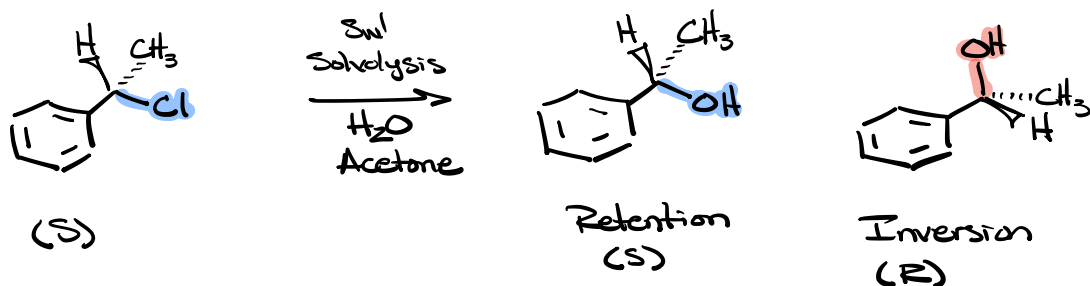
unimolecular (polar \neq) these strongly affected by solvent

\Rightarrow faster in polar solvents

\Rightarrow shut down in non-polar solvents

\oplus are not solvated by non-polar solvents.

Solvent on Stereochemical Selectivity S_N1



H_2O /Acetone
Ratio

100/0

41%

59%

40/60

47%

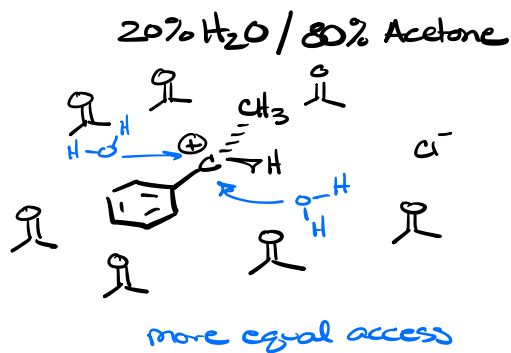
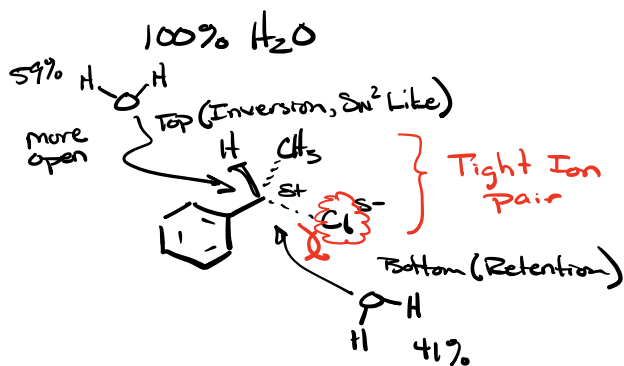
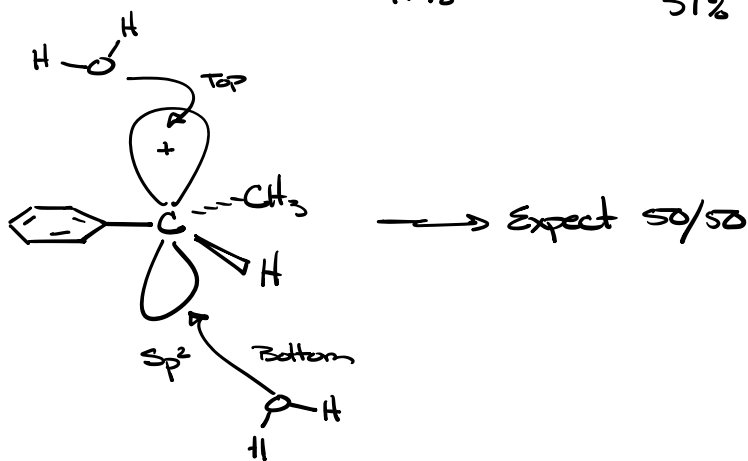
53%

20/80

49%

51%

↓
Closer to 50/50



Nucleophile

Relative nucleophilicity (How good a nucleophile)

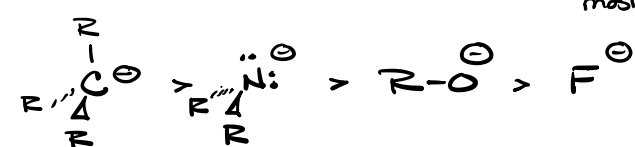


No super clear trend

Nucleophilicity decreases with increasing EN



Least EN



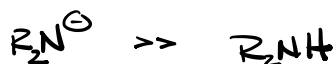
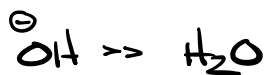
most EN element

Elements that hold e^- more tightly are worse nucleophile

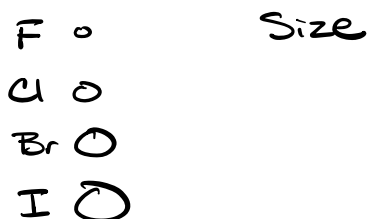
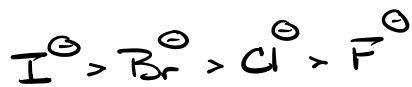
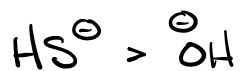
Best nuc

worst nuc

Anions more nucleophilic than their Conjugates

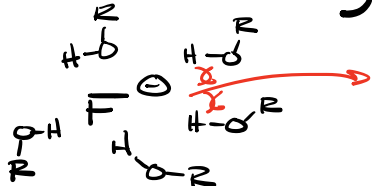


For protic Solvents, nucleophilicity increases going down a group

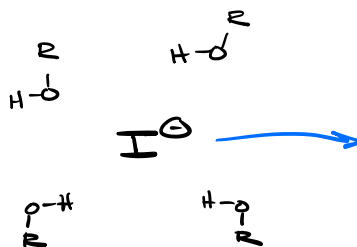


Something that is large is a better nuc ???

- ① Solvent
- ② Polarizability

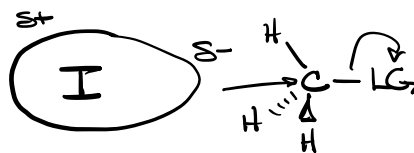


High charge density
Tight Solvent Cage



Low charge density
Less tightly solvated

Polarizability - Soft, Squishy, polarizable



Has easier time attacking substrate due to its ability to change shape

Factors

- ① Substrate ✓ 1°, 2°, 3°, Allylic (position of LG)
- ② { Leaving Group ✓
? Base / Nucleophile ✓
- ③ Solvent ✓
- ④ Temperature ✓

Leaving Group

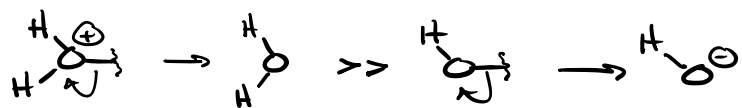
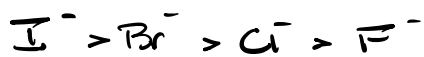
Better LG = faster Rxn

S_N'/E, LG has bigger impact

Good LG is a weak base

Weak base = very stable species

EWG
Resonance
Size

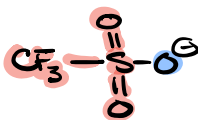


Really good LG are Tosylates

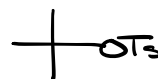
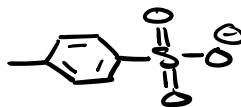


strongest

Triflate (Tf)

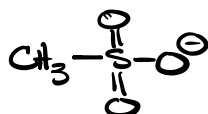


Tosylate (Ts)



weakest

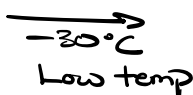
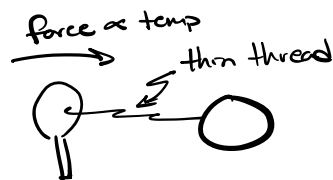
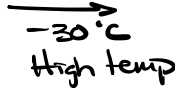
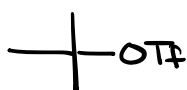
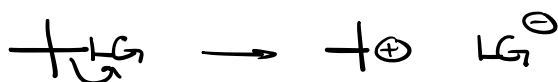
mesylate (Ms)



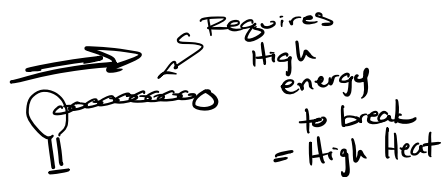
Temperature (Hard because it is relative to LG)

High \longleftrightarrow Low moving target

$\text{S}_\text{N}1/\text{E}_1$



no Rxn



Temp \propto stability of C^+
 stability of LG
 Solvent

Simple Guide

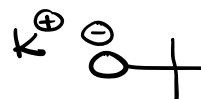
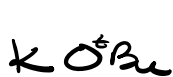
Δ = reflux in the solvent
= Highest possible temp
= High Temp

0°C & below is usually low temp

-30°C or -78°C are low temp
↑ ↑
NaCl/Ice dry ice/acetone

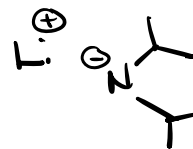
Base vs Nucleophile?

Bulky Base



LDA

(Lithium Diisopropyl)
Amide



These two are
only used as base,
they are non-nucleophilic
due to sterics

Base vs. Nucleophile depends on other factors

Is there a C⁺ (S_N¹/E₁)?

Temp High or Low?

Solvent?

Magic Sheet

NUCLEOPHILIC SUBSTITUTION AND ELIMINATION

The question is how do we discern when substitution is favored versus elimination? The answer is found partly in how we should think about reactions of alkyl halides.

*The characteristic reaction of alkyl halides (or alkyl tosylates) with a Lewis base is **elimination**, special conditions are required to promote substitution.*

Given here is a set of guidelines (not absolutes) that can be used to arrive at the probable solution to nucleophilic substitution/elimination problems.

	Substitution	Elimination
	S_N2	E2
substrate	benzyl = allyl > Me > 1° > 2° α -haloketone, α -haloester, α -halonitrile	3° > 2° > 1°
solvent	polar aprotic	polar aprotic
nucleophile	good nuc (weaker base than OH^-)	bulky or strong base $\gg OH^-$
leaving group	sulfonate > I^- > Br^- > Cl^-	sulfonate > I^- > Br^- > Cl^-
Temp	low	high
	S_N1	E1
substrate	3° > 2°	3° > 2° > 1°
solvent	polar protic	polar protic
nucleophile	weak nuc (no anions!)	any anionic base
leaving group	sulfonate > I^- > Br^- > Cl^-	sulfonate > I^- > Br^- > Cl^-
Temp	low	high

Classification of Nucleophiles

Very good nucleophile	I^- , HS^- , RS^-
Good nucleophile	Br^- , OH^- , RO^- , CN^- , N_3^-
Fair nucleophile	NH_3 , Cl^- , F^- , RCO_2^-
Weak nucleophile	H_2O , ROH
Very weak nucleophile	RCO_2H

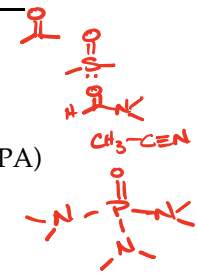
Nucleophilic Constants of Various Nucleophiles

Nucleophile	n_{CH_3I}	pK_a of conjugate acid
CH_3OH	0.0	-1.7
F^-	2.7	3.45
$CH_3CO_2^-$	4.3	4.8
Cl^-	4.4	-5.7
NH_3	5.5	9.25
N_3^-	5.8	4.75
$C_6H_5O^-$	5.8	9.89
Br^-	5.8	-7.7
CH_3O^-	6.3	15.7
OH^-	6.5	15.7
$(CH_3CH_2)_3N$	6.7	10.70
CN^-	6.7	9.3
I^-	7.4	-10.7
$(CH_3CH_2)_3P$	8.7	8.69
$C_6H_5S^-$	9.9	6.5

nucleophilicity constant
Acidity

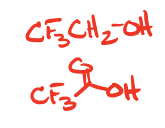
Solvents Which Promote $S_N2/E2$ (bimolecular)

- Acetone
- Dimethyl sulfoxide (DMSO)
- N,N*-Dimethylformamide (DMF)
- Acetonitrile
- Hexamethylphosphoramide (HMPA)



Solvents Which Promote $S_N1/E1$ (Unimolecular/Ionizing)

- Increasing nucleophilicity (solvolysis) ↑
- Ethanol
 - Methanol
 - 50% Aqueous Ethanol
 - Water
 - Acetic Acid
 - Formic Acid
 - Trifluoroethanol
 - Trifluoroacetic acid



Better nuc



Stronger base ↑

CH_3^-

↑

HO^-

↓

Weak base I^-

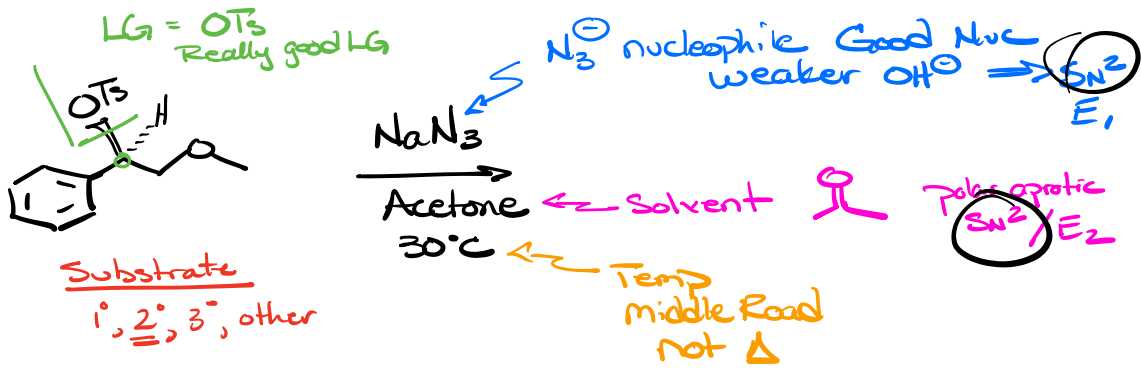
pK_a

CH_4 60

H_2O 15.7

9.3

IH -10.7



Substrate
 $1^\circ, 2^\circ, 3^\circ$, other
 2° benzylic Tosylate
 $\Rightarrow \text{SN}^2$

SN^2

