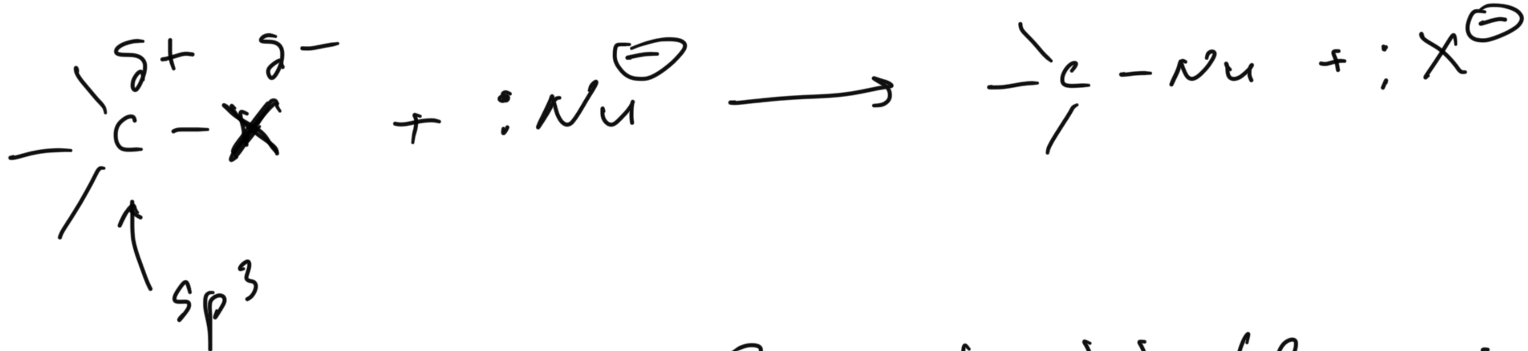
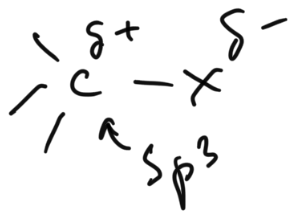
Alkyl halides: nucleophilic substitution

Reactant, leaving group, nucleophile, Lewis acid–base reaction



① reactant

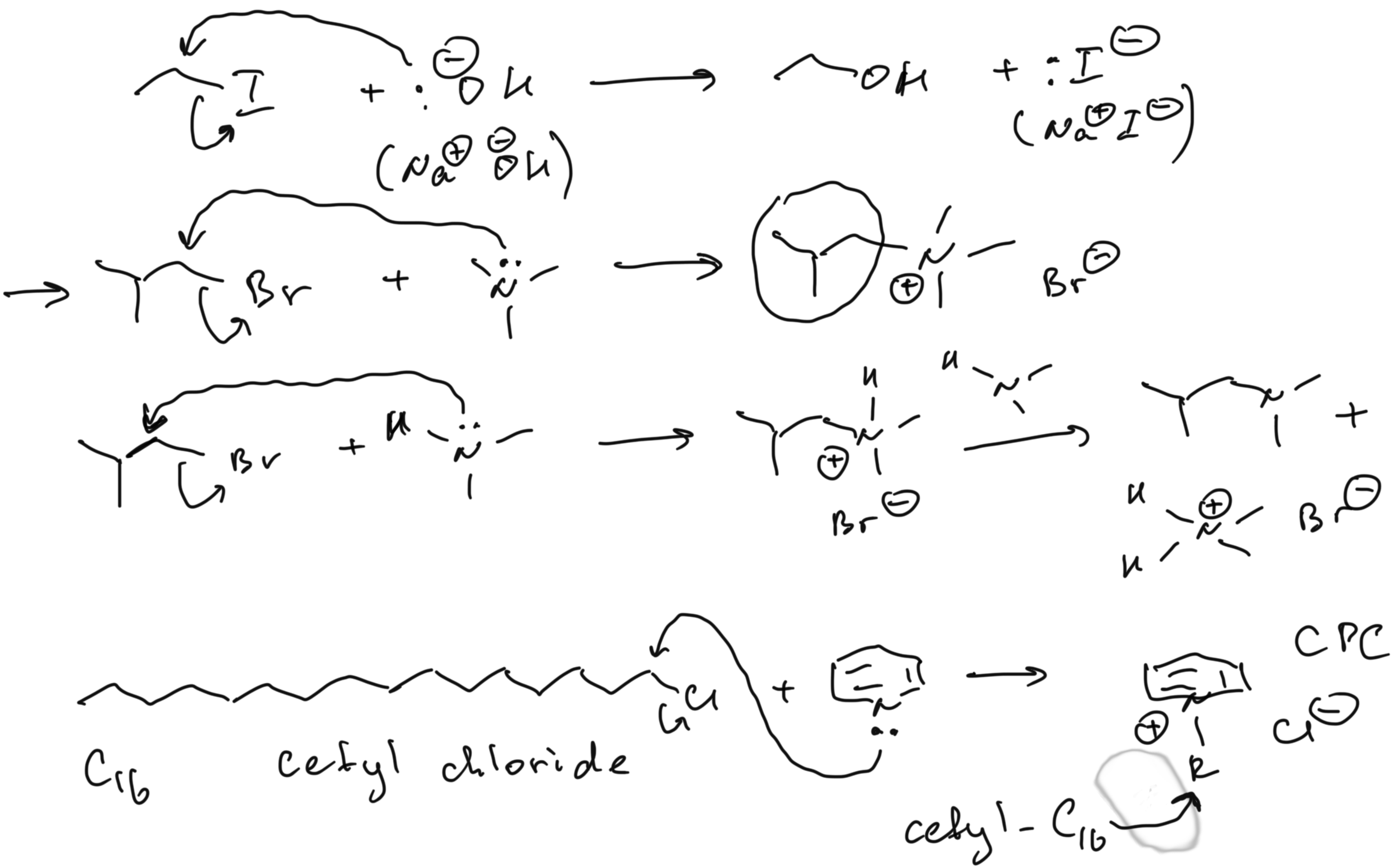


② $:Nu^{\ominus}$ – nucleophile (lone pair, π bond)

③ X – leaving group
(accept electrons:
halides, H_2O ($-C-\overset{\oplus}{O}H_2$),
N_2 ($-C-N_2^{\oplus}$)

Alkyl halides: nucleophilic substitution

Charged and neutral nucleophiles, curved arrows, proton transfer



Nucleophilic substitution: the leaving group

Basicity and leaving group ability

$$-\overset{|}{\underset{|}{\overset{\delta+}{C}}}-\overset{\delta-}{X} + :Nu^{\ominus} \longrightarrow -\overset{|}{\underset{|}{C}}-Nu + :\underline{X^{\ominus}}$$

Lewis acid-base reaction

weak base

- weaker bases are better leaving groups

more basic

H_2O vs NH_3

better leaving group

$F^{\ominus}$

$Cl^{\ominus}$

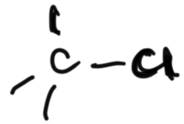
$Br^{\ominus}$

$I^{\ominus}$

basicity increases

leaving group ability increase

Nucleophilic substitution: the leaving group



Starting material	Leaving group	Conjugate acid	pK_a
R—Cl	√ Cl^-	HCl	−7
R—Br	√ Br^-	HBr	−9
R—I	√ I^-	HI	−10
R—OH_2^+	√ H_2O	H_3O^+	−1.7
X R—F	X F^-	HF	3.2
R—OH	X ^-OH	H_2O	15.7
R—NH_2	X $^-NH_2$	NH_3	38
R—H	X H^-	H_2	35
R—R	X R^-	RH	50

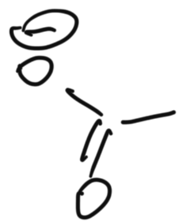
good

bad

Nucleophilic substitution: the nucleophile

Reactivity of bases and nucleophiles, basicity and nucleophilicity

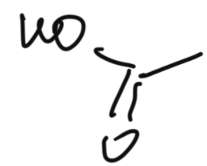
- a stronger base is, generally, a better nucleophile

$^{\ominus}OH$ vs 

stronger base

better nucleophile

$^{\ominus}OH$ vs H_2O

H_2O vs 

pKa 15.7 pKa 4.8

H_2O vs $H_3O^{\oplus}$

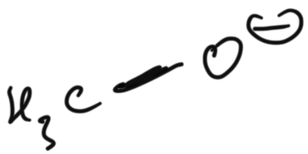
15.7 −1.7

- $CH_3^{\ominus}$ $NH_2^{\ominus}$ $OH^{\ominus}$ $F^{\ominus}$ basicity increases

nucleophilicity

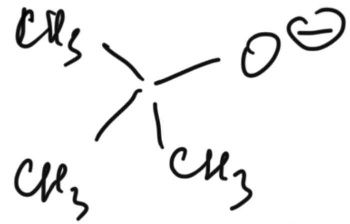
Nucleophilic substitution: the nucleophile

Steric effects and nucleophilicity, effect on basicity



methoxide

vs



t-butoxide

CH_3-OH vs t-Bu$-OH$

pK_a 15.5 pK_a 17.0

weaker base stronger base

BUT

$CH_3O^{\ominus}$ better Nu than t-Bu$O^{\ominus}$

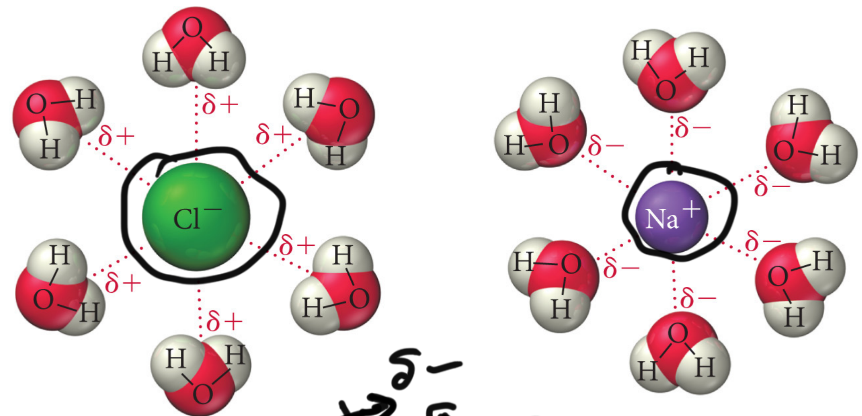
t-Bu$O^{\ominus}$ is bigger than $CH_3O^{\ominus}$

- sterics play role in nucleophilicity but not basicity (smaller Nu is better Nu)

Nucleophilic substitution: the nucleophile

Polar protic solvents, solvation of cations and anions, effect on nucleophilicity

two groups of solvents:



(1) polar protic solvents

H_2O, CH_3OH, t-BuOH

$\delta^+ H-\overset{\delta-}{O}-H \delta^+$

NaCl in water

(2) polar aprotic solvents

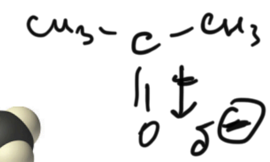
$CH_3-\overset{O}{\overset{\|}{C}}-CH_3$, $CH_3-\overset{O}{\overset{\|}{S}}-CH_3$, $CH_3-\underset{CH_3}{\underset{|}{N}}-\overset{O}{\overset{\|}{C}}-H$

acetone, dimethyl sulfoxide, dimethyl formamide

• polar protic solvents solvate both cations and anions

Nucleophilic substitution: the nucleophile

Polar aprotic solvents, solvation of cations, effect on nucleophilicity



polar protic solvents

$\boxed{F^{\ominus}}$

$Cl^{\ominus}$

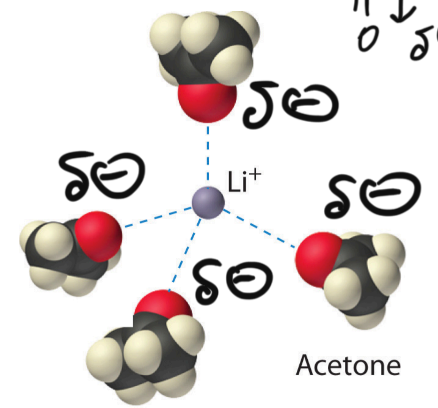
$Br^{\ominus}$

$\boxed{I^{\ominus}}$

nucleophilicity increases

polar aprotic solvents

nucleo-philicity



LiBr in acetone

$Br^{\ominus} \rightarrow$ naked

Nucleophilic substitution: mechanisms

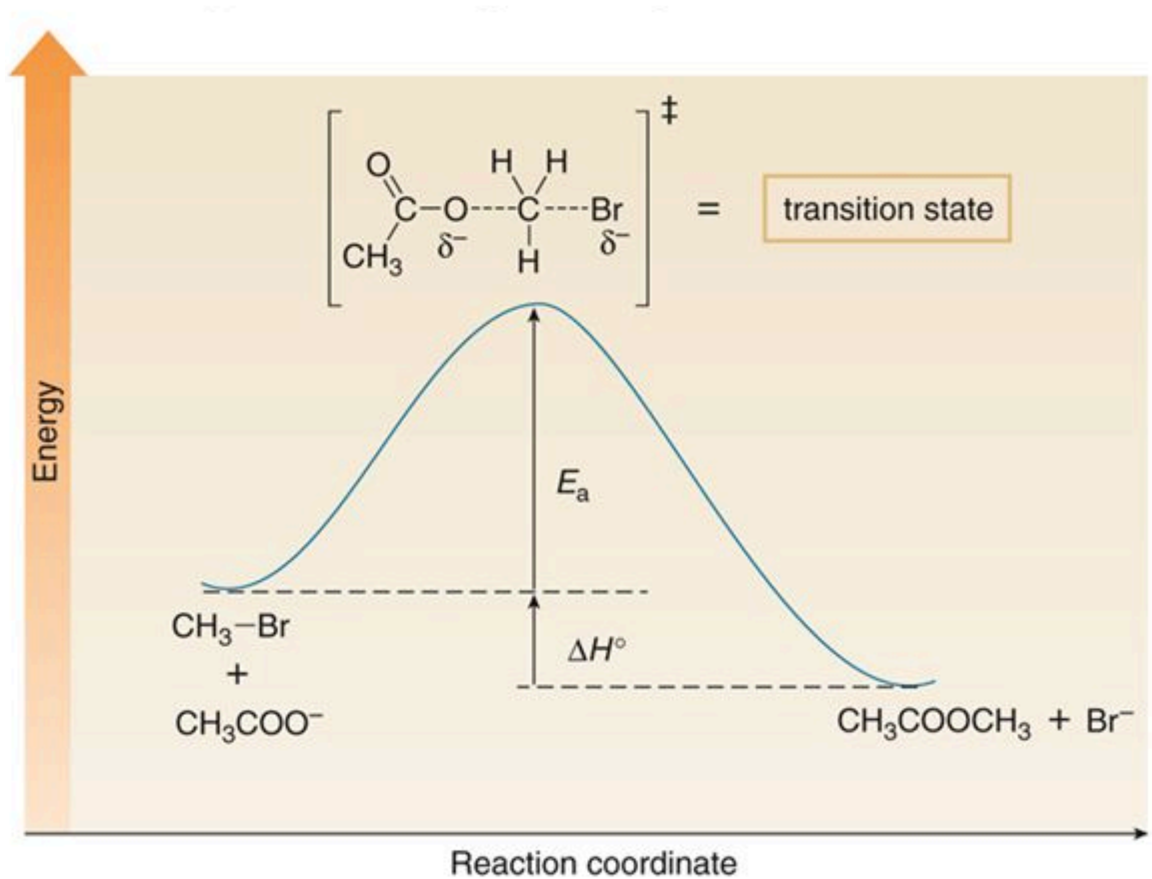
One step or two steps? Rate equations and implications

Nucleophilic substitution: the S_N2 mechanism

Substitution nucleophilic bimolecular, kinetics and mechanism

Nucleophilic substitution: the S_N2 mechanism

Substitution nucleophilic bimolecular, energy diagram



Nucleophilic substitution: the S_N2 mechanism

Frontside or backside? Stereochemistry of the S_N2 reaction, Walden inversion

Nucleophilic substitution: the S_N2 mechanism

Effect of the R group (1°, 2°, 3°) on the S_N2 reaction

Nucleophilic substitution: the S_N2 mechanism

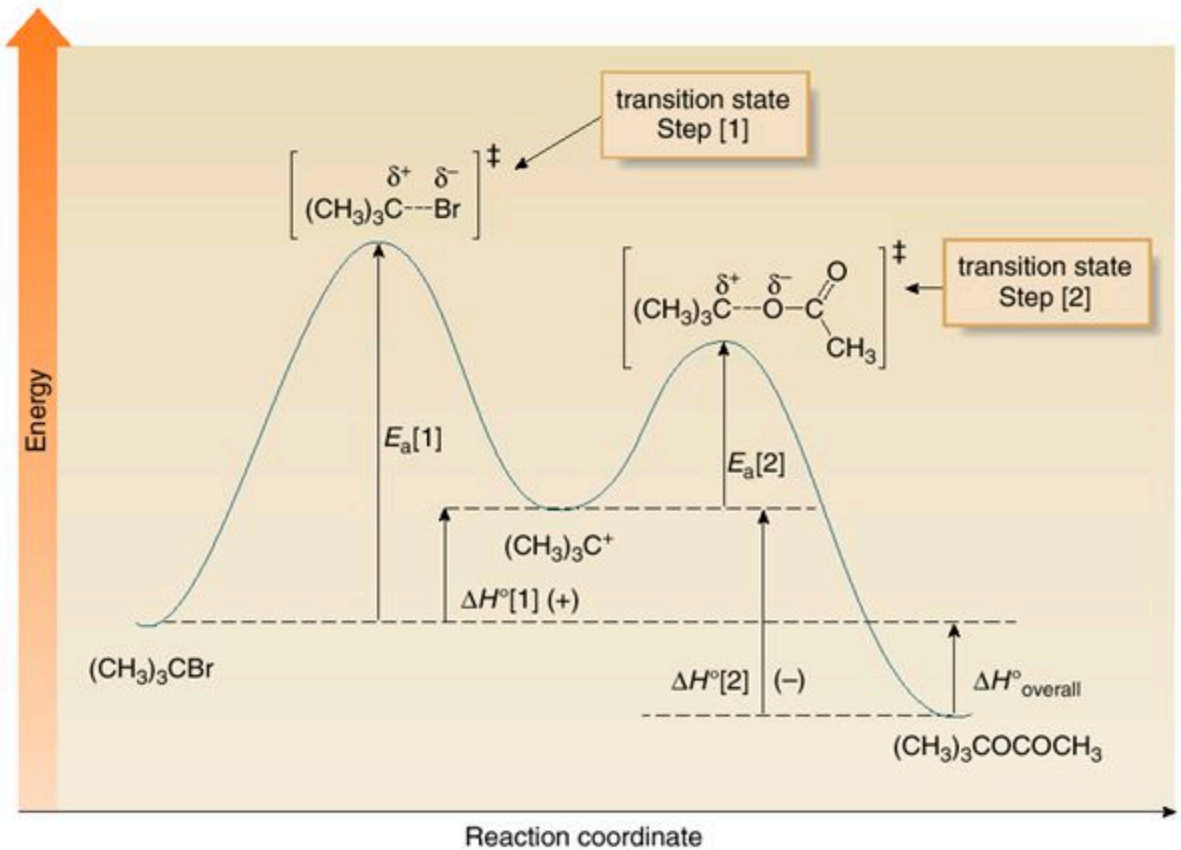
Effect of the R group (1°, 2°, 3°) on the S_N2 reaction

Nucleophilic substitution: the S_N1 mechanism

Substitution nucleophilic unimolecular, kinetics and mechanism

Nucleophilic substitution: the S_N1 mechanism

Substitution nucleophilic unimolecular, energy diagram



Nucleophilic substitution: the S_N1 mechanism

Stereochemistry of the S_N1 reaction, racemization