台灣大學開放式課程

有機化學乙

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Chapter 6
Ionic reactions of alkyl halides

※ Alkyl halides R-X

- ✓ Classification

CH_3X	RCH_2X	RR'CHX	RR'R"CX
methyl halides	1°	2°	3°

- ✓ Some physical properties

Me-F	Me-Cl	Me-Br	Me-I
1.39 Å	1.78	1.93	2.14
472 kJ/mol	350	293	239

Water insoluble, good organic solvents

CH_2Cl_2	$CHCl_3$	CCl_4
dichloromethane	chloroform	carbon tetrachloride

carcinogenic

※ Nucleophilic substitution reactions
親核性取代反應

leaving group

$$Nu:^{-} \quad + \quad R\text{-}X \quad \rightarrow \quad R\text{-}Nu \quad + \quad X:^{-}$$

nucleophile　substrate　product　halide ion

heterolysis occurs

例

$$HO:^{-} \quad + \quad CH_3\text{-}Cl \quad \rightarrow \quad CH_3\text{-}OH \quad + \quad Cl:^{-}$$

$$CH_3O:^{-} \quad + \quad CH_3CH_2\text{-}Br \quad \rightarrow \quad CH_3CH_2\text{-}OCH_3 \quad + \quad Br:^{-}$$

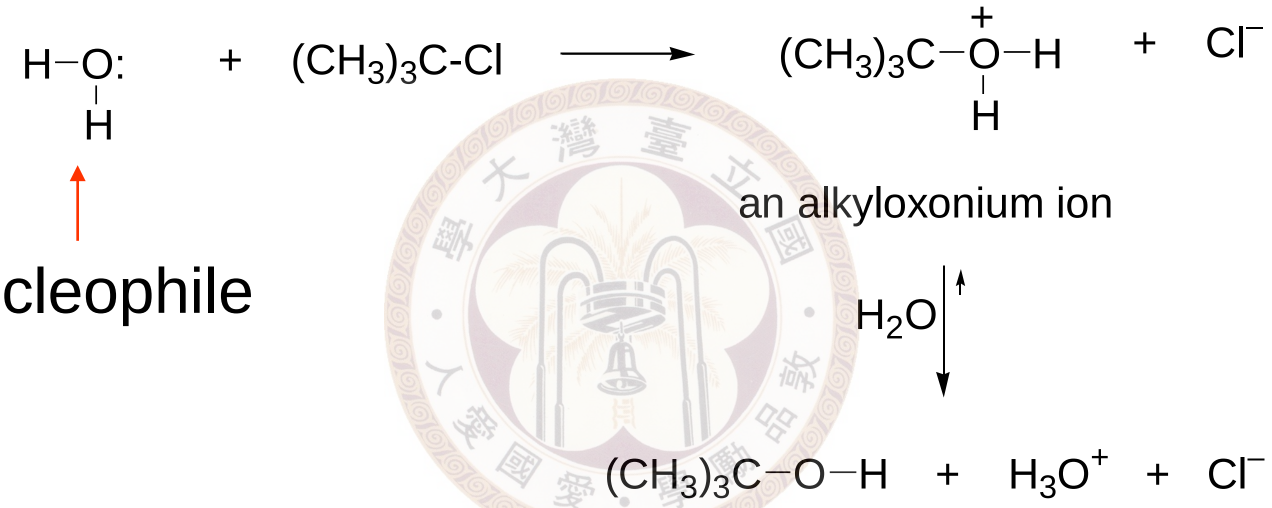
$$I:^{-} \quad + \quad CH_3CH_2CH_2\text{-}Cl \quad \rightarrow \quad CH_3CH_2CH_2\text{-}I \quad + \quad Cl:^{-}$$

◎ Nucleophiles:

any molecule that has an unshared electron pair

(not necessarily charged)

例



$$\underset{H}{\overset{}{H-\underset{|}{O}:}} \quad + \quad (CH_3)_3C\text{-}Cl \longrightarrow (CH_3)_3C-\overset{+}{\underset{\underset{H}{|}}{O}}-H \quad + \quad Cl^-$$

$$H_2O \; \downarrow\uparrow$$

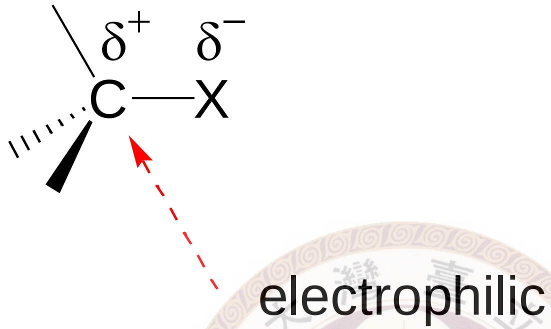
$$(CH_3)_3C-O-H \quad + \quad H_3O^+ \quad + \quad Cl^-$$

nucleophile

an alkyloxonium ion

hydronium ion

◎ Substrates: electrophiles



◎ Leaving groups:

leave as a relatively stable, weakly basic molecule or anion

Two types:

$$\mathrm{Nu{:}^-} \quad + \quad \mathrm{R{-}LVG} \quad \longrightarrow \quad \mathrm{Nu{-}R} \quad + \quad \mathrm{^-{:}LVG}$$

$$\mathrm{Nu{:}^-} \quad + \quad \mathrm{R{-}\overset{+}{L}VG} \quad \longrightarrow \quad \mathrm{Nu{-}R} \quad + \quad \mathrm{{:}LVG}$$

★ S_N2 reaction mechanism

例

$$H_3C{-}Cl \quad + \quad {}^{-}OH \quad \xrightarrow[H_2O]{60\ {}^{o}C} \quad H_3C{-}OH \quad + \quad Cl^{-}$$

$$\text{Rate} \propto [CH_3Cl][OH^-]$$

$$\text{Rate} = \underset{\substack{\uparrow \\ \text{rate constant}}}{k}\,[CH_3Cl][OH^-]$$

A second order reaction or bimolecular reaction

⇒ Likely involve the collision of CH_3Cl and OH^-

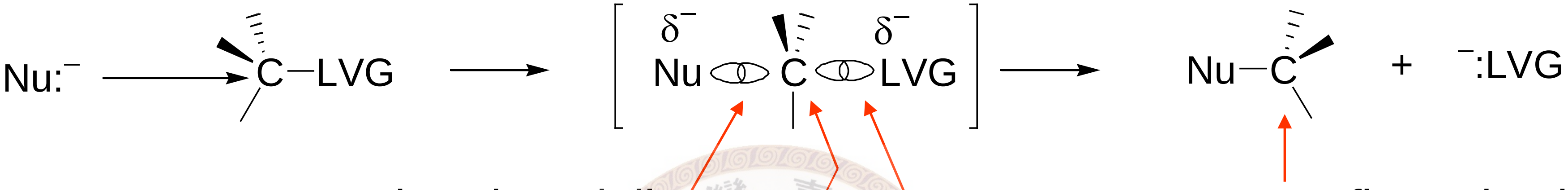
S_N2

substitution → S

nucleophilic → N

bimolecular → 2

★ Orientation: backside attack



bond partially formed

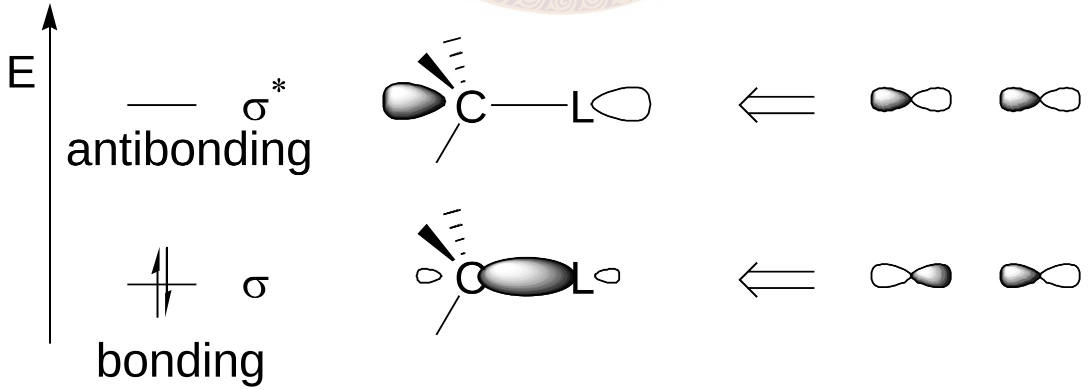
sp^2

bond partially broken

configuration is inverted

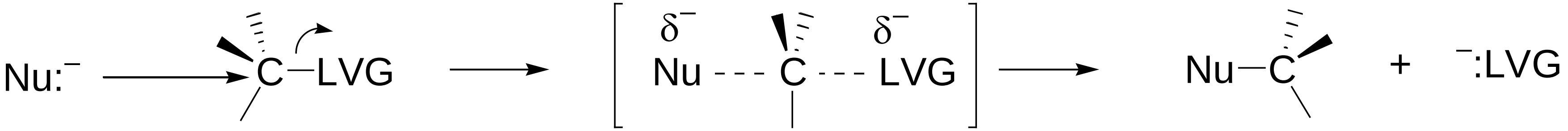
A concerted process:
bond breaking and bond formation occur at the same time

MO view:

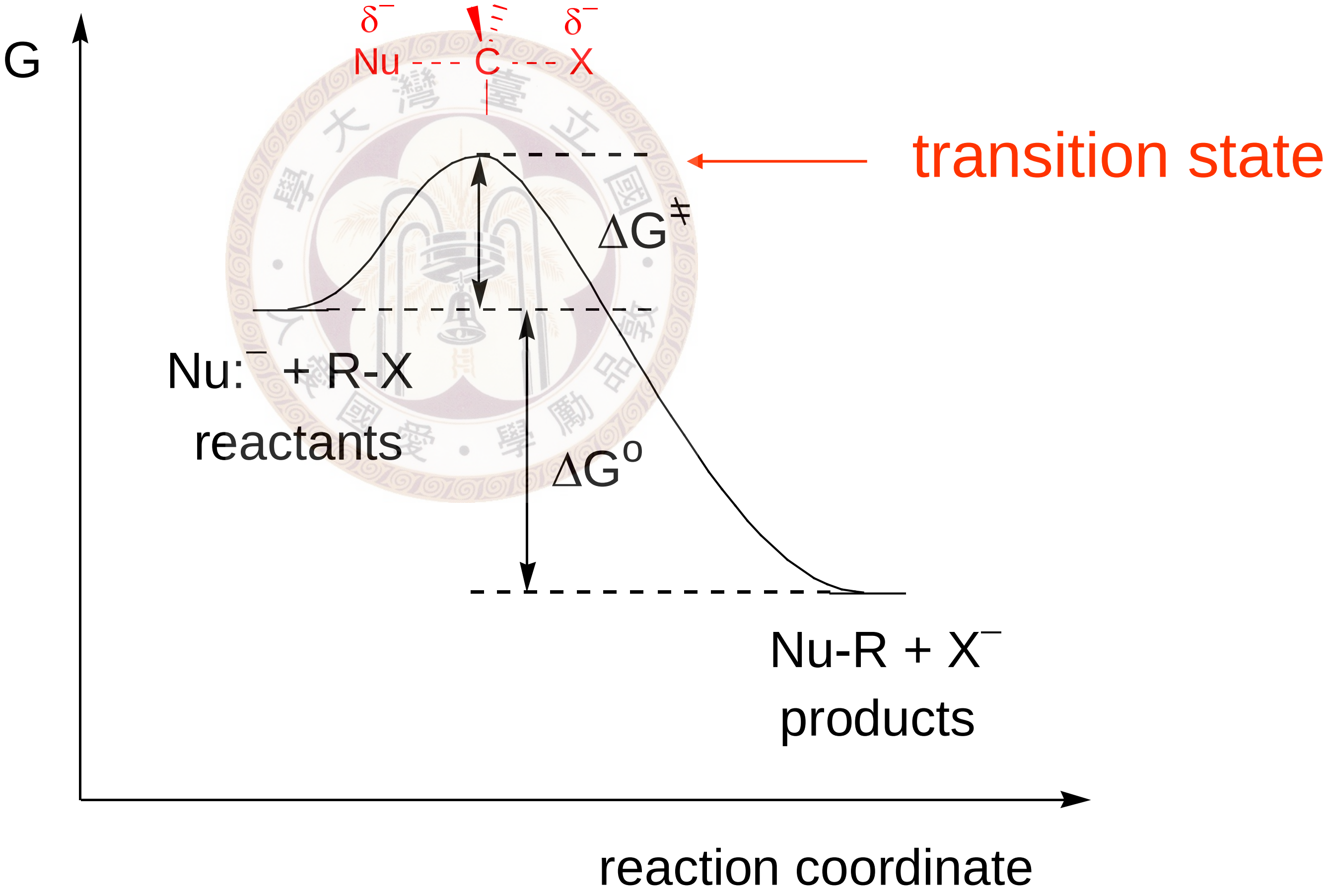


Nucleophile (electron rich) prefers to react with empty σ^* orbital

★★ Using arrows to represent electron flow ★★



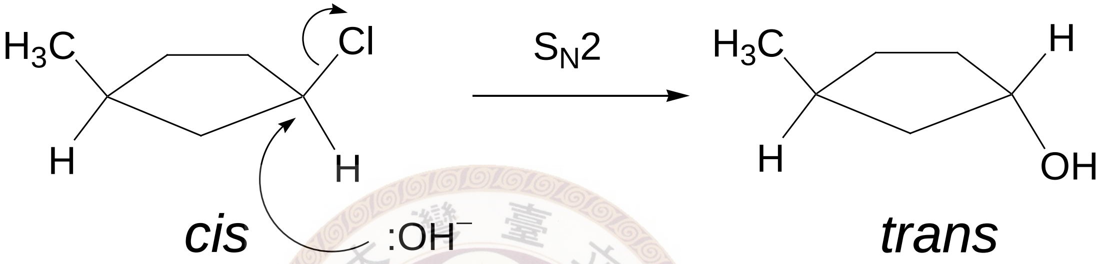
Energy profile:



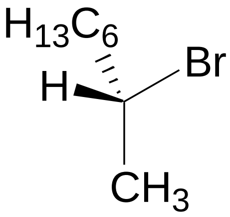
※ Stereochemistry of S_N2 reactions: inversion

Evidence:

●

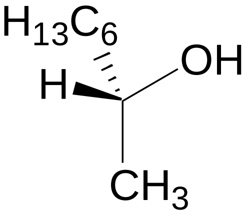


● Known:



$[\alpha]^{25}_{D} = -34.25^o$

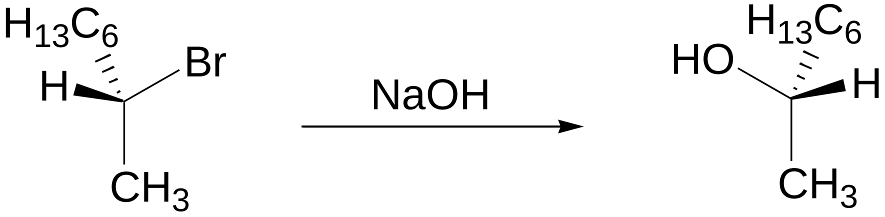
(*R*)-(–)-2-bromooctane



$[\alpha]^{25}_{D} = -9.90^o$

(*R*)-(–)-2-octanol

Experiment:



$[\alpha]^{25}_{D} = -34.25^o$

$[\alpha]^{25}_{D} = +9.90^o$

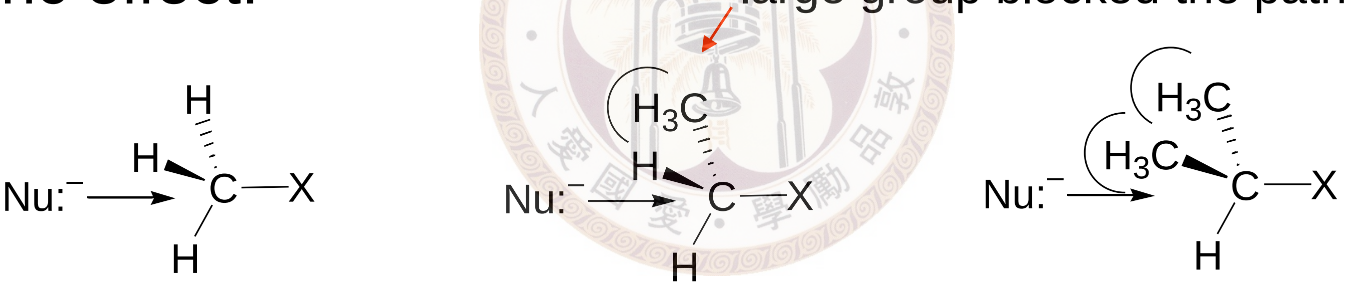
Complete inversion

※ Substrate: good or bad? (S_N2)

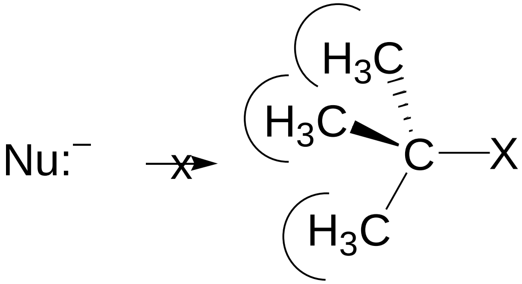
Relative rate of S_N2 reactions:

CH_3X	CH_3CH_2X	$(CH_3)_2CHX$	$(CH_3)_3CX$
30	1	0.02	~0

Steric effect:

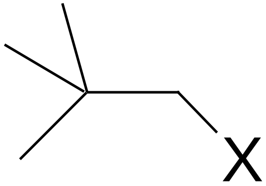


large group blocked the path of nucleophile



The steric hindrance is very high for tertiary halides

$(CH_3)_3CCH_2X$ $\equiv$



relative rate: 0.00001

Neopentyl halide: also very hindered

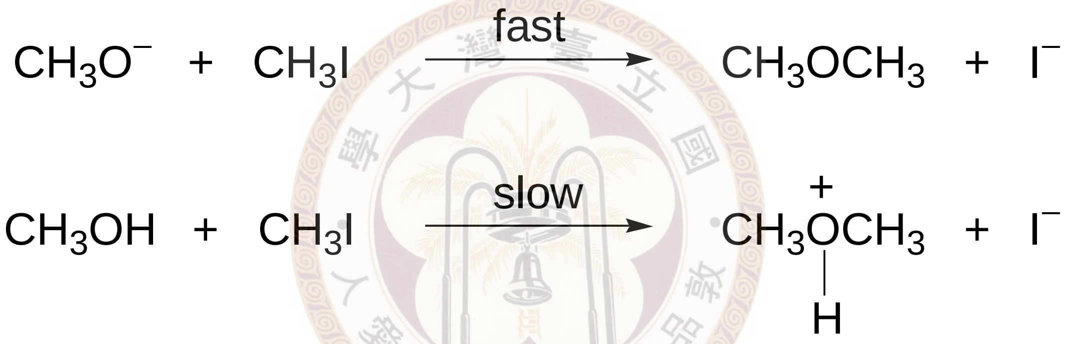
S_N2 reactivity:

Methyl > 1° > 2° > 3°

※ Nucleophiles: strong or weak?

Stronger nucleophile reacts faster

<1> Charged stronger than neutral (same atom)



$$CH_3O^- + CH_3I \xrightarrow{\text{fast}} CH_3OCH_3 + I^-$$

$$CH_3OH + CH_3I \xrightarrow{\text{slow}} CH_3\overset{+}{\underset{\substack{|\\H}}{O}}CH_3 + I^-$$

$CH_3O^- > CH_3OH$　　$OH^- > H_2O$

Same nucleophilic atom:

⇨ Nucleophilicity parallels basicity

$RO^- > HO^- >> RCOO^- > ROH > H_2O$

<2> In the same group: Size ↑ Nucleophilicity ↑

$I^- > Br^- > Cl^- > F^-$ (與鹼性相反)

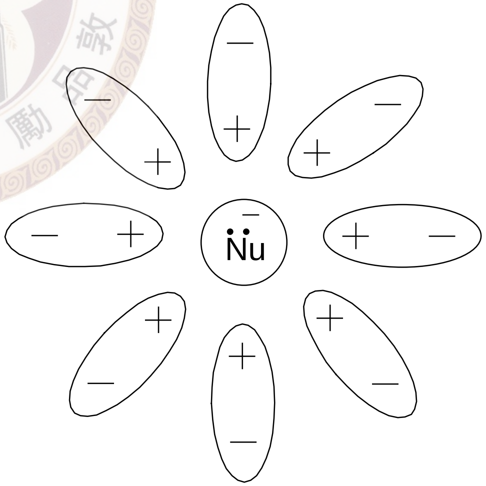
$RS^- > RO^-$

Reasons:

i size↑ solvation↓

nucleophile愈容易突破solvent的束縛

Solvation:



ii size↑ polarizability↑

ability to donate e⁻ ↑

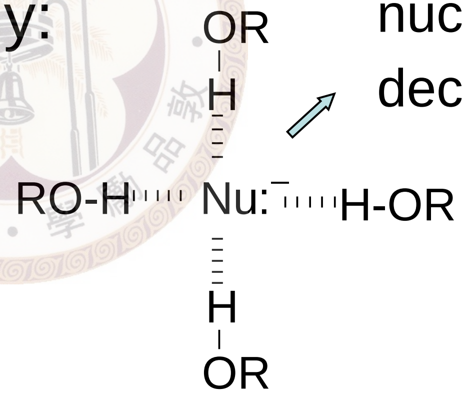
※ Solvent effects (S_N2)

◎ Polar protic solvents:

H_2O, CH_3CH_2OH, ……

hydrogen attached to a highly electronegative atom

solvate nucleophiles strongly:



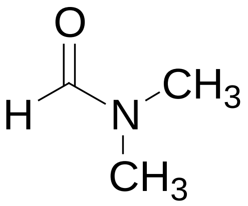
nucleophilicity decreases

Relative nucleophilicity in protic solvent:

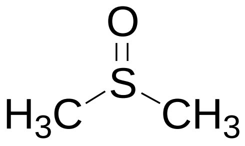
$HS^- > {}^-CN > I^- > OH^- > N_3^- > Br^- > CH_3CO_2^- > Cl^- > F^- > H_2O$

weak solvation

◎ Polar aprotic solvents

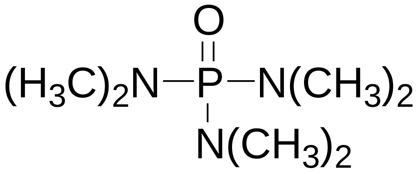


N,*N*-dimethylformamide
(DMF)



$H_3C{-}S({=}O){-}CH_3$

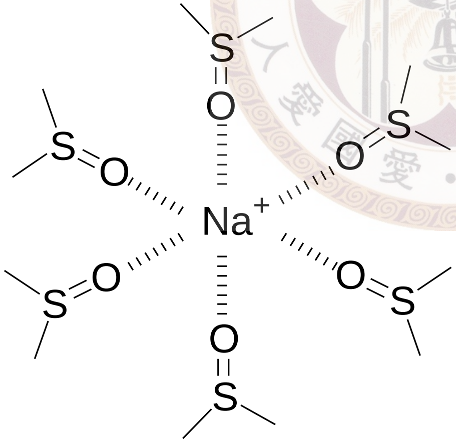
dimethyl sulfoxide
(DMSO)



$(H_3C)_2N{-}P({=}O)(N(CH_3)_2){-}N(CH_3)_2$

hexamethylphosphoramide
(HMPA)

Solvate cations but not anions



$Nu:^-$ ← naked
(not solvated)
very reactive

例 In DMSO: $F^- > Cl^- > Br^- > I^-$

↑ most basic

◎ Nonpolar solvents

Not important due to solubility problem

★ S_N1 reaction mechanism

例

$$(CH_3)_3C\text{-}Cl + {}^{-}OH \xrightarrow[H_2O]{\text{acetone}} (CH_3)_3C\text{-}OH + Cl^{-}$$

$$\text{Rate} \propto [t\text{-BuCl}]$$

$$\text{Rate} = k\,[t\text{-BuCl}]$$

A first order reaction: unimolecular

Rate has nothing to do with nucleophile

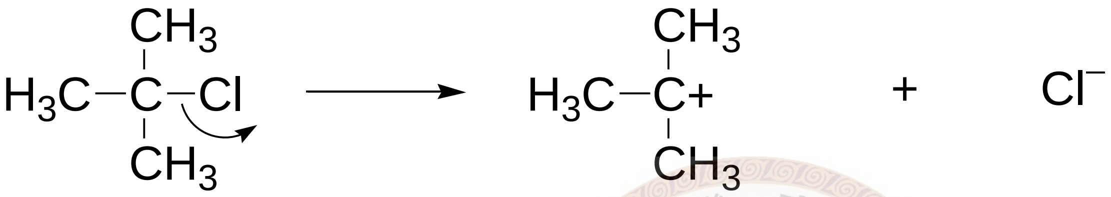
S_N1

↑

unimolecular

◎ Mechanism of S_N1 reaction: A stepwise process

Step 1



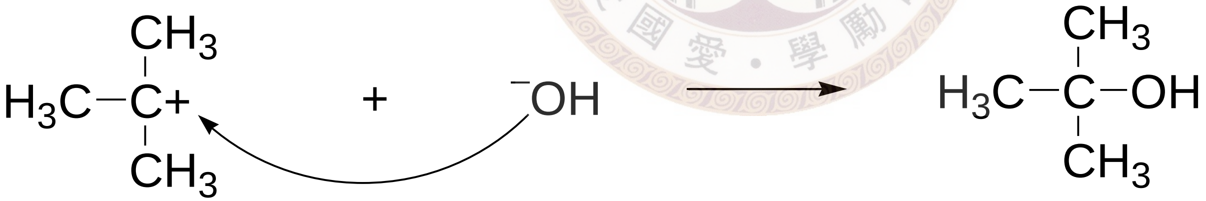
$$H_3C-\overset{CH_3}{\underset{CH_3}{C}}-Cl \longrightarrow H_3C-\overset{CH_3}{\underset{CH_3}{C}}{+} \quad + \quad Cl^-$$

slow

a carbocation
highly reactive intermediate

1. Only bond breaking
2. Formation of a high energy species
3. Charge separation

Step 2



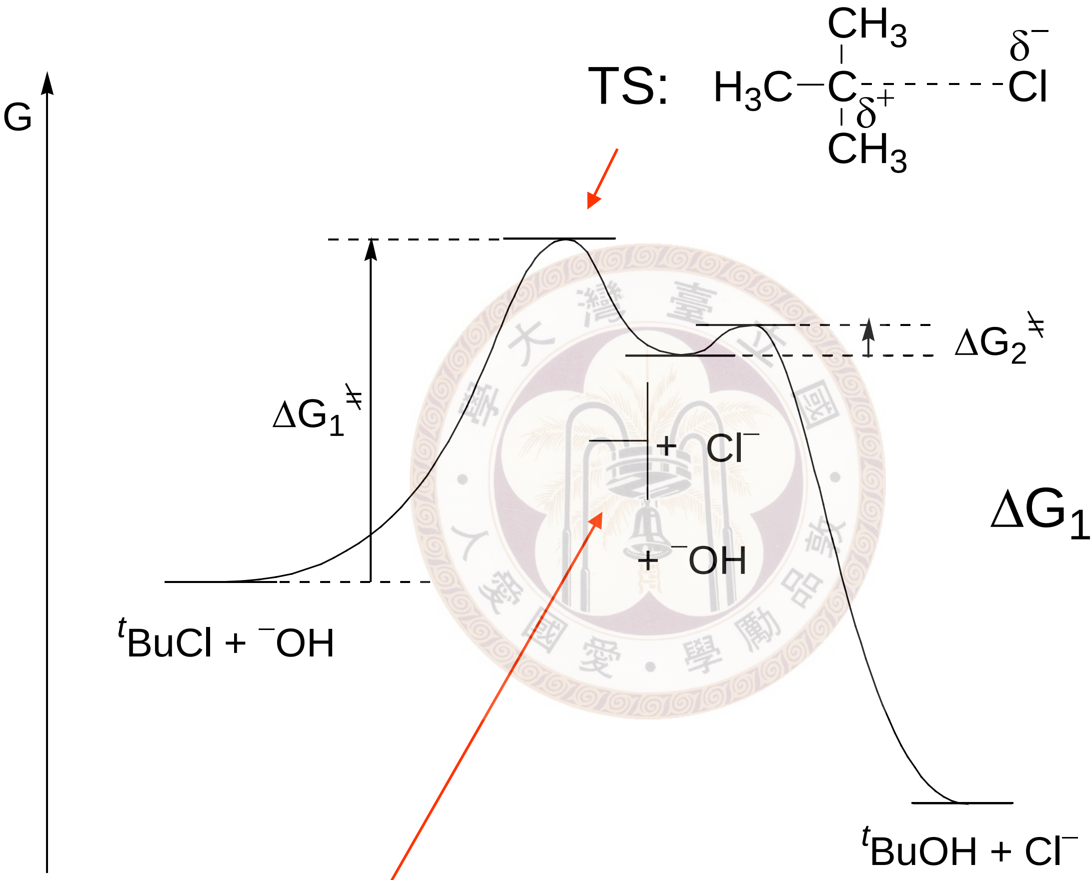
$$H_3C-\overset{CH_3}{\underset{CH_3}{C}}{+} \quad + \quad {}^-OH \longrightarrow H_3C-\overset{CH_3}{\underset{CH_3}{C}}-OH$$

fast

1. Only bond forming
2. Charge combination

The slowest step is the rate determining step (RDS)
The rate is only dependent on *t*-butyl chloride

◎ Energy profile of S_N1 reaction

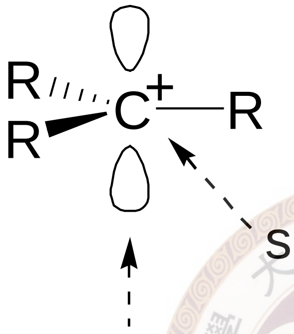


$\Delta G_1^{\ddagger} >> \Delta G_2^{\ddagger}$

Intermediate
not transition state

※ Carbocations

◎ Structure



sp^2

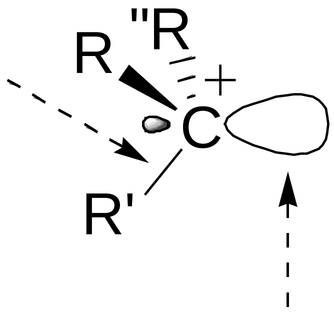
trigonal planar

empty p orbital ←

Better than using sp^3 orbital
Has less s character
Less electronegativity
More s used in bonding

Compare with: tetrahedral structure

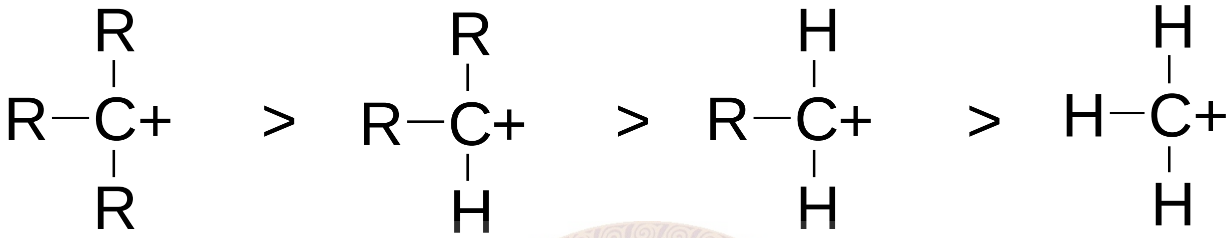
sp^3 used in bonding



← Not as good as above

empty sp^3

◎ Relative stability



$$R_3C^+ > R_2CH^+ > RCH_2^+ > CH_3^+$$

3^o 2^o 1^o methyl

most stable least stable

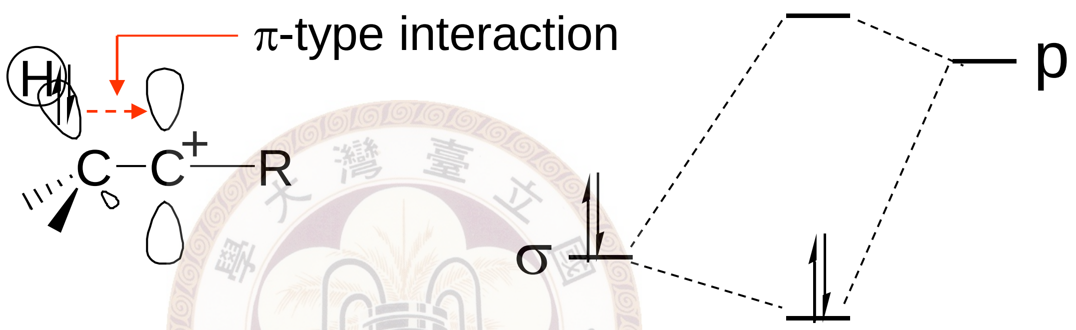
Reason:

Alkyl groups are considered as weak electron donating

→ More R groups, more stabilization

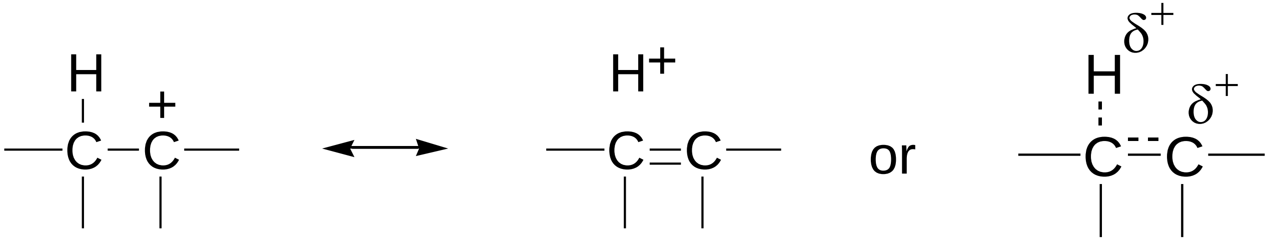
Why is alkyl group electron donating?

Hyperconjugation:



Weak π-type interaction between the filled σ orbital with the empty p orbital
(as if donating e⁻ from filled σ to empty p)

Valence bond view:



※ Substrate: good or bad? (S_N1)

Relative rate for S_N1:

$3^o > 2^o > 1^o >$ Methyl

Parallel carbocation stablity
But why?

Recall the rate determining step:

$$R\text{-}X \rightarrow R^+ + X^-$$

Wrong reason:

More stable carbocation → Faster reaction

★ Rate depends on activation energy, not product stability

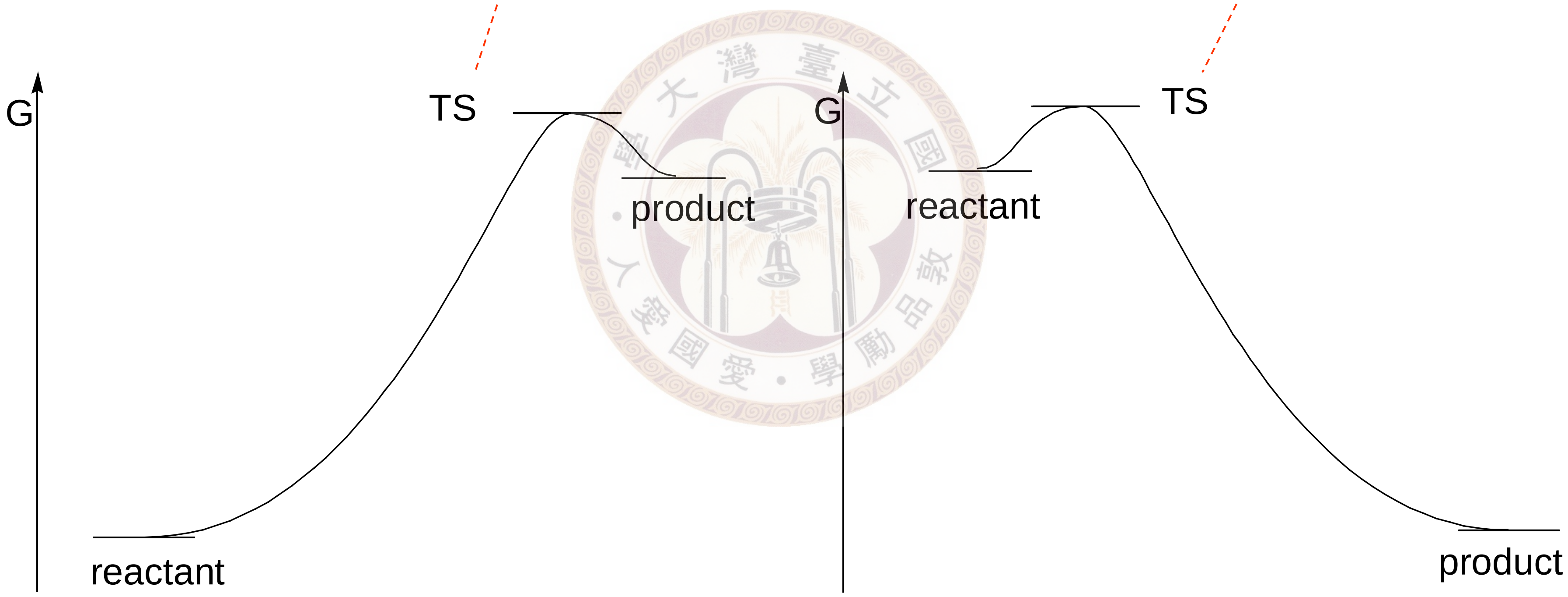
To estimate E_a, we need to know the TS energy

◎ How to estimate transition state energy?

Hammond-Leffler postulate:

For a highly endothermic reaction
TS structure mimics the product

For a highly exothermic reaction
TS structure mimics the reactant



Now for an highly endothermic reaction, we can use the product stability to estimate transition state energy

The rate determining step of S_N1:

$R\text{-}X \rightarrow R^+ + X^-$ highly endothermic

More stable carbocation

→ More stable TS
(TS has very high carbocation character)

→ Smaller E_a

→ Faster reaction

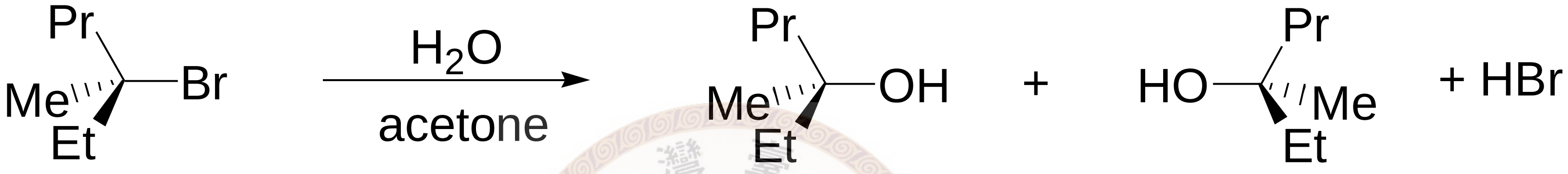
Relative rate for S_N1:

$3^o > 2^o > 1^o >$ Methyl

Tertiary substrate reacts faster

※ Stereochemistry of S_N1 reactions: racemization

Experiment:



one enantiomer
(optically active)

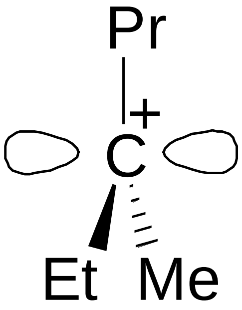
retention

inversion

1:1
a racemate
(optically inactive)

Reason:

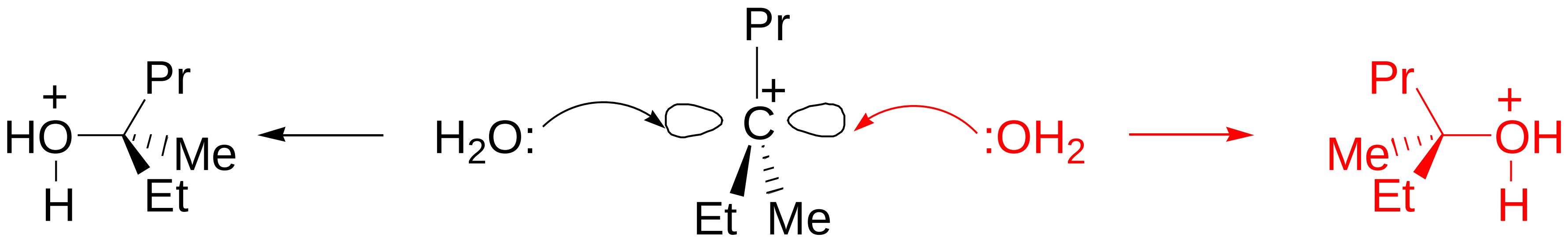
go through a trigonal planar carbocation



Has a plane of symmetry

⇨ Achiral (chirality lost)

⇨ Optical activity is lost



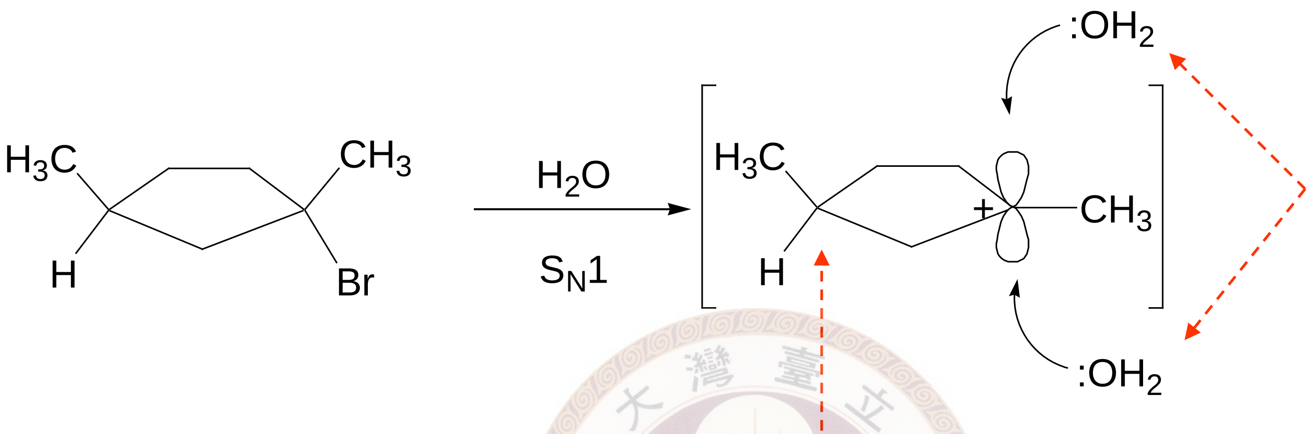
Attack of H_2O: equal rate from both faces
(the two approaches are enantiomeric)

★★ Important lesson:

Optically active product can not be obtained from optically inactive starting materials

Optically active product may be obtained from optically active starting materials

◎ S_N1 in the presence of another chiral center



diastereotopic approaches

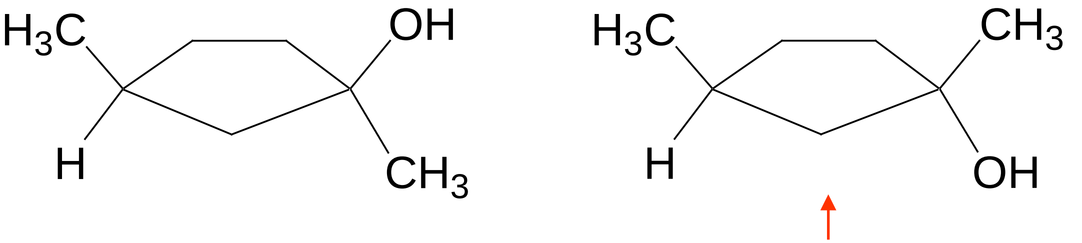
another chiral center

No plane of symmetry for the carbocation

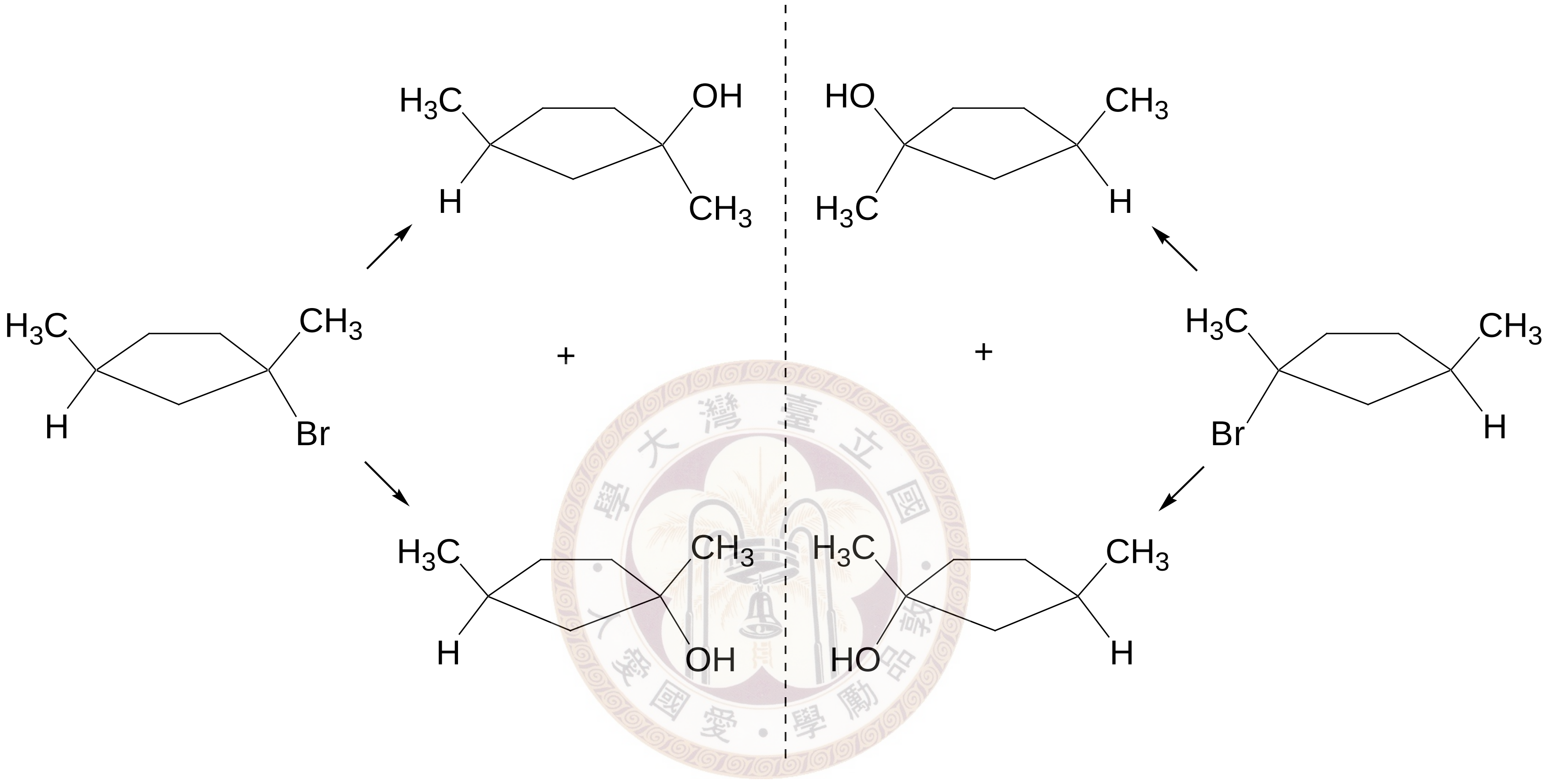
⇨ The two approaches are diastereomeric

⇨ The energy may be different

Obtain two diastereomeric products:



Expected to be major due to steric effect


H3C
OH
H
CH3
HO
CH3
H3C
H
H3C
CH3
H
Br
+
+
H3C
CH3
Br
H
H3C
CH3
H
OH
H3C
CH3
HO
H

◎ Solvolysis

When solvent is the nucleophile: solvolysis

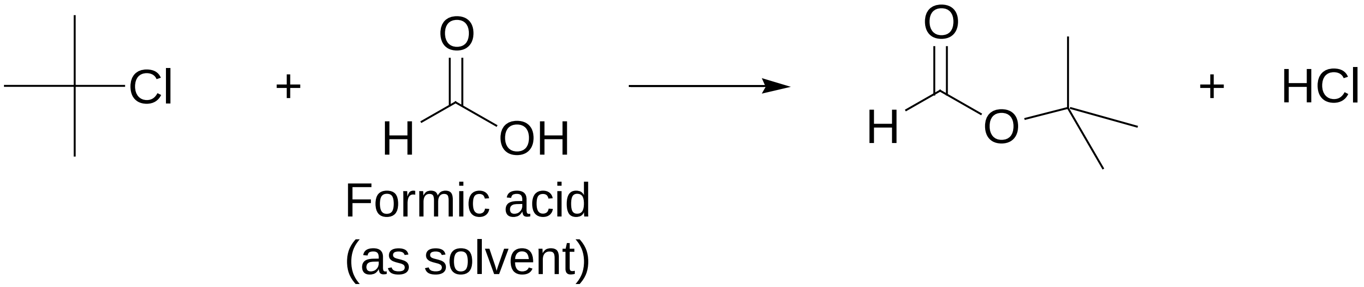
Hydrolysis:

$t\text{-BuBr} + H_2O \rightarrow t\text{-BuOH} + HBr$

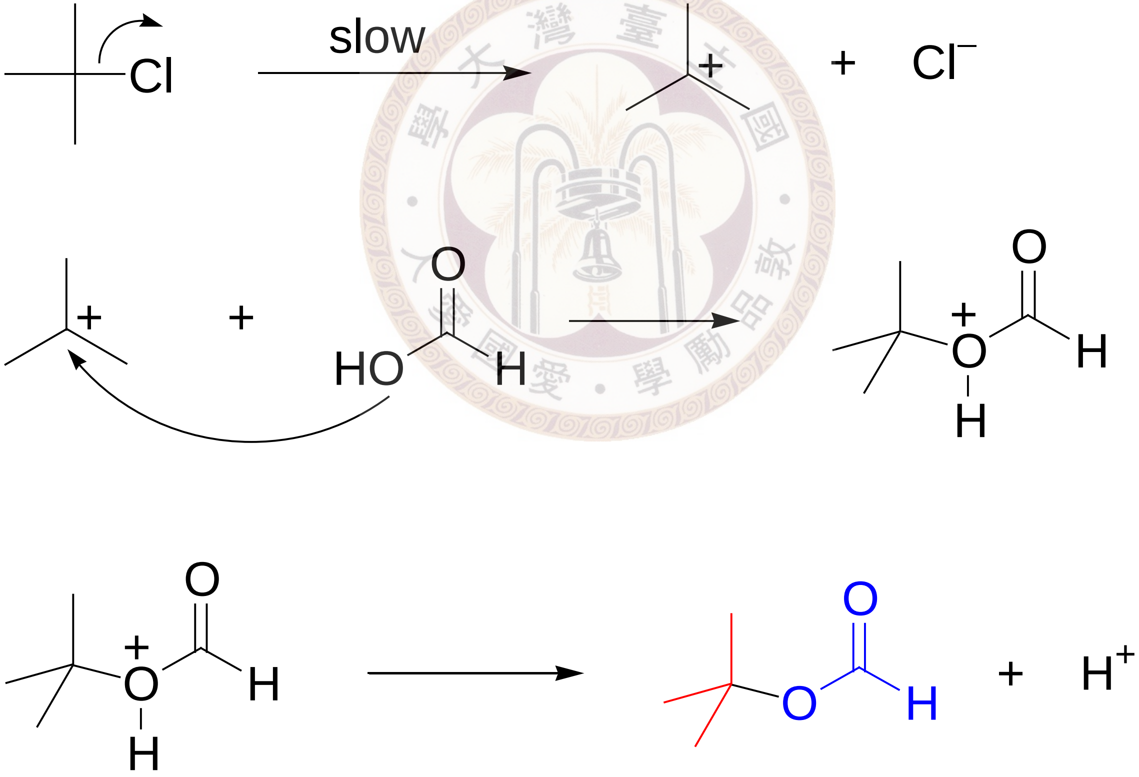
Methanolysis:

$t\text{-BuCl} + CH_3OH \rightarrow t\text{-BuOCH}_3 + HCl$

例


Cl
+
O
H
OH
Formic acid
(as solvent)
O
H
O
+
HCl

Mechanism:


Cl
slow
+
+
Cl⁻
+
+
O
HO
H
+
O
O
H
H
O
+
O
H
H
O
O
H
+
H⁺

※ Effect of nucleophile (S_N1)

Key concept:

Nucleophile not involved in RDS

→ No effect

※ Solvent effects (S_N1)

Key concept:

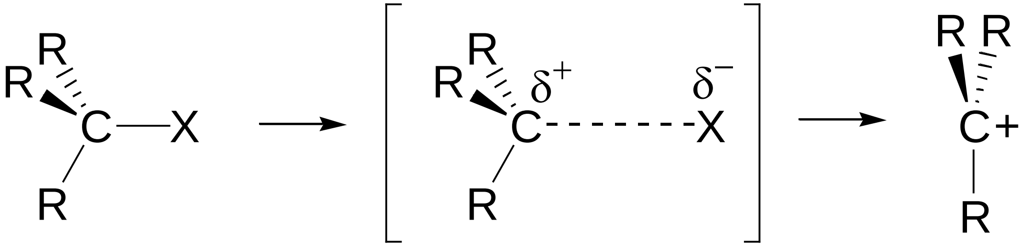
Charge separation is involved in RDS

Faster in polar solvent

Reasons:

- Polar solvent has higher ionizing power
  (dielectric constant is high)
  介電常數

- TS is more stabilized through solvation, $\Delta G^{\ddagger}$ lower

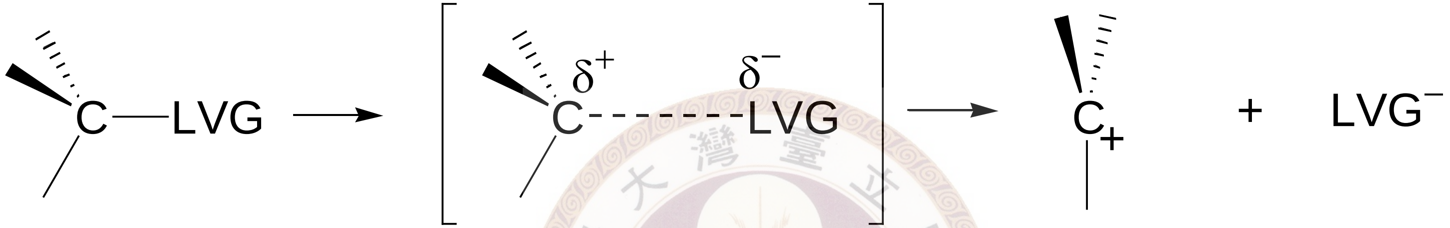


TS

has very high charge separation

※ The nature of leaving group

S_N1:



S_N2:

Key concept:

In both transition states:

negative charge developed on LVG

Better ability to stabilize negative charge

⟹ Better LVG

例 $I^- > Br^- > Cl^- \gg F^-$

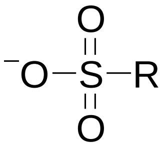
⟹ Weaker base → Better LVG

Recall:

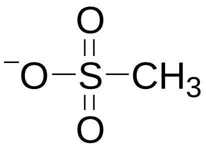
$$\underset{\text{acid}}{HA} \rightleftharpoons H^+ + \underset{\text{base}}{A:^-}$$

◎ Some other important good leaving groups

Sulfonates

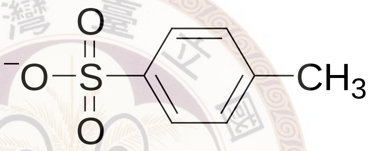


$^{-}O-S(=O)_2-R$



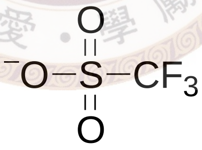
$^{-}O-S(=O)_2-CH_3$ ≡ ^{-}OMs

methanesulfonate
(mesylate)



≡ ^{-}OTs

p-toluenesulfonate
(tosylate)

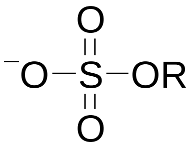


$^{-}O-S(=O)_2-CF_3$ ≡ ^{-}OTf

trifluoromethanesulfonate
(triflate)

A super LVG

Sulfates

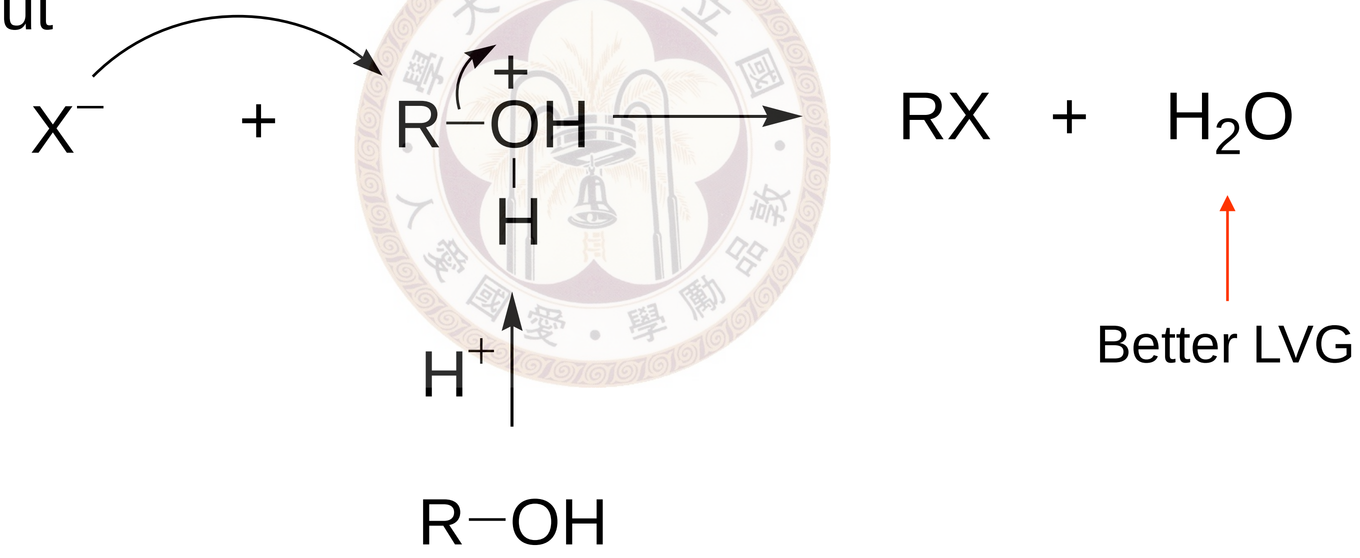


$^{-}O-S(=O)_2-OR$

H_2O is a better LVG than ${}^-OH$

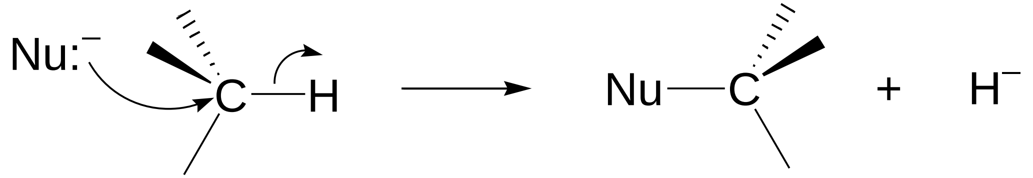
$$X^- + ROH \xrightarrow{\times} RX + {}^-OH$$

But

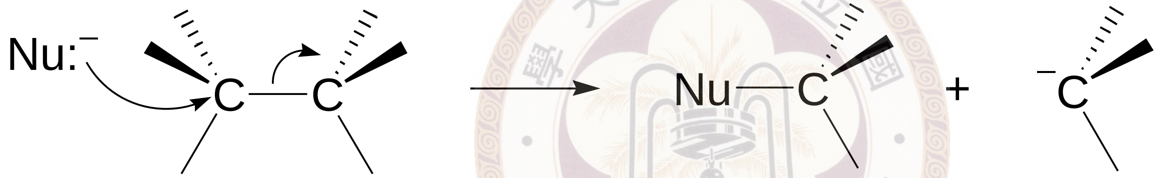


$$X^- + R-\overset{+}{O}H \rightarrow RX + H_2O$$

Common mistakes for beginners:

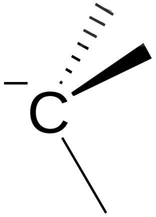


NO!



NO!

H^- and



are strong bases

⇨ bad LVGs

hydride

a carbanion

※ S_N1 vs S_N2

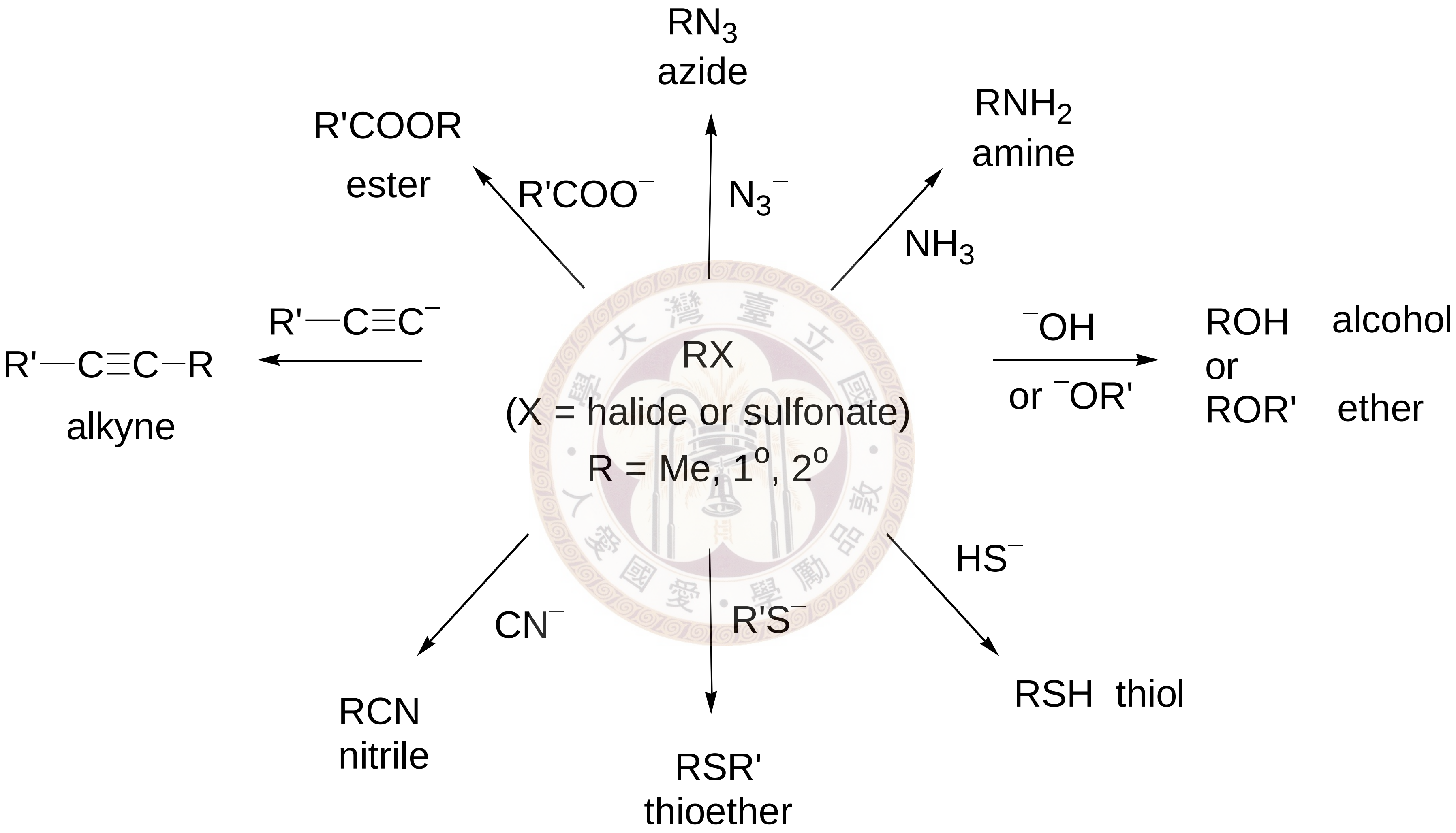
In general: $\underset{S_N1}{3^o} \quad \underbrace{2^o \quad 1^o \quad \text{methyl}}_{S_N2}$

*Never S_N2 for 3^o

S_N1 prefers:	stabilized carbocation polar solvent weak nucleophile good LVG
*Stereochemistry:	racemization

S_N2 prefers:	less steric hindrance polar aprotic solvent strong nucleophile (high conc. is better) good LVG
*Stereochemistry:	inversion

S_N2 reactions are useful in functional group transformations



RX

(X = halide or sulfonate)

R = Me, 1^o, 2^o

N_3^- → RN_3 azide

NH_3 → RNH_2 amine

^-OH or $^-OR'$ → ROH alcohol or ROR' ether

HS^- → RSH thiol

$R'S^-$ → RSR' thioether

CN^- → RCN nitrile

$R'—C{\equiv}C^-$ → $R'—C{\equiv}C—R$ alkyne

$R'COO^-$ → R'COOR ester

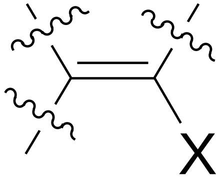
例 Finkelstein reaction:

$$\begin{array}{c}\text{RCl}\\ \text{or}\\ \text{RBr}\end{array} \xrightarrow[\text{acetone}]{\text{NaI}} \text{RI} + \left.\begin{array}{c}\text{NaCl}\\ \text{or}\\ \text{NaBr}\end{array}\right\}$$

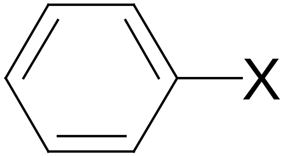
Insoluble in acetone; reaction is driven to the right-hand side

◎ Vinylic and phenyl halides:

unreactive in S_N1 or S_N2 reactions



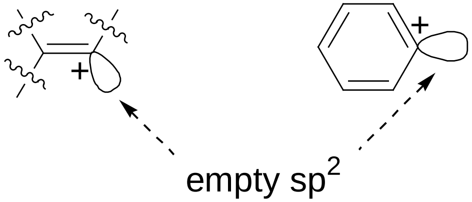
vinylic halide



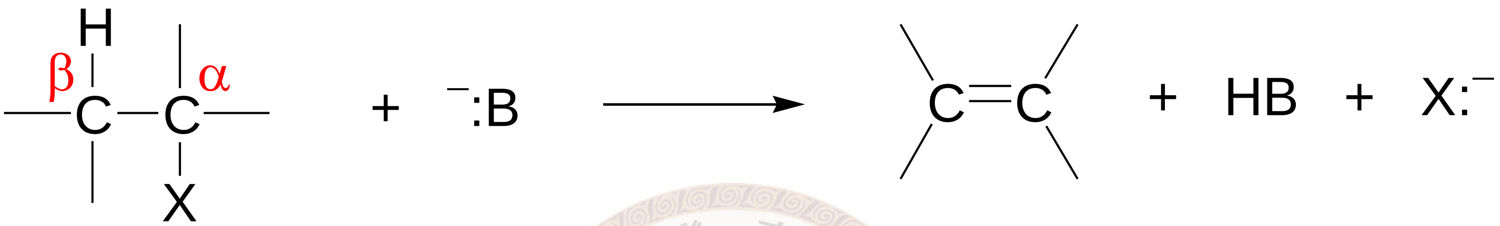
phenyl halide

Reasons:

- Stronger bond:
  carbon uses sp^2 orbital which has higher s character
  → hard to break (bad for S_N1 and S_N2)
- Backside is blocked (phenyl halide) or hindered (vinylic halide)
  (bad for S_N2)
- Vinyl carbocation and phenyl carbocation are less stable:
  empty sp^2 orbital which has higher s character
  (bad for S_N1)

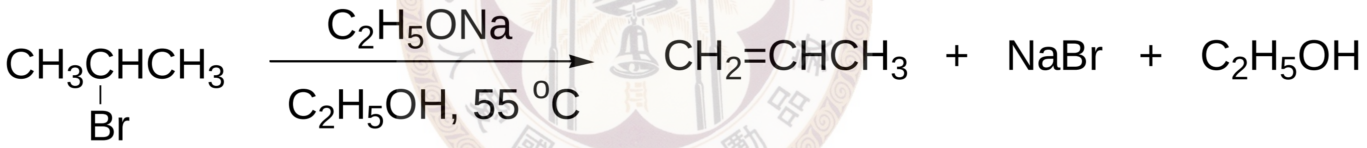


※ Elimination reactions (消去反應): dehydrohalogenations

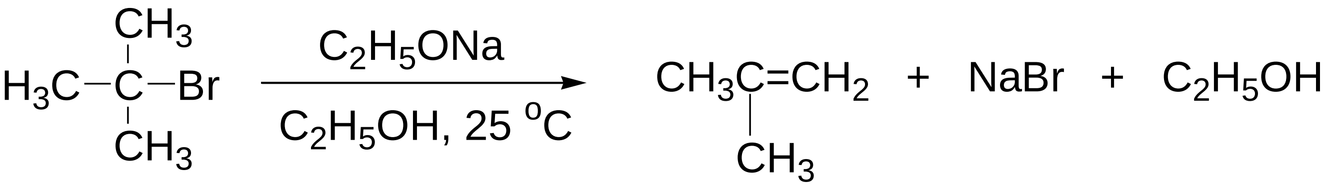


A β-elimination or 1,2-elimination reaction

例



$CH_3\underset{\underset{Br}{|}}{C}HCH_3 \xrightarrow[C_2H_5OH,\ 55\ ^oC]{C_2H_5ONa} CH_2{=}CHCH_3 + NaBr + C_2H_5OH$



$H_3C-\overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{C}}-Br \xrightarrow[C_2H_5OH,\ 25\ ^oC]{C_2H_5ONa} CH_3\underset{\underset{CH_3}{|}}{C}{=}CH_2 + NaBr + C_2H_5OH$

◎ The base

✓ $2ROH + 2Na \longrightarrow 2R\overset{-}{O}\overset{+}{Na} + H_2\uparrow$

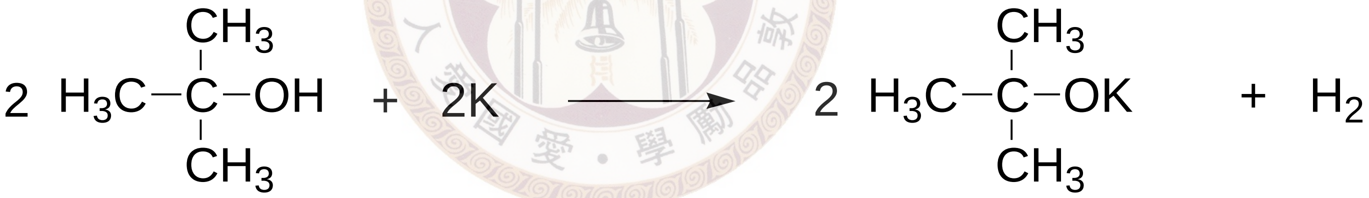
sodium
alkoxide

(an oxidation-reduction reaction)

例 $2CH_3CH_2OH + 2Na \longrightarrow 2CH_3CH_2ONa + H_2$

used in excess
(as solvent)

sodium
ethoxide ≡ NaOEt or EtONa



$$2\ H_3C-\underset{CH_3}{\overset{CH_3}{C}}-OH + 2K \longrightarrow 2\ H_3C-\underset{CH_3}{\overset{CH_3}{C}}-OK + H_2$$

potassium
tert-butoxide ≡ *t*-BuOK

✓ $ROH + NaH \longrightarrow RONa + H_2$

sodium
hydride
(a strong base)

※ The mechanism: E1 and E2

◎ E2

$$\underset{\text{Br}}{CH_3\overset{}{C}HCH_3} + {}^{-}OEt \longrightarrow CH_2{=}CHCH_3 + Br^{-} + EtOH$$

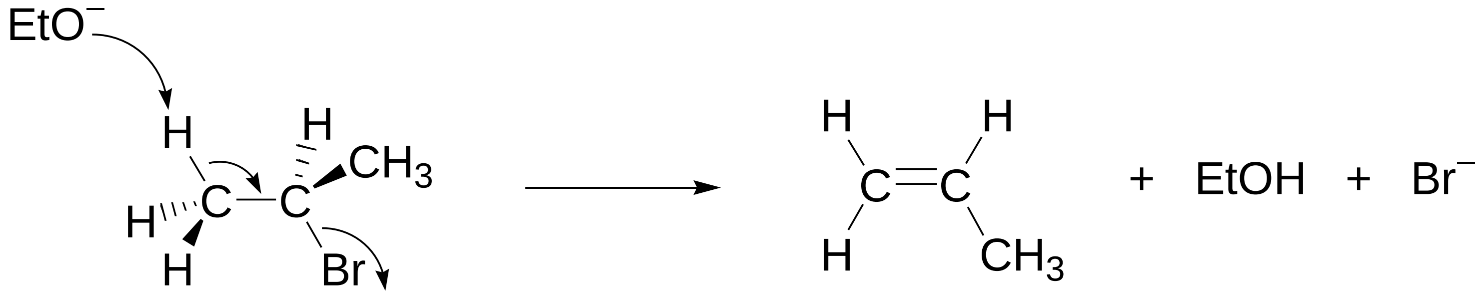
$$\text{Rate} \propto [CH_3CHBrCH_3][EtO^{-}]$$

$$\text{Rate} = k\,[CH_3CHBrCH_3][EtO^{-}]$$

A bimolecular elimination reaction (E2):

likely involves the collision of the two

★ E2 mechanism

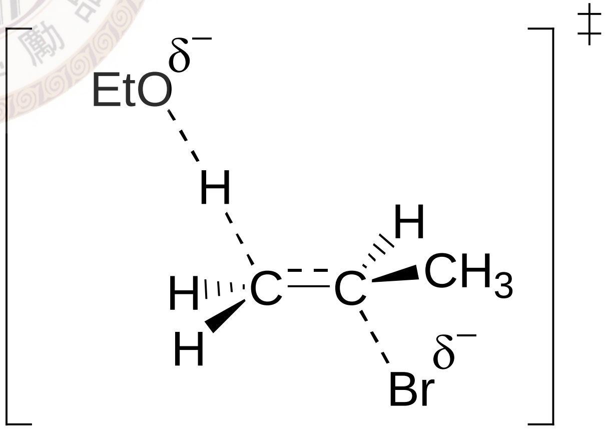


☆ Stereochemical requirement:

antiperiplanar for C-H and C-Br

(反式共平面)

Transition state:

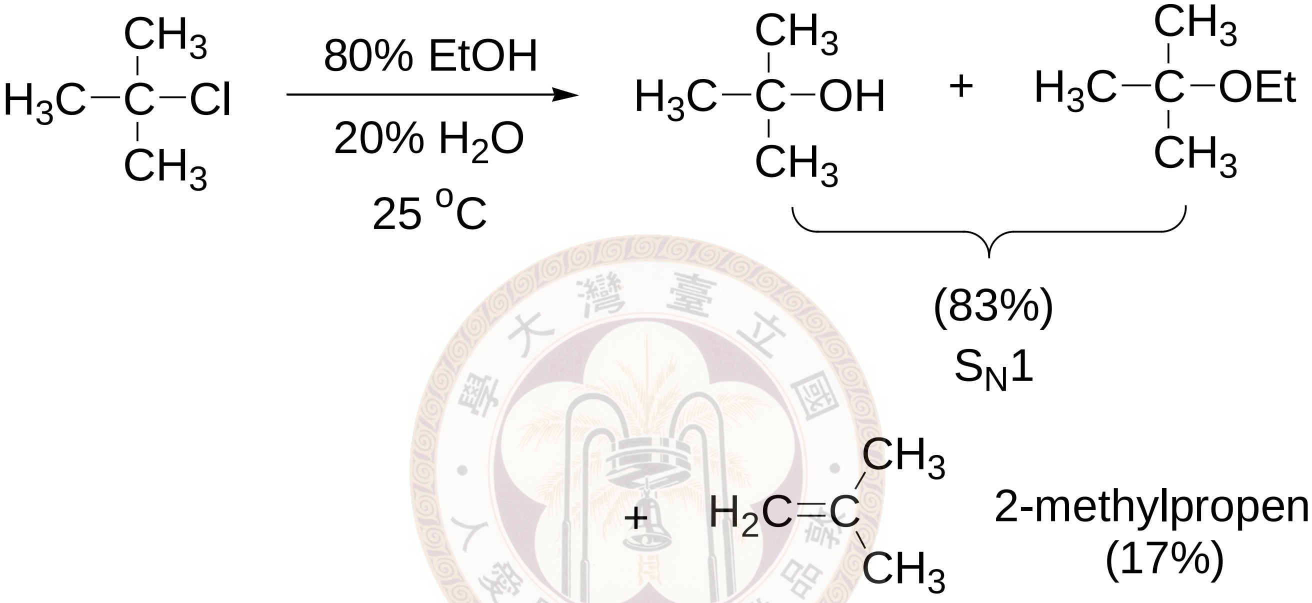


Partial bond breaking: C-H, C-Br

Partial bond formation: O-H, π

The reason for the stereochemical requirement is obvious

◎ E1



$$(CH_3)_3C{-}Cl \xrightarrow[\text{20\% } H_2O,\ 25\ ^{o}C]{\text{80\% EtOH}} \underbrace{(CH_3)_3C{-}OH + (CH_3)_3C{-}OEt}_{(83\%)\ S_N1} + H_2C{=}C(CH_3)_2$$

(83%)
S_N1

2-methylpropene
(17%)

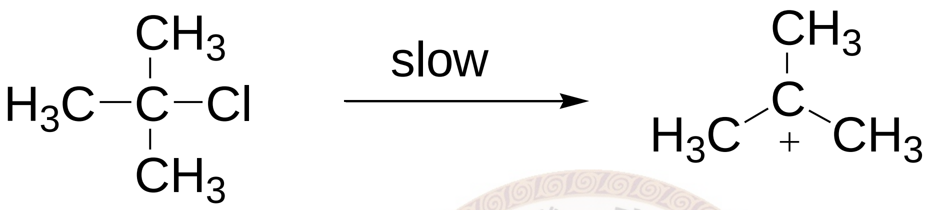
$$\text{Rate}_{\text{elim}} \propto [t\text{-BuCl}]$$

$$\text{Rate}_{\text{elim}} = k\,[t\text{-BuCl}]$$

An unimolecular elimination process → E1

★ E1 mechanism

Step 1



Step 2

The nature and concentration of the base is not important for E1

Stability of carbocation is important for E1

★ Substitution vs elimination

- ✓ 1^o halides

S_N2 vs E2

(1^o carbocation is not stable: S_N1 and E1 not possible)

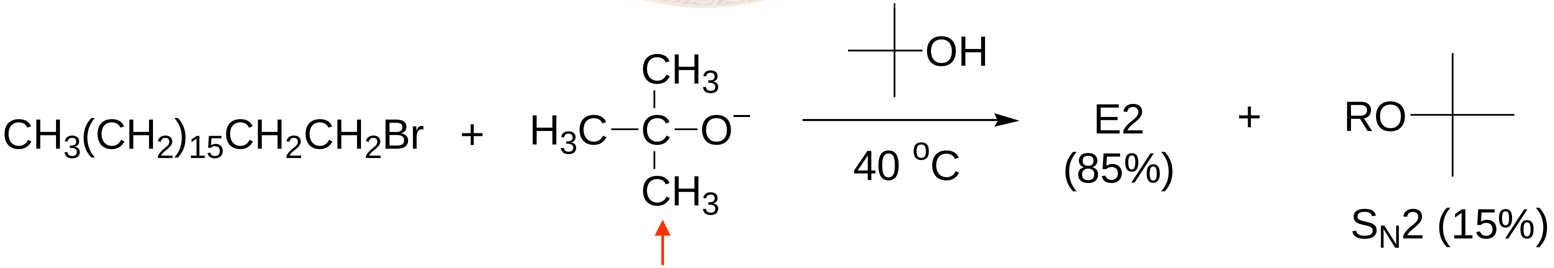
In general: S_N2 unless strong and hindered base is used

$$CH_3(CH_2)_{15}CH_2CH_2Br + CH_3O^- \xrightarrow[65\ ^oC]{CH_3OH} CH_3(CH_2)_{15}CH_2CH_2OCH_3$$

S_N2 (99%)

$+ \ CH_3(CH_2)_{15}CH{=}CH_2$

E2 (1%)



$$CH_3(CH_2)_{15}CH_2CH_2Br + H_3C{-}\overset{\displaystyle CH_3}{\underset{\displaystyle CH_3}{C}}{-}O^- \xrightarrow[40\ ^oC]{\text{(CH}_3)_3\text{COH}} \text{E2 (85\%)} + RO{-}C(CH_3)_3 \ \text{S}_N2\ (15\%)$$

A hindered base (bulky base)

Prefers to attack smaller H but not larger C (from backside)

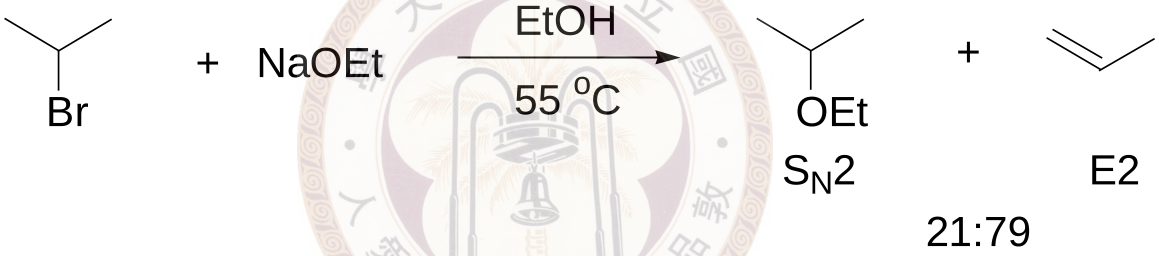
- ✓ 2^o halides

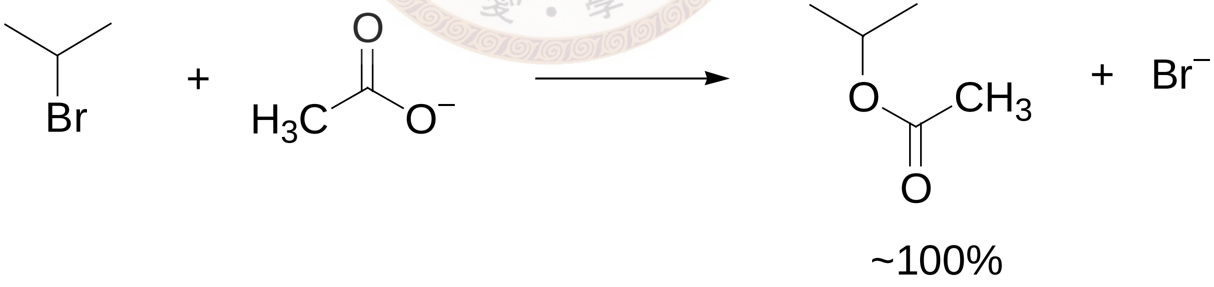
S_N2 vs E2

(2^o carbocation is not stable: S_N1 and E1 not easy)

Weak base: S_N2 (例: $RCOO^-$)

Strong base: E2 (例: RO^-)





Recall: there are weak bases but strong nucleophiles

RS^-, I^- → favor S_N2

- ✓ 3° halides

S_N1 vs (E1 + E2)

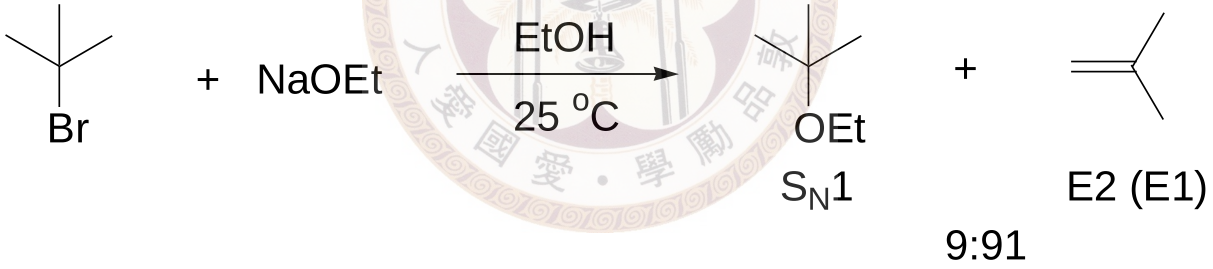
(S_N2 not possible for steric reason; E2 has no steric effect)

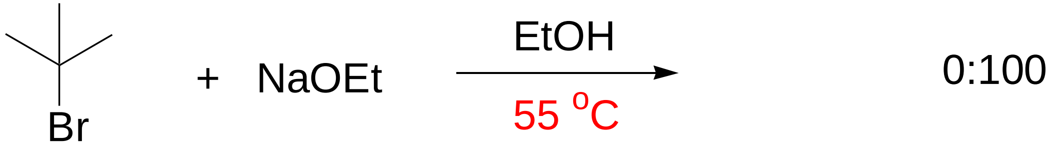
Weak base: S_N1 preffered over E1

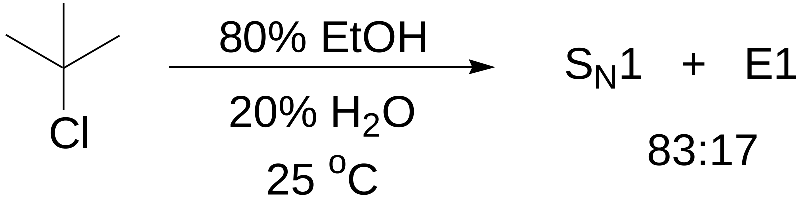
Strong base: (E1 + E2) preferred over S_N1

High T favors elimination

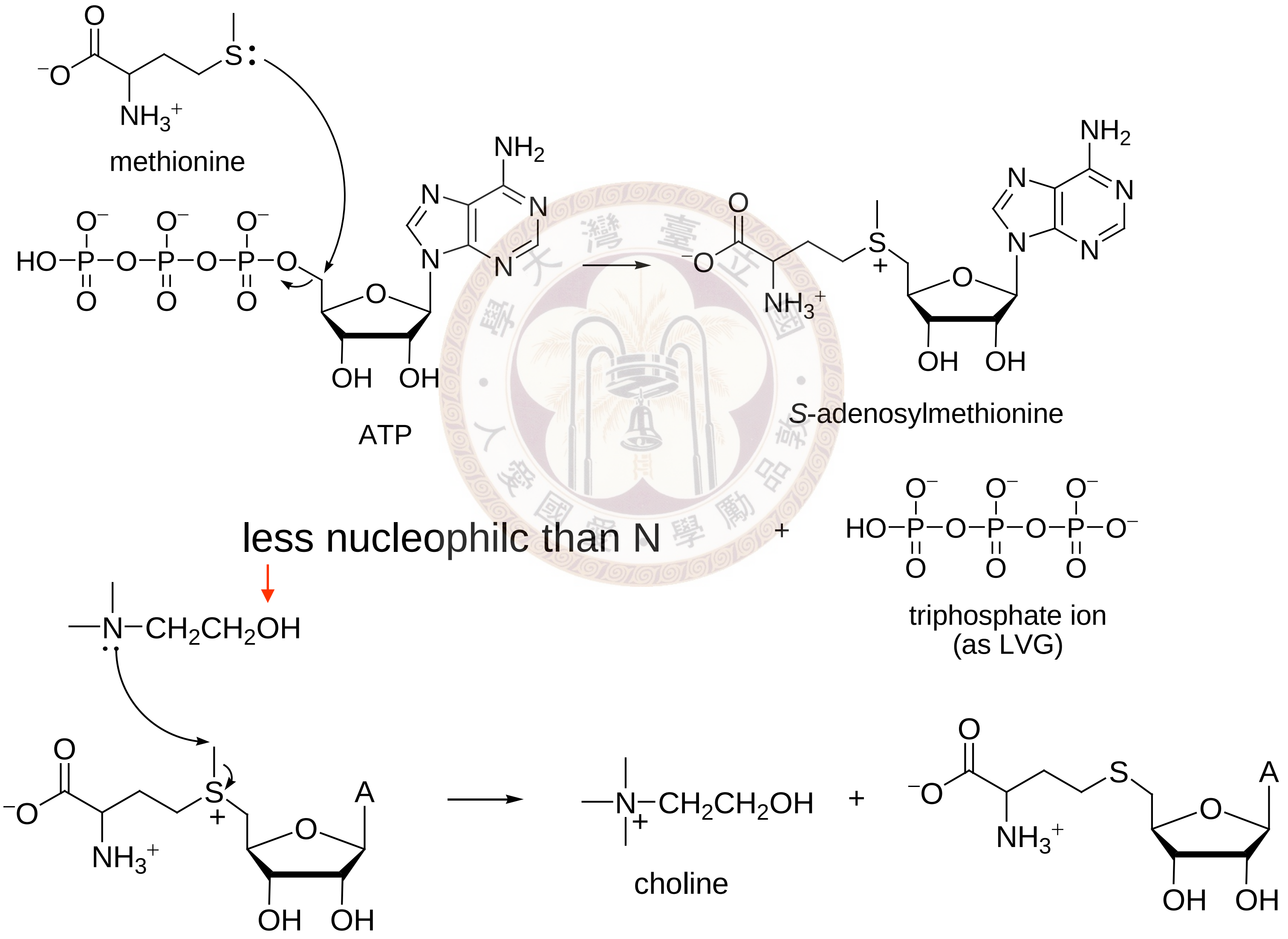
Reason: entropy is more positive for elimination ($\Delta G = \Delta H - T\Delta S$)







※ Biological relevance



less nucleophilc than N