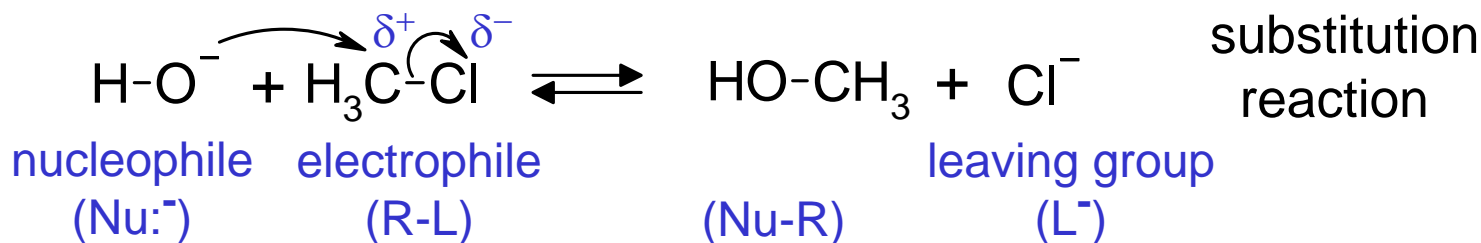
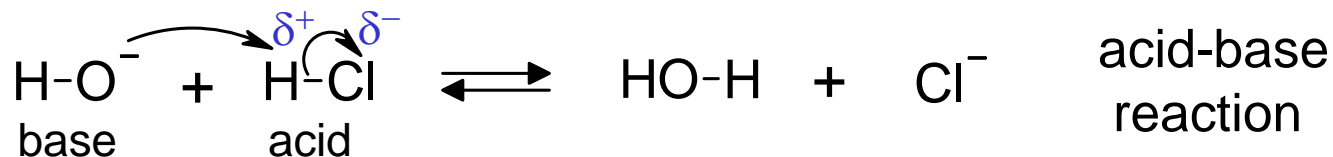


Chapter 8 Nucleophilic Substitutions

□ What to master

- ◆ Two Mechanisms of Substitution Reactions: S_N2 & S_N1
- ◆ Factors Controlling the Reactivities of Nucleophiles and Leaving Groups
- ◆ Factors Controlling the Substitution Reaction Rates
- ◆ Predicting Which Reaction Mechanism Will Occur
- ◆ Predicting the Products of Substitution Reactions
- ◆ Predicting the Stereochemistry of the Products
- ◆ Recognizing the Products from Competing Reactions
- ◆ Recognizing When a Rearrangement Reaction Occurs

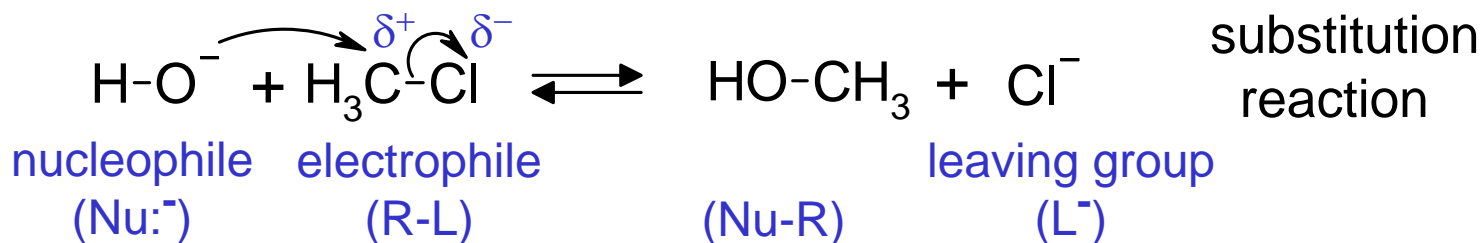
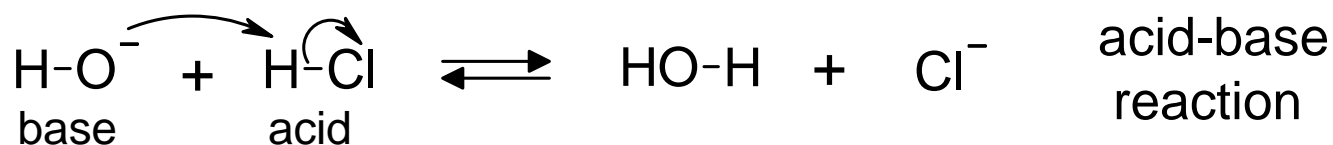
Chapter 8 Nucleophilic Substitutions (I)



□ Reaction mechanisms: S_N1 / S_N2

- ◆ bond-breakage first, then bond-formation
- ◆ bond-formation first, then bond-breakage
- ◆ simultaneous bond-breakage & bond-formation

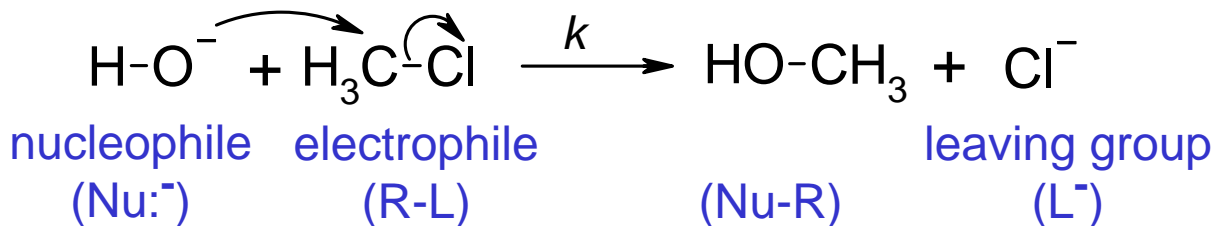
Nucleophilic Substitutions (II)



□ Proof for the mechanism: S_N1 / S_N2

- ◆ rate law & competing reactions
- ◆ stereochemistry: retention / inversion / racemization
- ◆ structure-activity relationship

Bimolecular Nucleophilic Substitution (S_N2)



□ rate = $k[\text{CH}_3\text{Cl}][\text{OH}^-]$; S_N2

◆ concerted mechanism: [📖 263 Figure 8.3](#)

□ stereochemistry: inversion, [📖 261 Figure 8.2](#)










◆ no change at other chirality centers: [📖 262 bottom](#)

□ energy profile: one maximum, [📖 260 Figure 8.1](#)

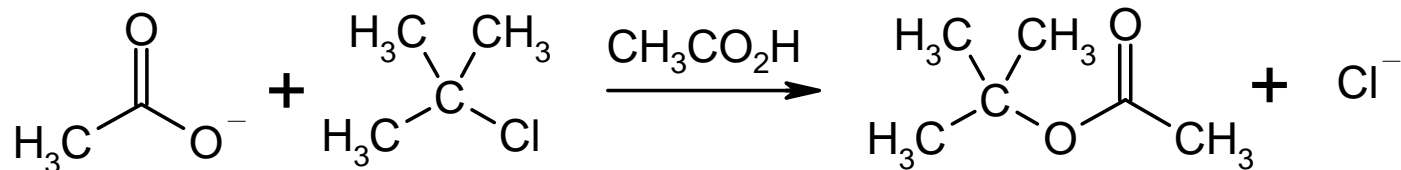
◆ one transition state (TS) and no intermediates

◆ *practice*: [📖 263 Problem 8.1](#)

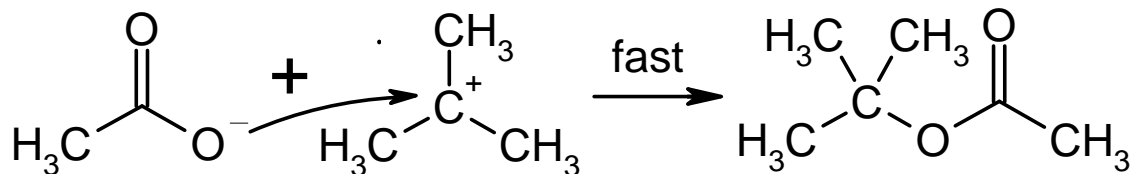
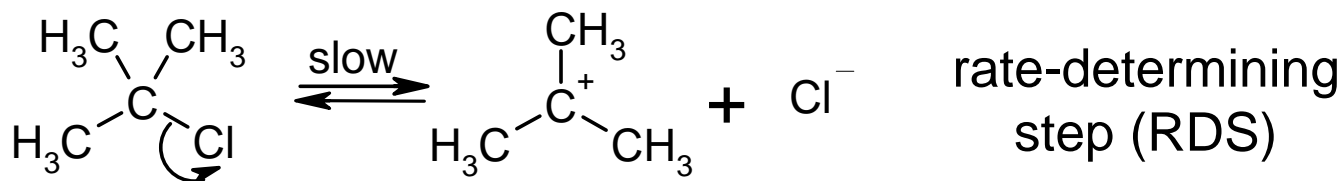
Effect of Substituents on S_N2 Reactions

- Steric effect:  264 [Table 8.1](#) &  265 [Figure 8.4](#)
 - ◆ more crowded TS:  [263 Figure 8.3](#)
 - ◆ the reactivity order:  [266 middle](#) &  [267 Figure 8.5](#)
- Electronic effect:  264 [Table 8.1](#) &  [266 bot.](#)
 - ◆ sp^2 transition state: resonance stabilization by conjugating p orbitals,  [263 Figure 8.3](#)
- *practice*:  [267-8 Problem 8.2 & 8.3](#)

Unimolecular Nucleophilic Substitution (S_N1)



$$\text{rate} = k[\text{t-BuCl}]; S_N1$$

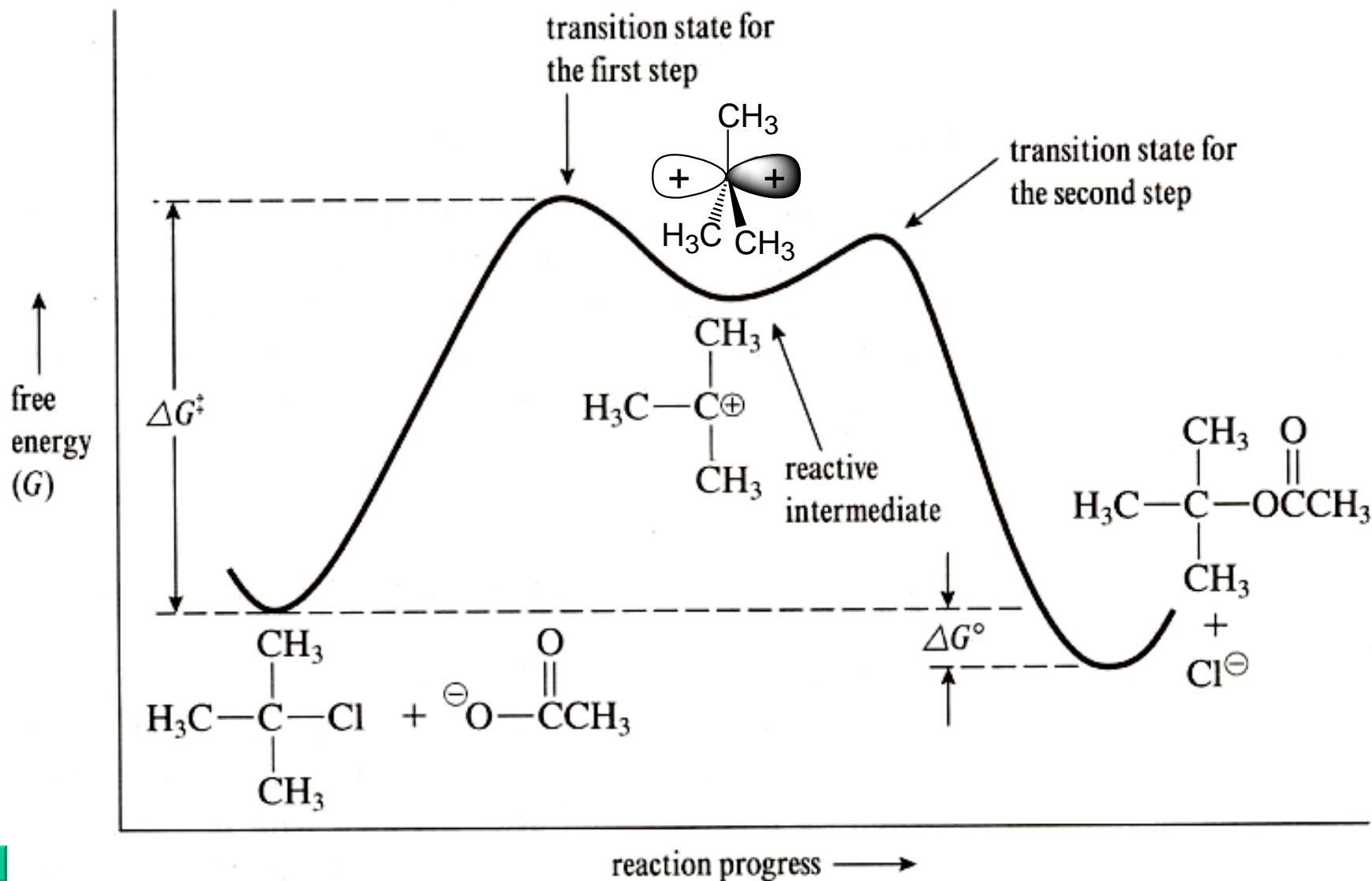


S_N1 Reactions (continued)







- Energy profile: two maxima, [📖 269 Figure 8.6](#)
 - ◆ carbocation intermediates: reactive & sp^2 , [📖 270 middle](#)
 - ◆ estimate of TS: Hammond postulate, [📖 271 Figure 8.7](#)
 - exergonic: reactant-like TS, endergonic: product-like TS

- Stereochemistry: racemization, [📖 276 Figure 8.8](#)
 - ◆ partial inversion: ion pair; [📖 277 Figure 8.9](#)
 - ◆ *practice*: [📖 278 Practice 8.1](#), [📖 279-80 Problems 8.8](#)






Energy profile of S_N1 reactions








Effect of Substituents on S_N1 Reactions

- Relative rates of S_N1 Reactions :  [272 Table 8.2](#)
- ◆ CH₃X: **only S_N2** reactions (too unstable CH₃⁺)
- ◆ relative stability of carbocations:  [272 middle](#)
 - e⁻-donating alkyl groups: hyperconjugation;  [273 top](#)
 - resonance stabilization: allyl & phenyl;  [273 bottom](#)
- ◆ *Focus On*: very stable triphenylmethyl cation;  [274-5](#)
- ◆ *practice*:  [275 Problems 8.6 & 8.7](#)

Effect of Leaving Groups

- the better the leaving group, the faster the reaction
 - ◆ acidity of the conjugate acid:  279 [Table 8.3](#)
 - ◆ alcohols as a leaving group: $-\text{OH}_2$ / $-\text{OSO}_2\text{R}$;  [280-281](#)
 - preparation of tosylates:  [281 bottom](#)
 - amines: not useful
 - ◆ correlation of the S_{N} reaction & stereochemistry:  [283 top](#)
 - ◆ *practice*:  280-1 Problems [8.9](#) & [8.10](#)

Effect of Nucleophiles on S_N2 Reactions

- No effect of nucleophiles on the rate of S_N1 reactions
- Strength of nucleophiles (nucleophilicity)
 1. parallel to basicity in the same period:  284; [Rule 1](#)
 2. increases down a column in the same group:  284; [Rule 2](#)
 3. decreases as the bulkiness increases:  285; [Rule 3](#)
- ◆ *practice*:  285 [Practice 8.2](#), [Problem 8.11](#) &  286 [8.12](#)





Effect of Solvent (I)

- Dissolving & inert to the reaction conditions
- Effect on the rate: polarity between **reactants** & **TS**
 - ◆ S_N1: polar TS **stabilized** by polar solvents, [📖 287 Figure 8.10](#)
 - ◆ S_N2: depending on the charge of nucleophiles
 - Nu⁻ : dispersed charge in TS: **slower** in polar solvents, [📖 287 mid](#)
 - Nu: : charged TS: **faster** in polar solvents, [📖 287 bottom](#)



Effect of Solvent (II)

- Protic vs aprotic solvents: hydrogen bonding ability
 - ◆ ROH / RNH₂ vs CH₃COCH₃ / DMF
 - Nu: : stabilized in protic solvents → higher ΔG^\ddagger (slower rate)
 - $\text{rate}_{\text{DMF}} : \text{rate}_{\text{MeOH}} = 1 \times 10^6$; [📖 288 top](#)
 - ◆ polar protic vs polar aprotic: [📖 288 Table 8.4](#)
 - nucleophilicity: in MeOH, I⁻ > Br⁻ > Cl⁻ vs in DMF, Cl⁻ > Br⁻ > I⁻
 - faster S_N1 reactions in a solvent with high ionizing power
 - ◆ *practice*: [📖 289 Practice 8.3, Problems 8.14 & 8.15](#)




Competition between S_N1 and S_N2







- S_N1: stable carbocations,  291 [Table 8.5](#)
 - ◆ tertiary carbons: tertiary carbocations
 - ◆ 2°/allylic/benzylic E⁺: high ionizing solvents & poor Nu:
- S_N2: favorable attack by Nu,  291 [Table 8.5](#)
 - ◆ less steric hindrance: primary carbons (RCH₂X)
 - ◆ 2°/allylic/benzylic E⁺: aprotic solvents & strong Nu:
 - ◆ *practice*:  290 [Practice 8.4](#) &  291 [Problem 8.16](#)

Intramolecular Substitution Reactions

- nucleophile & leaving group **within the same molecule**:
 - ◆ faster than **intermolecular** reactions: **cycles**;  [293 top](#)
 - favorable **cyclization** for 3-, 5- & 6-membered rings
 - ◆ $\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$ (the smaller ΔG^\ddagger , the faster the rate)
 - ΔS^\ddagger (distance factor): the smaller the ring, the faster the rate
 - ΔH^\ddagger (strain factor): the smaller the steric strain, the faster
 - ◆ **practice**:  [294 Problem 8.17](#)

Elimination & Rearrangement

- Removal of adjacent proton & leaving group
 - ◆ a nucleophile acting as a base
 - S_N2:  294 [Figure 8.11](#) ○ S_N1:  295 [Figure 8.12](#)
 - ◆ *practice*:  295 [Problems 8.18](#)

- Rearrangement in carbocations: S_N1
 - ◆ 1,2-hydride/alkyl shift: formation of a more stable (tertiary) carbocation,  295-6 &  299 [Focus On](#)
 - ◆ faster rearrangement:  296 [Figure 8.13](#)
 - ◆ allylic rearrangement: resonance structures;  297 [middle](#)
 - ◆ *practice*:  297 [Practice 8.5](#),  298 [Problems 8.20 & 8.21](#)

공부하는 방법

“그저 익숙하도록 읽는 것뿐이다. 글을 읽는 사람이, 비록 글의 뜻은 알았으나, 만약 익숙하지 못하면 읽자마자 곧 잊어버리게 되어, 마음에 간직할 수 없을 것은 틀림없다.

이미 읽고 난 뒤에, 또 거기에 자세하고 익숙해질 공부를 더한 뒤라야 비로소 마음에 간직할 수 있으며, 또 흐뭇한 맛도 있을 것이다.” - 퇴계 이황 (금장태 著)

