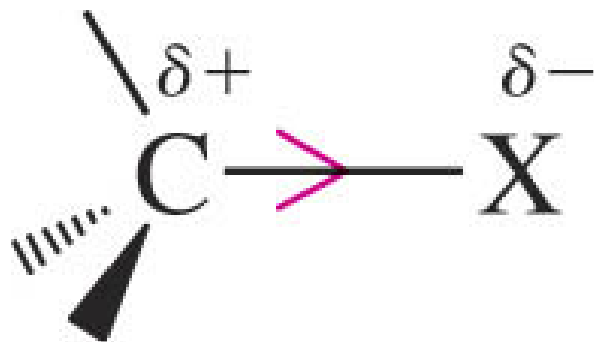
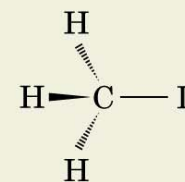
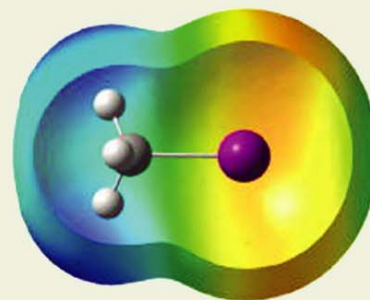
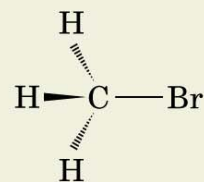
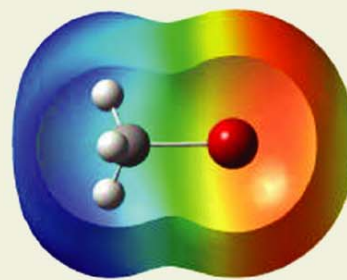
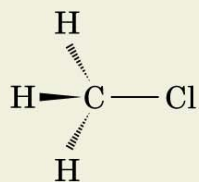
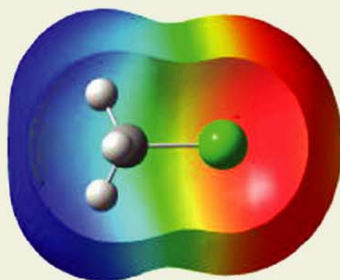
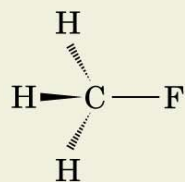
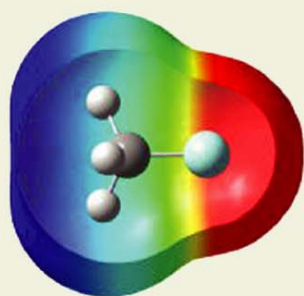


## 第6章 Ionic Reactions-Nucleophilic Substitution and Elimination Reaction of Alkyl Halides (鹵代烷烴的親核取代反應及消除反應)

1) 鹵代烷烴C-X鍵的極化(polarized):



由於C原子與X原子之間電負性的差異，造成了C-X鍵的極化，使得C帶partial positive charge，X帶partial negative charge. 此現象決定了鹵代烷烴的化學反應性.



C—X Bond  
length (Å)  
C—X Bond  
strength  
(kJ mol<sup>-1</sup>)

1.39

472

1.78

350

1.93

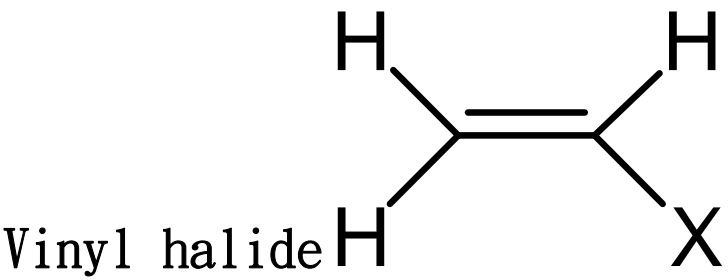
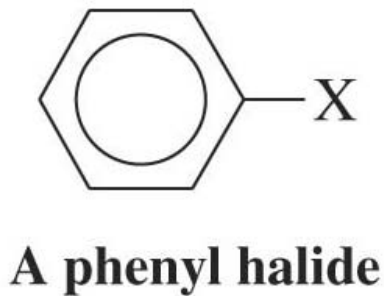
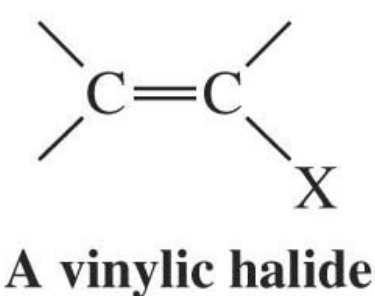
293

2.14

239

以CH<sub>3</sub>X為例，從F→I， C—X鍵的鍵長增加， 極化度降低， 鍵能減小。

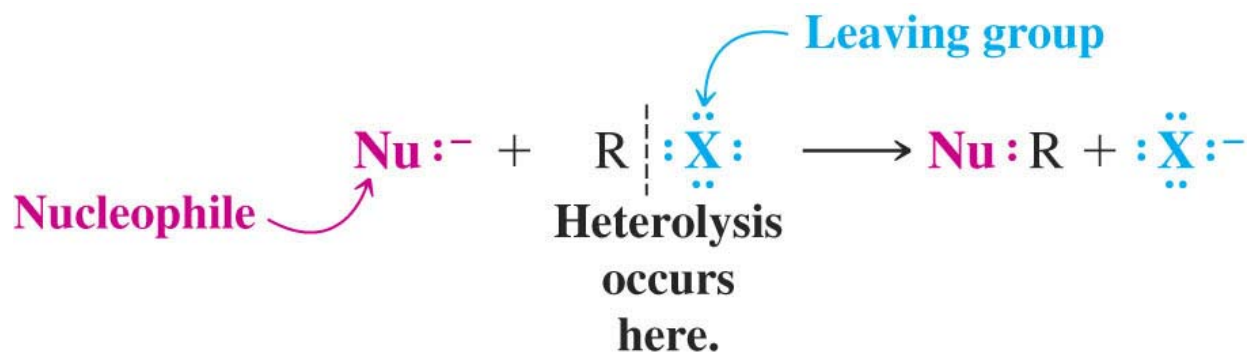
Organic halides 包括: alkyl halides; vinilic halides and aryl halides



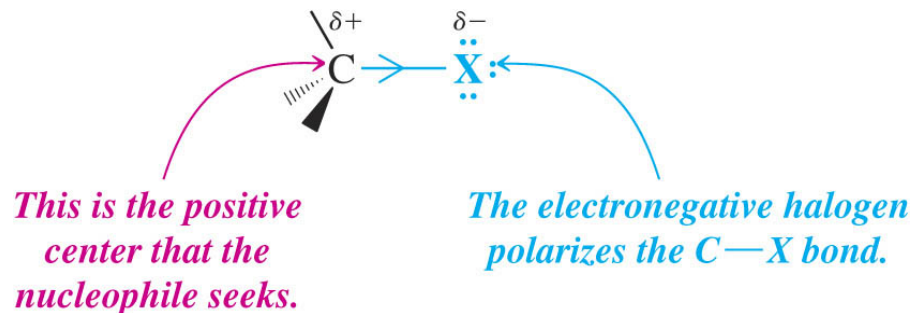
CH<sub>2</sub>Cl<sub>2</sub>: dichloromethane; CH<sub>3</sub>Cl: chloroform; CCl<sub>4</sub>: carbon tetrachloride

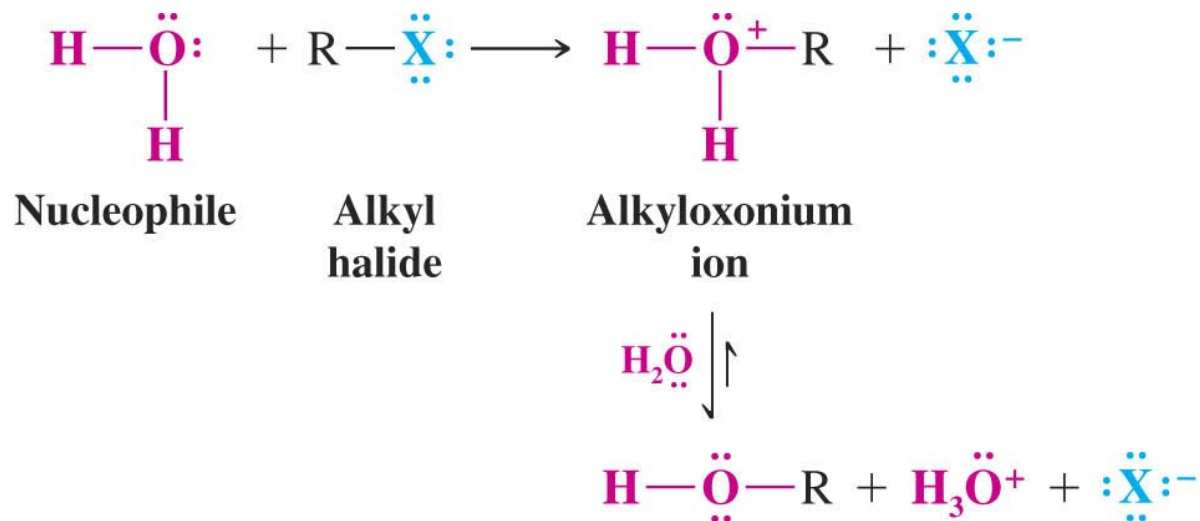
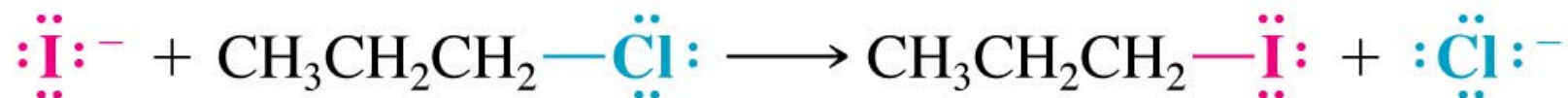
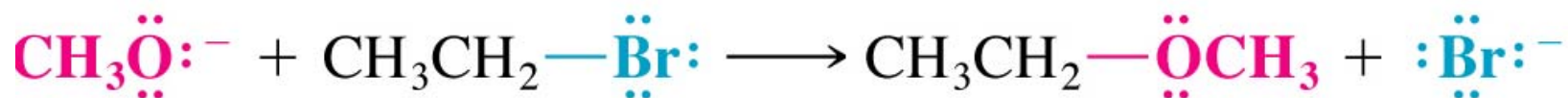
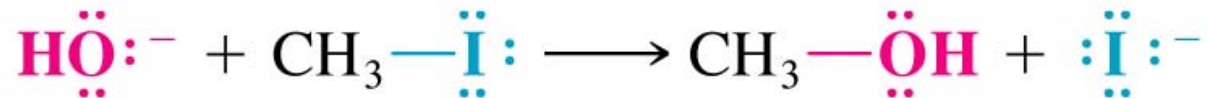
## 2) 有機反應中重要的一類反應-親核取代反應 (Nucleophilic substitution Reactions)

以RX為例：

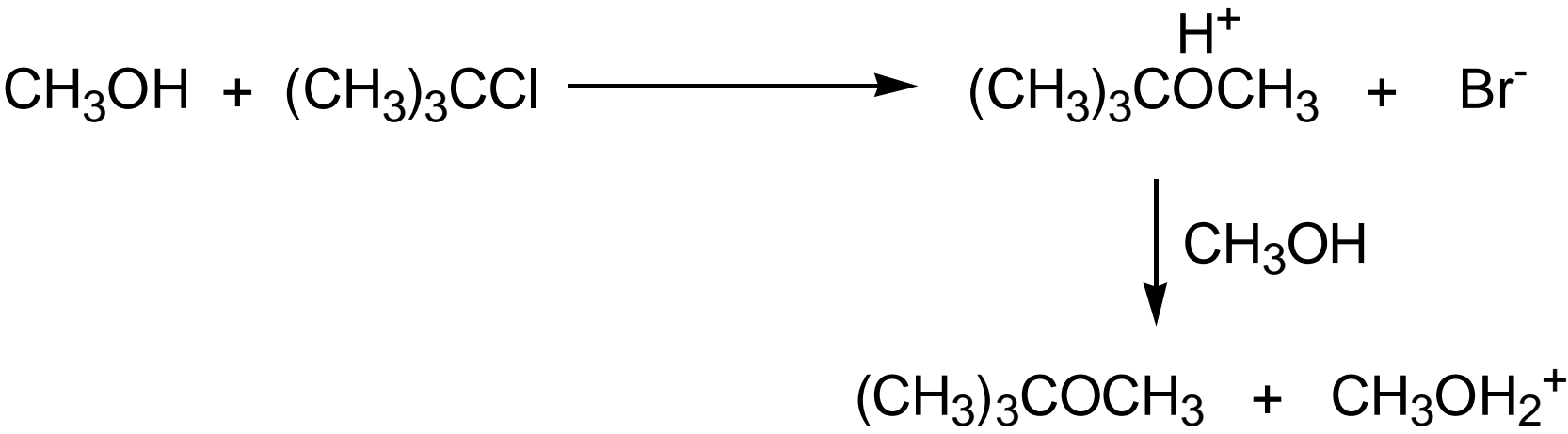


$\text{Nu}^-$  被稱為nucleophiles(親核試劑)，它為具有未成對電子的負電離子或分子。在反應中進攻底物的正電中心,取代底物 (substrates)中的離去基團 (leaving groups)。





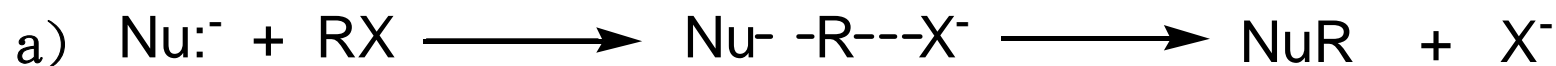
Exercise in page 242: Rewrite the reactions as net ionic reactions:



L<sup>-</sup> 被稱為leaving group (離去基), 好的離去基在離開底物後, 應為穩定的弱鹼離子.

### 3) S<sub>N</sub>2(Bimolecular nucleophilic substitution)親核取代反應

A) 親核取代反應可能的途徑:



在新鍵形成的同時, 舊鍵亦發生斷裂 (S<sub>N</sub>2)

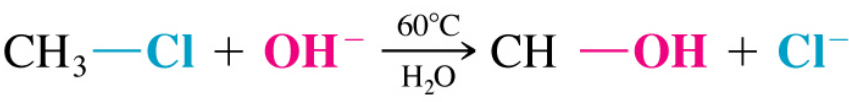
或者是:



RX先發生斷裂產正碳離子, 再受到親核試劑的攻擊 (S<sub>N</sub>1)

B) S<sub>N</sub>2反應的機制的探討:

a) 從反應的初始速度(initial rate)來證明反應機制: Second order reaction



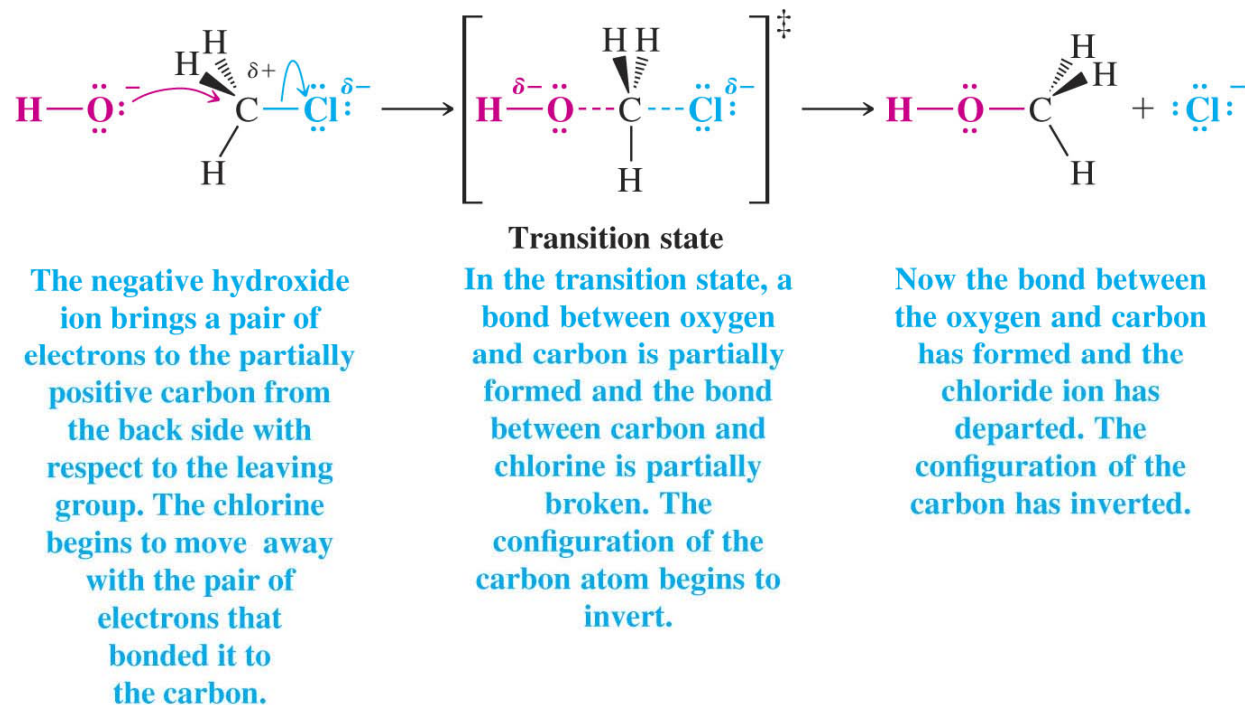
Experiment Number	Initial [CH <sub>3</sub> Cl]	Initial [OH <sup>-</sup> ]	Initial Rate (mol L <sup>-1</sup> s <sup>-1</sup> )
1	0.0010	1.0	4.9 × 10 <sup>-7</sup>
2	0.0020	1.0	9.8 × 10 <sup>-7</sup>
3	0.0010	2.0	9.8 × 10 <sup>-7</sup>
4	0.0020	2.0	19.6 × 10 <sup>-7</sup>

$$\text{Rate} = k[\text{CH}_3\text{Cl}][\text{OH}^-]$$

反應的初始速度與兩種反應物的濃度成正比，間接證明反應是由兩種分子碰撞而發生(second order).

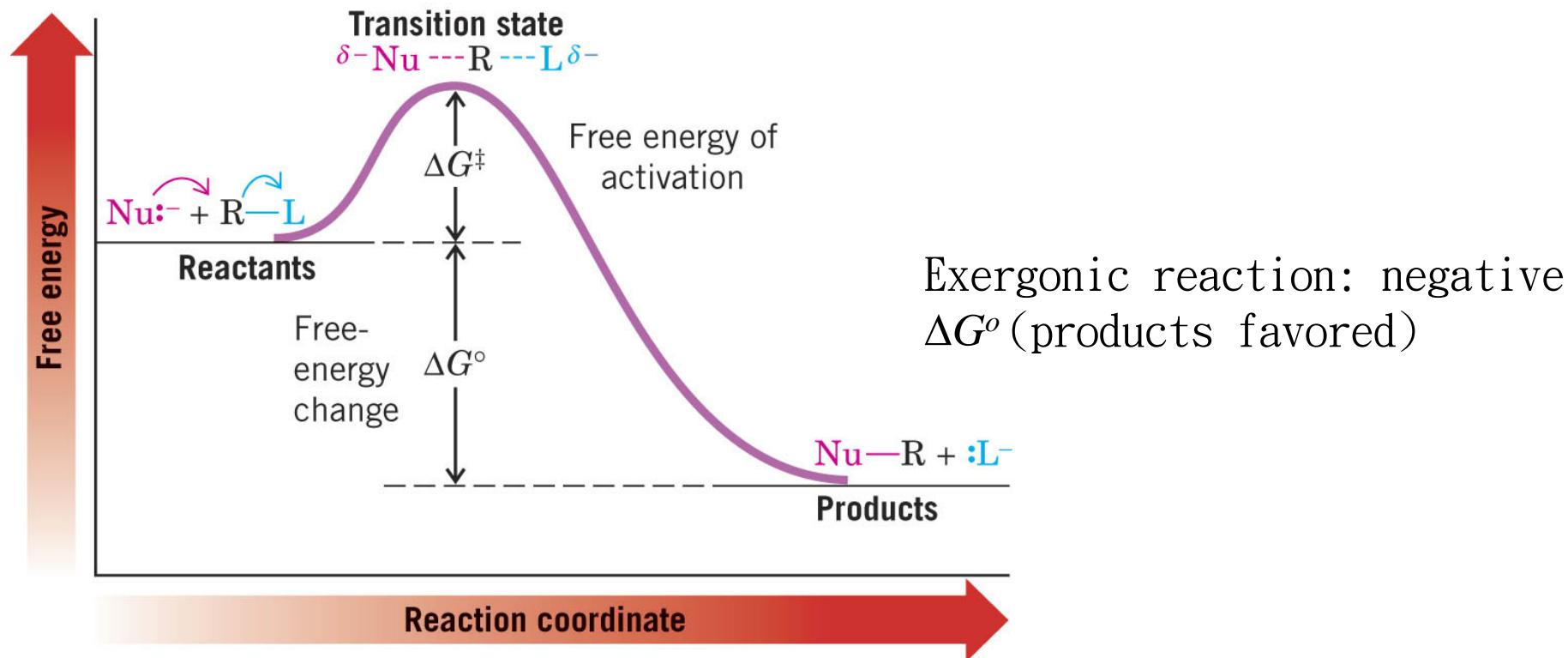


b) Sir Christopher Ingold 所提出的SN2反應機制：



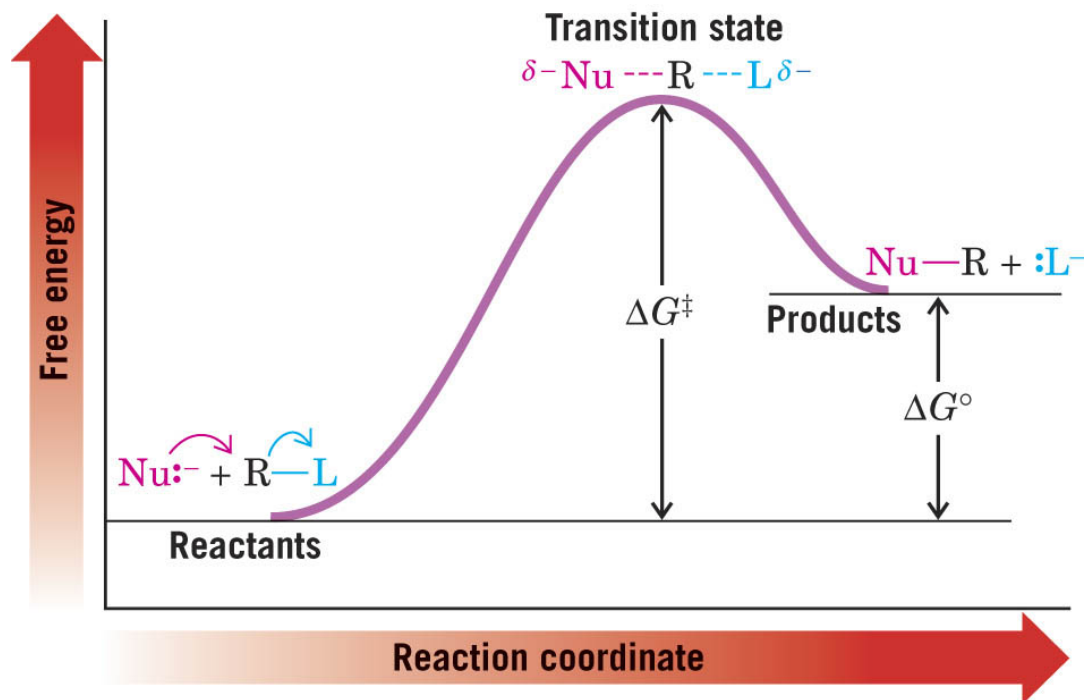
反應的過渡態：反應過程中所經歷的一種能量高而不穩定的狀態，它所對應的時間僅為 $10^{-12}$  S左右。反應的過渡態不是反應的中間體(intermediates).

### c) SN2反應能量之探討



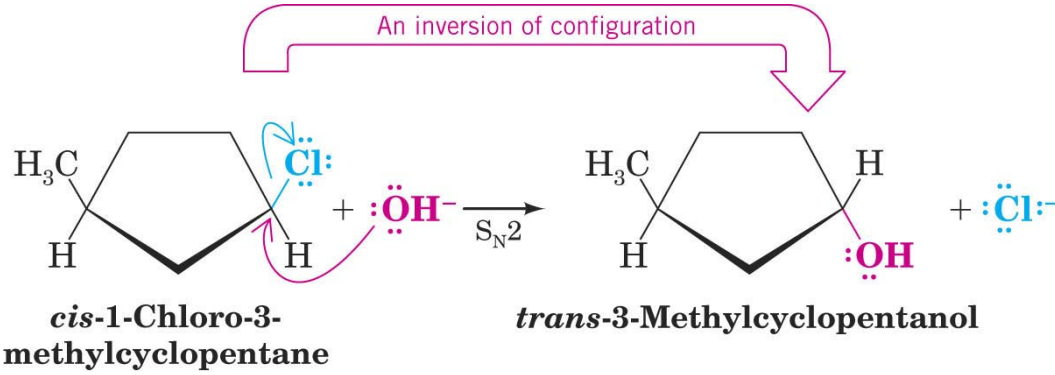
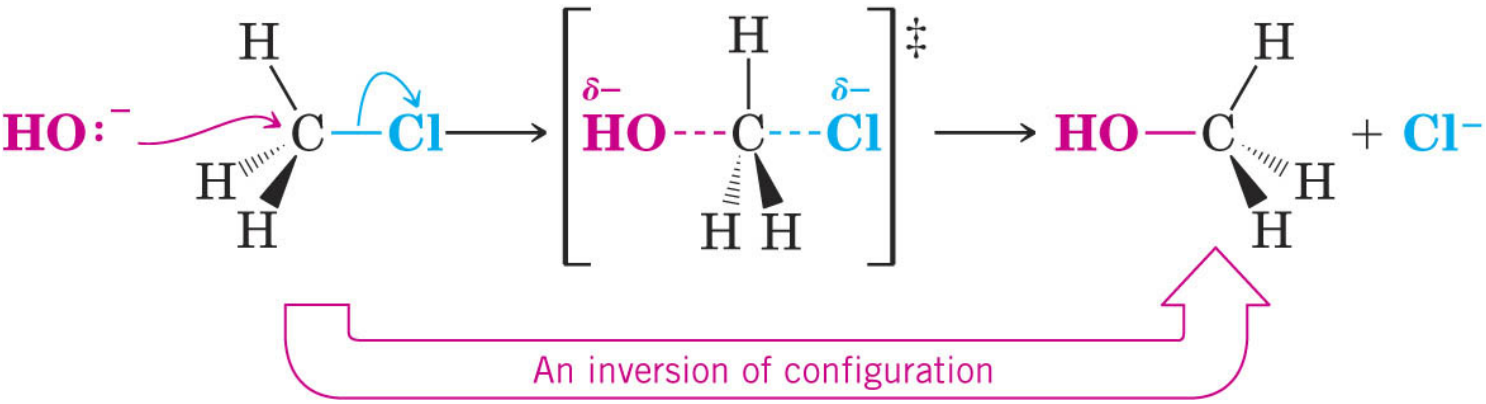
An energy barrier is evident because a bond is being broken in going to the transition state (which is the top of the energy barrier).

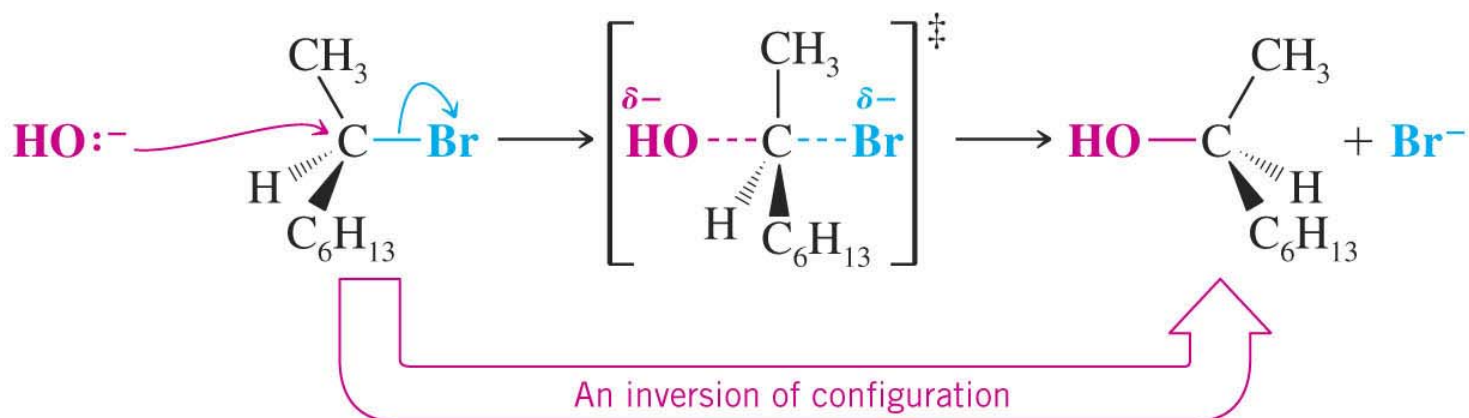
The difference in energy between starting material and the transition state is the free energy of activation ( $\Delta G^\ddagger$ ). The difference in energy between starting molecules and products is the free energy change of the reaction,  $\Delta G^\circ$ .



Endergonic reaction: positive  $\Delta G^\circ$  (products not favored)

d) SN2反應立體化學之探討：





**(R)-(-)-2-Bromooctane**

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

**Enantiomeric purity = 100%**

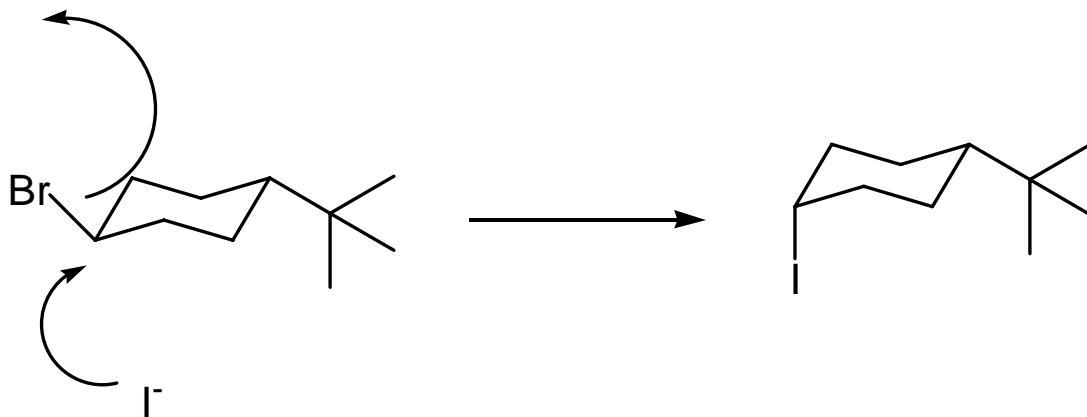
**(S)-(+)-2-Octanol**

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

**Enantiomeric purity = 100%**

課堂練習：

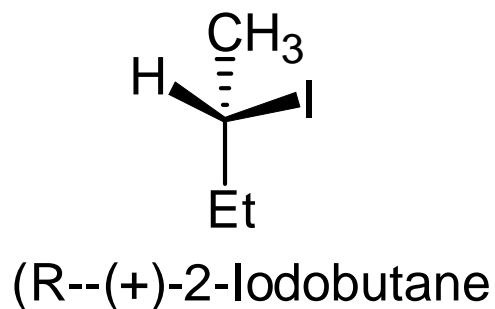
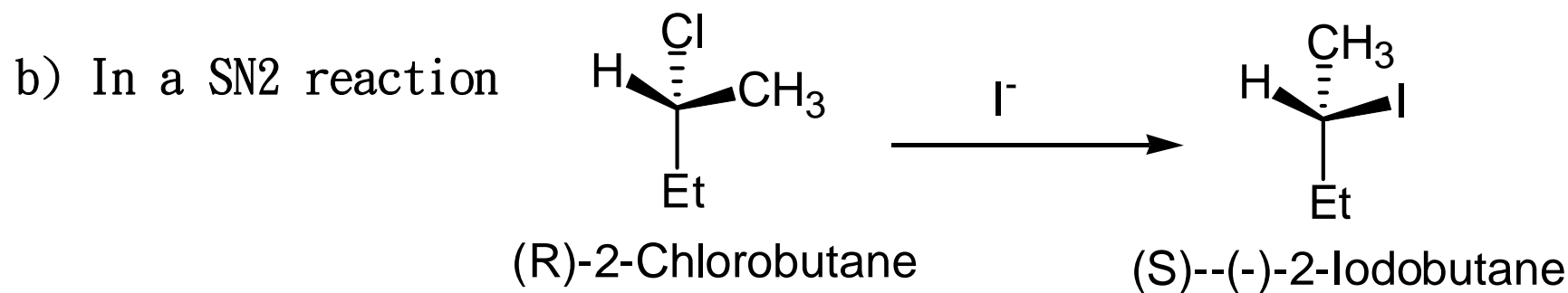
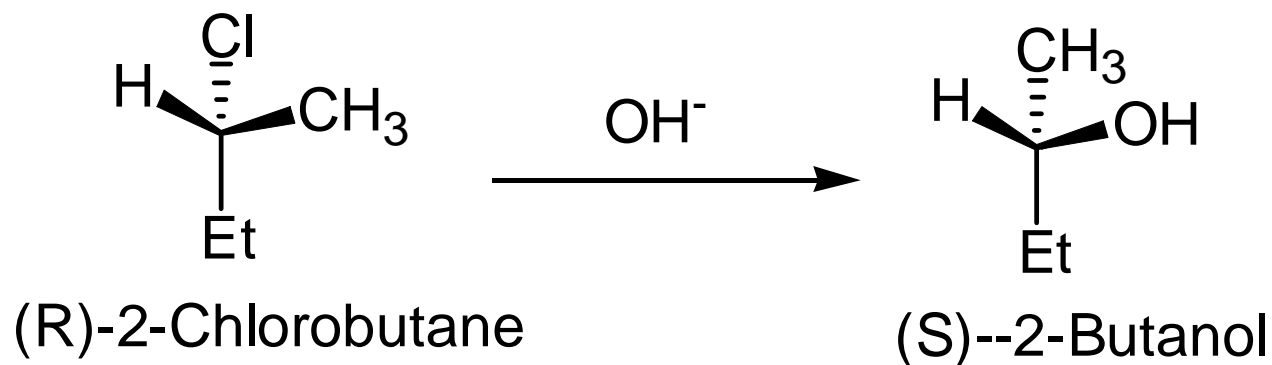
a) Page 250:



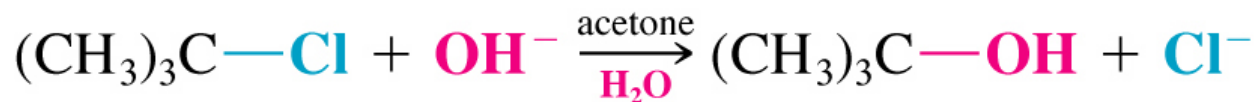
Thinking if this molecule is the chiral molecule?

b) Page 251:

a) In a  $S_N2$  reaction, based on the configuration of the product, deduce the configuration of the start material:



4)另一類親核取代反應：SN1(Unimolecular nucleophilic substitution)



$$\text{Rate} \propto [(\text{CH}_3)_3\text{CCl}]$$

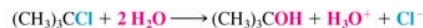
$$\text{Rate} = k[(\text{CH}_3)_3\text{CCl}]$$

產物的生成速度與 *tert*-butyl chloride 的濃度成正比，而與OH<sup>-</sup>的濃度無關。

可以據此推論，OH<sup>-</sup>並沒有參與到影響反應速度的過渡態當中。此類反應被稱之為SN1(Unimolecular nucleophilic substitution)

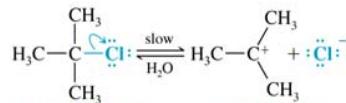
A) SN1反應的Mechanism:

Reaction:



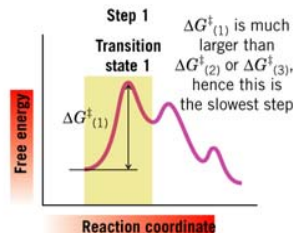
Mechanism:

Step 1



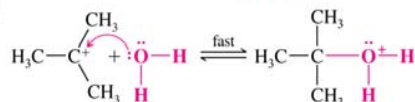
Aided by the polar solvent a chlorine departs with the electron pair that bonded it to the carbon.

This slow step produces the relatively stable  $3^\circ$  carbocation and a chloride ion. Although not shown here, the ions are solvated (and stabilized) by water molecules.



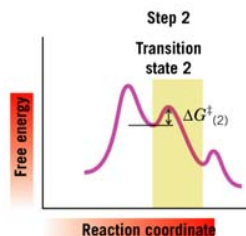
Intermediate 1

Step 2



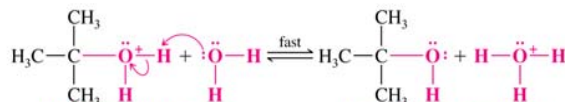
A water molecule acting as a Lewis base donates an electron pair to the carbocation (a Lewis acid). This gives the cationic carbon eight electrons.

The product is a *tert*-butyloxonium ion (or protonated *tert*-butyl alcohol).



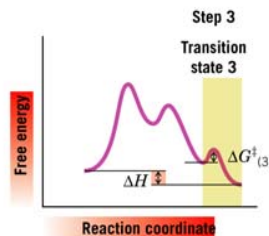
Intermediate 2

Step 3



A water molecule acting as a Brønsted base accepts a proton from the *tert*-butyloxonium ion.

The products are *tert*-butyl alcohol and a hydronium ion.

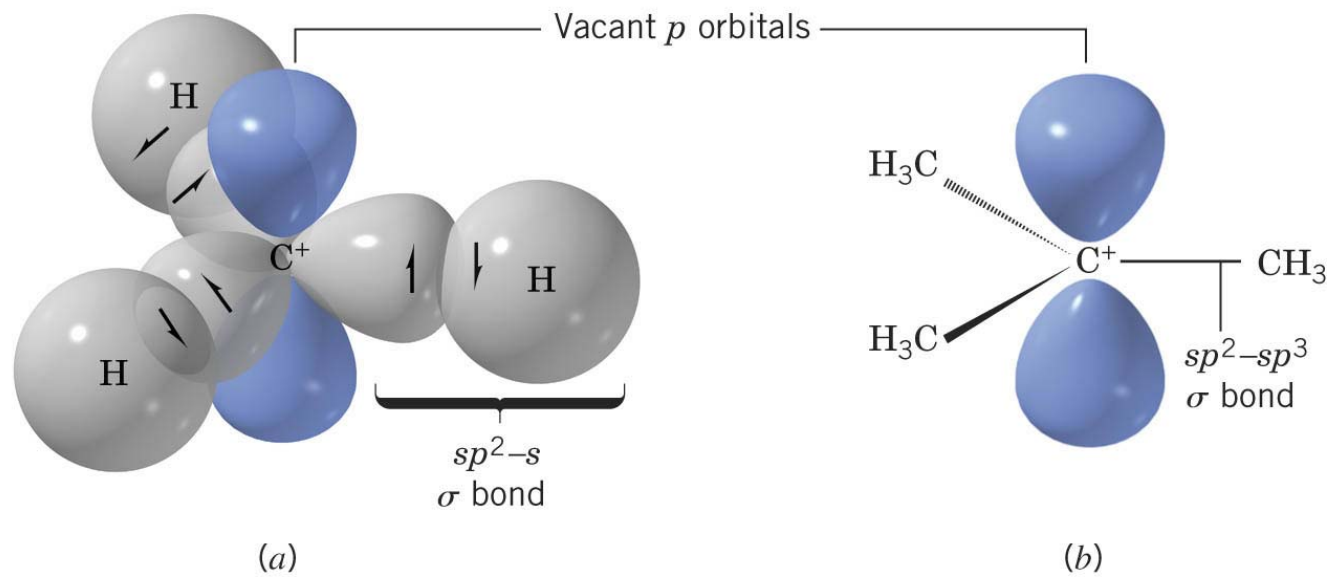


在多階段的反應中，最慢的反應過程通常決定整個反應的速度，它被稱之為rate-determining step;  $\Delta G^\ddagger$ 為最大。

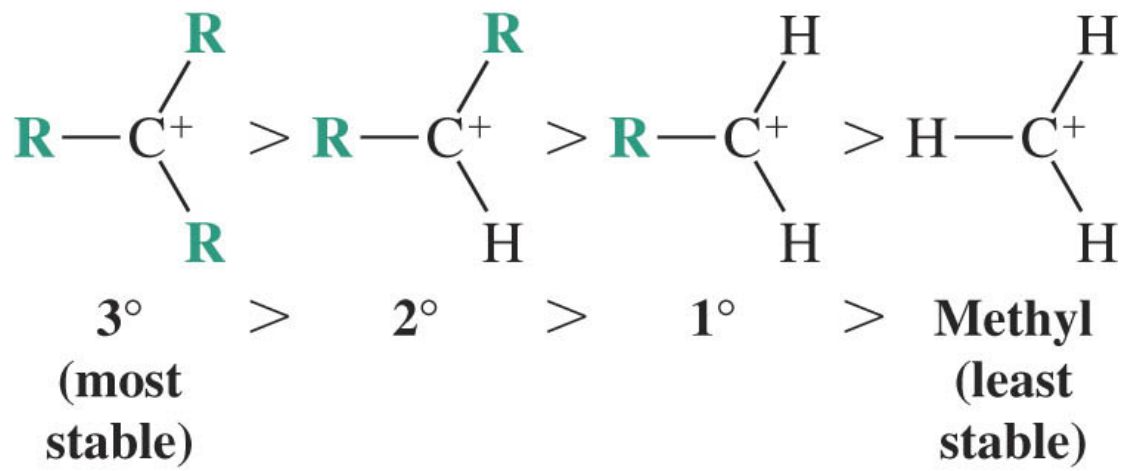
In the case above  $k_1 \ll k_2$  or  $k_3$ , and the first step is rate determining



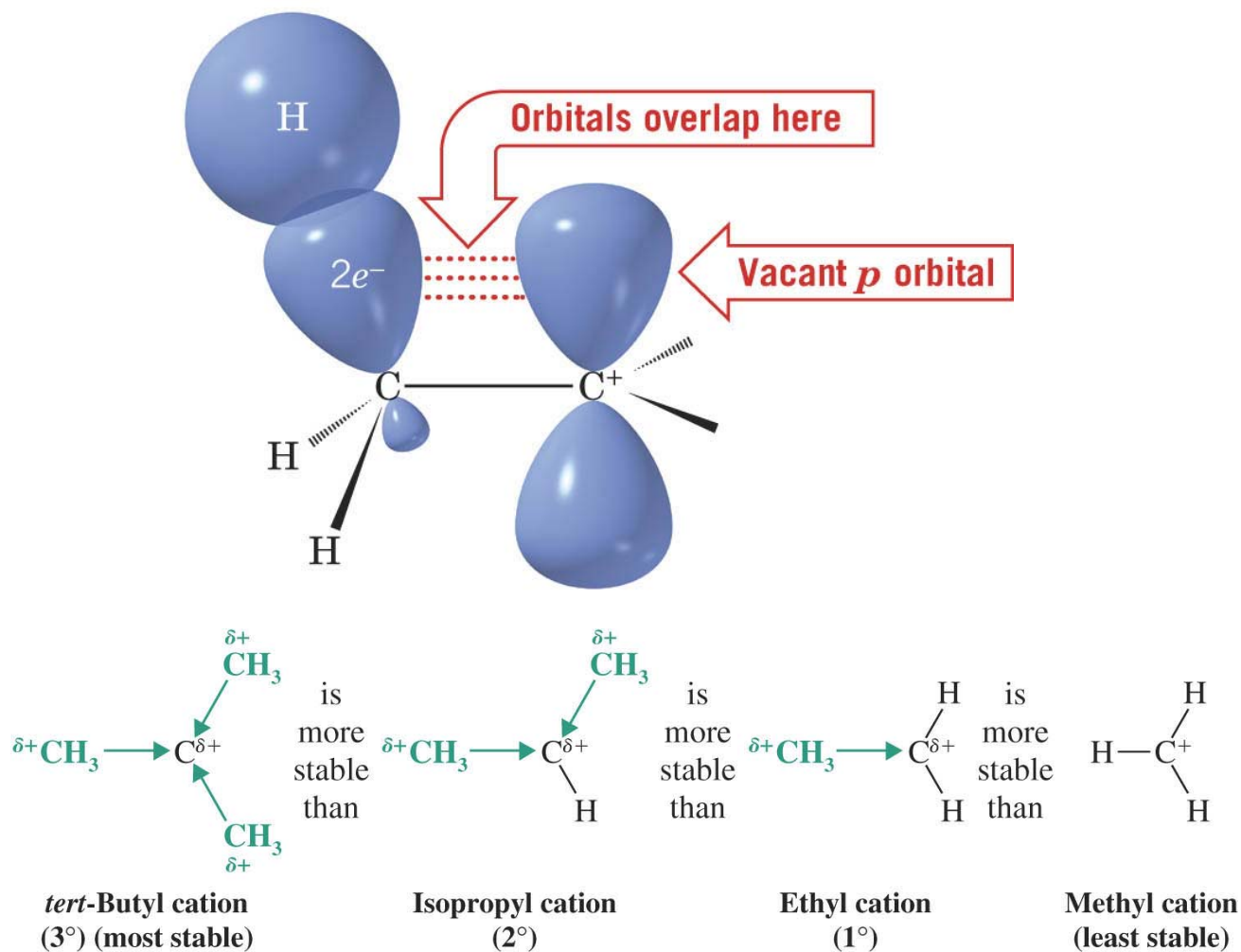
B) 正碳離子(carboncations)的結構及穩定性



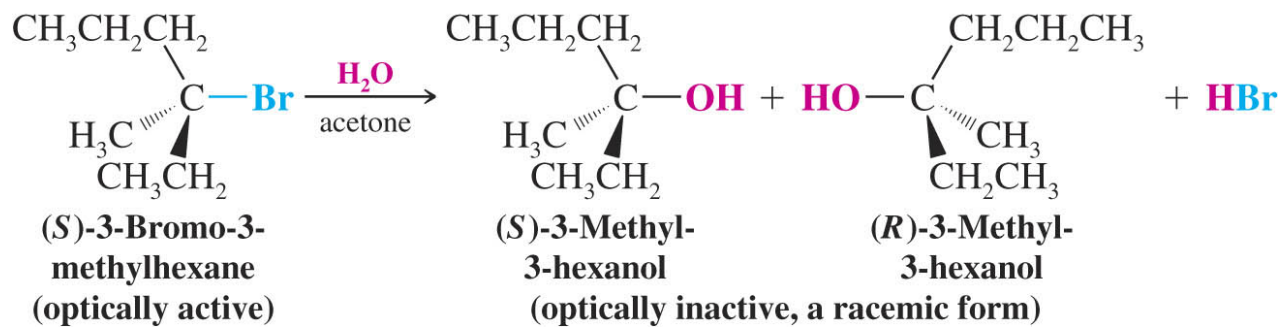
A carbocation has only 6 electrons, is  $sp^2$  hybridized and has an empty  $p$  orbital



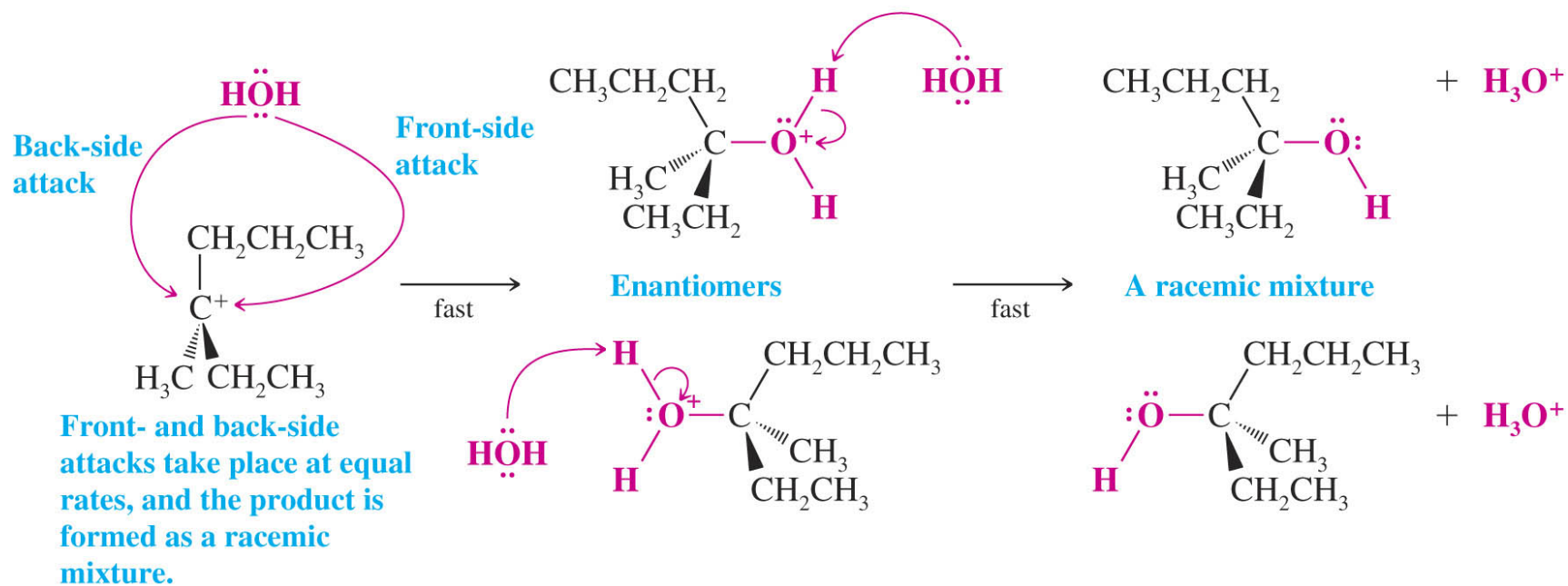
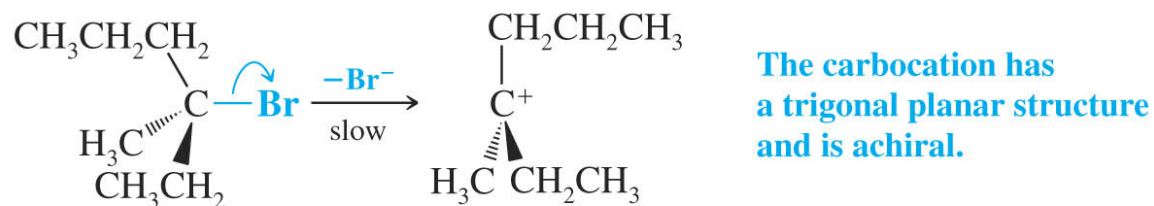
Hyperconjugation: stabilizes the carbocation by donation of electrons from an adjacent carbon-hydrogen or carbon-carbon  $\sigma$  bond into the empty  $p$  orbital (電子從C-H或C-C $\sigma$ 軌道分散到鄰近的未充滿p軌道, 可使得p軌道上的正電荷分散, 降低體系的能量, 穩定正碳離子)



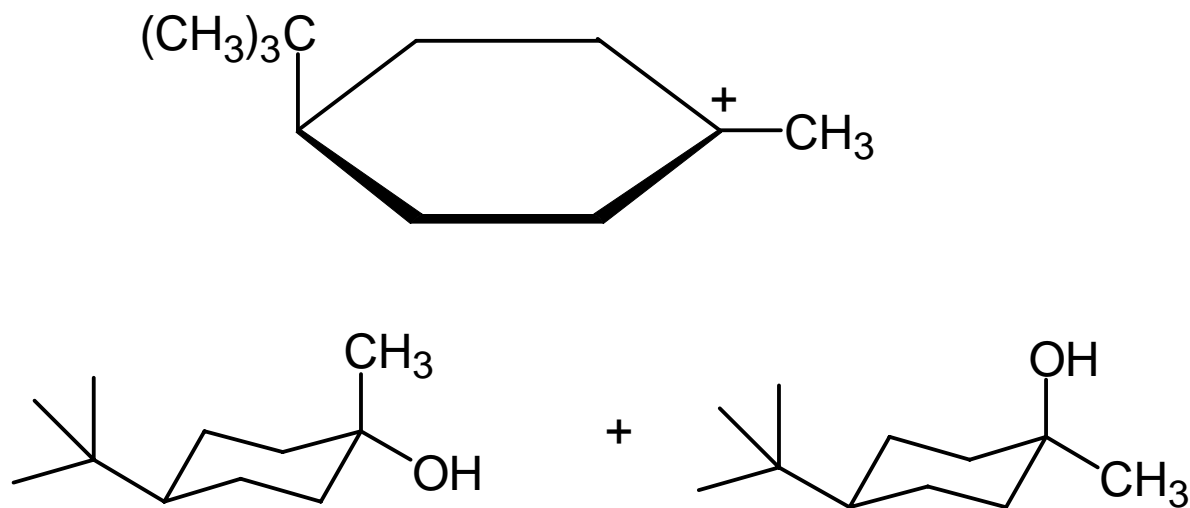
C) SN1反應立體化學之探討：



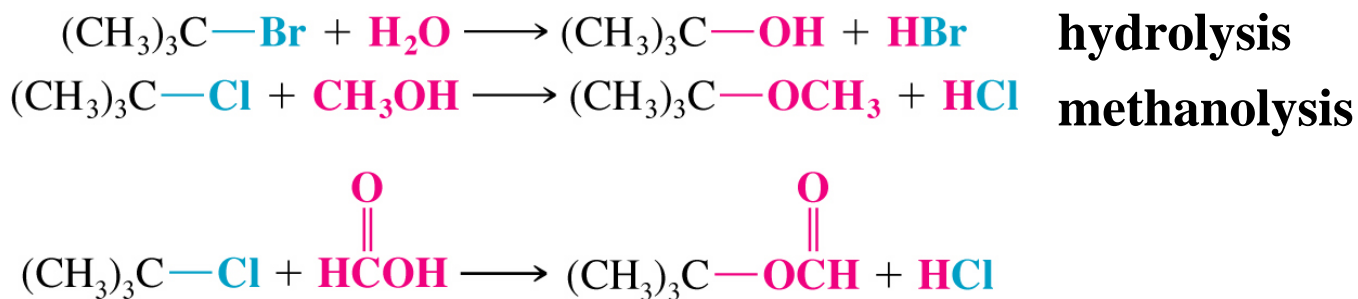
有光學活性的反應物經過化學反應後生成外消旋的產物，稱為：**Racemization**.



課堂練習:a) Page 257:

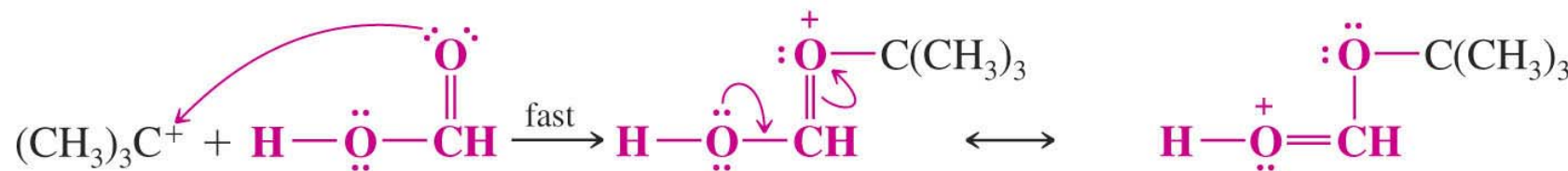


D) solvolysis: 鹵代烷烴與溶劑分子發生的親核取代反應

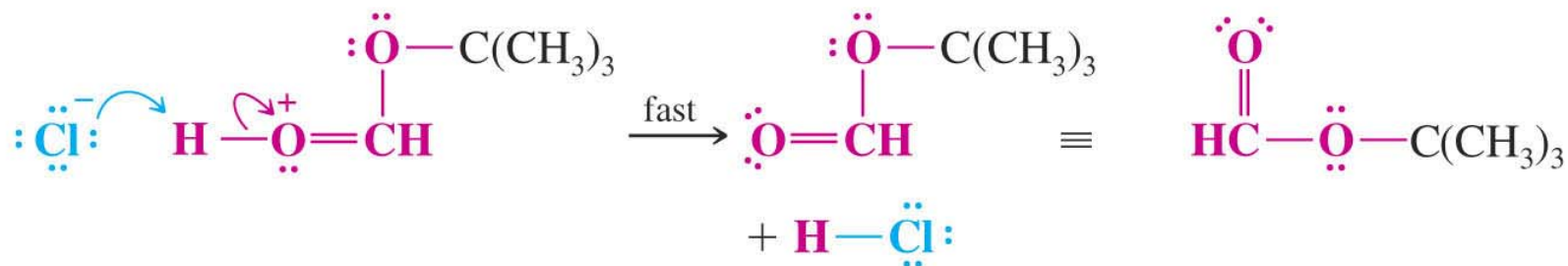




*Step 2*



*Step 3*



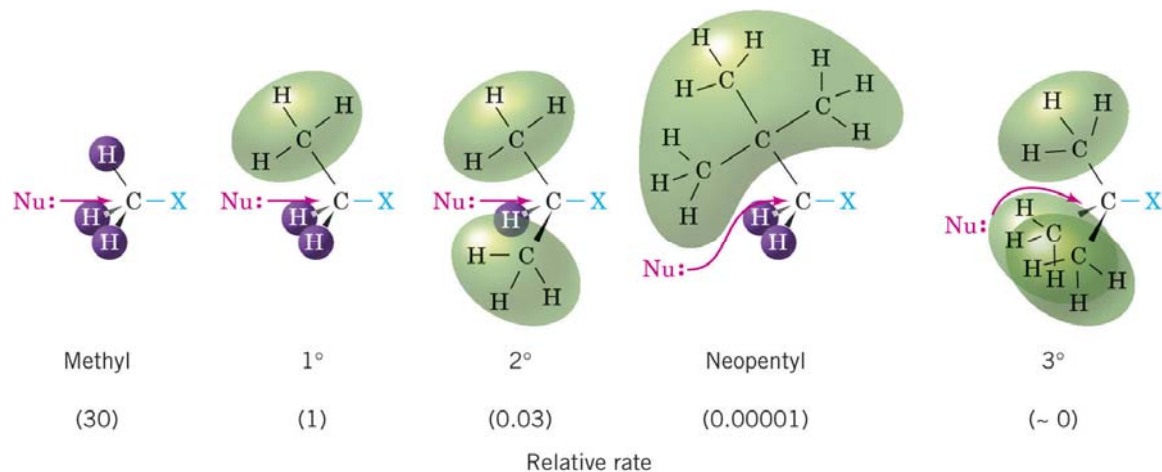
## 5) 決定SN1和SN2反應途徑的因素

### a) 底物結構(the structure of the substrate)

#### SN2 Reactions——steric effect

In SN2 reactions alkyl halides show the following general order of reactivity:

**Methyl > primary > secondary >> (tertiary — unreactive)**



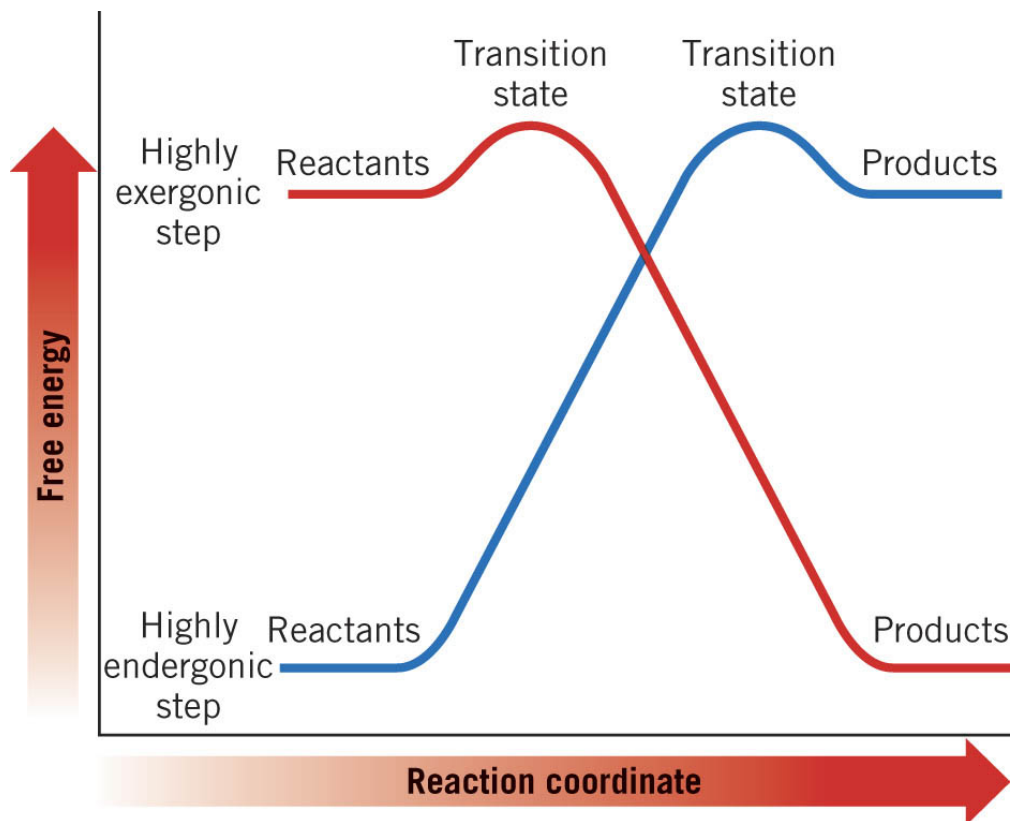
Steric hinderance: the spatial arrangement of the atoms or groups at or near a reacting site hinders or retards a reaction. In tertiary and neopentyl halides, the reacting carbon is too sterically hindered to react.

SN1 reactions—決定SN1反應的關鍵因素是看是否可以形成穩定的正碳離子。

Generally, a) for alkyl halides, only tertiary halides undergo SN1 reactions because only they can form relatively stabilized carbocations b) allylic halides and benzylic halides can also undergo SN1 reactions easily.

Explain (b)?





### *The Hammond-Leffler Postulate*

The transition state for an exergonic reaction looks very much like starting material

The transition state for an endergonic reaction looks very much like product

Generally the transition state looks most like the species it is closest to in energy

## 課堂練習:Page 261

b)親核試劑的濃度與強度 (concentration and strength of nucleophile):

SN1反應並不受親核試劑濃度及強度的影響

對SN2反應來講: 1) Rate is directly proportional to the concentration of nucleophile;

2) Stronger nucleophiles react faster:

$$\text{CH}_3\text{OH} + \text{CH}_3\text{I} \xrightarrow{\text{very slow}} \text{CH}_3\overset{+}{\text{O}}(\text{H})\text{CH}_3 + \text{I}^-$$
$$\text{CH}_3\text{O}^- + \text{CH}_3\text{I} \xrightarrow{\text{rapid}} \text{CH}_3\text{OCH}_3 + \text{I}^-$$

規則 1: A negatively charged nucleophile is always more reactive than its neutral conjugate acid

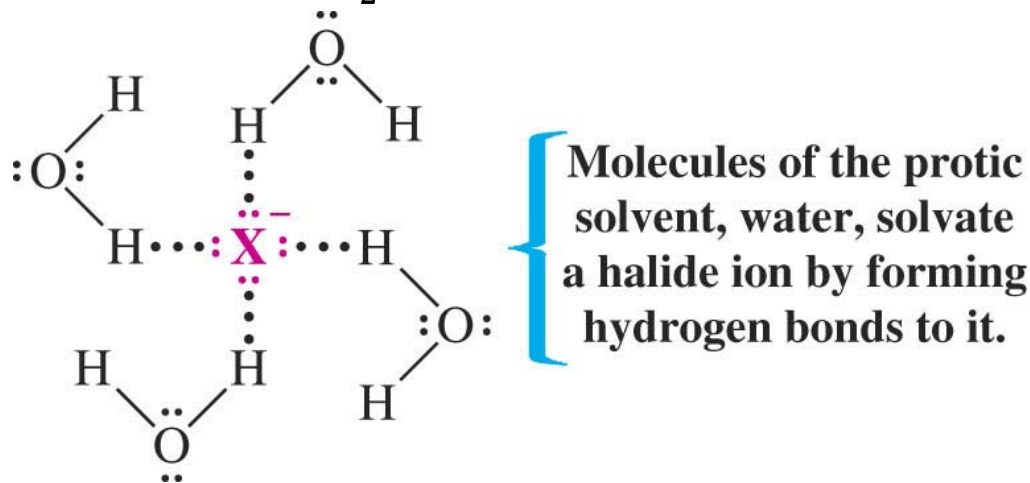
規則 2: When comparing nucleophiles with the same nucleophilic atom, nucleophilicities parallel basicities:



Note: the nucleophilicity and basicity are not measured in the same way ( $\text{OH}^-$  and  $\text{CN}^-$ ).

c) 溶剂对SN2反应的影响

1) In Protic solvent: having hydrogen attached to a strongly electronegative element (H<sub>2</sub>O, ROH...etc)

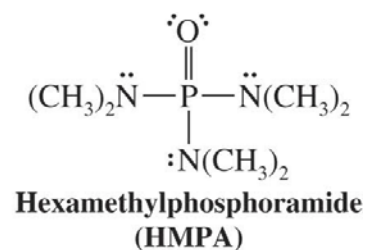
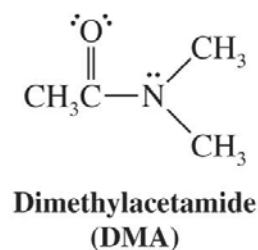
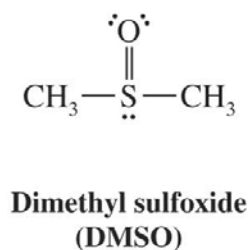
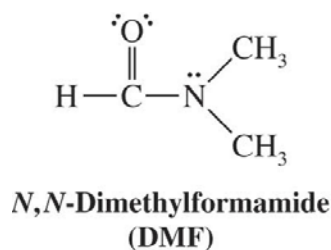


溶剂分子通过氢键聚集在亲核试剂周围，降低它和亲核性。

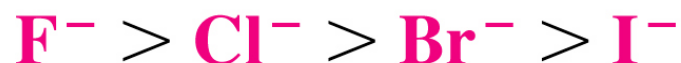
规则 3: 原子半径较小的亲核试剂易形成较强的氢键，而且较大的原子在质子型溶剂中极化性较强，较易于提供电子进行亲核进攻，为此：  
在protic solvent中：relative nucleophilicity:



2) In Aprotic solvent:



relative nucleophilicity:



課堂練習:Page 264

3)在Protic solvent中，SN1的反應速度會大大增強，因為溶劑對中間體正碳離子的穩定作用。

課堂練習:Page 265

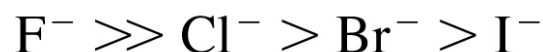
d)離去基團的性質:在SN1和SN2反應中， 好的離去基團應該是穩定的陰離子（弱鹼）或中性小分子。

規則 4:

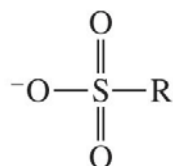
Leaving group ability of halides:



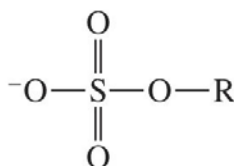
This trend is opposite to basicity (see Table in page 105):



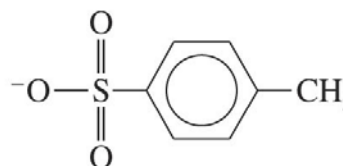
其他好的離去基團：



An alkanesulfonate ion



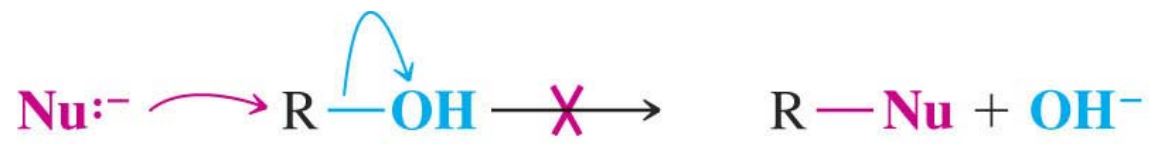
An alkyl sulfate ion



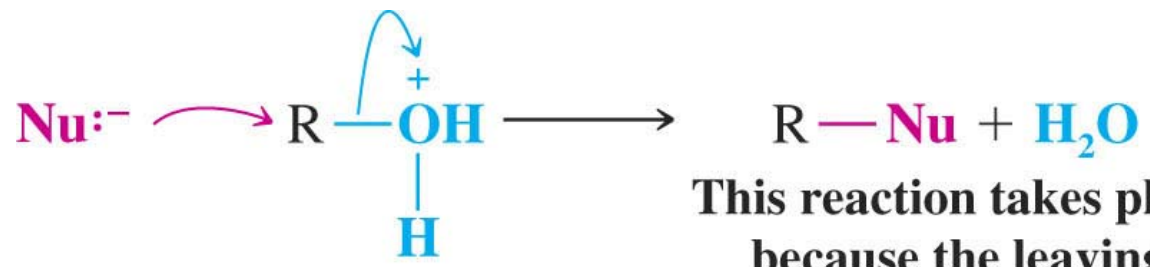
*p*-Toluenesulfonate ion

Triflate ion:  $\text{CF}_3\text{SO}_3^-$ ,

規則 5: 強鹼極少可能作為好的離去基團



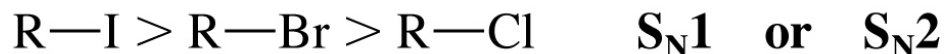
This reaction does not take place because the leaving group is a strongly basic hydroxide ion.



This reaction takes place because the leaving group is a weak base.

## Summary S<sub>N</sub>1 vs. S<sub>N</sub>2

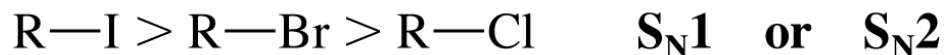
In both types of reaction alkyl iodides react the fastest because of superior leaving group ability



Factor	S <sub>N</sub> 1	S <sub>N</sub> 2
Substrate	3° (requires formation of a relatively stable carbocation)	Methyl > 1° > 2° (requires unhindered substrate)
Nucleophile	Weak Lewis base, neutral molecule, nucleophile may be the solvent (solvolysis)	Strong Lewis base, rate favored by high concentration of nucleophile
Solvent	Polar protic (e.g., alcohols, water)	Polar aprotic (e.g., DMF, DMSO)
Leaving group	<div>I &gt; Br &gt; Cl &gt; F for both S<sub>N</sub>1 and S<sub>N</sub>2</div> <div>(the weaker the base after the group departs, the better the leaving group)</div>	

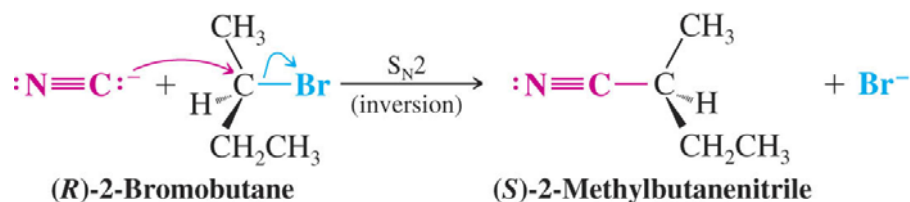
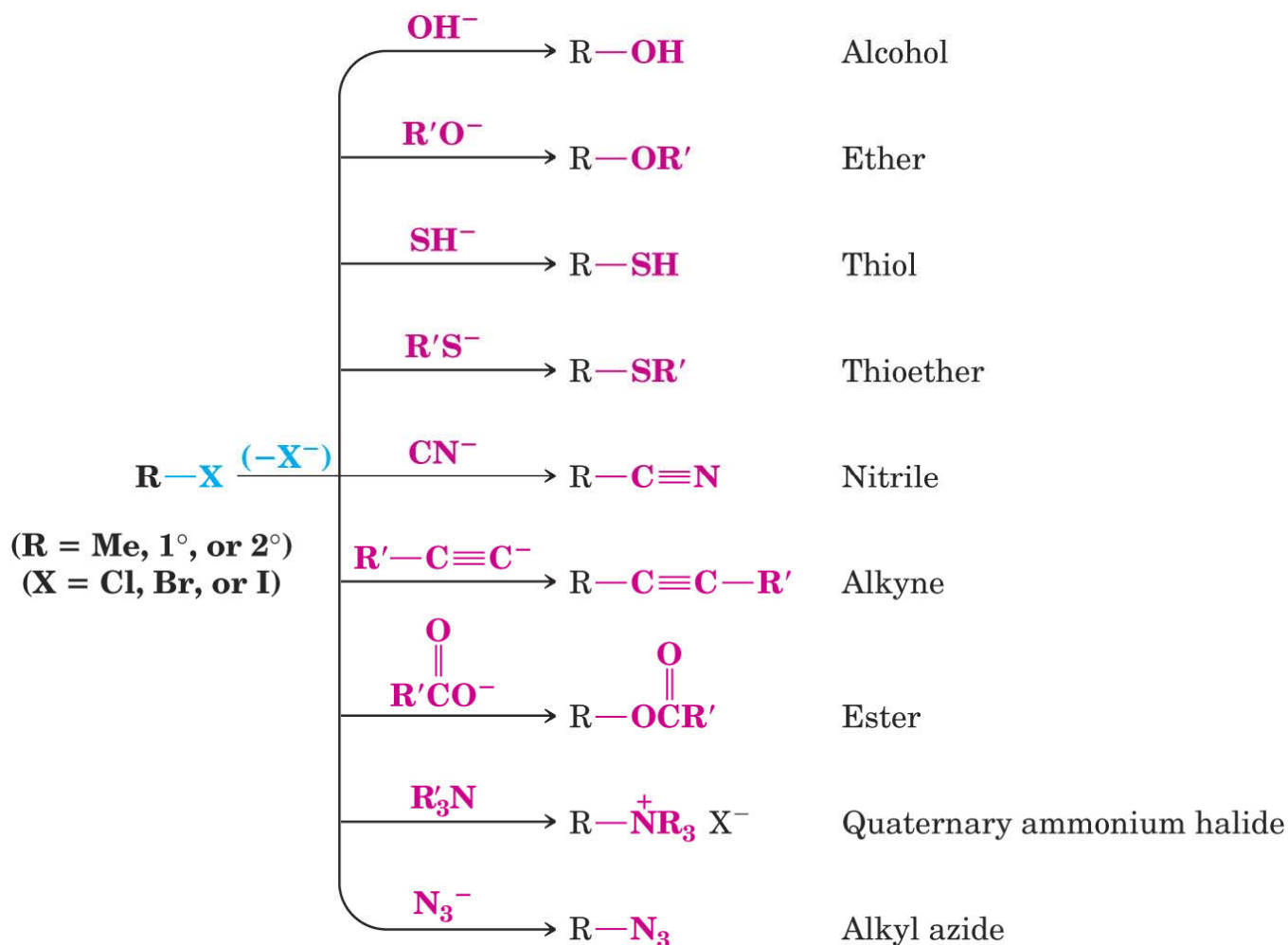
## SN1, SN2反應小結：

- 1)一般來講，能形成穩定正碳離子的底物 (tertiary halides), 親核性較弱的 nucleophiles, 以及 polar protic solvents 有利於 SN1 反應的發生. Such as solvolysis reactions of tertiary halides.
- 2)立體位阻小的底物 (methyl halides and primary halides), 親核性較強的 nucleophiles, polar aprotic solvent, 以及高濃度的 nucleophiles 則有利於 SN2 反應的發生.
- 3)離去基團的影響對 SN1 和 SN2 反應相同，即穩定的弱鹼離子為好的離去基



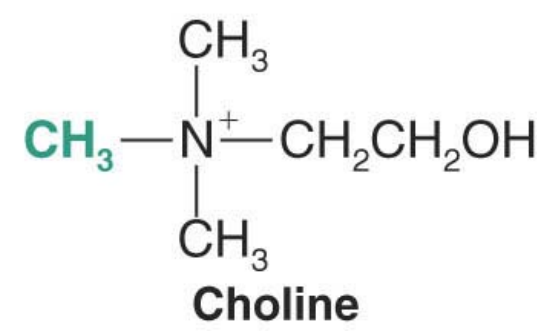
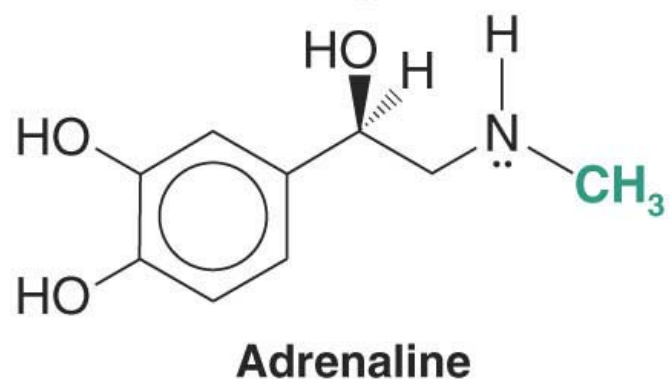
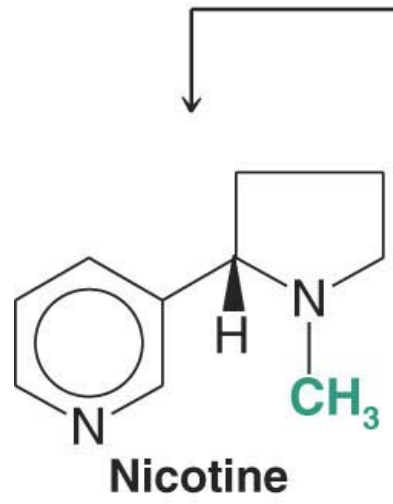
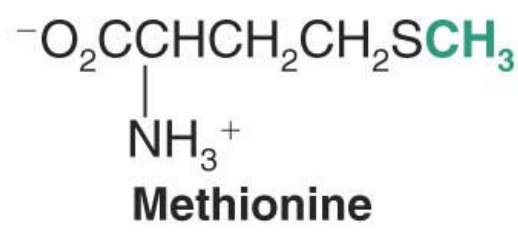


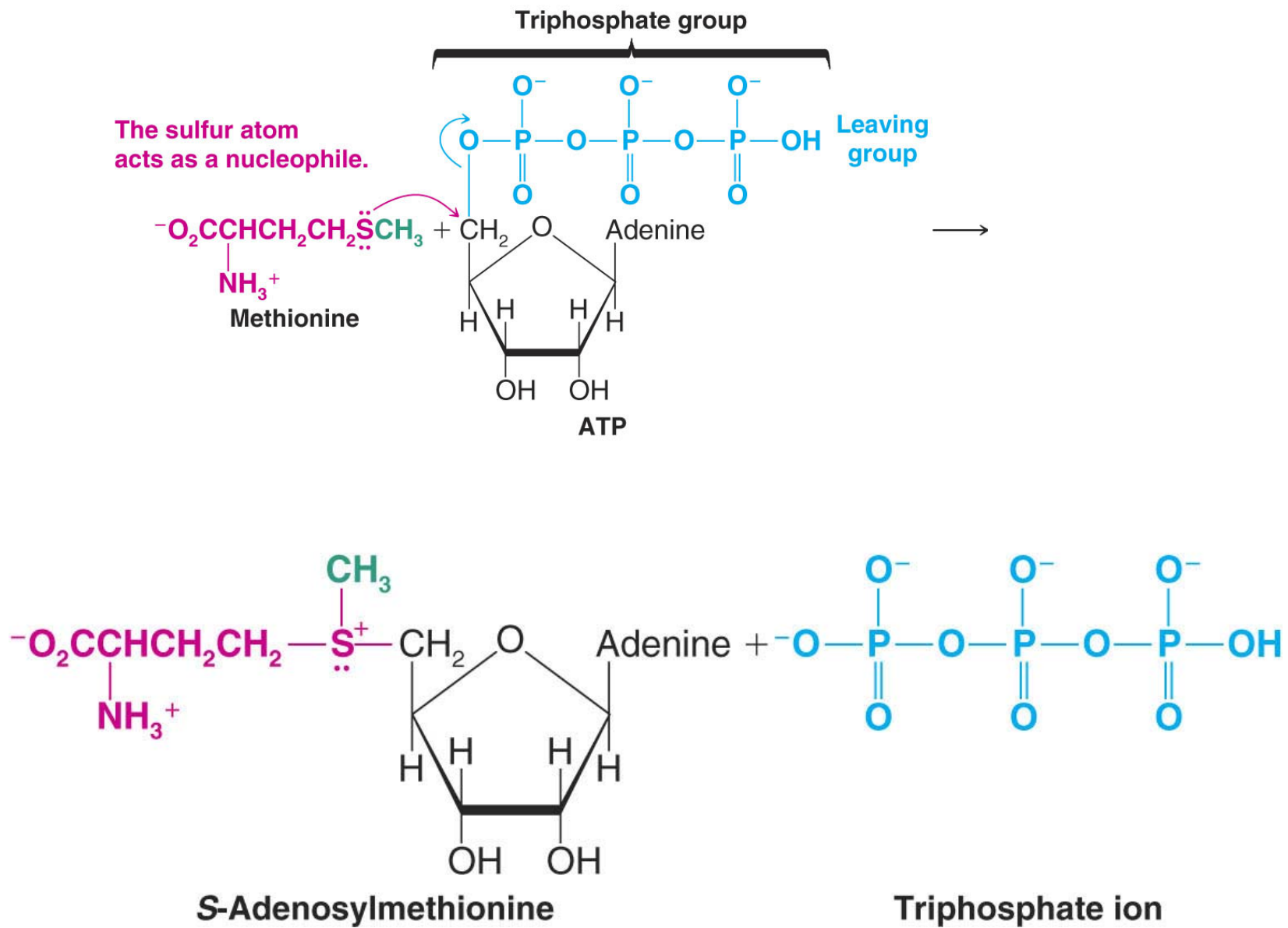
# Functional Group Transformations using SN2 Reactions:

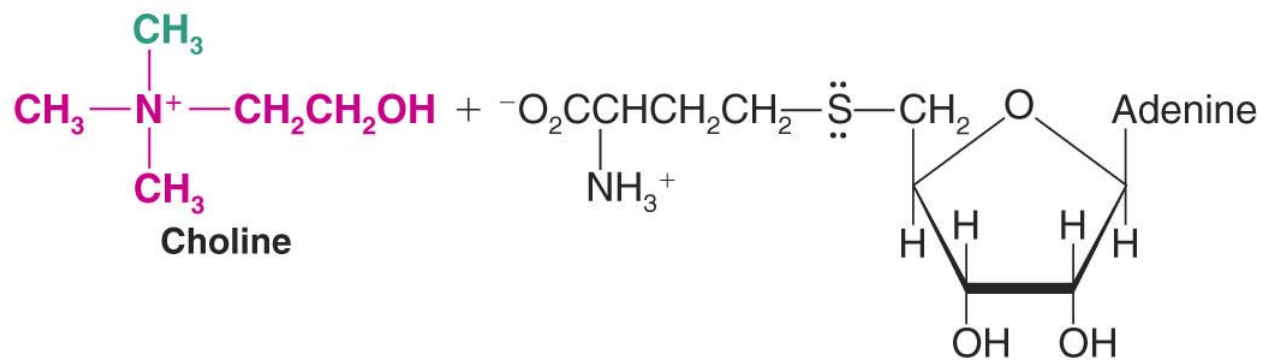
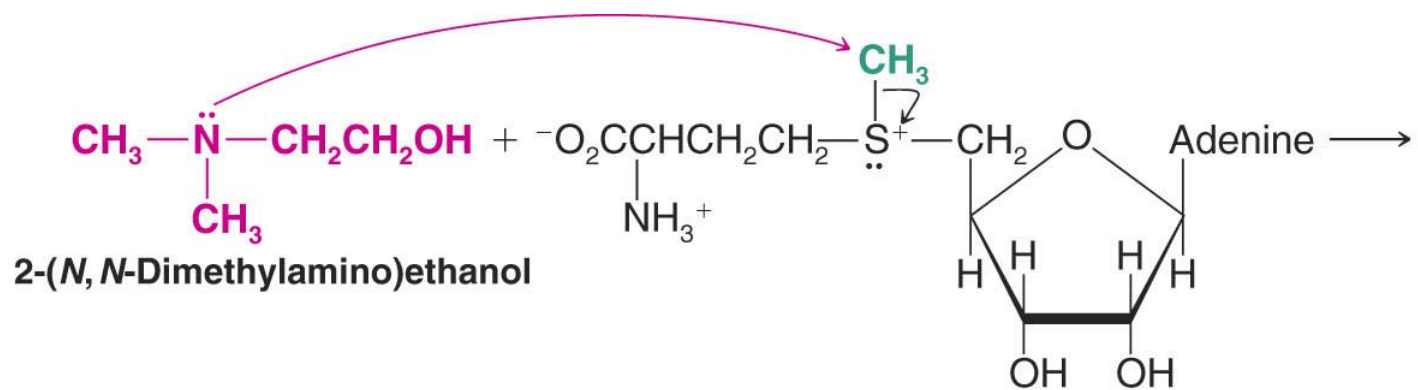


Stereochemistry can be controlled in SN2 reactions

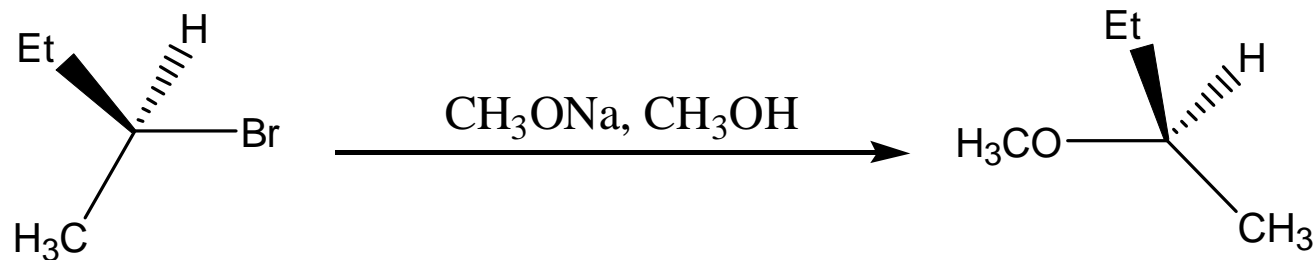
生化反應中SN2反應實例



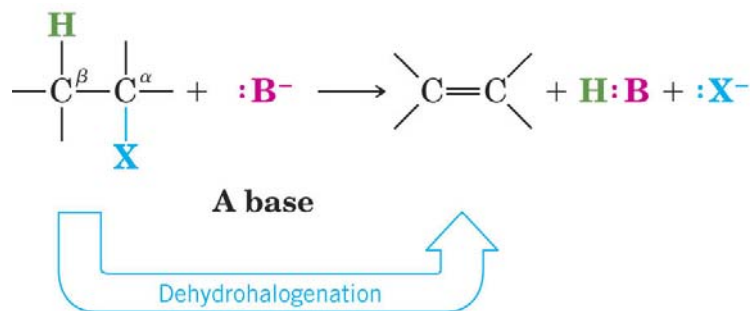




課堂練習: Page 270: Starting with (S)-2-bromobutane, outline syntheses of Each of the following compounds:



## 7) 鹵代烷烴的消除反應 (elimination reaction)



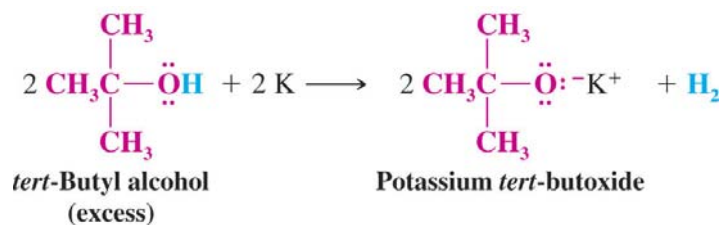
為製備烯烴的主要方法

Explain what is  $\alpha$  carbon and what is  $\beta$  carbon


$$2 \text{CH}_3\text{CH}_2\ddot{\text{O}}\text{H} + 2 \text{Na} \longrightarrow 2 \text{CH}_3\text{CH}_2\ddot{\text{O}}:^-\text{Na}^+ + \text{H}_2$$

Ethanol
Sodium ethoxide  
(excess)
dissolved in  

excess ethanol



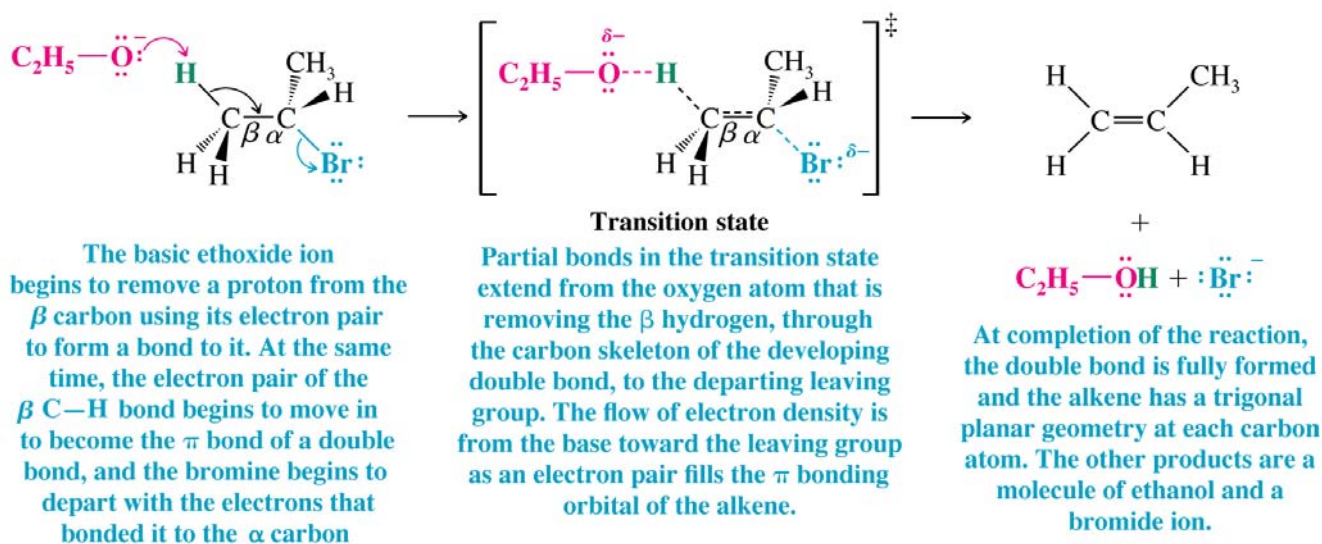
## a) E2消除反應的反應的機制

E<sub>2</sub>:

Reaction:



Mechanism:

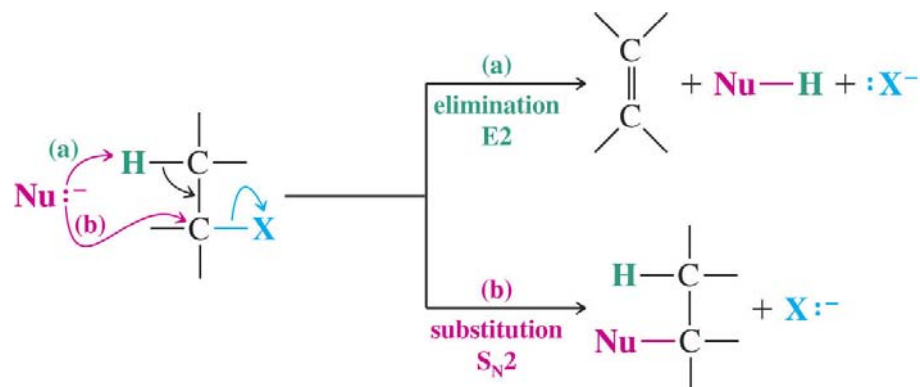


$$\text{Rate} \propto [\text{CH}_3\text{CHBrCH}_3][\text{C}_2\text{H}_5\text{O}^-]$$

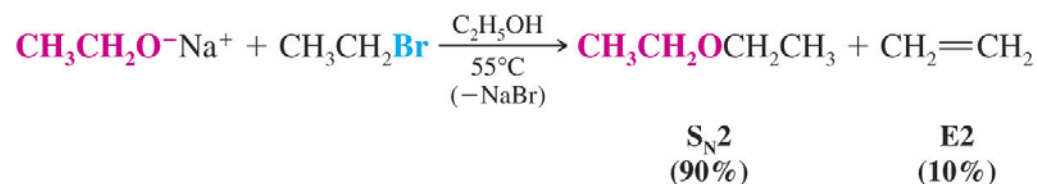
$$\text{Rate} = k[\text{CH}_3\text{CHBrCH}_3][\text{C}_2\text{H}_5\text{O}^-]$$

E<sub>2</sub> reaction involves concerted removal of the proton, formation of the double bond, and departure of the leaving group  
 The orientation of the hydrogen being removed and the leaving group is in the same plane.

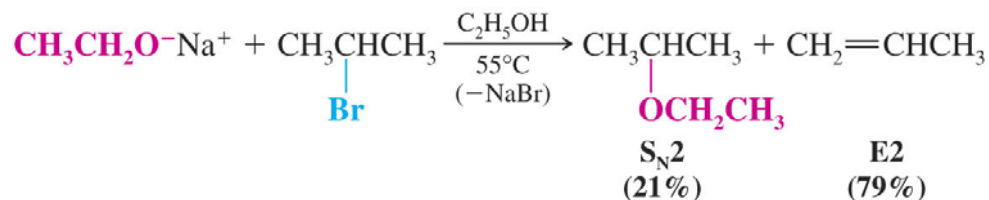
b) E2 versus SN2: 兩種反應均在高濃度的nucleophiles下容易發生。



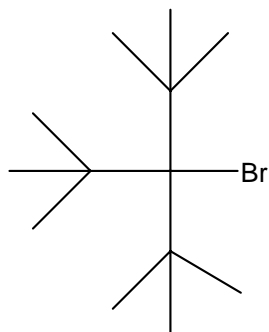
規則 1: 當底物為一級鹵代烷烴，在小體積強鹼條件下，SN2反應佔優勢。



規則 2: 當底物為二級鹵代烷烴，在強鹼條件下，E2反應佔優勢。

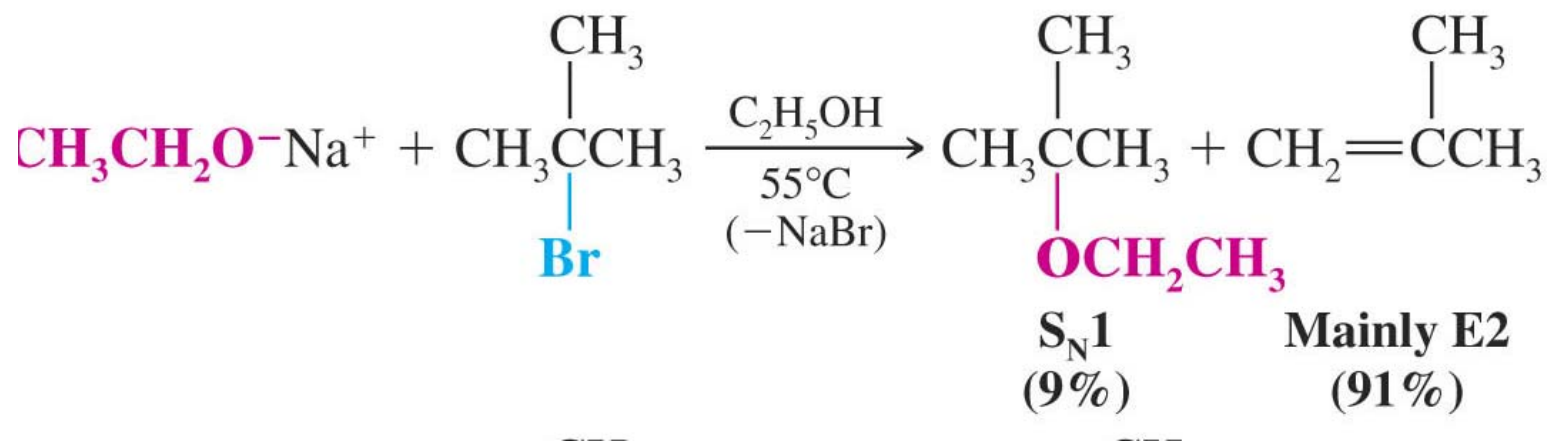






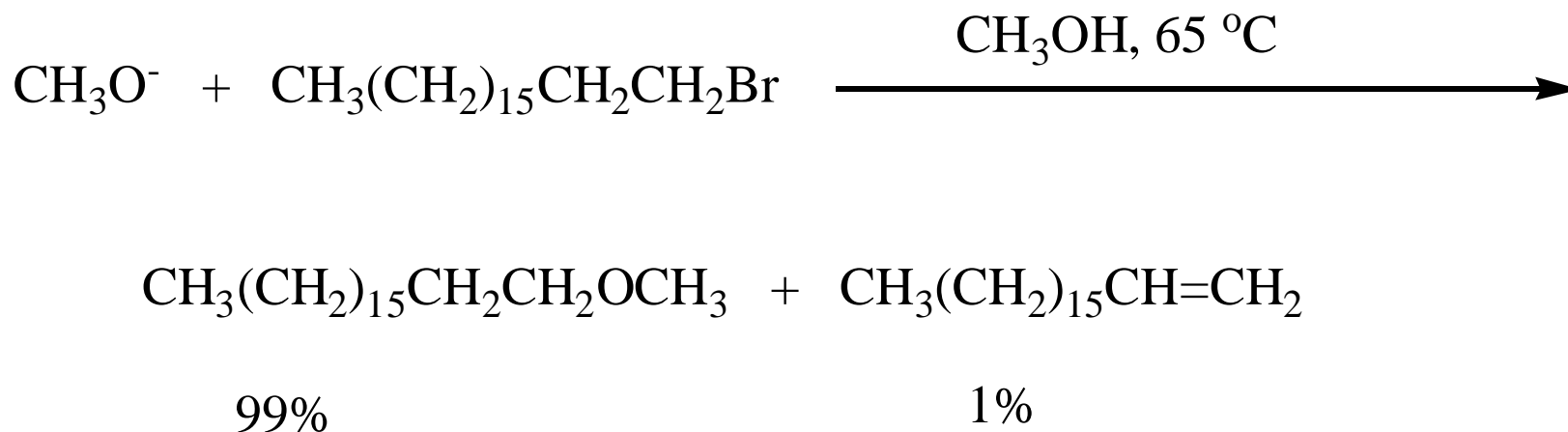
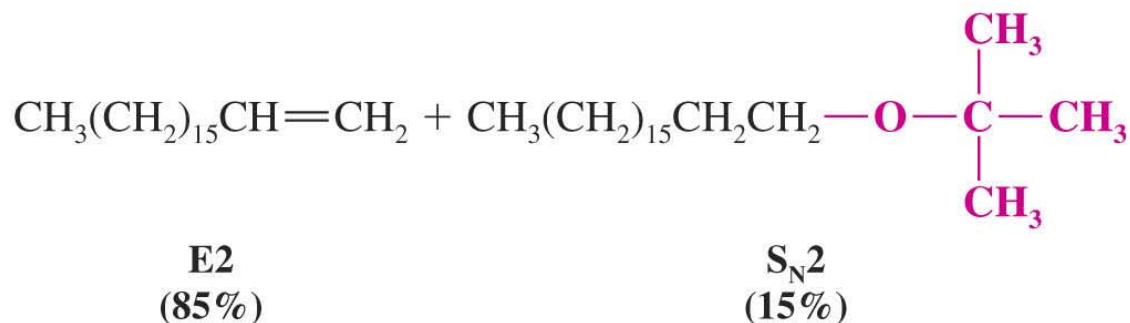
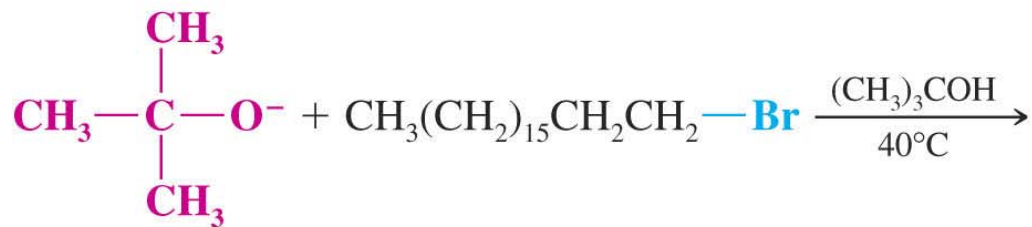
想一想此化合物會不會發生消去反應？

規則 3: 當底物為三級鹵代烷烴， $S_N2$ 反应几乎不会发生。在加熱強鹼條件下，消除反應占絕對優勢。



規則 4: 加熱條件有利於消除反應 (both E1 and E2) 的發生。

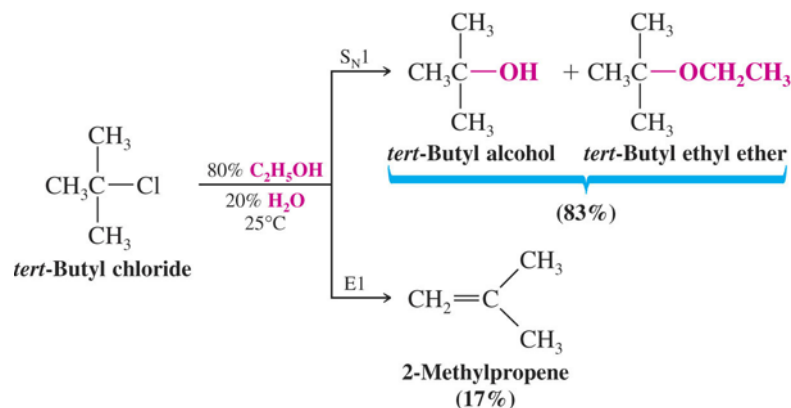
規則 5: 體積大的鹼有利於E2反應的發生



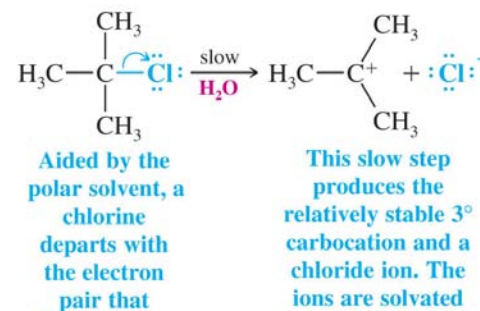
規則 6：低極化的強鹼（ $\text{NH}_2^-$ ,  $\text{CH}_3\text{O}^-$ , etc）有利於E2反應的發生；而高極化的弱鹼（ $\text{Cl}^-$ ,  $\text{CH}_3\text{CO}_2^-$ ）則有利於 $\text{S}_\text{N}2$ 反應的發生。

### c) E1 消除反應及其反應機制

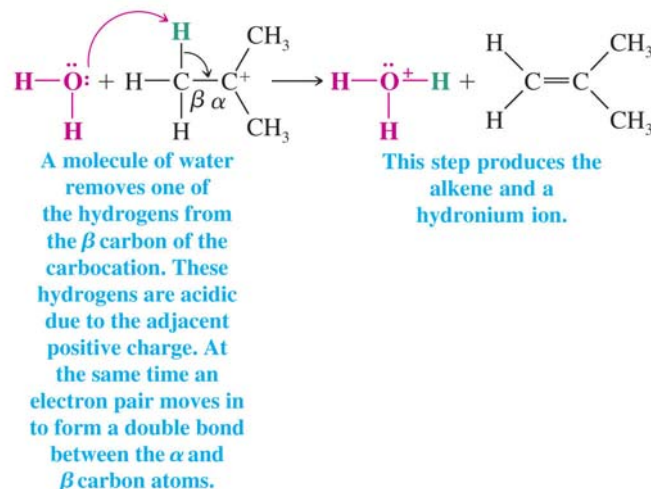
The E1 reaction competes with the S<sub>N</sub>1 reaction and likewise goes through a carbocation intermediate.



Step 1



Step 2

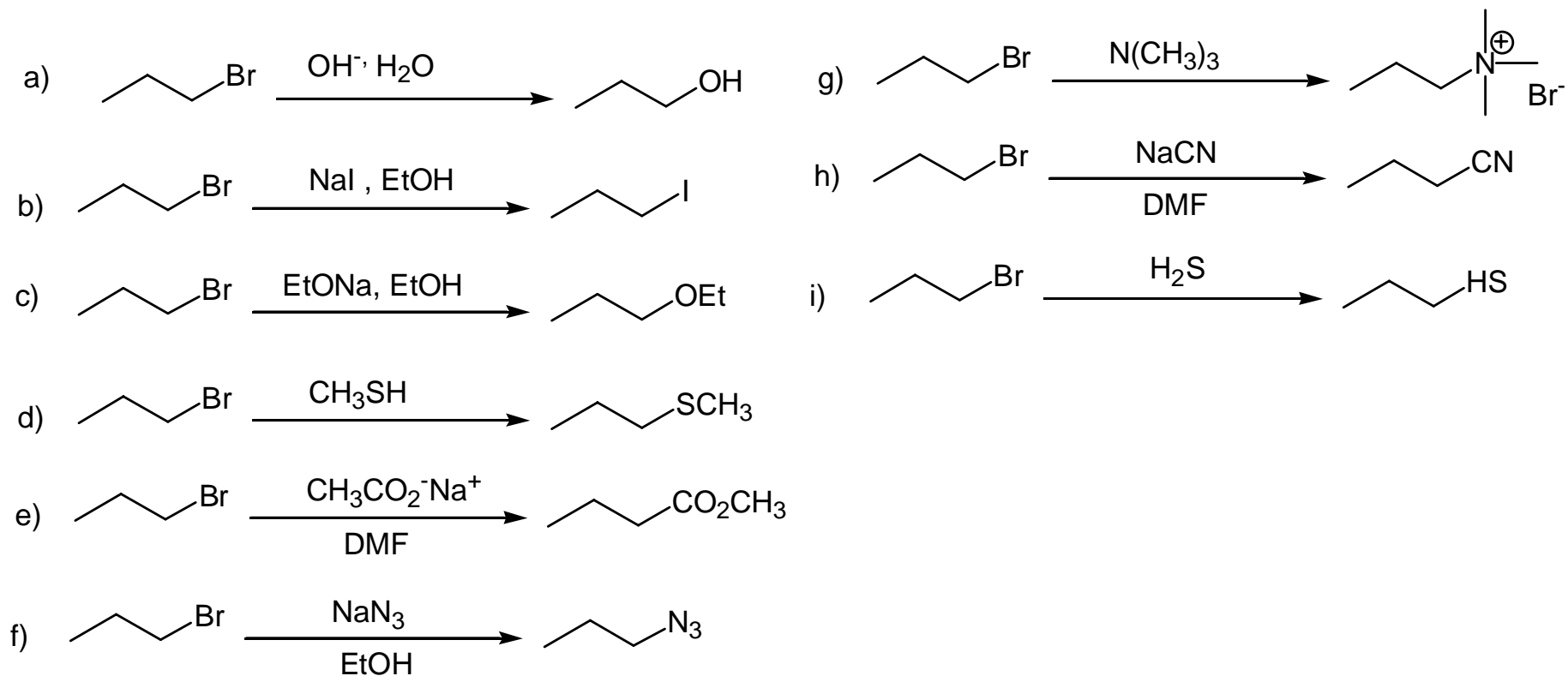


**d) E1 versus SN1: 加熱及強鹼有利於E1反應的進行**

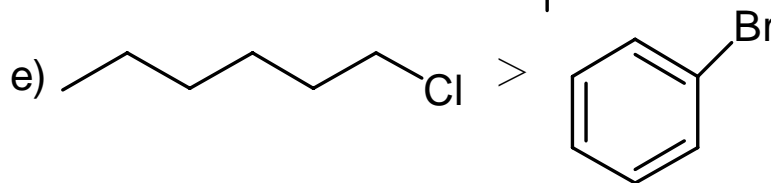
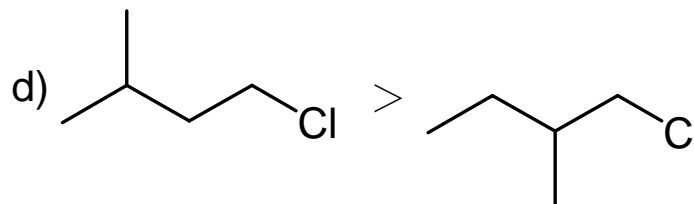
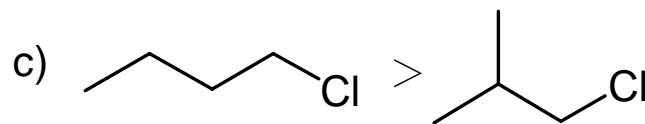
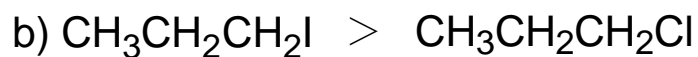
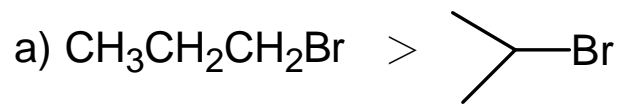
**課堂練習: 認真討論 cases on Page 278**

## 課堂練習

**6.13 Show how you might use a nucleophilic substitution reaction of propyl bromide to synthesize each of the following compounds.**



**6.14 Which alkyl halides would you expect to react more rapidly by an  $\text{S}_{\text{N}}2$  reaction**



**6.15 Which  $\text{S}_\text{N}2$  reaction of each pair would you expect to react more rapidly in protic solvent? Explain**

a) 1) > 2)

b) 2) > 1) 原子半徑較小的親核試劑易形成較強的氫鍵

c) 2) > 1) 原子半徑較小的親核試劑易形成較強的氫鍵

d) 2 > 1) the concentration of nucleophile is higher

**6.16 Which  $\text{S}_\text{N}1$  reaction of each pair would you expect to react more rapidly in protic solvent? Explain**

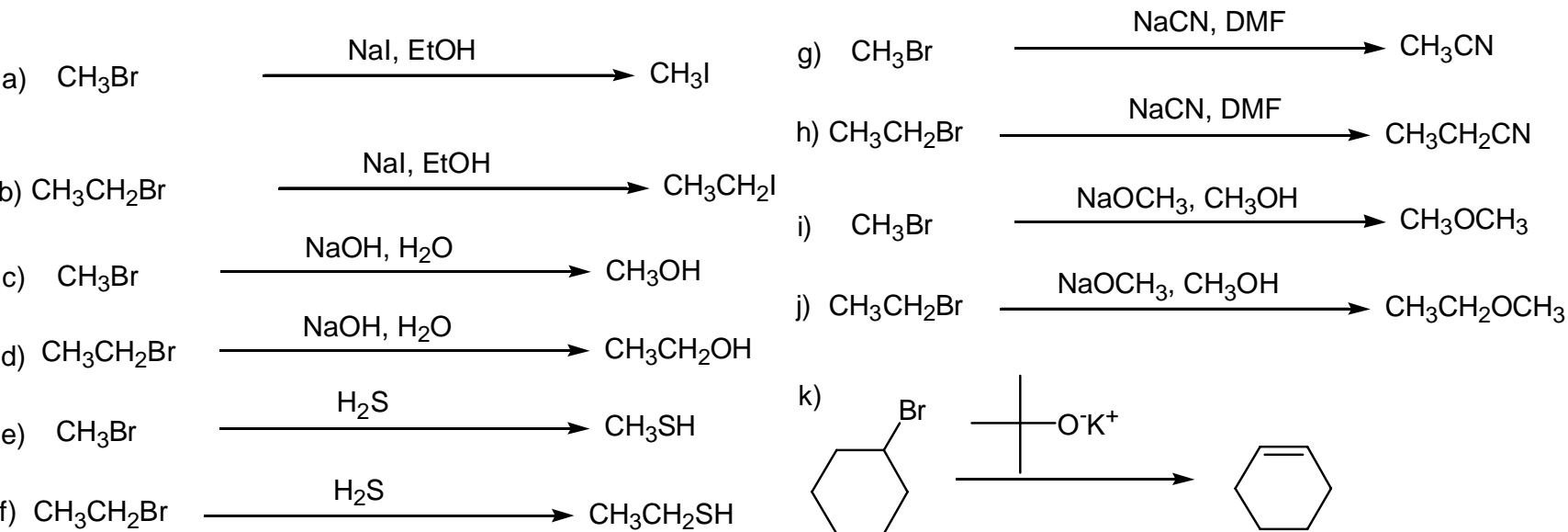
a) 2) > 1): Br is better leaving group

b) 1) > 2): CH<sub>3</sub>OH is weaker base (see page 105)

c) 2) > 1): concentration

d) about the same; e) 1) > 2)

## 6.17 synthesize the following compounds:



## 6.18

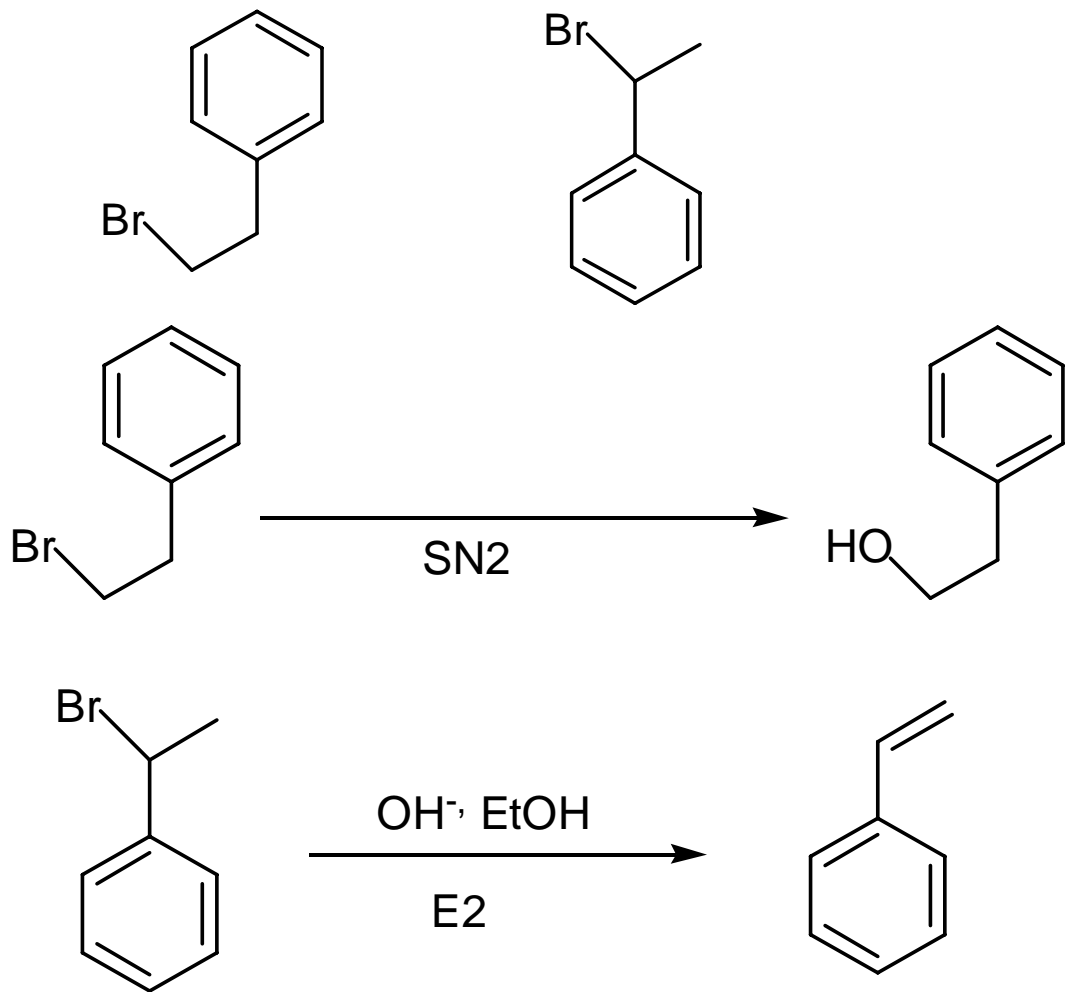
a) Strong base can not be as leaving group.

b) same as above

c) same as above

d) ??? e) CH<sub>3</sub>O<sup>-</sup> is a strong base f) the formation of NH<sub>4</sub><sup>+</sup> and CH<sub>3</sub>OH

**6.19 Which compound is more suitable for preparing styrene by dehydrohalogenation using KOH in ethanol?**

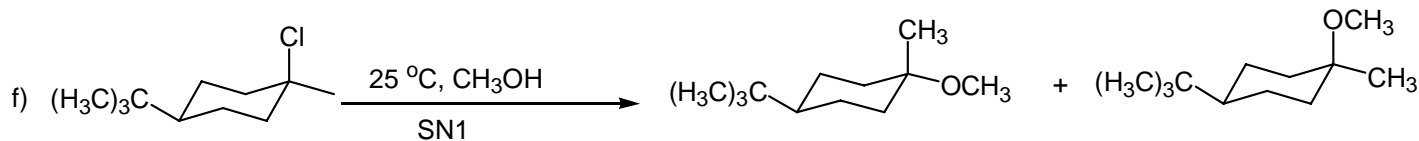
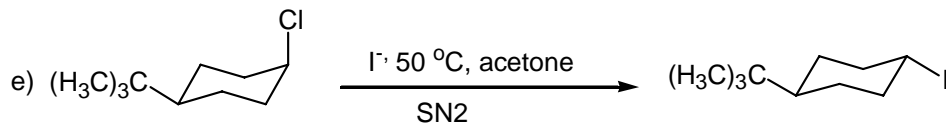
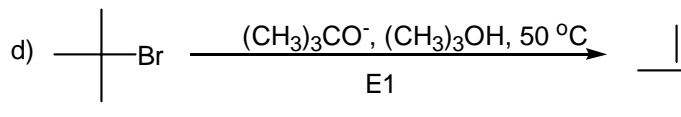
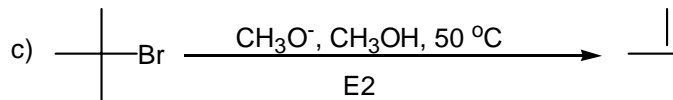
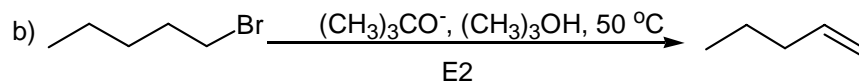
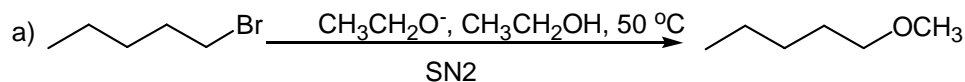


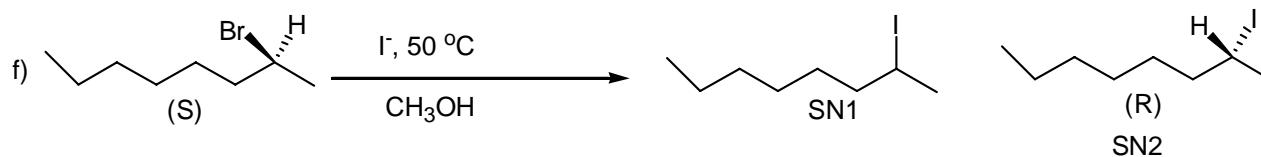
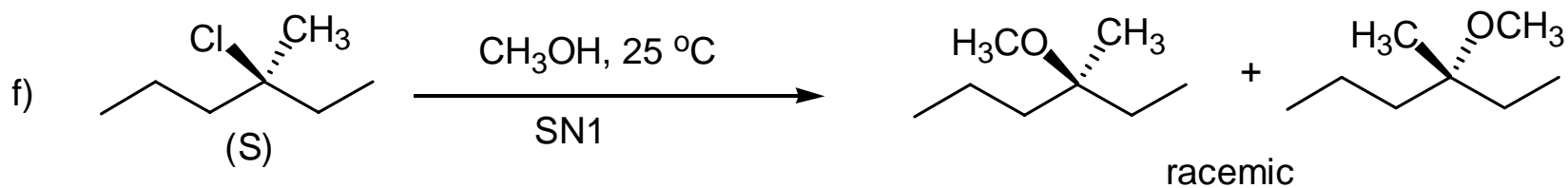
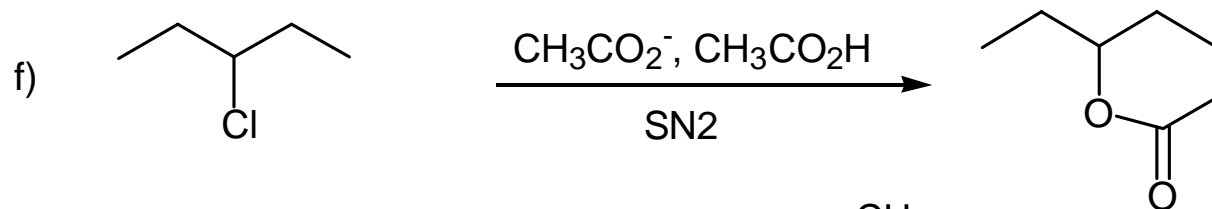
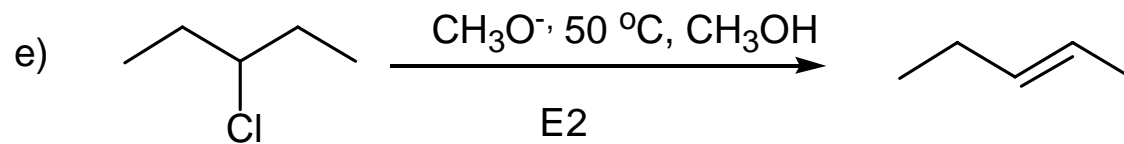


## 6.20 Which of the following reaction is more suitable for the preparation of $\text{CH}_3\text{OCH}(\text{CH}_3)_2$

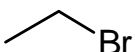
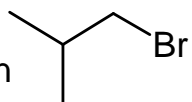
Answer: 2) Is better than 1), because 對於1)來說；消除反應佔優勢。

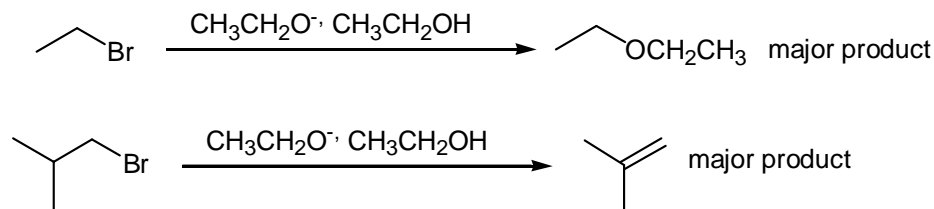
## 6.21 write the major product:





## 6.23 Explain:

In SN2 reaction,  is more than 10 times faster than  because of the less steric hindrance



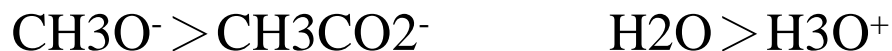
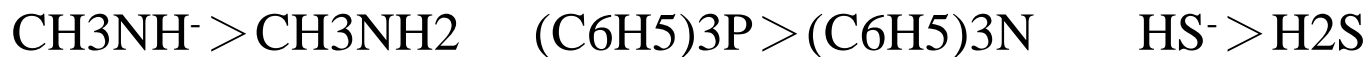
對isobutyl bromide來講，SN2反應會受到部分立體阻礙，故E2反應在強鹼條件下佔優勢

## 6.24

**Answer: SN2**

## 6.25

**Answer: in protic solvent; nucleophilicity:**



**6.33 Give the structure of the products:**

