Lecture 4

Alkyl Halides, Substitutions on Saturated Carbons

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Organic Mechanisms

Basic Organic Reactions, Electron Effects

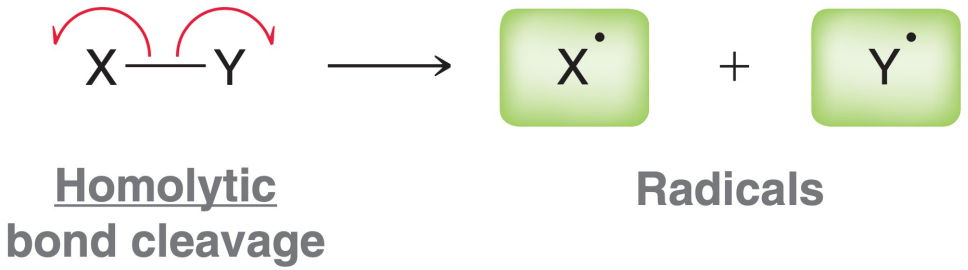
- 基本有机反应

自由基反应(free radical reaction)

离子型反应(ionic reaction)

协同反应(concerted reaction)

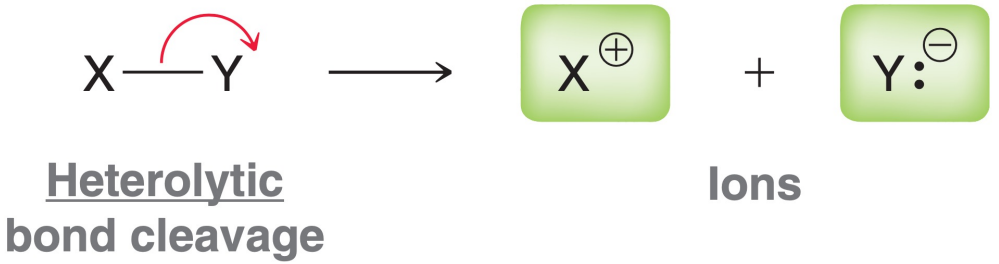
- 自由基反应(free radical reaction)



均裂(homolysis)产生自由基(free radical)

分子均裂产生自由基而引发的反应称为自由基反应

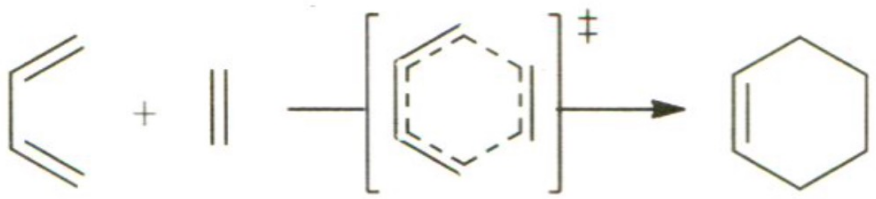
- 离子型反应(ionic reaction)



异裂(heterolysis)产生离子

分子异裂产生阴阳离子而引发的反应称为离子型反应

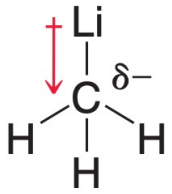
- 协同反应(concerted reaction)

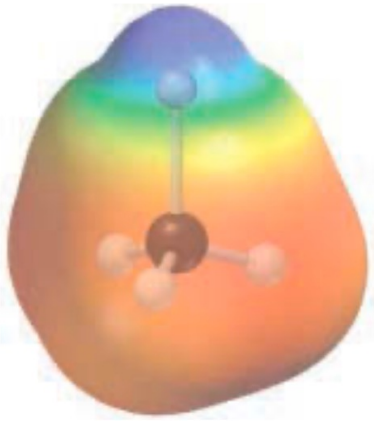


在反应过程中，旧键断裂和新键形成在同一步完成的反应称为协同反应

- 亲核试剂与亲电试剂

Methyllithium



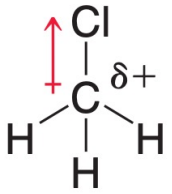


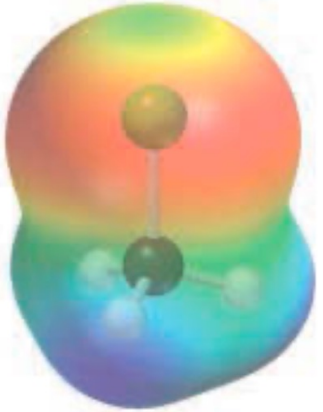
The carbon atom is electron rich

碳原子中心富电子

亲核试剂(nucleophile)

Methyl chloride

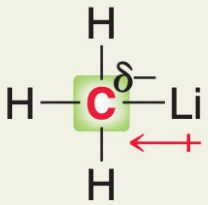
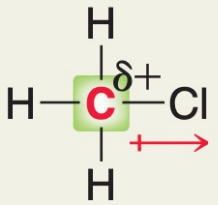
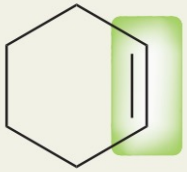




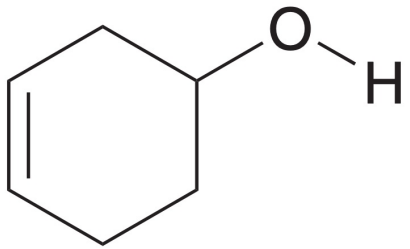
The carbon atom is electron deficient

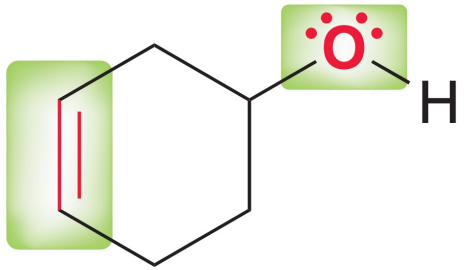
碳原子中心贫电子

亲电试剂(electrophile)

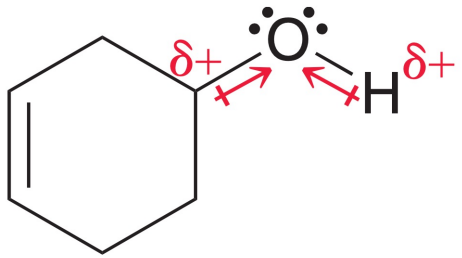
NUCLEOPHILES		ELECTROPHILES	
FEATURE	**EXAMPLE**	**FEATURE**	**EXAMPLE**
Inductive effects		Inductive effects	
Lone pair		Empty *p* orbital	
π Bond			

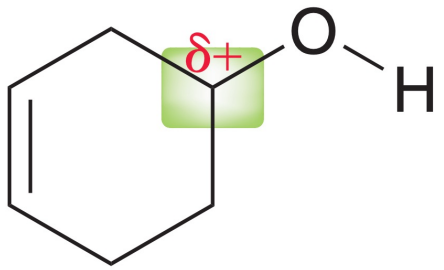
- Practice: identify all nucleophilic centers and all electrophilic centers in the following compound:





nucleophilic centers



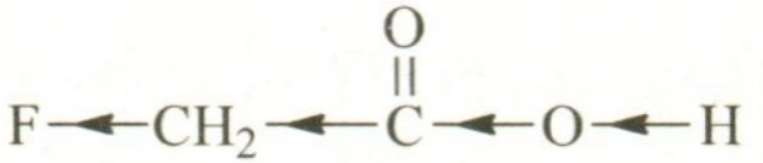


electrophilic center

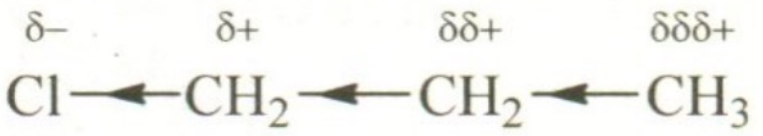
- 有机化学中的电子效应

  - 诱导效应(inductive effect)
  - 共轭效应(conjugation effect)
  - 超共轭效应(hyperconjugation)
  - 场效应(field effect)

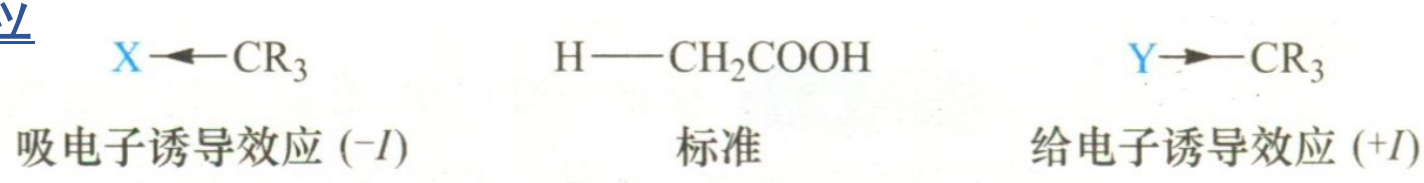
- 诱导效应(inductive effect)
  - 电子沿着原子链传递



  - 作用随距离增长迅速下降，一般只考虑**三根键**的影响



  - 以**乙酸的α氢作为标准**，如取代基的**给电子能力比其强**，则具有给电子诱导效应



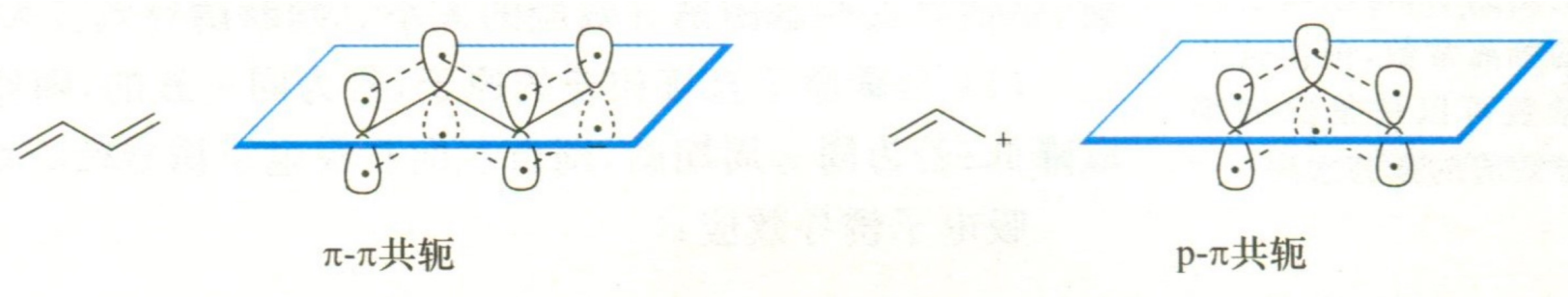
- 比较诱导效应的大小和方向
  - 与碳原子直接相连的原子，**电负性越大**，吸电子诱导效应**越强**
  - 与碳原子直接相连的基团，**不饱和程度越大**，吸电子诱导效应**越强**
  - 基团带**正电荷-吸电子**；**负电荷-给电子**；具有**配位键-吸电子**

$$-\overset{+}{N}R_3 > -NO_2 > -CN > -COOH > -COOR > -\overset{O}{\overset{\|}{C}}R\ (或\ -\overset{O}{\overset{\|}{C}}H)$$

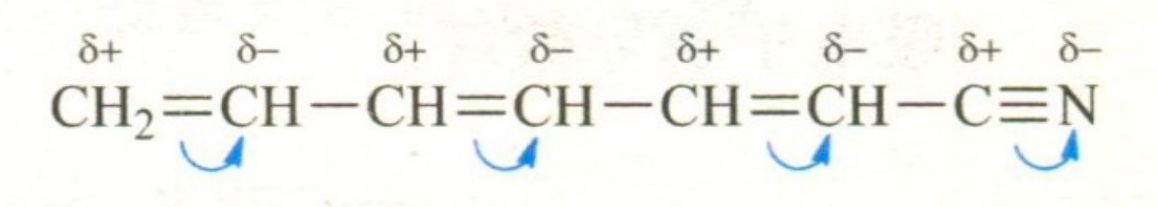
$$> -F > -Cl > -Br > -I > -C{\equiv}CH > -OCH_3\ (或\ -OH)$$

$$> -C_6H_5 > -CH{=}CH_2 > H$$

- 共轭(conjugation)
  - **单双键交替(π-π)**或**双键碳的相邻原子上有轨道(p-π)**的体系称为共轭体系(conjugated system)
  - 在共轭体系中，π电子（p电子）的运动范围会扩展到整个体系，即电子发生**离域(delocalized)**



- 共轭效应(conjugation effect)
  - 在共轭体系中，由于原子间的相互影响而使体系内的π电子（或p电子）分布发生变化的电子效应称作共轭效应
  - 共轭体系上能**降低**体系π电子云密度的基团有**吸电子共轭效应**；共轭体系上能**增高**体系π电子云密度的基团有**给电子共轭效应**
  - 特点：只能在共轭体系中传递；无论共轭体系有多大，共轭效应**始终能贯穿于整个共轭体系中**



- 吸电子/给电子共轭效应
  - 含有**孤对电子的原子**构成的基团，如N、O、F、S、Cl、Br、I构成的基团：羟基(-OH)、氨基(-NH_3)、卤素(-X)，这类基团一般为给电子共轭效应
  - 含有**重键**的基团：只有该基团第一个原子构成不饱和键，才有共轭效应，形如**-A=B**，如果**A的电负性大于B**，那么它就有**给电子共轭效应**，比如：亚氨基(-N=CR_2)；
  - 反之，即**A的电负性小于B**，就是**吸电子共轭效应**，比如：甲酰基(-CHO)、羧基(-COOH)、硝基(-NO_2)

- Practice: analyze electron effects of the underline groups:

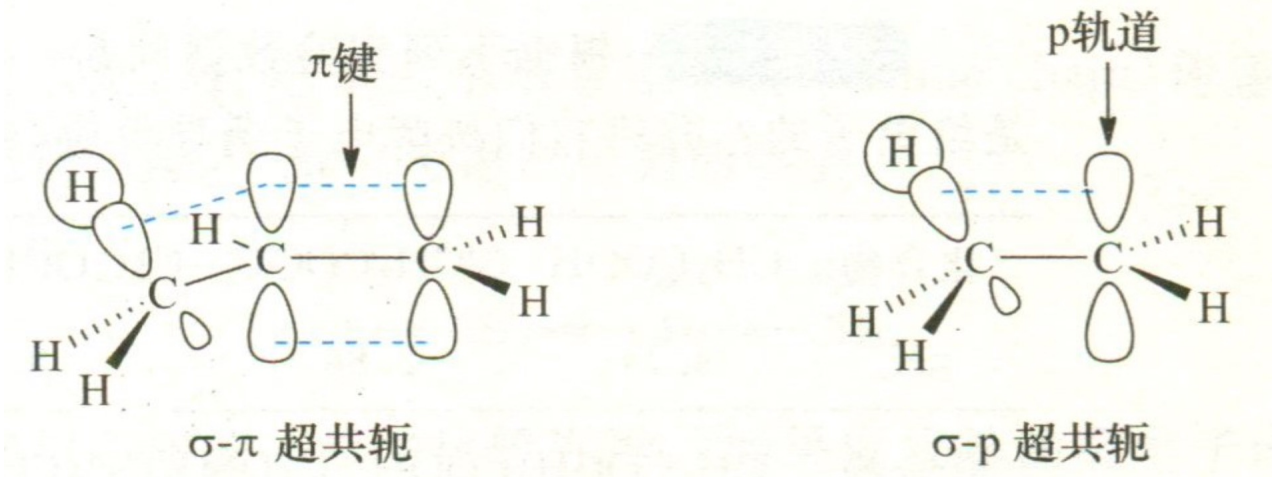
(i) $CH_2=CH-\underline{C\equiv N}$ (ii) $CH_2=CH-\underline{NO}$ (iii) $CH_2=CH-\underline{N(CH_3)_2}$

(i) $CH_2=\underset{H}{C}\rightarrow\underline{C\equiv N}$ 有吸电子诱导效应和吸电子共轭效应。

(ii) $CH_2=\underset{H}{C}\rightarrow\underline{N=O}$ 有吸电子诱导效应和吸电子共轭效应。

(iii) $CH_2=\underset{H}{C}\rightarrow\underline{N(CH_3)_2}$ 有吸电子诱导效应和给电子共轭效应。

- 超共轭效应(hyperconjugation)
  - **C-H的σ轨道**与**C=C的π轨道（或其旁边碳上的p轨道）接近平行**时的体系称为超共轭体系
  - 在超共轭体系中，C-H的σ键与π键（或p轨道）也会产生电子的离域现象，这种现象称为超共轭效应

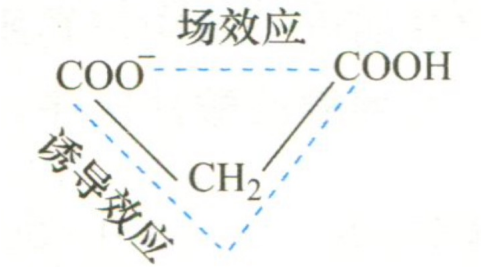


- 超共轭效应(hyperconjugation)
  - 在超共轭效应中，C-H的σ键是**给电子**的
  - 超共轭效应比共轭效应小得多
  - π轨道或p轨道相邻基团超共轭效应的大小次序：

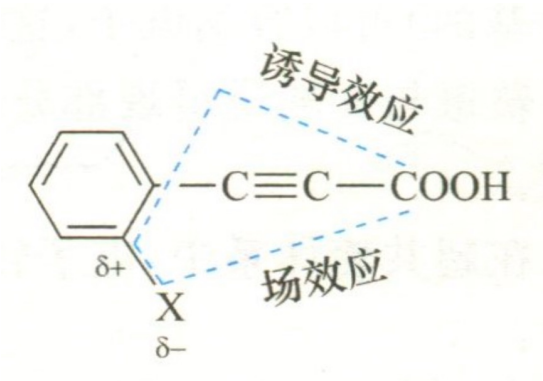
$$CH_3- > RCH_2- > R_2CH-$$

  - 超共轭效应的表示方式：

- 场效应(field effect)
  - 取代基在空间中产生电场，对附近的基团产生影响的效应称为场效应

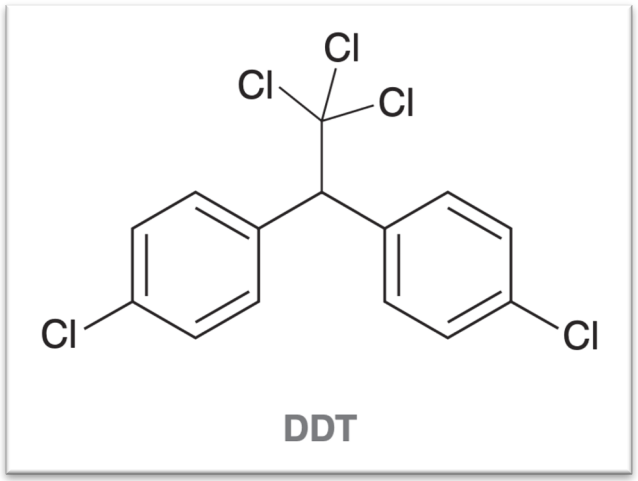


  - 场效应与诱导效应的作用可能相反



Alkyl Halides

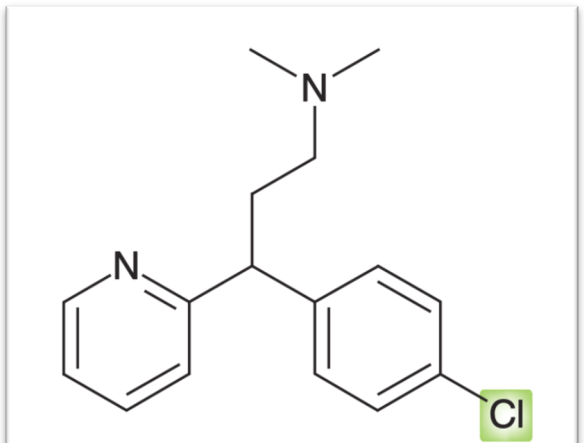
Nomenclature of Alkyl Halides, Physical Properties



DDT

dichlorodiphenyltrichloroethane

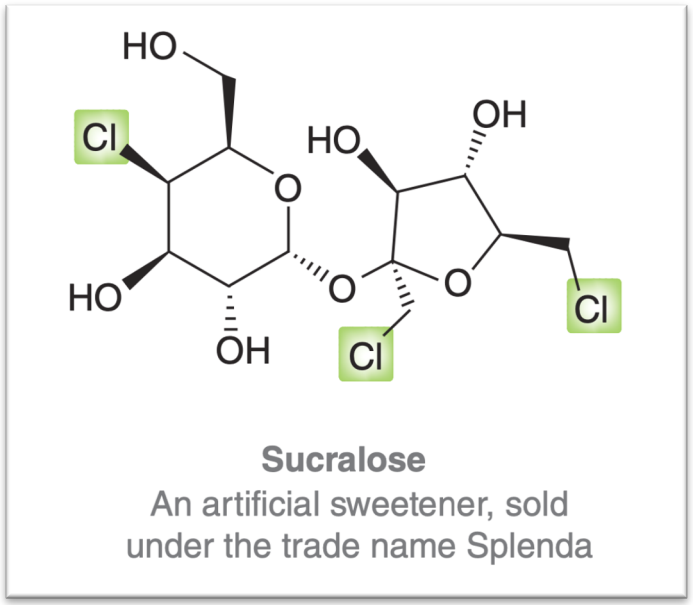
双对氯苯基三氯乙烷



Chlorpheniramine

An antihistamine, sold under the trade name Chlor-Trimeton

氯苯那敏【扑尔敏】

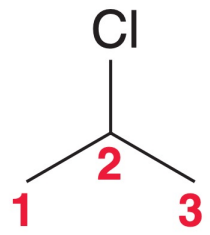


Sucralose

An artificial sweetener, sold under the trade name Splenda

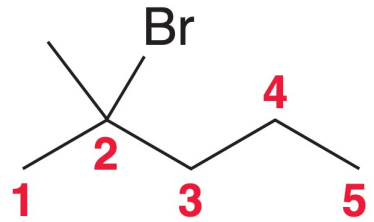
三氯蔗糖

- 卤代烃的系统命名
  - 卤代烃的命名法与普通烷烃大致相同
  - 命名时，将卤原子当作取代基
  - 卤原子的前缀：fluoro-, chloro-, bromo-, iodo-



2-Chloropropane

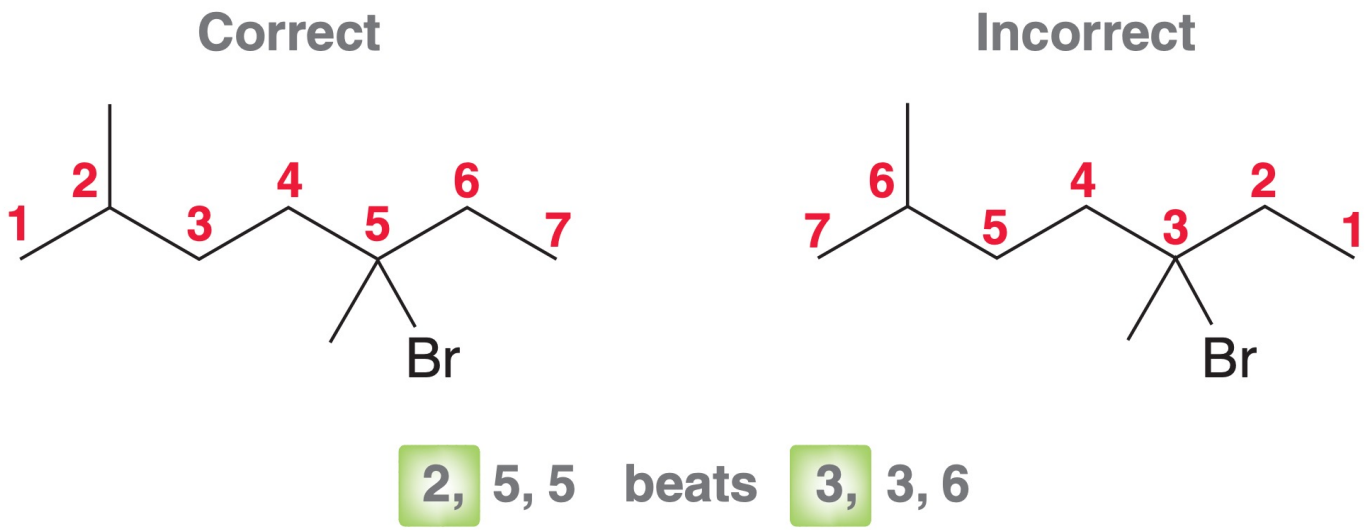
2-氯丙烷



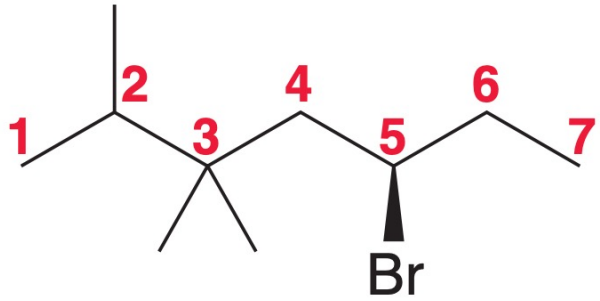
2-Bromo-2-methylpentane

2-溴-2甲基戊烷

- 尽可能让取代基（包括卤原子）位序最小



- 手性中心的构型必须指明

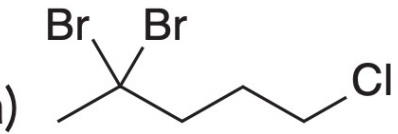


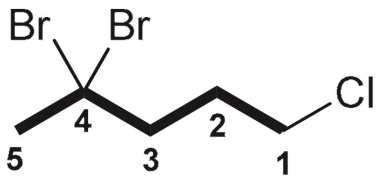
(*R*)-5-Bromo-2,3,3-trimethylheptane

(*R*)-5-溴-2,3,3-三甲基庚烷

- Practice: assign a systematic name for each of the following compounds:

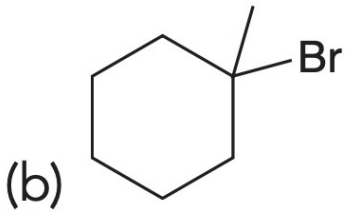
(a)

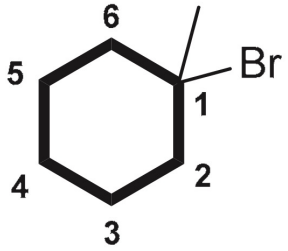




4,4-dibromo-1-chloropentane

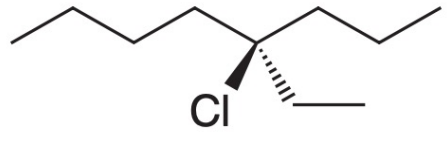
(b)

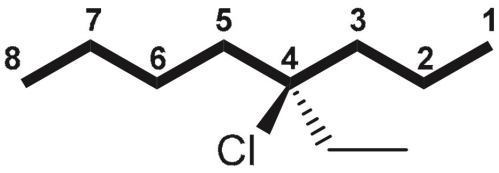




1-bromo-1-methylcyclohexane

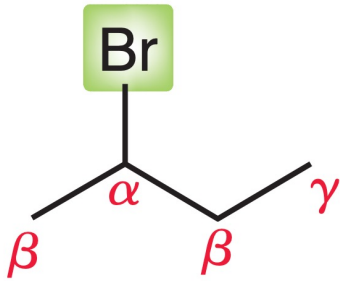
(c)



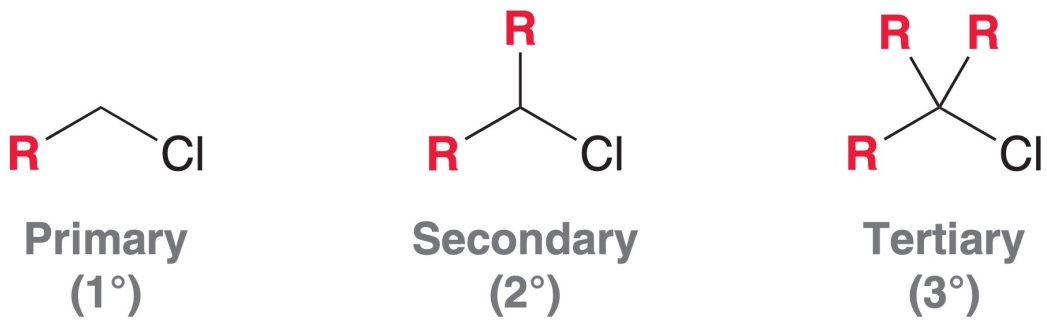


(*R*)-4-chloro-4-ethyloctane

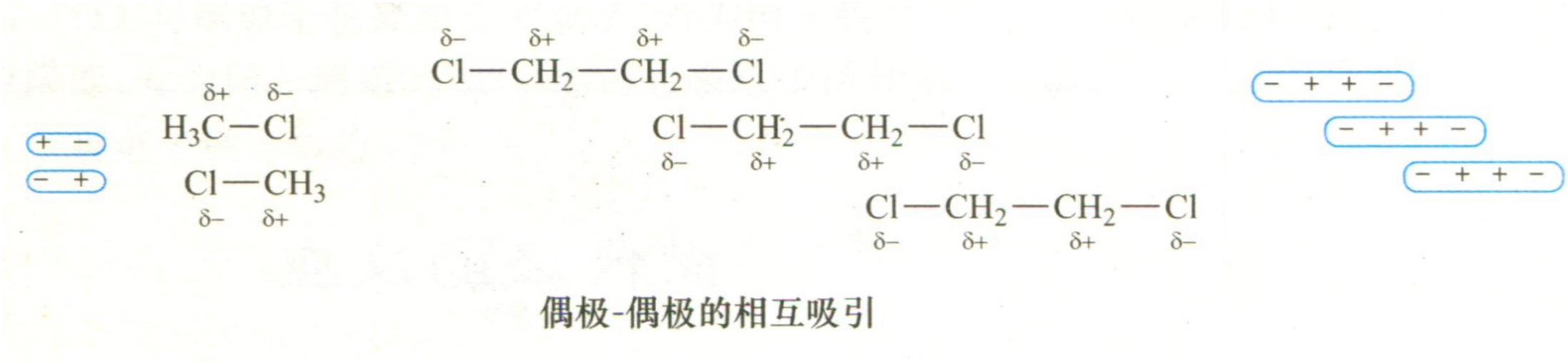
- α位，β位，γ位



- 卤代烃的级数



- 卤代烃的分子间力：取向力(dipole-dipole interactions)



	氟化物		氯化物		溴化物		碘化物	
	沸点/℃	相对密度(d_4^{20})	沸点/℃	相对密度(d_4^{20})	沸点/℃	相对密度(d_4^{20})	沸点/℃	相对密度(d_4^{20})
$CH_3—X$	−78.4		−24.2		3.6		42.4	2.279
$CH_3CH_2—X$	−37.7		12.3		38.4	1.440	72.3	1.933
$CH_3CH_2CH_2—X$	−2.5		46.6	0.890	71.0	1.335	102.5	1.747
$(CH_3)_2CH—X$	−9.4		34.8	0.859	59.4	1.310	89.5	1.705
$CH_3CH_2CH_2CH_2—X$	32.5	0.779	78.4	0.884	101.6	1.276	130.5	1.617
$CH_3CH_2CH(CH_3)—X$	25.3	0.766	68.3	0.871	91.2	1.258	120	1.595
$(CH_3)_2CHCH_2—X$	25.1		68.8	0.875	91.4	1.261	121	1.605
$(CH_3)_3C—X$	12.1		50.7	0.840	73.1	1.222	$100_{分解}$	
$CH_3CH_2CH_2CH_2CH_2—X$			108	0.883	130	1.223	157	1.517
 —X			142.5	1.000	165			
CH_2X_2	−52		40	1.336	99	2.49	$180_{分解}$	3.325
CHX_3	−83		61	1.489	151	2.89	升华	4.008
CX_4	−128		77	1.595	189.5	3.42	升华	4.32

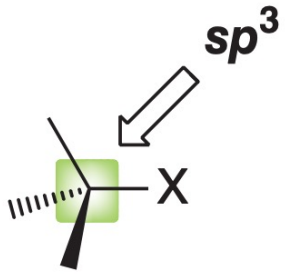
Substitutions on Saturated Carbons

S_N2, S_N1, Factors Determining Which Reaction Predominates,

Synthesis Route Design – Functional Group Transformation,

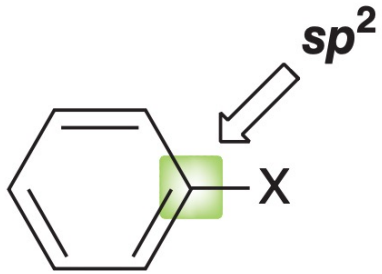
*Nucleophilic Substitution in Biochem

- 卤代烃



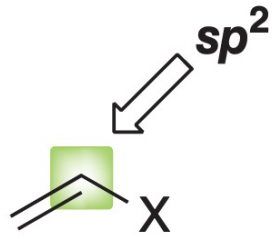
Alkyl halide

卤代（烷）烃



Aryl halide

卤代（芳）烃



Vinyl halide

卤代（烯）烃

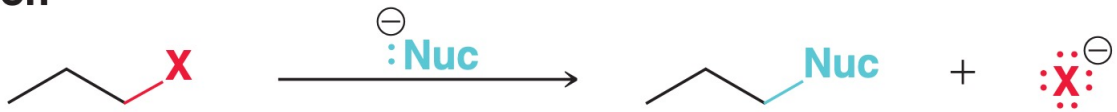
not saturated!

为什么没有F？

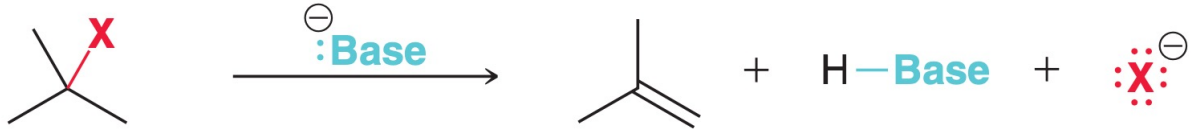
(X = Cl, Br, or I)

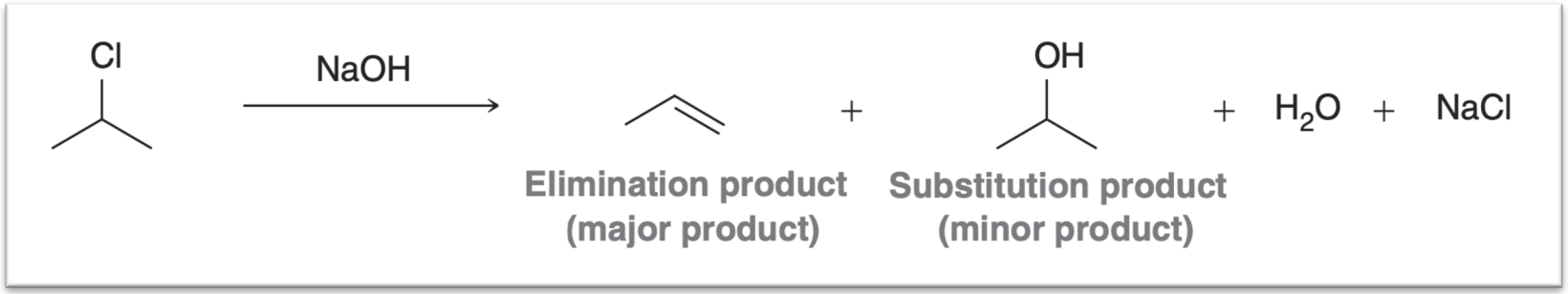
- 卤代烃的反应

Substitution

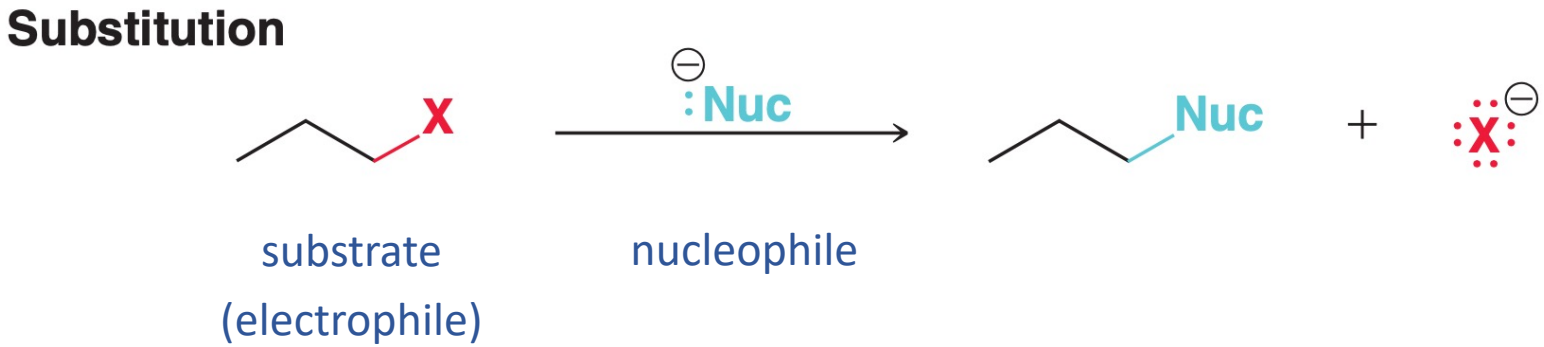


Elimination



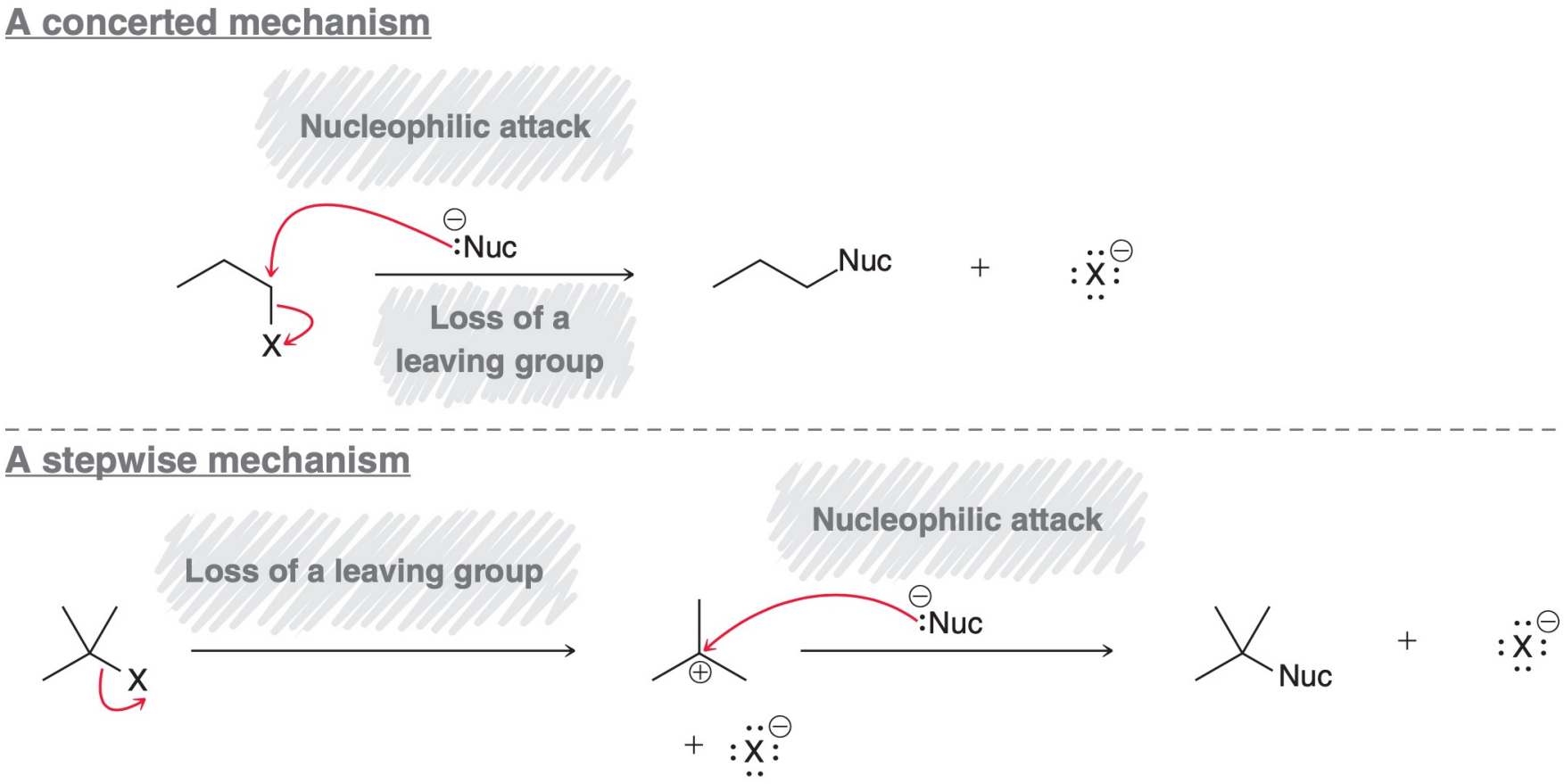


- 卤代烃的亲核取代反应(nucleophilic substitution reaction)

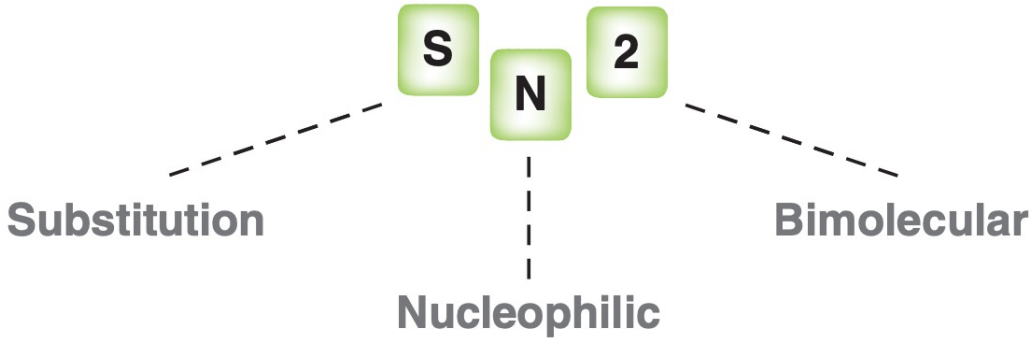


- Back to 1930s…

S_N2 reaction



- What is S_N2?



$$\text{Rate} = k\,[\text{alkyl halide}]\,[\text{nucleophile}]$$

- Practice

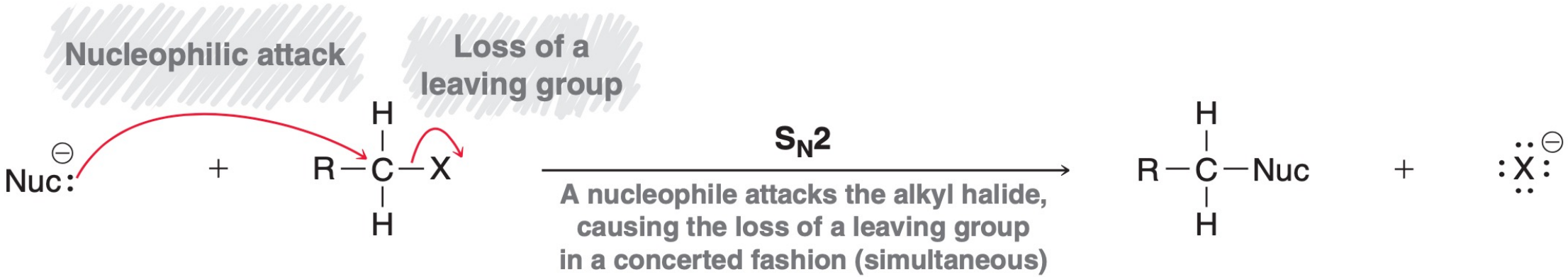
7.2 The following substitution reaction exhibits second-order kinetics, and is therefore presumed to occur via an S_N2 process:

(a) What happens to the rate if the concentration of 1-iodopropane is tripled and the concentration of sodium hydroxide remains the same?

(b) What happens to the rate if the concentration of 1-iodopropane remains the same and the concentration of sodium hydroxide is doubled?

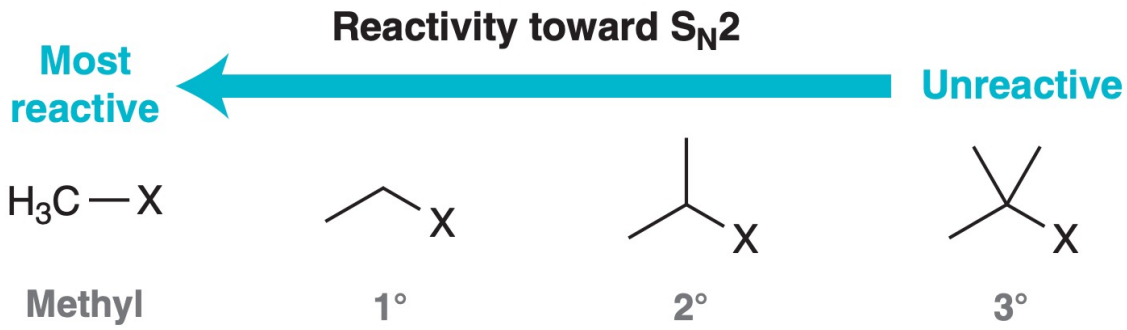
(c) What happens to the rate if the concentration of 1-iodopropane is doubled and the concentration of sodium hydroxide is tripled?

- **The S_N2 Mechanism**



- Practice: identify the nucleophile and substrate, then draw a mechanism for the following reaction:

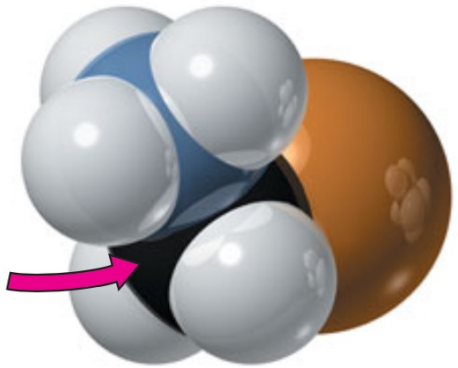
- S_N2反应的速率
  - 位阻越小，反应越快



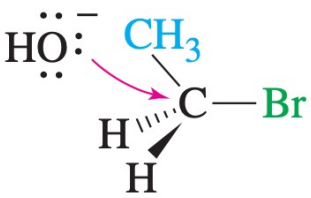
  - 基团越易离去，反应越快

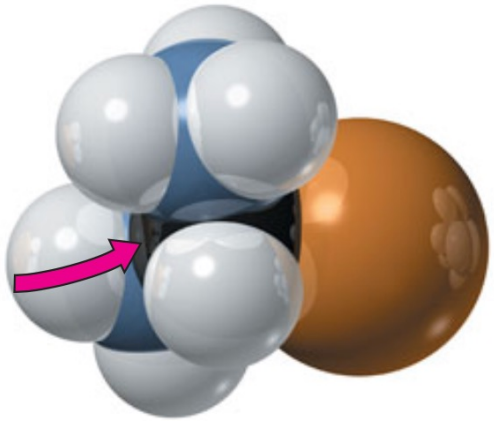
$$I^{\ominus} > Br^{\ominus} > Cl^{\ominus}$$

- 底物位阻对反应速率的影响

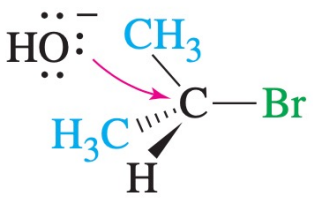


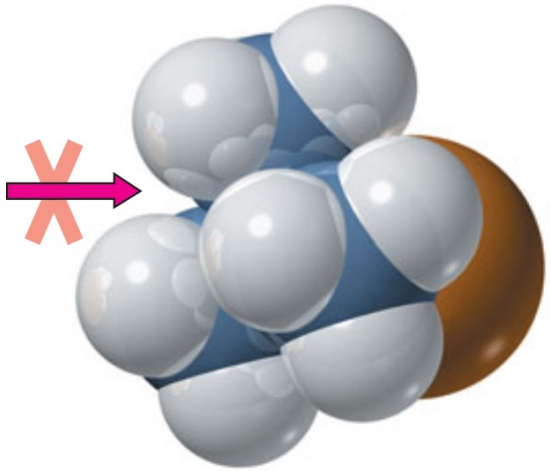
ethyl bromide (1°)
attack is easy



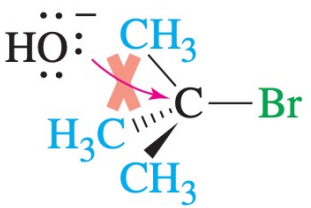


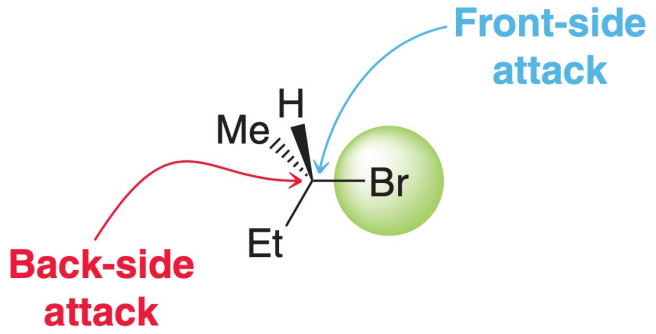
isopropyl bromide (2°)
attack is possible



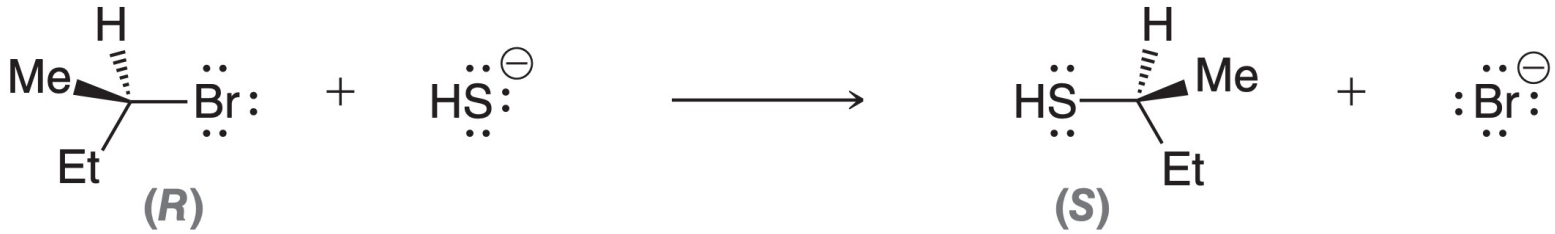


tert-butyl bromide (3°)
attack is impossible



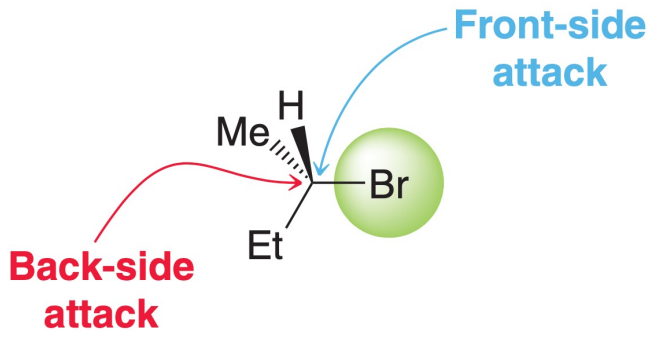


- S_N2反应伴随立体构型翻转[Walden inversion]

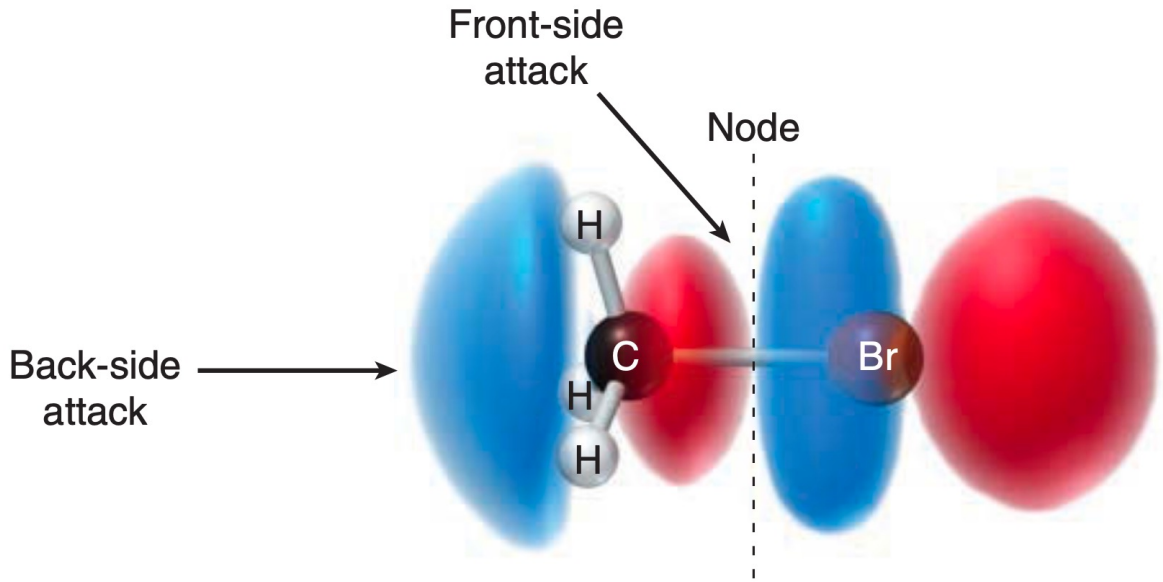


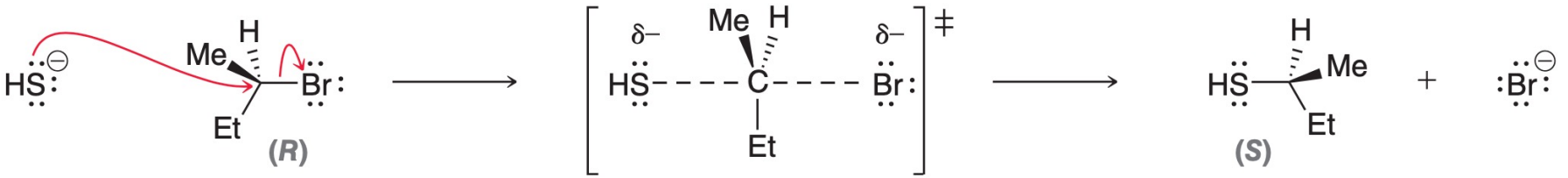
立体专一性

stereospecificity



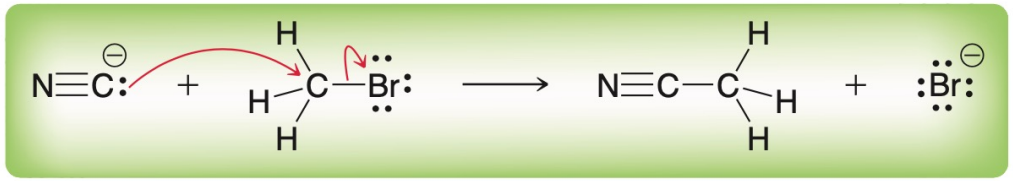
- 背面进攻的位阻更小&轨道对称性匹配

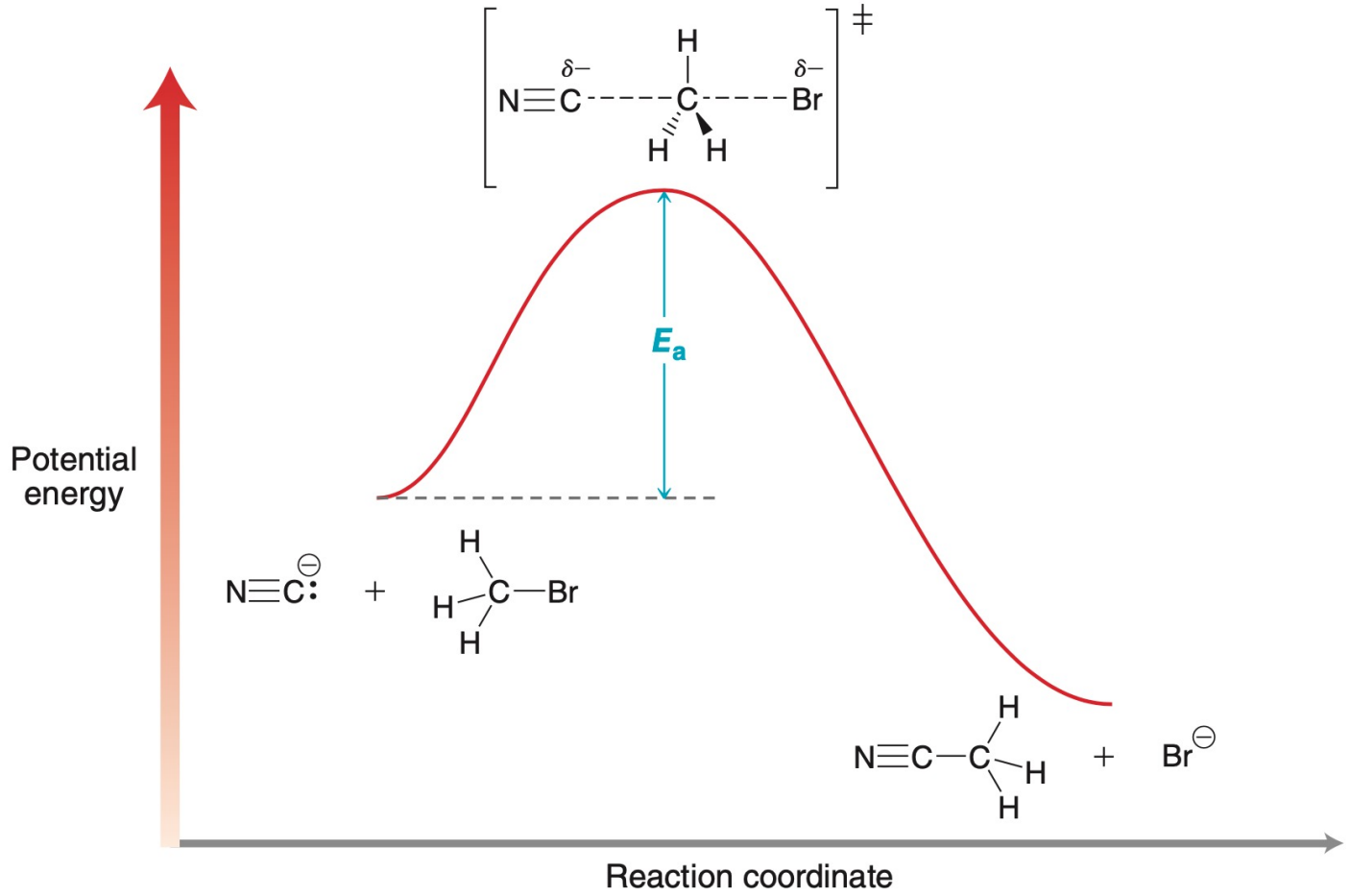




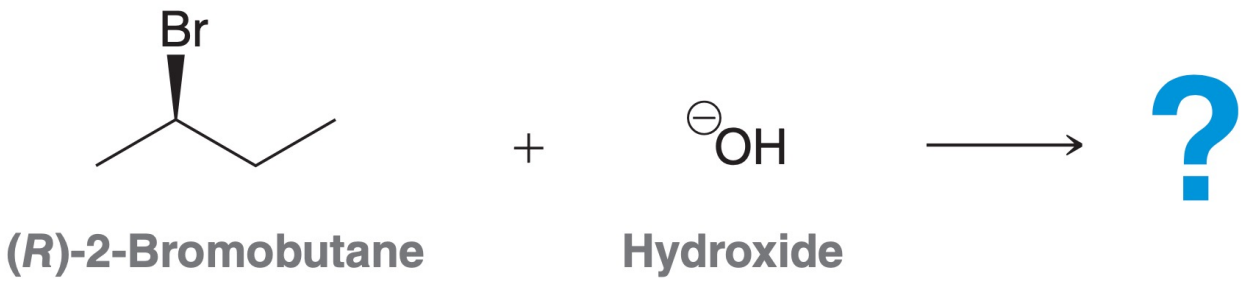
过渡态(transition state)

- 反应历程

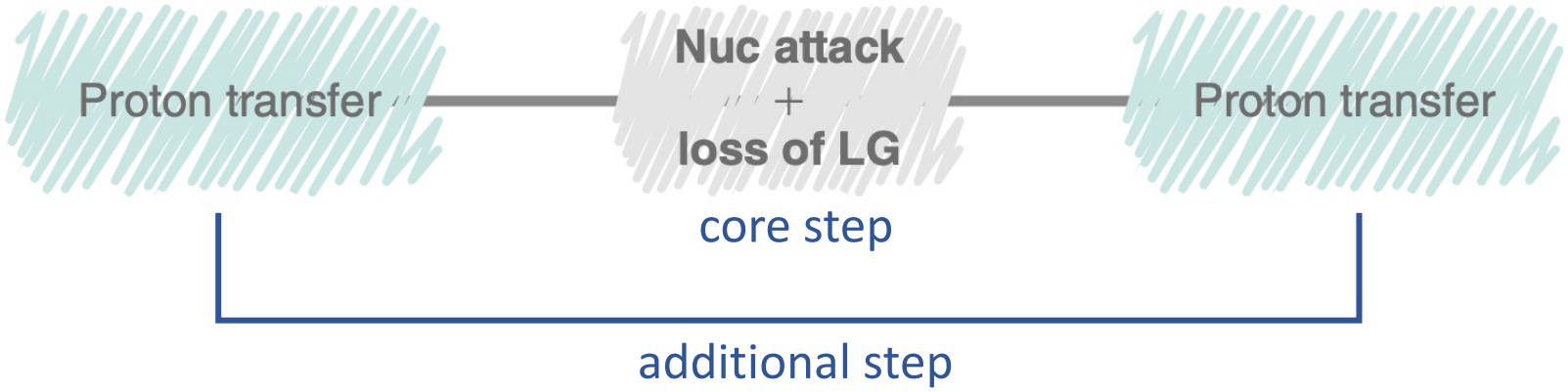




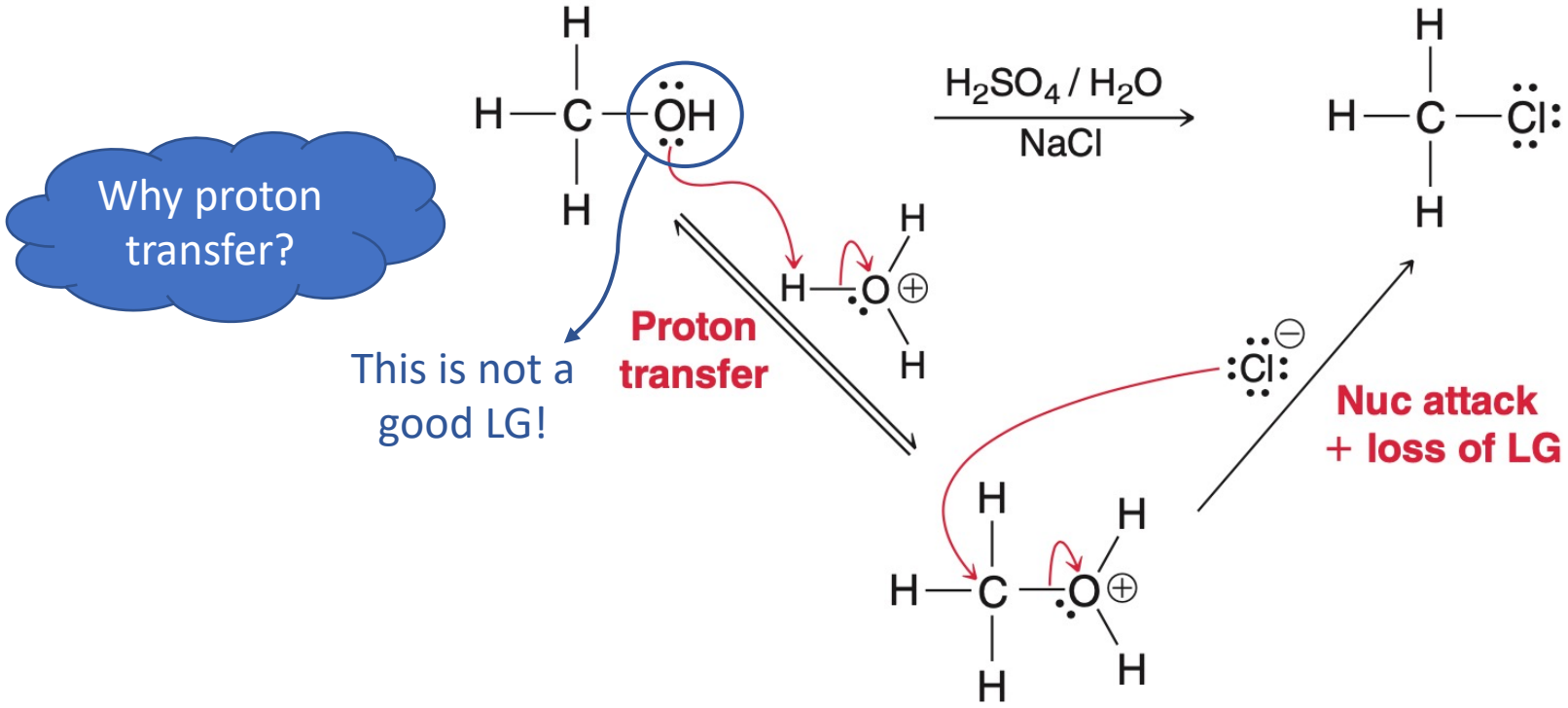
- Practice: draw the S_N2 product that is obtained when (*R*)-2-bromobutane reacts with a hydroxide ion.



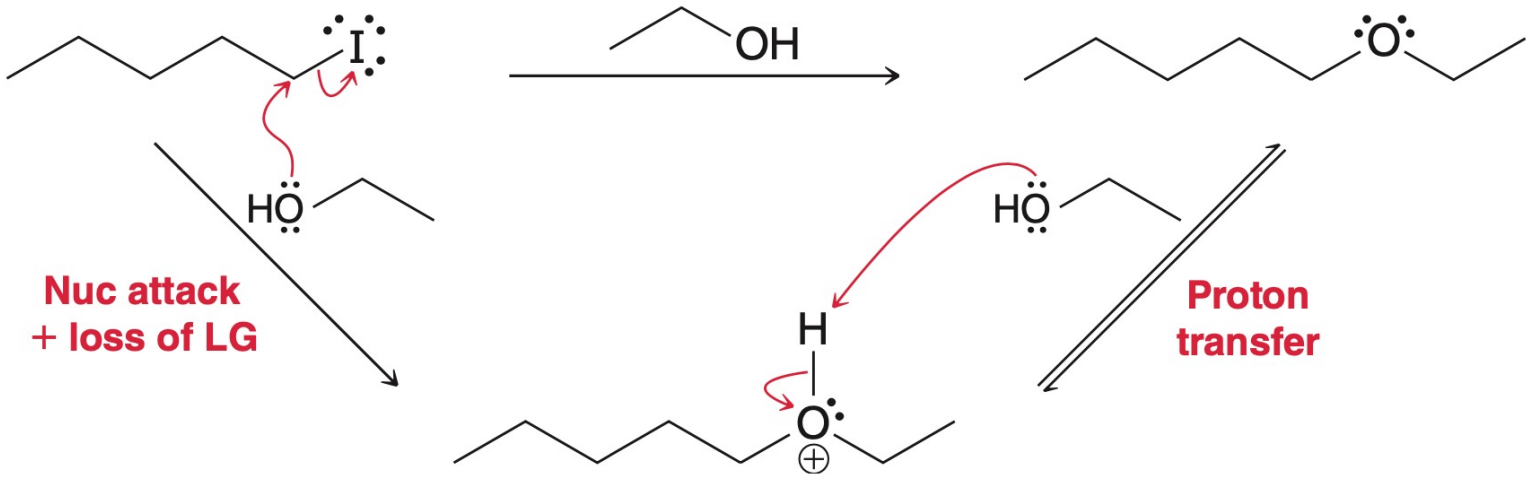
- Additional steps for S_N2



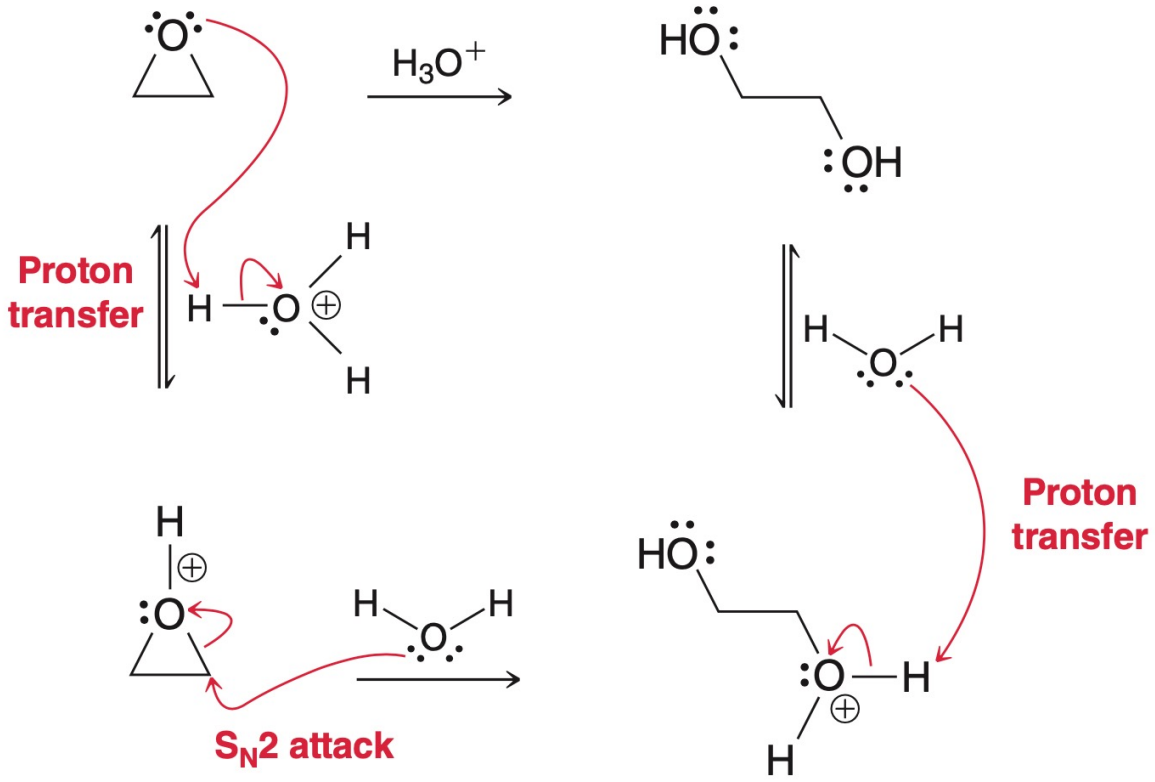
- Proton transfer at the beginning



- Proton transfer at the end

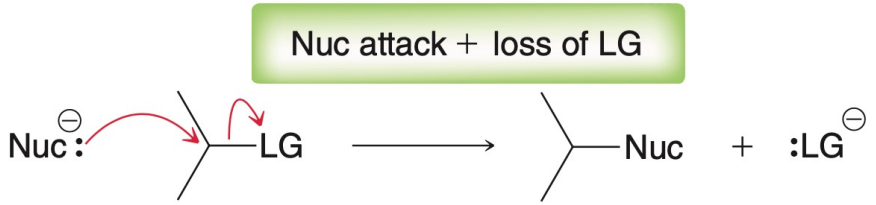


- Proton transfer before and after the core process



- The complete S_N2 process

One concerted step



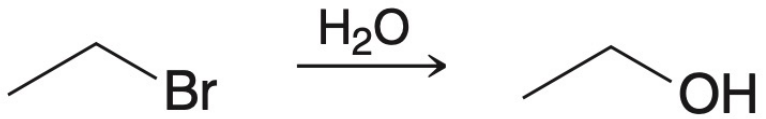
An S_N2 process is comprised of just one concerted step in which the nucleophile attacks with simultaneous loss of the leaving group.

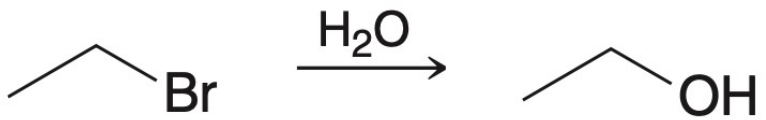
Possible additional steps

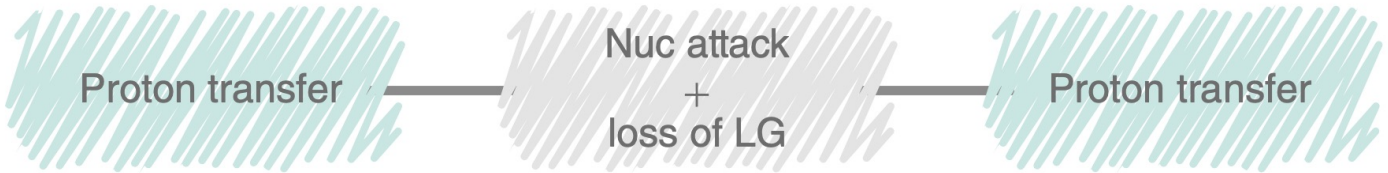
If the substrate is an alcohol, then the OH group must be protonated before it can leave.

If the nucleophile is neutral, a proton transfer is required to remove the positive charge that is generated.

- Practice: ethyl bromide was dissolved in water and heated, and the following solvolysis reaction was observed to occur slowly, over a long period of time. Propose a mechanism for this reaction.





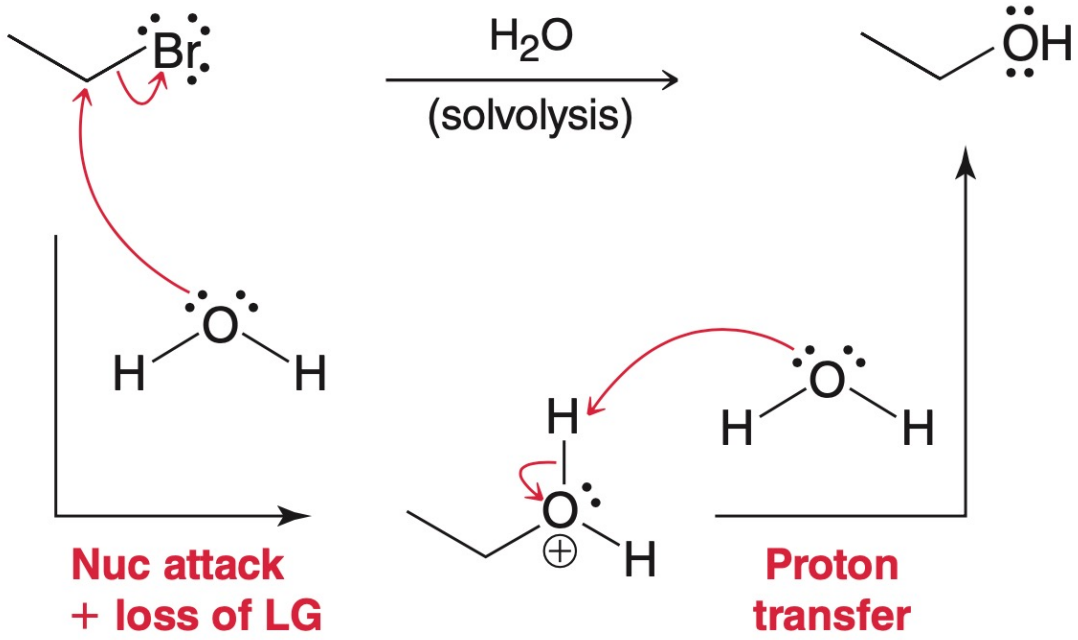


Does the LG need to be protonated first?

No. Bromide is a good LG.

Is the nucleophile neutral?

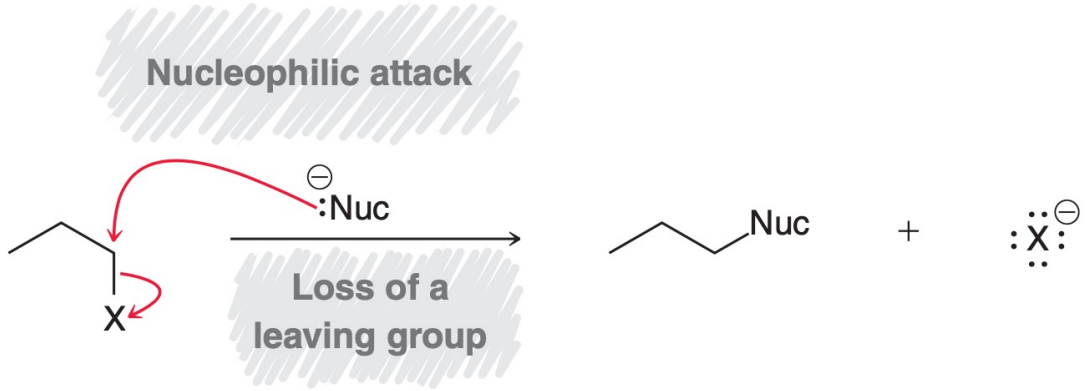
Yes. We will therefore need a proton transfer at the end of the mechanism in order to remove the positive charge.


Br
H_2O
(solvolysis)
OH
O
H
H
H
O
H
O
H
H
Nuc attack
+ loss of LG
Proton
transfer

- Back to 1930s…

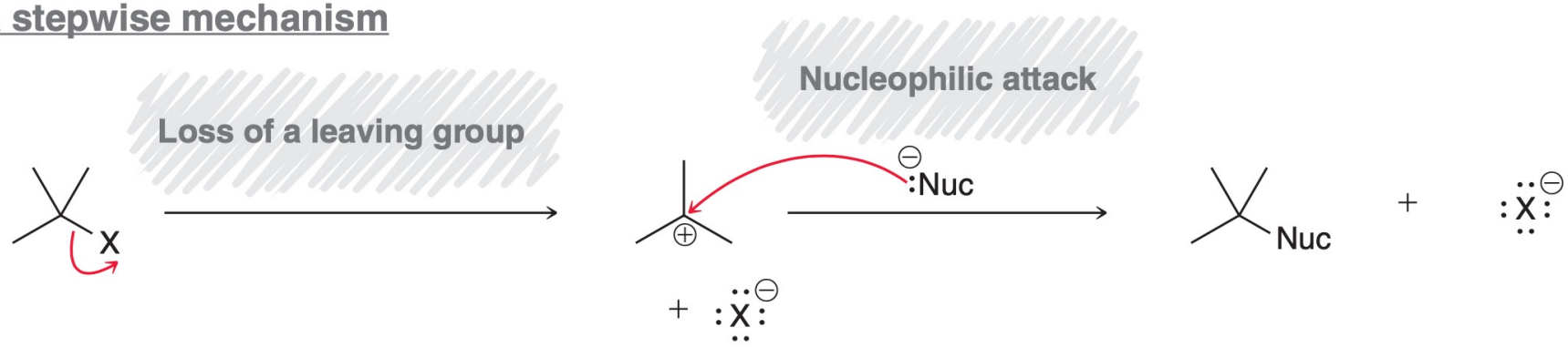
A concerted mechanism

S_N2 reaction

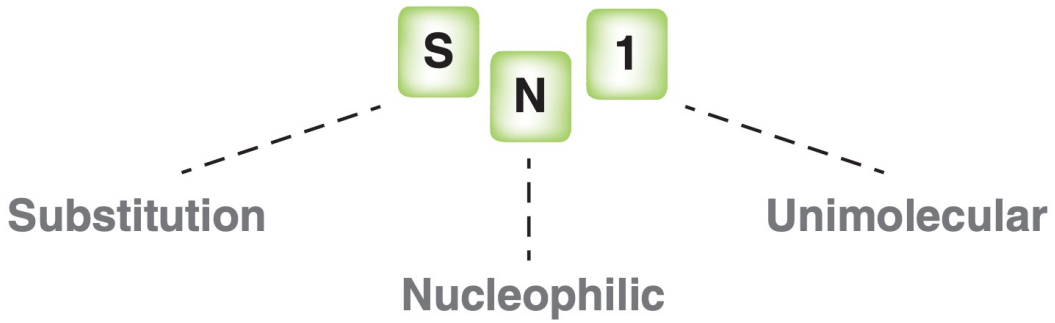


A stepwise mechanism

S_N1 reaction

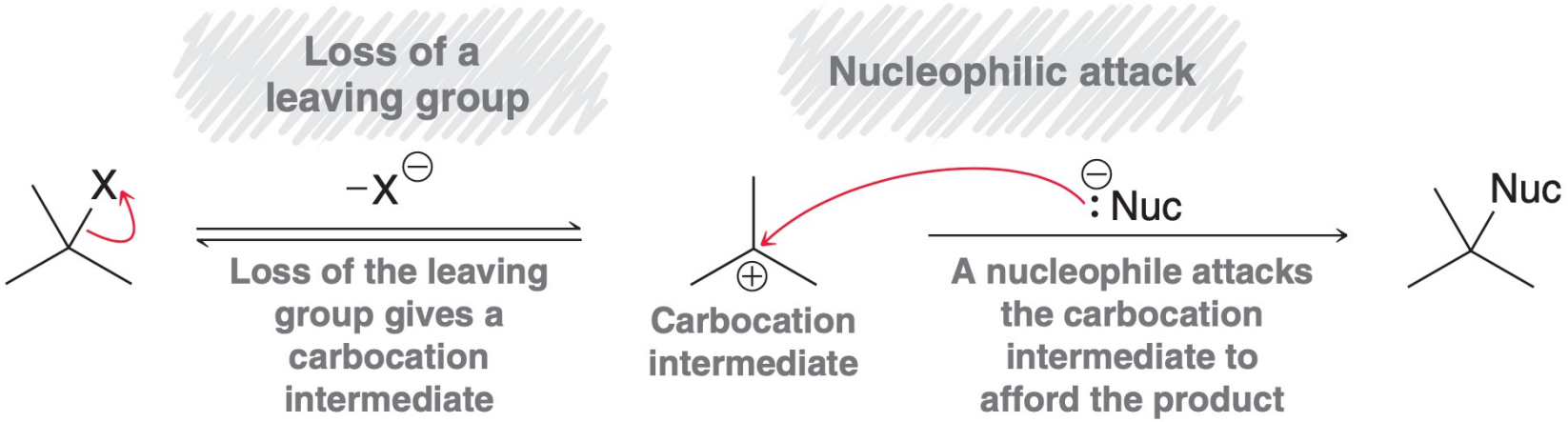


- What is S_N1?

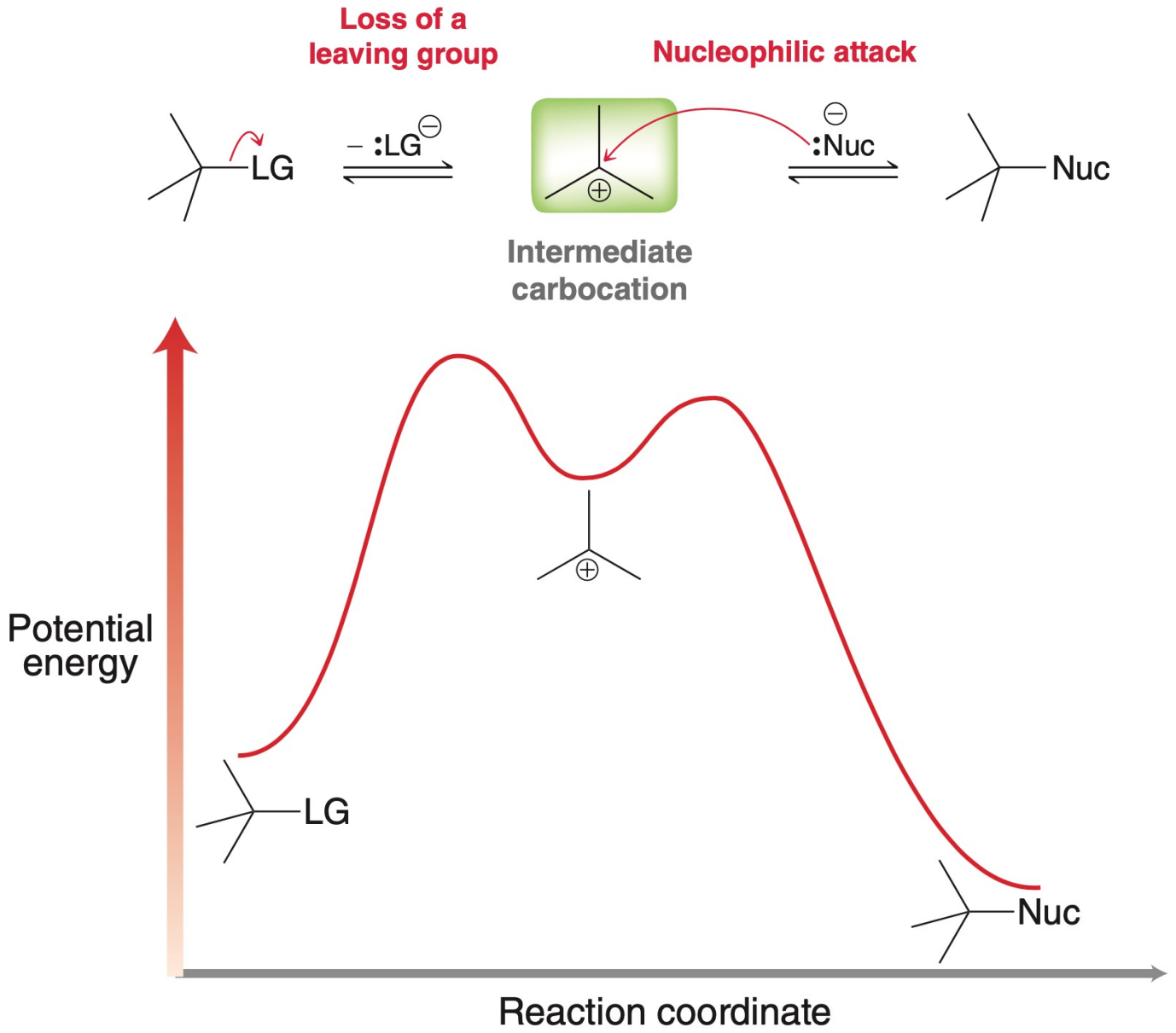


$$\text{Rate} = k\,[\text{substrate}]$$

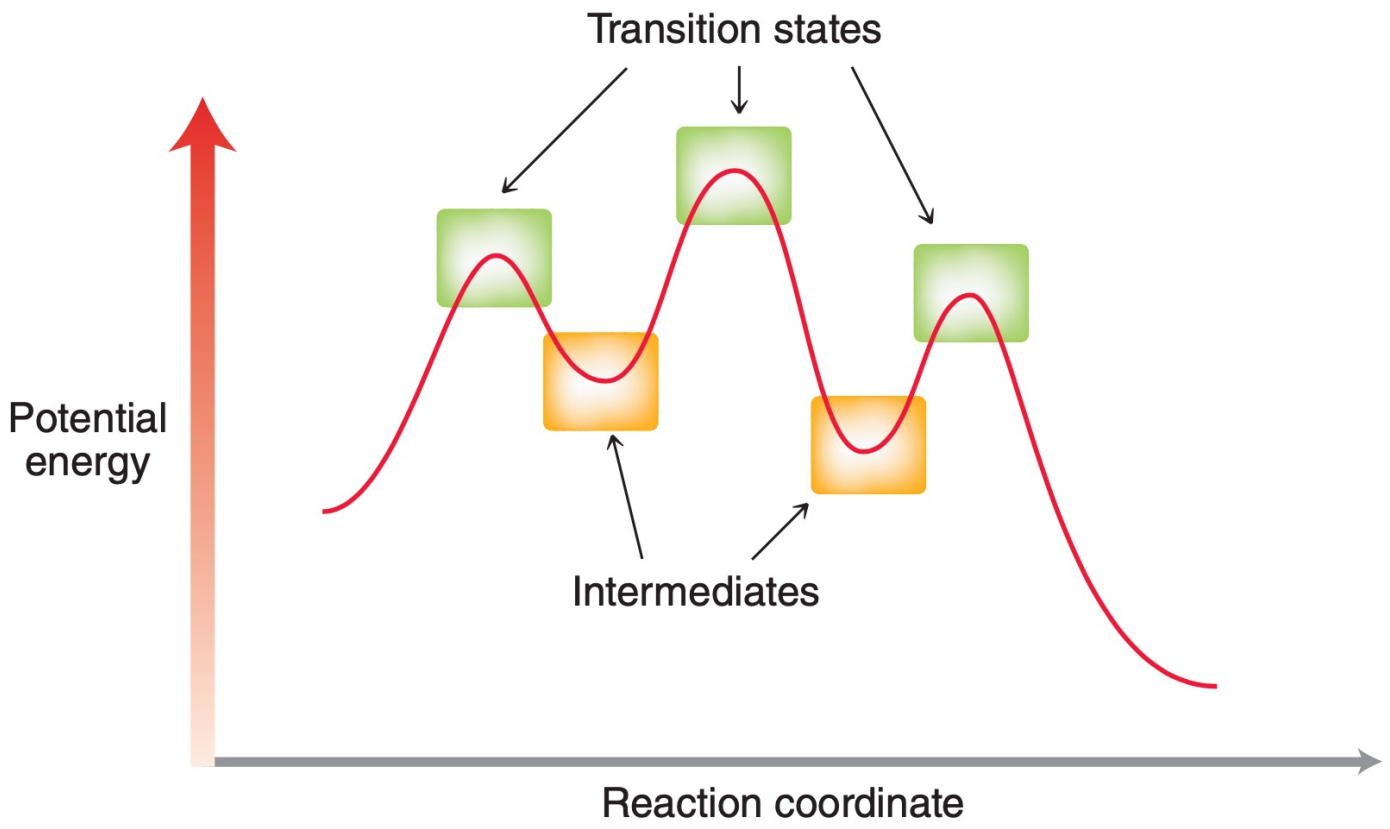
- **The S_N1 Mechanism**



- 反应历程


Loss of a leaving group
Nucleophilic attack
LG
:LG
:Nuc
Nuc
Intermediate carbocation
Potential energy
LG
Nuc
Reaction coordinate

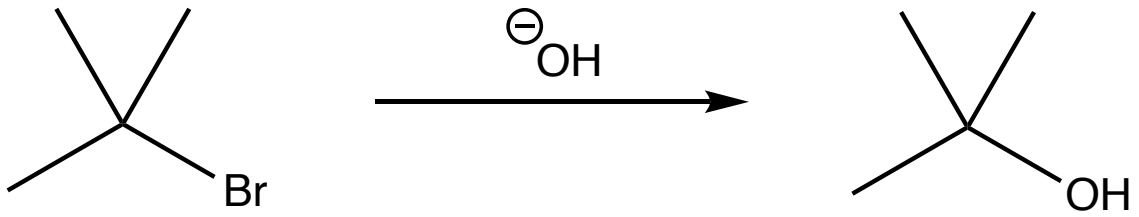
- 过渡态(transition state)与中间体(intermediate)



过渡态：能量高，不可被分离

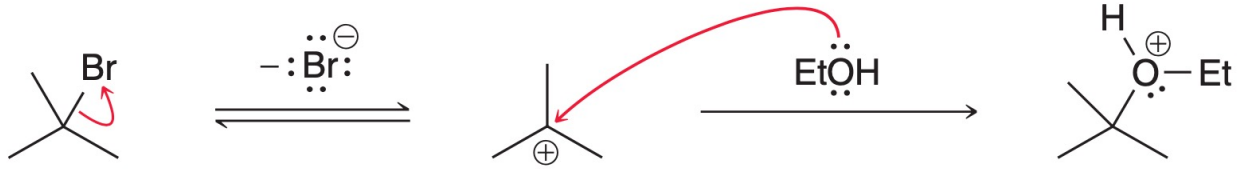
中间体：能量低，可被分离

- Practice: identify the nucleophile and substrate, then draw a mechanism for the following reaction:

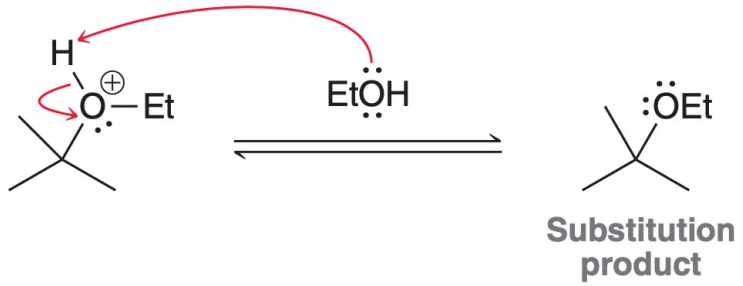


- 溶剂解反应(solvolysis reaction)

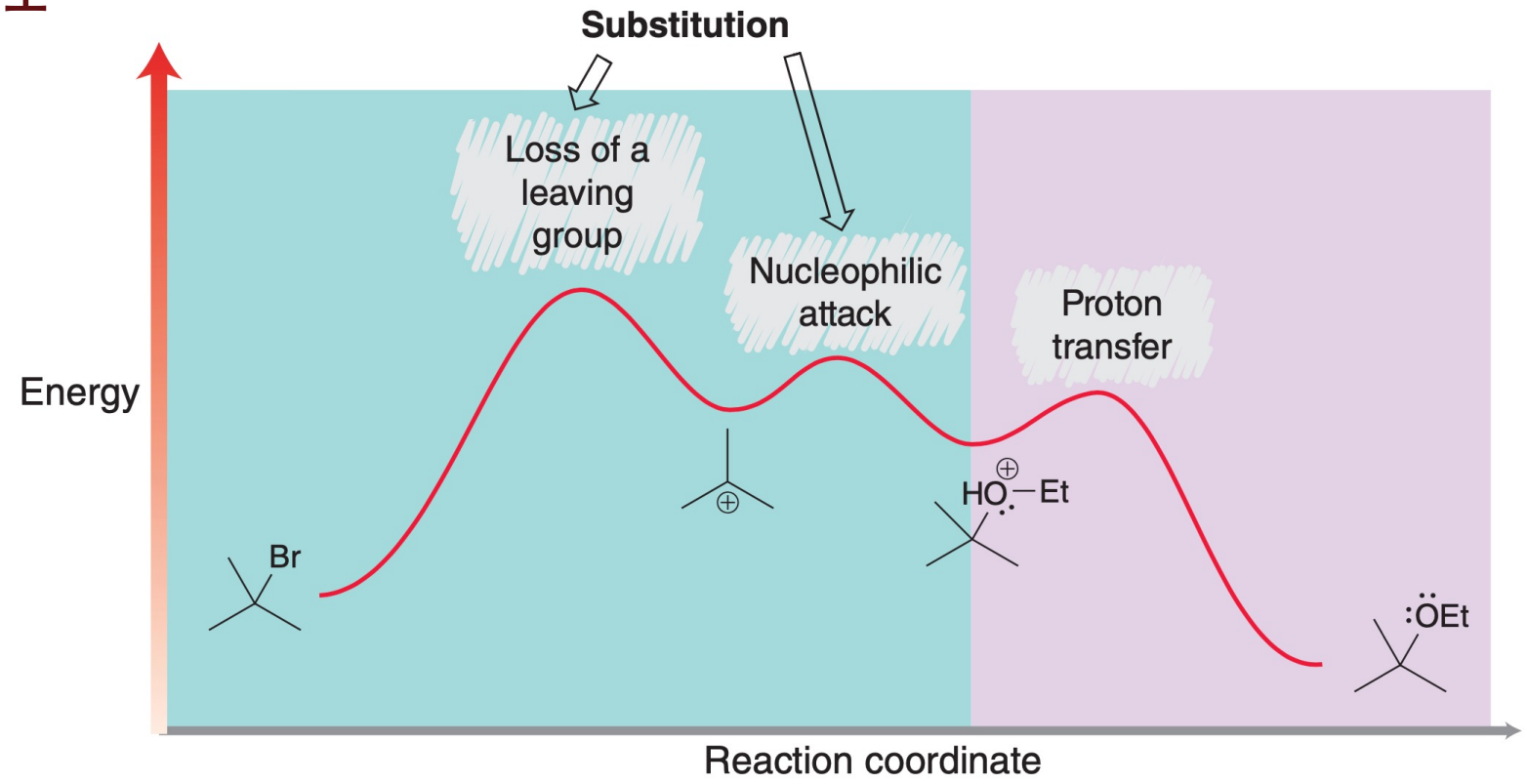
step 1. S_N1 process



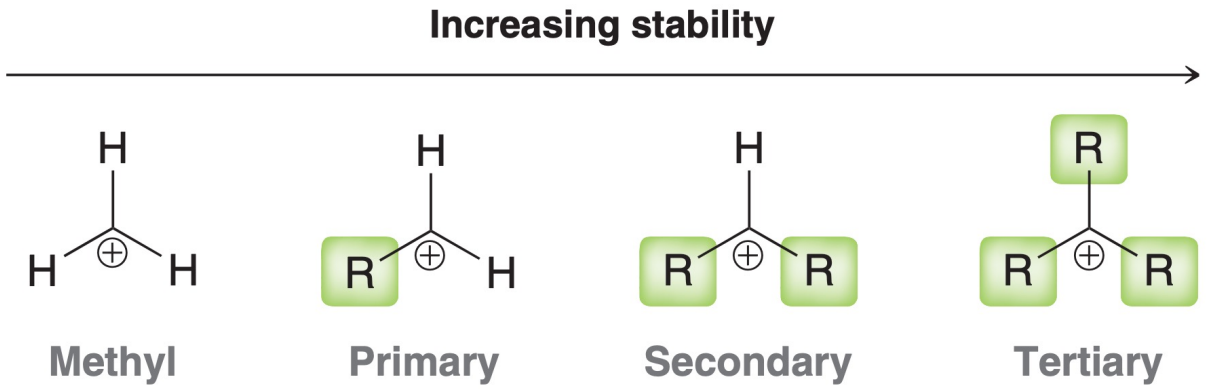
step 2. proton transfer



- 反应历程


Substitution
Loss of a leaving group
Nucleophilic attack
Proton transfer
Energy
Br
HO—Et
:ÖEt
Reaction coordinate

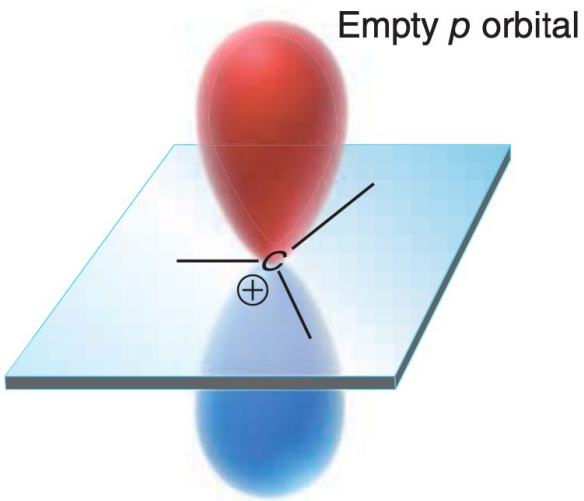
- S_N1反应的速率
  - 碳正离子越稳定，反应越快



  - 基团越易离去，反应越快

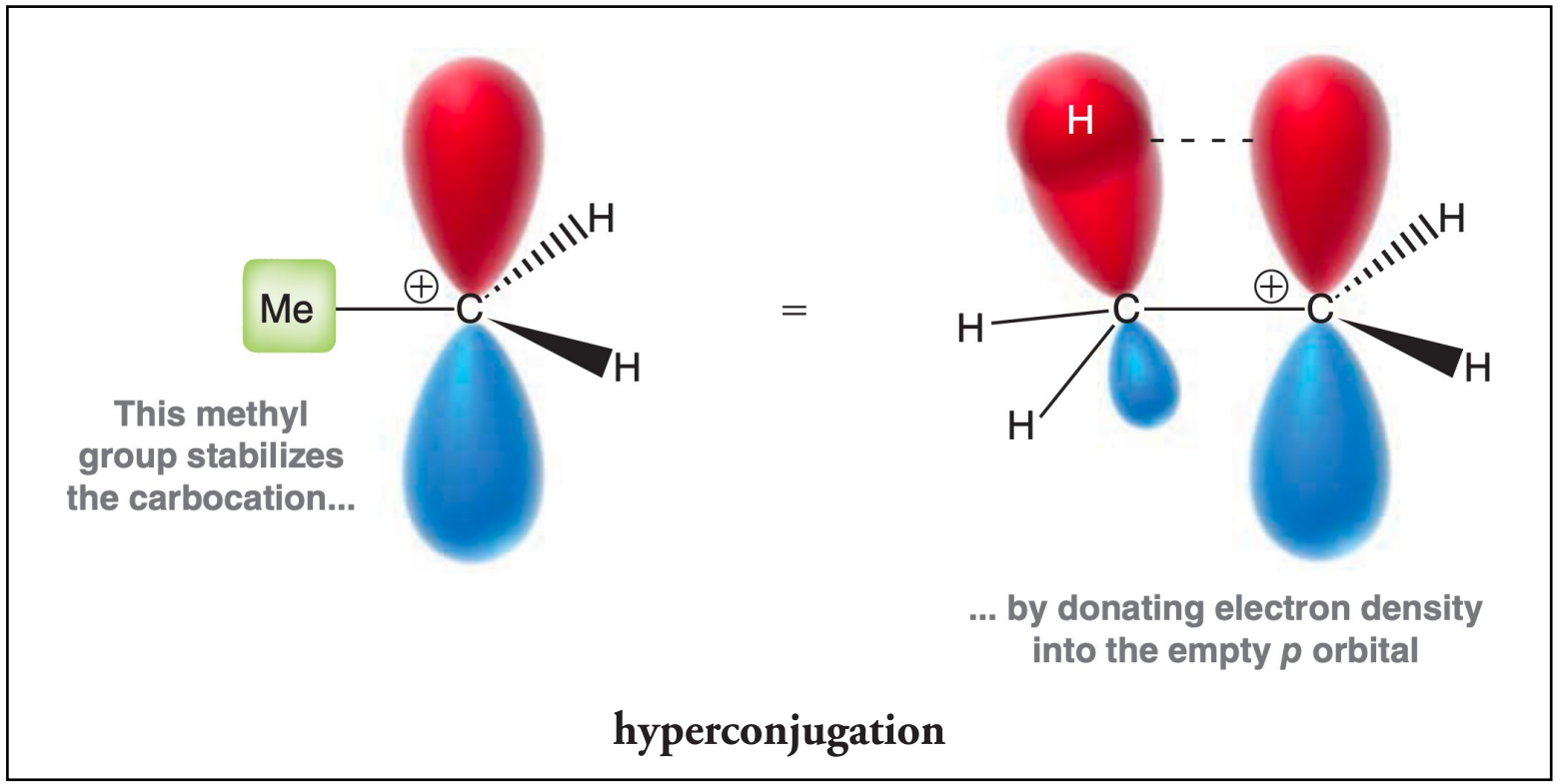
$$I^{\ominus} > Br^{\ominus} > Cl^{\ominus}$$

- 碳正离子(carbocation)

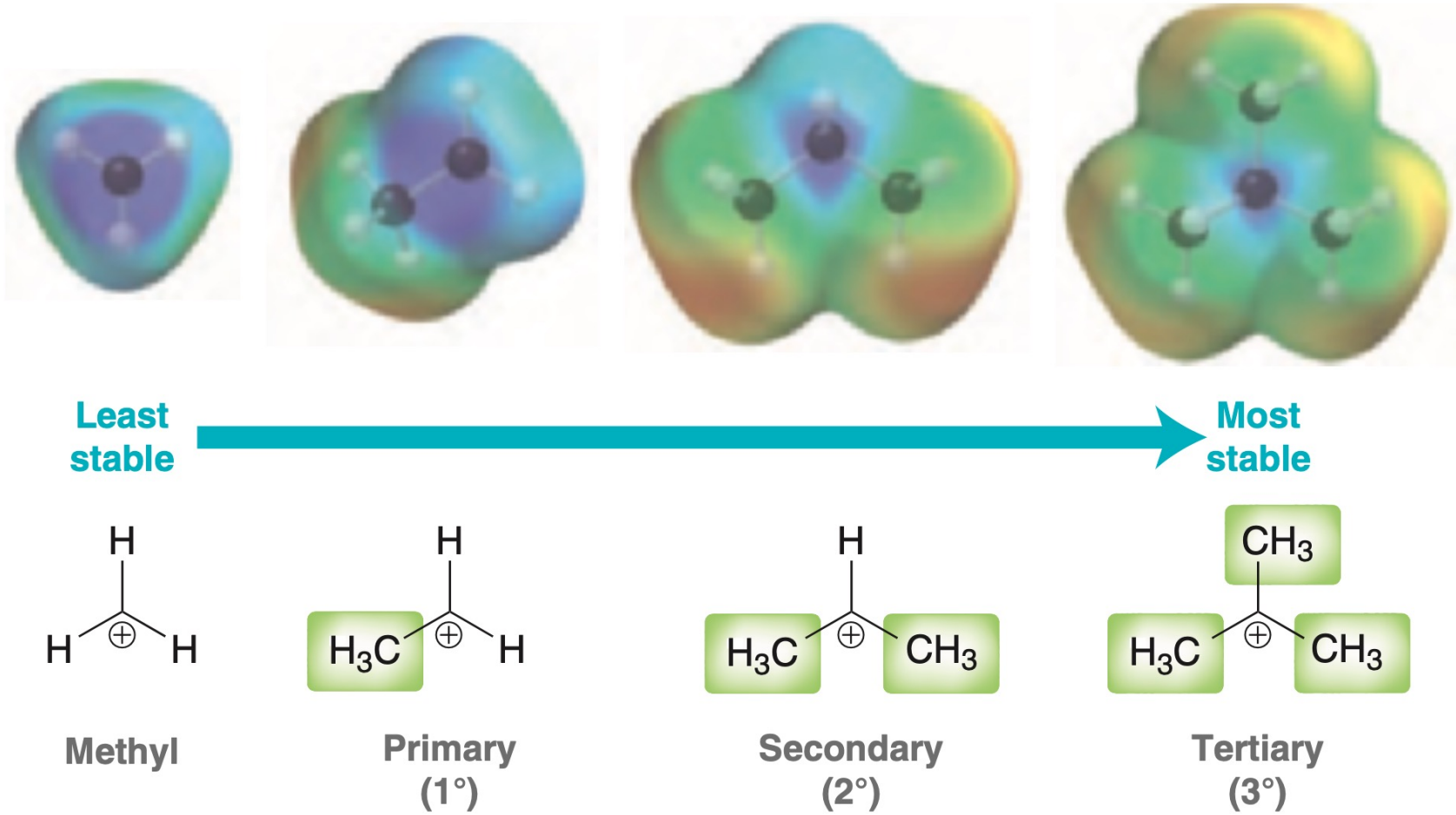


呈sp^2杂化

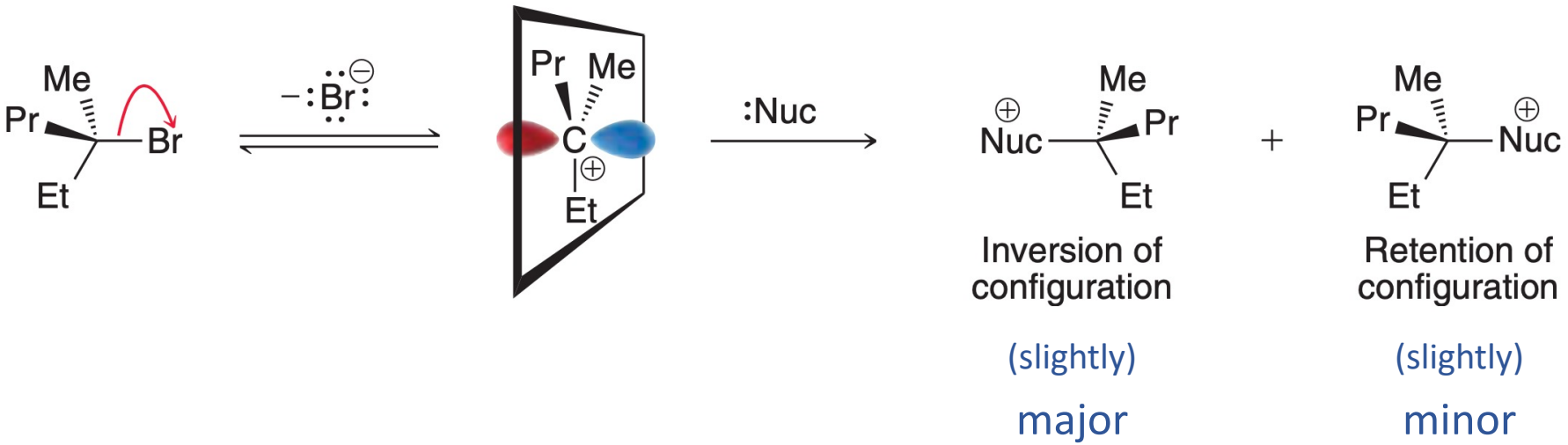
平面三角形



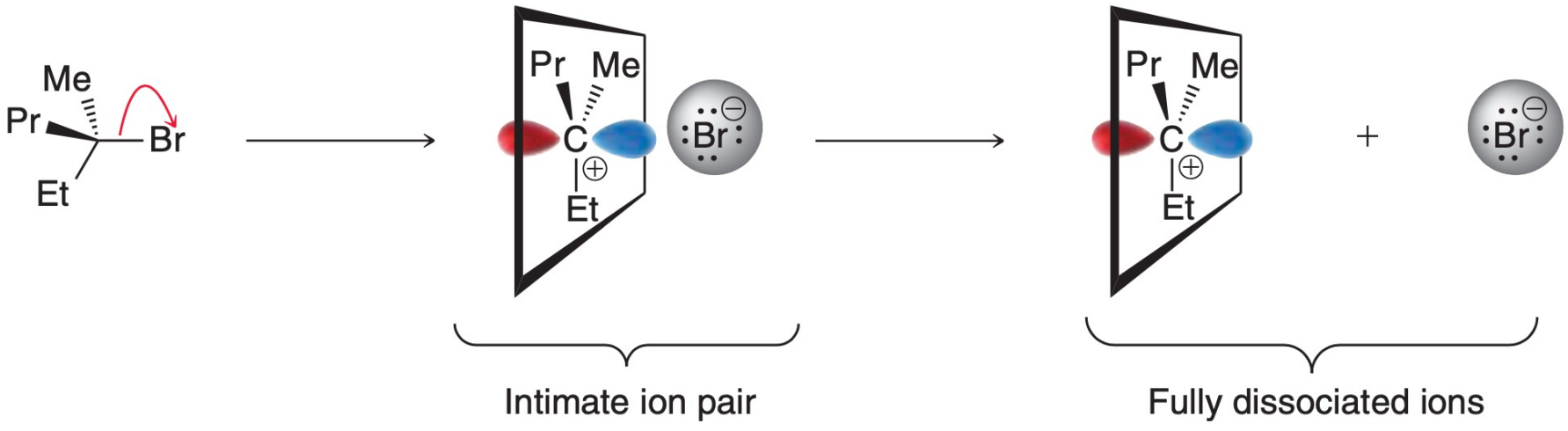
- 烷基能够稳定碳正离子


Least stable
Most stable
H
H
H
Methyl
H
H3C
H
Primary (1°)
H
H3C
CH3
Secondary (2°)
CH3
H3C
CH3
Tertiary (3°)

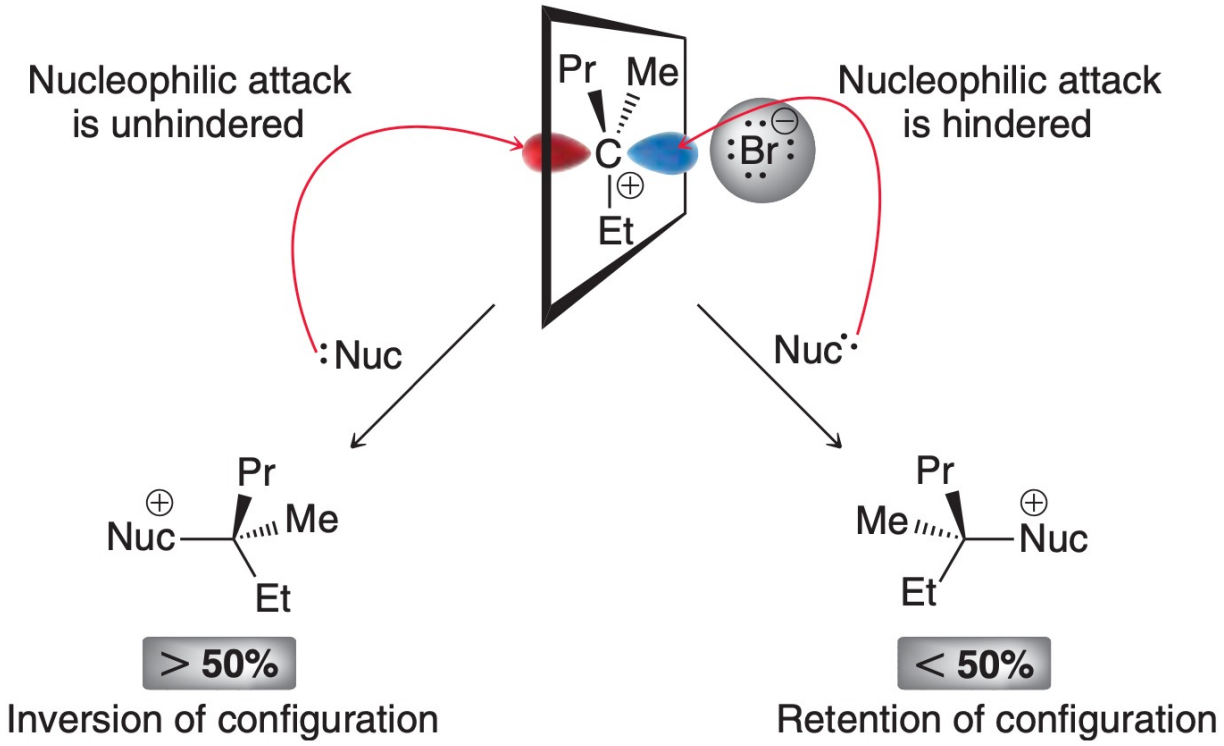
- S_N1反应得到完全消旋产物……?



- Winstein离子对机理

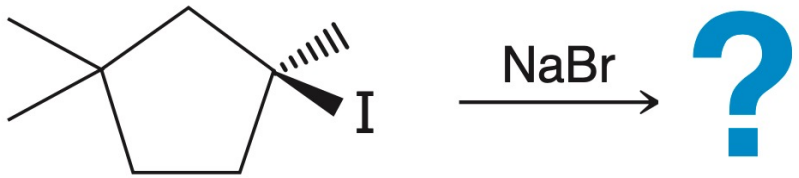


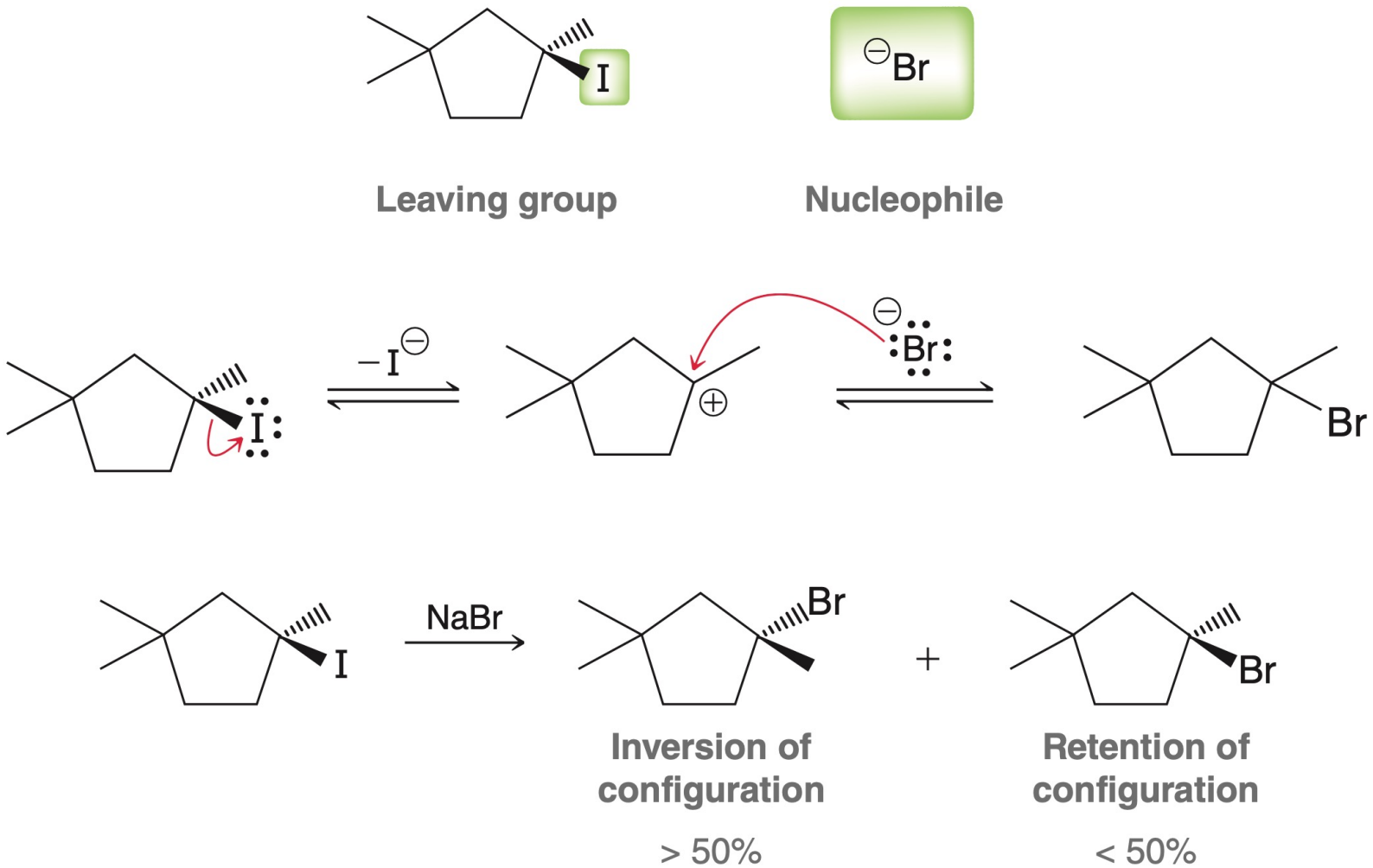
- Winstein离子对机理



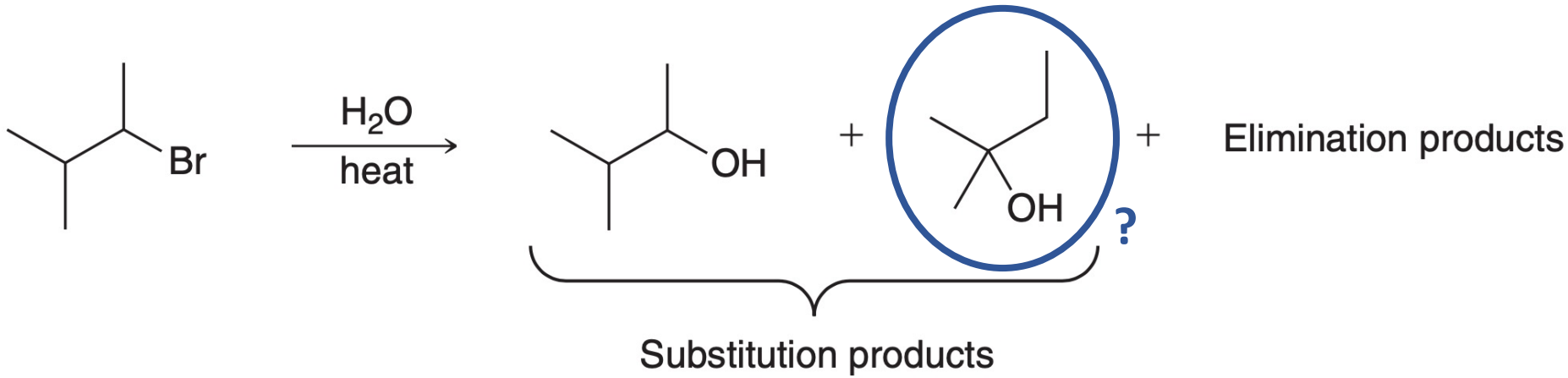
处于紧密离子对阶段时，生成的产物偏向于构型翻转

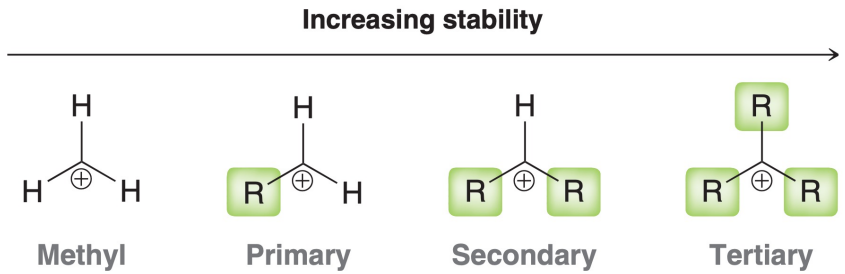
- Practice: draw the products of the following S_N1 reaction:



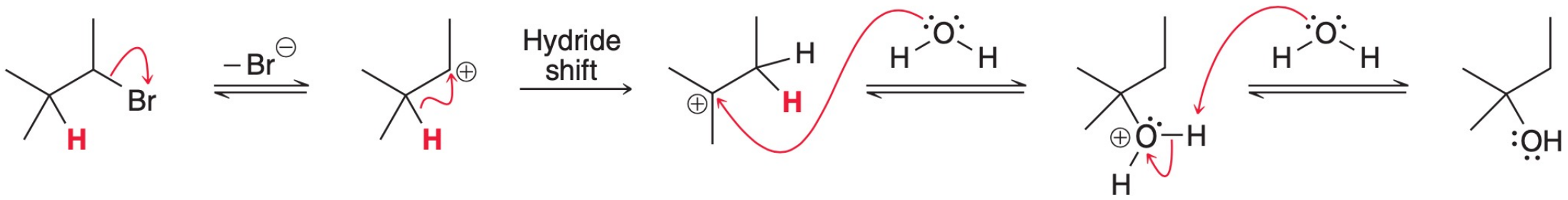

I
Br
Leaving group
Nucleophile
I
−I
Br
Br
I
NaBr
Br
Br
Inversion of configuration
> 50%
Retention of configuration
< 50%

- S_N1中的重排(rearrangement)过程

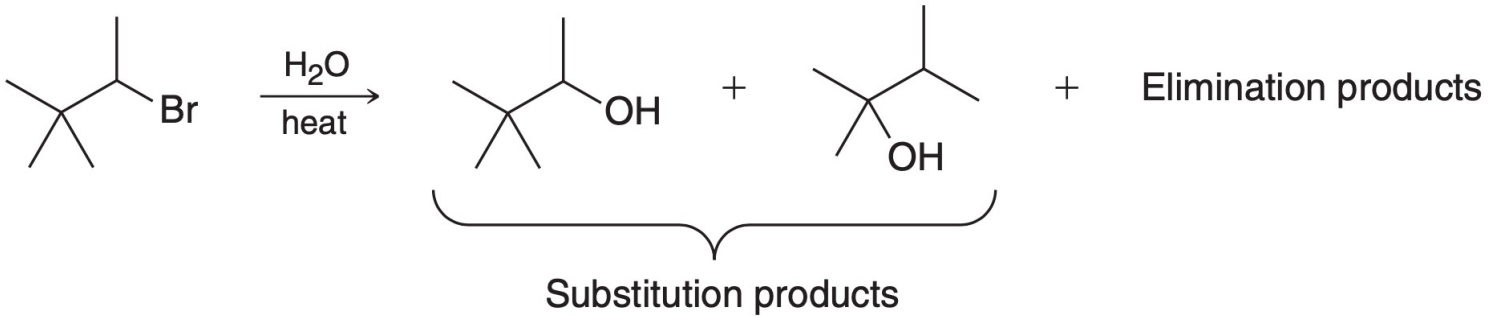


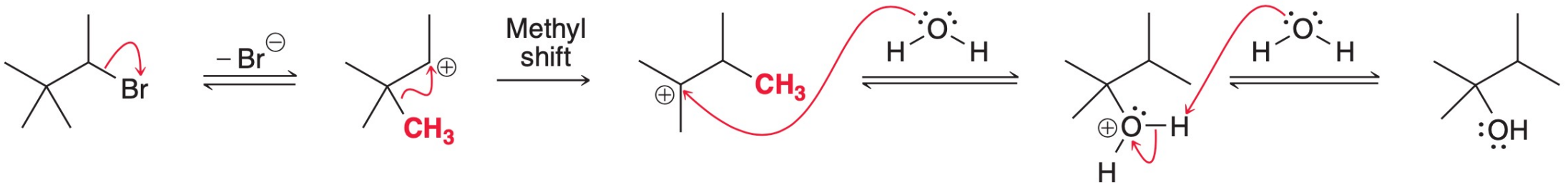


- 氢迁移(hydride shift)

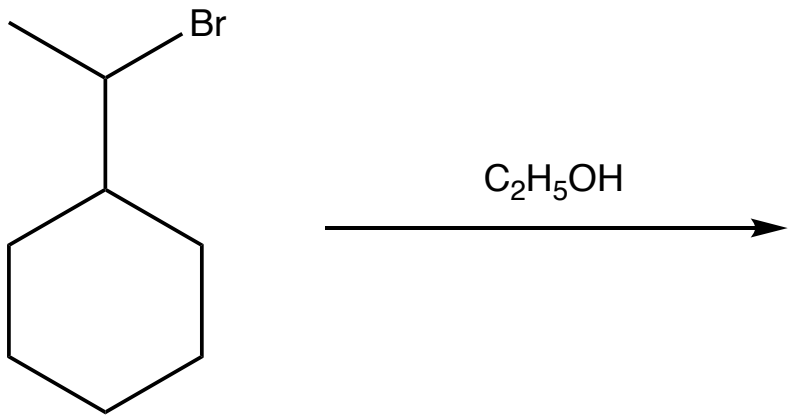


- 甲基迁移(methyl shift)



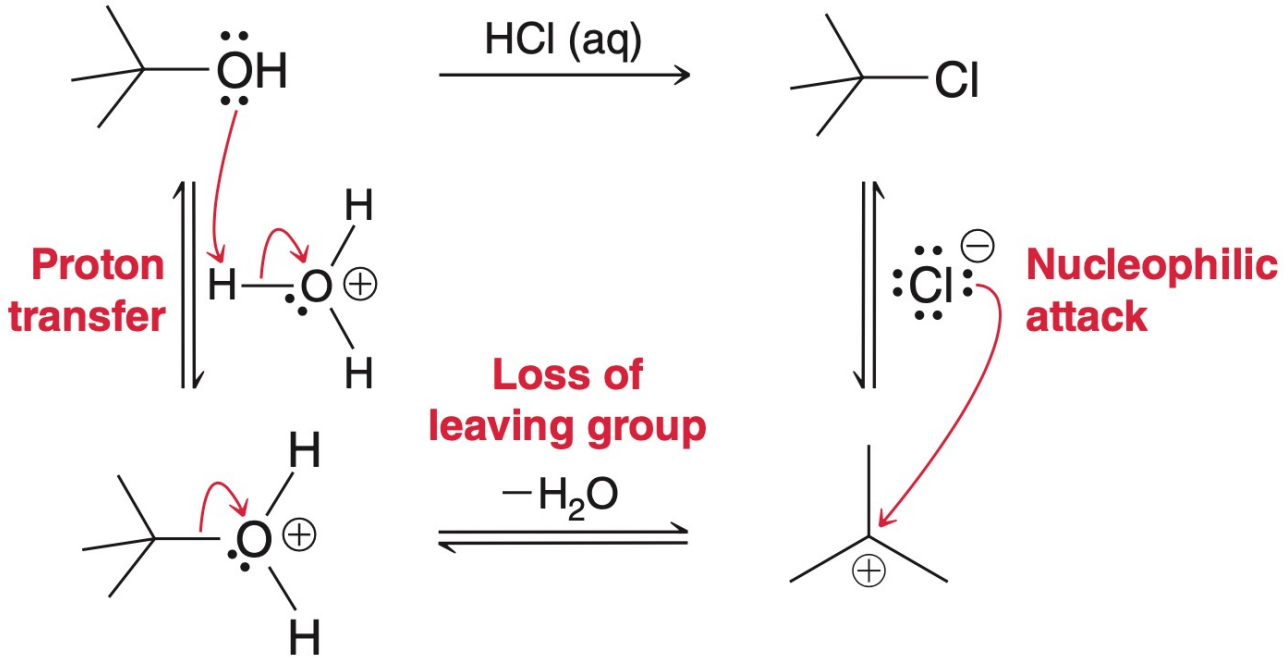


- Practice: predict the S_N1 product, and draw a mechanism for the following reaction.

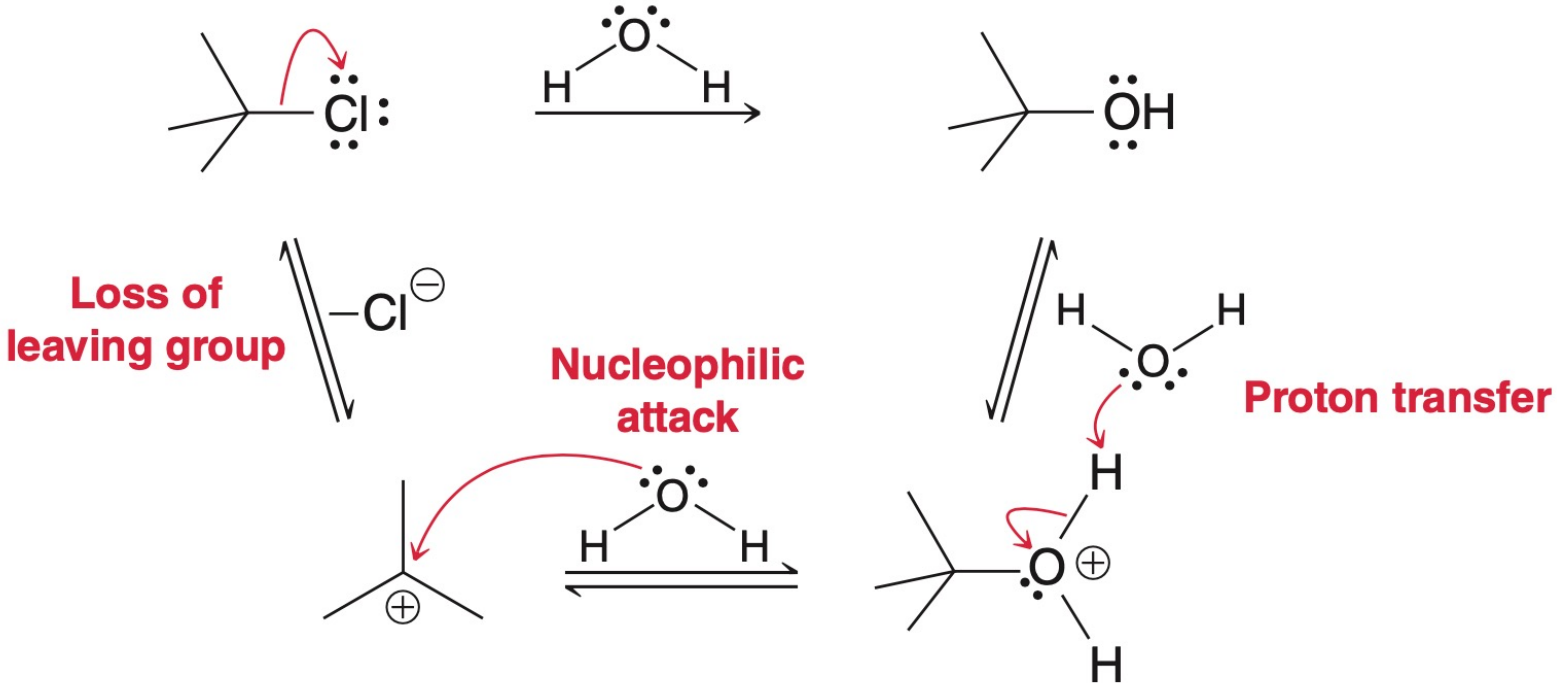


- Additional steps for S_N1

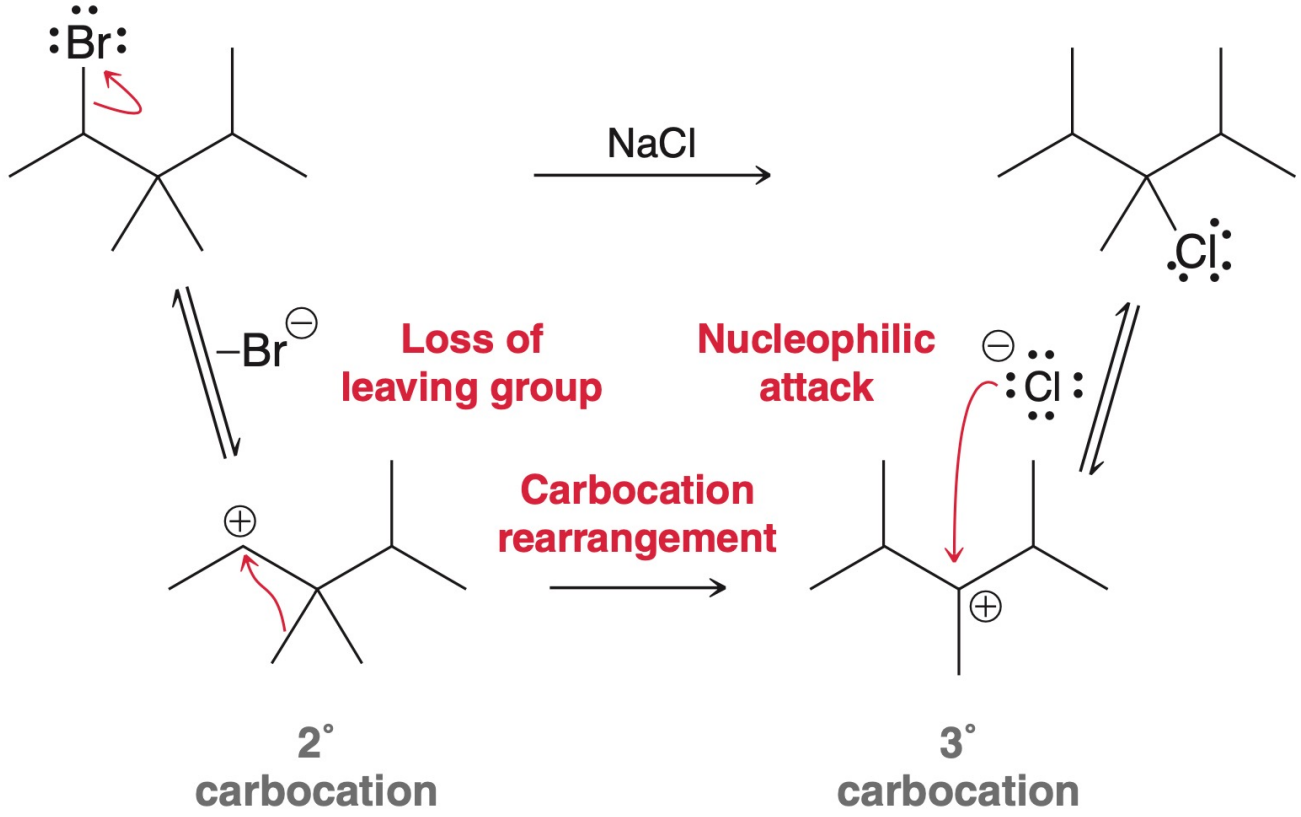
- Proton transfer at the beginning



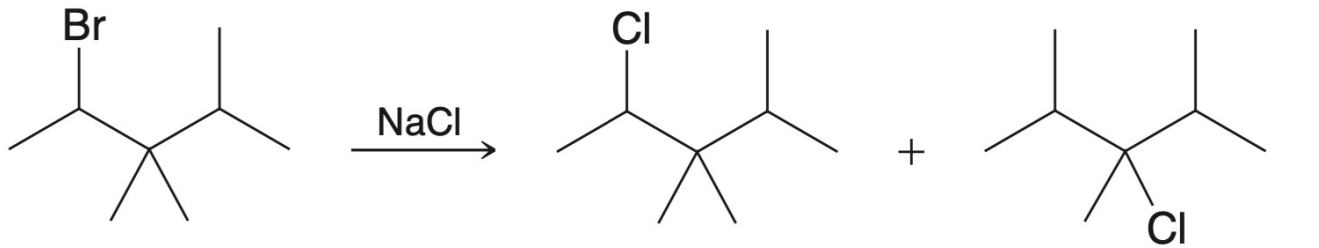
- Proton transfer at the end



- Carbocation rearrangement



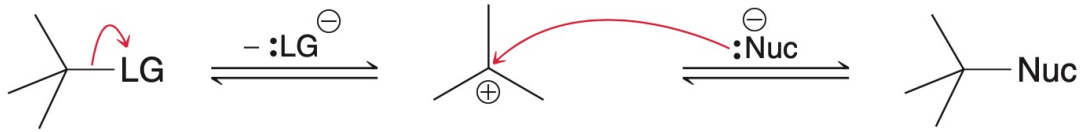
- Rearrangement results mixtures



- The complete S_N1 process

Loss of LG Nuc attack

Two core steps



In the first core step of an S_N1 process, the leaving group leaves to form a carbocation.

In the second core step of an S_N1 process, a nucleophile attacks the carbocation.

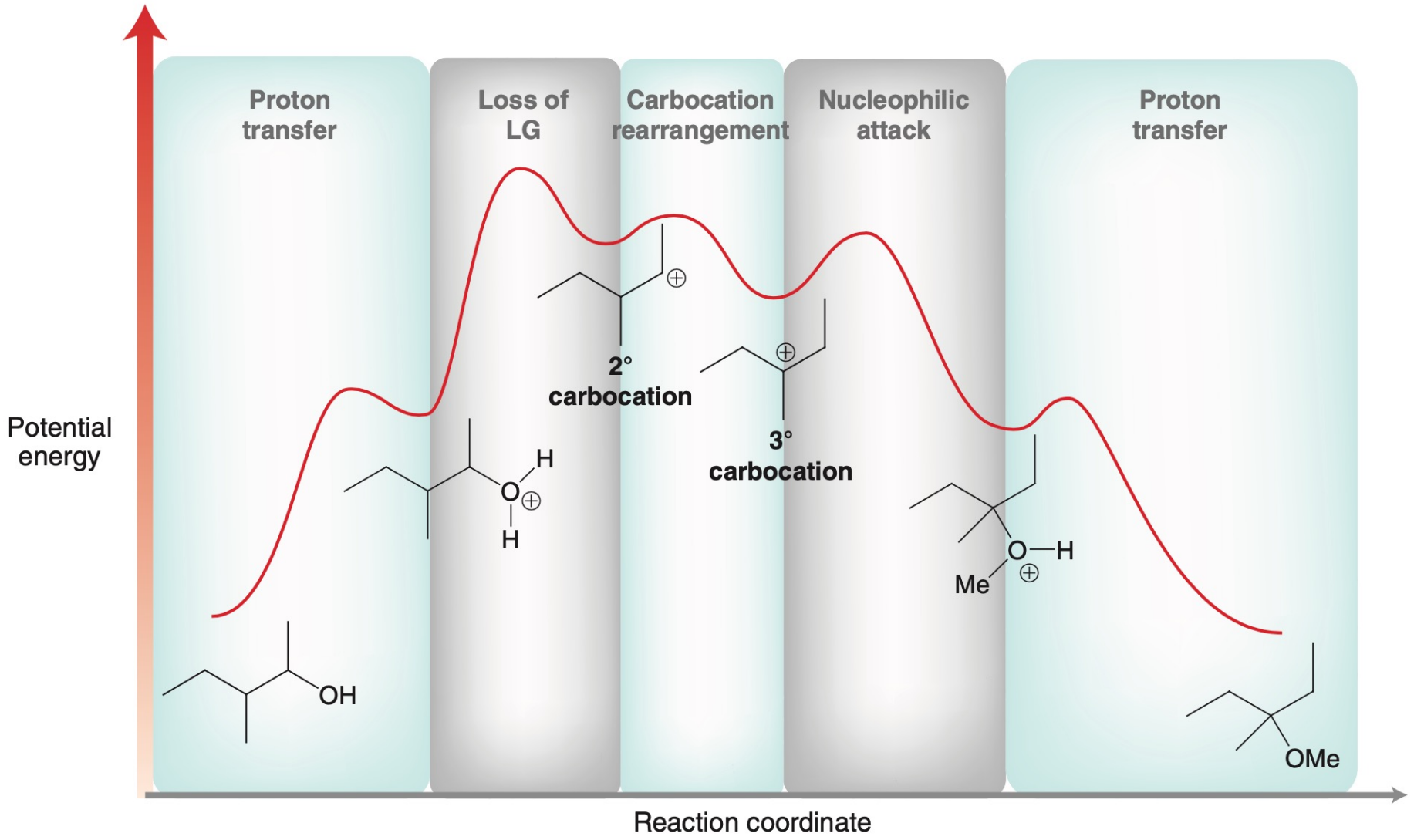
Proton transfer — Loss of LG — Carbocation rearrangement — Nuc attack — Proton transfer

If the substrate is an alcohol, then the OH group must be protonated before it can leave.

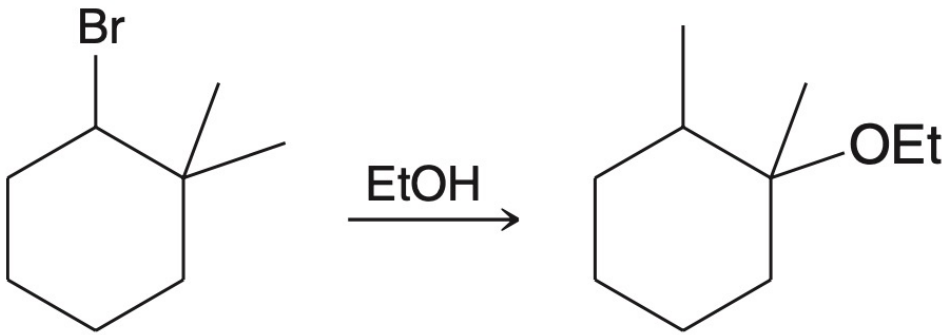
If the carbocation initially formed can rearrange to generate a more stable carbocation, then a rearrangement will occur.

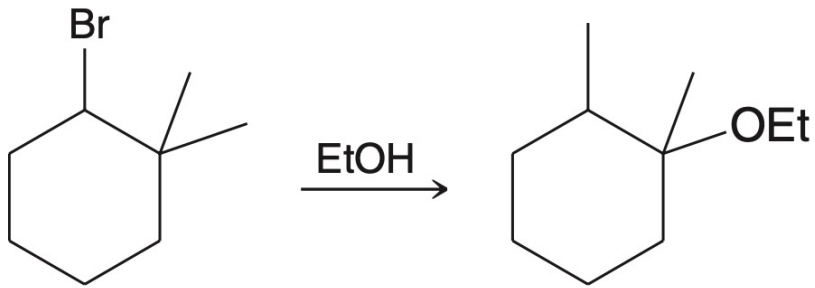
If the nucleophile is neutral, a proton transfer is required to remove the positive charge that is generated.

Possible additional steps


Proton transfer
Loss of LG
Carbocation rearrangement
Nucleophilic attack
Proton transfer
Potential energy
2° carbocation
3° carbocation
OH
H
O
H
O—H
Me
OMe
Reaction coordinate

- Practice: draw the mechanism of the following S_N1 process:





Proton transfer — Loss of LG — Carbocation rearrangement — Nuc attack — Proton transfer

Does the LG need to be protonated before it can leave?

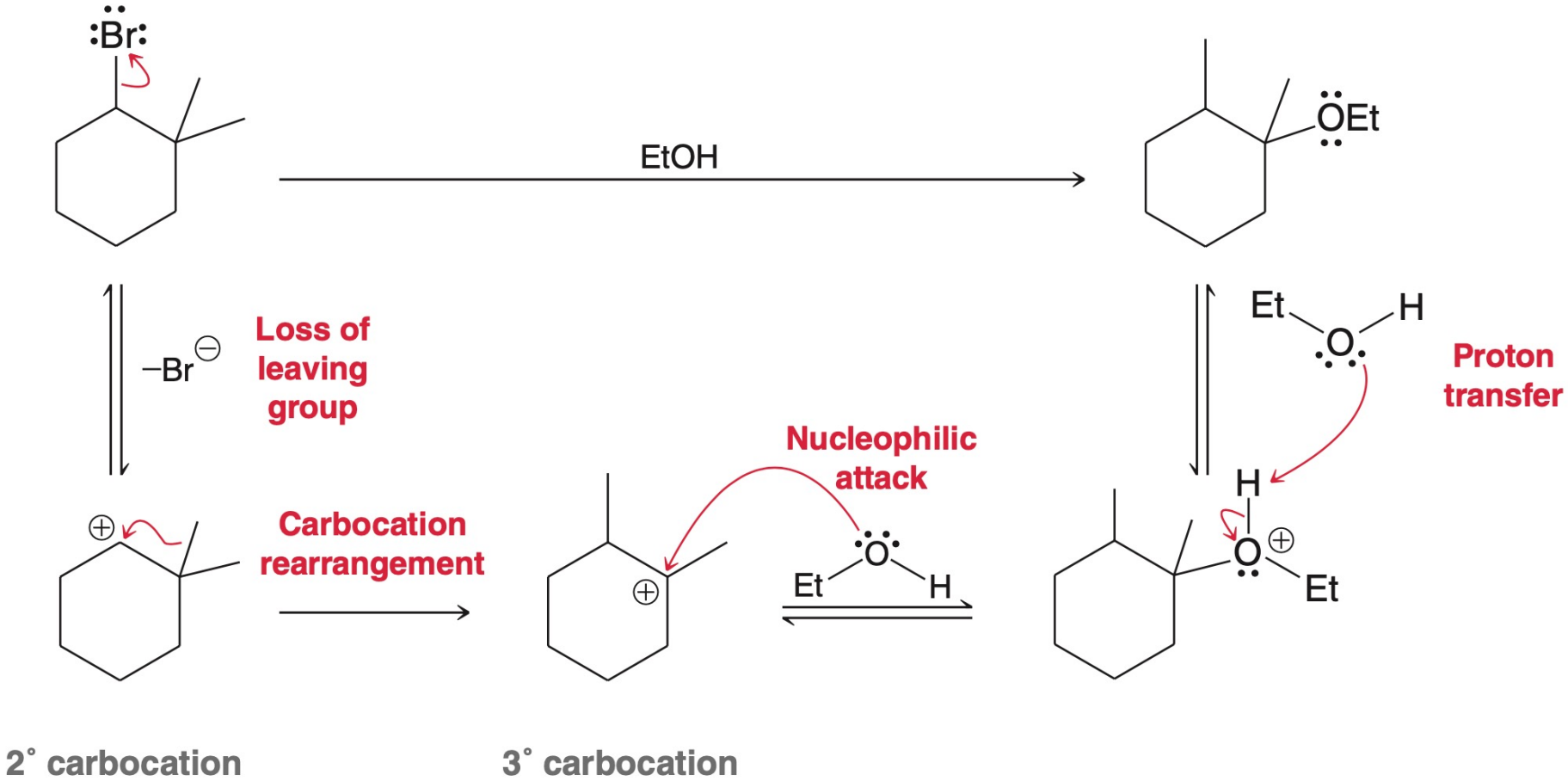
No. Bromide is a good LG.

Is the nucleophile ultimately positioned at a different location than the leaving group?

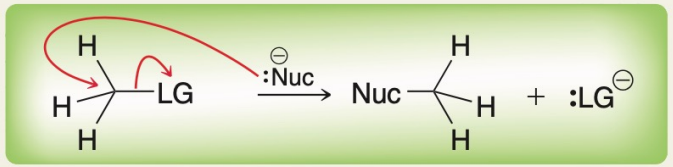
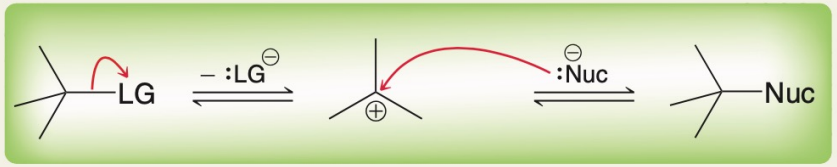
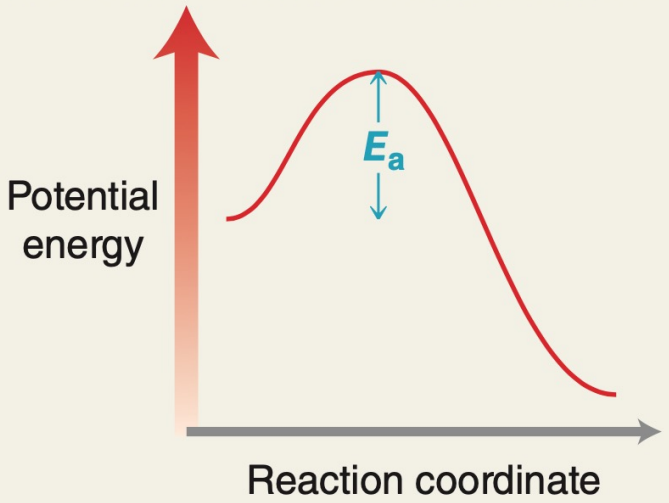
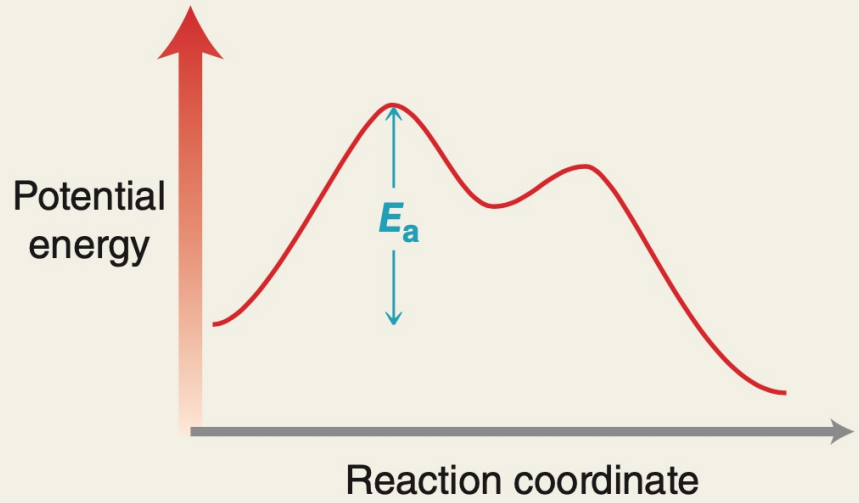
Yes. This indicates a carbocation rearrangement.

Is the nucleophile neutral?

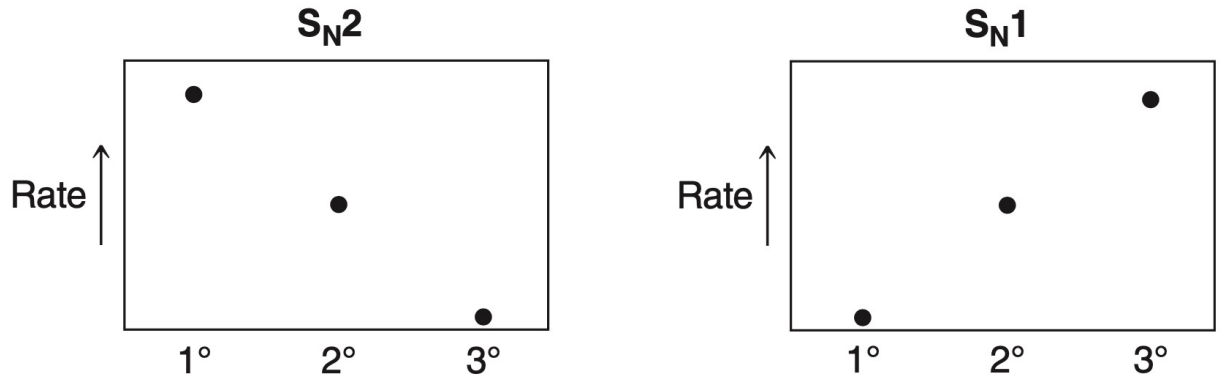
Yes. We will therefore need a proton transfer at the end of the mechanism in order to remove the positive charge.

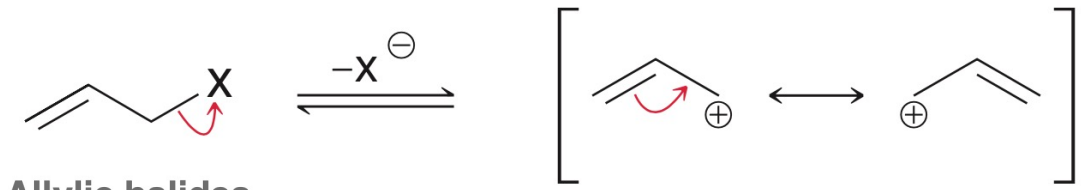

:Br:
EtOH
OEt
–Br
Loss of leaving group
Et
O
H
Proton transfer
Nucleophilic attack
H
O
Et
Carbocation rearrangement
Et
O
H
2˚ carbocation
3˚ carbocation

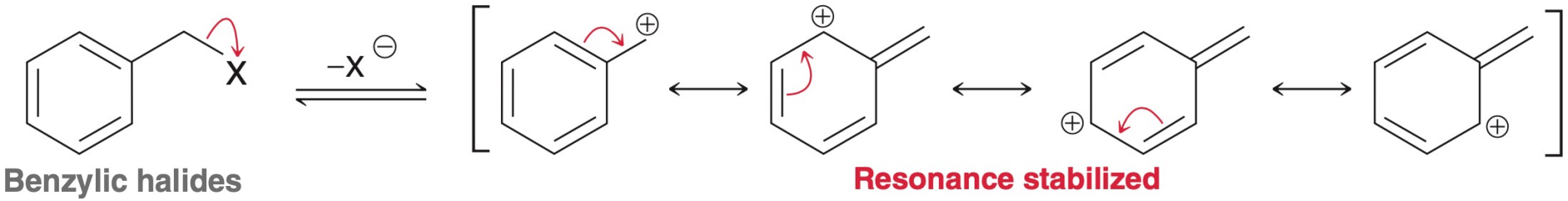
Comparison between S_N1 & S_N2

	S_N2	S_N1
Mechanism		
Energy diagram		
Rate equation	Rate = *k* [substrate] [nucleophile]	Rate = *k* [substrate]
Rate of reaction	Methyl > 1° > 2° > 3°	3° > 2° > 1° > methyl
Stereochemistry	Inversion of configuration	Racemization (with slight preference for inversion due to ion pairs)

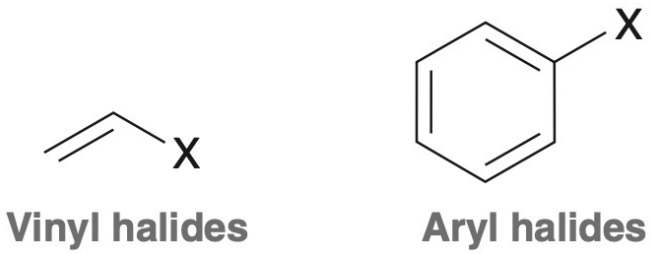
- The Substrate



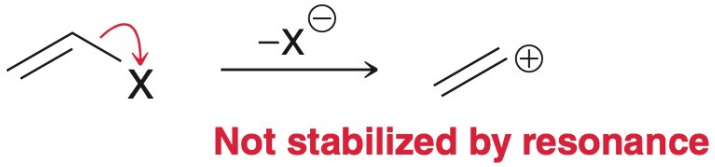




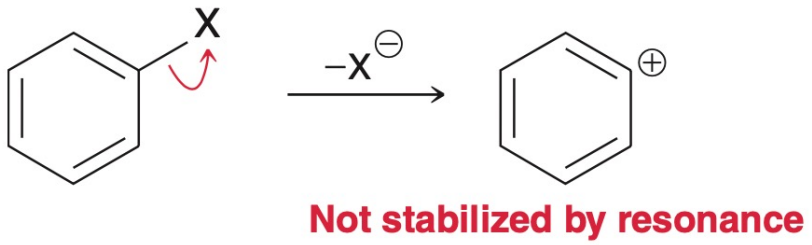
- Vinyl halides and aryl halides are unreactive in substitution reactions



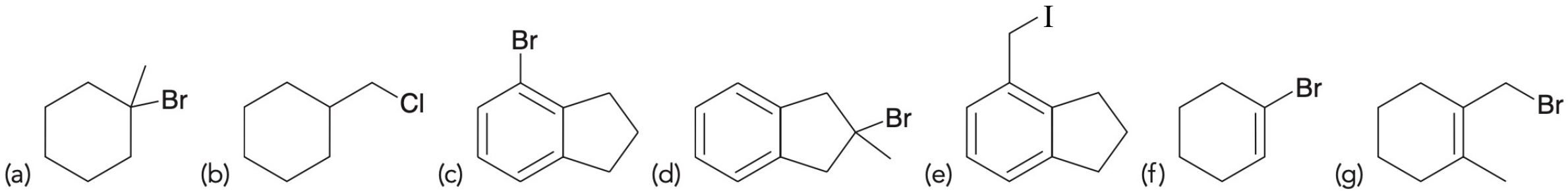
既存在位阻妨碍S_N2



又不能形成稳定的碳正离子进行S_N1



- Practice: identify whether each of the following substrates favors S_N2, S_N1, both, or neither:



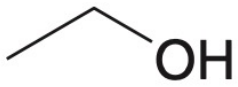
- The Nucleophile
  - a strong nucleophile favors S_N2
  - a weak nucleophile disfavors S_N2 (and thereby allows S_N1 to compete successfully – S_N1 does not depend a lot on nucleophile strength)

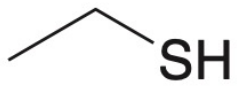
Common nucleophiles

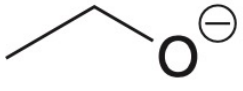
Strong			Weak
$I^{\ominus}$	$HS^{\ominus}$	$HO^{\ominus}$	$F^{\ominus}$
$Br^{\ominus}$	H_2S	$RO^{\ominus}$	H_2O
$Cl^{\ominus}$	RSH	$N{\equiv}C^{\ominus}$	ROH

强亲核试剂一般具有较强的(Lewis)碱性和较大的极化能力

- Practice: does each of the following nucleophiles favor S_N2 or S_N1?

(a) 

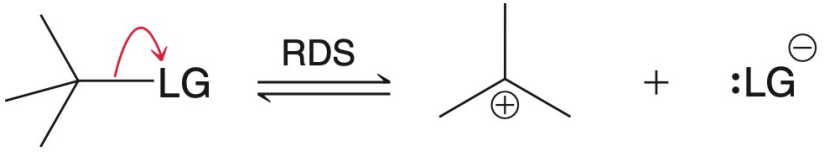
(b) 

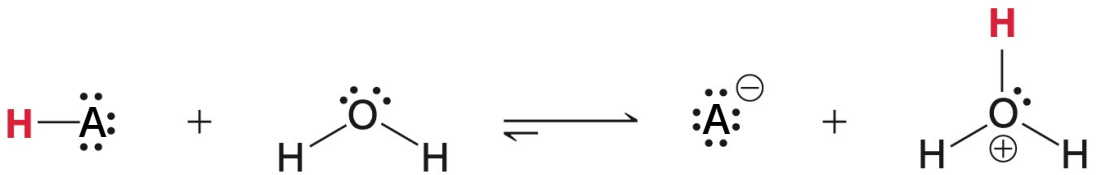
(c) 

(d) NaOH

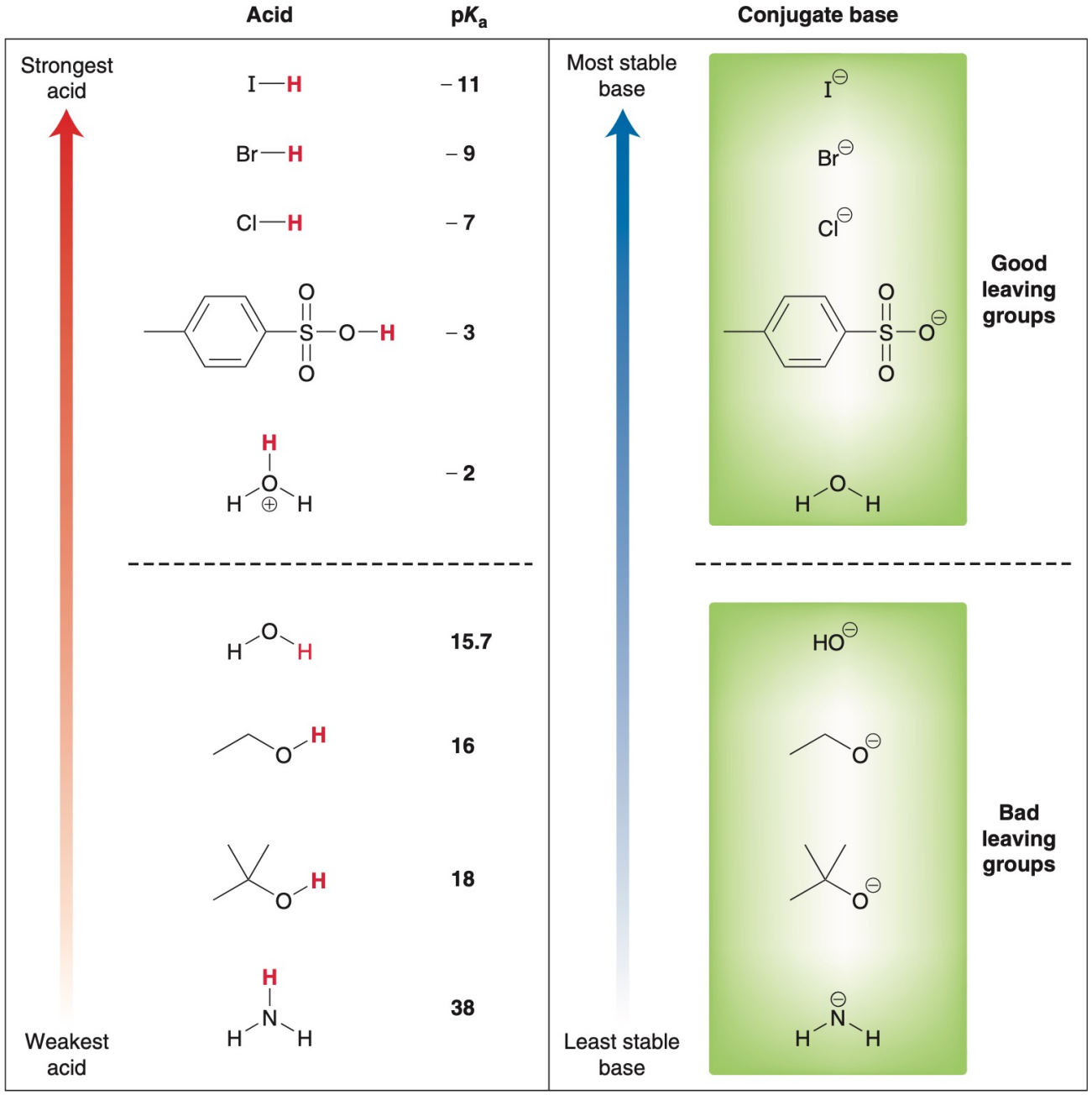
(e) NaCN

- The Leaving Group

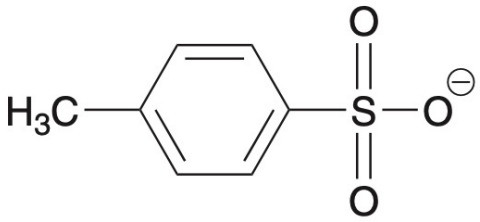
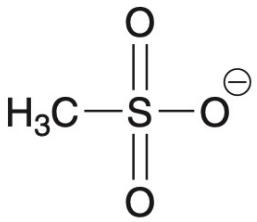
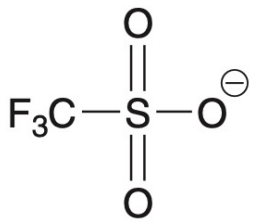




强酸的共轭碱是较好的离去基团



- Sulfonate ions can also be good leaving groups

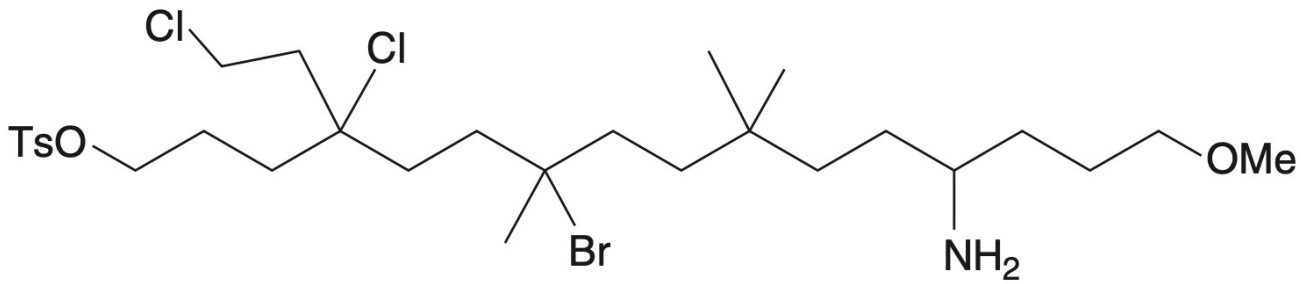
Halides			Sulfonate ions		
					
Iodide	**Bromide**	**Chloride**	**Tosylate**	**Mesylate**	**Triflate**

- Practice

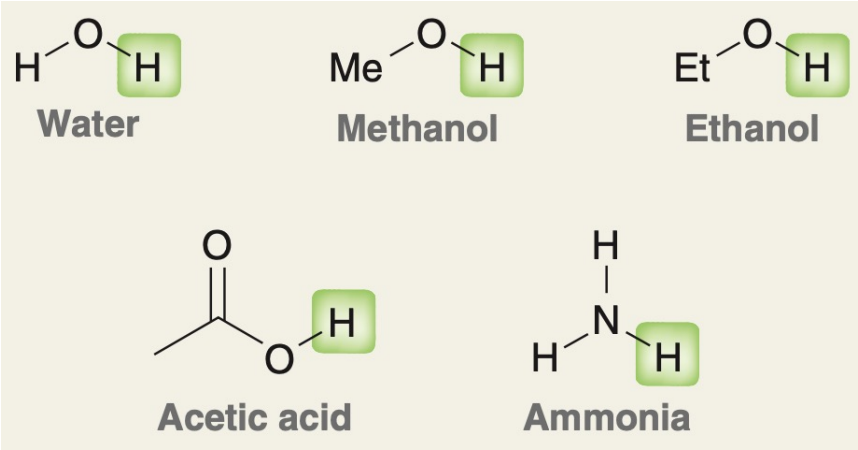
7.28 Consider the structure of the compound below.

(a) Identify each position where an S_N2 reaction is likely to occur if the compound were treated with hydroxide.

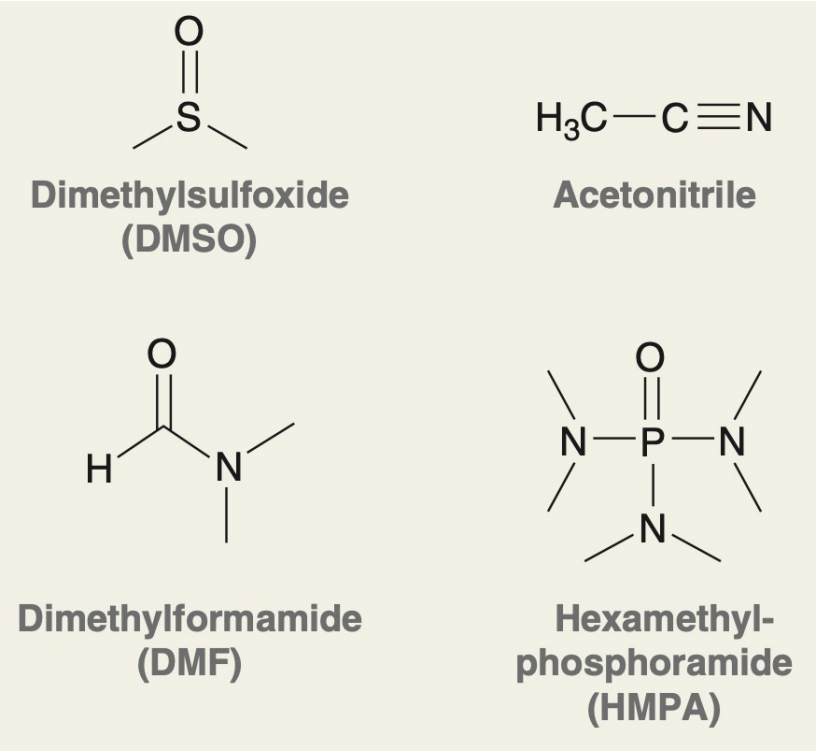
(b) Identify each position where an S_N1 reaction is likely to occur if the compound were treated with water.



- The Solvent

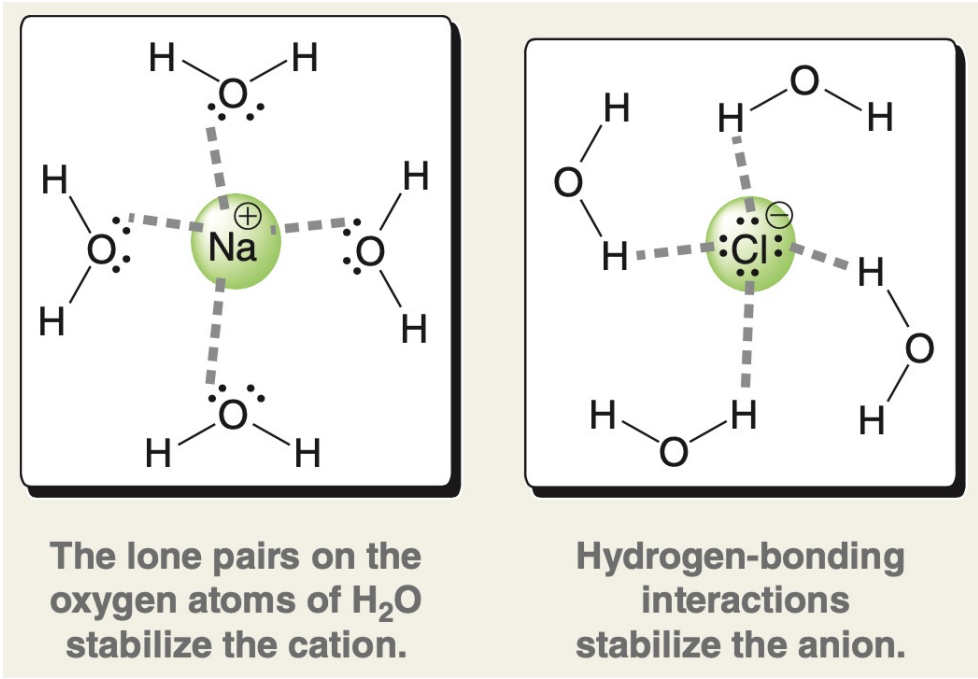


protic solvent
质子性溶剂

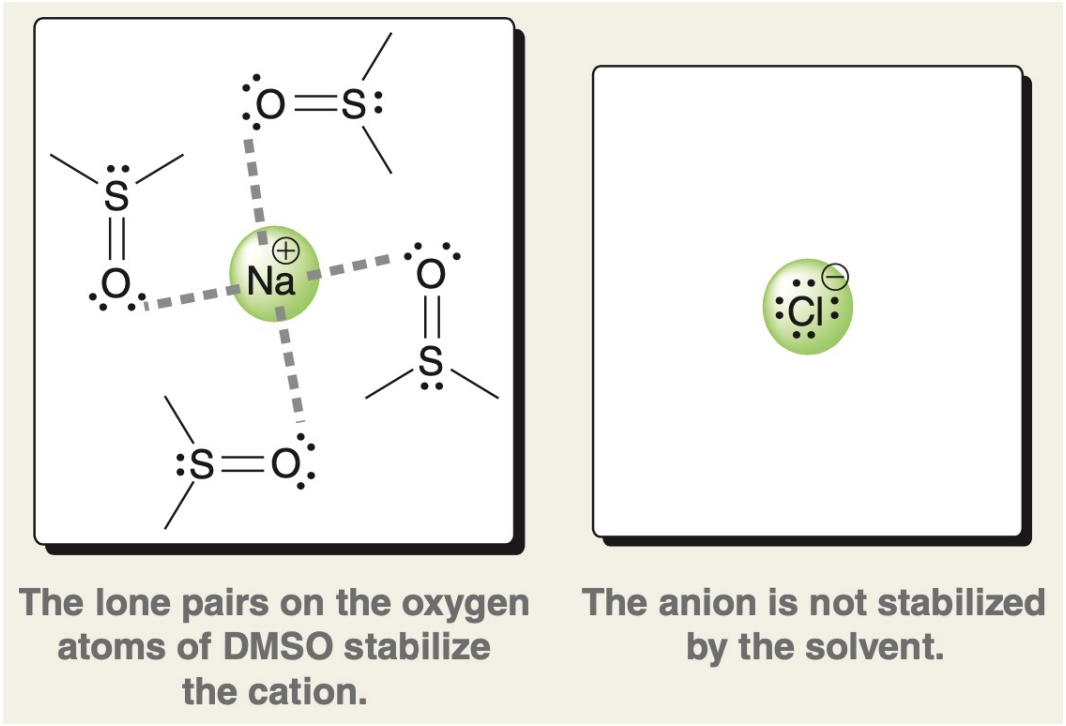


polar aprotic solvent
非质子极性溶剂

protic solvent



polar aprotic solvent



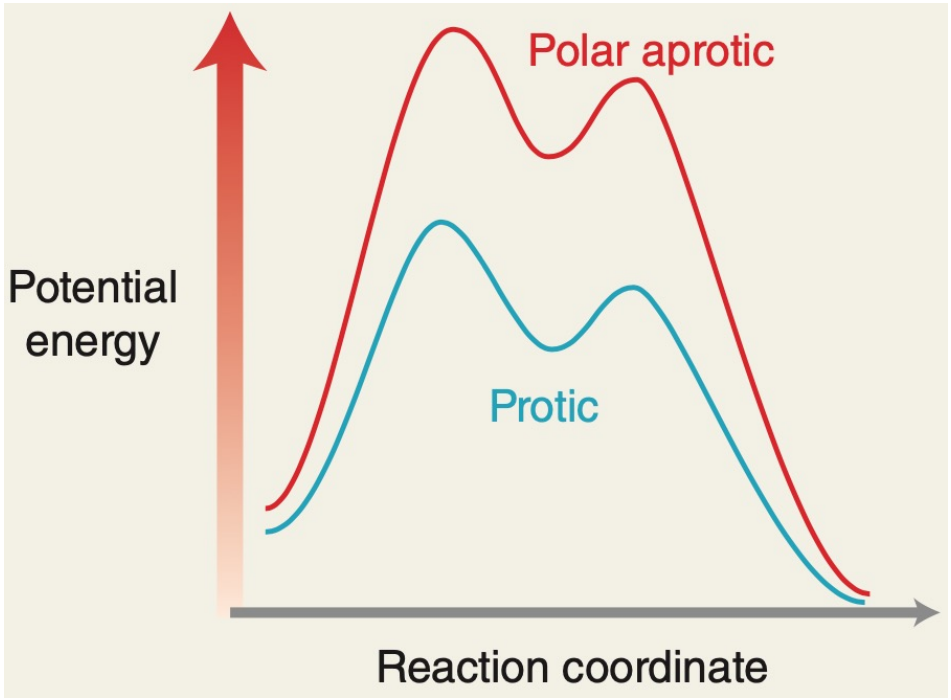
阴、阳离子均被溶剂化

有利于S_N1 – 稳定中间体及过渡态

阳离子被溶剂化

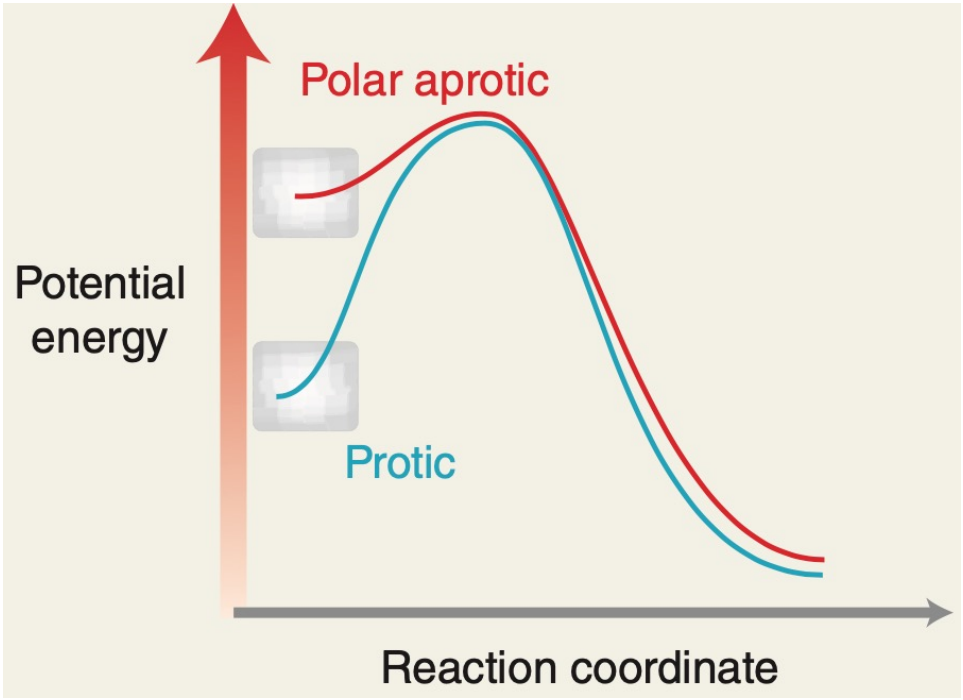
有利于S_N2 – 较高能量的阴离子减小所需活化能

for S_N1



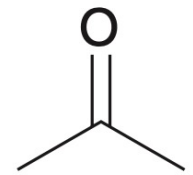
protic solvents favor the reaction

for S_N2



polar aprotic solvents favor the reaction

- Practice: when used as a solvent, will acetone favor an S_N2 or an S_N1 mechanism? Explain.

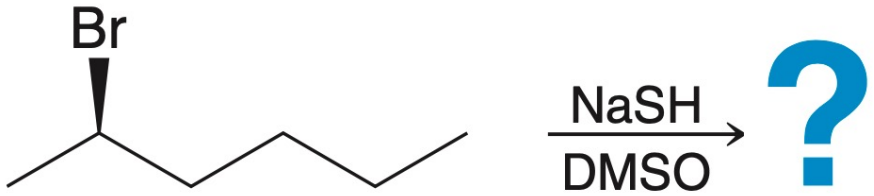


Acetone

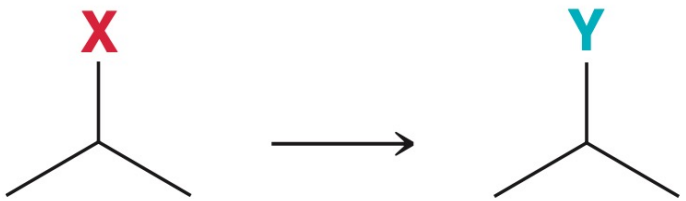
- **Summary**

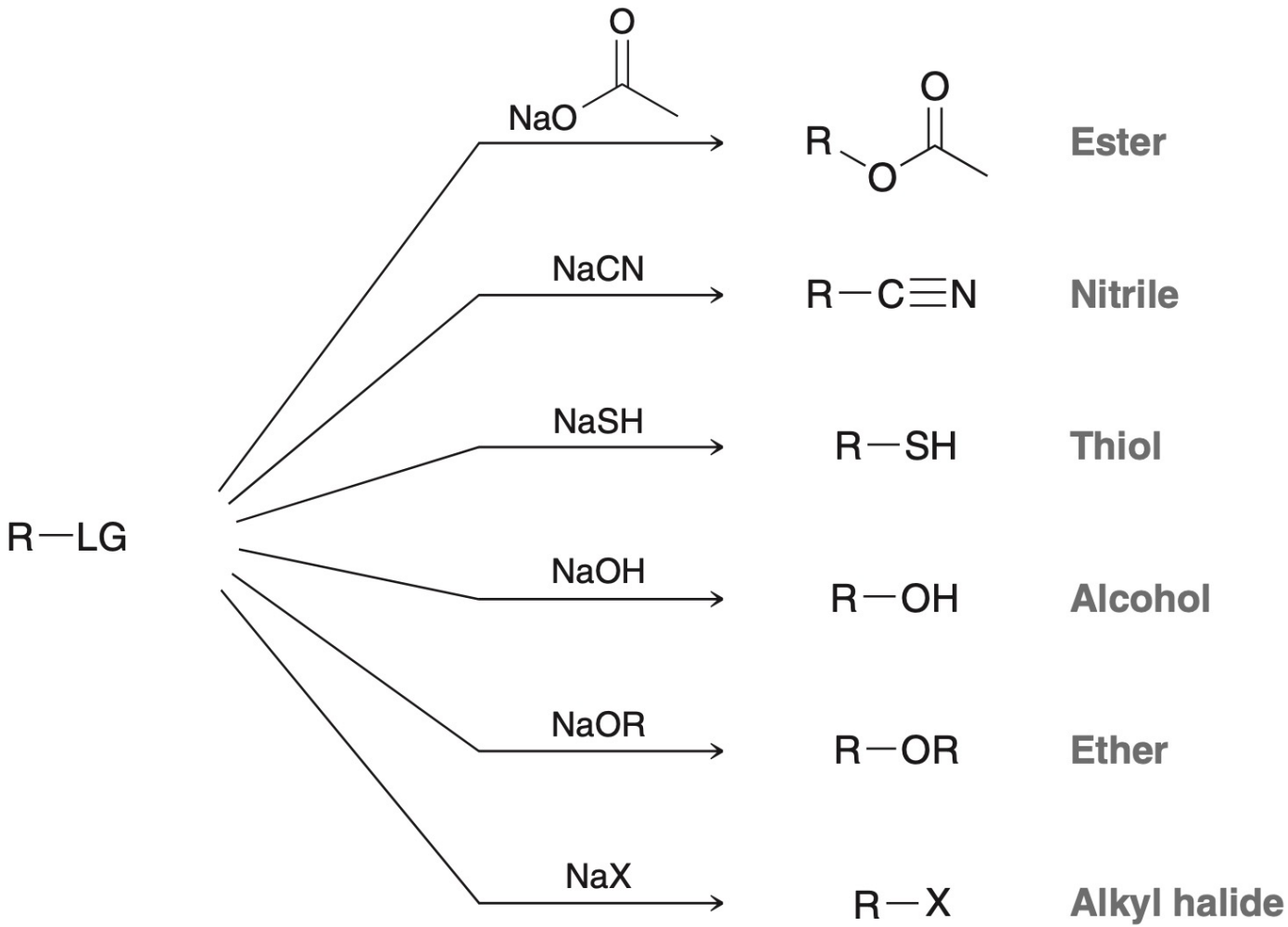
FACTOR	FAVORS S_N2	FAVORS S_N1
Substrate	Methyl or primary	Tertiary
Nucleophile	Strong nucleophile	Weak nucleophile
Leaving group	Good leaving group	Excellent leaving group
Solvent	Polar aprotic	Protic

- Practice: determine whether the following reaction proceeds via an S_N1 or an S_N2 mechanism and then draw the product(s) of the reaction:



- 合成设计初步——官能团的转化

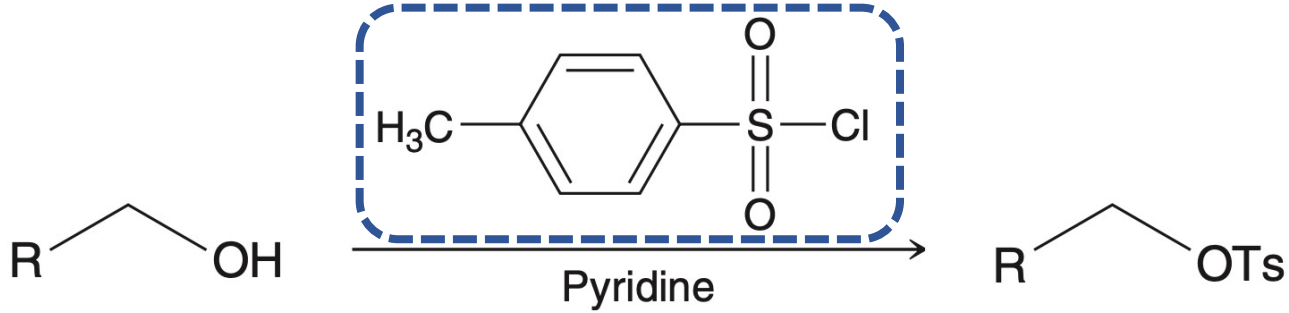



R—LG
NaO
O
R
O
O
Ester
NaCN
R—C≡N
Nitrile
NaSH
R—SH
Thiol
NaOH
R—OH
Alcohol
NaOR
R—OR
Ether
NaX
R—X
Alkyl halide

- 利用TsCl完成醇到其它官能团的转化(S_N2 process)

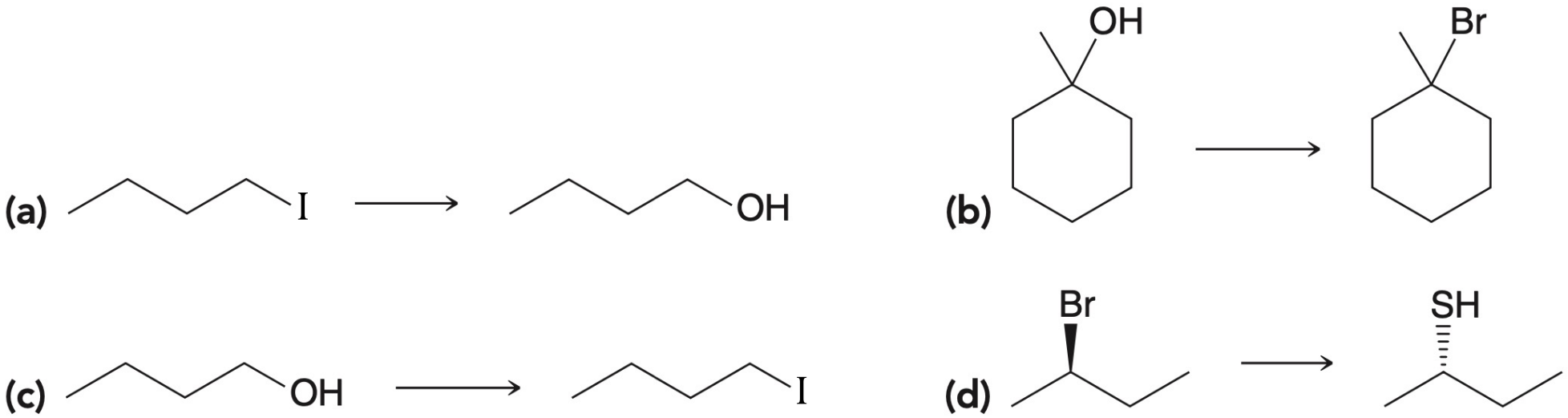
对甲苯磺酰氯

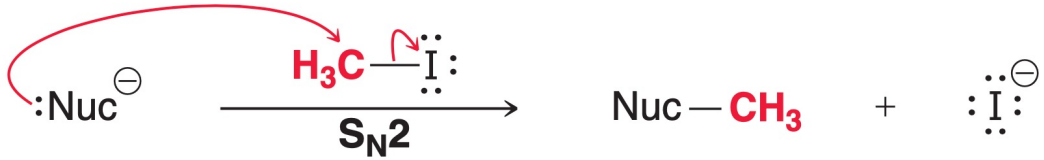
TsCl



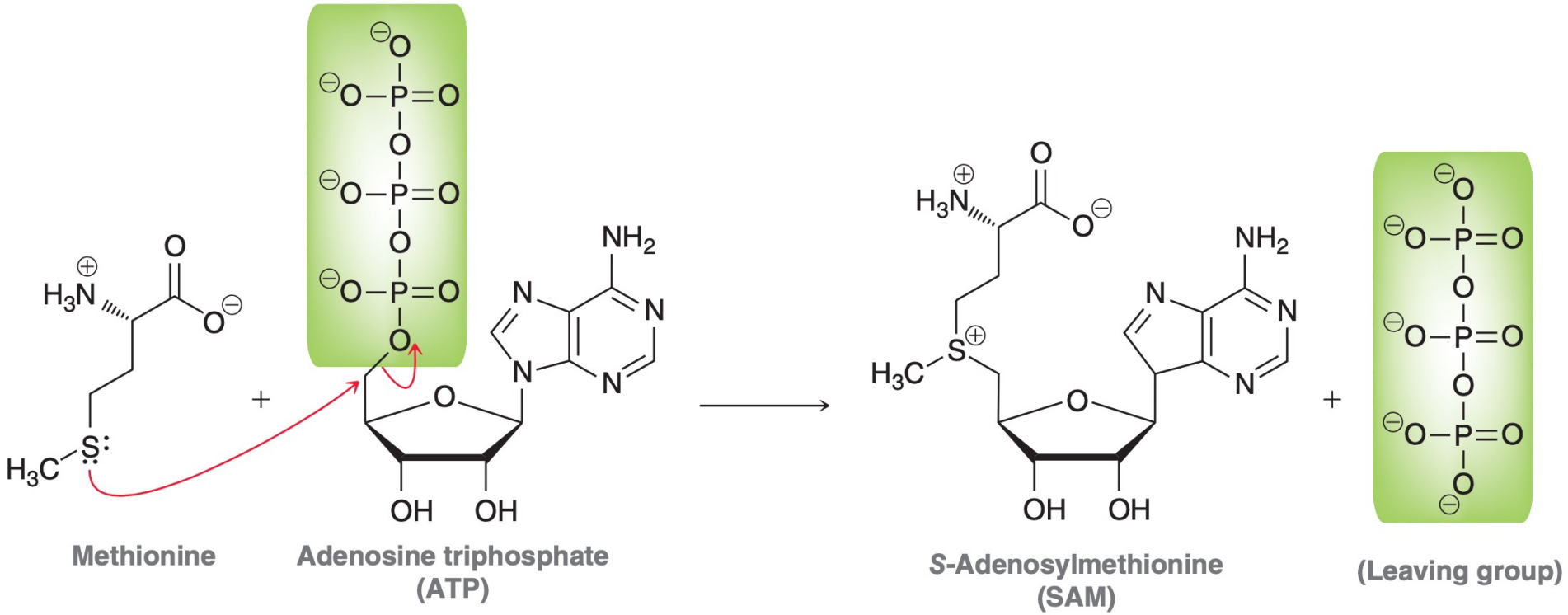
OTs是好的离去基团

- Practice: identify the reagents you would use to accomplish each of the following transformations:

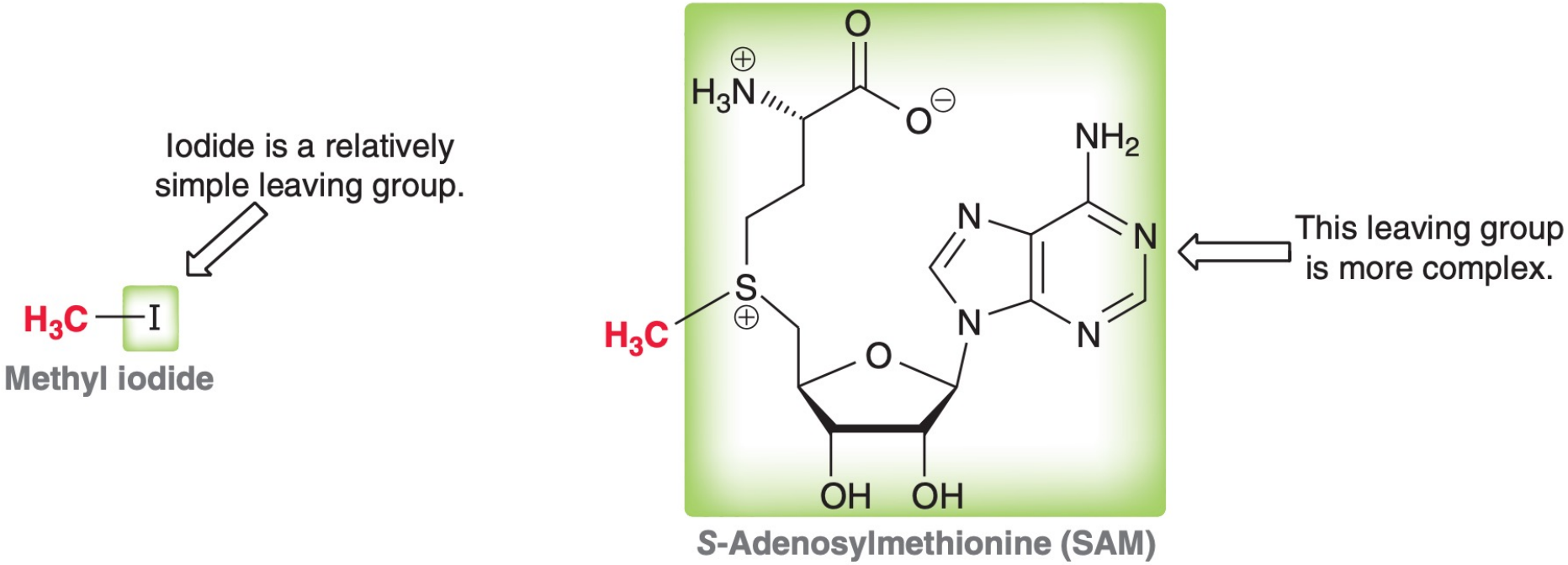




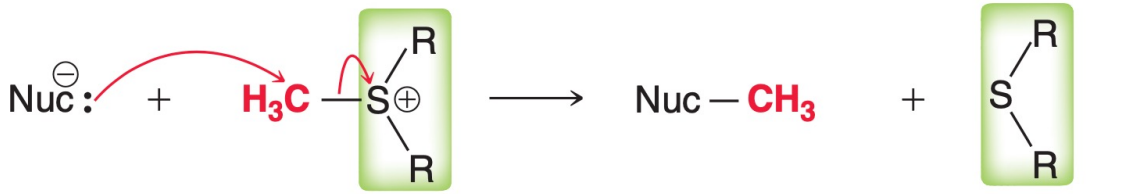
- S_N2 reactions in biological systems – methylation



- SAM – the biological equivalent of methyl iodide

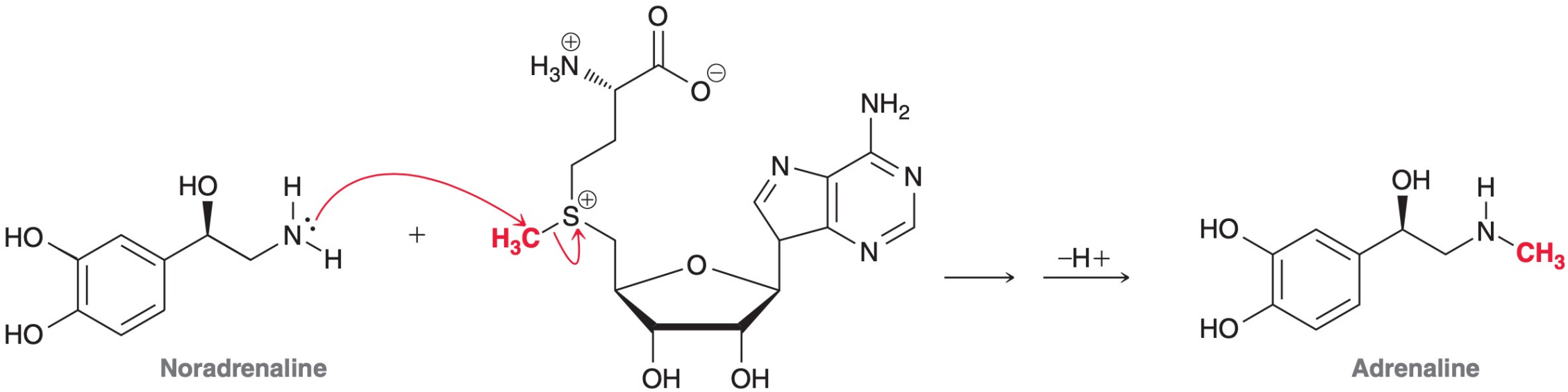


- Biosynthesis reactions included SAM



S-Adenosylmethionine (SAM)

Excellent LG



Noradrenaline

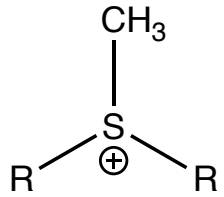
去甲肾上腺素

Adrenaline

肾上腺素

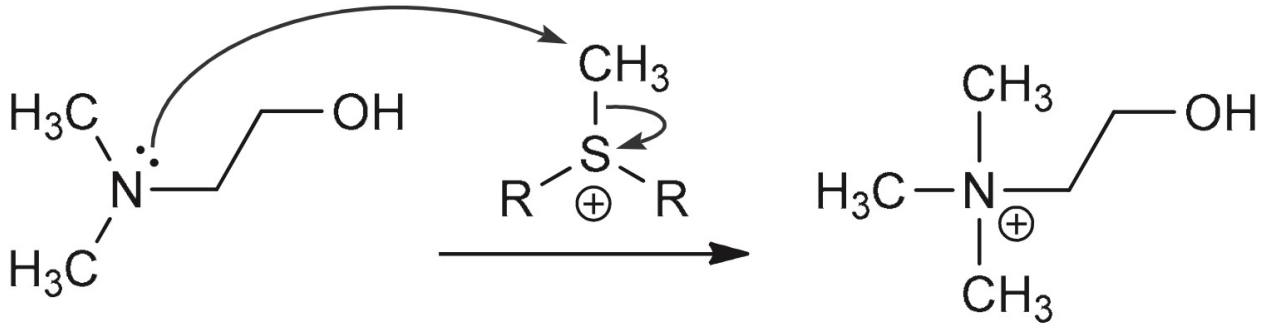
- Practice: choline is a compound involved in neurotransmission. The biosynthesis of choline involves the transfer of a methyl group from SAM. Draw a mechanism for this transformation:

hint: try to use



as an abbreviation for SAM

- Practice: choline is a compound involved in neurotransmission. The biosynthesis of choline involves the transfer of a methyl group from SAM. Draw a mechanism for this transformation:



The nitrogen atom functions as a nucleophilic center and attacks the electrophilic methyl group in SAM, forming an ammonium ion.