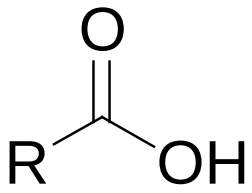
台灣大學開放式課程

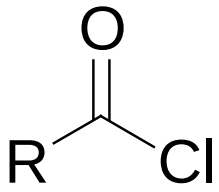
有機化學乙

蔡蘊明　教授

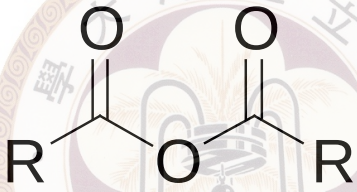
Chapter 17
Carboxylic acids and their derivatives



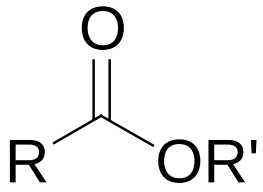
carboxylic acid (羧酸)



acyl chloride
(acid chloride; 醯氯)

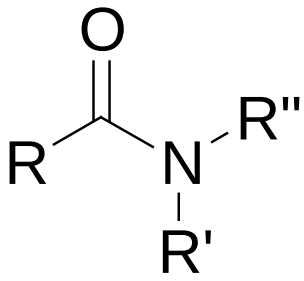


acid anhydride
(酸酐)



ester (酯)

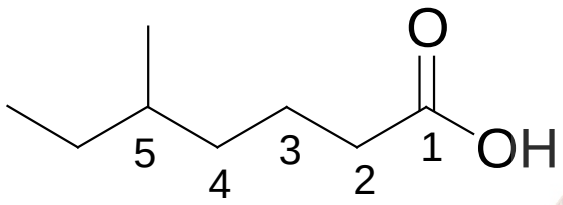
R−C≡N nitrile (腈)



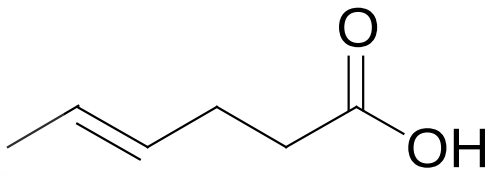
amide (醯胺)

※ Carboxylic acids

◎ Nomenclature

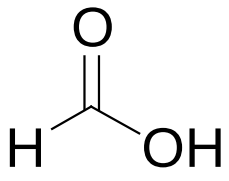


5-methylheptan**oic acid**

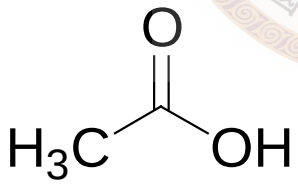


trans-4-hexenoic acid

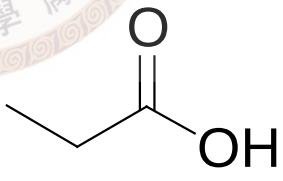
Common names:



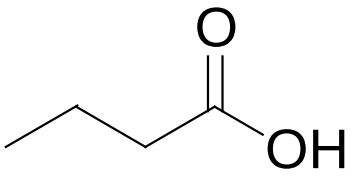
formic acid



acetic acid



propionic acid



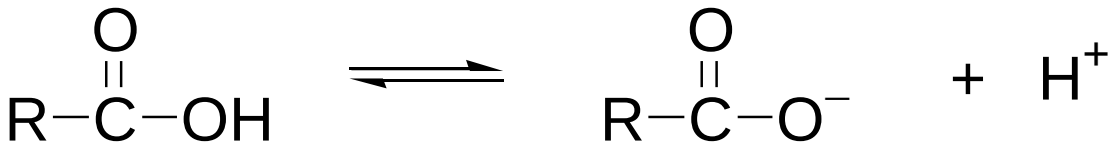
butyric acid

◎ Properties

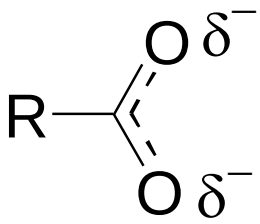
polar, soluble in water when small

intermolecular hydrogen bonding:

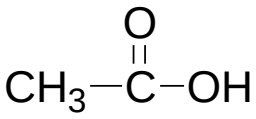
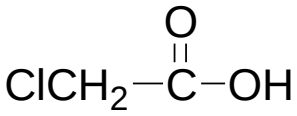
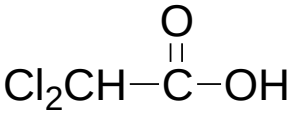
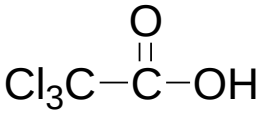
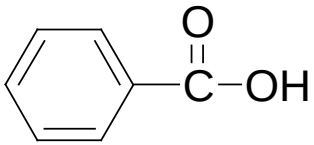
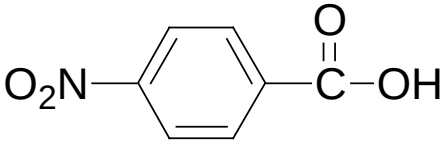
◎ Acidity of carboxylic acids

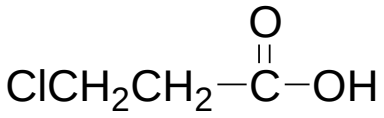


resonance stabilized



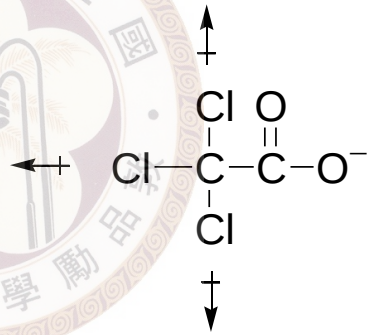
The negative charge is delocalized over the two oxygens

	p*K*a
	4.75
	2.85
	1.48
	0.70
	4.19
	3.41

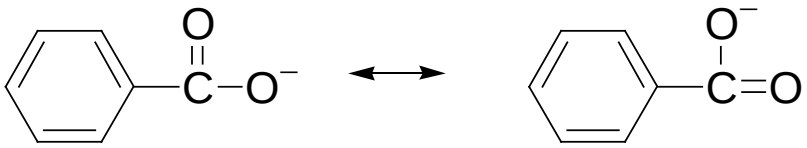


3.98

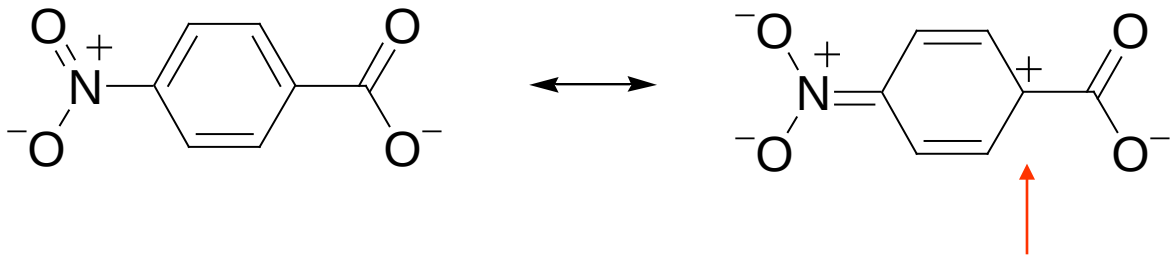
inductive effect is distance dependent



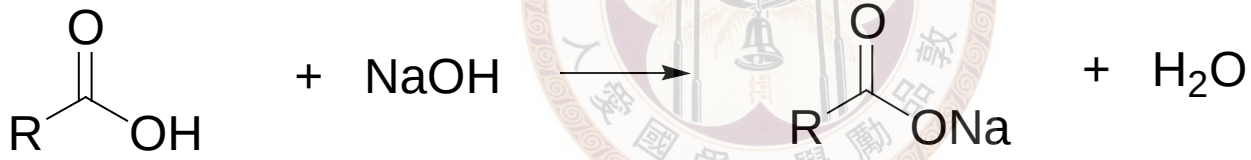
Inductively stabilized by the EWGs

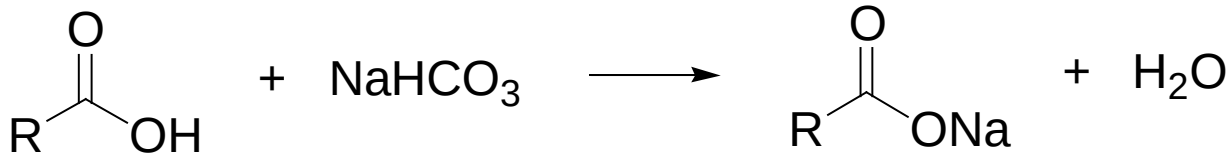


benzene ring not participated in resonance behaves as an EWG (sp^2)



Inductive effect is transmitted through resonance

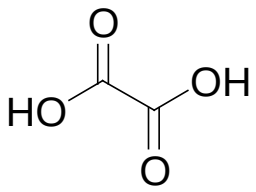
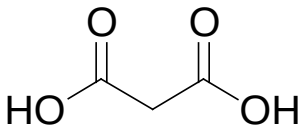
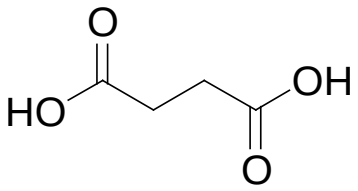
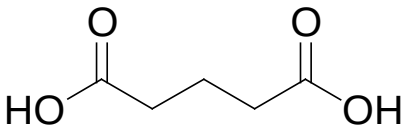
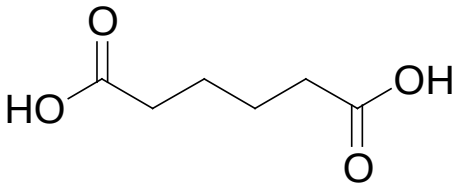


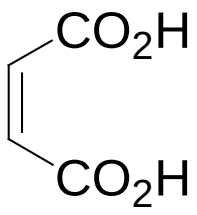


water soluble

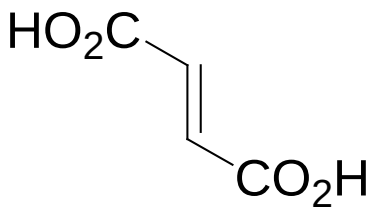
◎ Dicarboxylic acids

IUPAC: alkanedioic acid

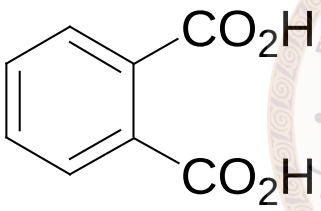
		common name	pK_{a1}	pK_{a2}
	ethanedioic acid	oxalic acid	1.2	4.2
		malonic acid	2.9	5.7
		succinic acid	4.2	5.6
		glutaric acid	4.3	5.4
		adipic acid	4.4	5.6



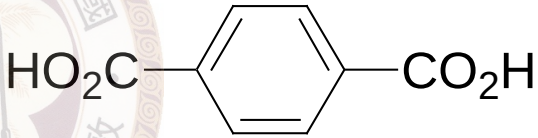
maleic acid



fumaric acid

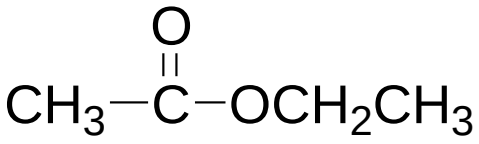


phthalic acid

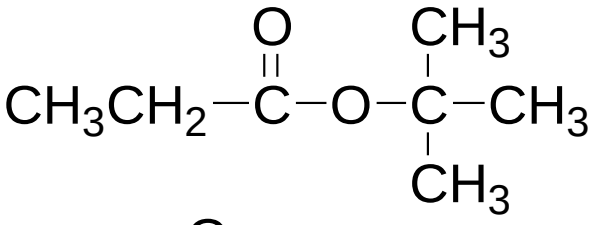


terephthalic acid

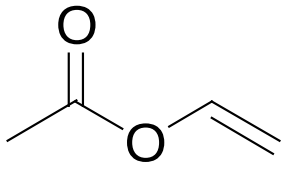
※ Esters



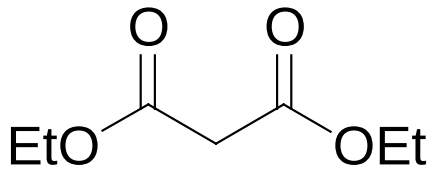
ethyl ethanoate (ethyl acetate)



t-butyl propanoate



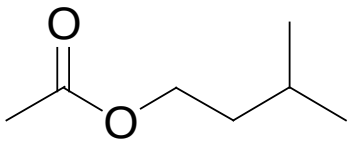
ethenyl ethanoate (vinyl acetate)



diethyl malonate

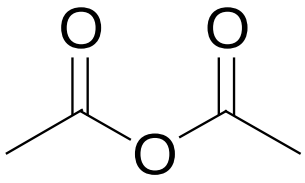
✓ Polar, but with no intermolecular hydrogen bonding

✓ With pleasant ordor

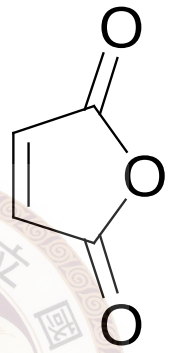


isopentyl acetate
(banana flavor)

※ Carboxylic anhydrides



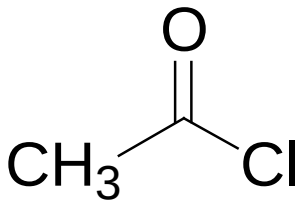
acetic anhydride
(ethanoic anhydride)



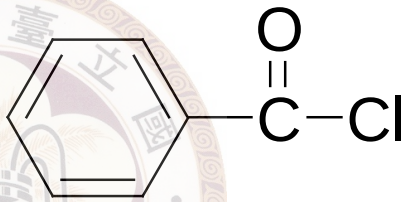
maleic anhydride

※ Acid chlorides

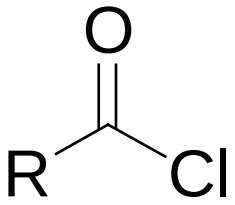
ic → yl



acetyl chloride
(ethanoyl chloride)

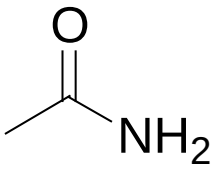


benzoyl chloride

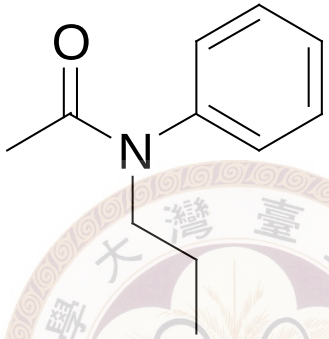


acyl chloride

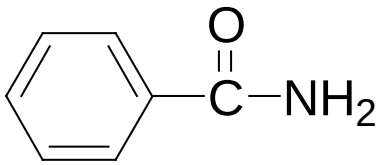
※ Amides



acetamide
(ethanamide)

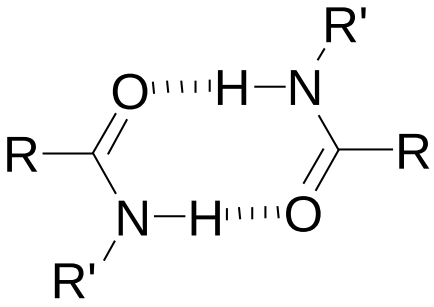


N-phenyl-*N*-propylacetamide

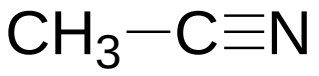


benzamide

✓ Amides can form intermolecular hydrogen bonding

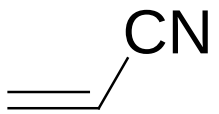


※ Nitriles

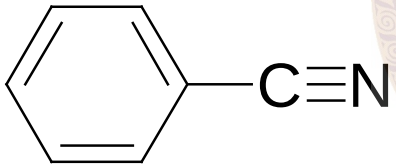


ethanenitrile
(acetonitrile)

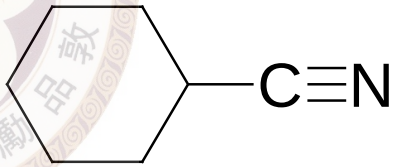
butanenitrile



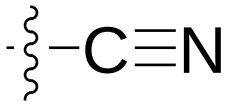
acrylonitrile



benzenecarbonitrile
(benzonitrile)



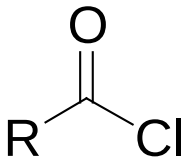
cyclohexanecarbonitrile



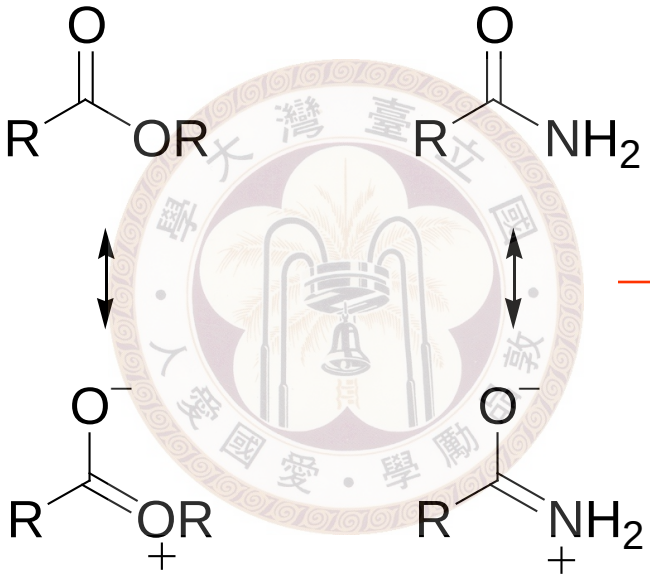
cyano group

※ Spectroscopic properties

✓ IR

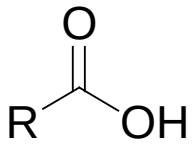


1780-1850

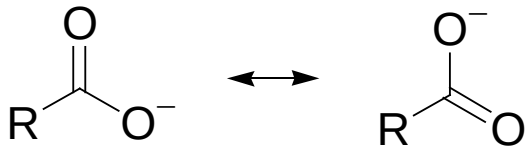


1730 1650-1680

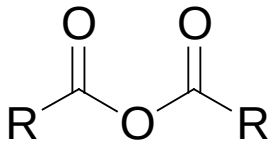
strong amide resonance increases single bond character of C=O



1710
(hydrogen bonded)

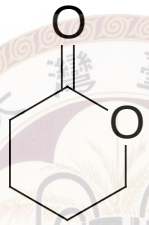


1550-1630

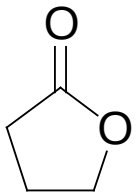


1820, 1760

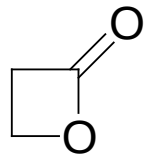
Lactone:



1735

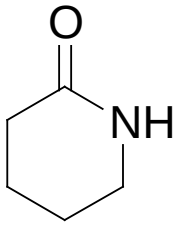


1770



1840

Lactam:



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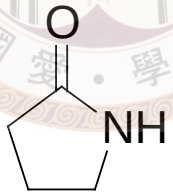

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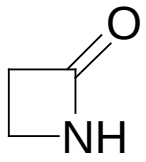
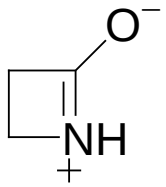
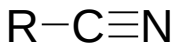




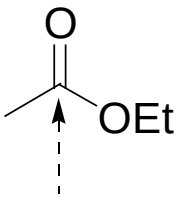
1745

too strain

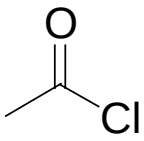


2250

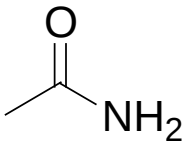
✓ ^{13}C NMR



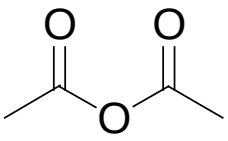
170.7



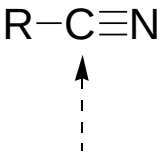
170.3



172.6

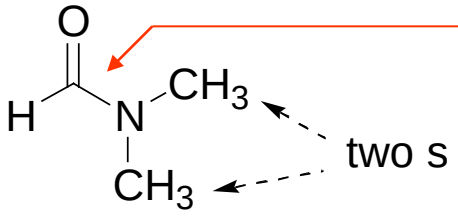


166.9



117.4

✓ ^{1}H NMR



C-N has double bond character
→ hindered rotation

※ Preparation of carboxylic acids

✓ Oxidation of alkenes

$$RCH{=}CHR' \xrightarrow[2)\ H_3O^+]{1)\ KMnO_4,\ OH^-,\ \Delta} RCO_2H + R'CO_2H$$

✓ Oxidation of aldehydes or primary alcohols

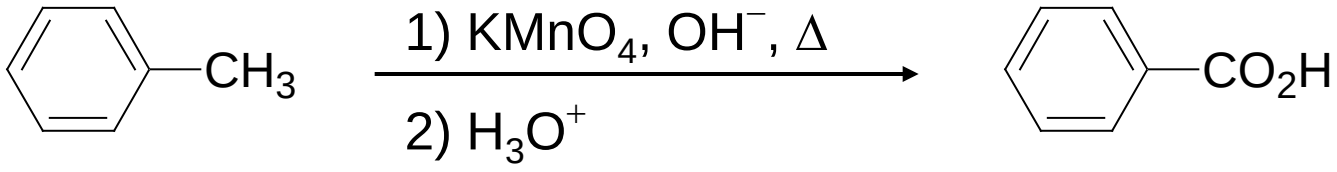
$$RCHO \xrightarrow[2)\ H_3O^+]{1)\ Ag_2O \text{ or } Ag(NH_3)_2^{+}\ ^-OH} RCO_2H$$

or Jones, $KMnO_4$ …

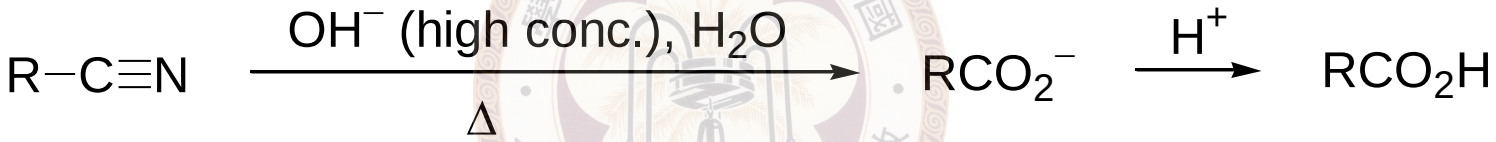
$$RCH_2OH \xrightarrow[2)\ H_3O^+]{1)\ KMnO_4,\ OH^-,\ \Delta} RCO_2H$$

or Jones

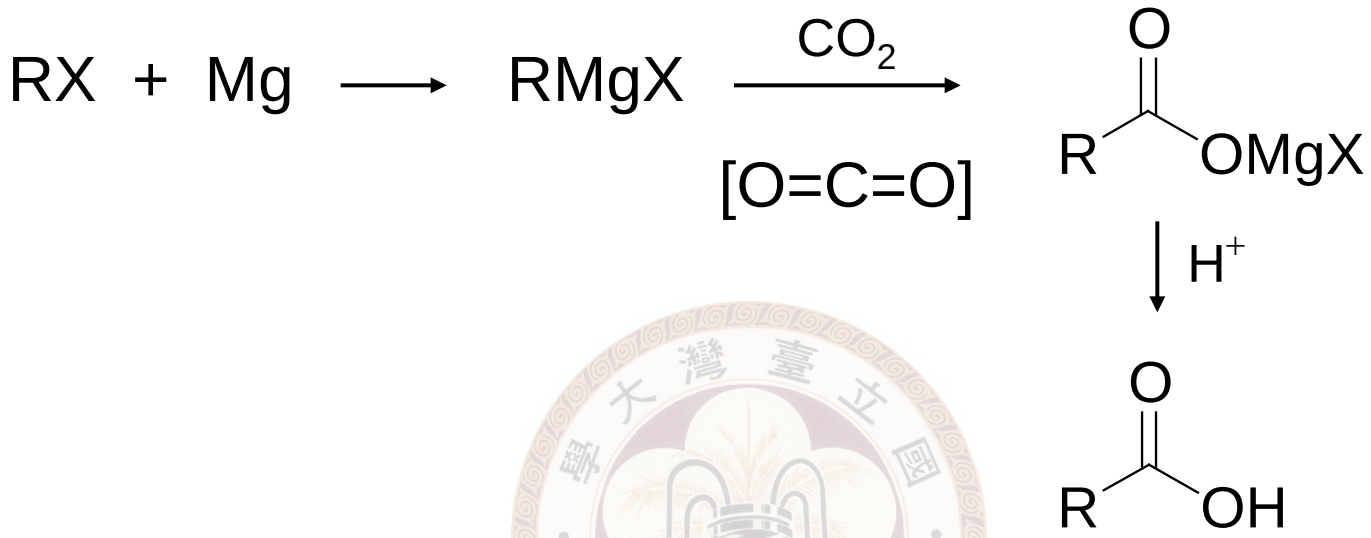
✓ Side-chain oxidation of aromatic compounds



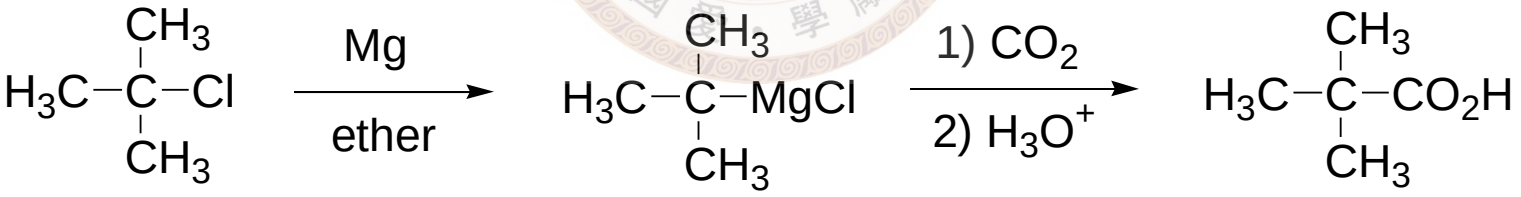
✓ Hydrolysis of nitriles

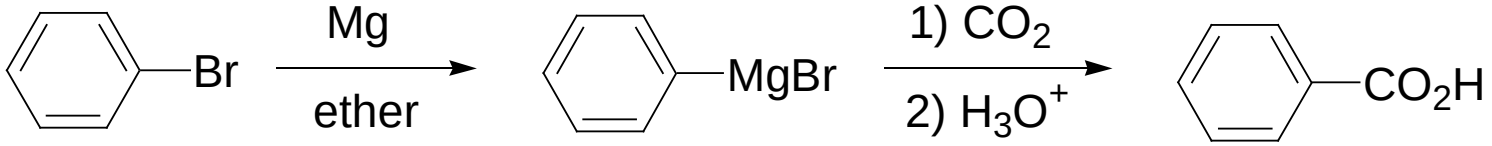


✓ From Grignard reagent

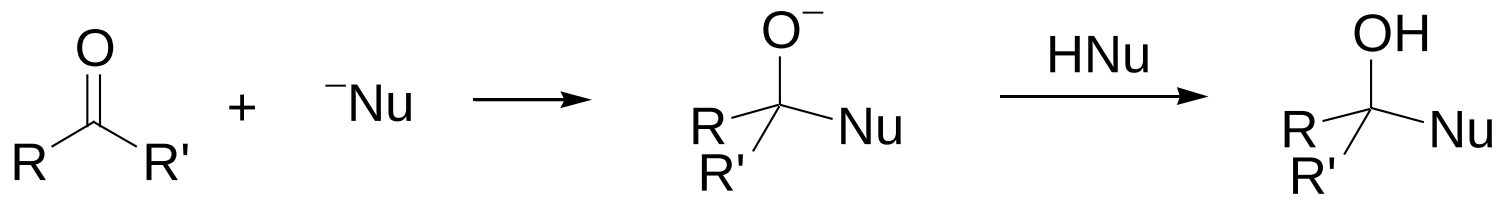


Applications:



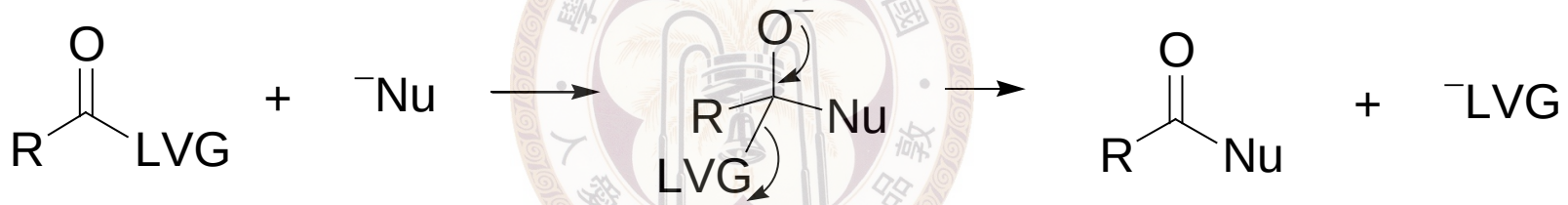


※ Nucleophilic substitution at acyl carbon



addition product

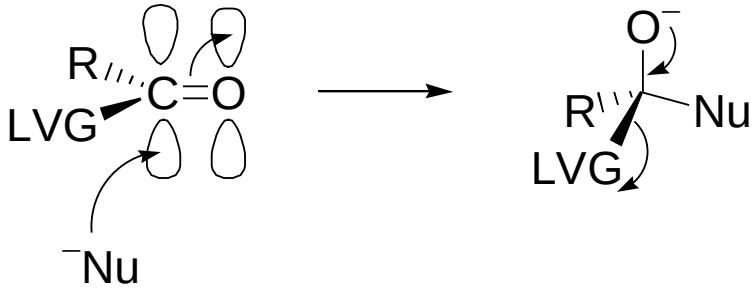
With a better LVG



a tetrahedral intermediate

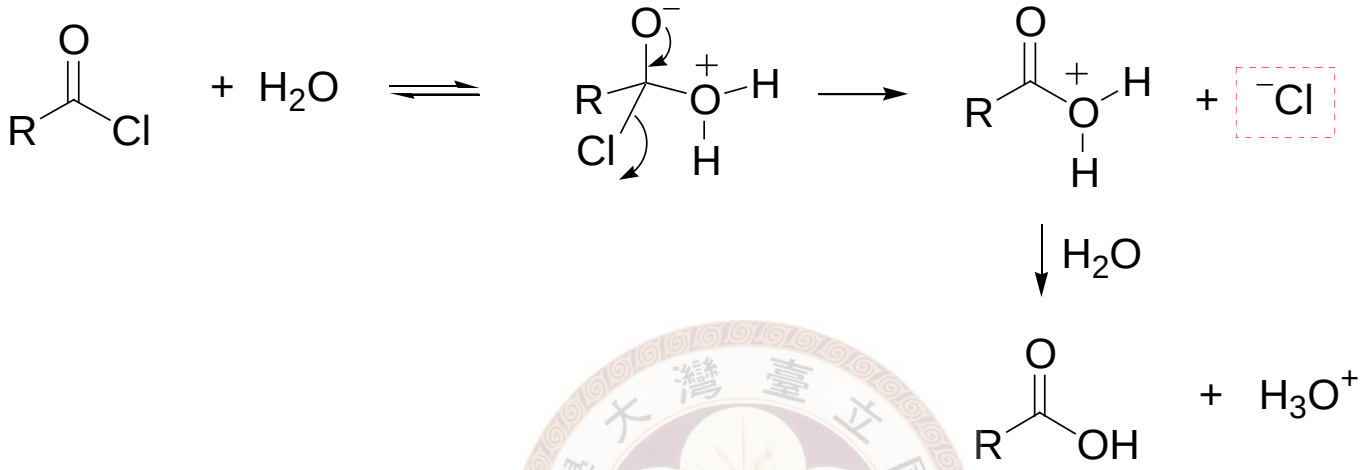
overall substitution

*This is an example of addition followed by elimination

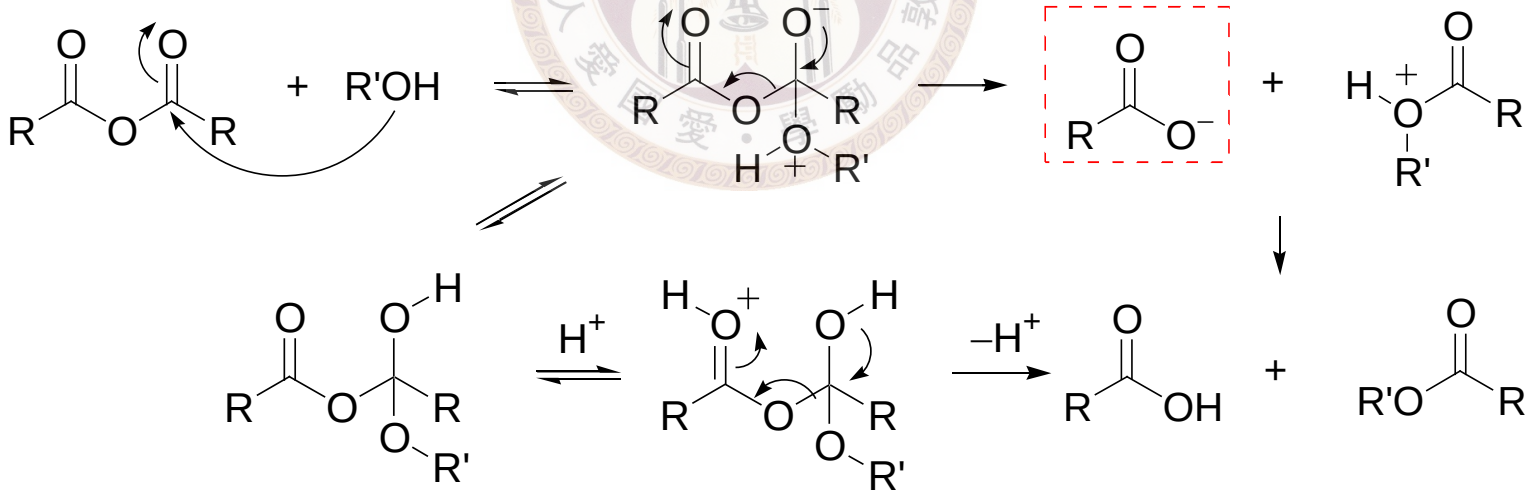


Not a direct displacement

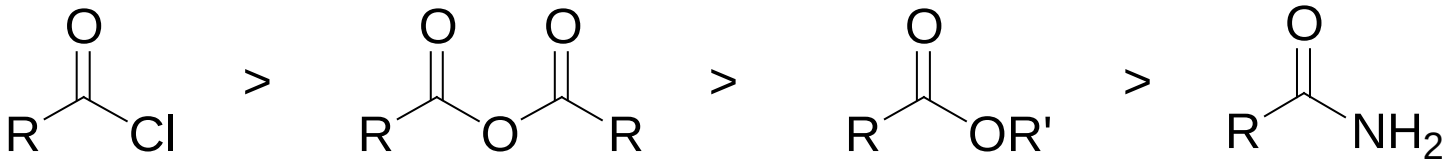
✓ Acyl chloride



✓ Acid anhydride



✓ Relative reactivity



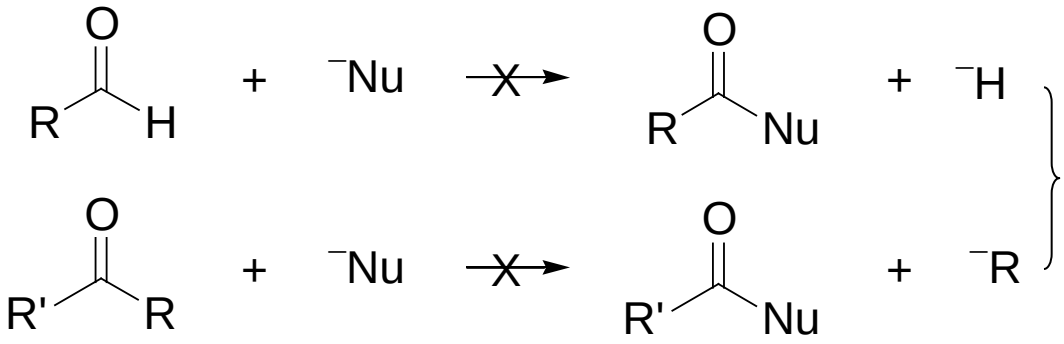
LVG: Cl^- $^-OR'$ $^-NH_2$

basicity

Reacivity parallels leaving group ability

It is possible to convert the one with higher reactivity to a lower one but not the reverse

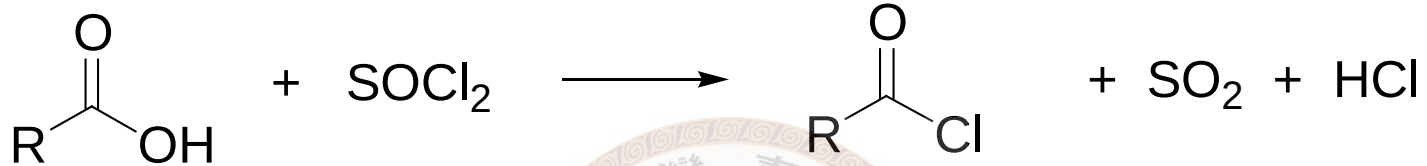
Note:



very bad LVG

※ Acyl chloride

◎ Preparation

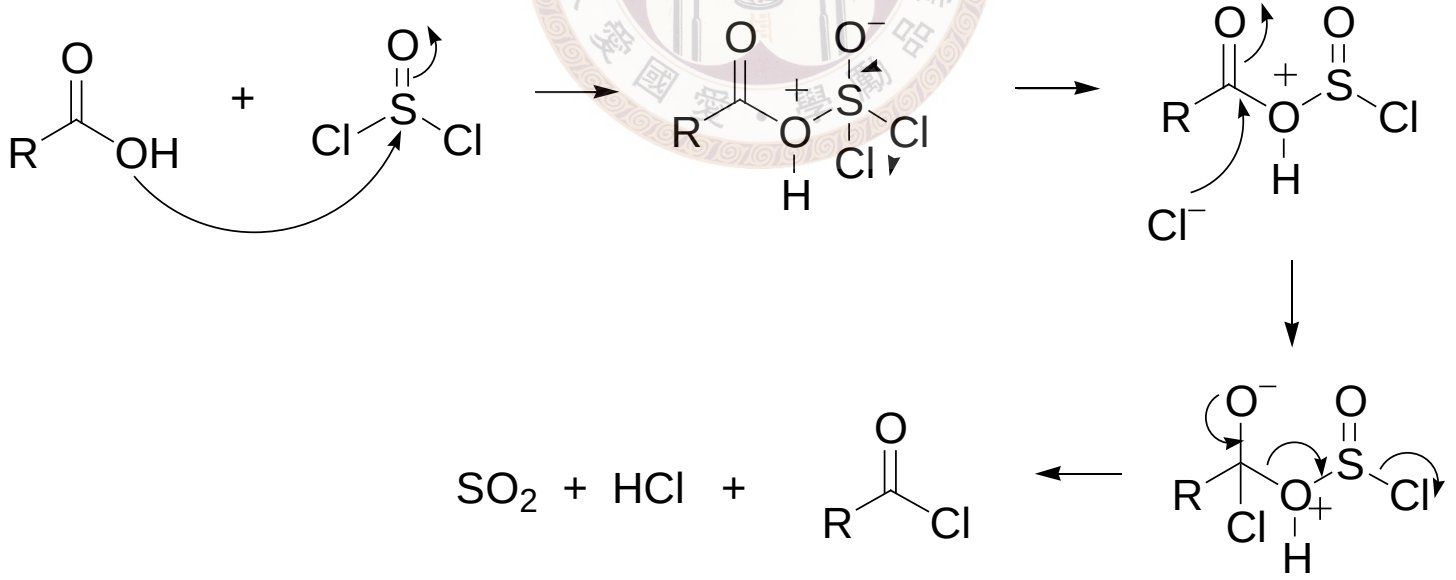


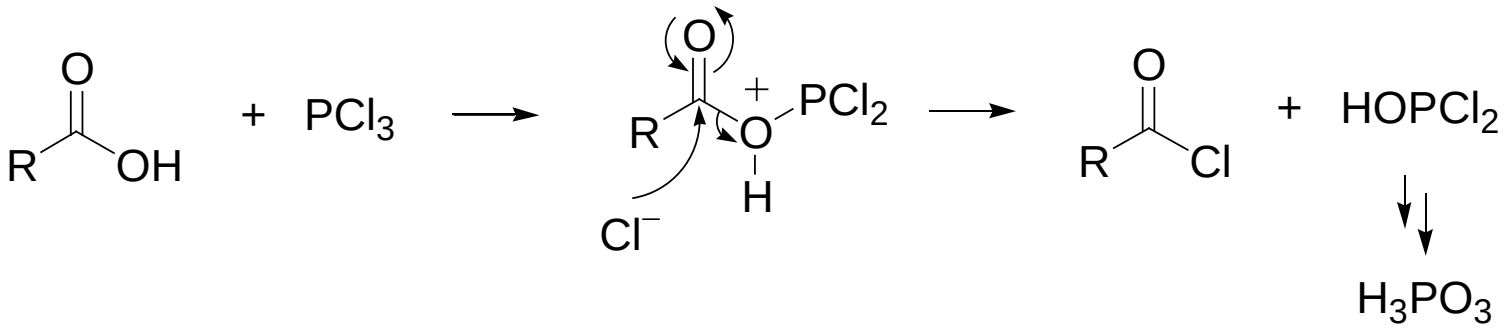
thionyl chloride

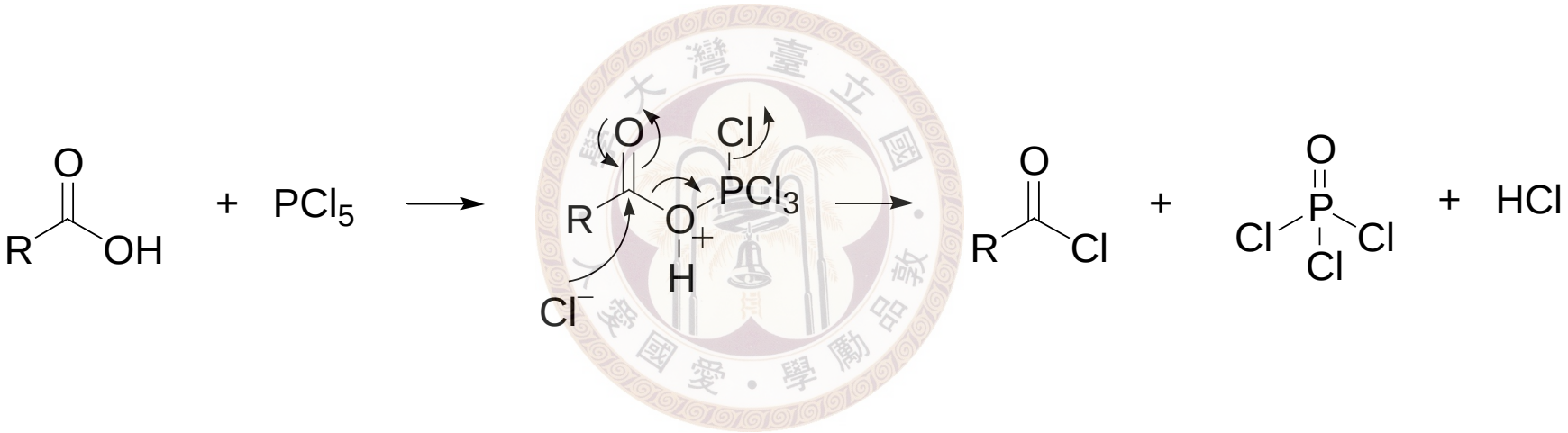
PCl_3 phosphorous trichloride

PCl_5 phosphorous pentachloride

Mechanism:

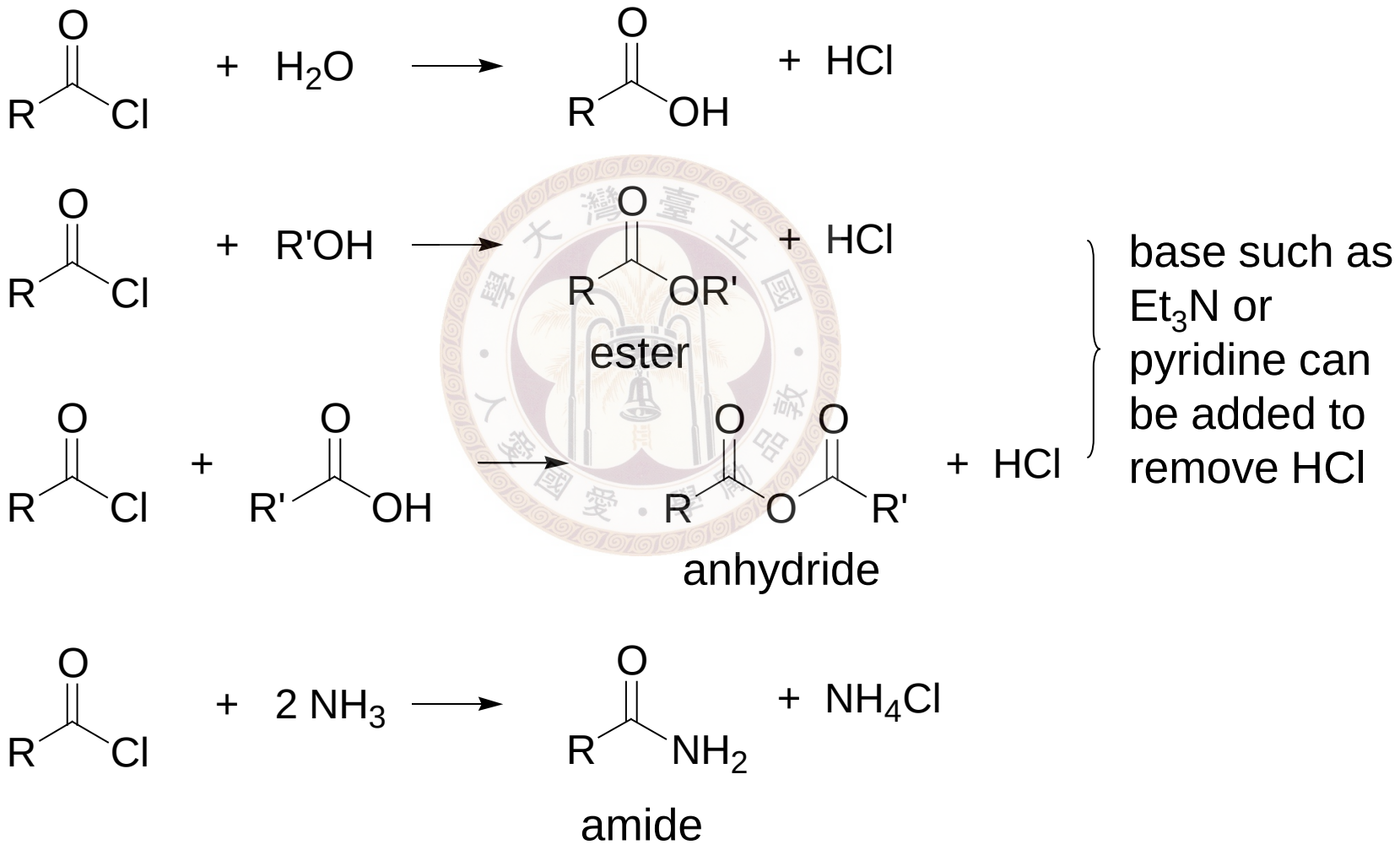



O
R
OH
+ PCl3
O
R
O
+
PCl2
H
Cl−
O
R
Cl
+ HOPCl2
H3PO3


O
R
OH
+ PCl5
O
Cl
PCl3
R
O
+
H
Cl−
O
R
Cl
+
O
P
Cl
Cl
Cl
+ HCl

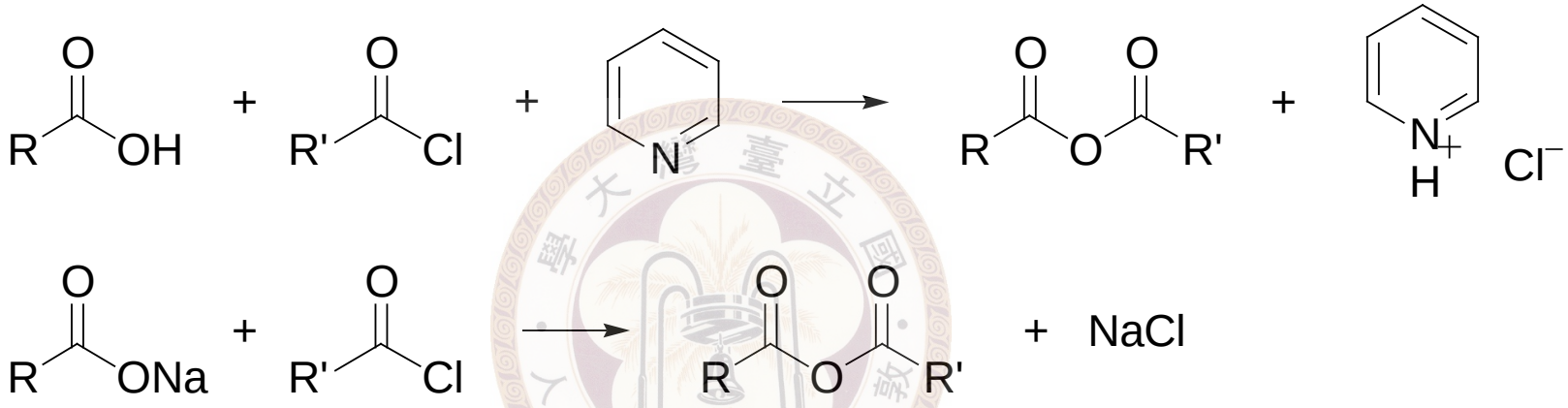
◎ Reactions of acyl chlorides

Reacts with water easily

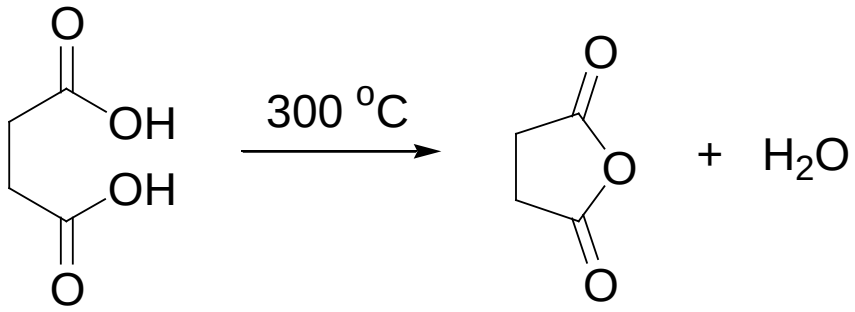


※ Carboxylic acid anhydrides

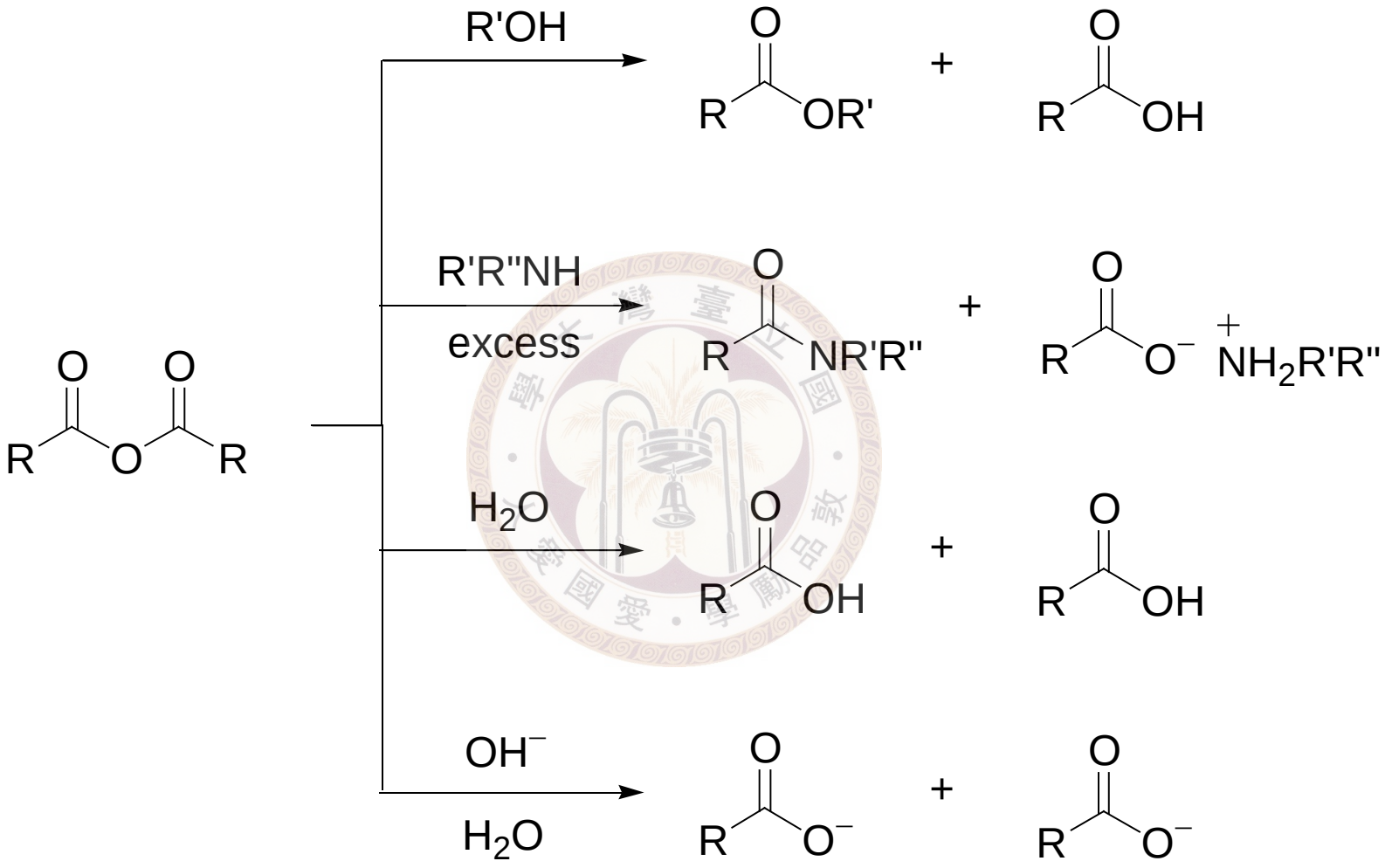
◎ Synthesis



For cyclic anhydrides (five- or six-membered ring)



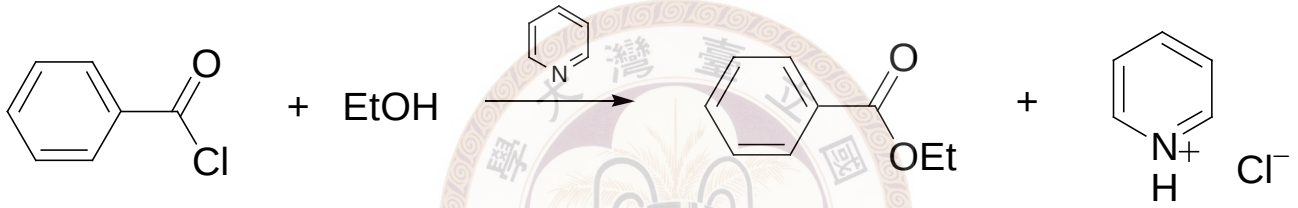
◎ Reactions



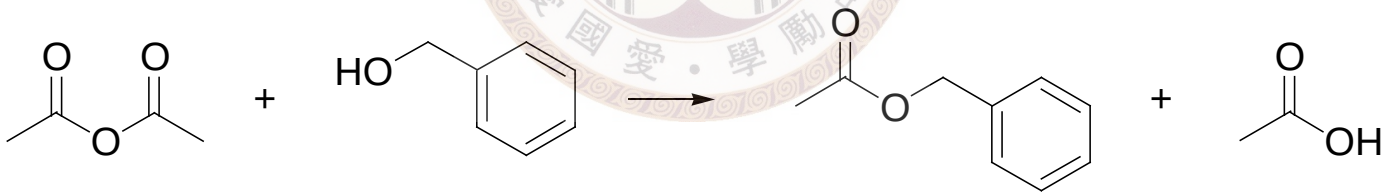
※ Esters

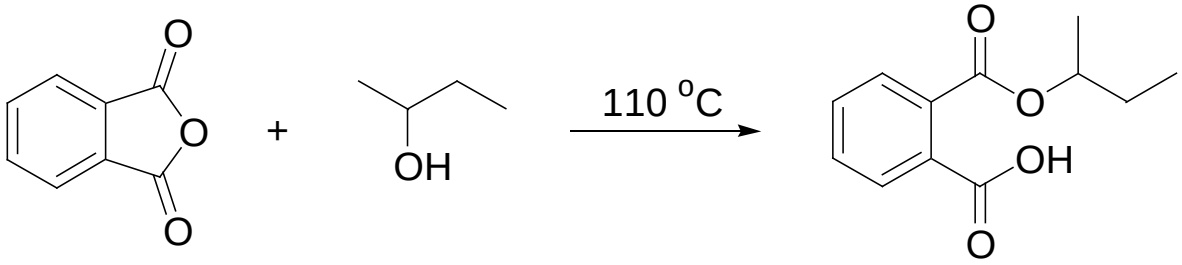
◎ Preparation

✓ From acid chloride

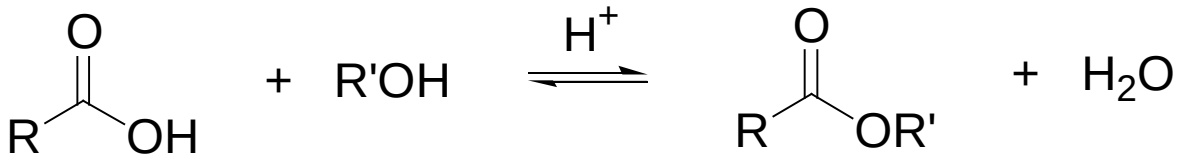


✓ From carboxylic acid anhydrides





✓ Fischer esterification

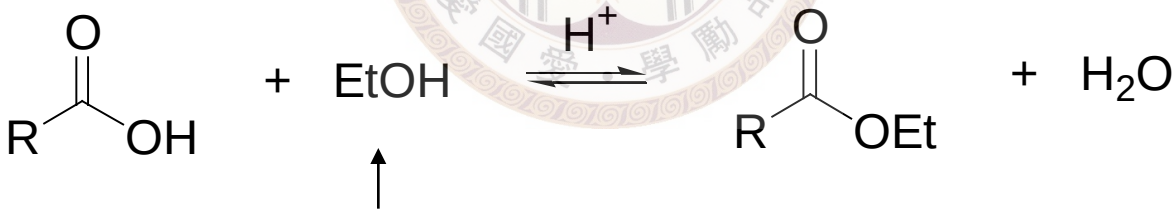


To drive the equilibrium to the right

→ remove water

ex.: azeotropically remove water with benzene or use drying reagent such as $CuSO_4$

例

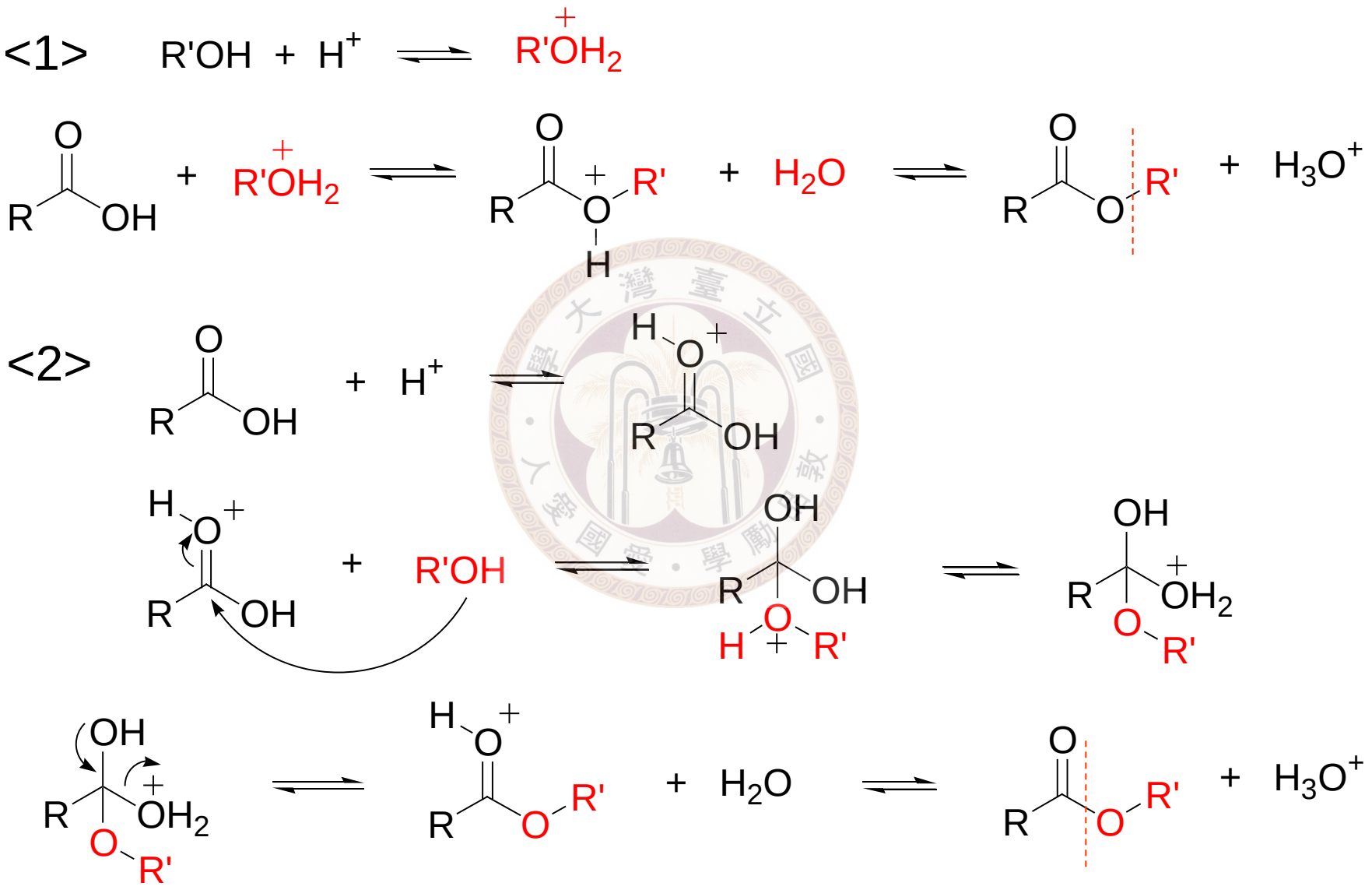


Used as solvent

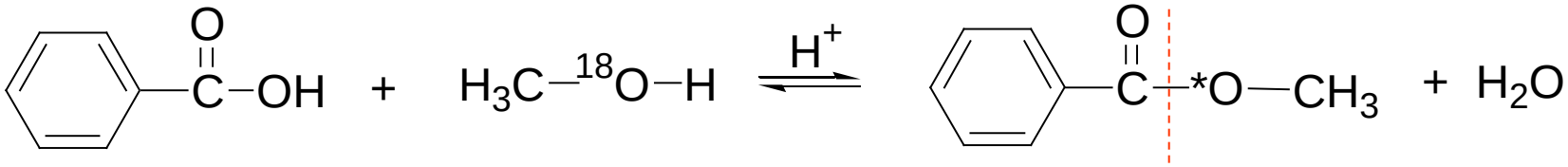
→ equilibrium shifts to the right

Not practical for expensive alcohol

Mechanism: two possibilities



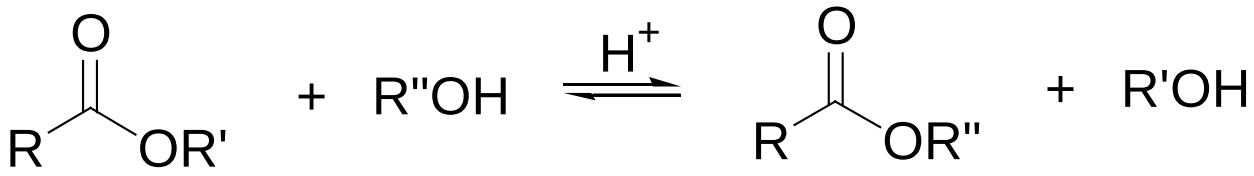
Q: How can we differentiate the two?
Solution: perform a labeling experiment



The second mechanism is correct

Note: the reverse reaction of Fischer esterification is acid catalyzed hydrolysis of ester

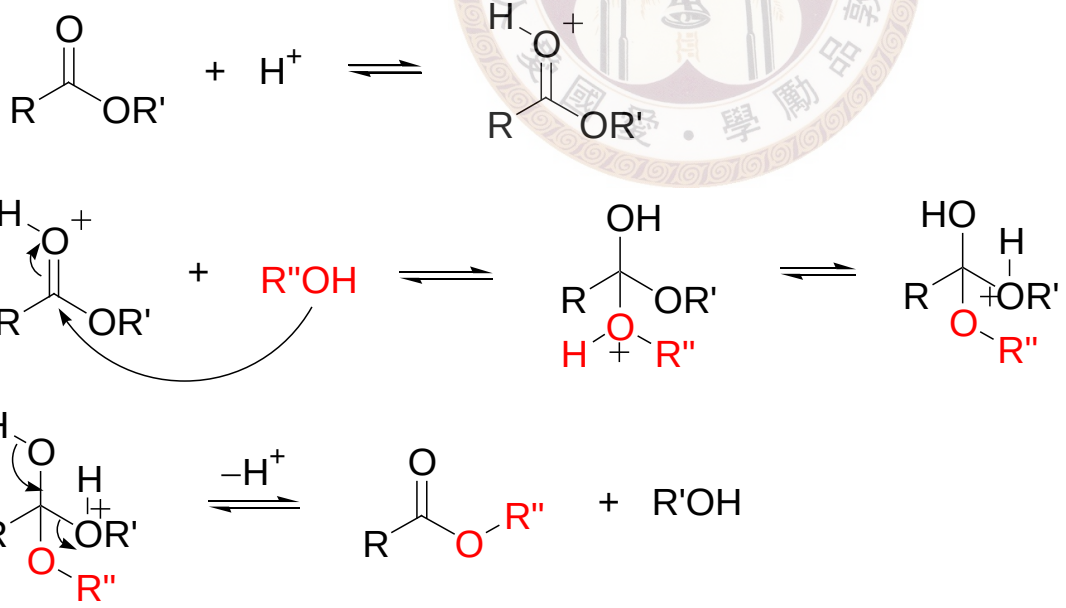
✓ Transesterification



To drive the equilibrium:

- use excess R”OH
- in case of a volatile R’OH, use distillation to remove it

Mechanism:

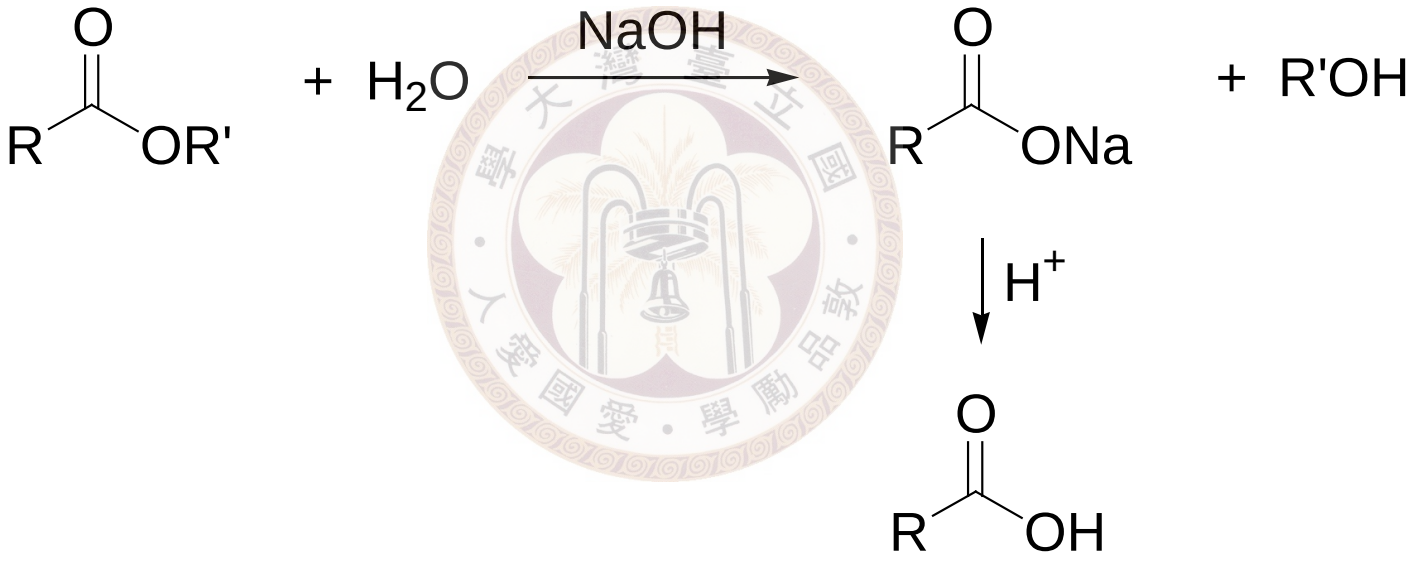


◎ Reactions

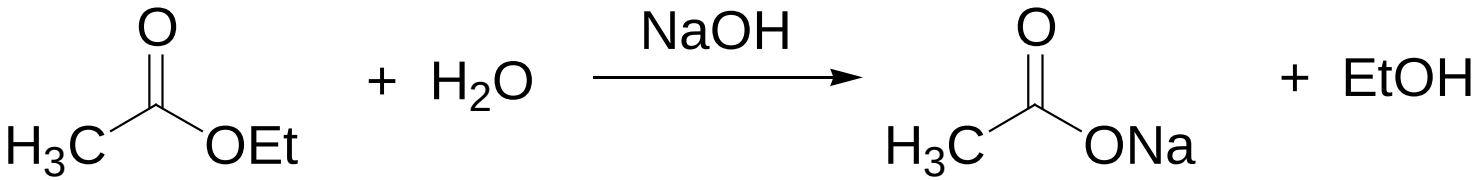
✓ Saponification (皂化反應)

base promoted ester hydrolysis

(more popular method for ester hydrolysis)



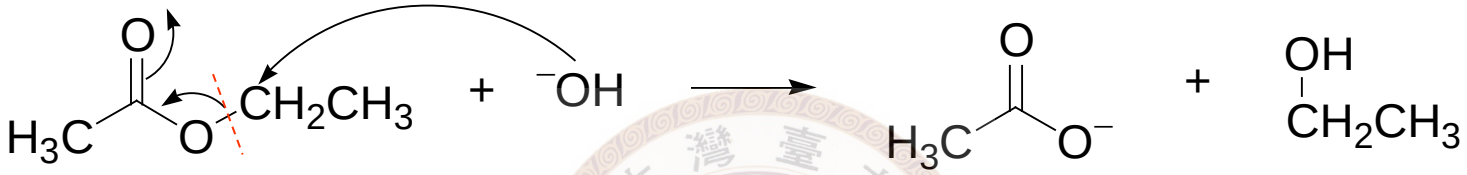
例



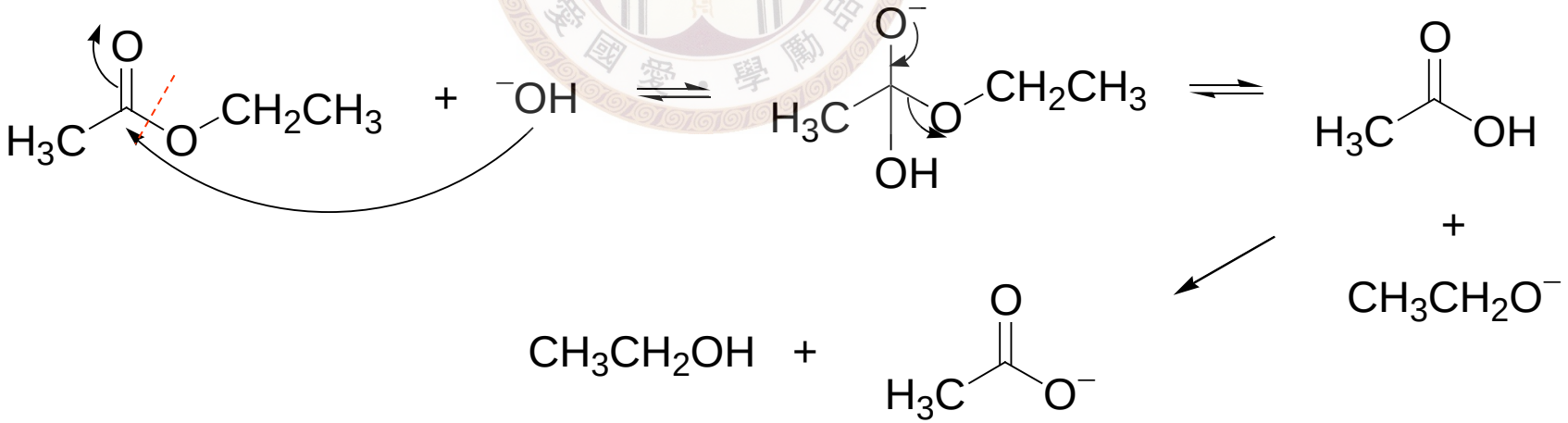
Mechanism?

two possibilities

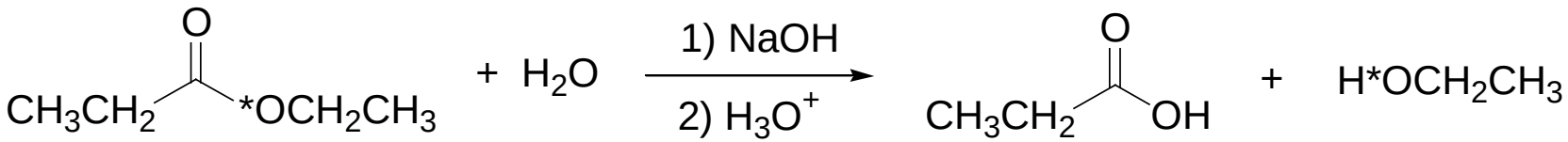
<1>



<2>

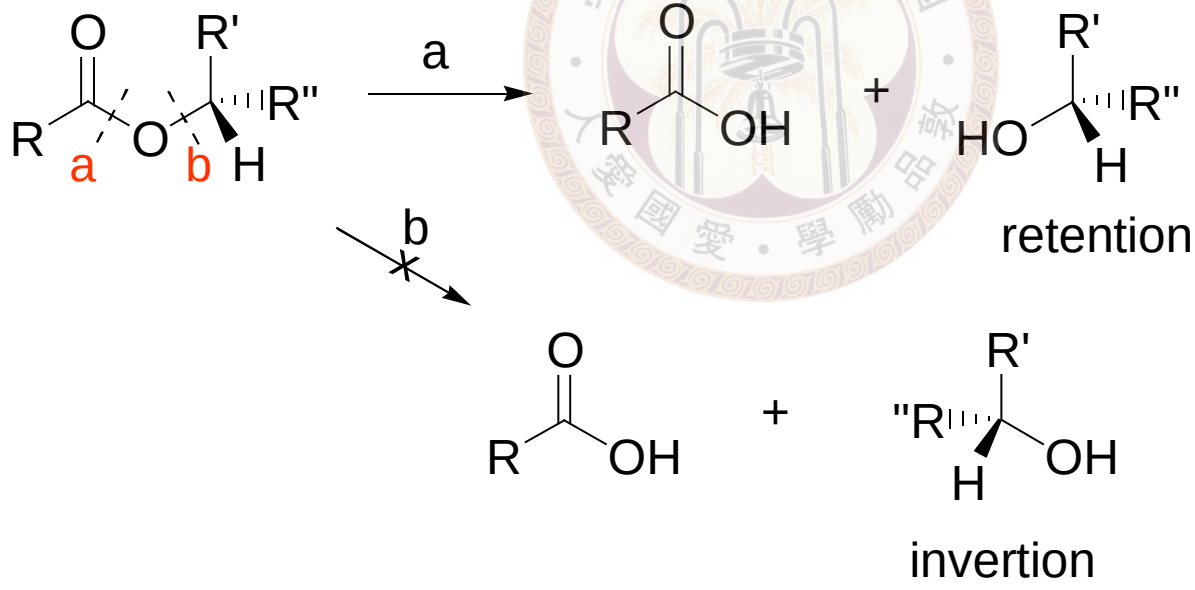


Experiment:

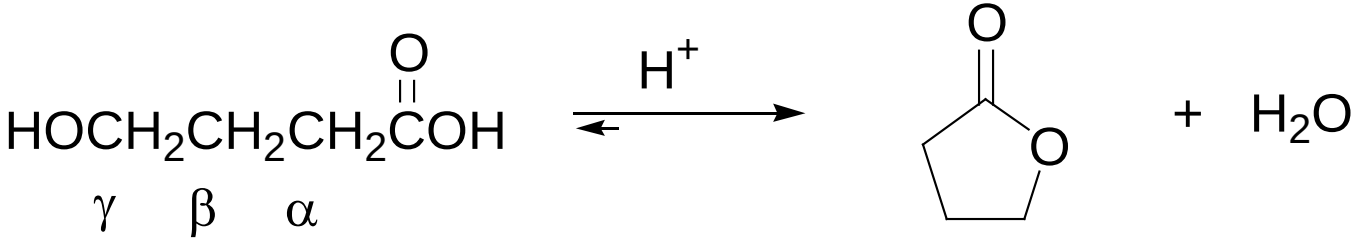


Answer: acyl substitution

*Other evidence:

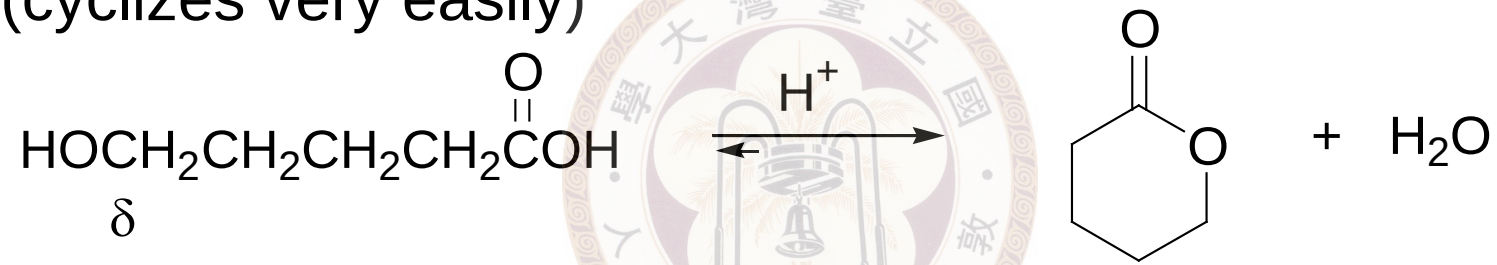


◎ Lactones (內酯)

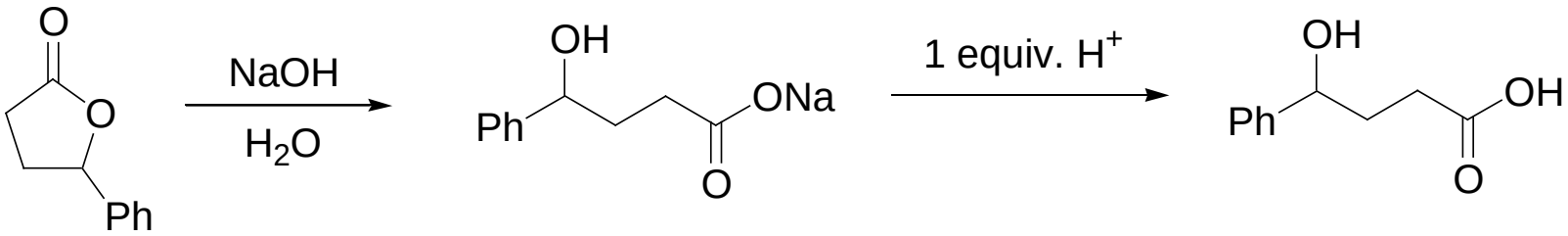


γ-hydroxy acid
(cyclizes very easily)

γ-lactone



δ-lactone

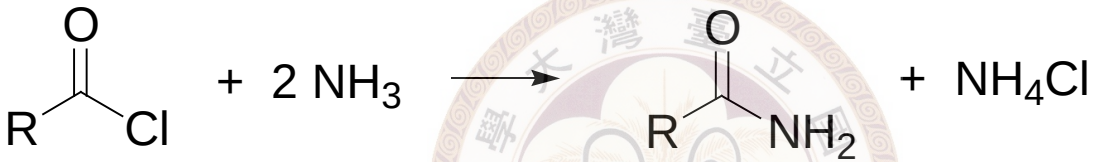


control of the amt.of H^+ is critical
otherwise cyclizes back

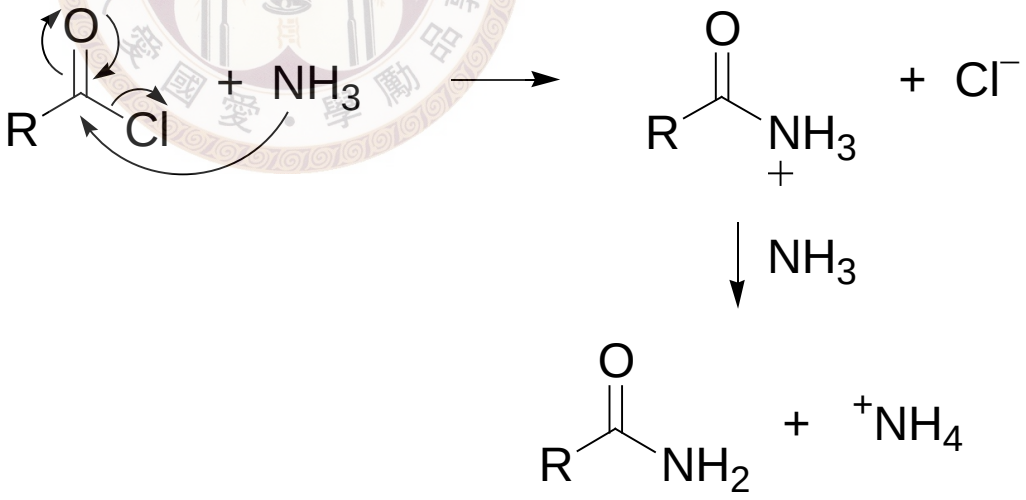
※ Amides

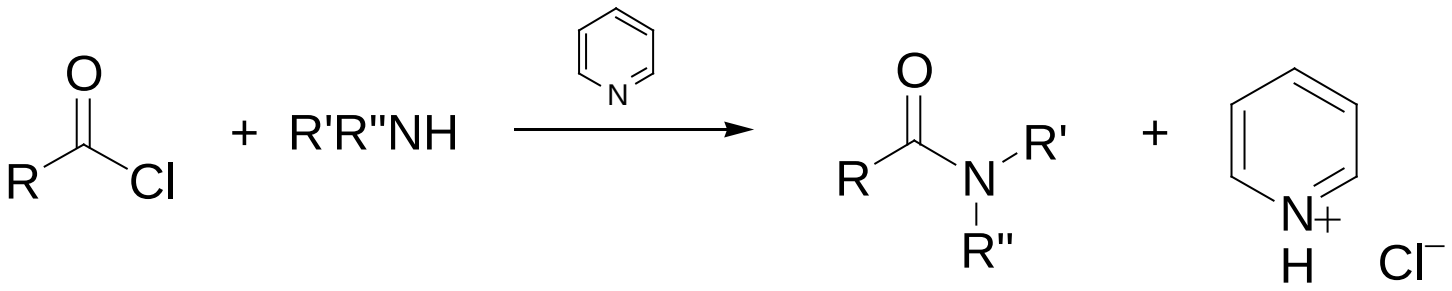
◎ Preparation

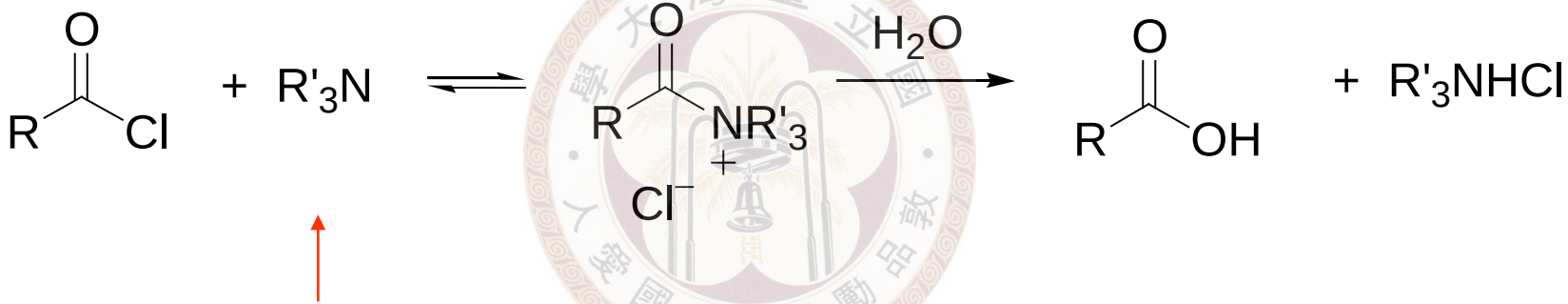
✓ From acyl chlorides



Mechanism:



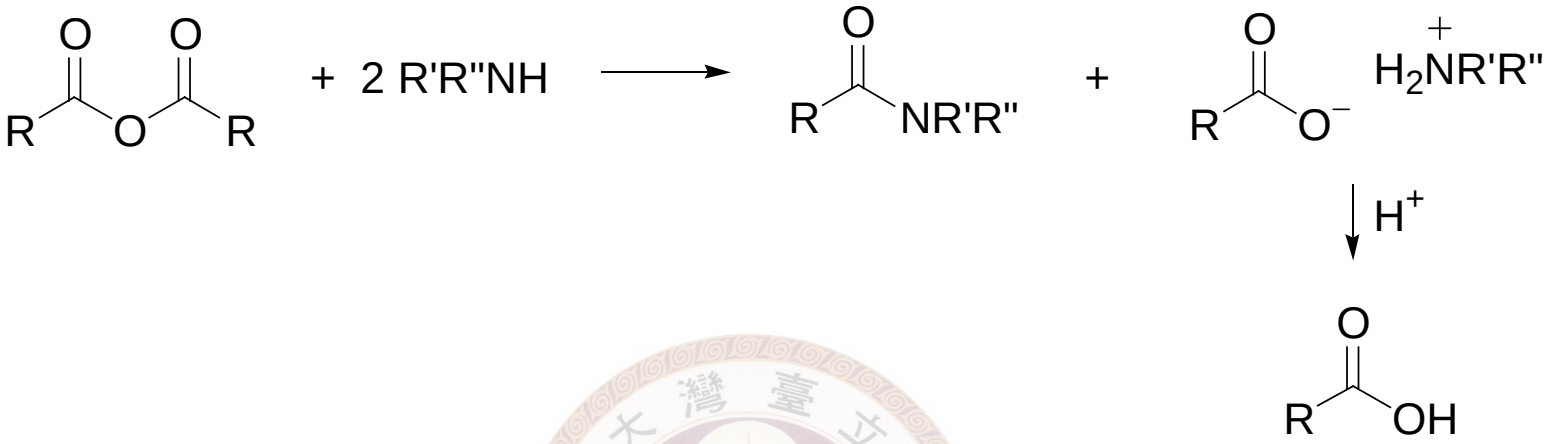




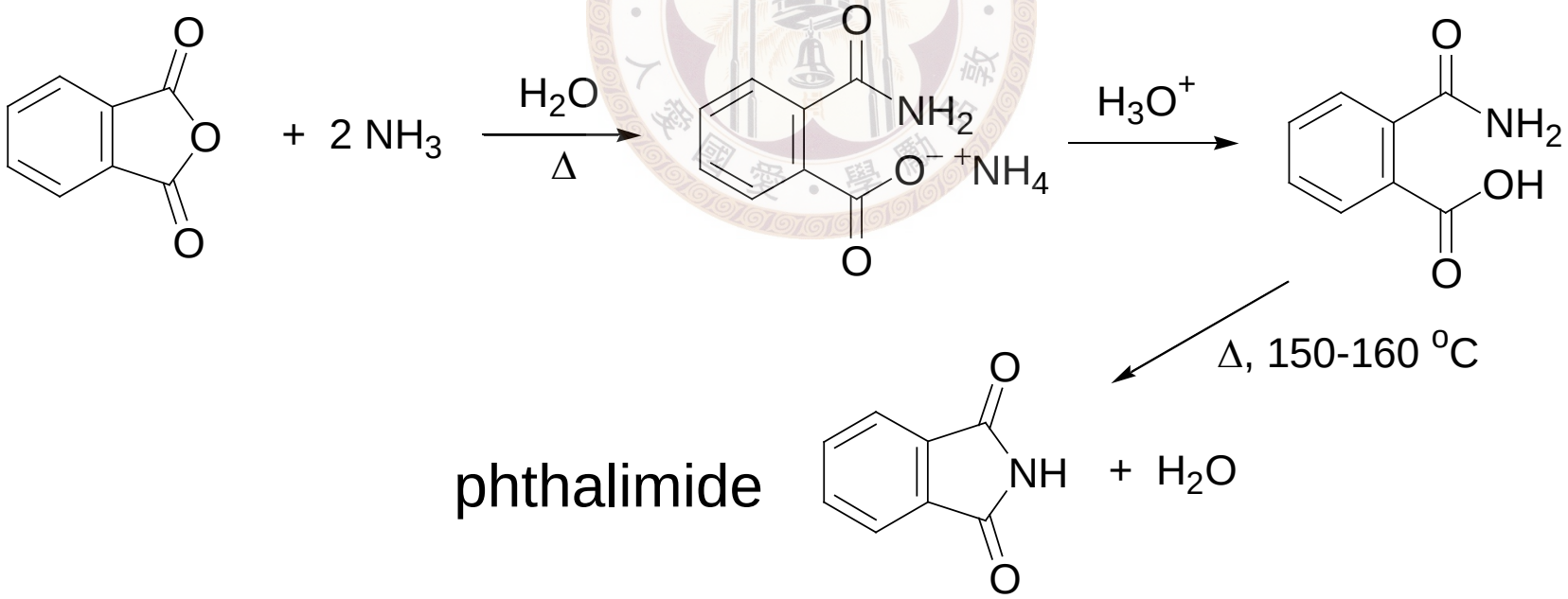
3º amine does not react

→ can be used as a base to remove acid

✓ From anhydrides

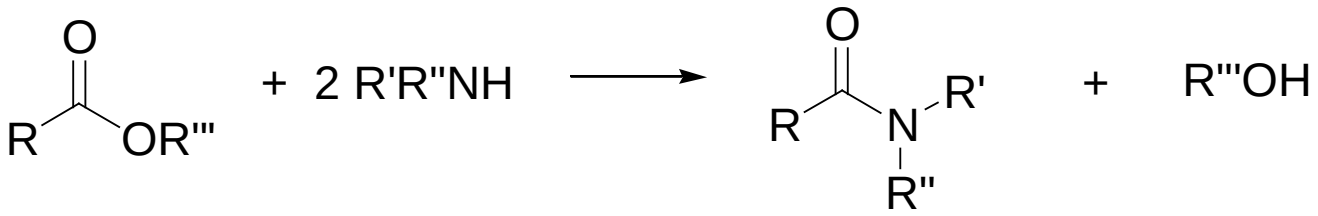


Cyclic anhydride → imide

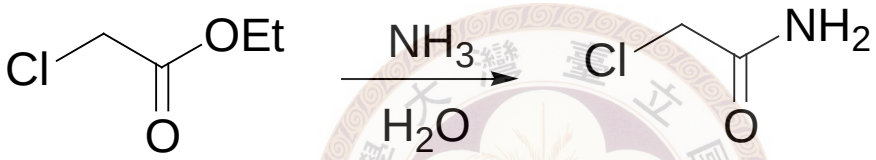


phthalimide

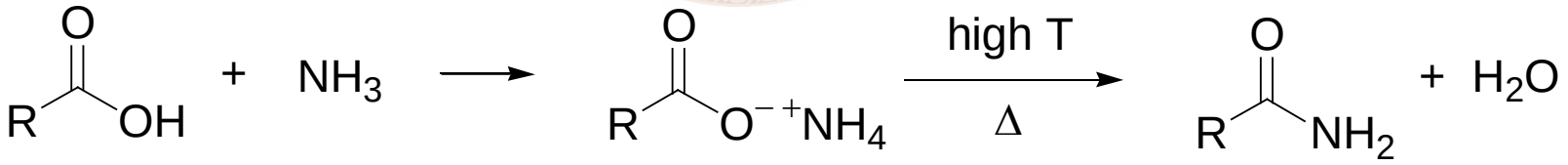
✓ From esters



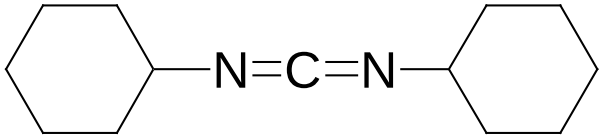
例



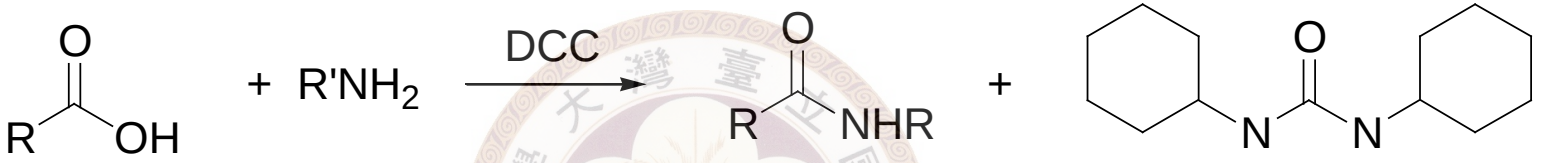
✓ From carboxylic acids



☆ DCC method



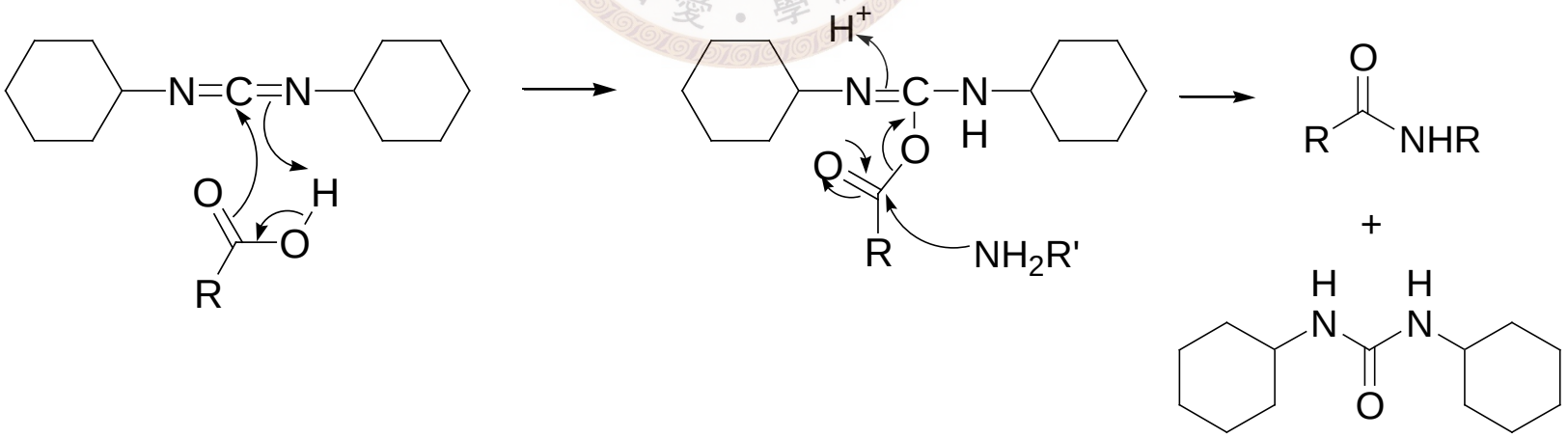
N,N'-dicyclohexylcarbodiimide (DCC)



*This is a neutral way to prepare amides

N,N'-dicyclohexylurea

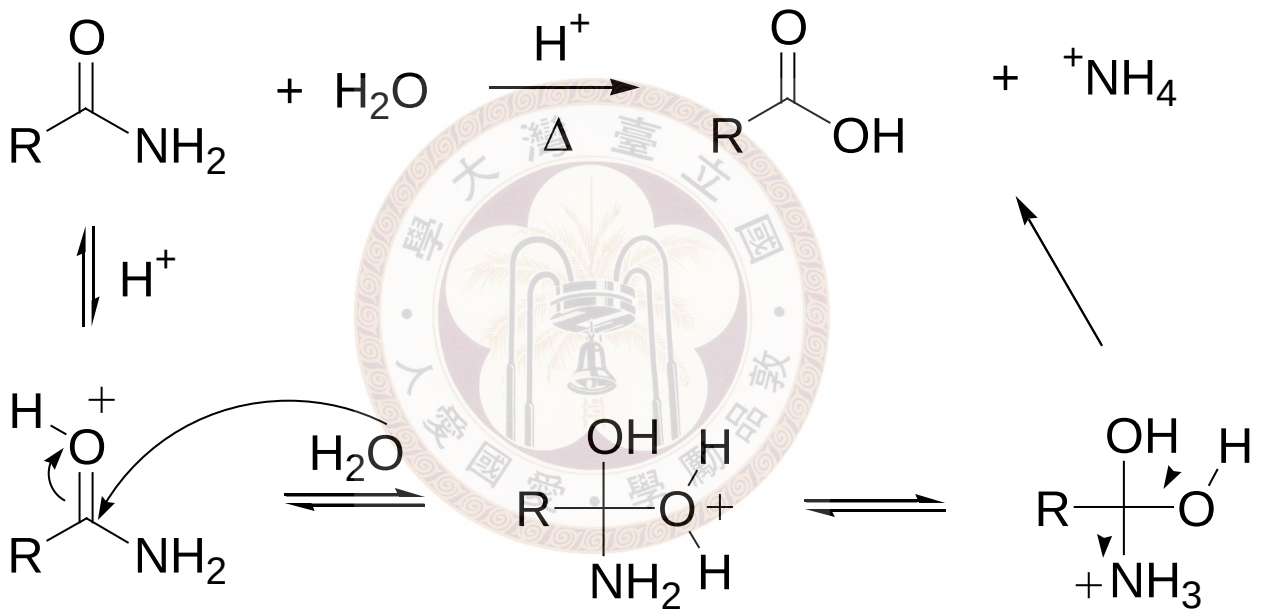
Mechanism:



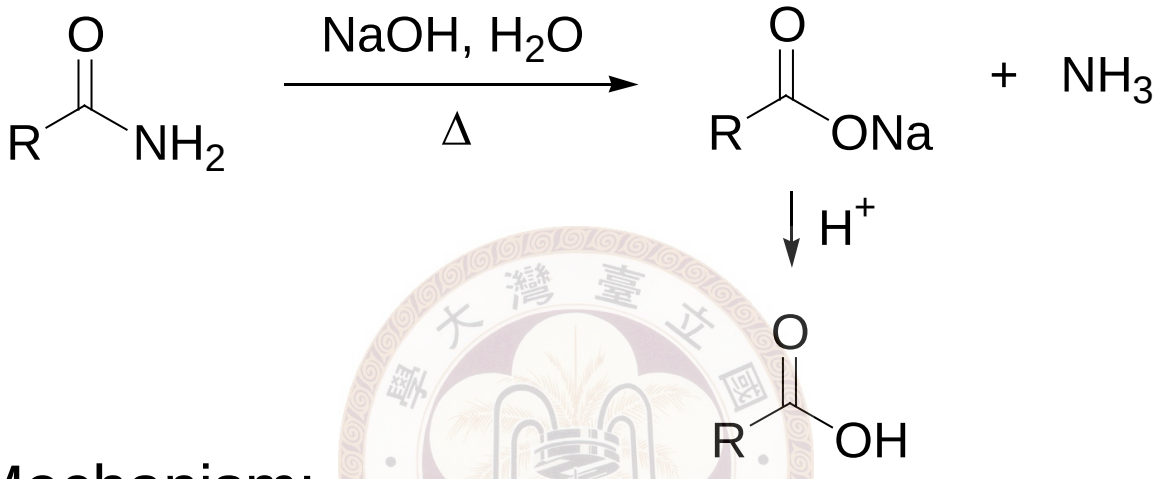
◎ Reactions

✓ Hydrolysis

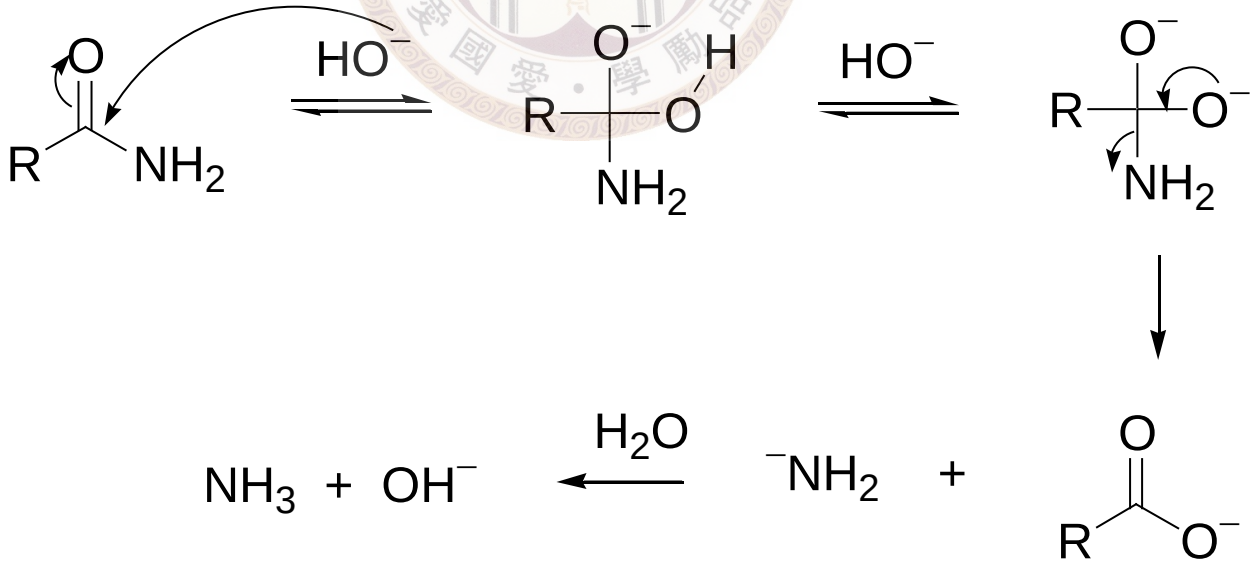
△ Acidic condition:



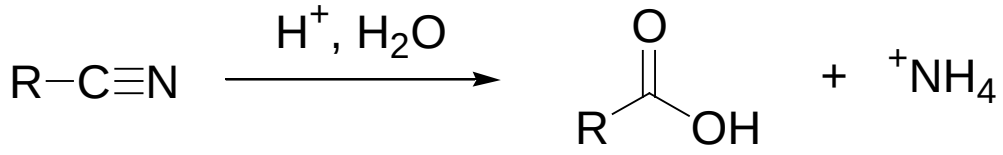
△ Basic condition:

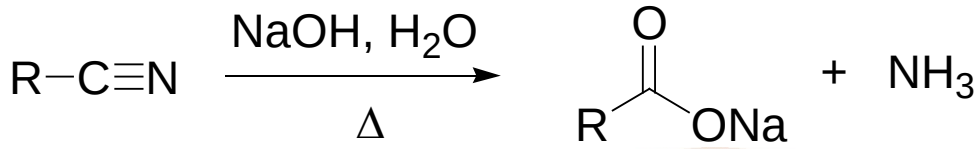


Mechanism:

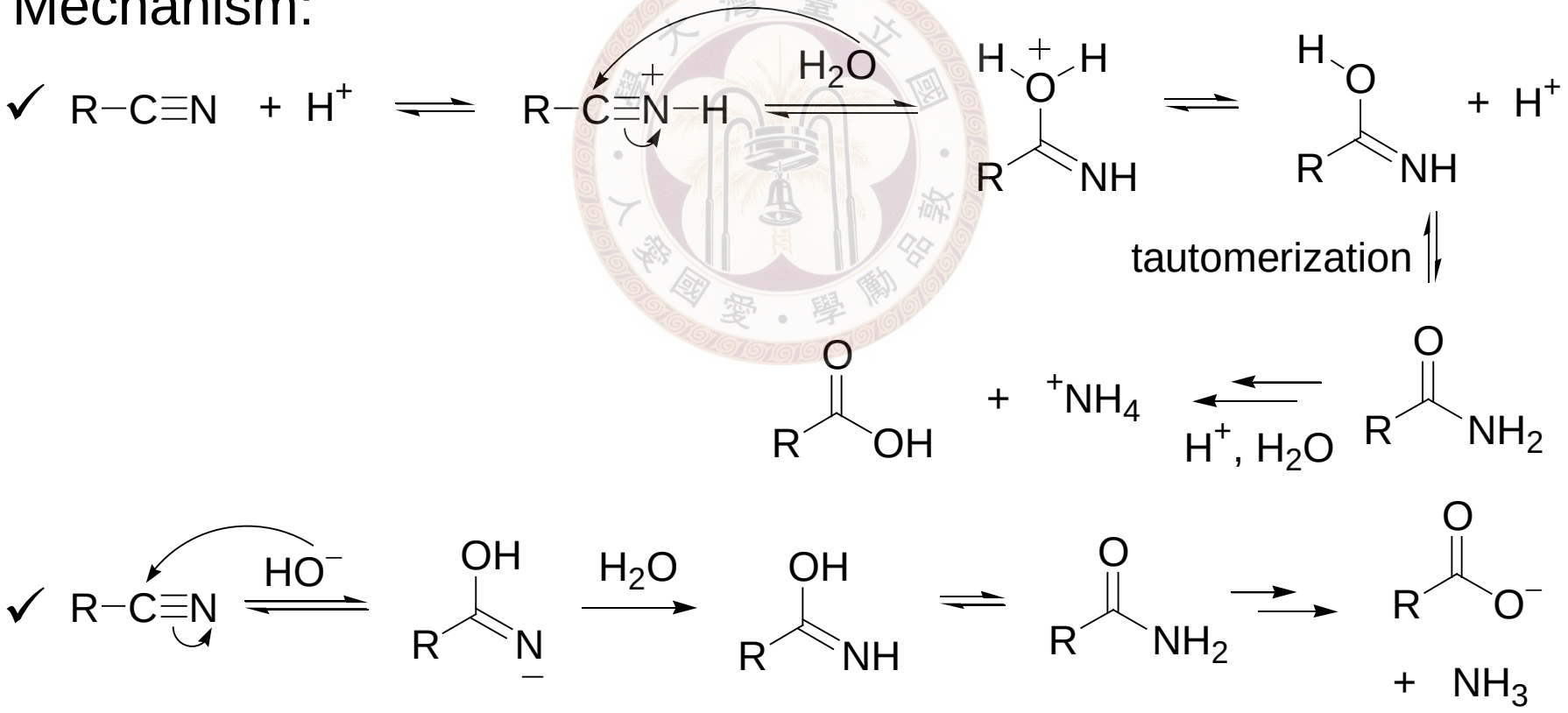


◎ Hydrolysis of nitriles

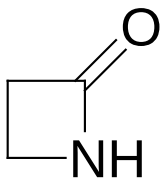




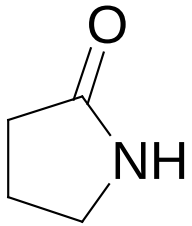
Mechanism:



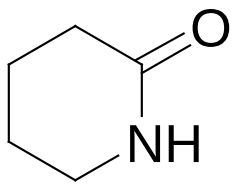
◎ Lactams: cyclic amides



β-lactam

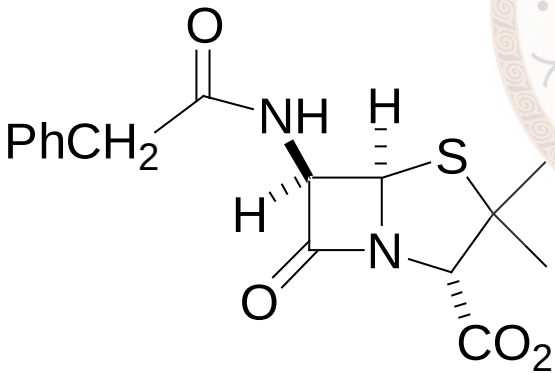


γ-lactam



δ-lactam

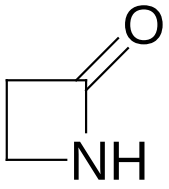
The β-lactam antibiotics



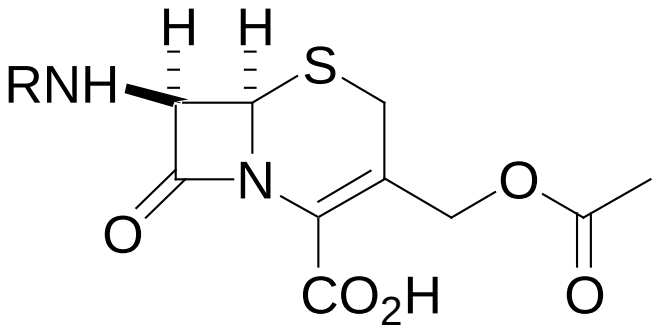
Penicillin G ← penam

IR 1770-1780 cm^{-1}

cf.

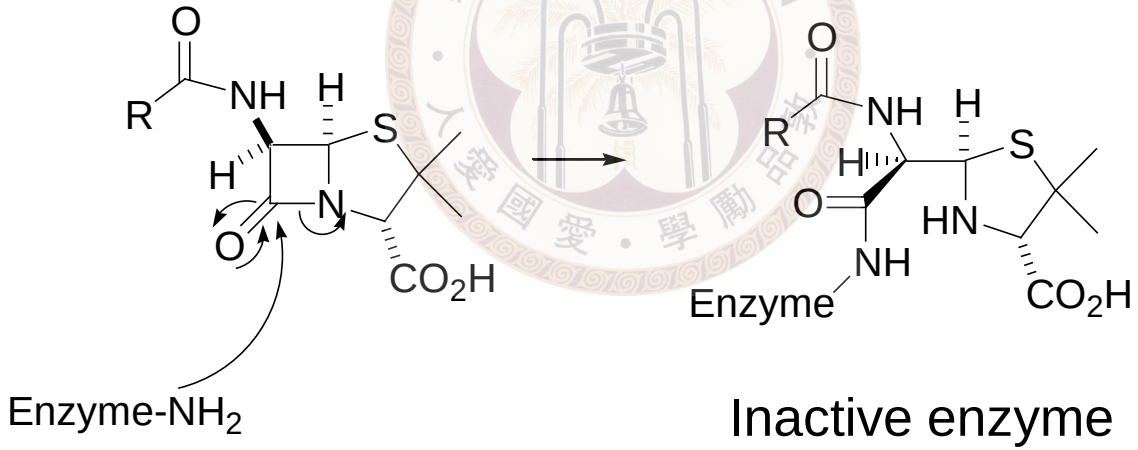


1745 cm^{-1}



Cephalosporins ← cepham

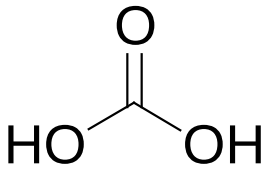
Biologically:



Inactive enzyme

Essential for bacterial cell wall synthesis

※ Carbonic acid derivatives



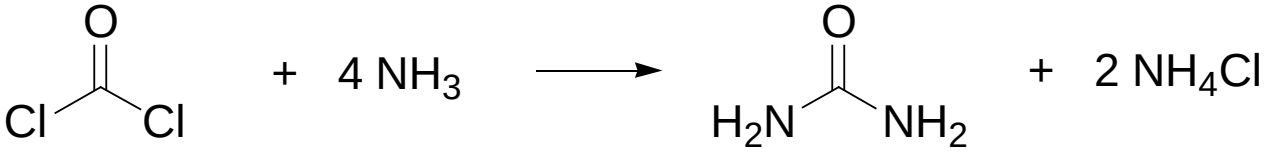
carbonic acid (H_2CO_3)

◎ Dialkyl carbonate

carbonyl dichloride (phosgene)

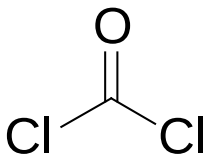
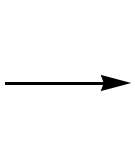
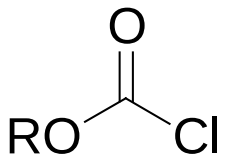
diethyl carbonate

◎ Urea



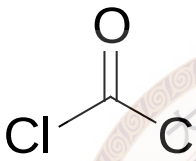
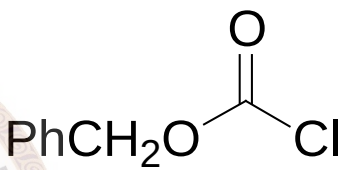
urea

◎ Alkyl chloroformate

✓ ROH +    + HCl

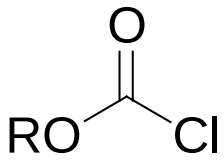
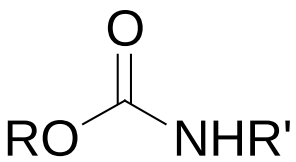
alkyl chloroformate

例

$PhCH_2OH$ +   + HCl

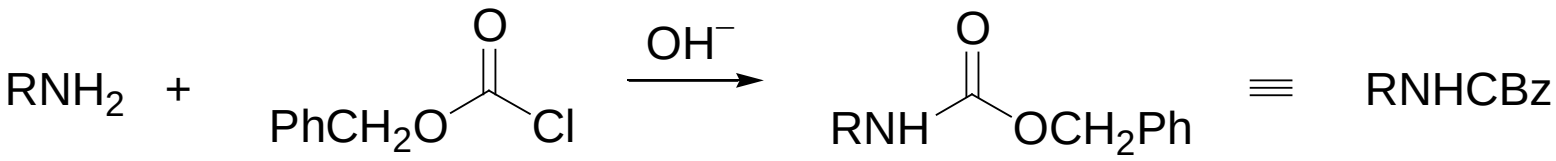
benzyl chloroformate

◎ Carbamate

 + $R'NH_2$ $\xrightarrow{OH^-}$ 

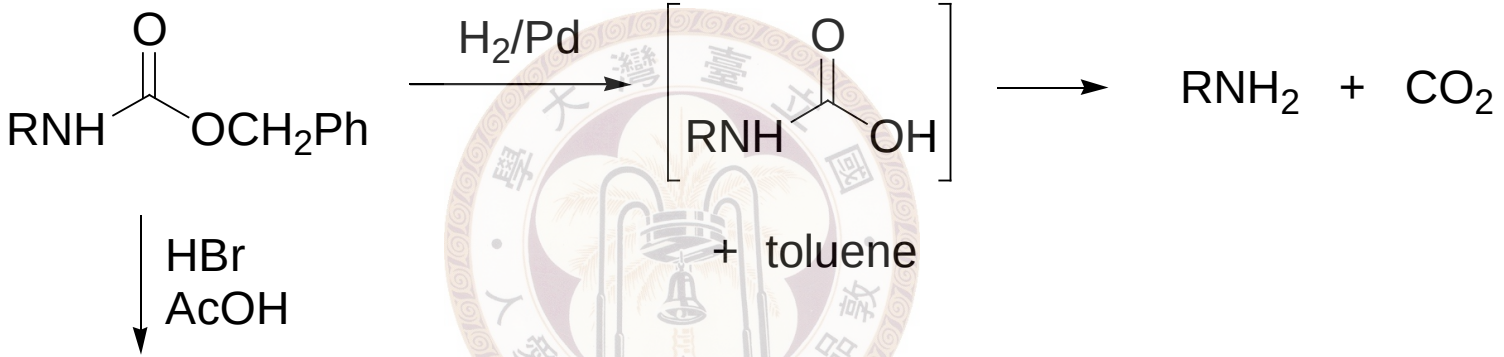
carbamate
or urethane

★ Carbamate used as a protecting group for amines

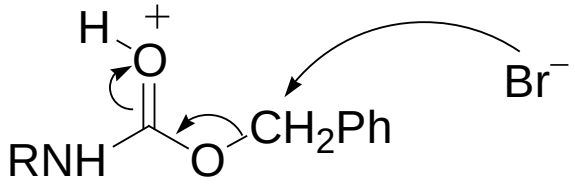


a CBz protected amine

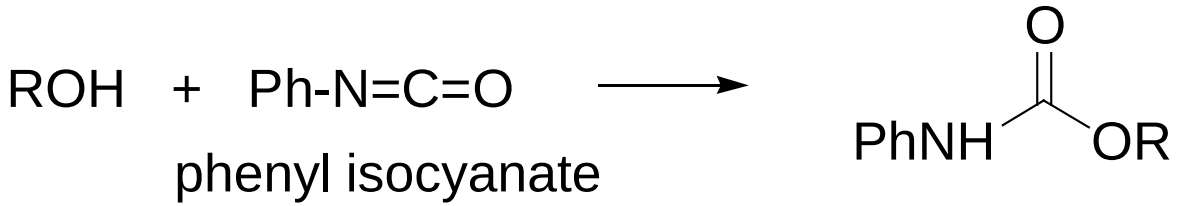
Deprotection:



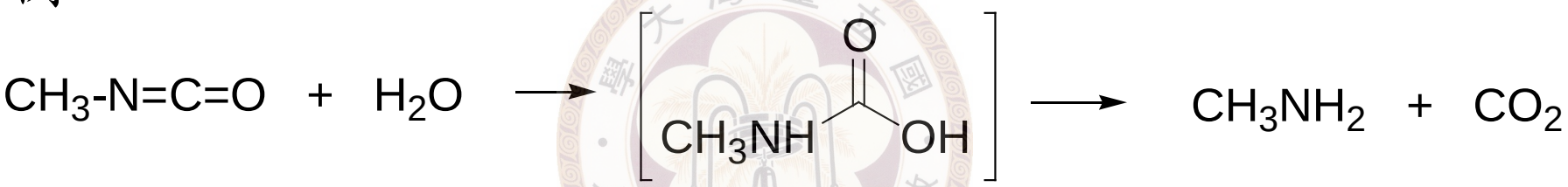
Mechanism:

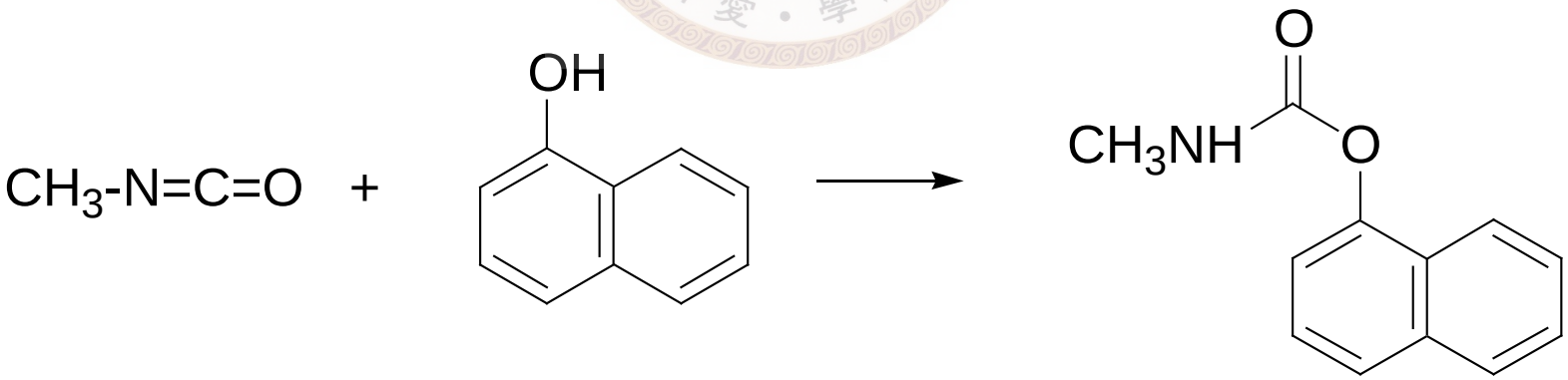


✓ From isocyanate

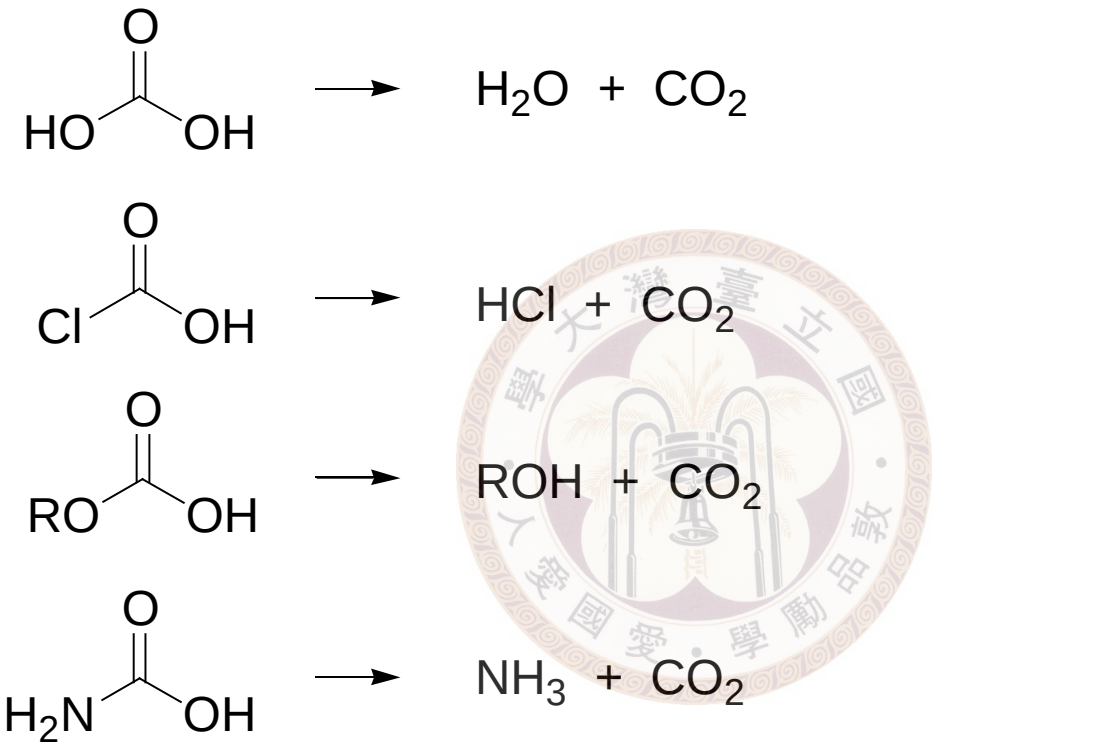


例

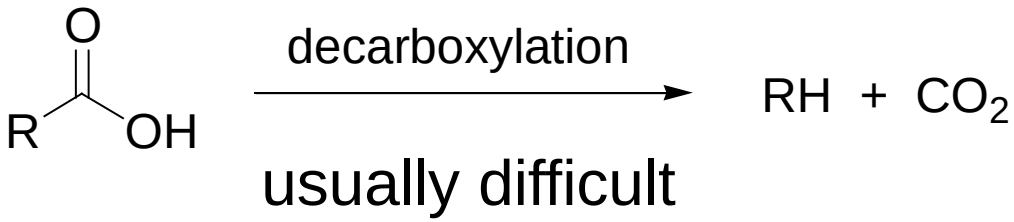




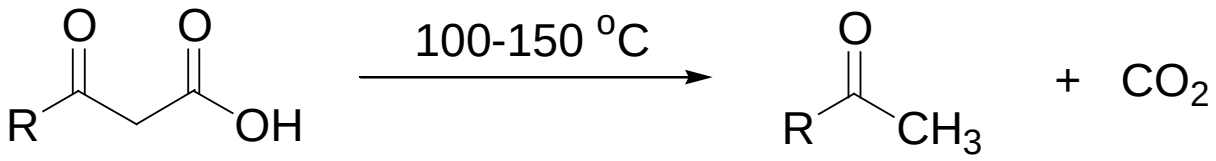
※ Decarboxylation of carboxylic acids



But

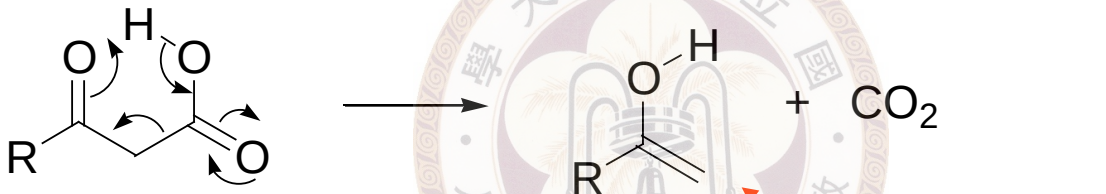


◎ Decarboxylation of β-keto acids

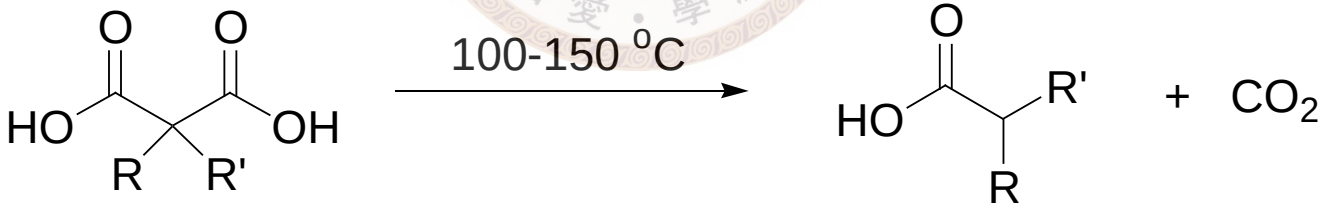


a β-keto acid

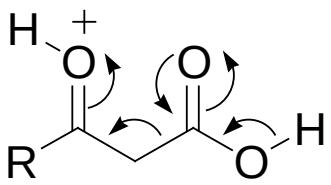
Mechanism:



✓

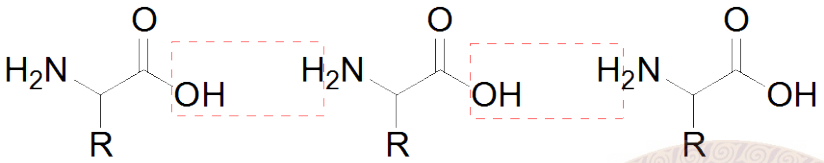


✓ Catalyzed by acid:

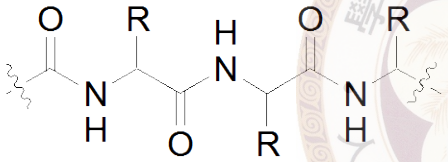


※ Step growth polymer

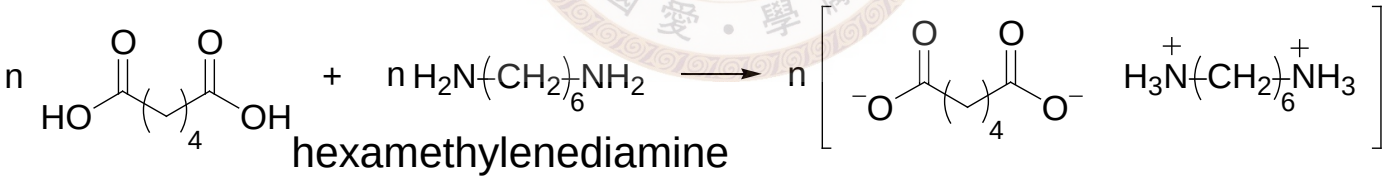
◎ Polyamides



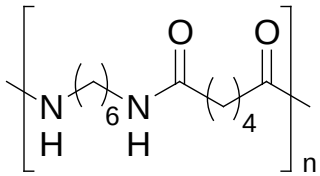
Also called condensation polymer



polypeptide

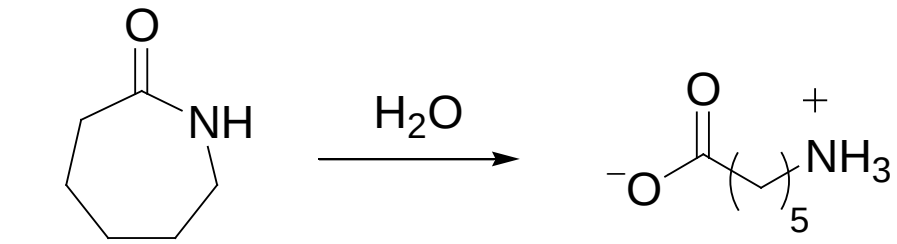


hexamethylenediamine

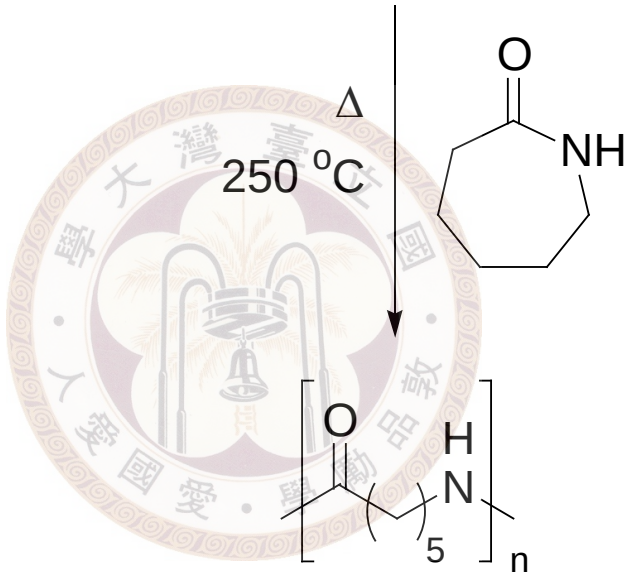


+ (2n–1) H_2O

Nylon 6,6



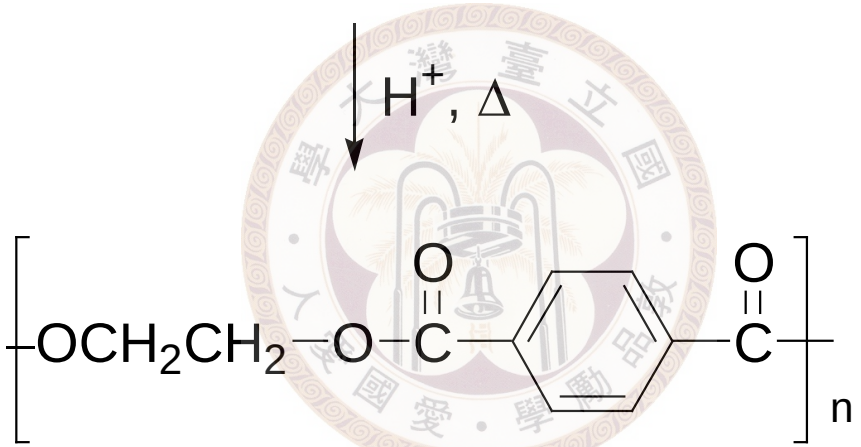
ε-caprolactam



Nylon 6

◎ Polyester

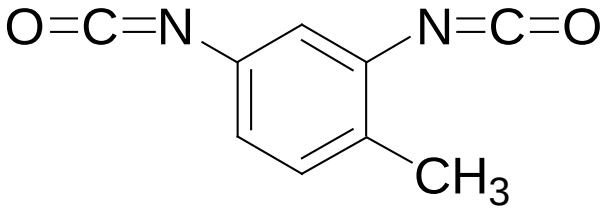
terephthalic acid



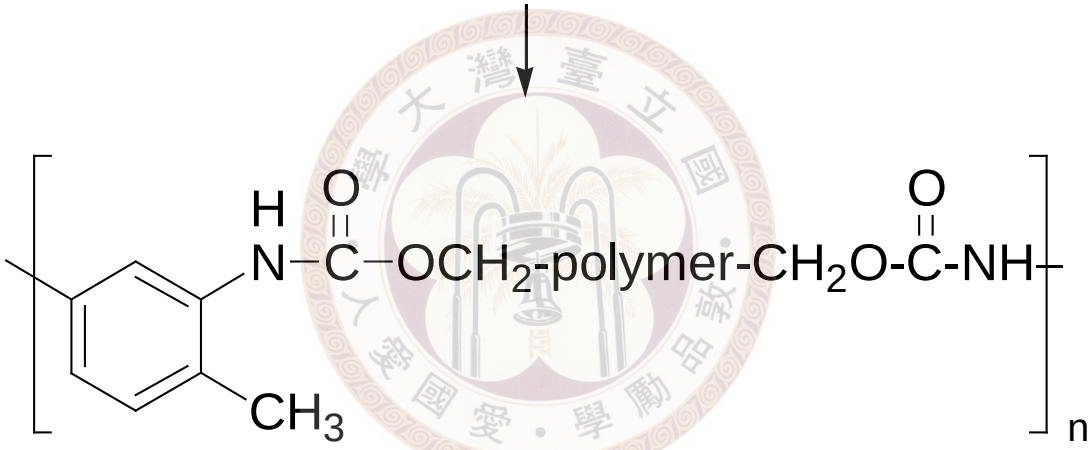
Poly (ethylene terephthalate)
(Dacron or PET)

◎ Polyurethanes

$HOCH_2$-polymer-CH_2OH +



toluene 2,4-diisocyanate



Formation of foams:

$$R{-}N{=}C{=}O + H_2O \longrightarrow R\text{-}NH_2 + CO_2\uparrow$$