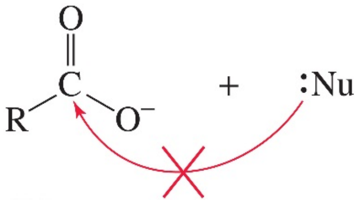
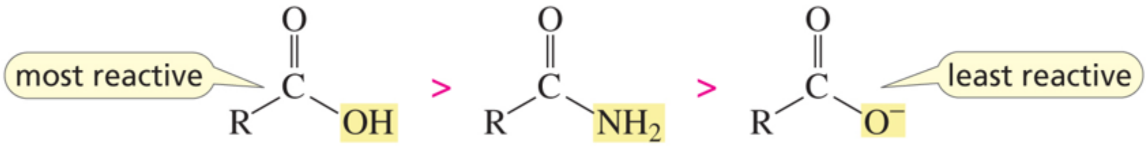
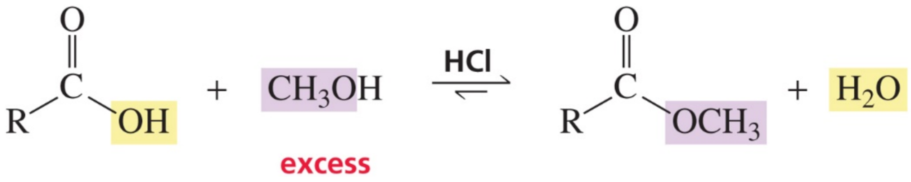
Rxn of RCOOH

- RCOOH for nu-philic add'n-elim'n rxn
  - reactive only in acidic form
    - basic form [COO⁻, carboxylate ion] refuses Nu:

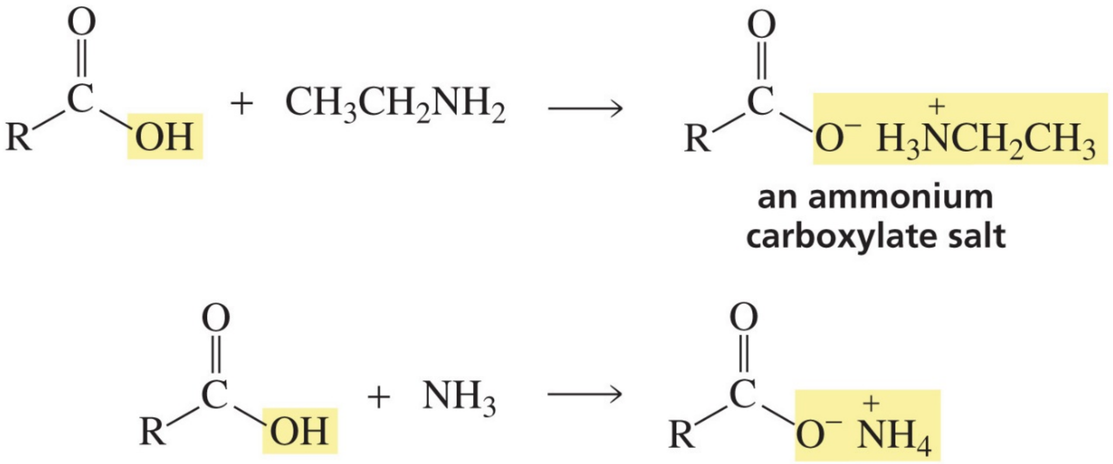




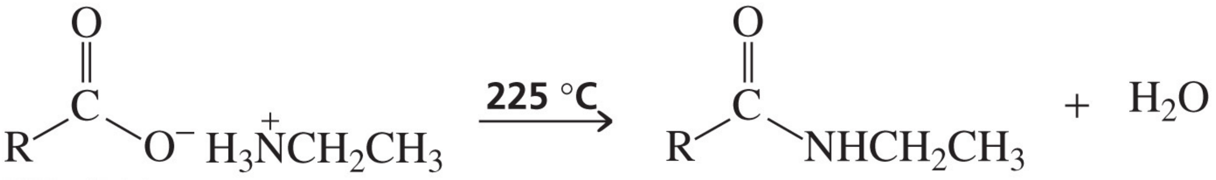
  - similar reactivity as ester ← $HO^- \approx RO^-$
- Fischer esterification
  - exact reverse of (acid-cat) hydrolysis of ester 🕮p739 sl#26
  - need xs ROH for forwarding



- RCOOH + amine (or ammonia) →
  - an acid-base reaction, not an add’n-elim’n

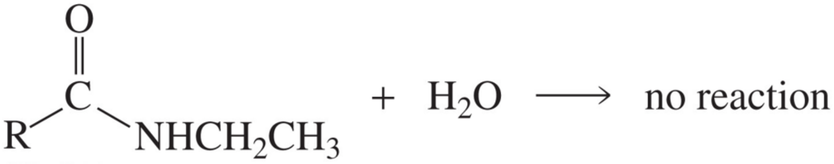


  - further to amide when heated



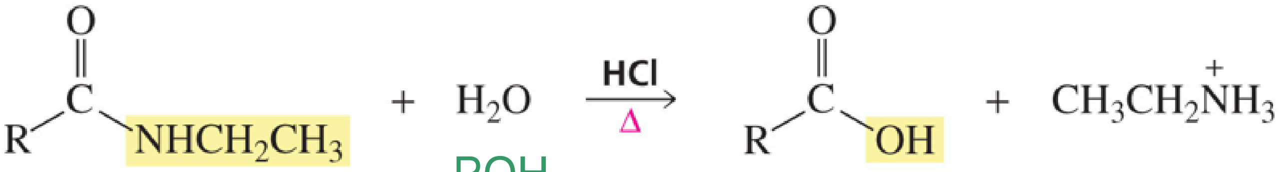
Rxn of amides

- amides not reactive as-it-is
  - $^-NH_2$, ^-NHR, $^-NR_2$ are very strong bases. → not leaving



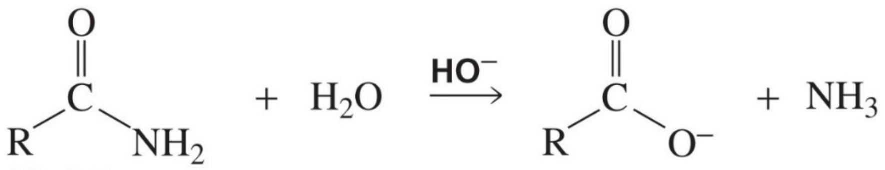
Cl^-, ROH

- acid-catalyzed hydrolysis (and alcoholysis)



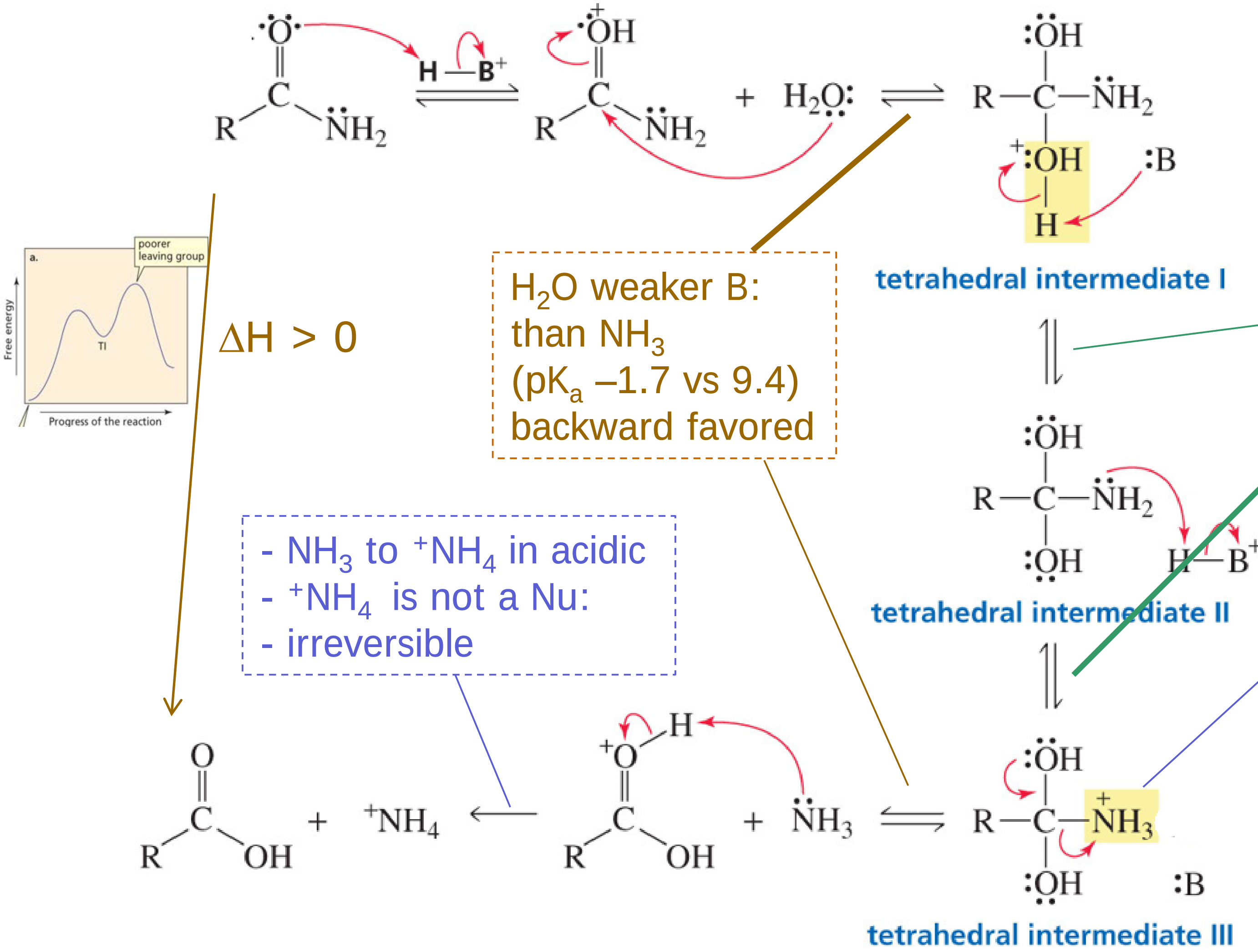
ROH

- hydroxide-ion-promoted hydrolysis



- mechanism for acid-catal’d hydrolysis

p749
unsuccessively?
unsuccessfully



$\Delta H > 0$

H_2O weaker B:
than NH_3
(pK_a –1.7 vs 9.4)
backward favored

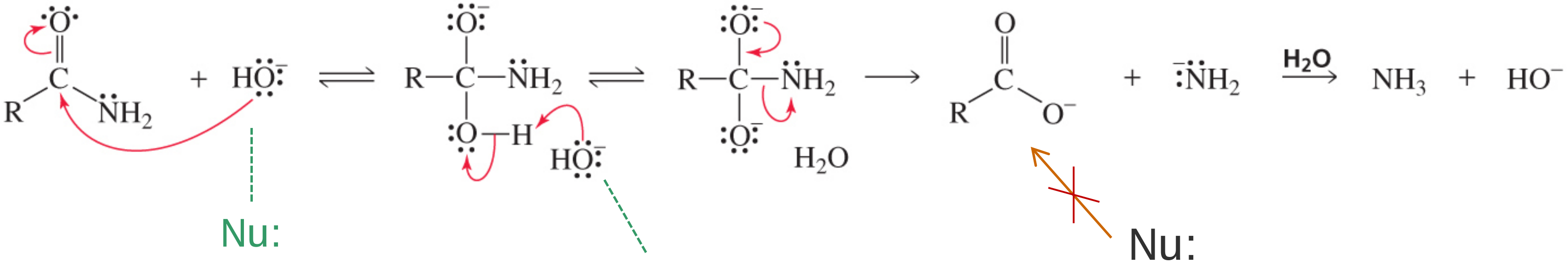
:NH_2 stronger B:
than :OH →
protonated more
→ forward favored

- NH_3 to $^+NH_4$ in acidic
- $^+NH_4$ is not a Nu:
- irreversible

NH_3 weaker B:
than ^-OH
($pK_a(NH_4^+) = 9.4$)
→ NH_3 leaves.

if no acid [catalyst],
^-OH leaves [NR].
$pK_a(NH_3) = 35$

- mechanism for OH^--promoted hydrolysis



Nu:
(promoter, reactant)

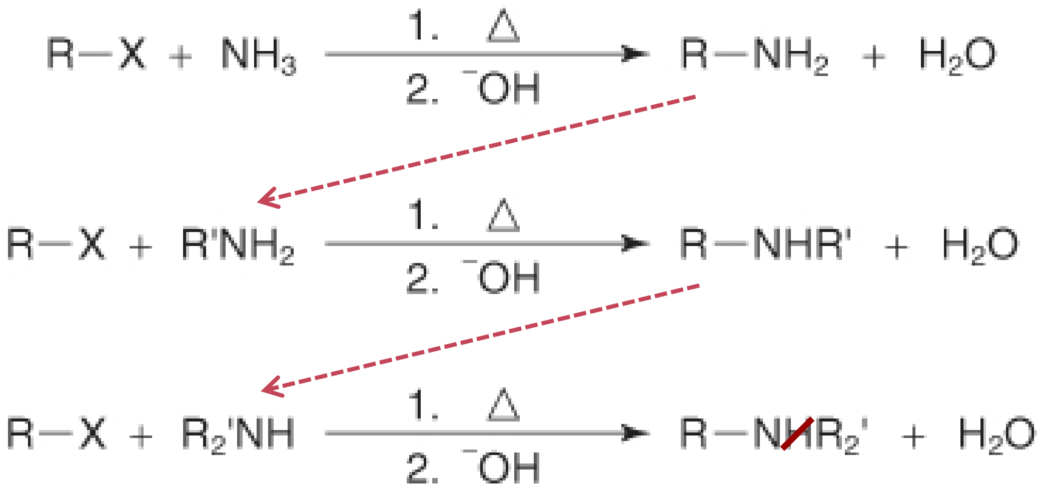
This ^-OH is a catalyst.

Nu:

- heated in strongly basic condition
  - At low pH, ^-OH leaves.
    - ^-OH weaker B: than $^-NH_2$
  - At high pH, $^-NH_2$ leaves.
    - $^-NH_2$ weaker B: than O^{2-}.
    - The reaction is 2nd order in ^-OH. ~ one reactant + one catalyst
- irreversible

Hydrolysis of imide to amine

- synthesis of amine by S_N of R-X with ammonia?

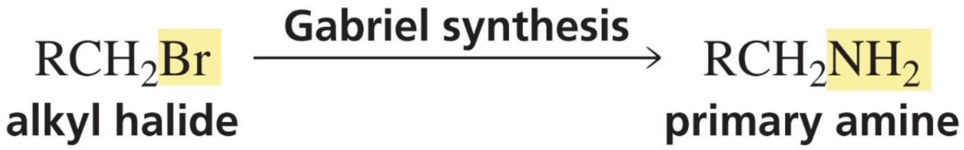


$$R{-}X + NH_3 \xrightarrow[2.\ ^{-}OH]{1.\ \Delta} R{-}NH_2 + H_2O$$

$$R{-}X + R'NH_2 \xrightarrow[2.\ ^{-}OH]{1.\ \Delta} R{-}NHR' + H_2O$$

$$R{-}X + R_2'NH \xrightarrow[2.\ ^{-}OH]{1.\ \Delta} R{-}N\cancel{H}R_2' + H_2O$$

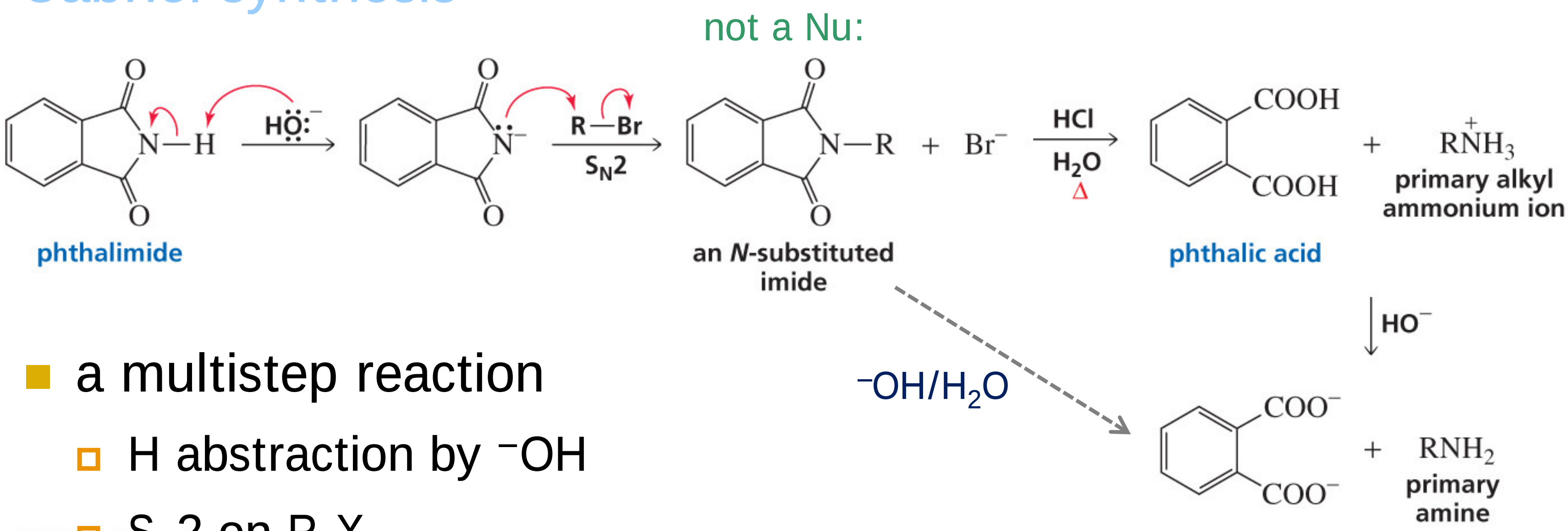
  - multiple alkylation problem ← RNH_2 better Nu: than NH_3
- Gabriel synthesis (instead)



$$\underset{\textbf{alkyl halide}}{RCH_2Br} \xrightarrow{\textbf{Gabriel synthesis}} \underset{\textbf{primary amine}}{RCH_2NH_2}$$

  - using phthalimide instead of ammonia

Gabriel synthesis



- a multistep reaction
  - H abstraction by ^{-}OH
  - S_N2 on R-X
  - hydrolysis
    - acid-catalyzed then ^{-}OH ~ through ammonium salt to amine
    - ^{-}OH-promoted then H_2O ~ through amide ion to amine
- useful (or necessary) for preparing 1° amine
  - no polyalkylation ← one N-R ← one N-H

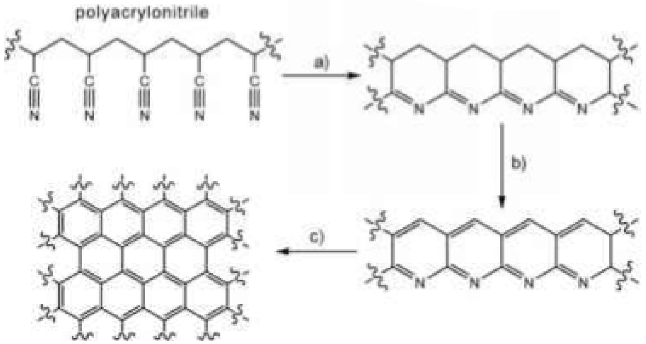
not a Nu:

Nitriles

= compounds containing cyano group [C≡N]

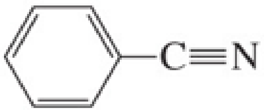
- no carbonyl, but hydrolyzed to COOH

- nomenclature
  - alkanenitrile ← --ic acid
  - –onitrile ← --ic acid
  - – cyanide

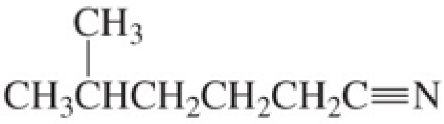


$CH_3C\equiv N$

ethanenitrile
acetonitrile
methyl cyanide



benzenecarbonitrile
benzonitrile
phenyl cyanide

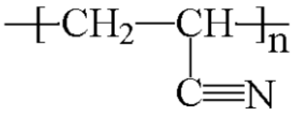


$$CH_3\overset{\displaystyle CH_3}{\overset{|}{C}}HCH_2CH_2CH_2C\equiv N$$

5-methylhexanenitrile
δ-methylcapronitrile
isohexyl cyanide

$CH_2{=}CHC\equiv N$

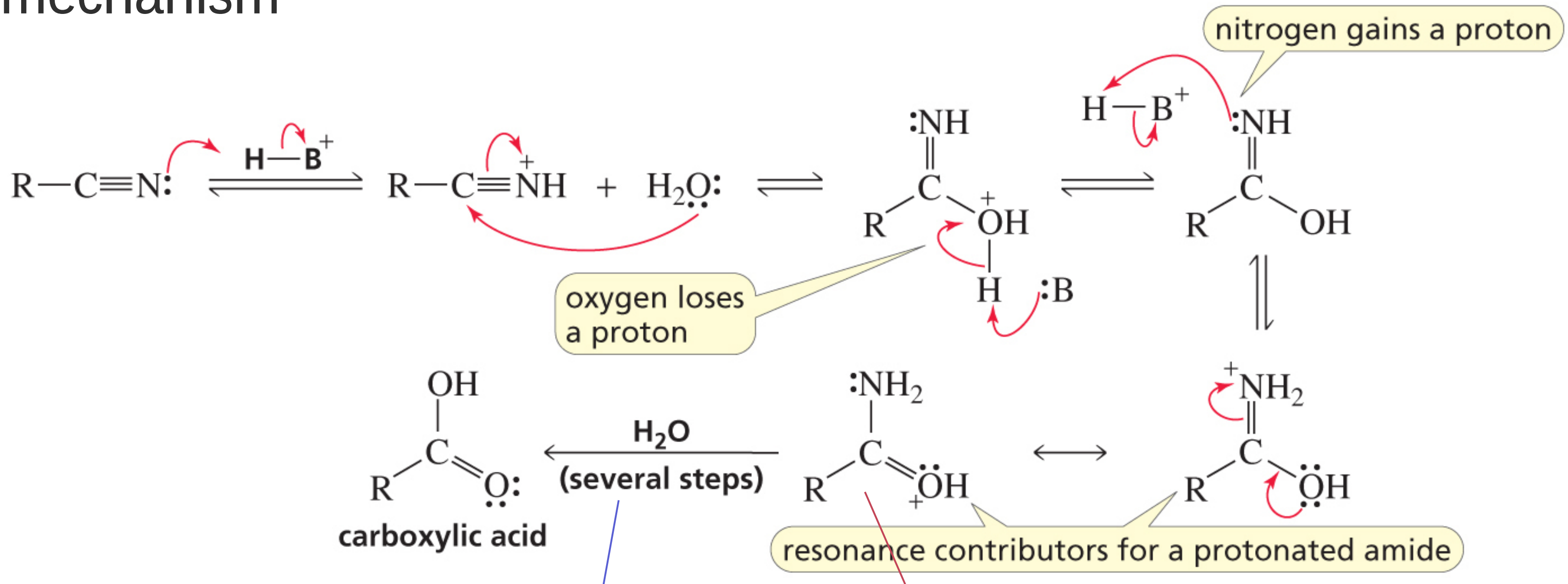
propenenitrile
acrylonitrile



$$-\!\!\left[CH_2-\underset{\underset{\displaystyle C\equiv N}{|}}{CH} \right]\!\!-_n$$

PAN

- hydrolysis of nitriles
  - (acid-catal’d) hydrolysis through (protonated) amide
    - even harder than amide hydrolysis ~ need acid and heat
  - mechanism

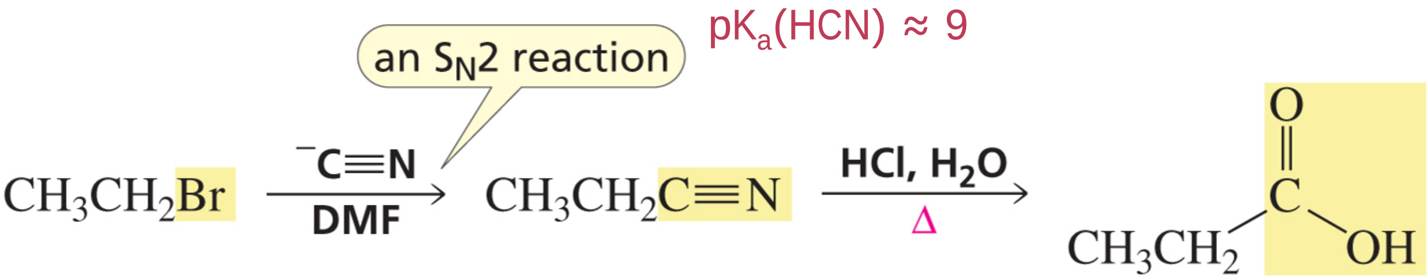


hydrolysis of amide

📖p748 sl#34

protonated amide

- preparation of RCOOH from RX (thru RCN)
  - S_N2 with CN^- from KCN or NaCN
  - then to RCOOH



$pK_a(HCN) \approx 9$

an S_N2 reaction

$$CH_3CH_2Br \xrightarrow[\text{DMF}]{^-C\equiv N} CH_3CH_2C\equiv N \xrightarrow[\Delta]{HCl,\ H_2O} CH_3CH_2COOH$$

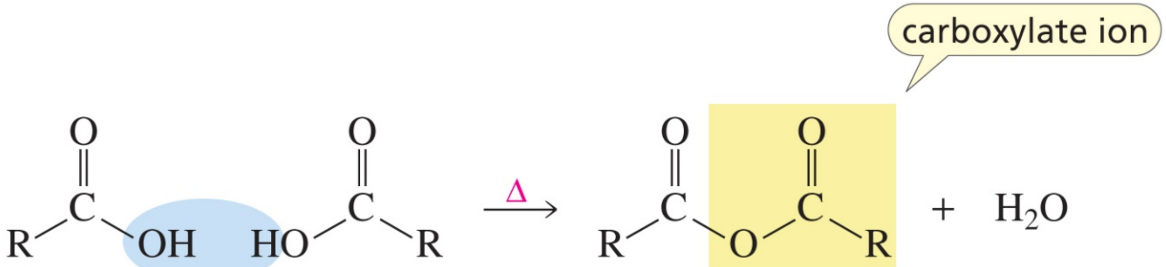
- (catalytic) hydrogenation to 1° amine

$$RC\equiv N \xrightarrow[\text{Raney nickel}]{H_2} RCH_2NH_2$$

Acid anhydrides

= acid ‘without water’ [酸無水物] ≠ anhydrous acid

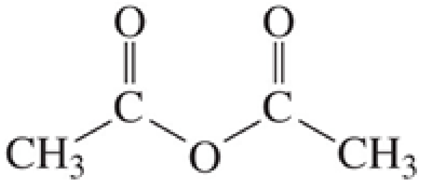
- two acids – water → two acyl linked by O
- an RCOOH derivative with carboxylate group



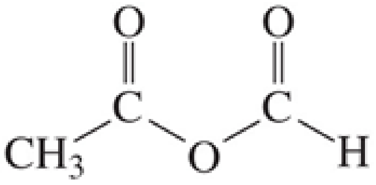
$$RCOOH + HOOCR \xrightarrow{\Delta} RCOOCOR + H_2O$$

an acid anhydride

- nomenclature
  - alkanoic anhydride; -- anhydride

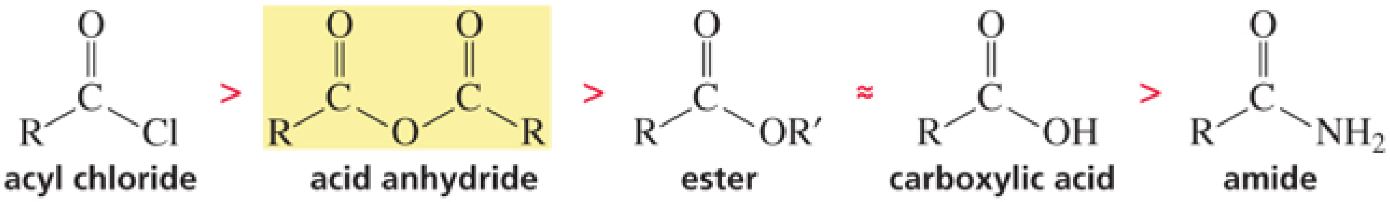


ethanoic anhydride
acetic anhydride
a symmetrical anhydride



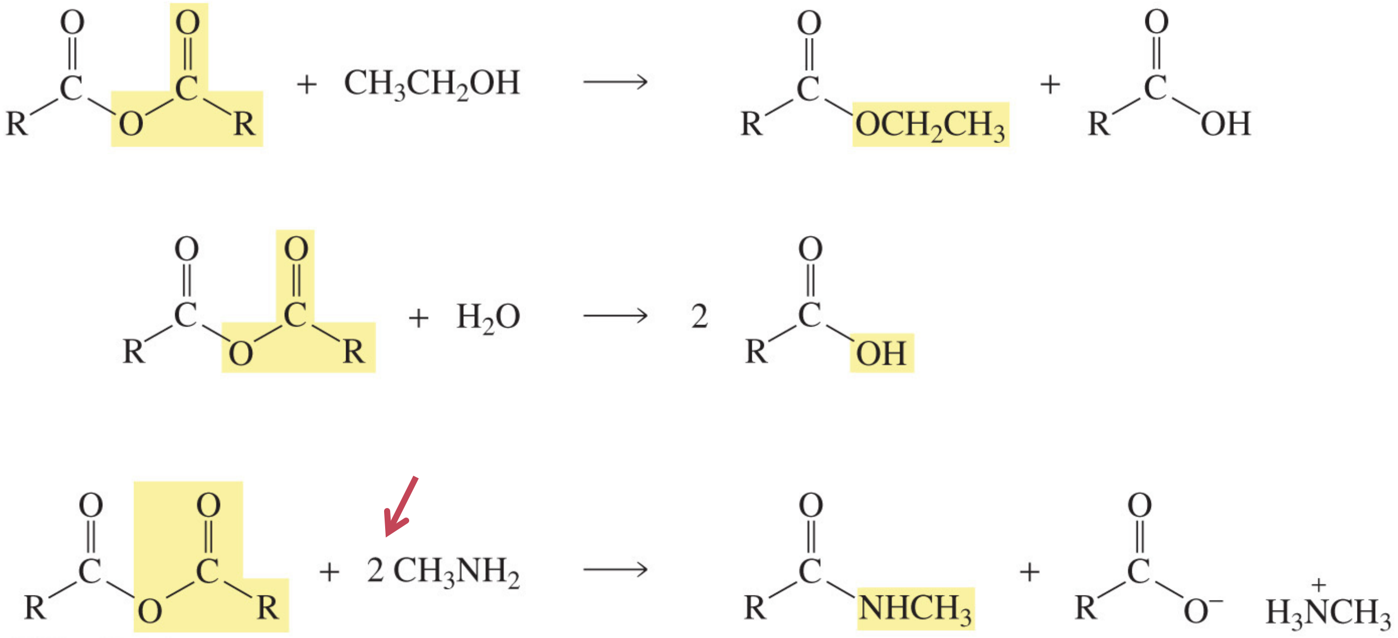
ethanoic methanoic anhydride
acetic formic anhydride
a mixed anhydride

- reactivity of add'n-elim'n

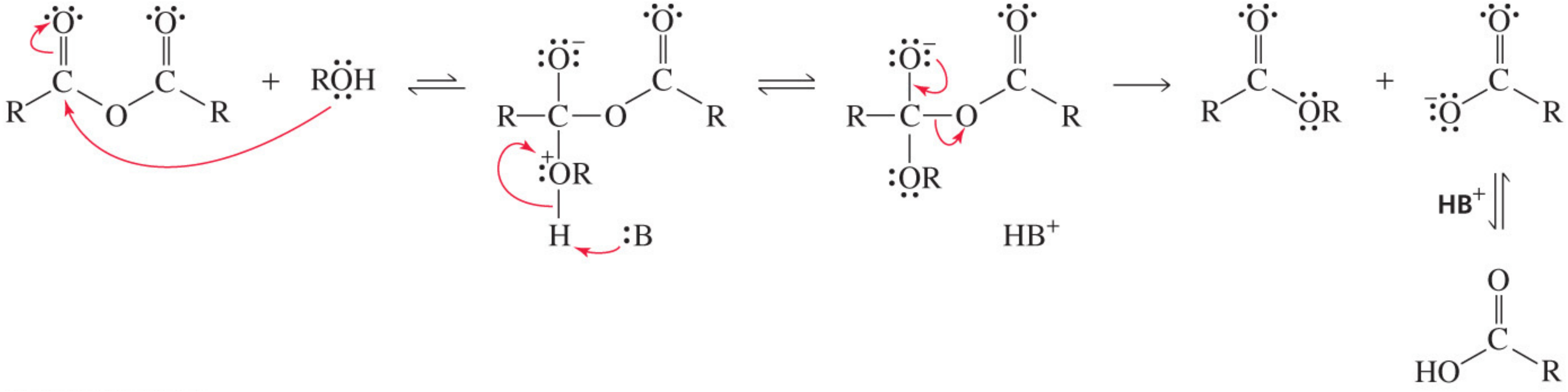


$pK_a(RCOOH) \approx 5$

- reactions



- mechanism
  - follows general mechanism



Dicarboxylic acid

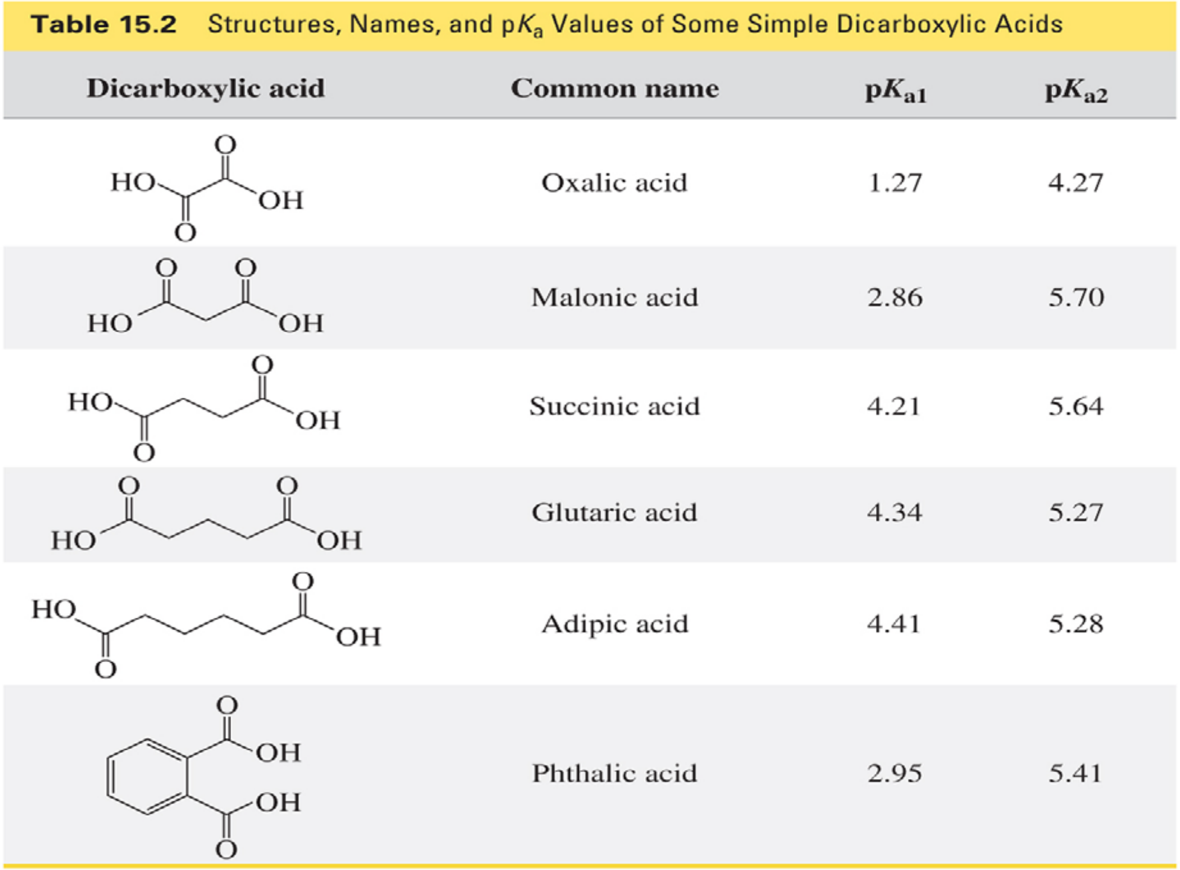
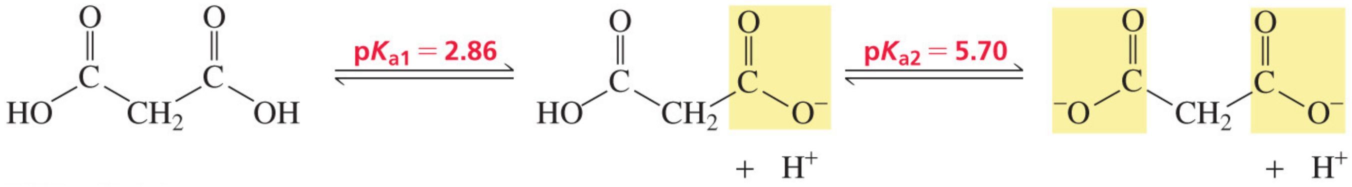


Table 15.2 Structures, Names, and pK_a Values of Some Simple Dicarboxylic Acids

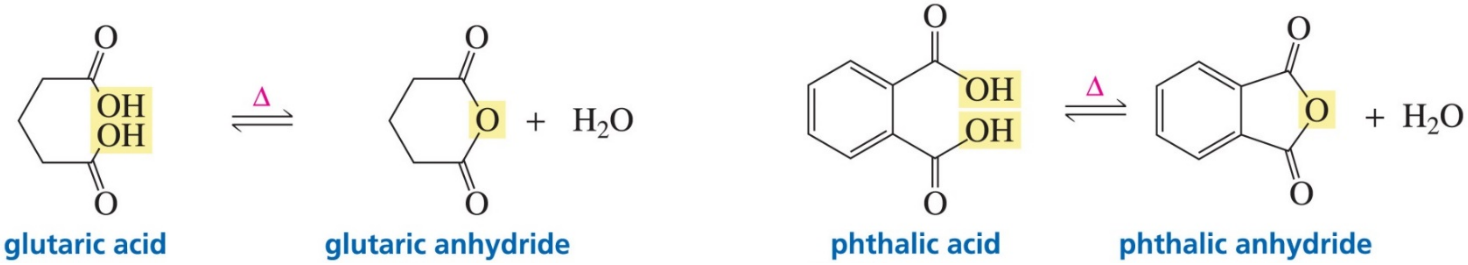
Dicarboxylic acid	Common name	pK_{a1}	pK_{a2}
	Oxalic acid	1.27	4.27
	Malonic acid	2.86	5.70
	Succinic acid	4.21	5.64
	Glutaric acid	4.34	5.27
	Adipic acid	4.41	5.28
	Phthalic acid	2.95	5.41

isophthalic
terephthalic

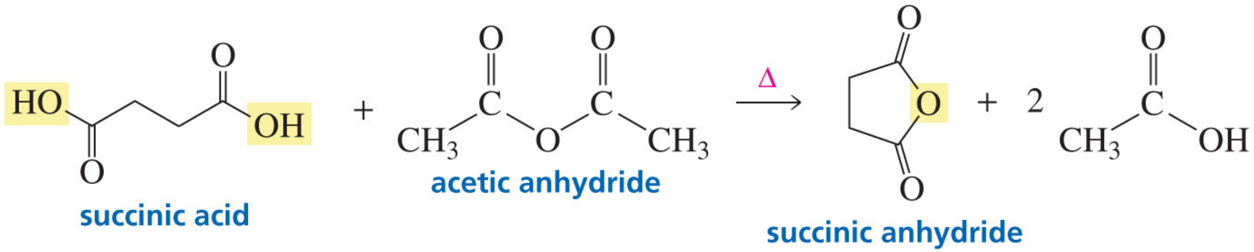
- inductive effect (of COO) on pK_a
- two pK_a's



- cyclic anhydride from dicarboxylic acid
  - when 5- or 6-membered ring possible



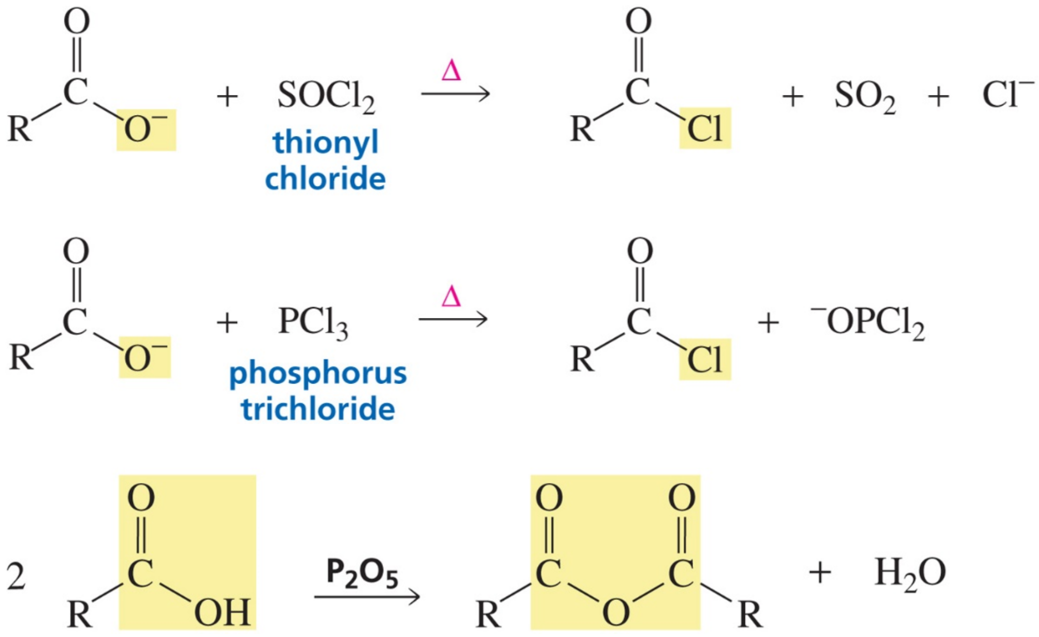
  - mechanism? add’n-elim’n
  - can be catalyzed by acetic anhydride or chloride



    - how? changing L   Problem 46 p759

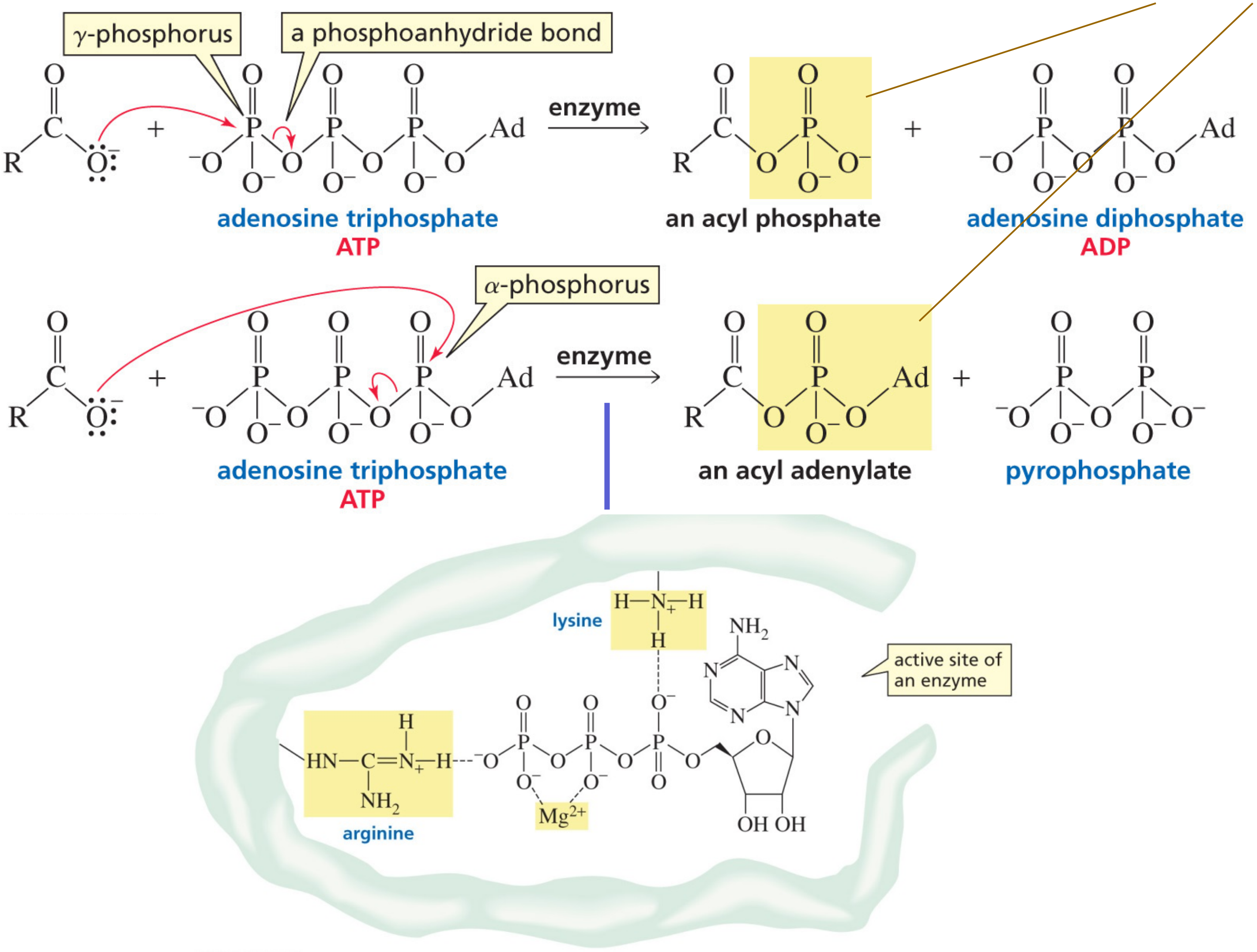
Activating RCOOH

- RCOOH more readily available than others, but
  - poor leaving –OH in add'n-elim'n rxn
  - esp at (physiological, blood) pH of 7.4 (in basic form $–O^–$)
- activating to RCOX or anhydride
  - just like converting –OH to –X in S_N



Activating RCOOH in biosynthesis

- to acyl phosphate or adenylate using ATP

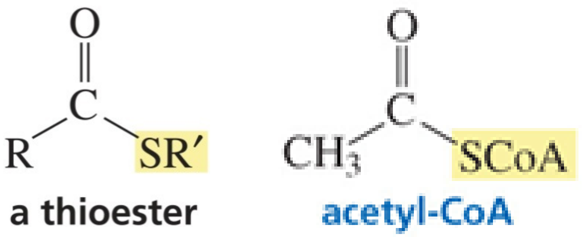


good leaving

- to thioester like acetyl-CoA
  - more reactive

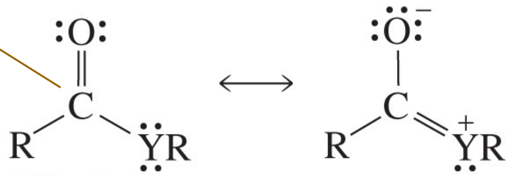
← localized δ+ and weaker B:

← size and size



a thioester

acetyl-CoA

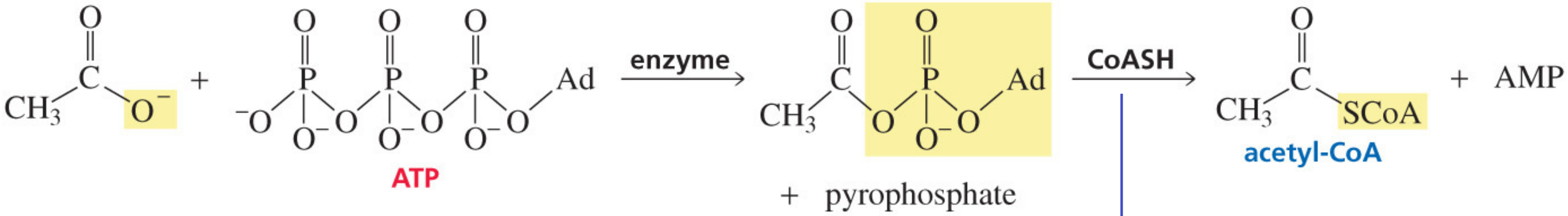


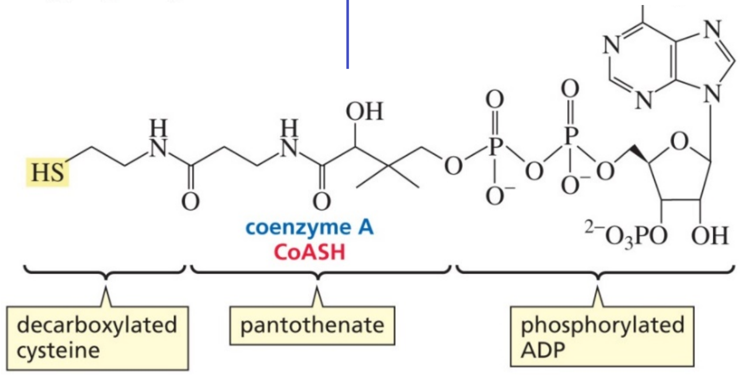
CH_3CH_2SH

p*K*a = 10.5

CH_3CH_2OH

p*K*a = 15.9





Summary

- 2 classes of carbonyls ~ RCOOH deriv’s vs A&K
- nomenclature
- relative reactivity ← basicity of $Z:^-$
- reactions
  - acyl chloride, ester, acid, amide, imide, nitrile, anhydride
  - equilibrium
  - (tetrahedral) intermediate
  - catalyzed vs promoted