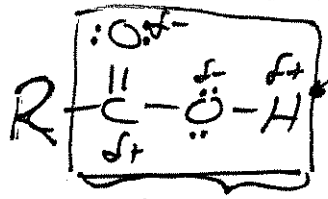
Chapter 15 Carboxylic Acids and their Derivatives. Acyl-Transfer Reactions

Carboxylic Acids:



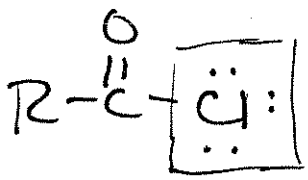
acidic

Carboxyl group

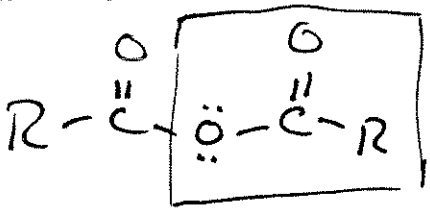
Condensed structural formula

RCO_2H or $RCOOH$

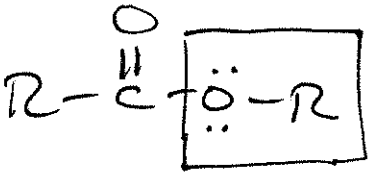
Carboxylic Acid Derivatives



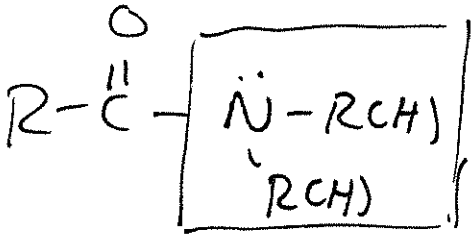
acid chlorides



acid anhydrides



esters



amides

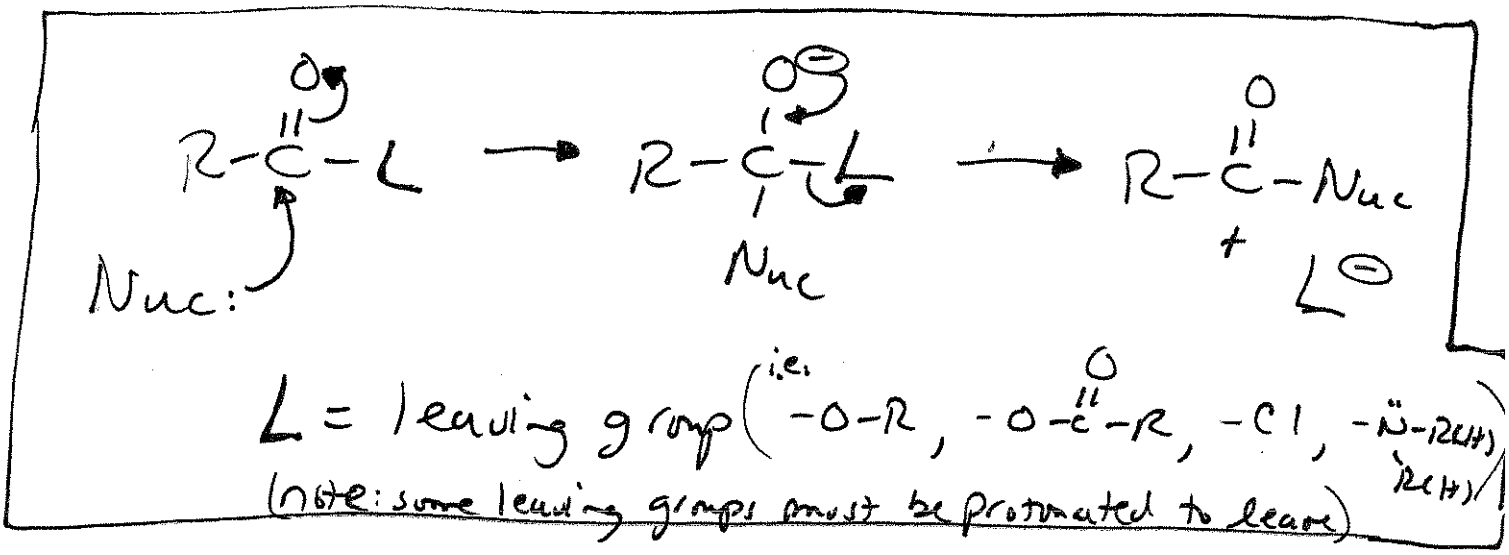
$-Cl$, $-O-\overset{O}{\overset{\|}{C}}-R$, $-O-R$, $-N(R)(R)$

are good leaving groups or can be converted to good leaving groups by protonation

Carboxylic Acid Derivatives

→ have a $-\overset{O}{\overset{\|}{C}}-$ group bonded to an atom with at least 1 nonbonding pair of electrons on it.

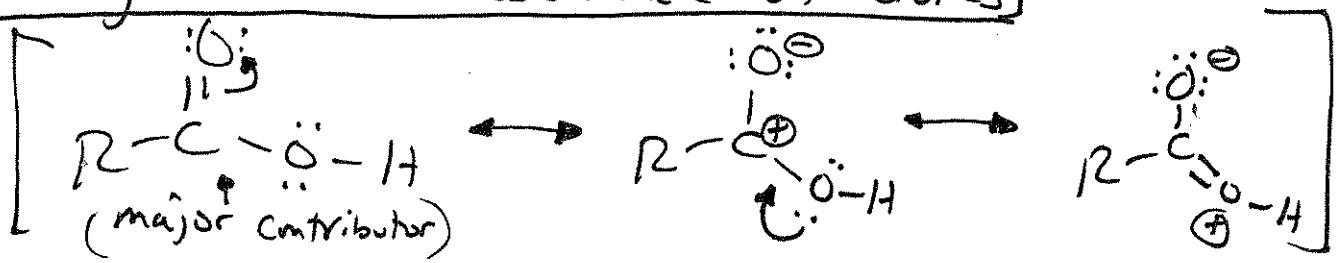
- Carboxylic Acids + Derivatives undergo Nucleophilic Substitution rather Than Nucleophilic Addition like aldehydes + Ketones ($R-\overset{O}{\overset{\|}{C}}-H$ or $R-\overset{O}{\overset{\|}{C}}-R$)



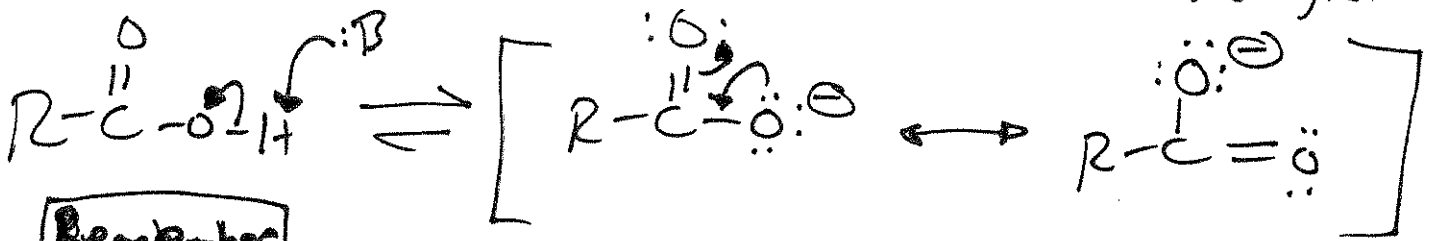
L = leaving group (i.e. $-O-R$, $-O-\overset{O}{\overset{\|}{C}}-R$, $-Cl$, $-\ddot{N}-R(H)$, $R(H)$)

(note: some leaving groups must be protonated to leave)

Carboxylic Acid Resonance Structures



- In carboxylic acids The ⊕ charge is delocalized onto C and O (2 right hand resonance structures). Therefore, The carboxylic acid carbonyl group is less electrophilic Than Ketones + aldehyde carbonyls.



Remember

- Carboxylate ion stabilized by resonance (thats why its H is more easily lost Than in alcohols)

Stabilities of Carboxylic Acids + Acid Derivatives

p598

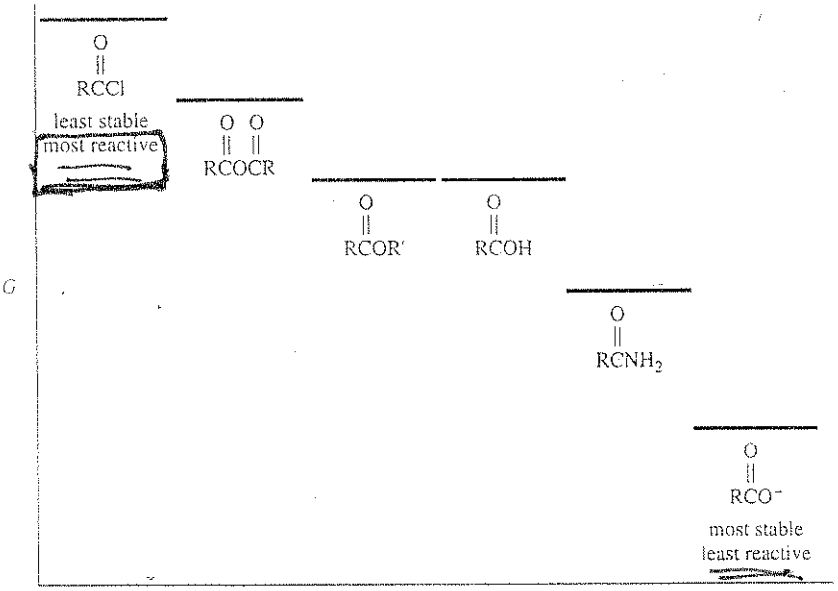


Figure 14.1
Relative stabilities of acid derivatives.

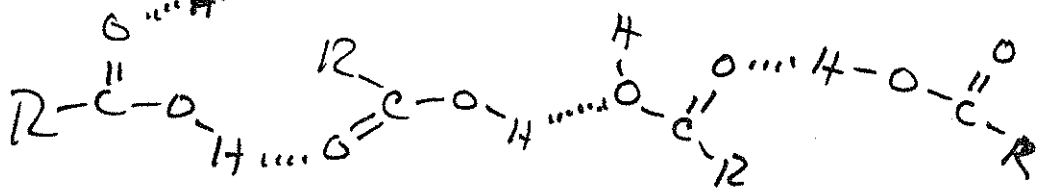
- Reactivities decrease as the resonance stabilization increases.

ex: an acid chloride ($R-\overset{O}{\overset{\|}{C}}-Cl$) will react with an appropriate Nucleophile to form any of the derivatives below it in Fig 14.1. Why?
Because it goes from a High energy state to a lower energy state during the rxn.

In contrast, can't easily form an acid chloride from $R-\overset{O}{\overset{\|}{C}}-NH_2$, for example.
(It's Thermodynamically unfavorable)

Carboxylic Acids; $R-\overset{O}{\overset{\|}{C}}-O-H$

- Can be hydrogen bond donors & acceptors



- C=5 or less on carboxylic acids or diacids → very soluble in water

  C>5 → solubility goes down (# C↑ sol.↓

- Can convert insoluble carboxylic acids to be soluble. (insoluble in H_2O) How?

  → deprotonate w/ a base to make a salt

Nomenclature of Carboxylic Acids + Their Derivatives

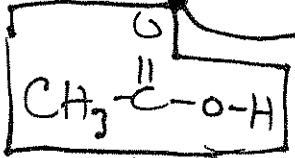
Carboxylic Acids

→ replace "e" in parent name with "oic acid"

→ substituents - name + # for location

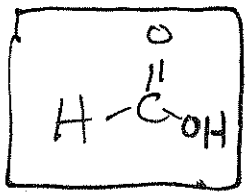
$-\overset{O}{\overset{\|}{C}}-O-H$ always 1st carbon atom of the chain

- Simplest carboxylic acids →



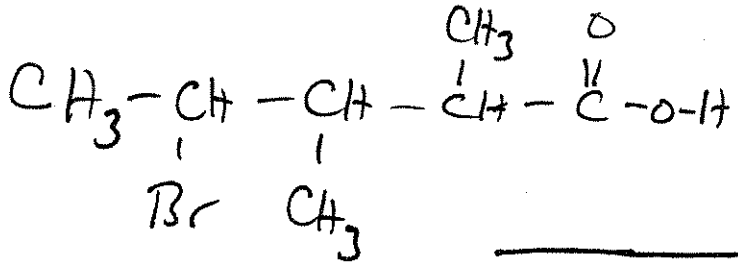
common → acetic acid

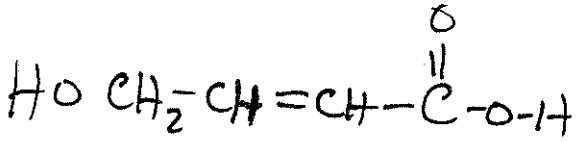
IUPAC → ethanoic acid



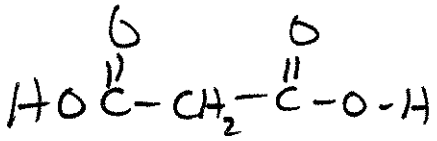
formic acid

methanoic acid



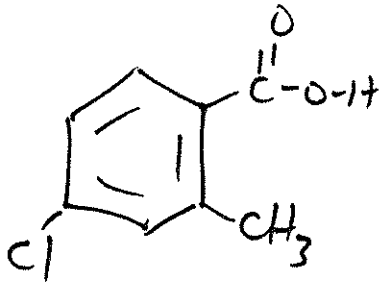


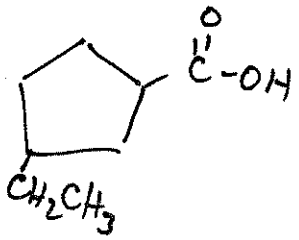
- if have 2 carboxylic acids in 1 molecule → use "dioic acid" (+ leave "e" in parent name)



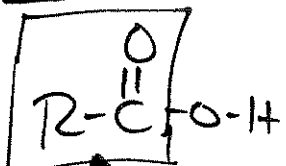
Common name: malonic acid

- carboxylic acid group attached to cycloalkane → add "carboxylic acid" to name of hydrocarbon



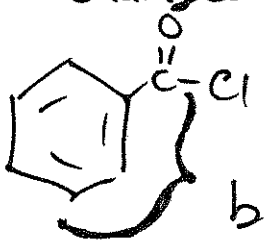


Acyl Groups, Acid Chlorides + Anhydrides



acyl group

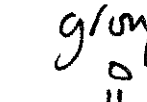
"ic" ending at end of carboxylic acid parent name changed to "yl"

ex 

benzoyl group

an acid chloride

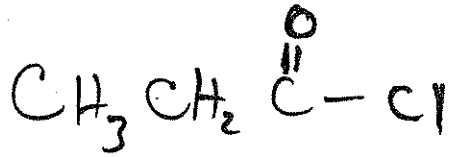
benzoyl chloride



acetyl group

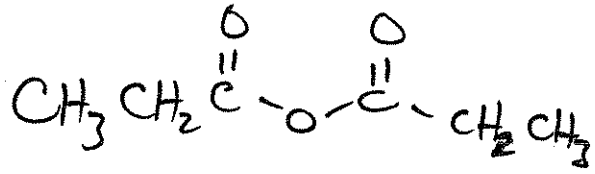
Acid chloride

Acyl group

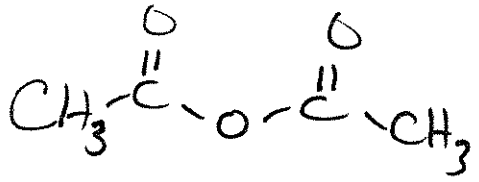


_____ _____

Anhydrides – substitute "anhydride" for "acid" in parent carboxylic acid name



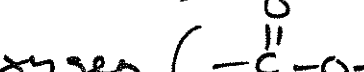
propanoic anhydride

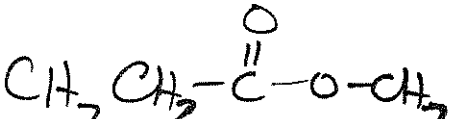


_____ (IUPAC)

_____ (Common)

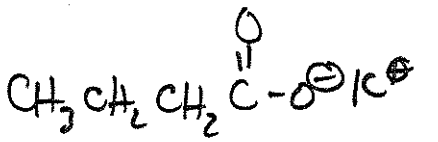
Salts & Esters

- Name of the cation (in salts) or the organic group attached to the oxygen () in esters precedes the name of the acid AND the "ic acid" ending is changed to "ate"

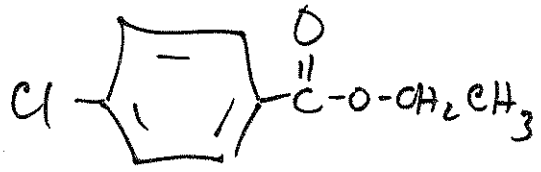
ex: 

methyl propanoate (IUPAC)

methyl propionate (common)



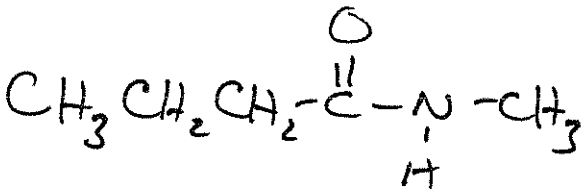
_____ (IUPAC)



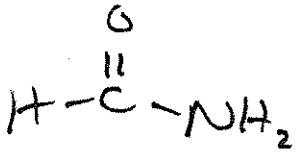
_____

Amides, Imides + Nitriles

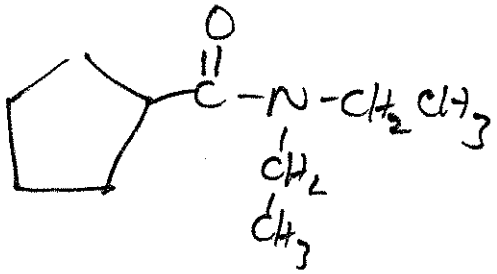
- **amides** - replace "oic acid" with "amide"
  or "carboxylic acid" with "carboxamide"
  - alkyl substituents on the amide Nitrogen - name by using "N-alkyl name"



_____

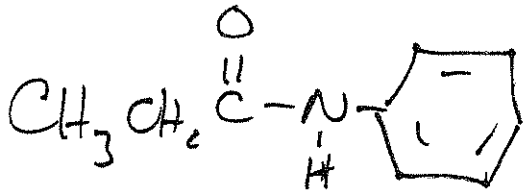


{ _____ (IUPAC)
_____ (Common)



_____

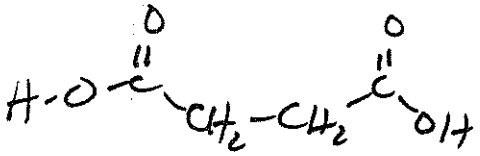
- if substituent on the nitrogen is a phenyl group then the name is changed to "anilide"
  (common)



_____

Imides – are cyclic amides produced from dicarboxylic acids

ex



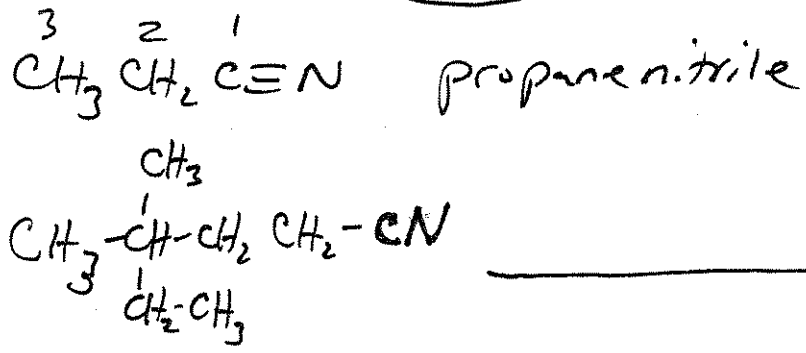
succinic acid (common name)

succinimide

Nitriles

– add suffix "nitrile" to parent hydrocarbon name

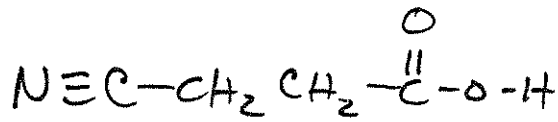
– count the carbon of the –C≡N group when numbering chain

ex 

propanenitrile

- if –C≡N group is on a cycloalkane → use suffix "carbonitrile"

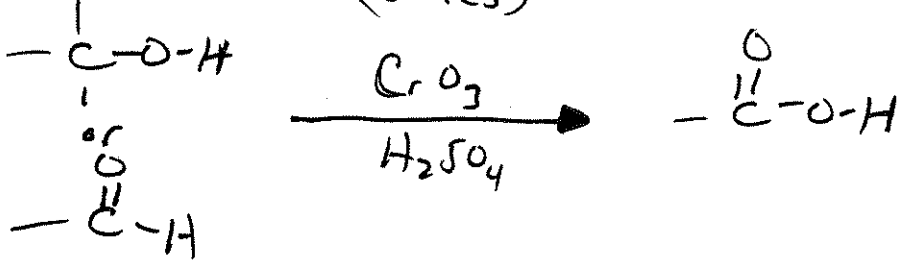
- when –C≡N group a substituent → use "cyano" (with other higher priority groups present)



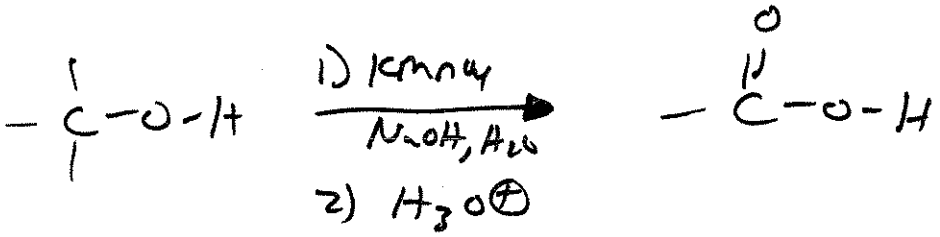
Preparation of Carboxylic Acids

Review 1° alcohols + aldehydes → carboxylic acid

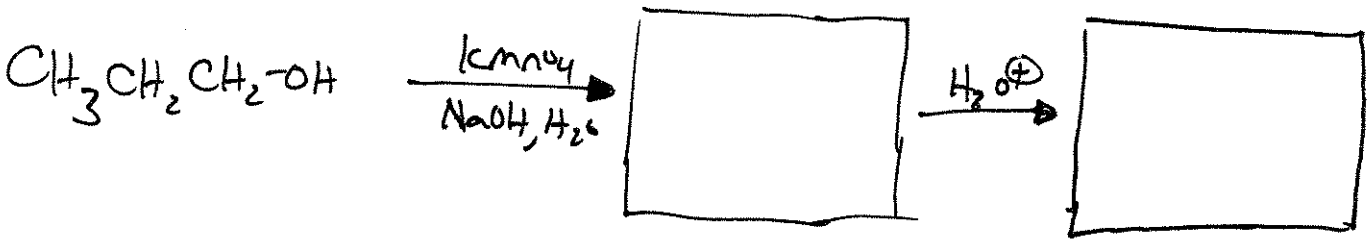
(Jones)



- Another method (better)



ex

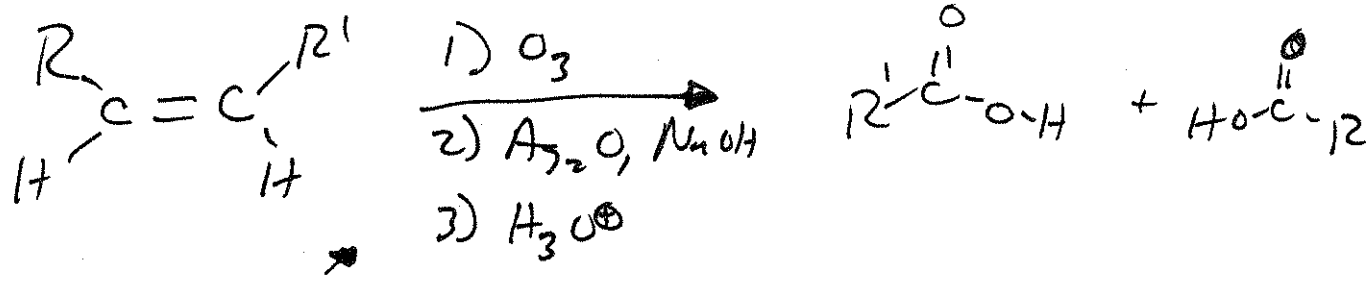


- $KMnO_4$ will also oxidize aldehydes to carboxylic acids

Tollens Reagent – **mild** use to convert aldehydes to carboxylic acids

Ag_2O, $NaOH$, H_2O

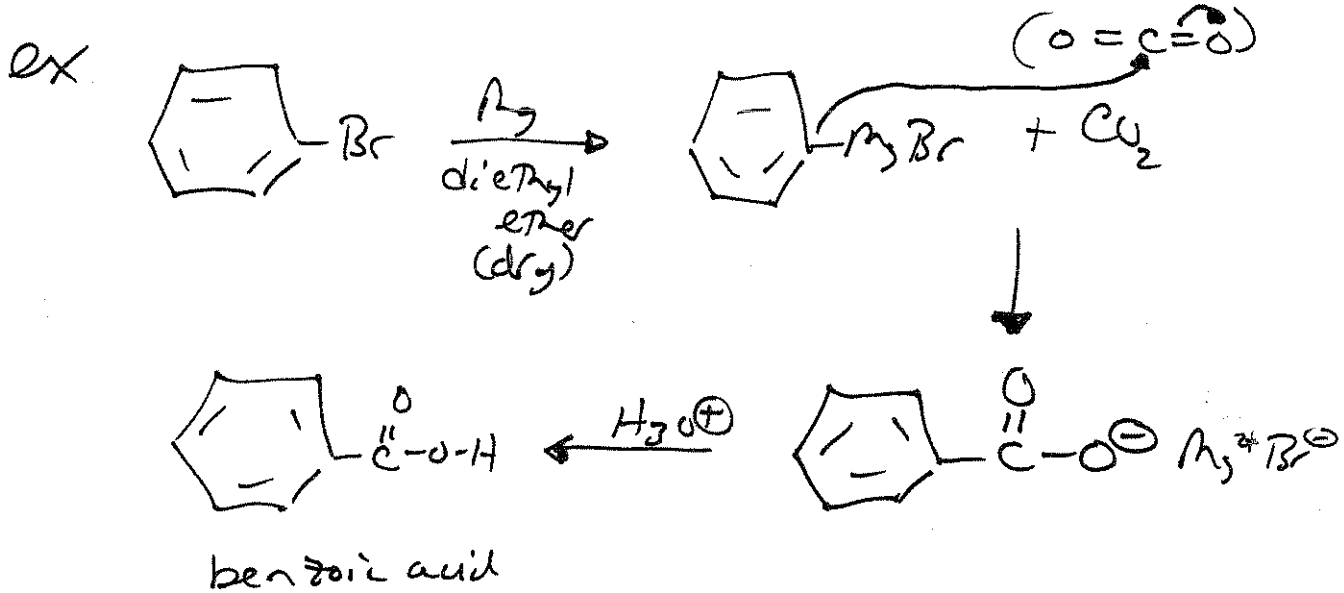
↑ alkene would react w/ $KMnO_4$



- ozonolysis under oxidative workup conditions

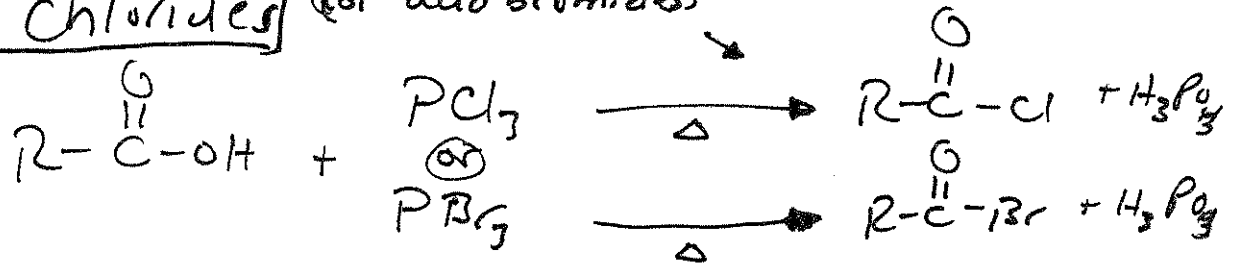
- A Grignard reagent + CO_2 $\xrightarrow[2)\ H_3O^{\oplus}]{}$ carboxylic acid

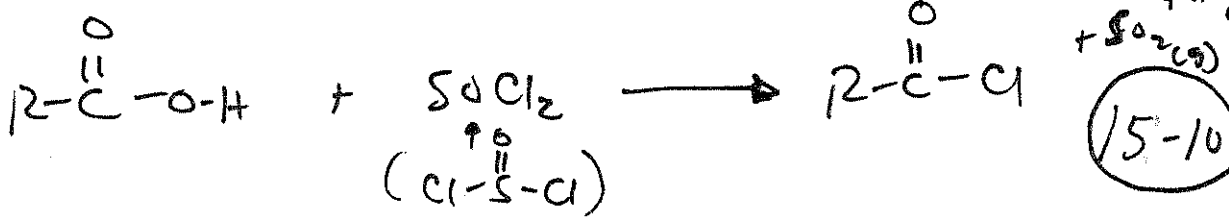
ex



Converting Carboxylic Acids into Acid Chlorides + Acid Anhydrides

Acid chlorides (or acid bromides)

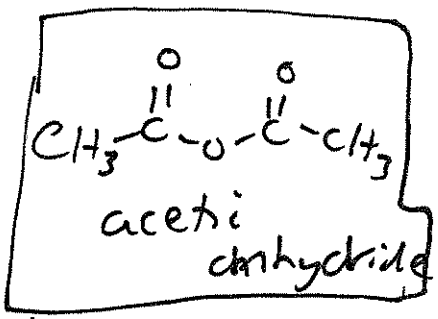




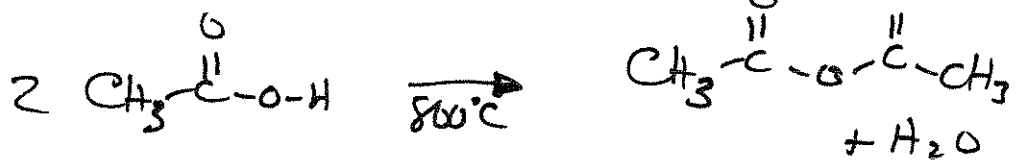
15-10

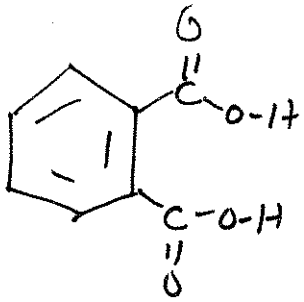
Acid Anhydrides

- most important and most used

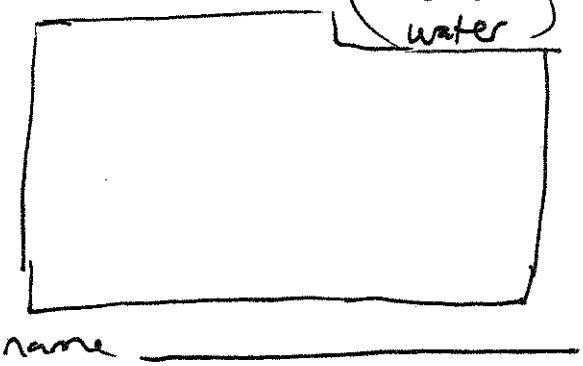


- one way to prepare acetic anhydride → heat acetic acid to 800°C

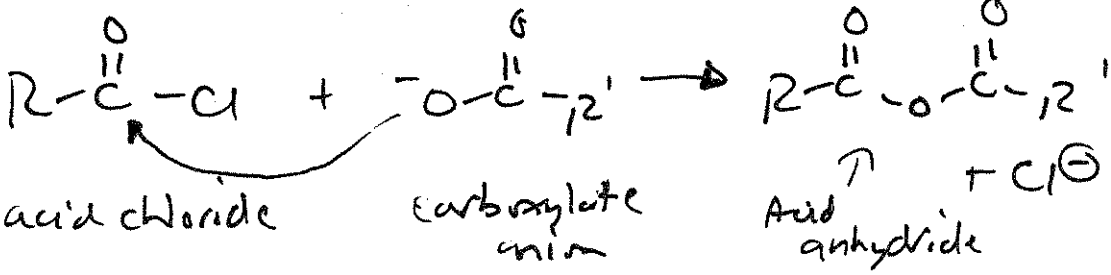




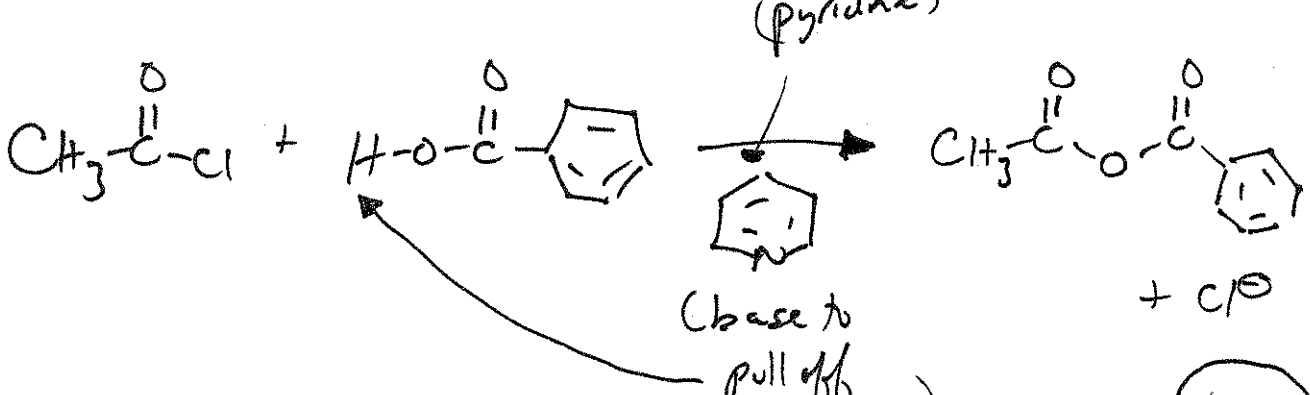
heat →



Most general anhydride synthetic method:



ex:



Reactions of Carboxylic Acid Derivatives w/ H_2O

Hydrolysis

Acid chlorides: $R-\overset{O}{\overset{\|}{C}}-Cl + H_2O \longrightarrow R-\overset{O}{\overset{\|}{C}}-O-H + HCl$

Anhydrides: $R-\overset{O}{\overset{\|}{C}}-O-\overset{O}{\overset{\|}{C}}-R' + H_2O \longrightarrow R-\overset{O}{\overset{\|}{C}}-O-H + R'-\overset{O}{\overset{\|}{C}}-OH$

Esters: $R-\overset{O}{\overset{\|}{C}}-O-R' + H_2O \xrightarrow[\text{or}]{H^{\oplus}} R-\overset{O}{\overset{\|}{C}}-OH + H-O-R$

$\xrightarrow[\Delta]{1)\ OH^- \quad 2)\ H_3O^{\oplus}}$

- **Saponification** → ester hydrolysis in basic soln

Nitriles:

review: $R-Cl + Na^{\oplus}CN^{\ominus} \longrightarrow R-CN + Cl^{\ominus}$ (S_N2)

hydrolysis

$R-C\equiv N \xrightarrow[H^{\oplus}]{H_2O}$ * lower temp * less time $\rightarrow R-\overset{O}{\overset{\|}{C}}-NH_2$

$\xrightarrow[H^{\oplus}]{H_2O}$ * higher temp * more time $\rightarrow R-\overset{O}{\overset{\|}{C}}-O-H$

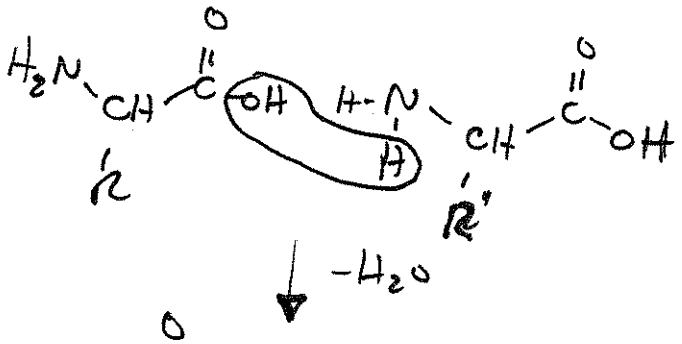
also: $R-C\equiv N \xrightarrow[H_2O]{NaOH} R-\overset{O}{\overset{\|}{C}}-O^{\ominus} \xrightarrow{H_3O^{\oplus}} R-\overset{O}{\overset{\|}{C}}-O-H$

Δ

Amides:

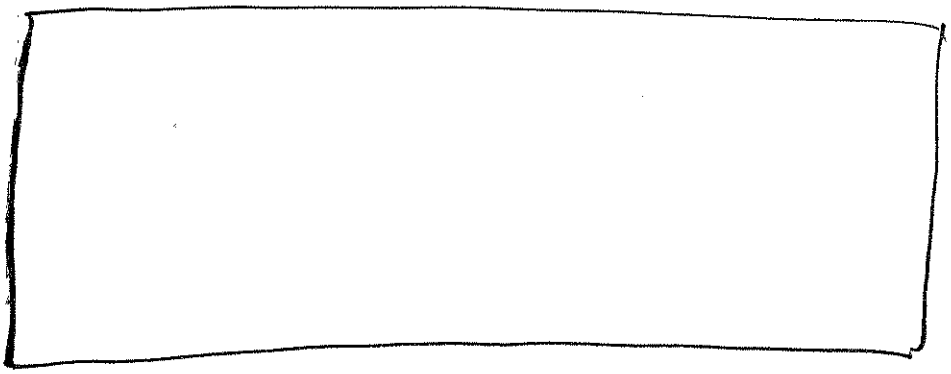
- amide hydrolysis is more difficult than esters, acid chlorides + anhydride hydrolysis
- biologically important amides → **peptide linkages in proteins**

2-amino acids:

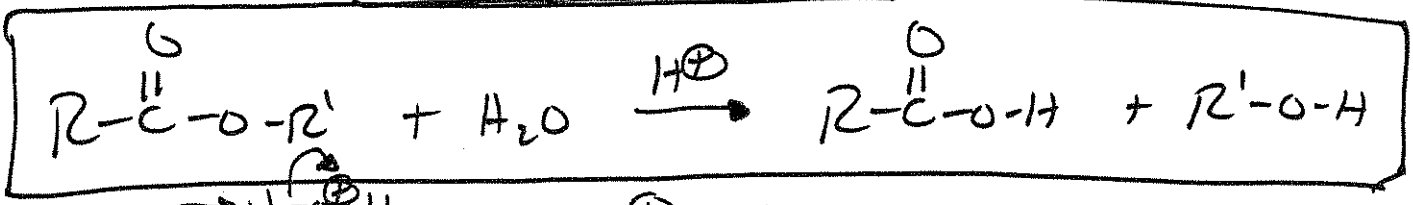


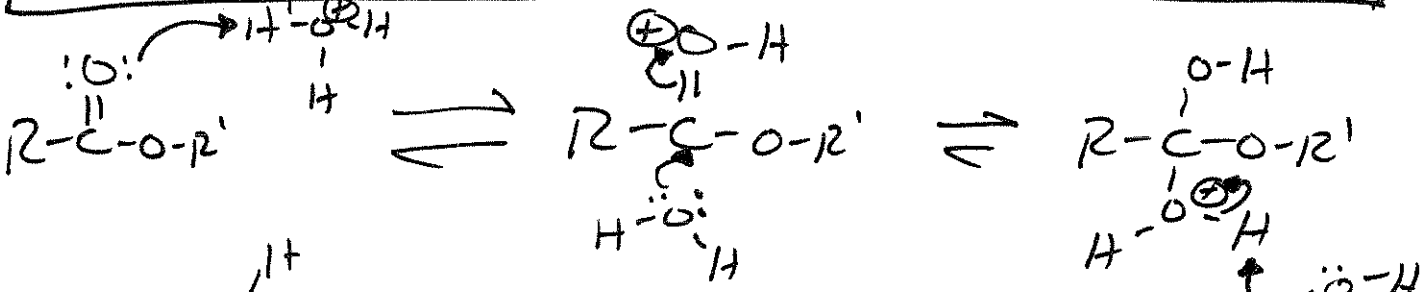
amide (peptide) linkage

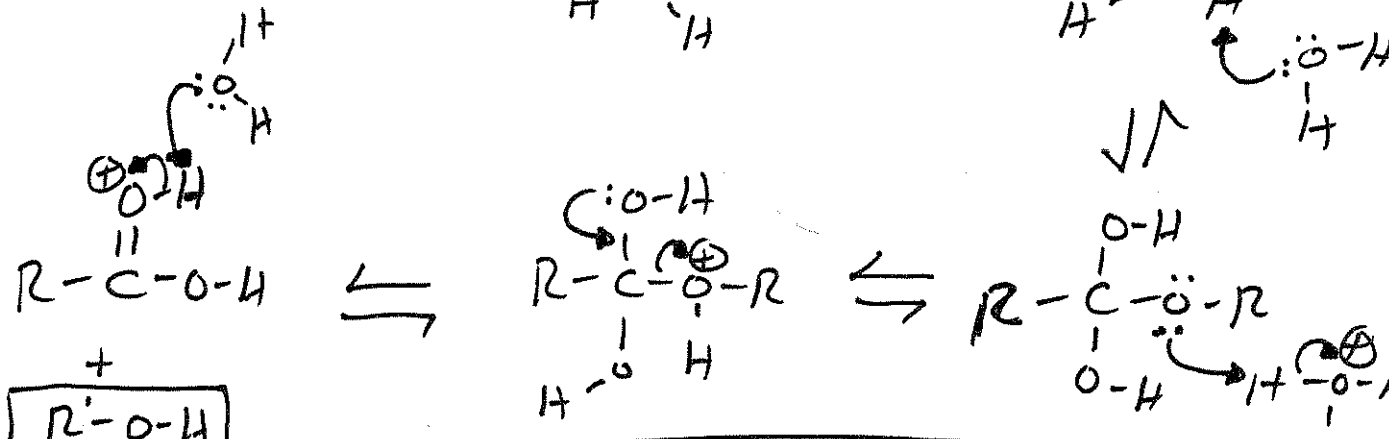
$H^{\oplus}$, H_2O Δ amide hydrolysis

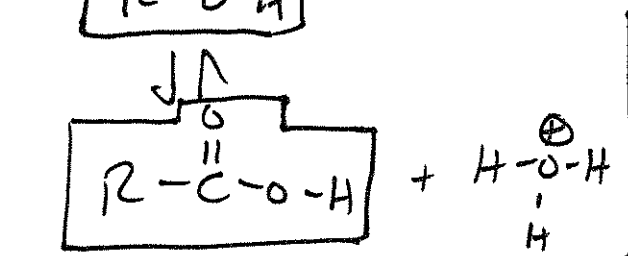


Acid Catalyzed Ester Hydrolysis Mechanism

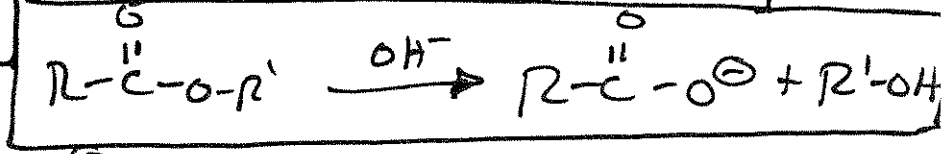


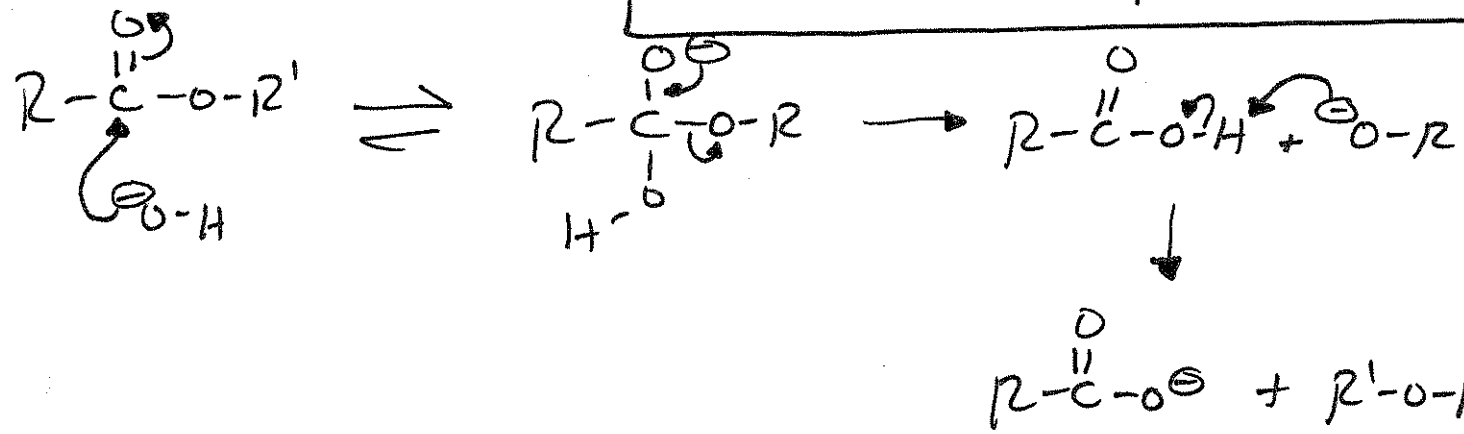




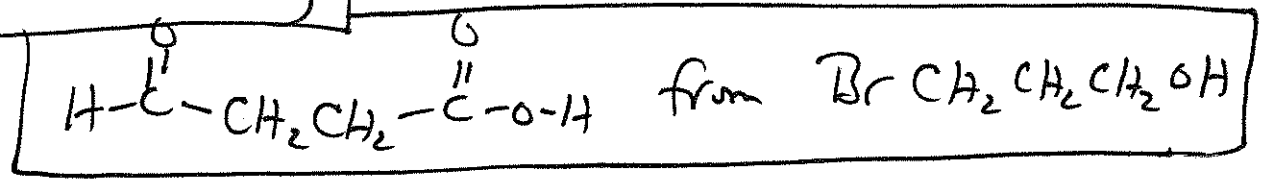


Base Catalyzed Ester Hydrolysis Mechanism



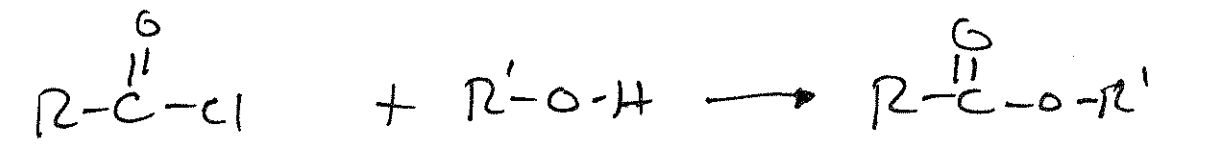


Problem Solving

Make:  from $BrCH_2CH_2CH_2OH$

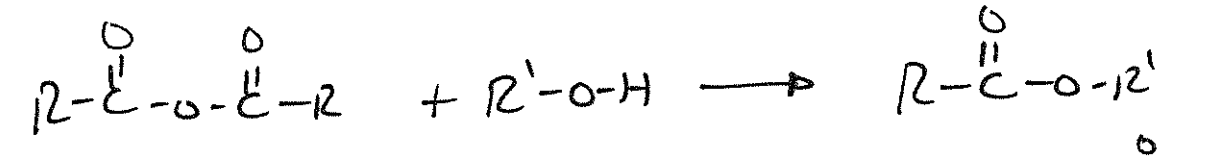
Reactions of Carboxylic Acids and Derivatives with Alcohol Nucleophiles

To make esters:



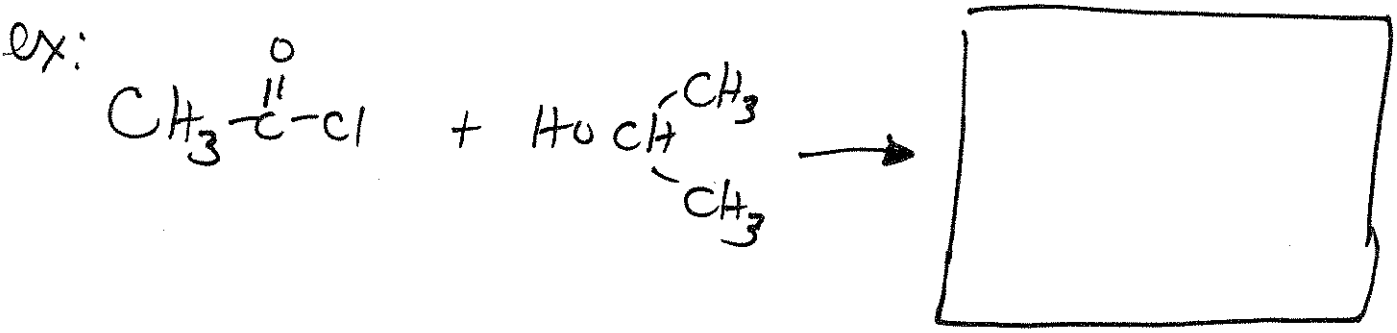
acid chloride

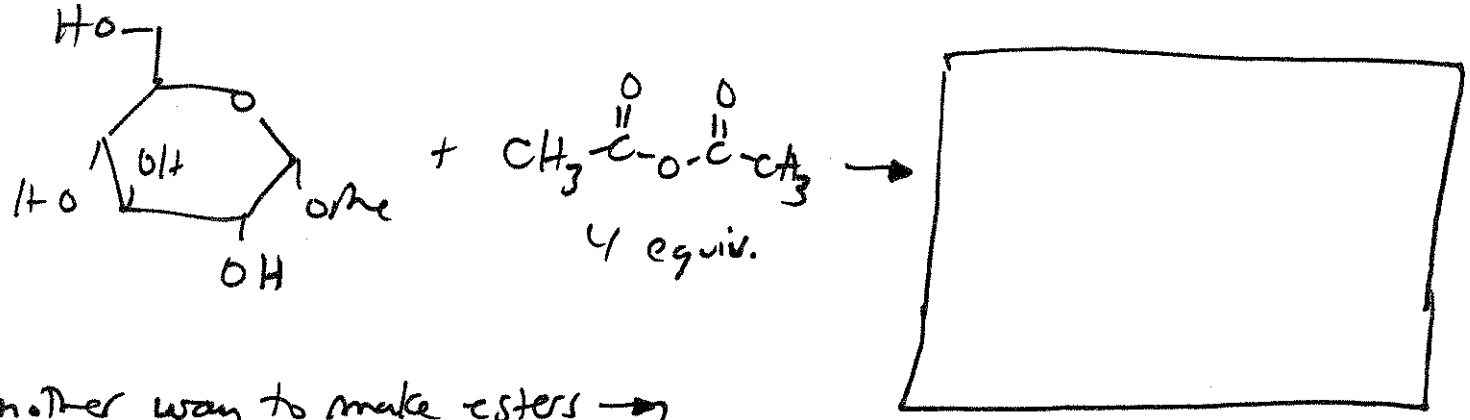
or



acid anhydride

ex:

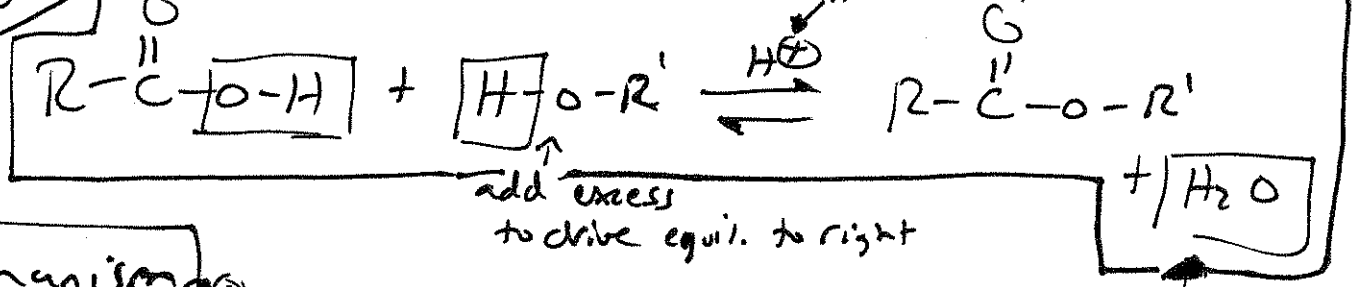




Another way to make esters →

Fischer Esterification

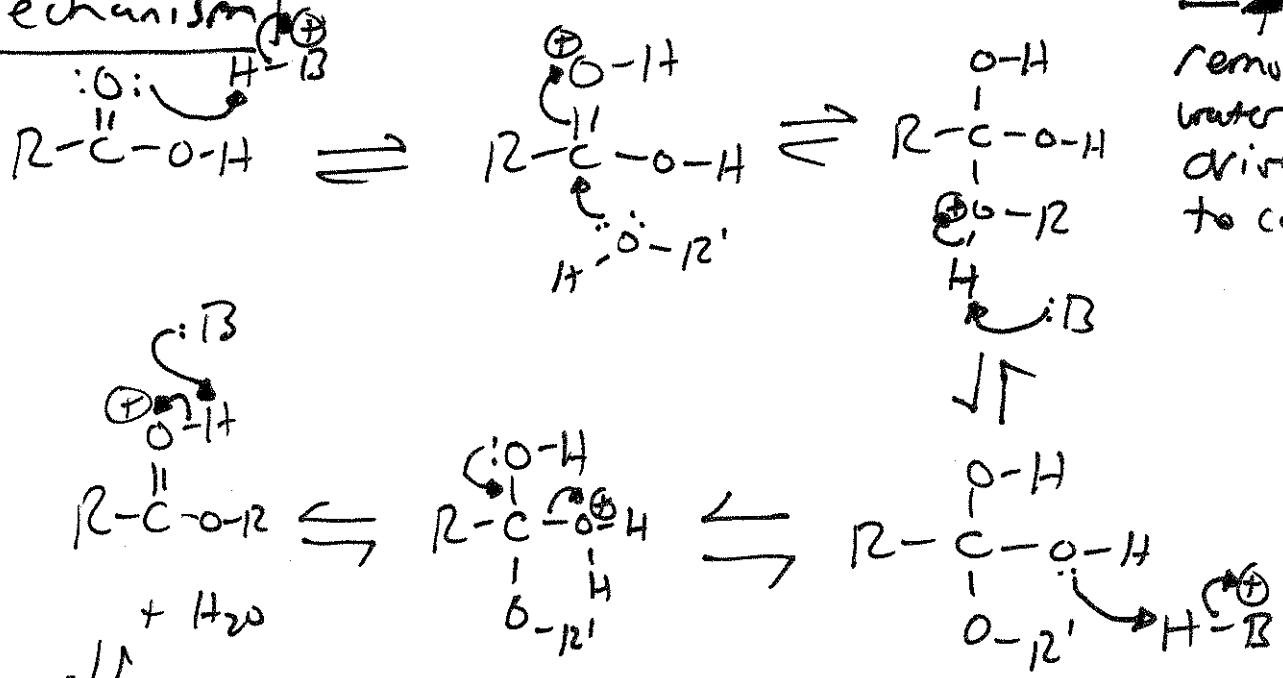
Carboxylic acid + alcohol + $H^{\oplus}$ catalyst (HCl or H_2SO_4)



add excess to drive equil. to right

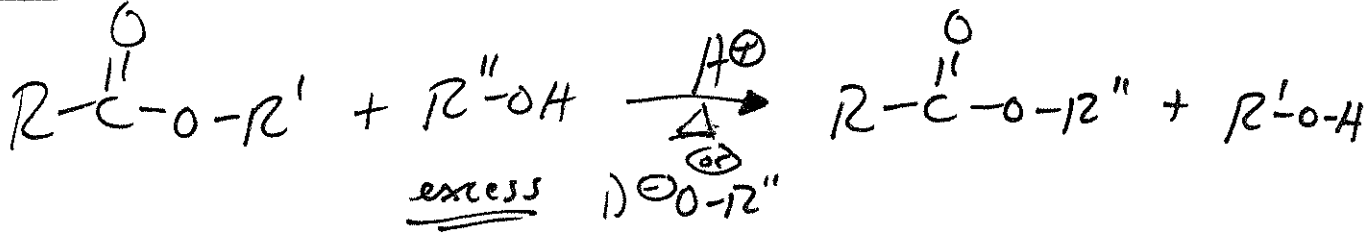
remove water to drive rxn to completion

Mechanism

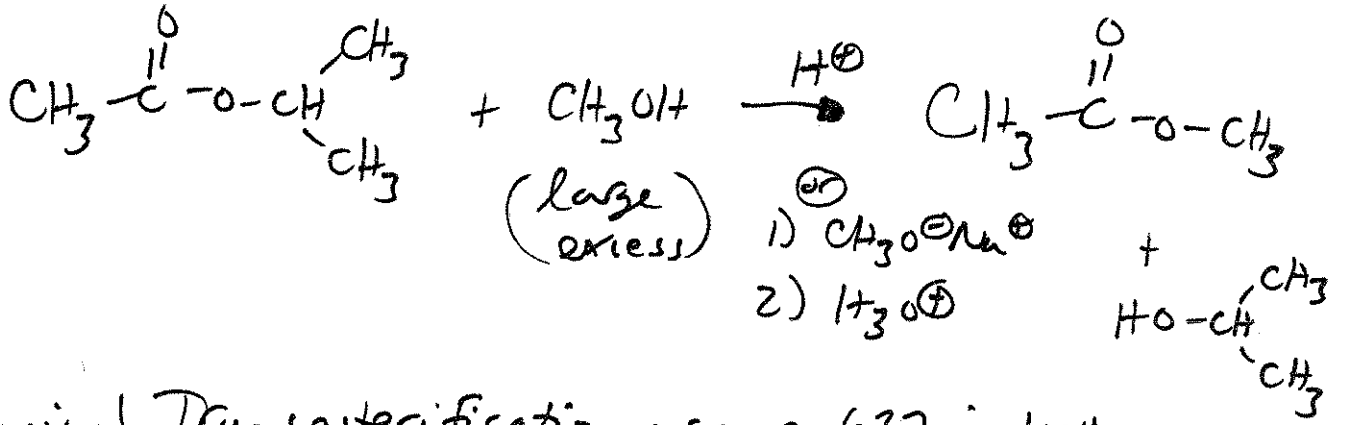


Reverse of Acid Catalyzed Hydrolysis of Esters

Transesterification ← conversion of one ester to another ester

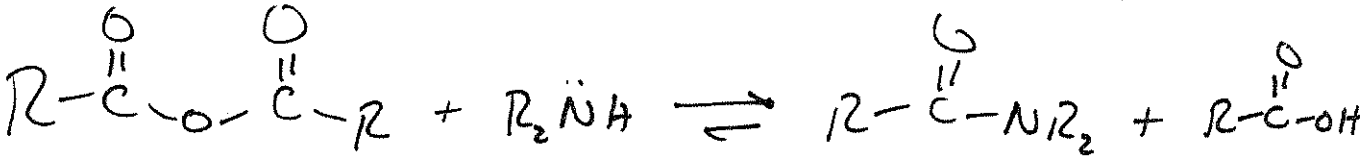


ex:

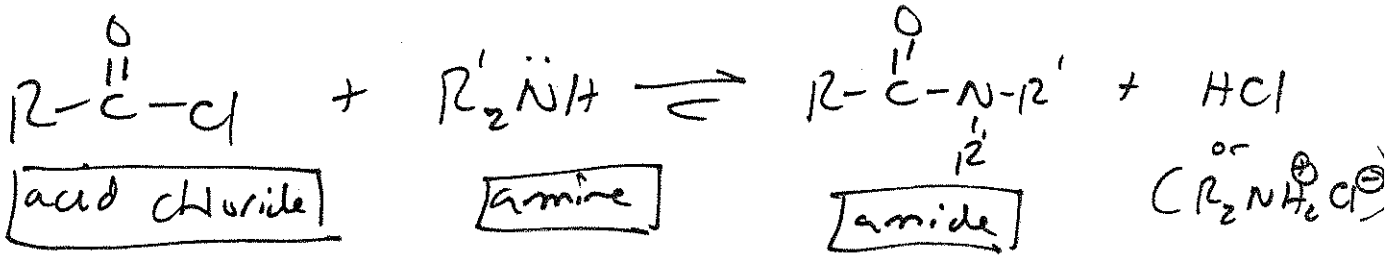


* Biological Transesterification → see pg 637 in text (Triesters → acetyl CoA)

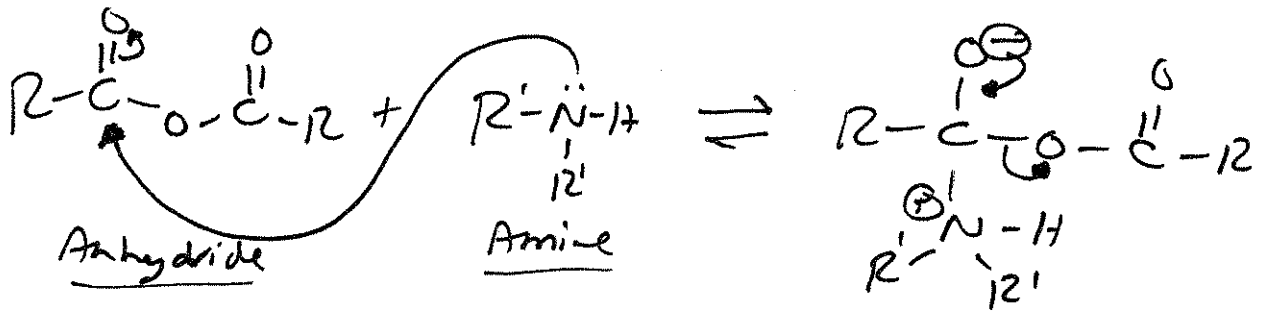
Reactions of Carboxylic Acids + Derivatives with Ammonia or Amine Nucleophiles

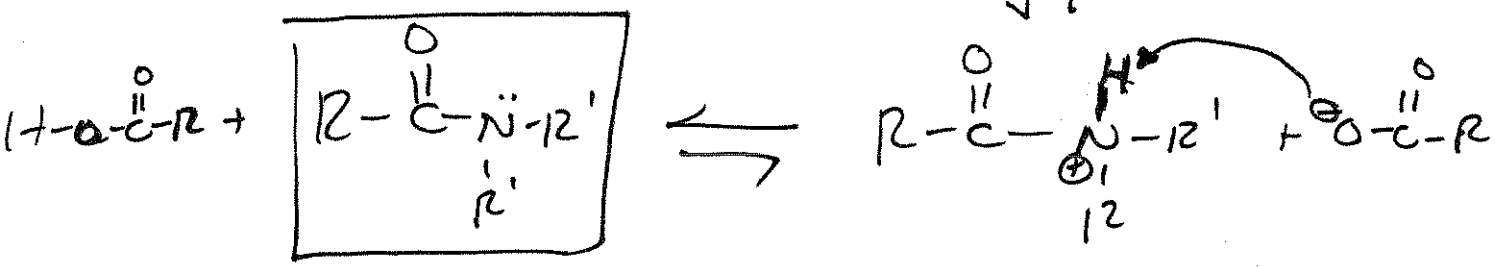


or

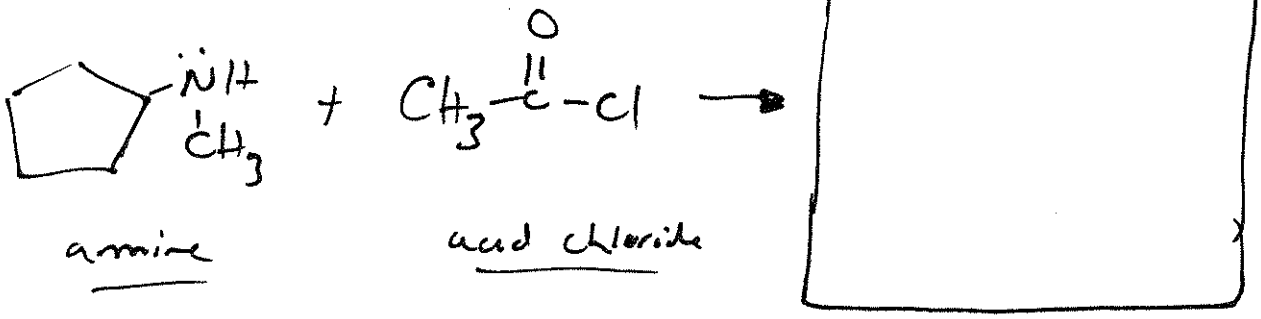


Mechanism to Make Amide from Amine + Anhydride

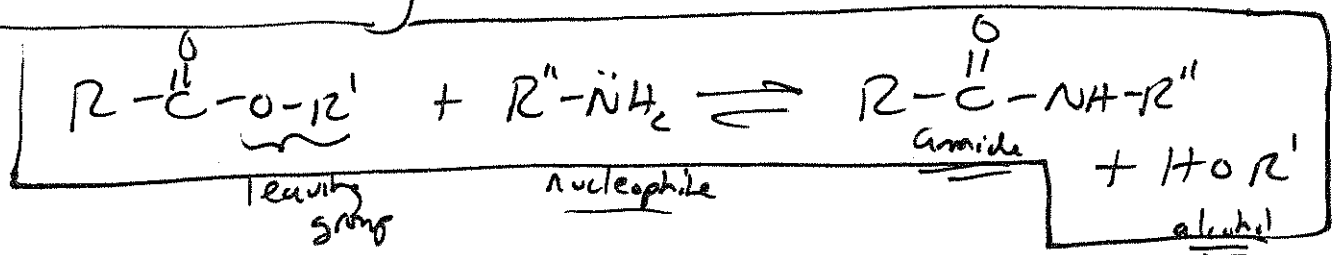




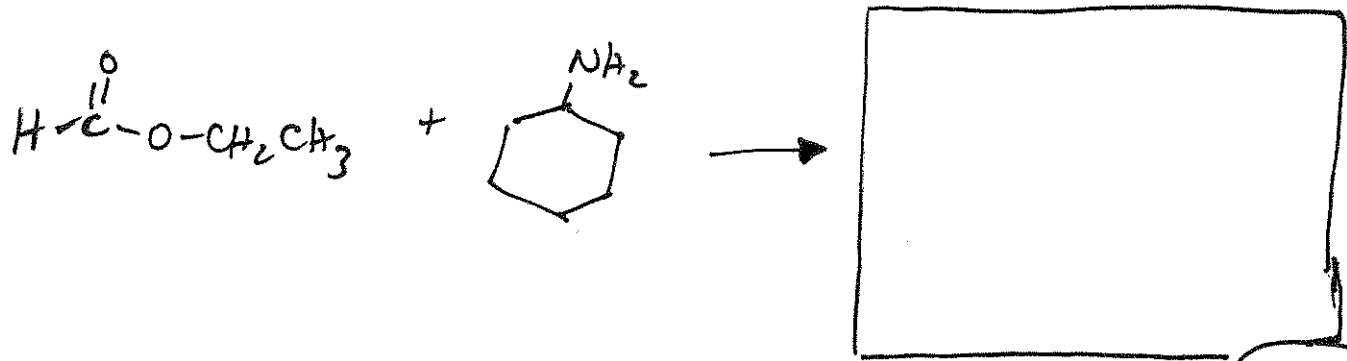
ex:



Esters to Amides



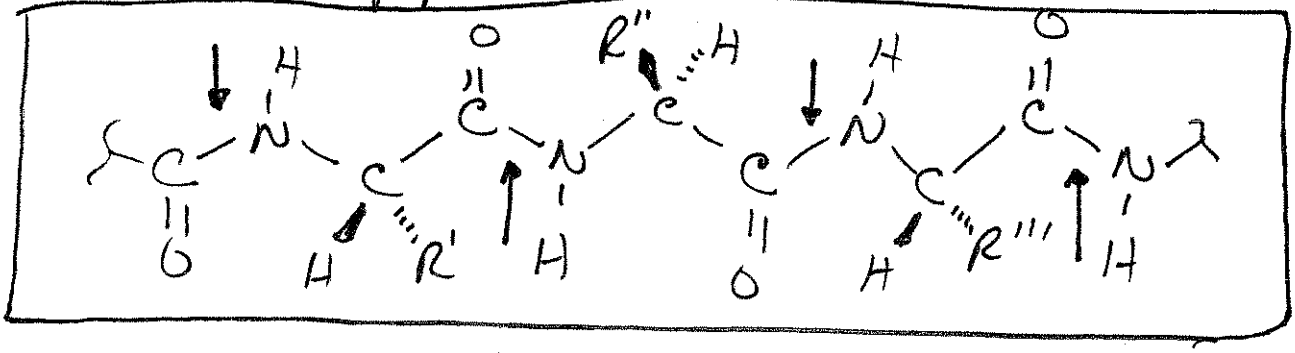
ex



Acyl-Transfer Reactions in Biological Systems

→ Synthesis of Peptides with Acyl-Transfer Rxns

Amide bonds link amino acids together to form peptides + proteins (arrows show amide bonds)



R', R'' + R''' = different amino acid side chains

- (See pp 983 + 985 for amino acid structures)

← Don't need to know these

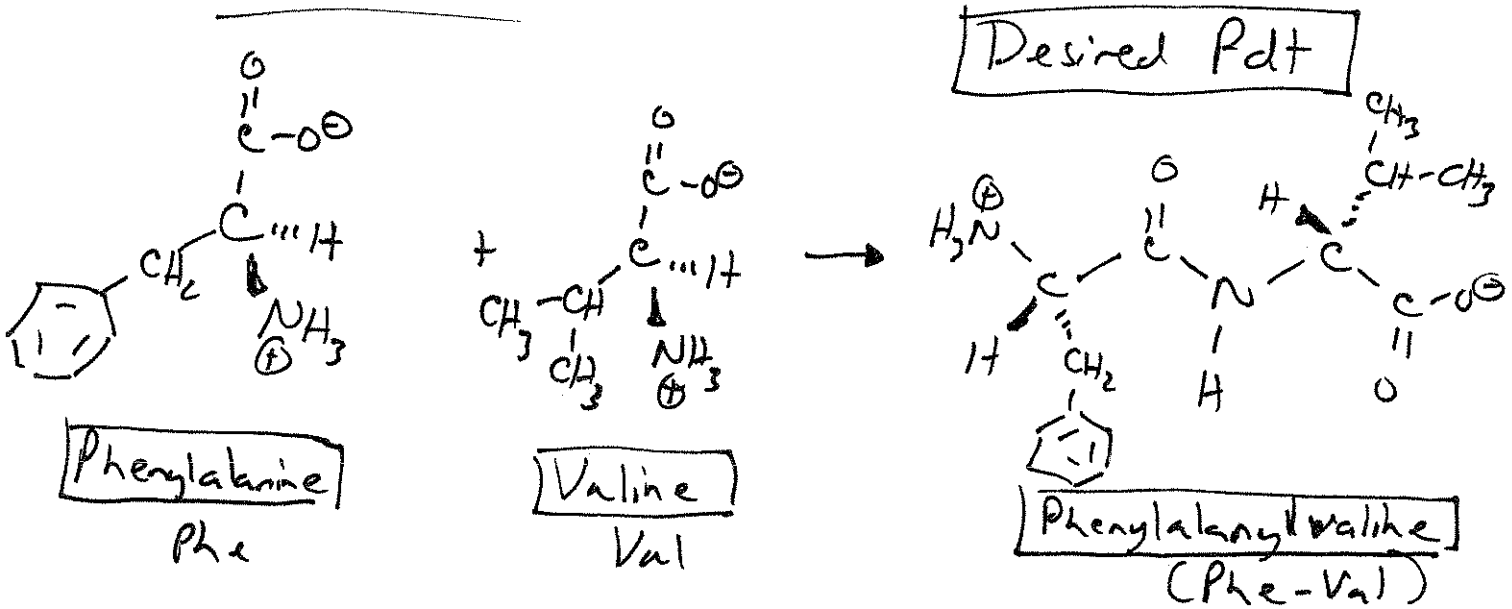
Peptides: smaller molecules with less amino acids linked together by amide bonds

Proteins: much larger molecules with many amino acids linked by peptide bonds

* Remember: amide bonds also known as peptide linkages (or bonds) in peptides + proteins

- Many different peptides + proteins have important biological activities.

Let's say we want to make the dipeptide Phenylalanylvaline (Phe-Val) from phenylalanine and valine:



- Is this the only product that will form if one mixes phenylalanine + valine together??

→ No - can also get valylphenylalanine (Val-Phe) or two valines linked (Val-Val) or two phenylalanines linked (Phe-Phe) together.

(4 dipeptides + also small amts of tri & tetra peptides as well)

- Will these peptide bonds (above) form easily??

→ No - reactions of a carboxylic acid + an amine is not the best way to make an amide bond.

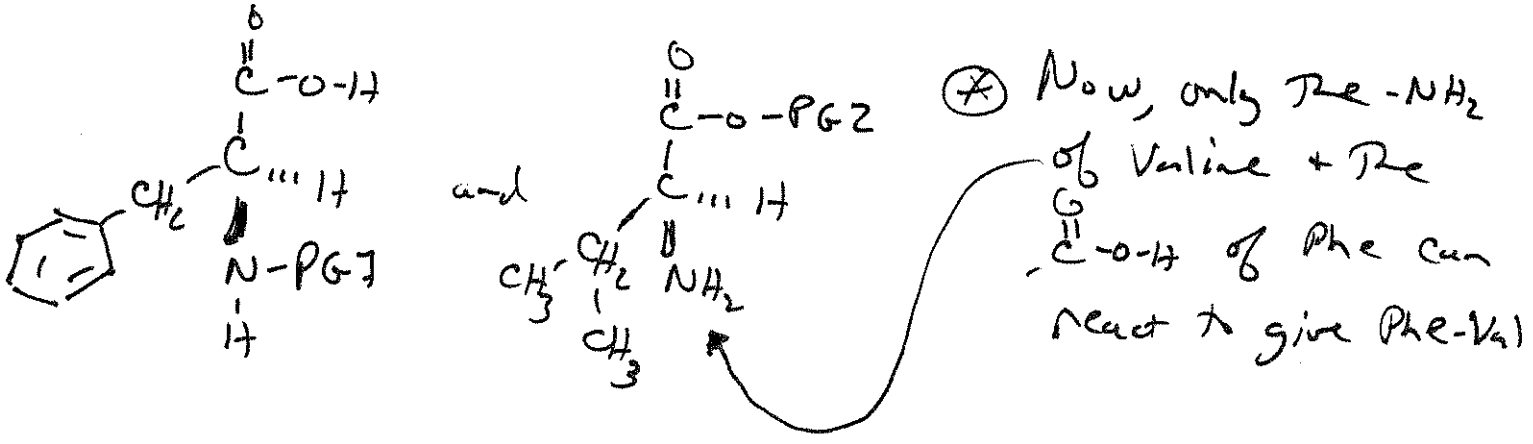
- To make only Phe-Val we need to a) link the amino acids together in a very specific way + b) we need a better rxn to make the peptide linkage (other than $\ce{-C(=O)-OH}$ + $\ce{R-NH2}$) (How do we do this? 15-20)

How do we do this?

1st – we need to use appropriate protecting groups,

2nd – we need to convert $-\overset{O}{\overset{\|}{C}}-O-H$ group to a more reactive functional group so peptide bonds are more readily made.

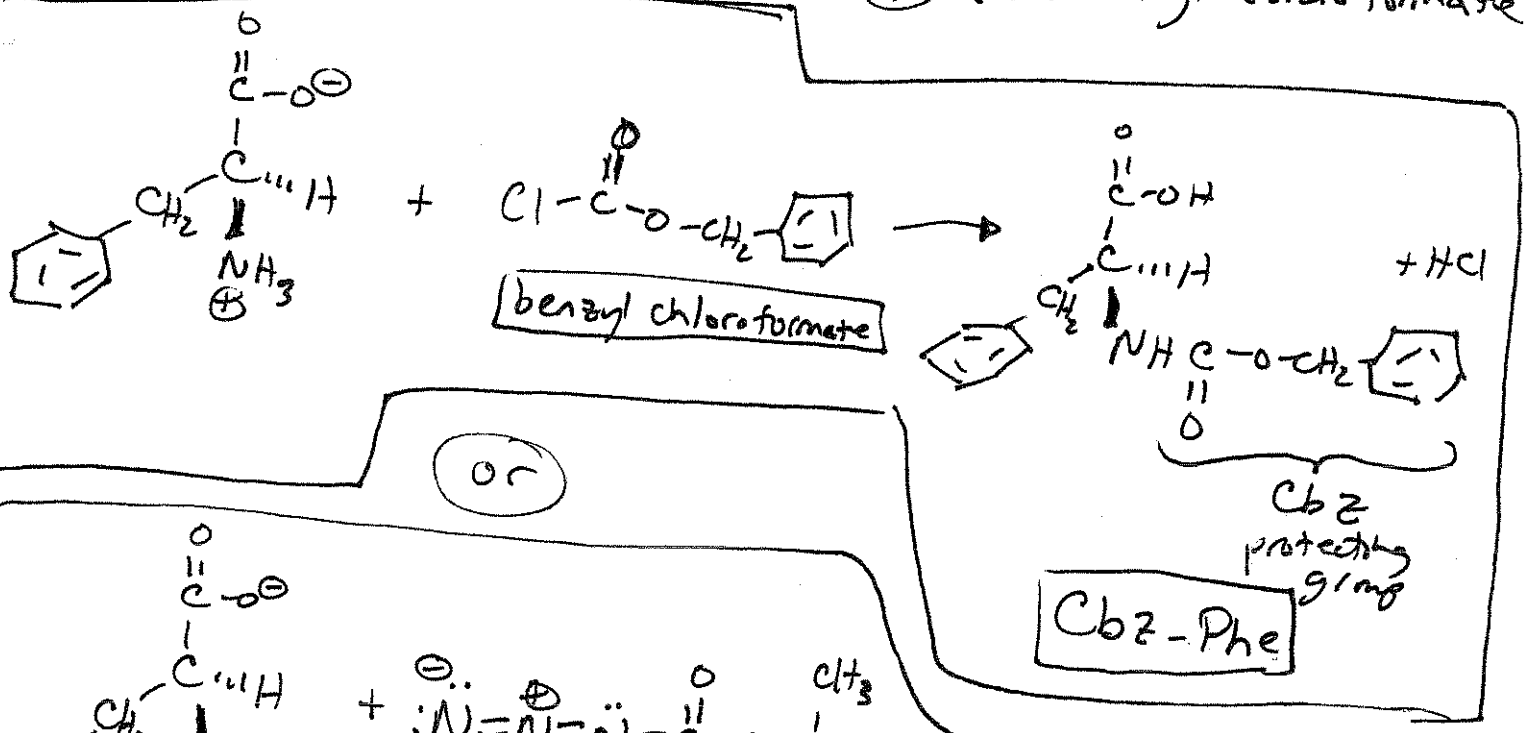
- To make Phe-Val:
  - a) need to protect the amino group on Phe w/ Protecting Group #1 (PG-1) so that it's no longer very nucleophilic
  - b) need to protect the carboxylic acid of Valine. Why?? (PG-2)
    → So that one valine molecule won't react with another valine molecule.



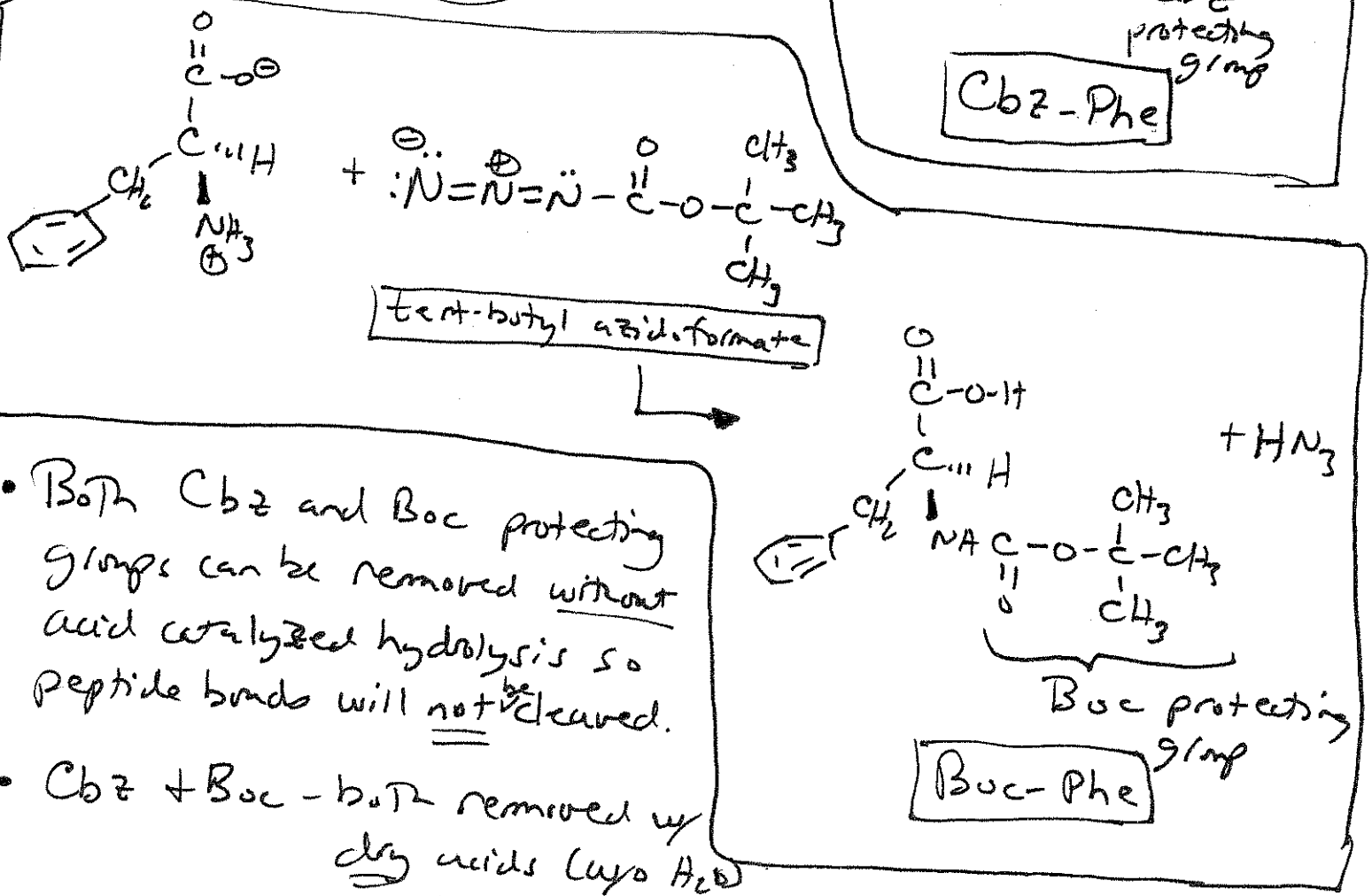
- Protecting groups should be easy to put on AND easy to remove with a rxn that won't cleave amide bonds. Why?

→ To protect amino group of Phe – use a benzyl chloroformate

(or) tert-butyl azido formate



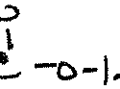
or

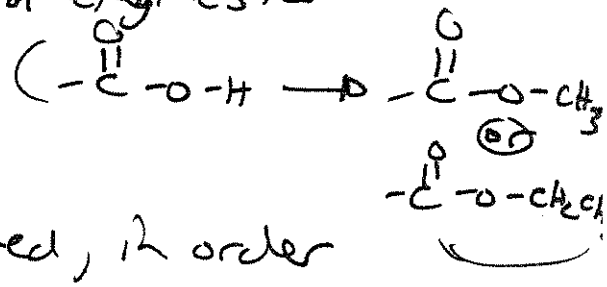


- Both Cbz and Boc protecting groups can be removed without acid catalyzed hydrolysis so peptide bonds will not be cleaved.
- Cbz + Boc – both removed w/ dry acids (w/o H_2O) or in the case of Cbz it can also be removed by catalytic hydrogenation

See Mechanisms on pp 632 + 633 for Cbz + Boc Protecting Group Removal

R Don't need to know mechanism

- To protect the carboxylic acid of Valine (PG-2)
  Change  into a methyl or ethyl ester

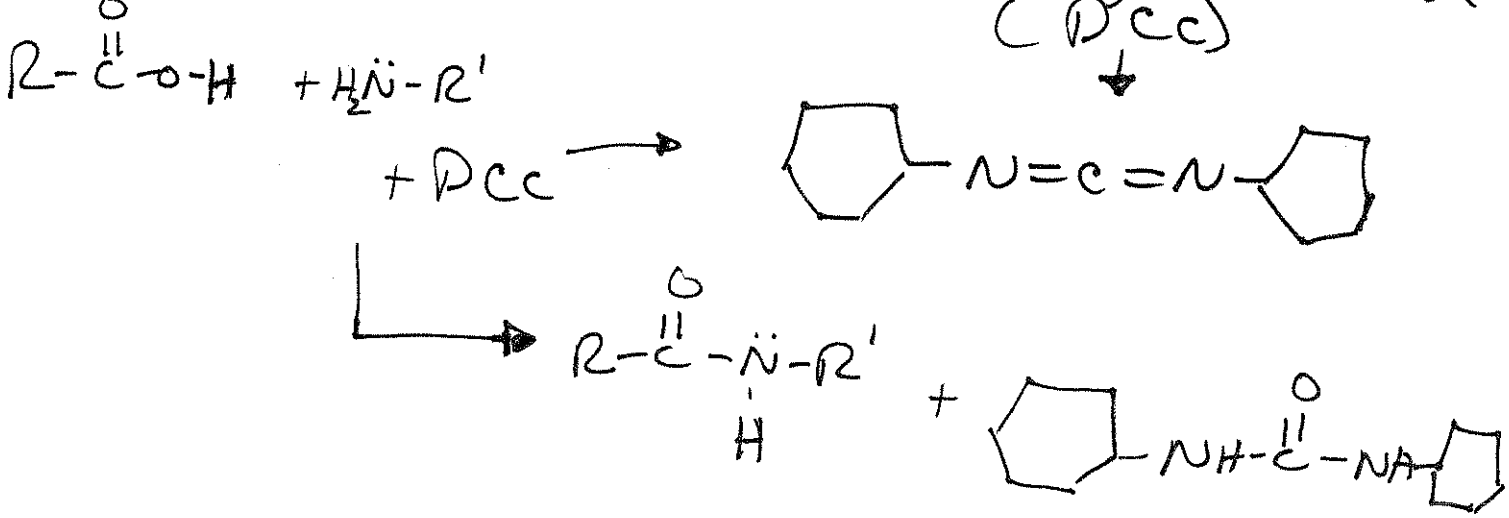


- Remember, earlier it was stated, in order make the desired Phe-Val in high yield we need to do two things:
  1) use appropriate protecting groups, +
  2) convert the carboxylic acid to a more reactive functional group so a peptide bond is more readily formed.

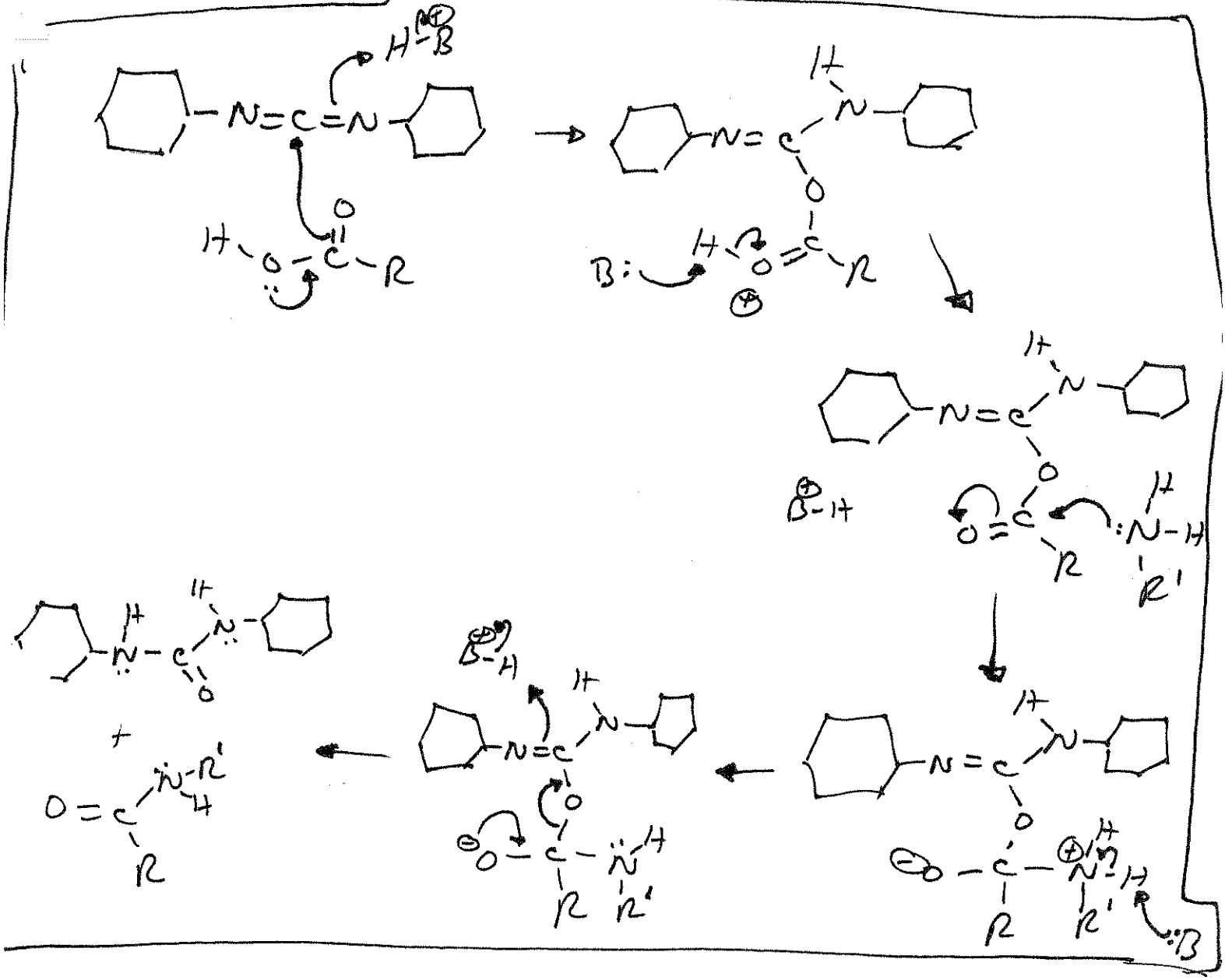
⇓

Use dicyclohexylcarbodiimide (DCC)

General Rxn



Mechanism of Carboxylic Acid Activation by DCC



- Can also make carboxylic acid more reactive by making The p-nitrophenyl ester (see pg 635 in text)

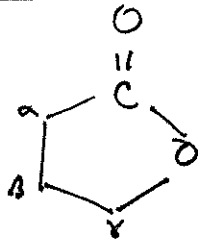
(or)

esters of N-hydroxysuccinimide (see p 636 in text) which will react more readily with The amine

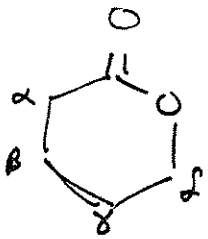
ICIP - BIOLOGICAL TRANSESTERIFICATIONS ← Don't need to know! (15-24)
(p 637 + top of p 638 in text)

(However, you could still read This section if you like)

Lactones → cyclic esters

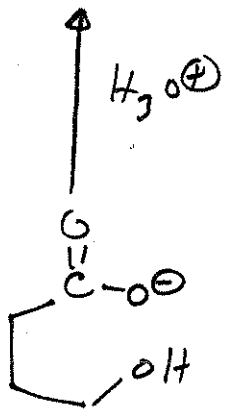


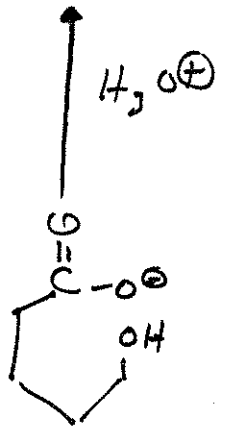
γ-lactone



δ-lactone

- These types of lactones form spontaneously under acidic conditions (via Fischer esterification)





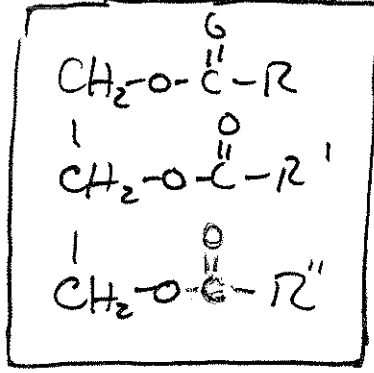
- pg 625-626
  - → esters in the perfume industry
  - → esters in antibiotics (macrolide antibiotics)
- pg 48 in lab manual
  - → esters in flavorings

Lipids, Fats, Oils and Waxes

Lipids – all are long chain hydrocarbons (rings or long chains) that many times have other functional groups present as well

examples: α + β-carotene, Vit. A, Vit. D, Vit. E & K, cholesterol

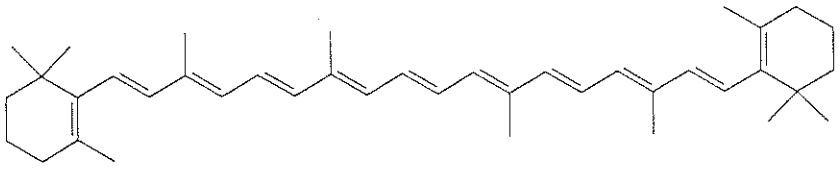
- Some lipids are **FATS & OILS** (triglycerides)
  - → glycerol + long chain carboxylic acids



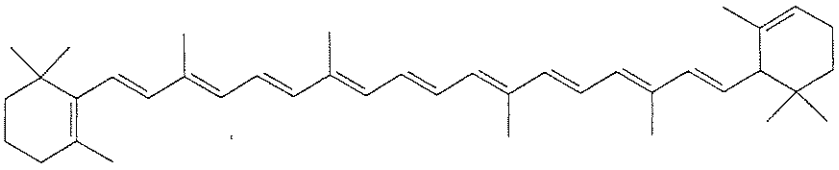
R, R' + R'' = long chain

Oils = R's are mostly unsaturated

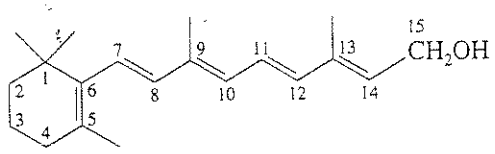
Fats = R's mostly (if not all) saturated



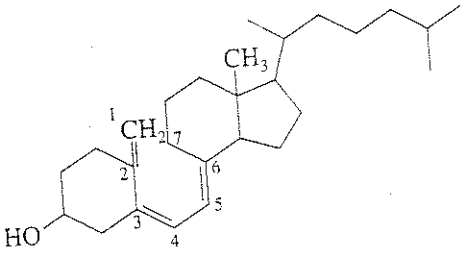
β-carotene



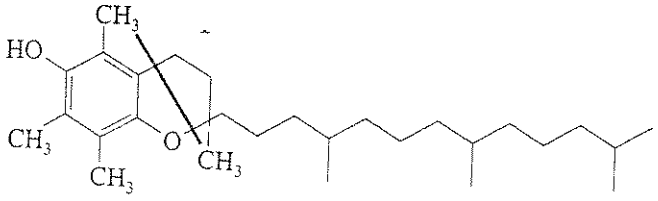
α-carotene



vitamin A
retinol



vitamin D_3
cholecalciferol

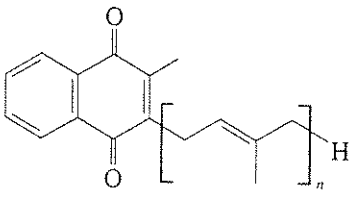


a trimethylhydroquinone

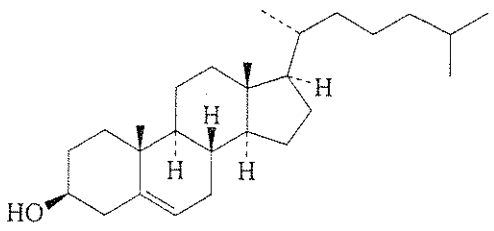
diterpenoid side chain

a phytyl group

α-tocopherol, or vitamin E

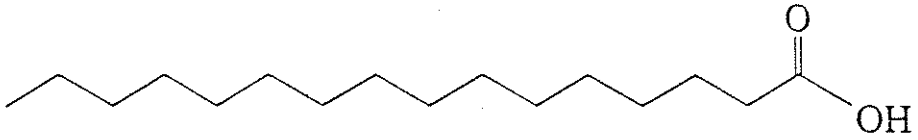


vitamin K_2
menaquinones
$n = 6, 7, 8,$ or 9

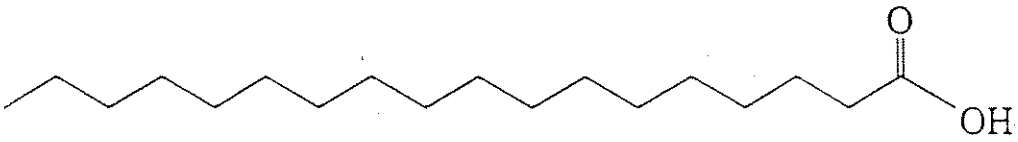


cholesterol

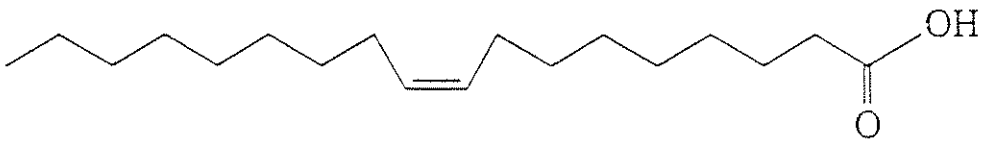
15-26



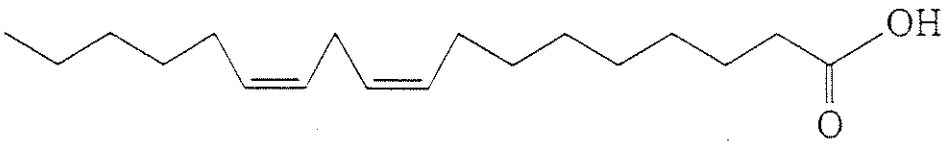
palmitic acid
hexadecanoic acid
mp 62.9 °C



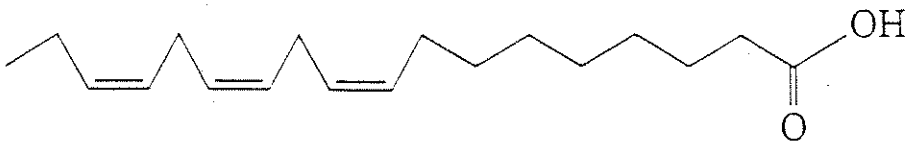
stearic acid
octadecanoic acid
mp 69.6 °C



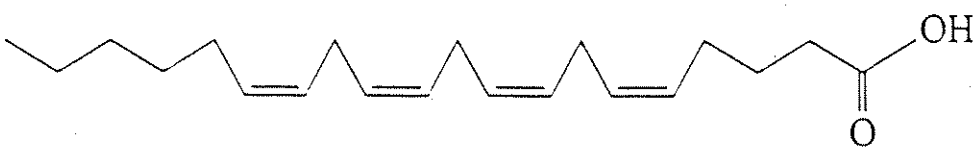
oleic acid
(*Z*)-9-octadecenoic acid
mp 13 °C



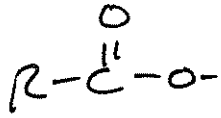
linoleic acid
(9*Z*, 12*Z*)-9,12-octadecadienoic acid
mp −5 °C



linolenic acid
(9*Z*, 12*Z*, 15*Z*)-9,12,15-octadecatrienoic acid
mp −16 °C



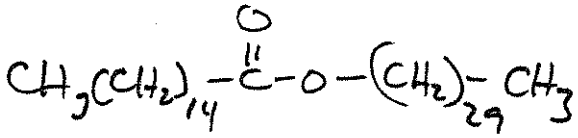
Waxes → long chain esters



R + R' = very long chain

R = 16-36 carbons

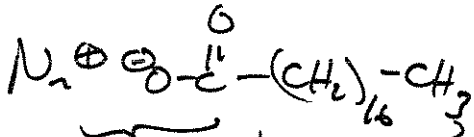
ex:



← in beeswax

Surface Active Compounds: Soap

Soap = $K^{\oplus}$ or $Na^{\oplus}$ salt of a fatty acid



← sodium stearate

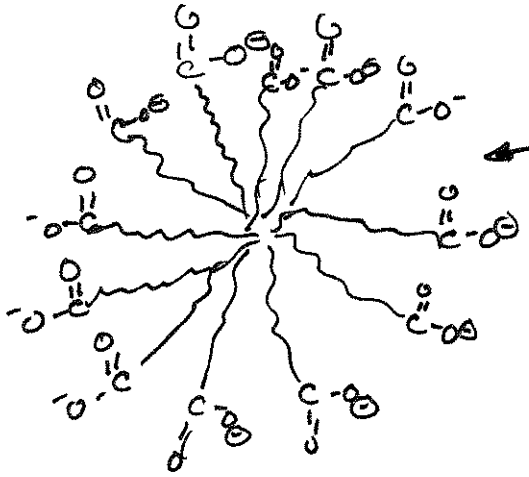
hydrophilic head

hydrophobic tail (lipophilic – attracted to oils)

- Soap in water (at certain concentrations) → forms micelles

micelles ⇒ 100-200 soap molecules with their polar "heads" on the surface + their "tails" enclosed within

bath tub ring → Mg^{2+} + Ca^{2+} salts of carboxylic acids, ppt out + leave soap scum



grease – (hydrophobic) dissolves inside soap micelle