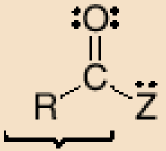
CARBOXYLIC ACIDS AND DERIVATIVES

Chapters 20, 21
Organic Chemistry, *8th Edition*
John McMurry

CARBOXYLIC ACIDS DERIVATIVES

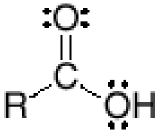
General structure



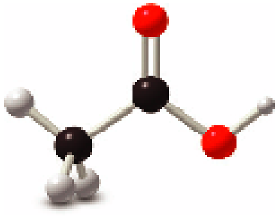
acyl group

Z = electronegative atom

Z = OH

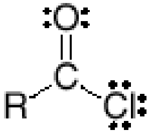


carboxylic acid

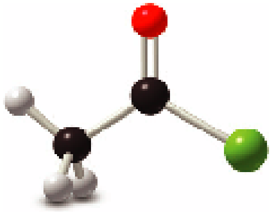


R = CH_3
acetic acid

Z = Cl

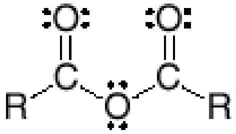


acid chloride

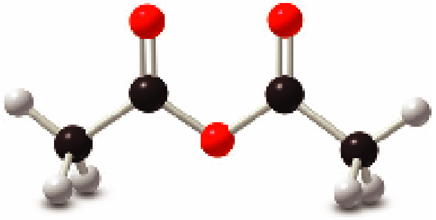


R = CH_3
acetyl chloride

Z = OCOR



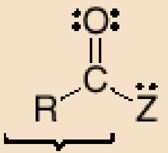
anhydride



R = CH_3
acetic anhydride

CARBOXYLIC ACID DERIVATIVES

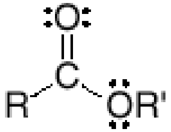
General structure



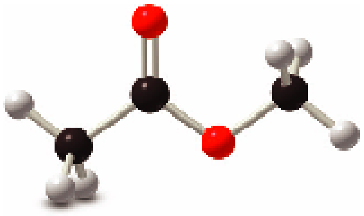
acyl group

Z = electronegative atom

Z = OR'

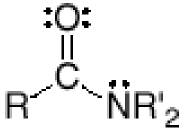


ester

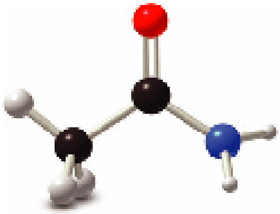


R = R' = CH_3
methyl acetate

Z = NR'_2



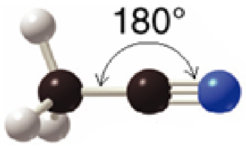
R' = H or alkyl
amide



R = CH_3, R' = H
acetamide

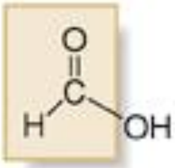
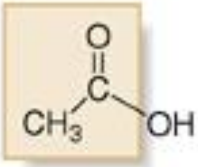
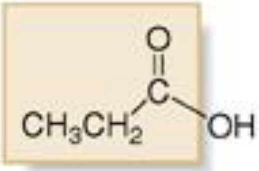
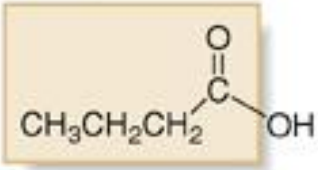
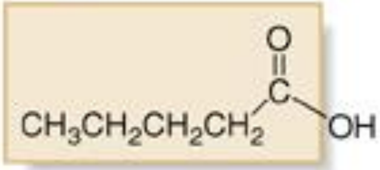
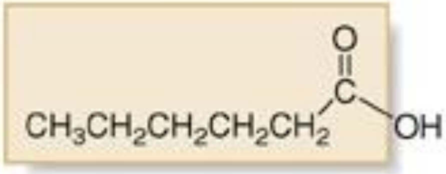
$R-C\equiv N$

nitrile



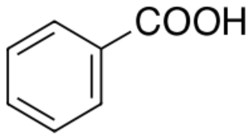
R = CH_3
acetonitrile

CARBOXYLIC ACIDS - NOMENCLATURE

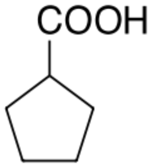
	IUPAC	**COMMON NAMES**	
	Acido metanoico	acido formico	
	Acido etanoico	acido acetico	
	Acido propanoico	acido propionico	προτοσ πιον (primo grasso)
	Acido butanoico	acido butirrico	
	Acido pentanoico	acido valerico	
	Acido esanoico	acido caproico	

CARBOXYLIC ACIDS
IUPAC NOMENCLATURE

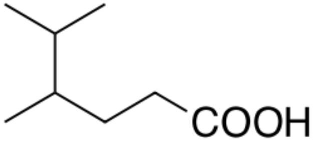
heptanoic acid



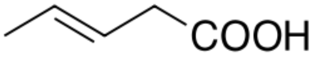
benzoic acid



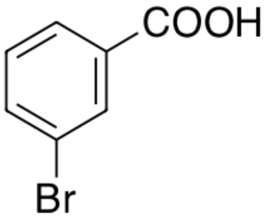
cyclopentane carboxylic acid



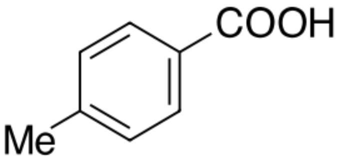
4,5-dimethyl hexanoic acid



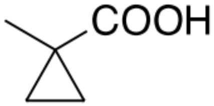
3-pentenoic acid



3-bromobenzoic acid



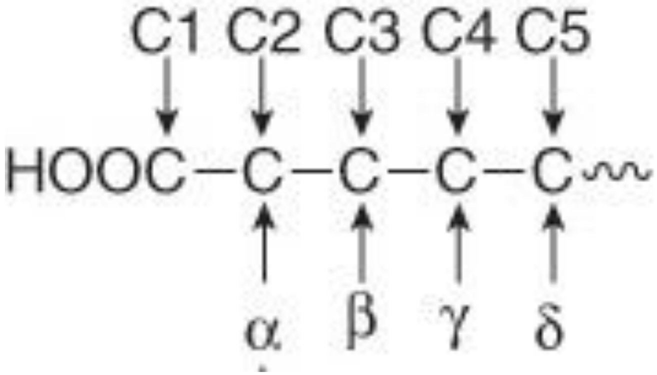
p-toluic acid

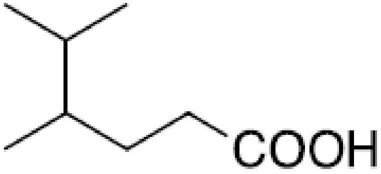


1-methyl-cyclopropanecarboxylic acid

NOMENCLATURE-COMMON NAMES

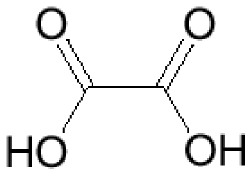
- In common names often greek letters are used to define the substituents position.



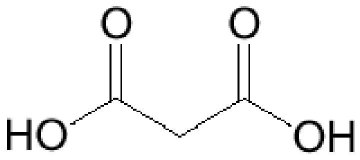


4,5-dimethyl hexanoic acid
γ,δ-dimethyl hexanoic acid

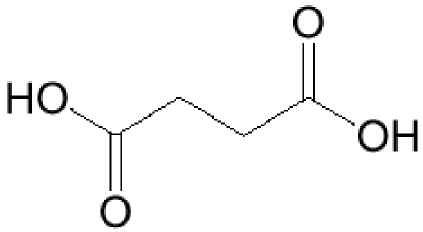
NOMENCLATURE-POLYIACIDS



oxalic acid
(ethanedioic acid)



malonic acid
(propanedioic acid)

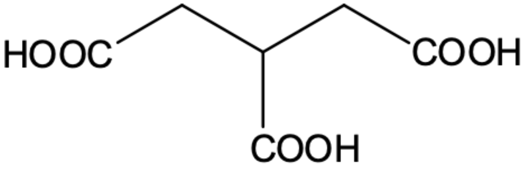


succinic acid
(butanedioic acid)

Oxalis acetosella

Malon

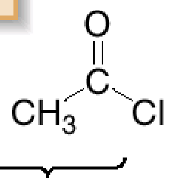
Succinum (ambra)



propane-1,2,3-tricarboxylic acid

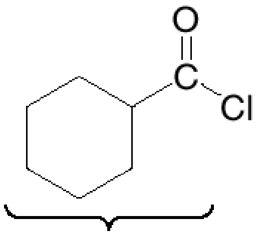
ACID CHLORIDES: NOMENCLATURE

Naming acid chlorides



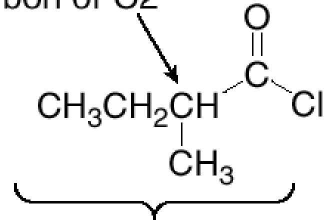
derived from
acet*ic acid*

acetyl chloride



derived from
cyclohexane*carboxylic acid*

cyclohexanecarbonyl chloride

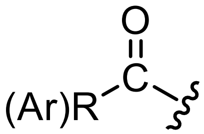


α carbon or C2

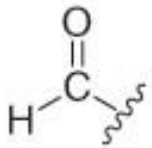
derived from
2-methylbutano*ic acid*
or
α-methylbutyr*ic acid*

2-methylbutanoyl chloride
or
α-methylbutyryl chloride

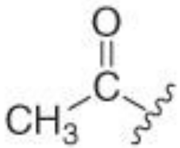
ACYL GROUPS



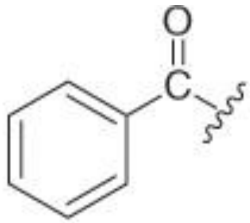
generic acyl group



formyl group

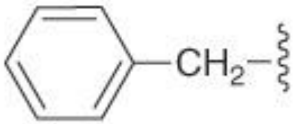


acetyl group



benzoyl group

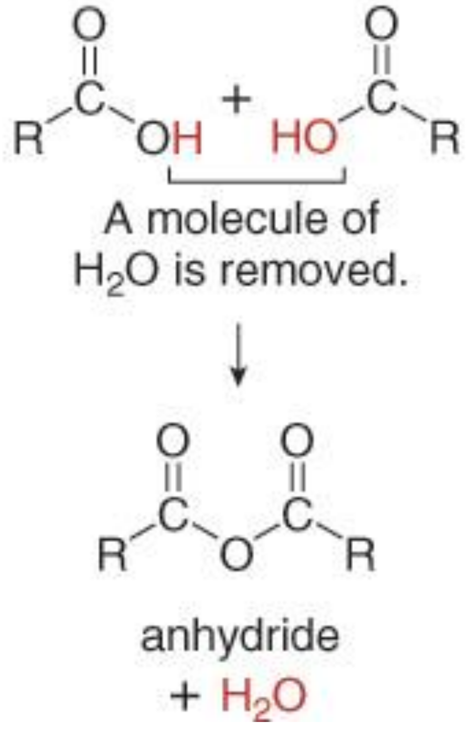
Do not confuse a **benzyl** group with a **benzoyl** group.



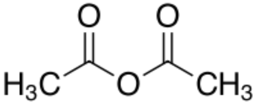
benzy*l* group

ANHYDRIDES

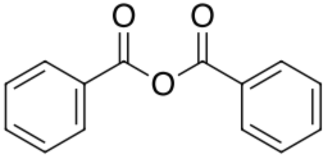
The word anhydride means *without water.* Removing one molecule of water from two molecules of carboxylic acid forms an anhydride.



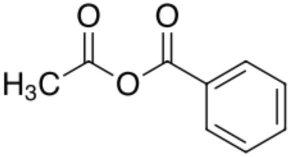
ANHYDRIDES: NOMENCLATURE



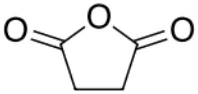
acetic anhydride



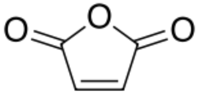
benzoic anhydride



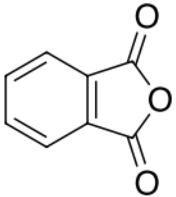
acetic benzoic anhydride



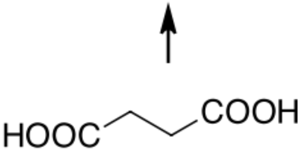
succinic anhydride



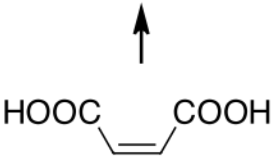
maleic anhydride



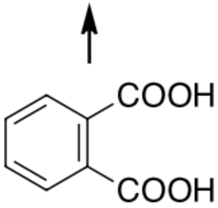
phthalic anhydride



succinic acid

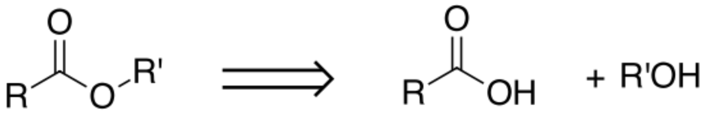


maleic acid

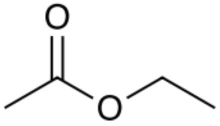


phthalic acid

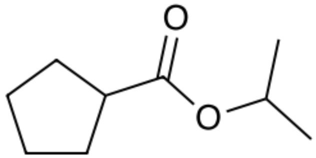
ESTERS: NOMENCLATURE



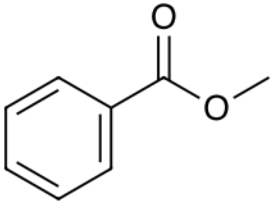
Esters are the (formal) condensation products of an acid and an alcohol



Ethyl acetate

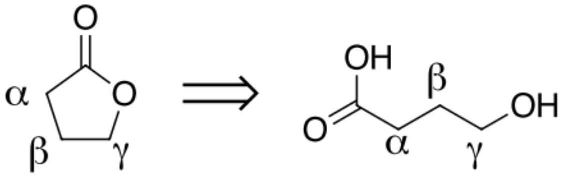


Isopropyl cyclopentanecarboxylate



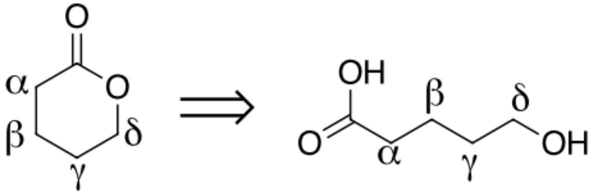
Methyl benzoate

Lactones are cyclic esters



Butyrolactone
(a γ-lactone)

4-hydroxybutanoic acid
(a γ-hydroxyacid)



Valerolactone
(a δ-lactone)

5-hydroxypentanoic (valeric) acid
(a δ-hydroxyacid)

INTERESTING ESTERS

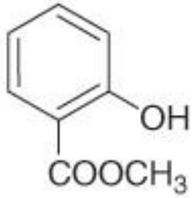
Many low molecular weight esters have pleasant and very characteristic odors.

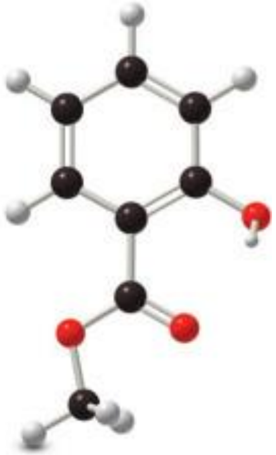
$CH_3COOCH_2CH_2CH(CH_3)_2$

isoamyl acetate
odor of banana

$CH_3CH_2CH_2COOCH_2CH_3$

ethyl butyrate
odor of pineapple



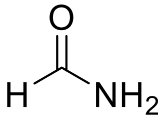


methyl salicylate
oil of wintergreen

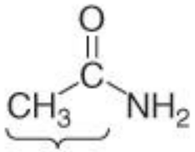
AMIDES: NOMENCLATURE

All 1° amides are named by replacing the *-ic acid*, *-oic acid*, or *-ylic acid* ending with the suffix amide.

Naming 1° amides



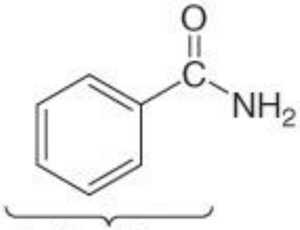
derived from
formic (methanoic) acid
formamide
(methanamide)



derived from
acet*ic acid*

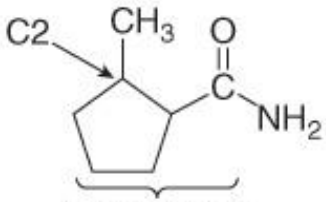
acetamide

ethanamide



derived from
benz*oic acid*

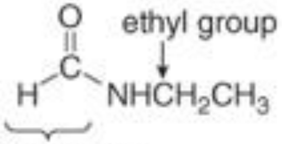
benzamide



derived from
2-methylcyclopentanecarbox*ylic acid*

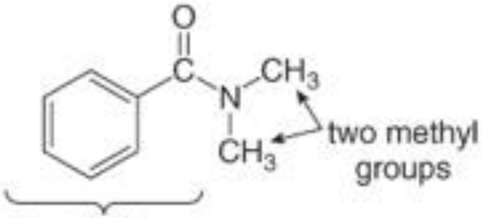
2-methylcyclopentanecarboxamide

2° and 3° amides are named as N-substituted (2°) or N,N-disubstituted (3°) derivatives of 1° amides



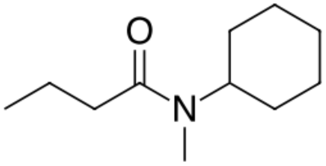
derived from
form*ic acid*

N-ethylformamide



derived from
benz*oic acid*

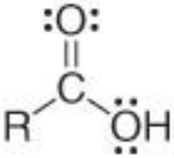
N,*N*-dimethylbenzamide



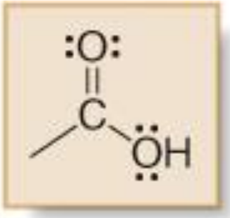
derived from
butanoic acid

N-cyclohexyl-*N*-methylbutanamide

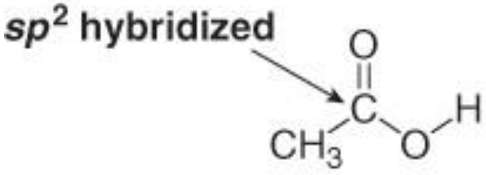
CARBOXYLIC ACIDS - STRUCTURE AND BONDING



carboxylic acid

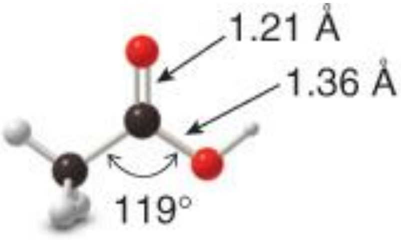


carboxy group



acetic acid

=



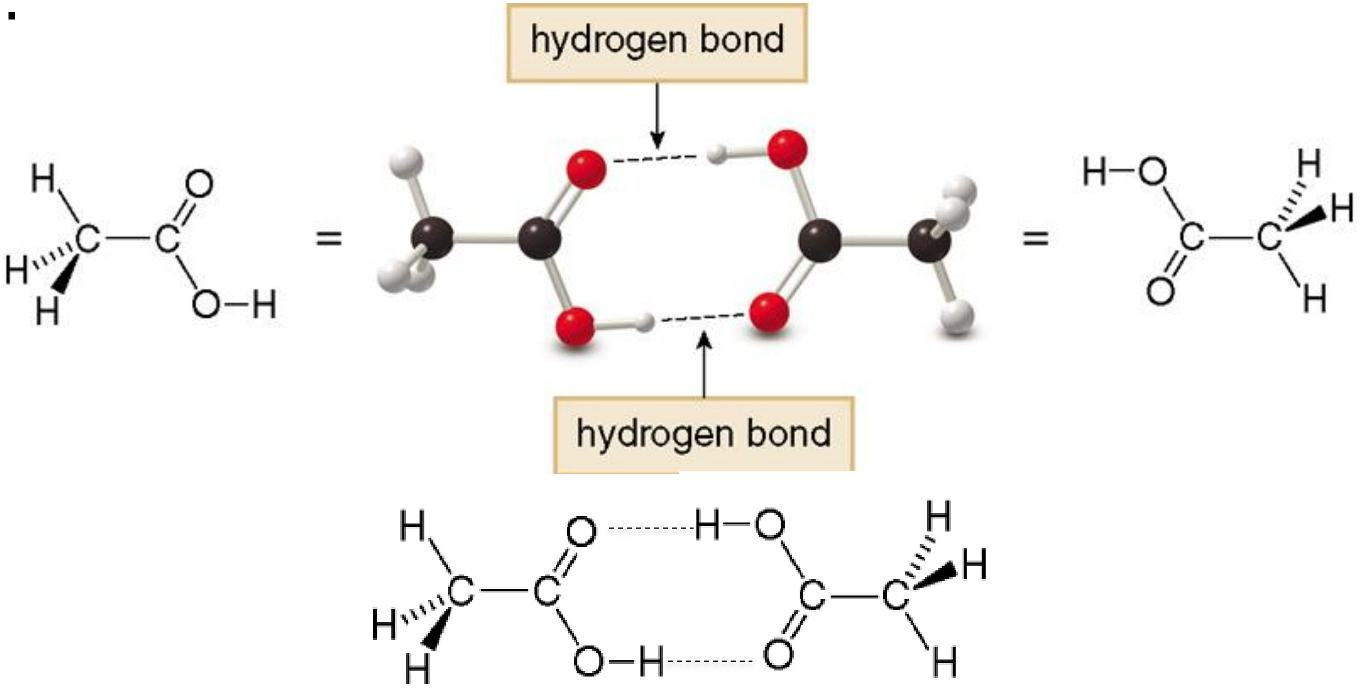
The C=O is shorter than the C−O.

PHYSICAL PROPERTIES

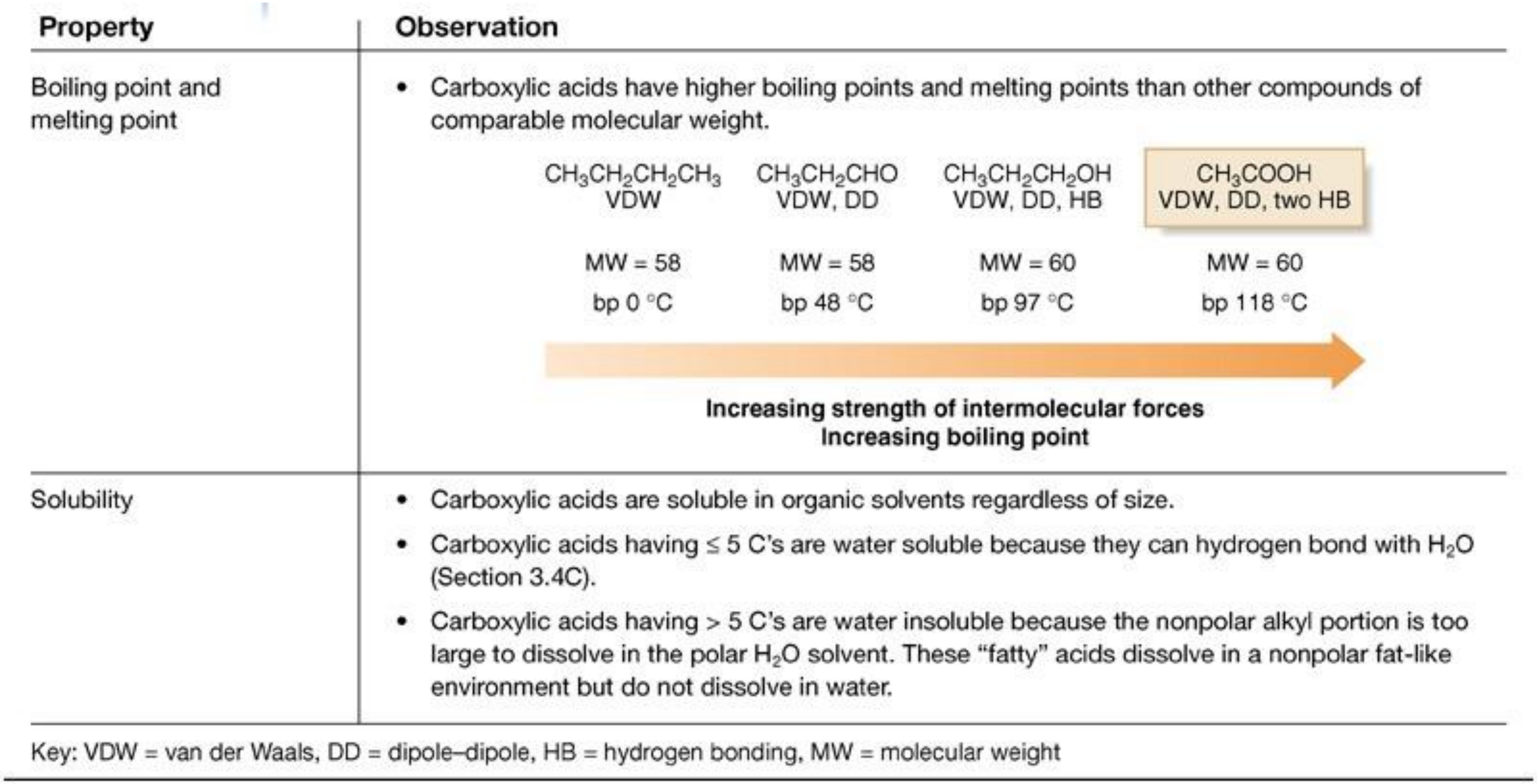
- Carboxylic acids exhibit dipole-dipole interactions because they have polar C—O and O—H bonds.

- They also exhibit intermolecular hydrogen bonding.

- In the gas phase and in apolar solvents, carboxylic acids often exist as dimers held together by two intermolecular hydrogen bonds.



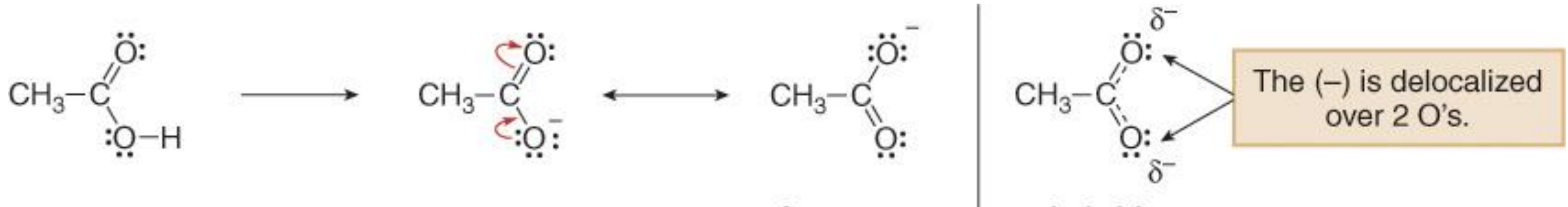
PHYSICAL PROPERTIES



Property	**Observation**
Boiling point and melting point	- Carboxylic acids have higher boiling points and melting points than other compounds of comparable molecular weight. $CH_3CH_2CH_2CH_3$ VDW MW = 58 bp 0 °C CH_3CH_2CHO VDW, DD MW = 58 bp 48 °C $CH_3CH_2CH_2OH$ VDW, DD, HB MW = 60 bp 97 °C CH_3COOH VDW, DD, two HB MW = 60 bp 118 °C **Increasing strength of intermolecular forces** **Increasing boiling point**
Solubility	- Carboxylic acids are soluble in organic solvents regardless of size. - Carboxylic acids having ≤ 5 C's are water soluble because they can hydrogen bond with H_2O (Section 3.4C). - Carboxylic acids having > 5 C's are water insoluble because the nonpolar alkyl portion is too large to dissolve in the polar H_2O solvent. These "fatty" acids dissolve in a nonpolar fat-like environment but do not dissolve in water.

Key: VDW = van der Waals, DD = dipole–dipole, HB = hydrogen bonding, MW = molecular weight

ACIDITY OF CARBOXYLIC ACIDS



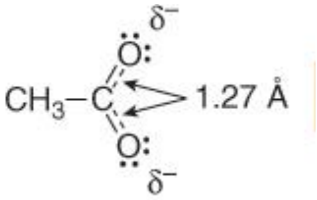
The (–) is delocalized over 2 O's.

acetic acid

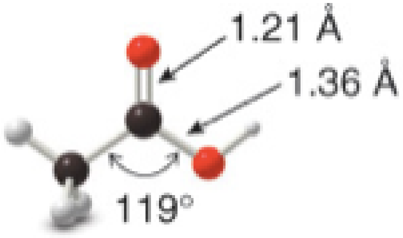
two resonance structures for acetate, the conjugate base

hybrid

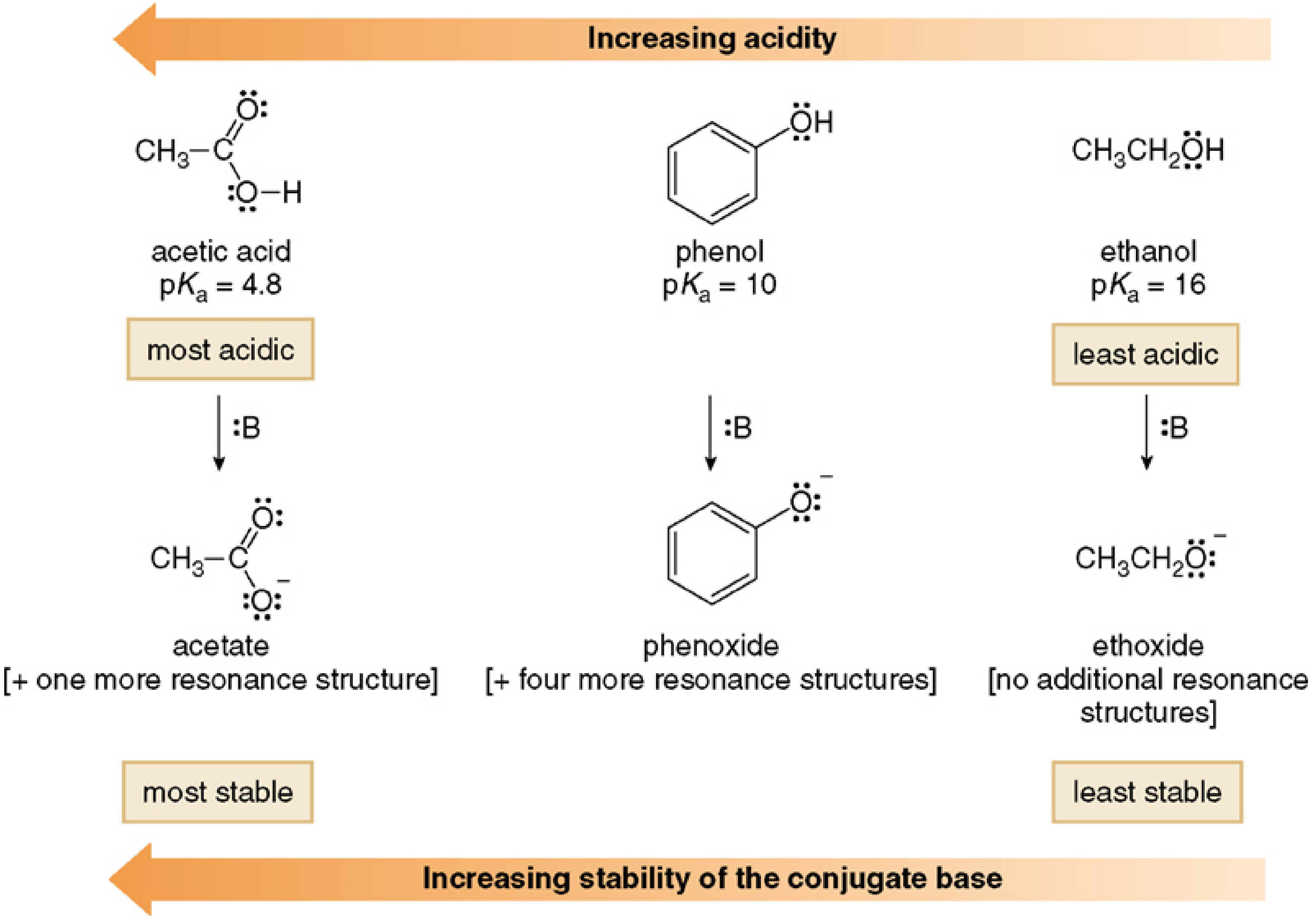
The acetate anion has two C—O bonds of equal length (1.27 Å) and intermediate between the length of a C—O single bond (1.36 Å) and C=O (1.21 Å).



acetate hybrid



CARBOXYLIC ACIDS—STRONG ORGANIC BRØNSTED-LOWRY ACIDS



acetic acid
pK_a = 4.8

most acidic

acetate
[+ one more resonance structure]

most stable

phenol
pK_a = 10

phenoxide
[+ four more resonance structures]

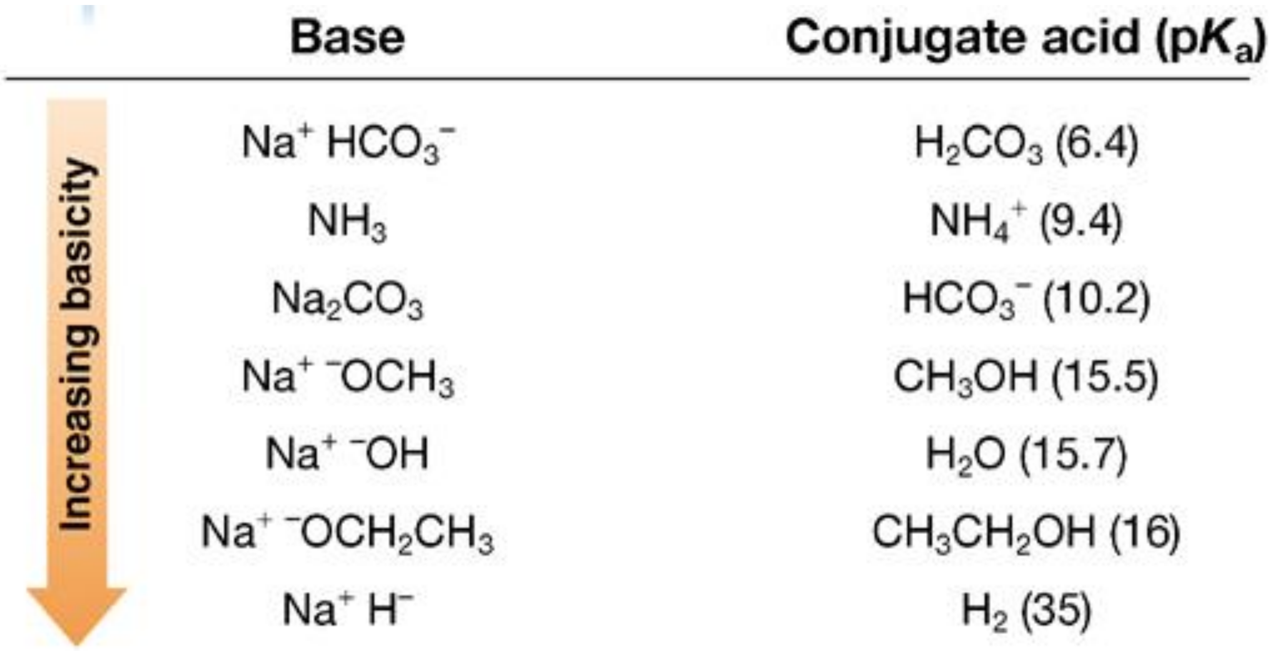
ethanol
pK_a = 16

least acidic

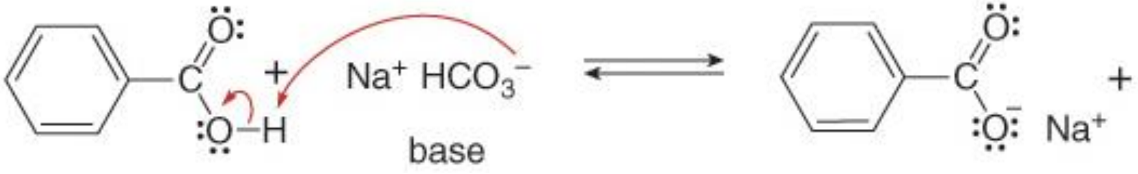
ethoxide
[no additional resonance structures]

least stable

CARBOXYLIC ACIDS—STRONG ORGANIC BRØNSTED-LOWRY ACIDS



Base	Conjugate acid (pK_a)
$Na^+ HCO_3^-$	H_2CO_3 (6.4)
NH_3	NH_4^+ (9.4)
Na_2CO_3	HCO_3^- (10.2)
$Na^+ \,^-OCH_3$	CH_3OH (15.5)
$Na^+ \,^-OH$	H_2O (15.7)
$Na^+ \,^-OCH_2CH_3$	CH_3CH_2OH (16)
$Na^+ H^-$	H_2 (35)



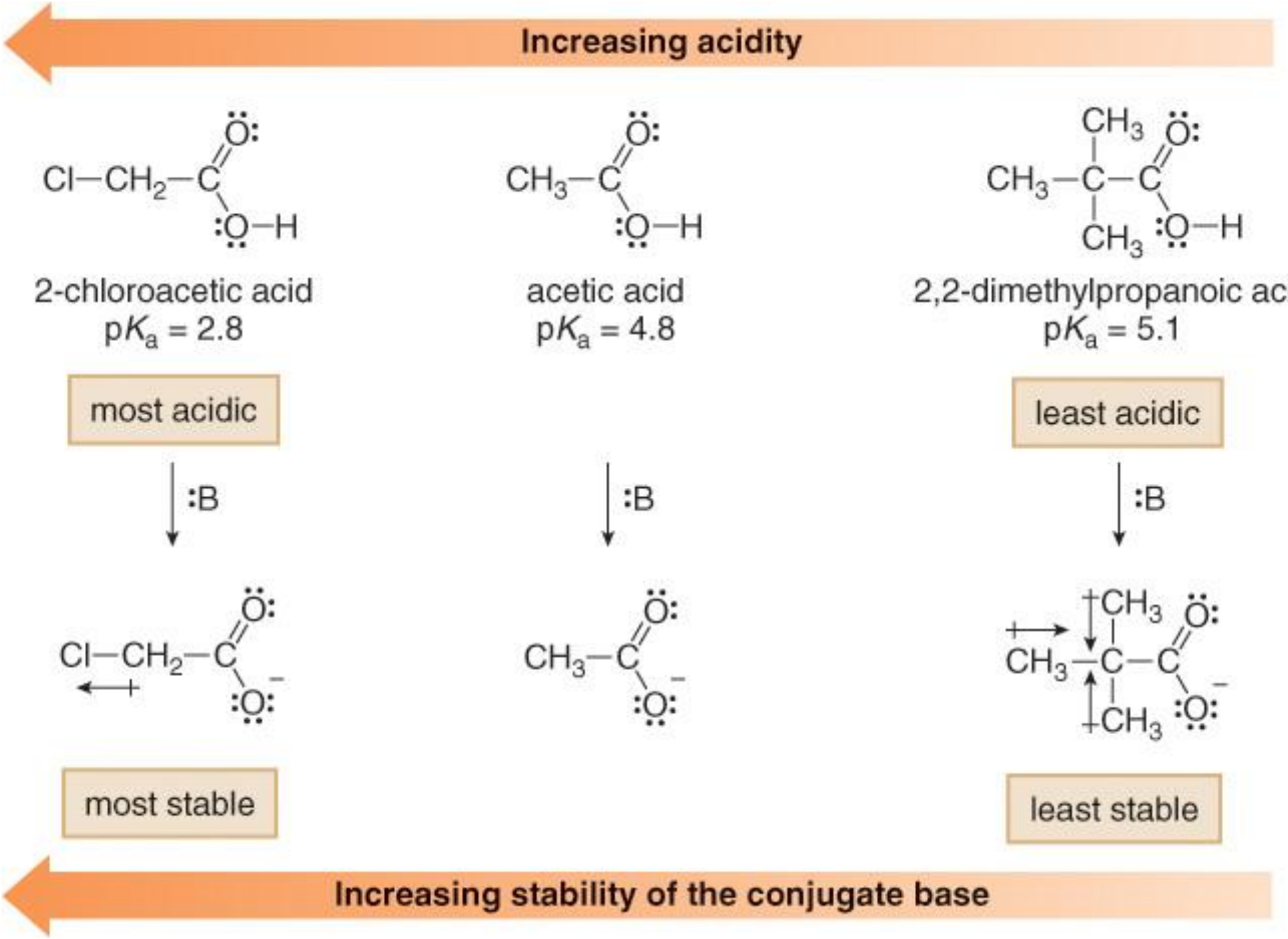
H_2CO_3

acido benzoico
Acido più forte
pKa = 4.2

Acido più debole
pKa = 6.4

THE INDUCTIVE EFFECT IN ALIPHATIC CARBOXYLIC ACIDS

- **Electron-withdrawing groups stabilize a conjugate base, making a carboxylic acid more acidic.**
- **Electron-donating groups destabilize the conjugate base, making a carboxylic acid less acidic.**



Increasing acidity

2-chloroacetic acid
pK_a = 2.8
most acidic

acetic acid
pK_a = 4.8

2,2-dimethylpropanoic acid
pK_a = 5.1
least acidic

most stable

least stable

Increasing stability of the conjugate base

THE INDUCTIVE EFFECT IN ALIPHATIC CARBOXYLIC ACIDS

- **The larger the number of electronegative substituents, the stronger the acid.**

$ClCH_2{-}COOH$
pK_a = 2.8

$Cl_2CH{-}COOH$
pK_a = 1.3

$Cl_3C{-}COOH$
pK_a = 0.9

Increasing acidity
Increasing number of electronegative Cl atoms

- **The more electronegative the substituent, the stronger the acid.**

$ClCH_2{-}COOH$
pK_a = 2.8

$FCH_2{-}COOH$
pK_a = 2.6

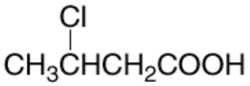
stronger acid

F is more electronegative than Cl.

- **The closer the electron-withdrawing group to the COOH, the stronger the acid.**

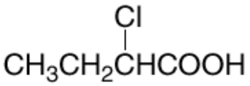
$ClCH_2CH_2CH_2COOH$

4-chlorobutanoic acid
pK_a = 4.5



$CH_3\overset{\overset{\textstyle Cl}{|}}{C}HCH_2COOH$

3-chlorobutanoic acid
pK_a = 4.1



$CH_3CH_2\overset{\overset{\textstyle Cl}{|}}{C}HCOOH$

2-chlorobutanoic acid
pK_a = 2.9

Increasing acidity
Increasing proximity of Cl to COOH

SUBSTITUTED BENZOIC ACIDS

D = Electron-donor group

This acid is less acidic than benzoic acid.

p$K_a > 4.2$

D destabilizes the carboxylate anion.

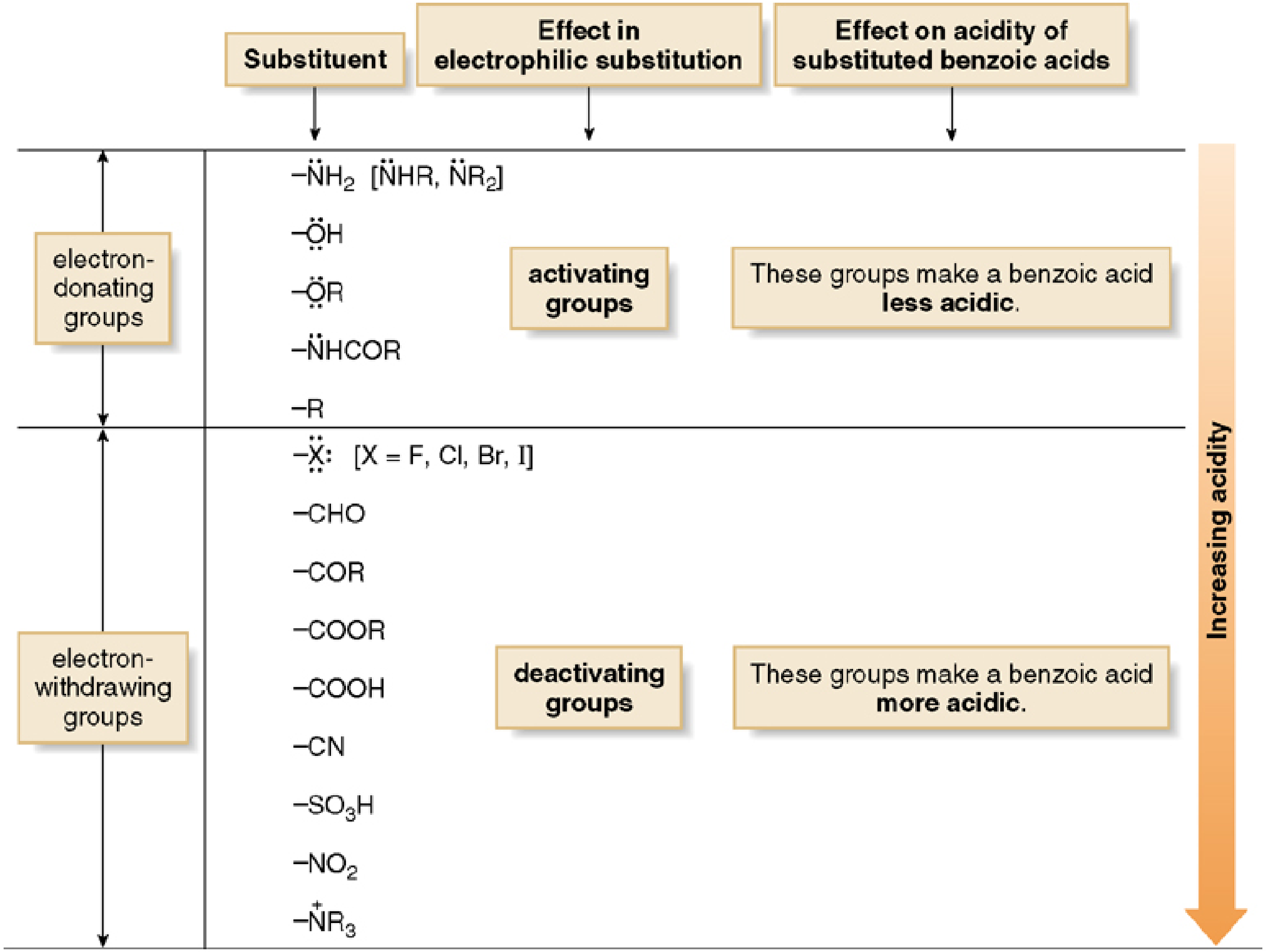
W = Electron-withdrawing group

This acid is more acidic than benzoic acid.

p$K_a < 4.2$

W stabilizes the carboxylate anion.

SUBSTITUTED BENZOIC ACIDS

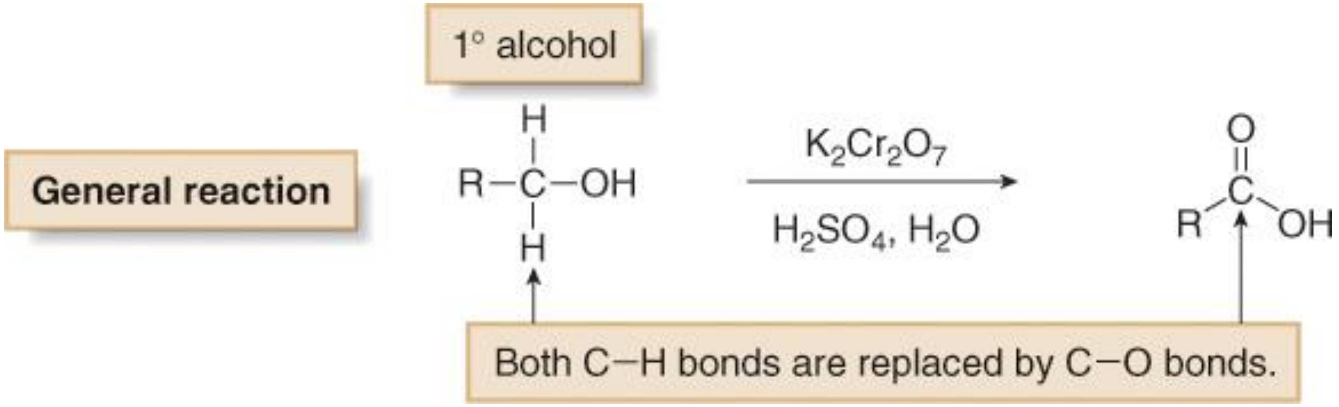


	Substituent	Effect in electrophilic substitution	Effect on acidity of substituted benzoic acids
electron-donating groups	$-\ddot{N}H_2$ [$\ddot{N}HR$, $\ddot{N}R_2$] $-\overset{..}{\underset{..}{O}}H$ $-\overset{..}{\underset{..}{O}}R$ $-\ddot{N}HCOR$ $-R$	**activating groups**	These groups make a benzoic acid **less acidic**.
electron-withdrawing groups	$-\overset{..}{\underset{..}{X}}:$ [X = F, Cl, Br, I] $-CHO$ $-COR$ $-COOR$ $-COOH$ $-CN$ $-SO_3H$ $-NO_2$ $-\overset{+}{N}R_3$	**deactivating groups**	These groups make a benzoic acid **more acidic**.

Increasing acidity

PREPARATION OF CARBOXYLIC ACIDS

[1] Oxidation of 1° alcohols

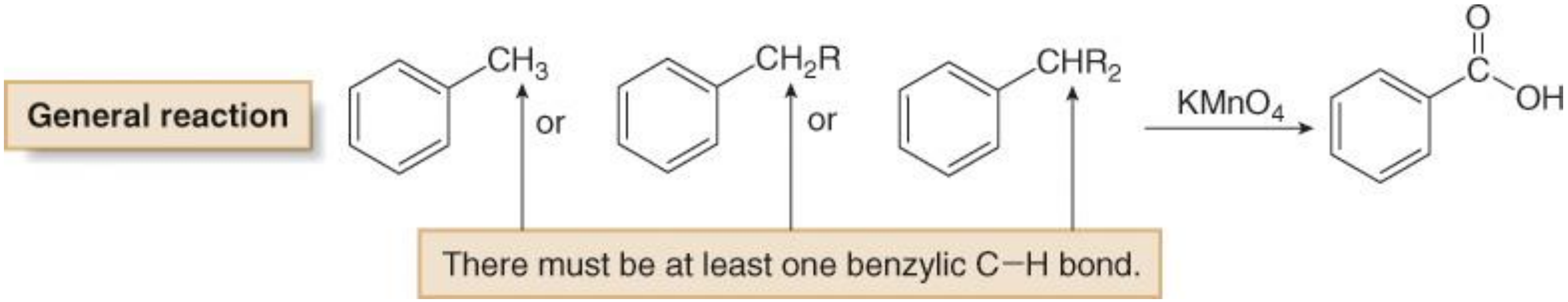


General reaction

1° alcohol

Both C–H bonds are replaced by C–O bonds.

[2] Oxidation of alkyl benzenes

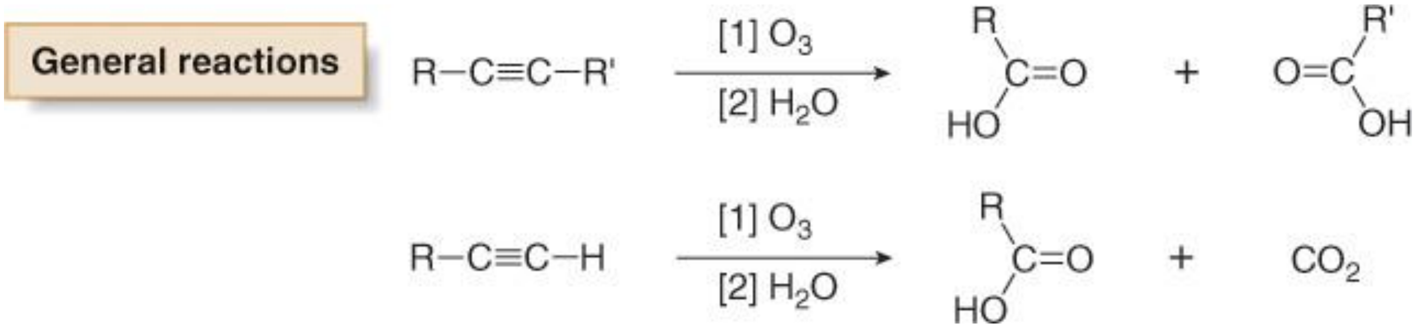


General reaction

There must be at least one benzylic C–H bond.

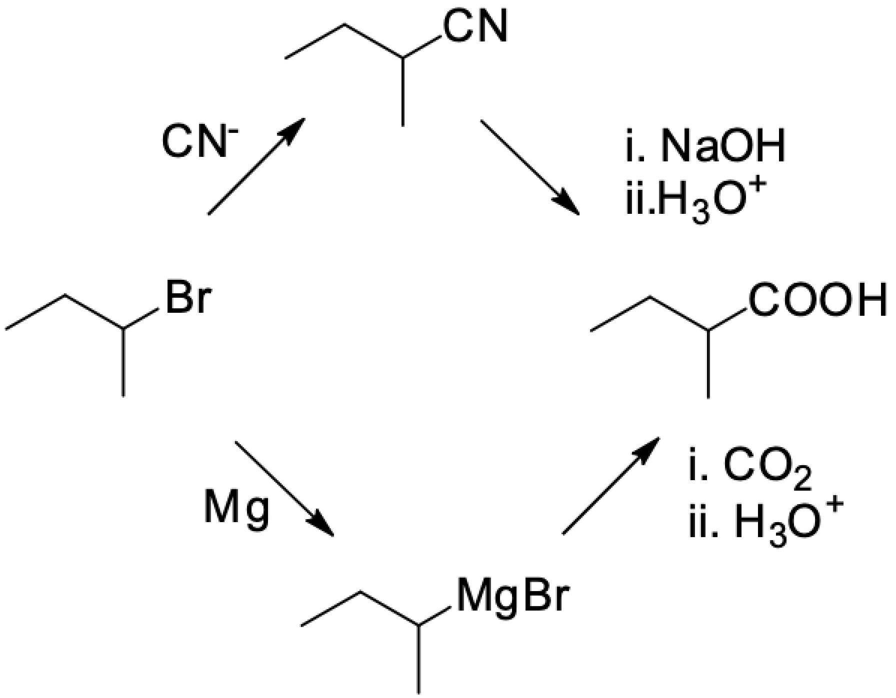
PREPARATION OF CARBOXYLIC ACIDS

[3] Oxidative cleavage of alkenes and alkynes

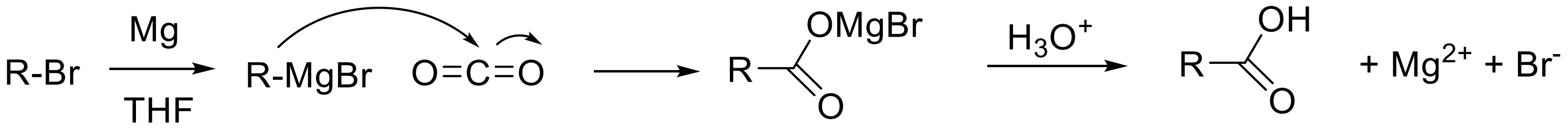


PREPARATION OF CARBOXYLIC ACIDS

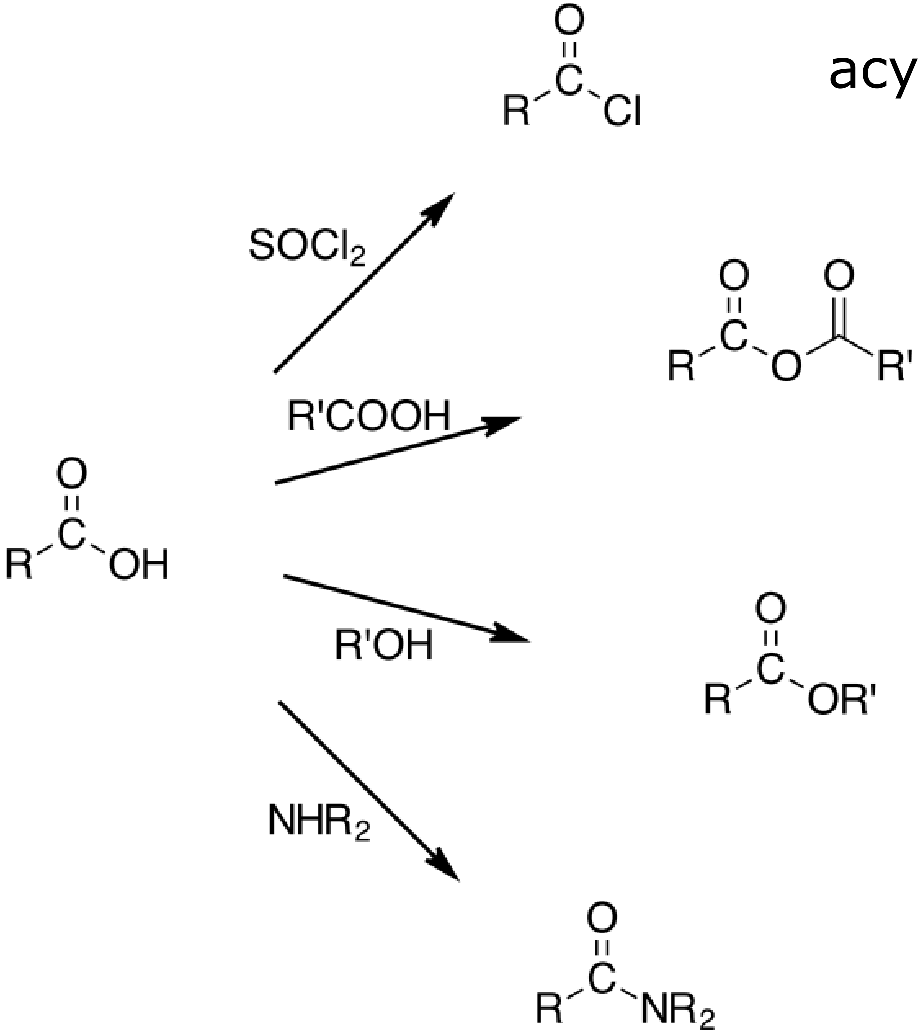
[4] From alkyl halides



Carbonatation (carboxylation) of Grignard reagents



REACTIONS OF CARBOXYLIC ACIDS



acyl chloride

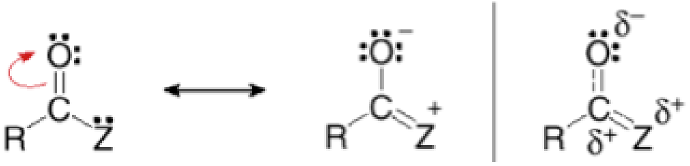
anhydride

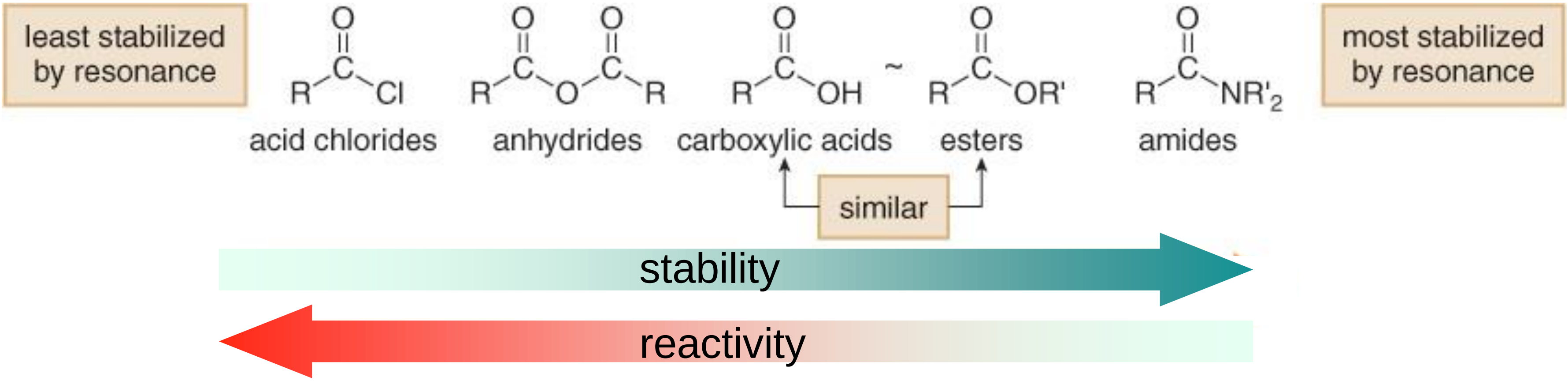
ester

amide

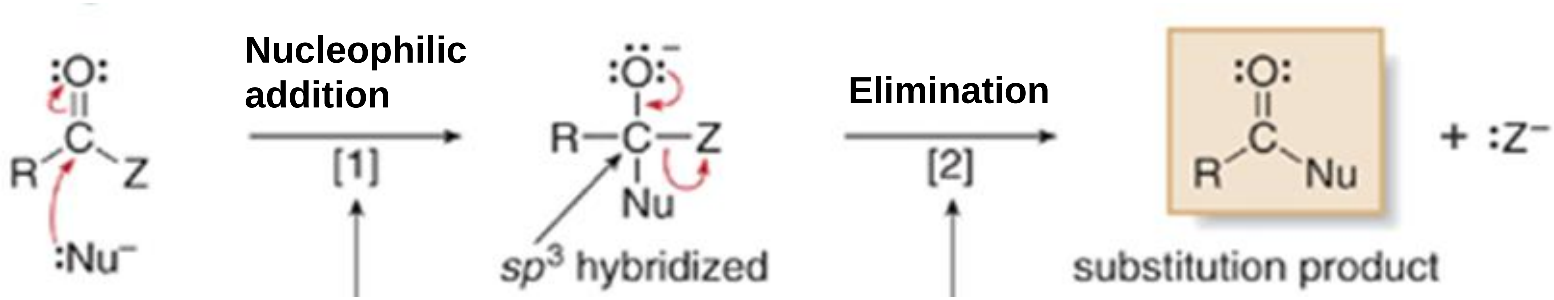
DERIVATIVES: STRUCTURE AND BONDING

- Three resonance structures stabilize carboxylic acid derivatives (RCOZ) by delocalizing electron density.





REACTION OF CARBOXYLIC ACID DERIVATIVES: NUCLEOPHILIC ACYL SUBSTITUTION

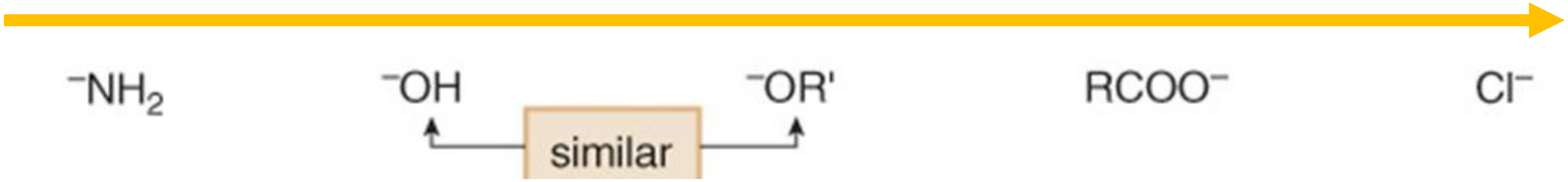


[Z = OH, Cl, OR, NH_2]

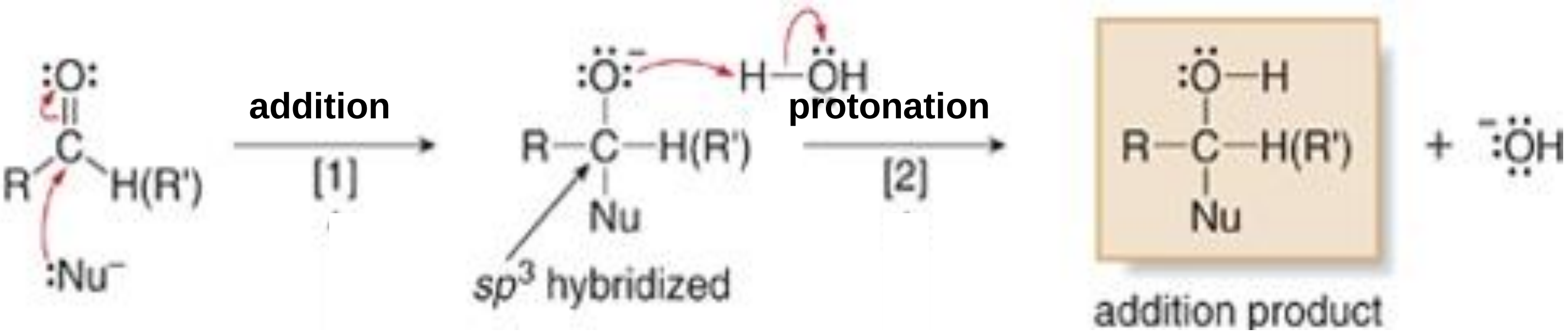
Z must be a better leaving group than Nu

Nucleophilic Acyl Substitution = Nucleophilic Addition + Elimination (S_NAE)

Leaving group ability

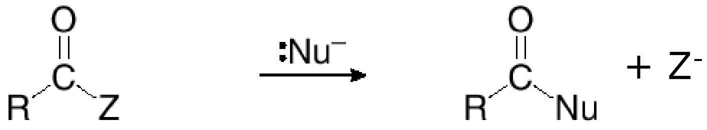


COMPARISON WITH NUCLEOPHILIC ADDITION TO CARBONYL COMPOUNDS



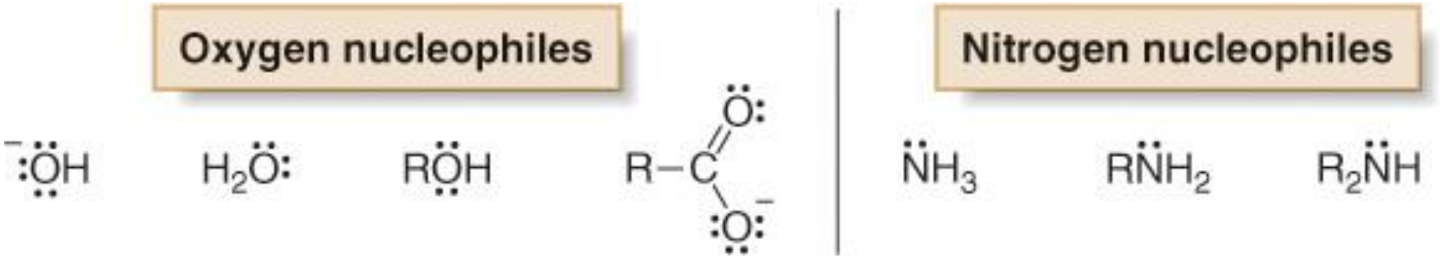
R'^- and H^- are not leaving group

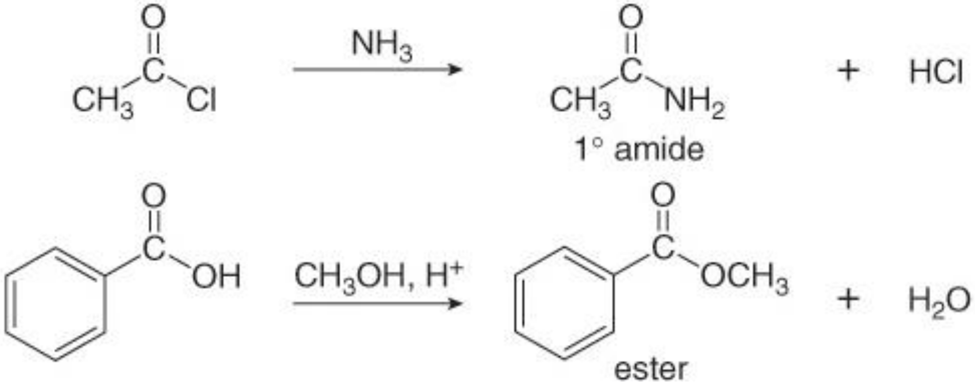
Nucleophilic Acyl Substitution



Z = OH, Cl, OR, NH_2

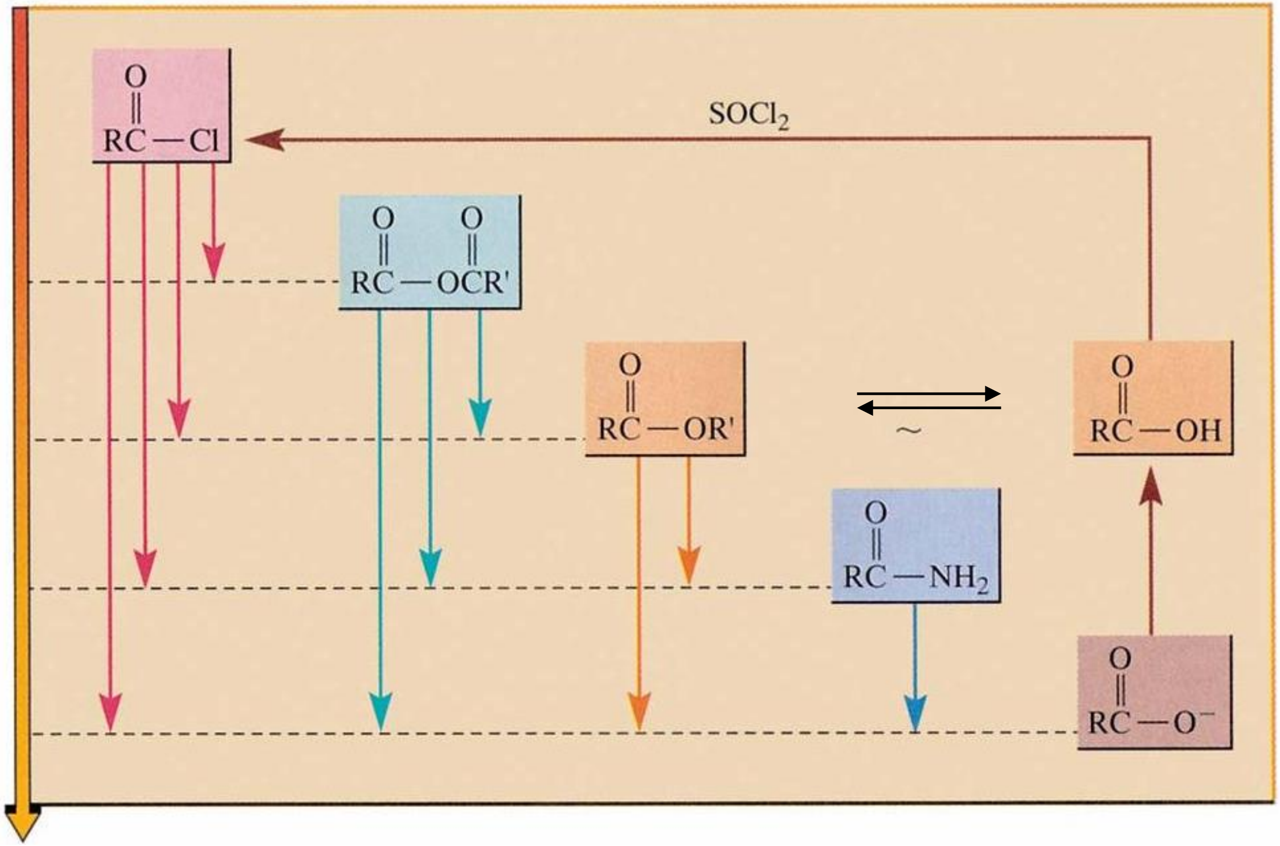
The nucleophiles



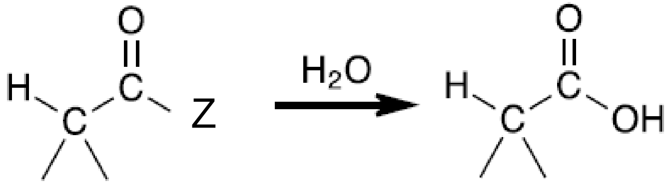


The leaving group is substituted by the nucleophile. With neutral nucleophiles a proton is removed to give a neutral product.

Nucleophilic Acyl Substitution



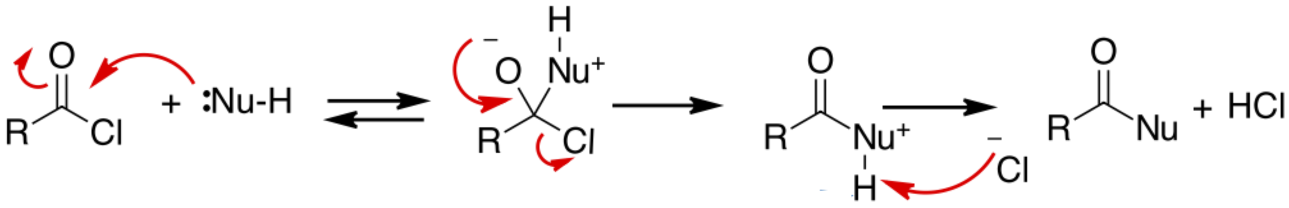
Interconvertion of carboxylic acid derivatives: a more reactive derivative can be transformed in a less reactive. For example, all derivatives can be hydrolyzed to carboxylic acids.

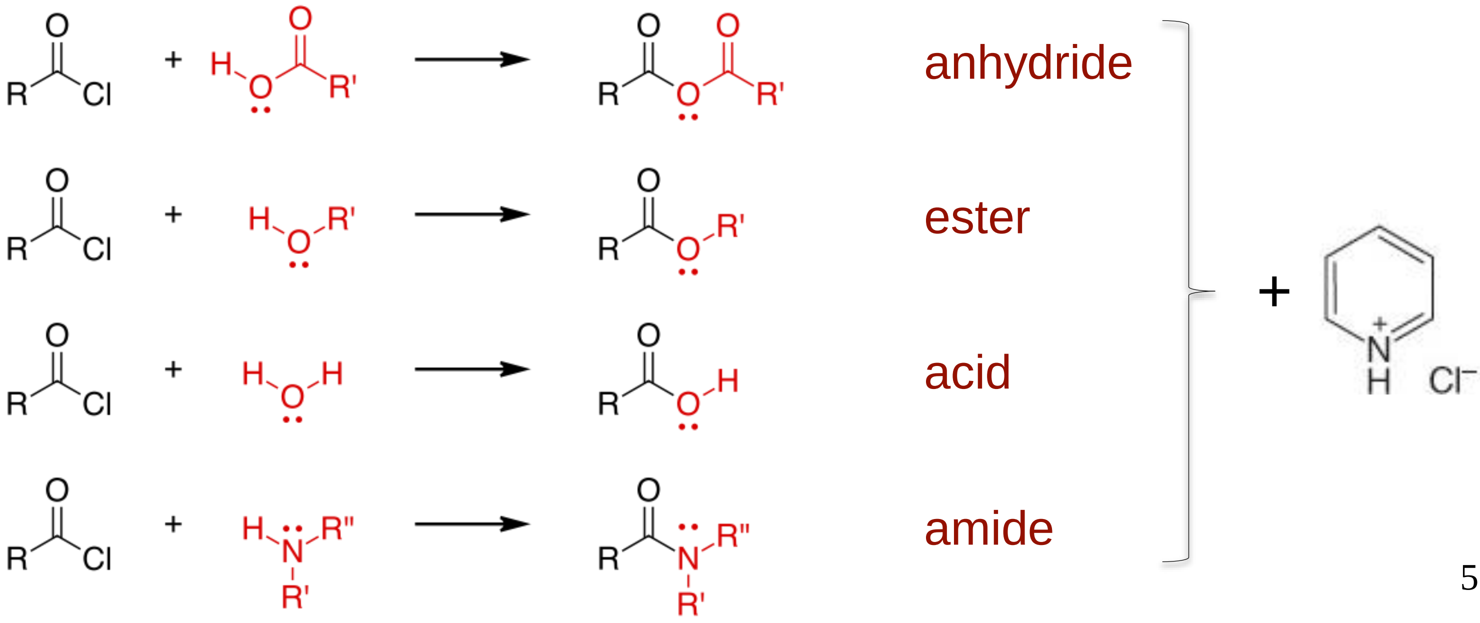


Z = Cl, OCOR, OR, NR_2

ACID CHLORIDES: REACTIONS

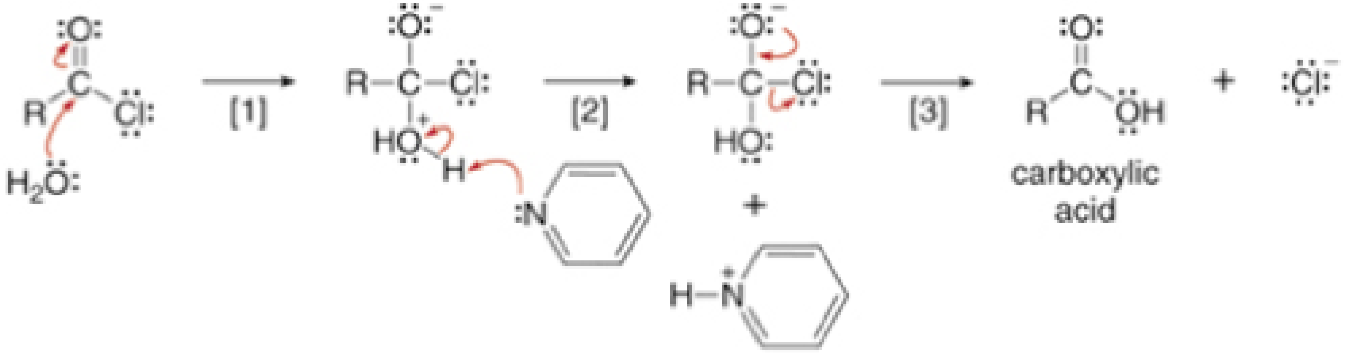
- Acyl chlorides are the most reactive among carboxylic acid derivatives
- A weak, non nucleophilic, base like pyridine is often added to the reaction mixture to remove the byproduct HCl.
- Acyl chlorides are easily decomposed by water
- Catalysis is not required



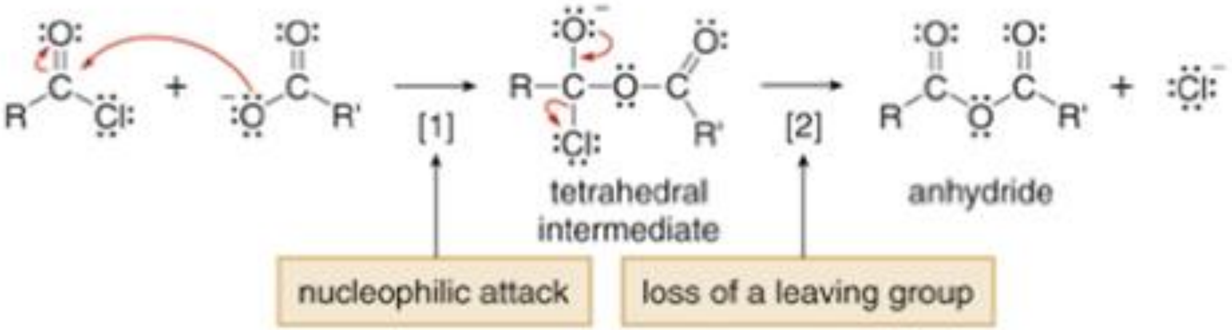


ACID CHLORIDES: REACTIONS

Hydrolysis:

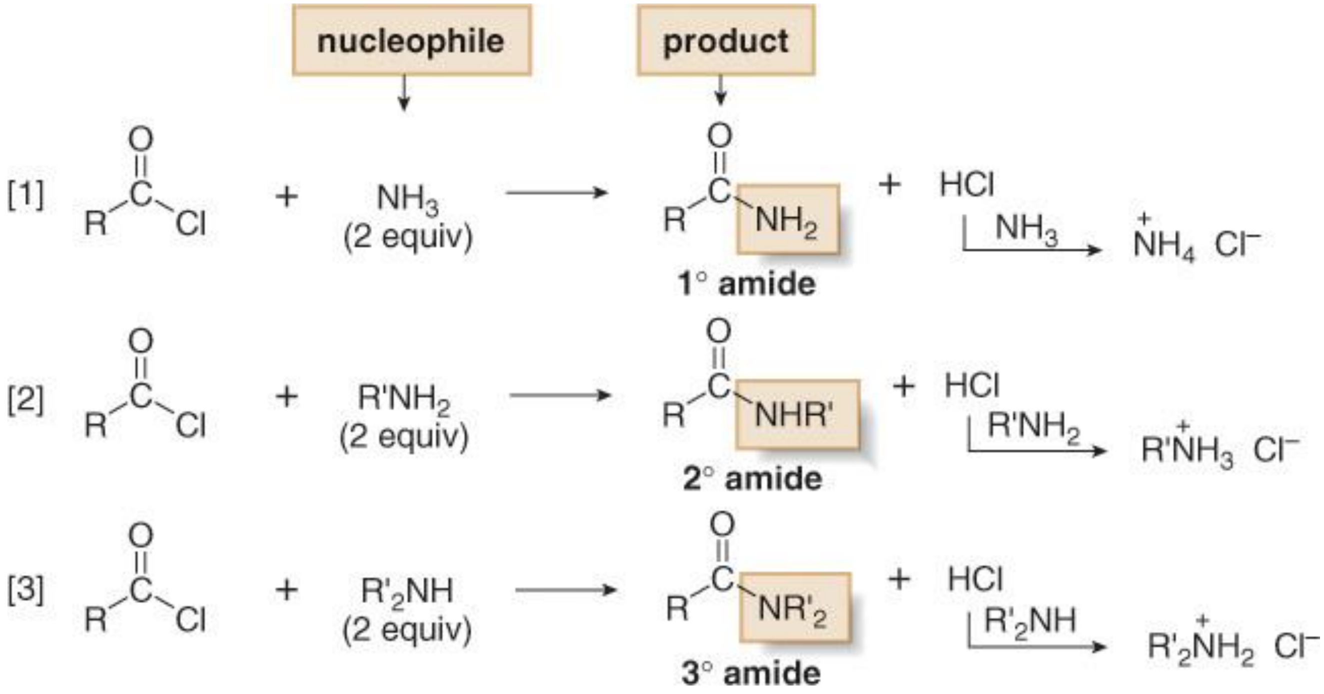


Formation of anhydrides:



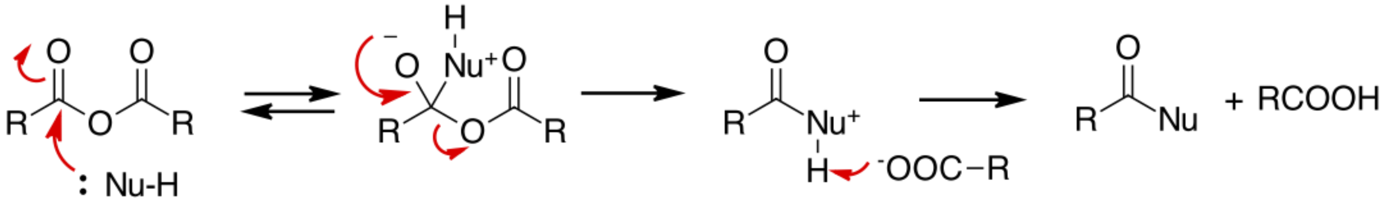
Reaction of Acid Chlorides with amines

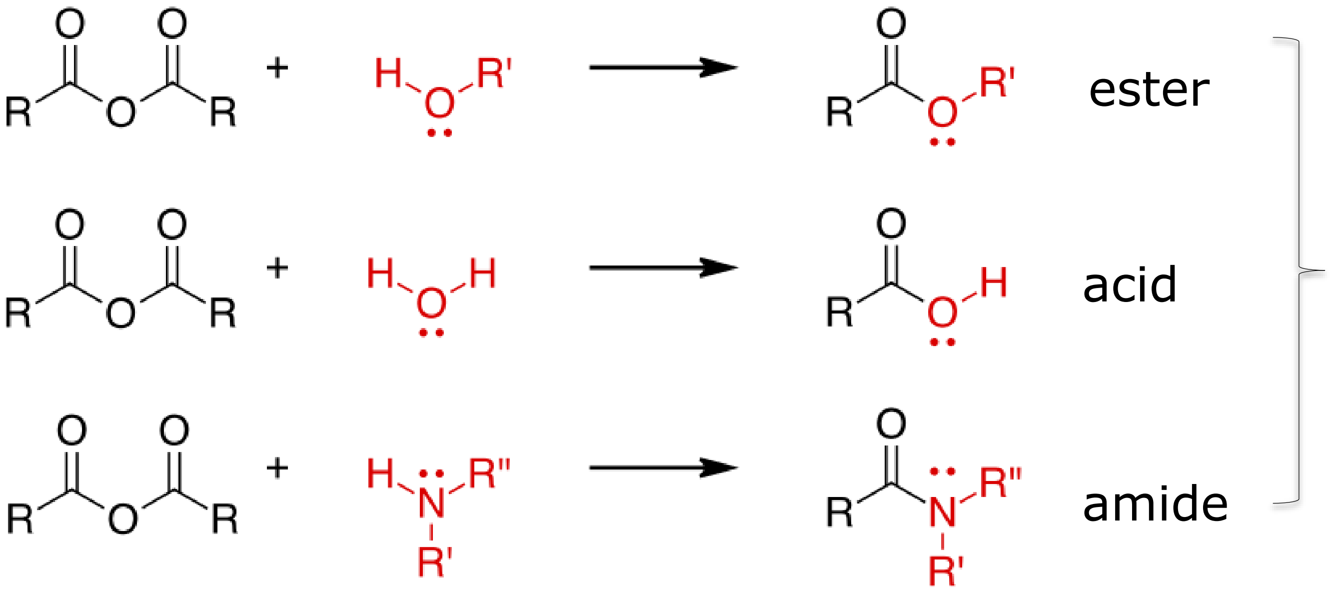
- Acid chlorides react with ammonia and 1° and 2° amines to form 1°, 2° and 3° amides respectively.
- Two equivalents of NH_3 or amine are used.
- One equivalent acts as the nucleophile to replace Cl, while the other reacts as a base with the HCl by-product to form an ammonium salt.



ANHYDRIDES: REACTIONS

- Anhydrides are strong acylating agents
- A weak acid is formed as by-product.
- Anhydrides are readily decomposed by water.
- Catalysis is not required.





ester

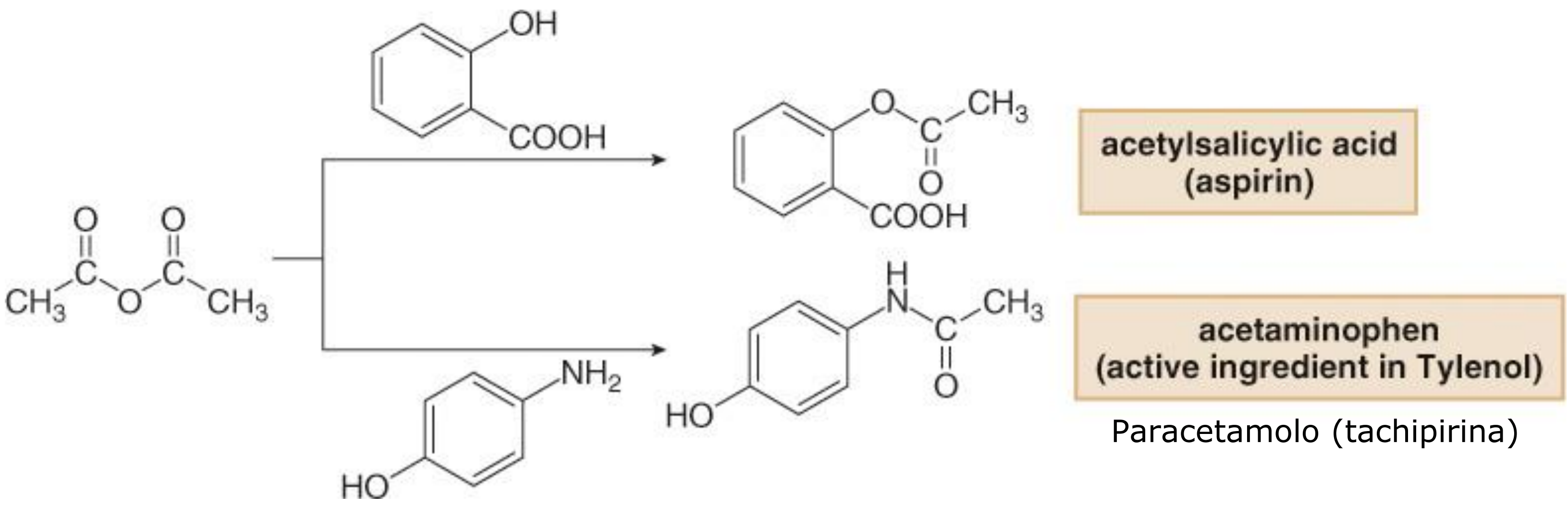
acid

amide

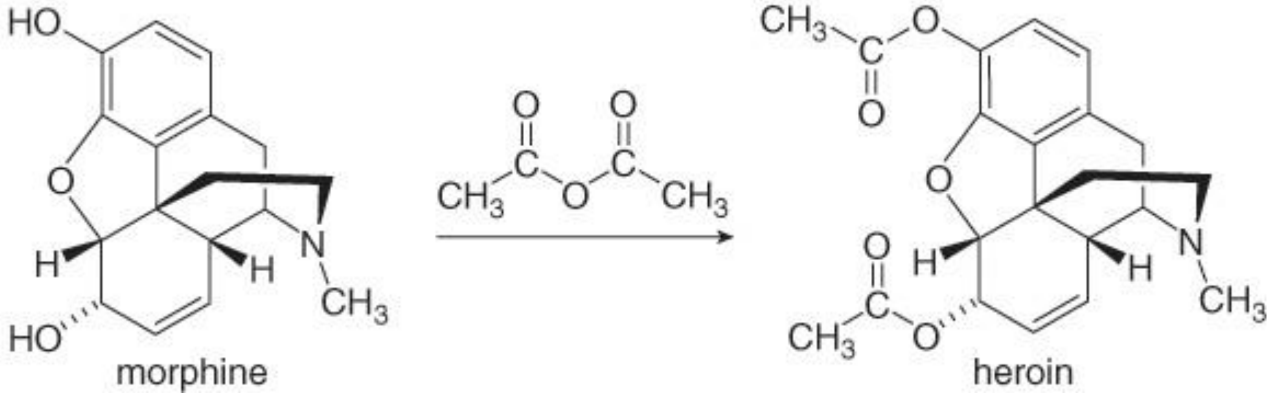
+ RCOOH

REACTIONS OF ANHYDRIDES

Anhydrides are very common acylating agents for the synthesis of esters and amides:

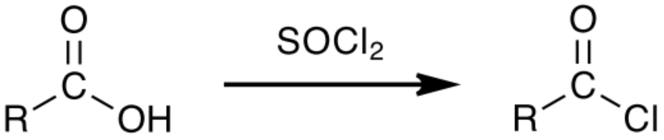


Paracetamolo (tachipirina)

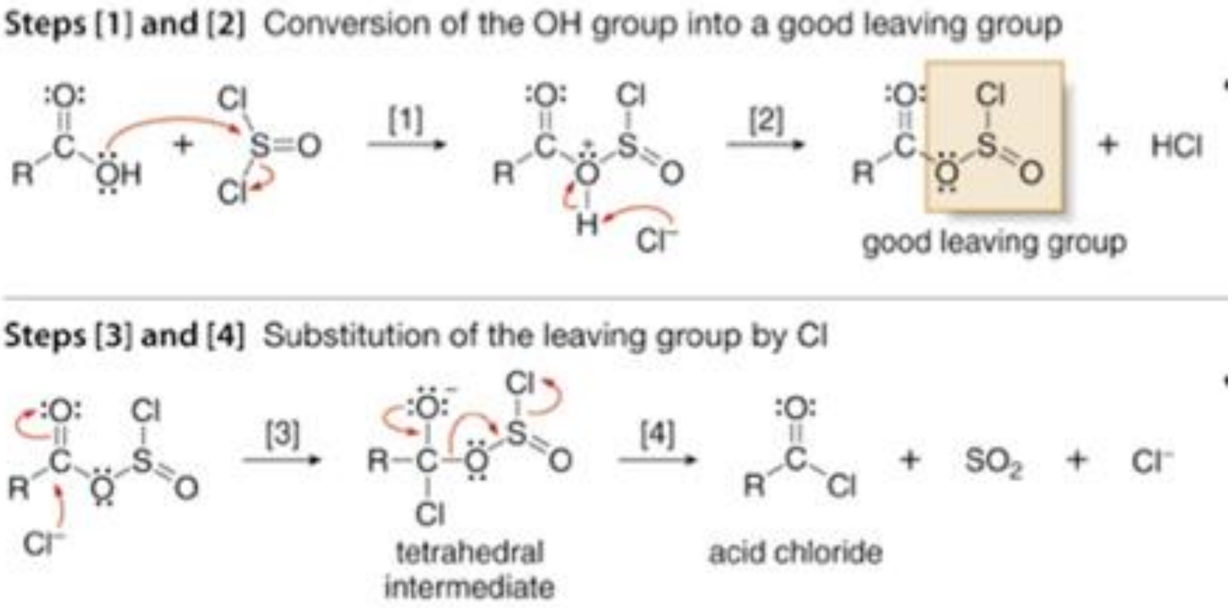


REACTION OF CARBOXYLIC ACIDS: SYNTHESIS OF ACYL CHLORIDES

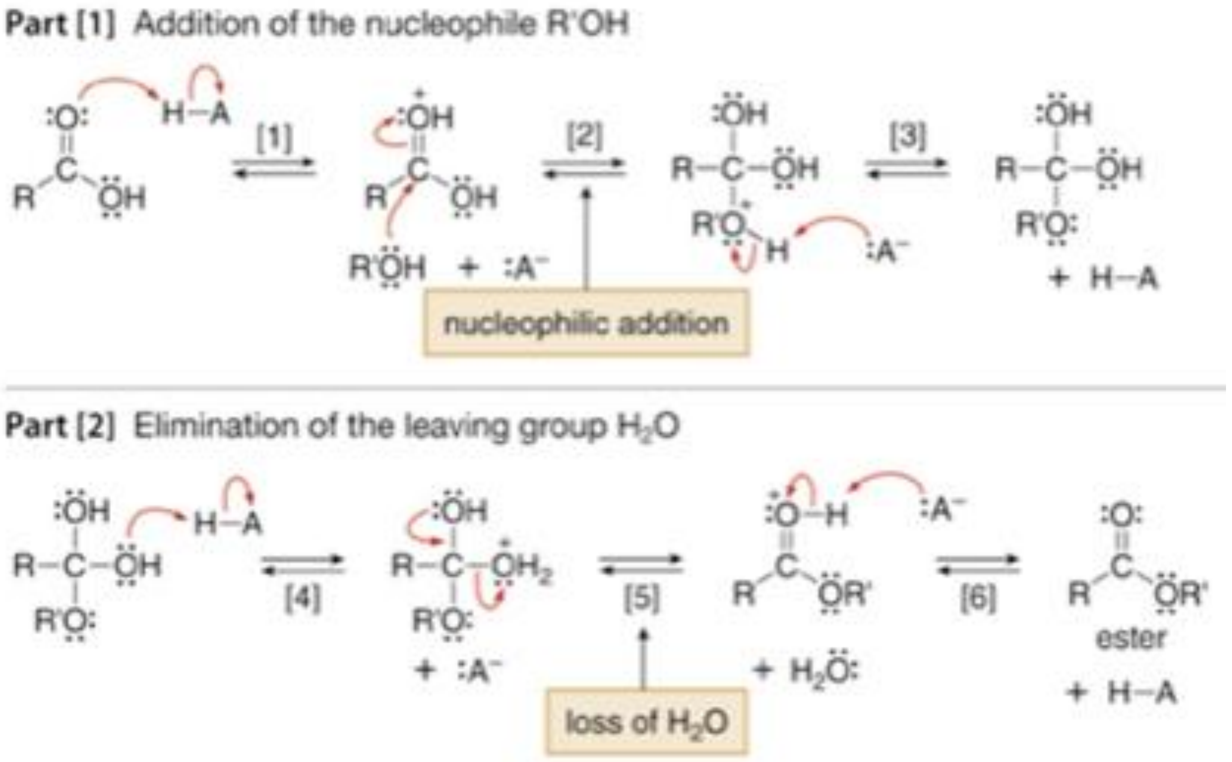
By the reaction of a carboxylic acid with thionyl chloride ($SOCl_2$).



$$RCOOH \xrightarrow{SOCl_2} RCOCl$$



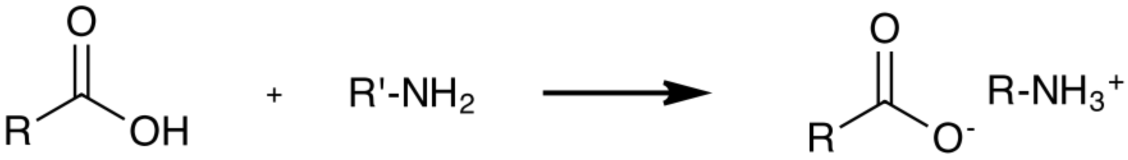
CARBOXYLIC ACIDS: FISCHER ESTERIFICATION



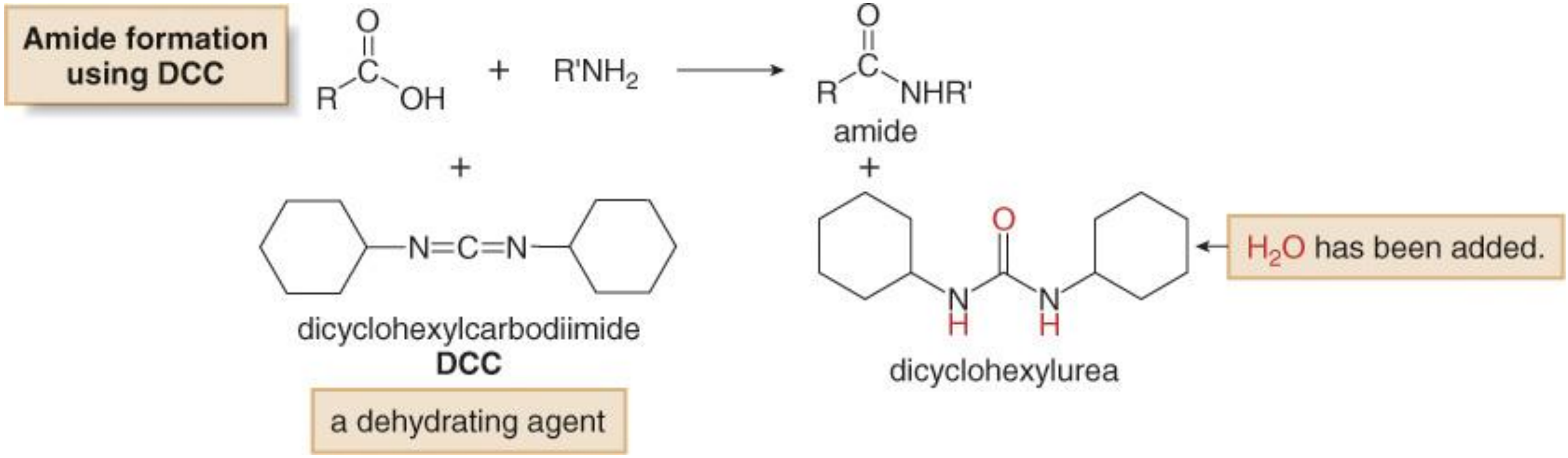
The reaction is an equilibrium, so it is driven to the right by using excess alcohol or by removing water as it is formed.

AMIDES FROM CARBOXYLIC ACIDS

Carboxylic acids cannot be converted into amides by reaction with NH_3 or an amine.

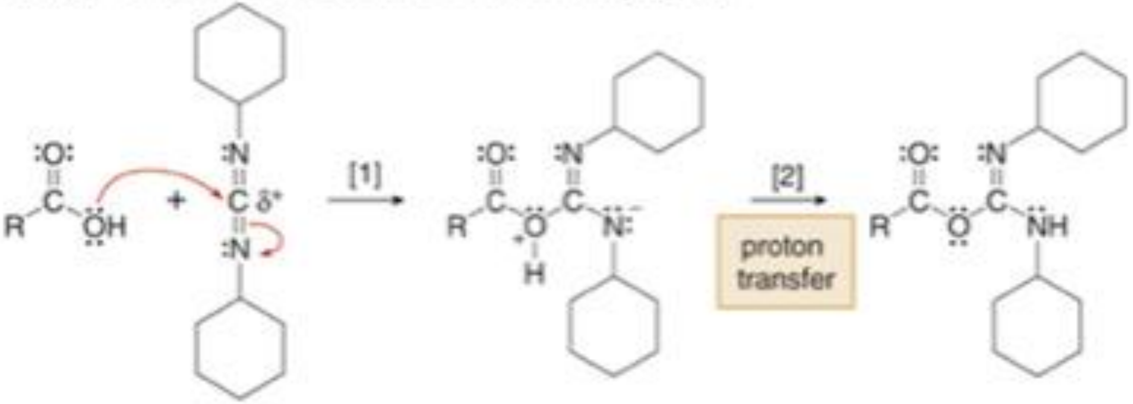


Carboxylic acids are converted into amides by reaction with NH_3 or an amine in the presence of a condensing agent (DCC).

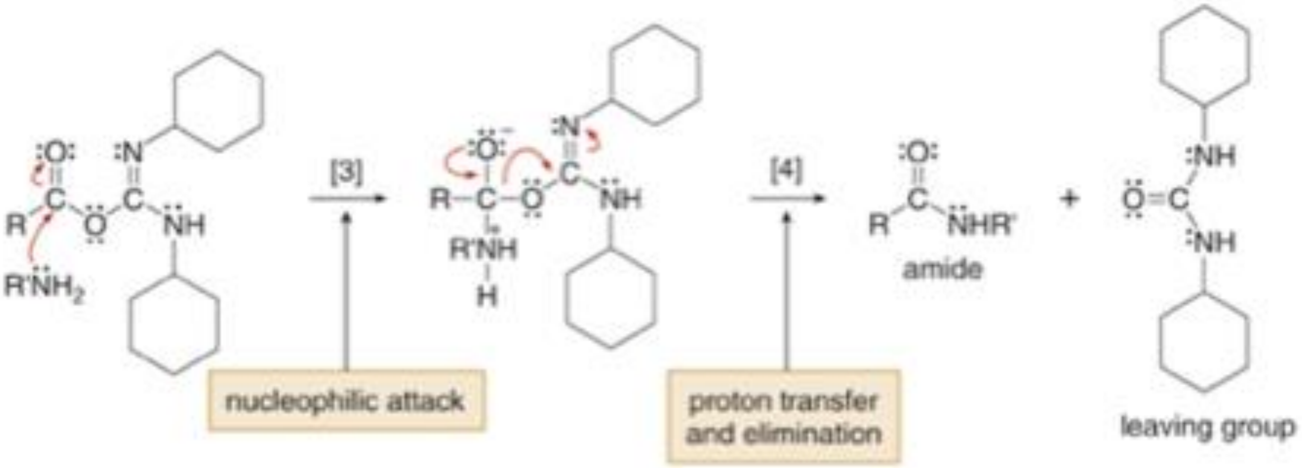


REACTIONS OF CARBOXYLIC ACIDS: AMIDES

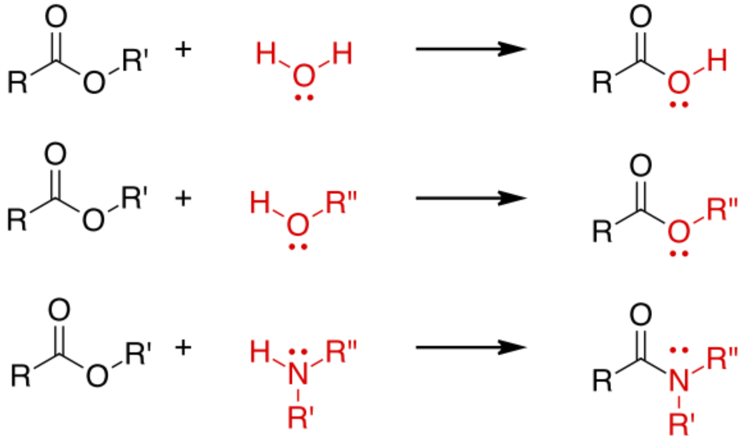
Part [1] Conversion of OH into a better leaving group



Part [2] Addition of the nucleophile and loss of the leaving group



ESTERS: REACTIONS

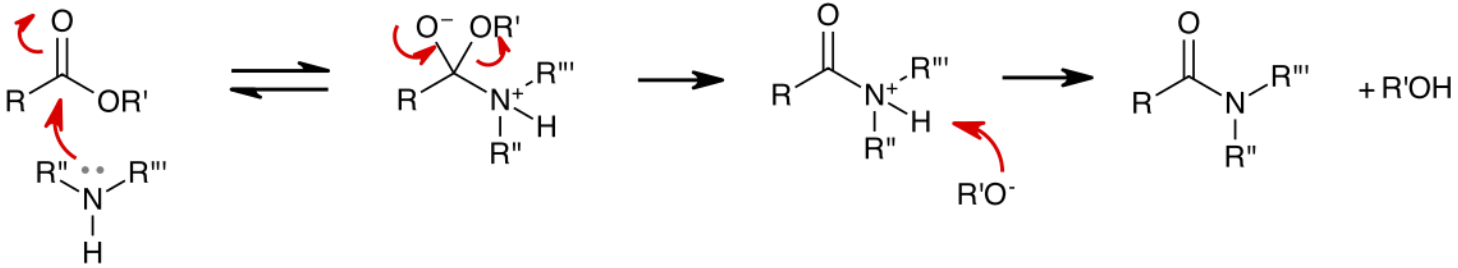


acid H⁺, H_2O or OH^-

transesterification H⁺, ROH or RO^-

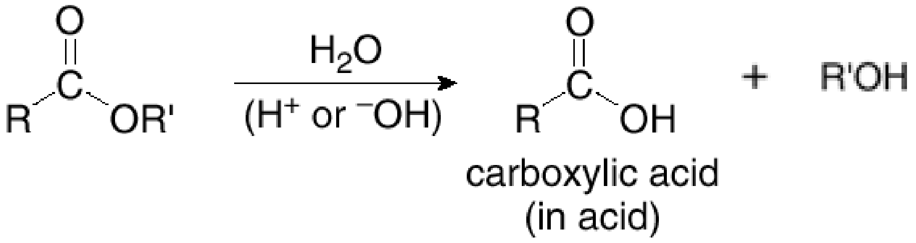
amide

Mechanism of amide formation

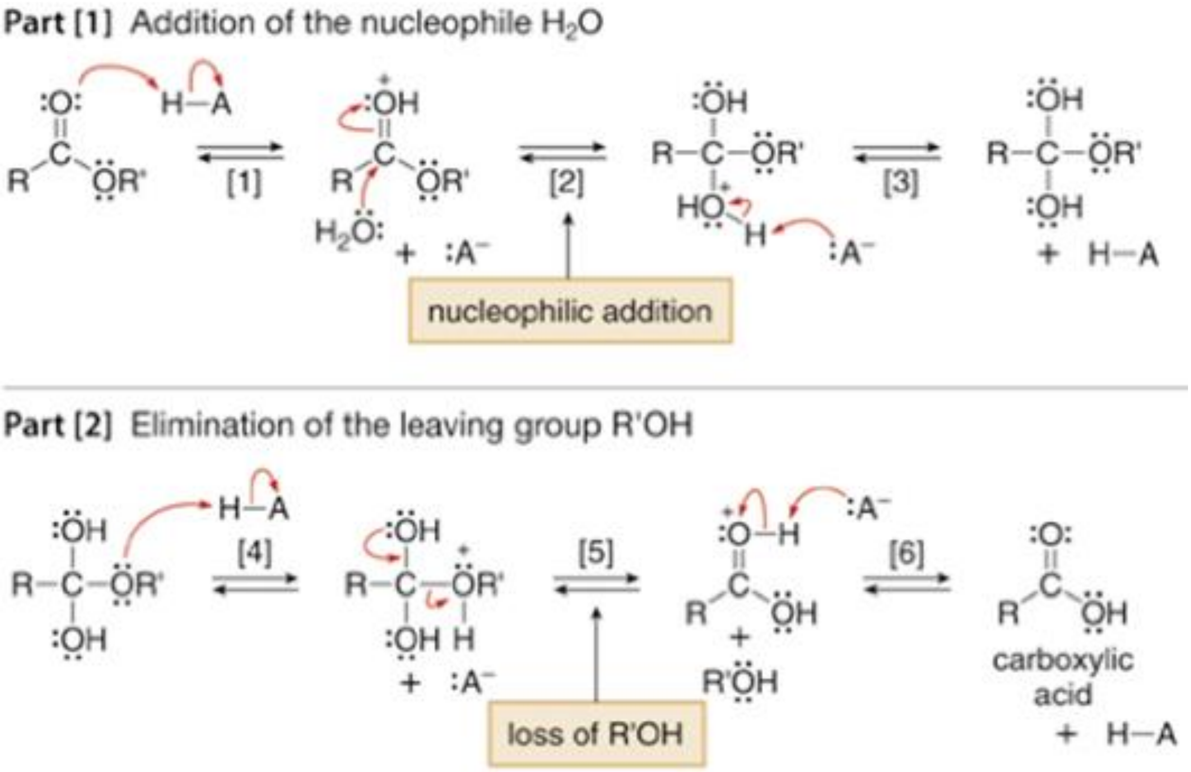


ESTERS: REACTIONS

Ester hydrolysis

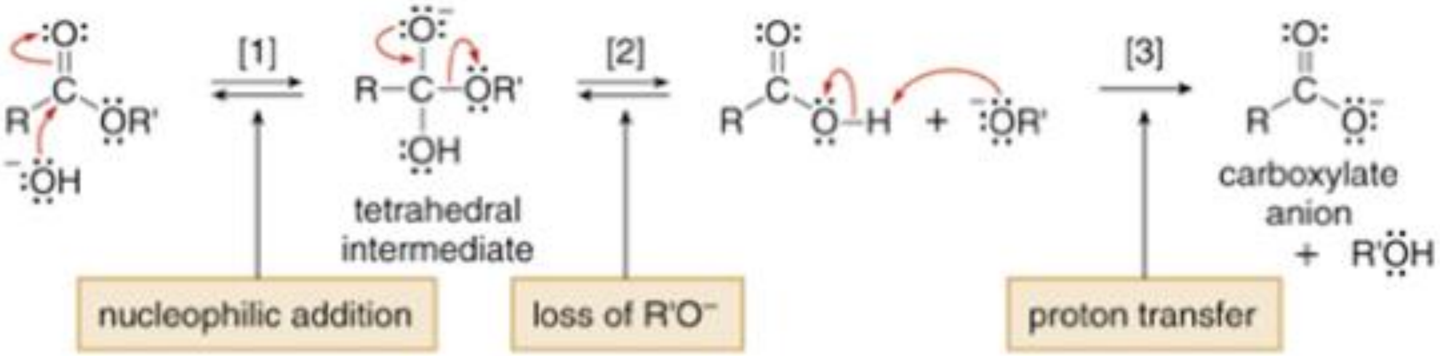


Acid hydrolysis



ESTERS: REACTIONS

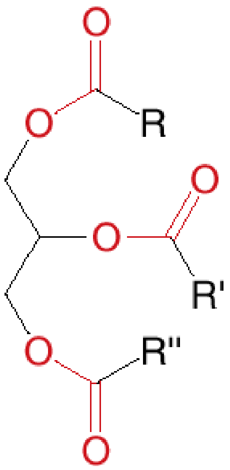
- Basic hydrolysis of an ester is also called saponification.



- Hydrolysis is base promoted, <u>not</u> base catalyzed, because the base (OH^-) is the nucleophile that adds to the ester and forms part of the product. It participates in the reaction and is not regenerated later.

Lipids

- Each triacylglycerol is a triester, containing three long hydrocarbon side chains.
- Unsaturated triacylglycerols have one or more double bonds in their long hydrocarbon chains, whereas saturated triacylglycerols have none.



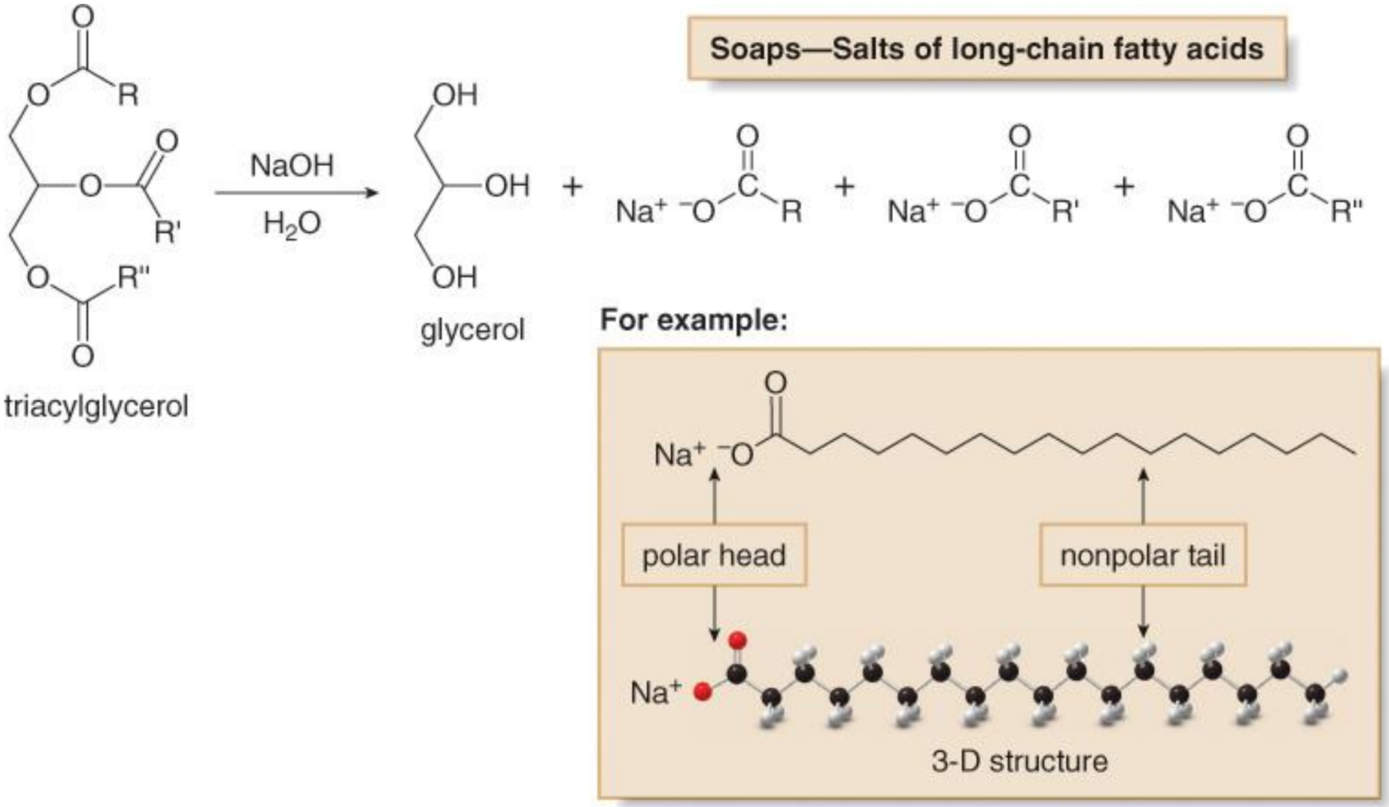
R groups have 11–19 C's.

[Three ester groups are labeled in red.]

triacylglycerol
the most common type of lipid

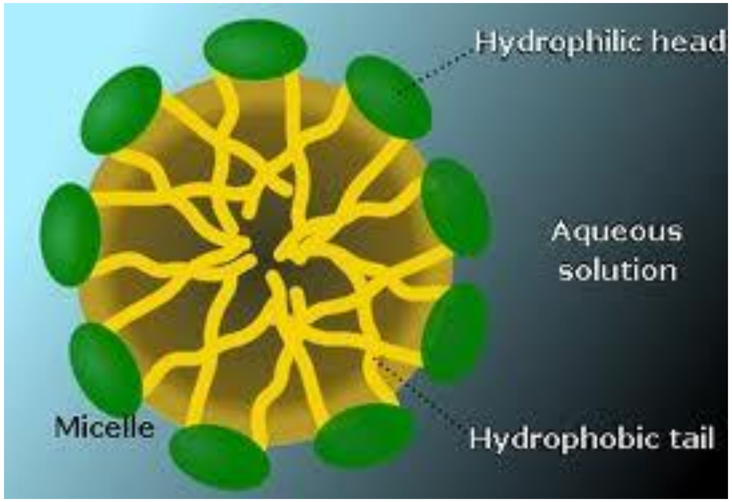
LIPID HYDROLYSIS

Soap is prepared by the basic hydrolysis or saponification of a triacylglycerol. Heating an animal fat or vegetable oil with aqueous base hydrolyzes the three esters to form glycerol and sodium salts of three fatty acids. These carboxylate salts are soaps.



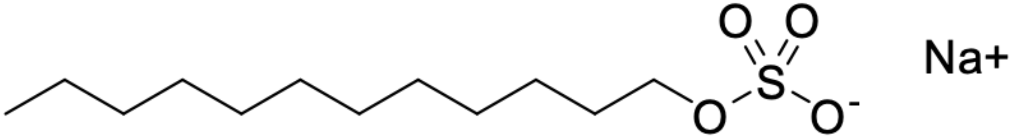
SOAP

- Soap molecules self-aggregate in water to form micelles

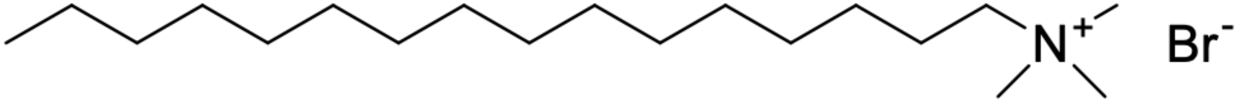


Micelles are water-soluble because the heads are hydrophilic.
Fats and oils from dirt dissolve in the hydorphobic core and are taken into solution

- Synthetic detergents



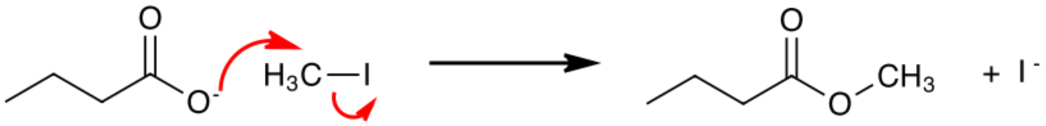
sodium laurylsulfate
SDS



cetyltrimethylammonium bromide
CTAB

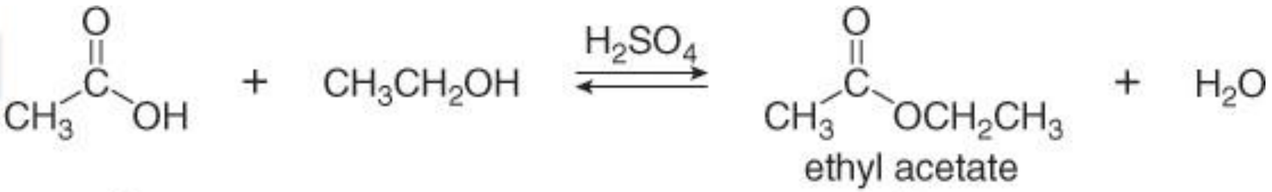
ESTERS FROM CARBOXYLIC ACIDS

- SN2 (mainly for methyl esters).

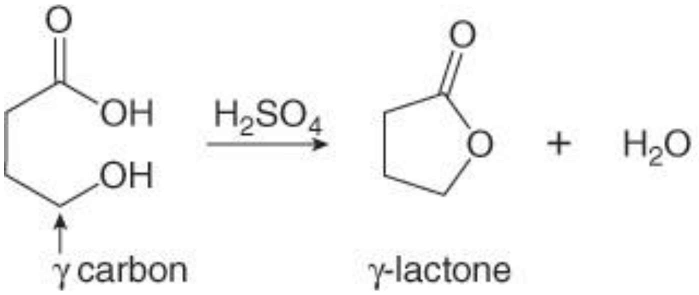


- Fischer esterification.

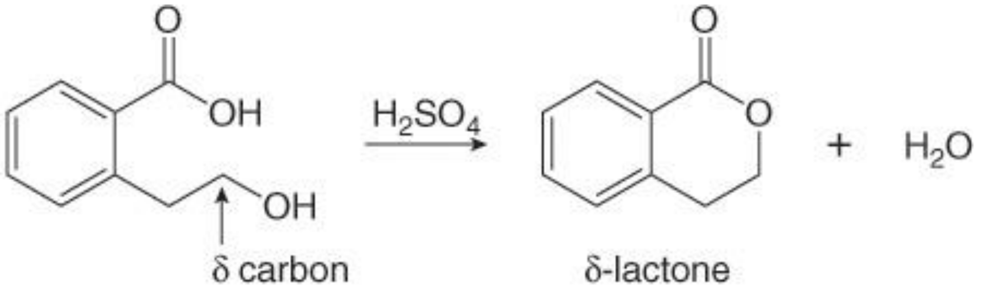
Examples



ethyl acetate

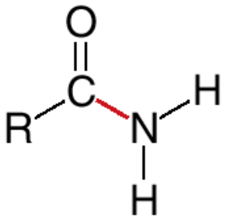


γ-lactone

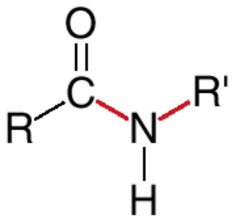


δ-lactone

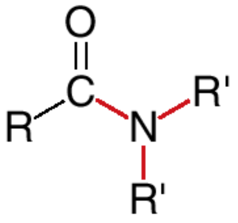
AMIDES: STRUCTURE



1° amide
1 C—N bond

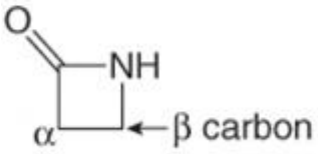


2° amide
2 C—N bonds

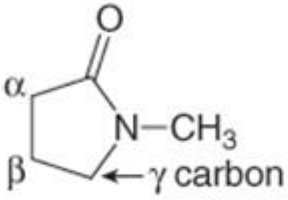


3° amide
3 C—N bonds

Lactams–Cyclic amides



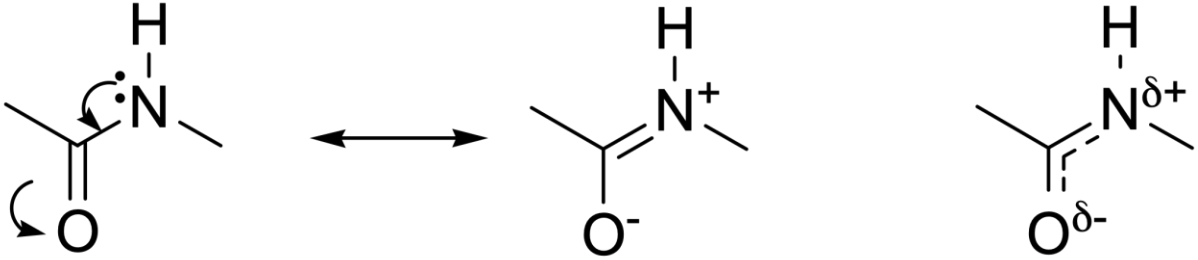
β-lactam



γ-lactam

AMIDES: STRUCTURE

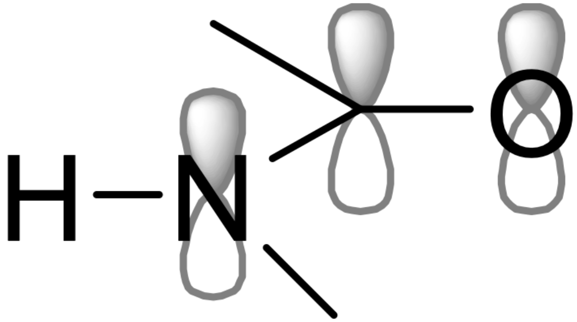
Amide resonance



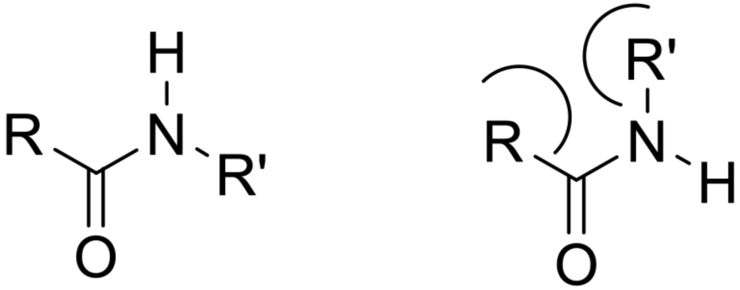
C, N, O: sp^2

planar

restricted rotation

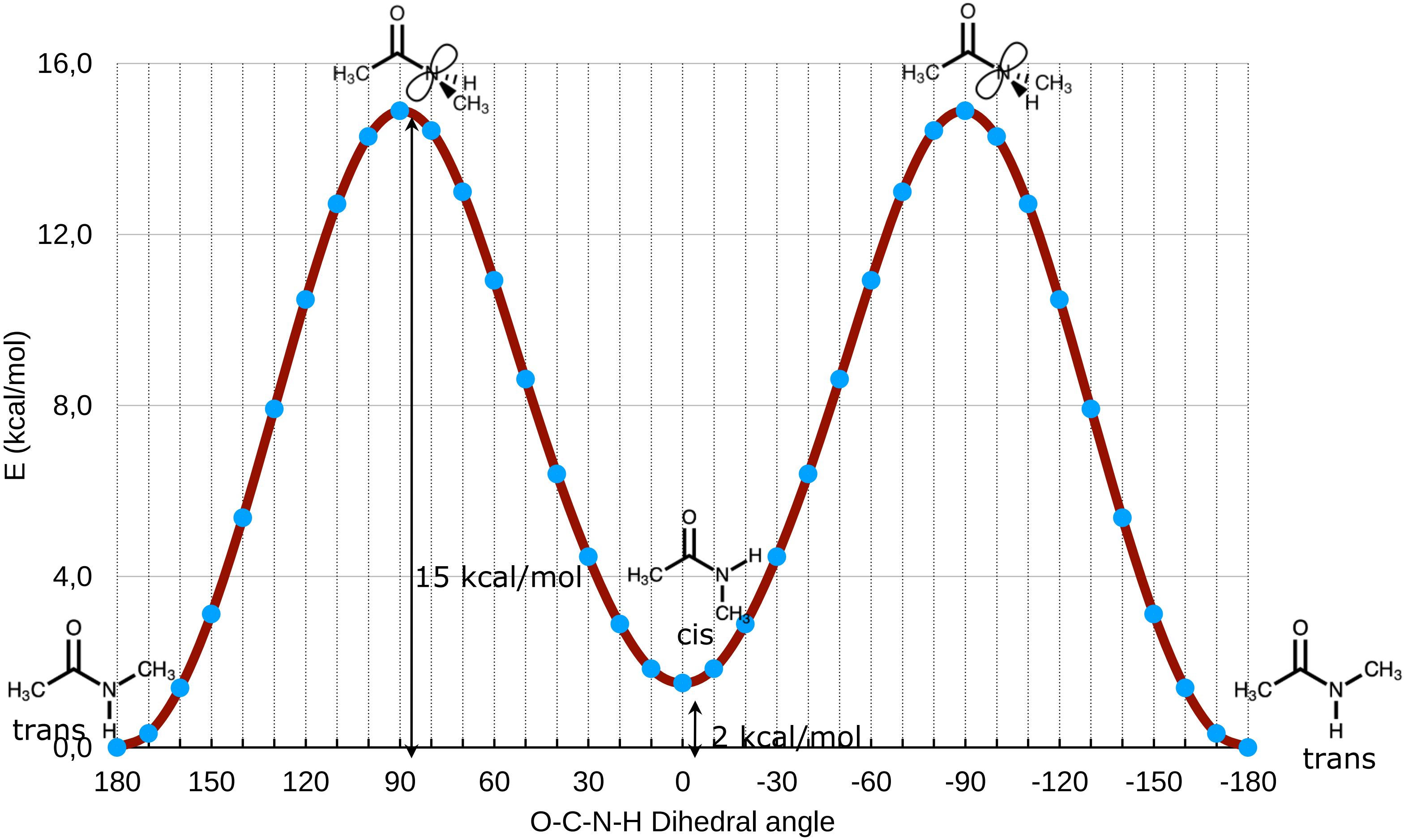


Trans amides are more stable than cis amides

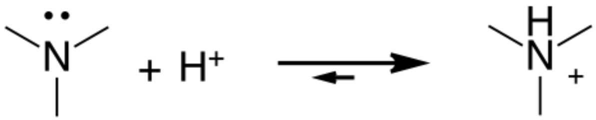


N-METHYLACETAMIDE

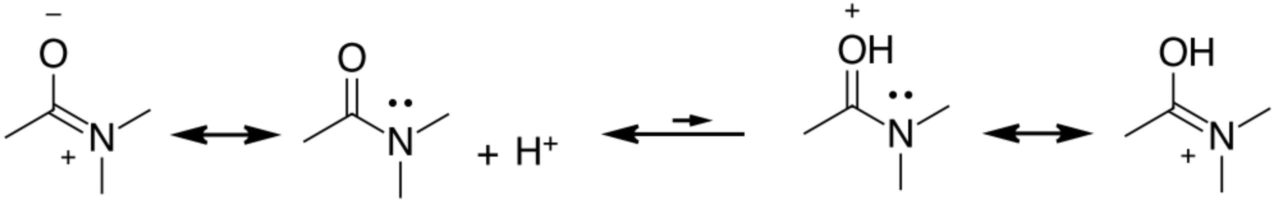
- The rotational barrier is unusually high in amides (15-20 kcal/mol) due to the partial double bond character of the C-N bond.
- Trans-amides are more stable than cis-amides.



AMIDES: BASICITY



pKa = 9

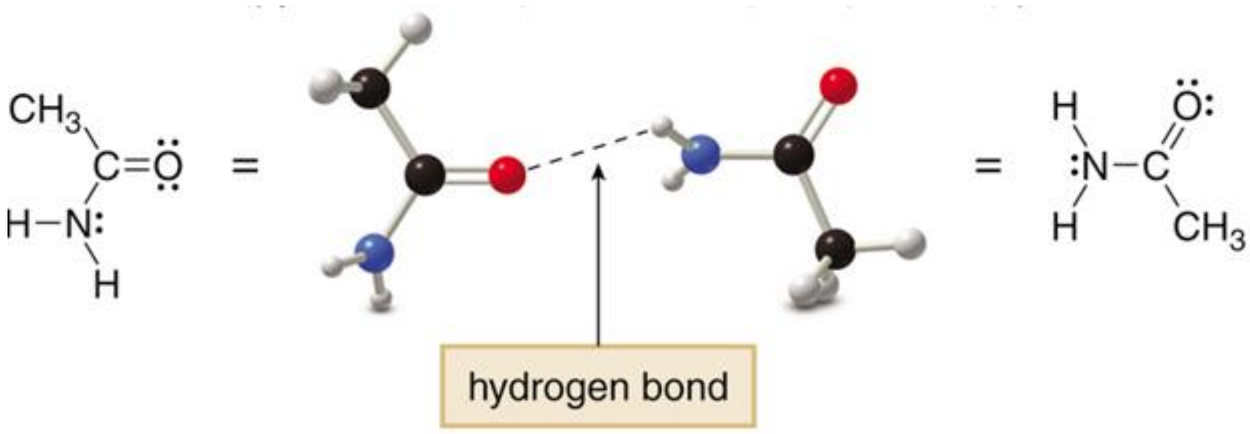


pKa = -1

DERIVATIVES: PHYSICAL PROPERTIES

- Because all carbonyl compounds have a polar carbonyl group, they exhibit dipole-dipole interactions.

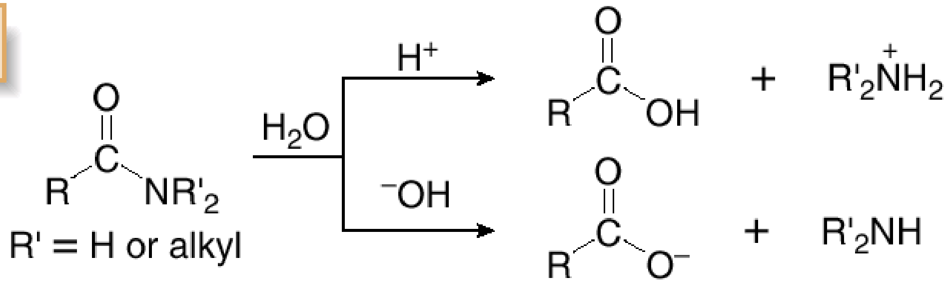
- Because they contain one or two N—H bonds, 1° and 2° amides are capable of intermolecular hydrogen bonding.



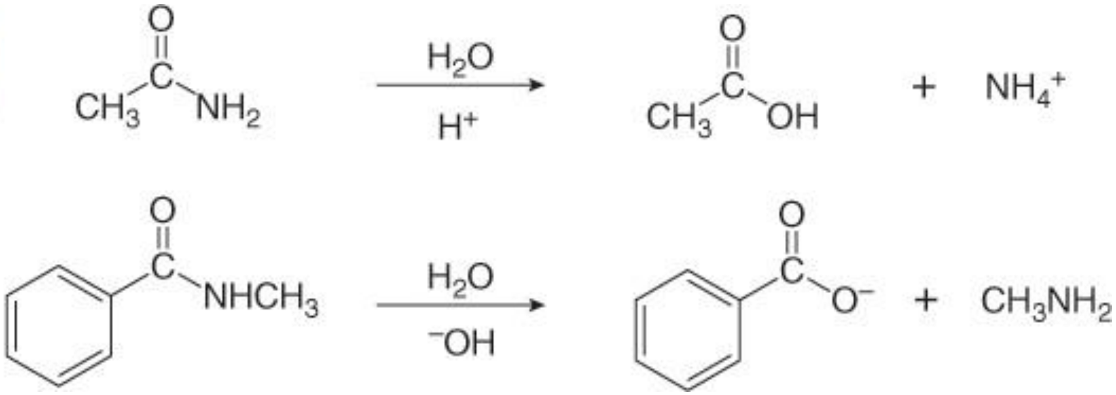
AMIDES: REACTIONS

Amides are the least reactive of the carboxylic acid derivatives.

Amide hydrolysis

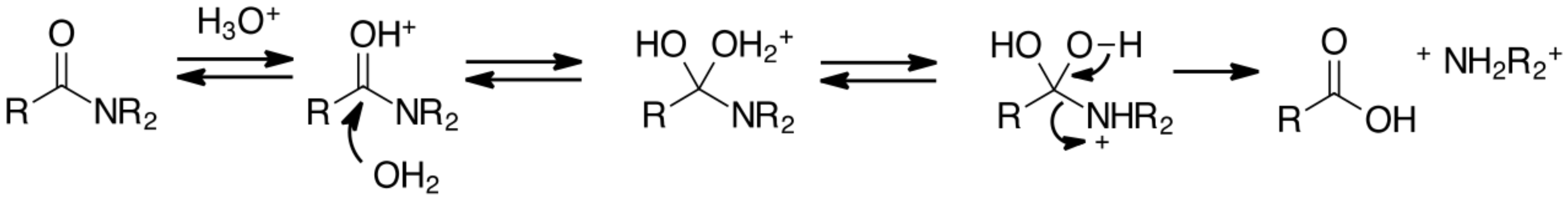


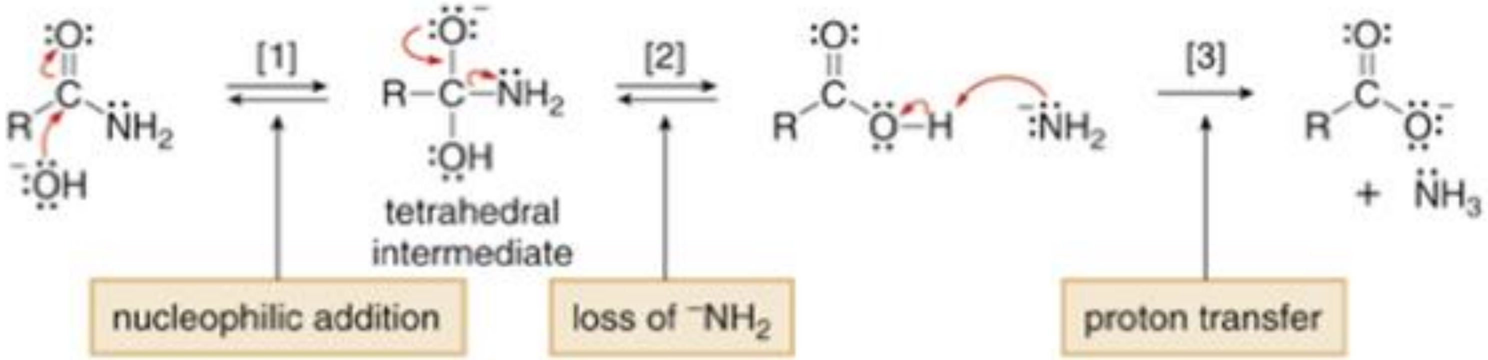
Examples



AMIDES: REACTIONS

The mechanism of amide hydrolysis is exactly the same as the mechanism of ester hydrolysis.



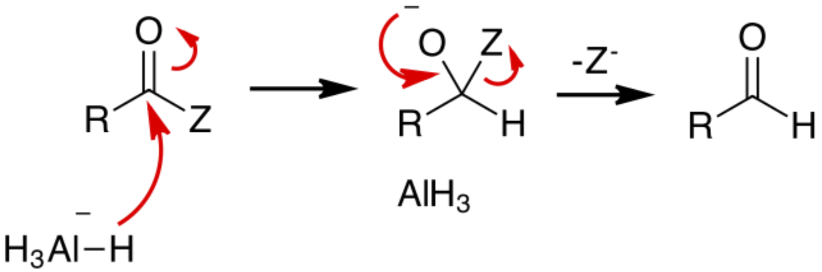


Amide hydrolysis is hard in acid because the nucleophile (H_2O) and the electrophile (amide) are poor.
Amide hydrolysis is hard in base because the electrophile and the leaving group (NR_2^-) are poor.

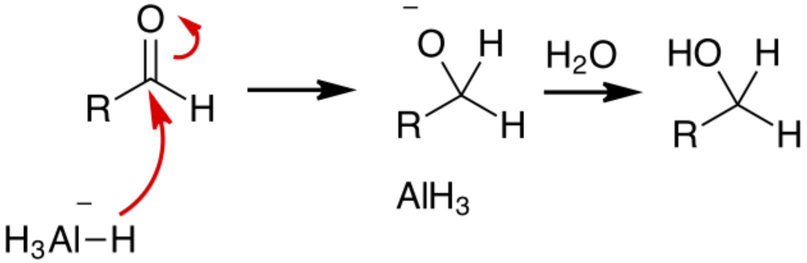
REDUCTION: ACID CHLORIDES, ANHYDRIDES AND ESTERS

Acid chlorides, anhydrides, carboxylic acids and esters are reduced to 1^{ry} alcohols by Al hydrides, e.g. $LiAlH_4$
A two-step reaction:

1. Nucleophilic acyl substitution



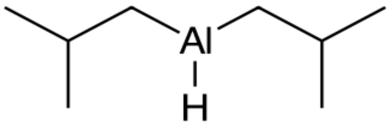
2. Nucleophilic addition



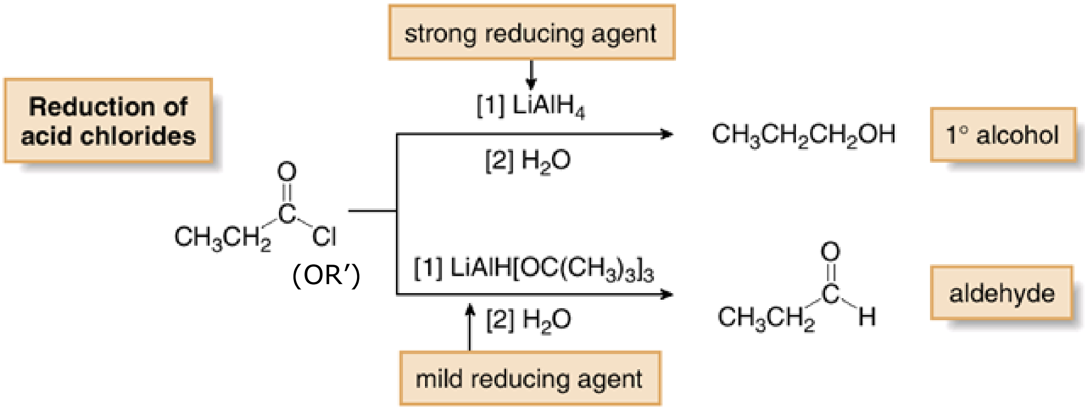
Z = Cl, OH, OCOR, OR’

REDUCTION OF ACID CHLORIDES, ANHYDRIDES AND ESTERS

- $LiAlH_4$ is a strong reducing agent that reduces acids, acid chlorides, anhydrides and esters to primary alcohols.
- Diisobutylaluminum hydride ($[(CH_3)_2CHCH_2]_2AlH$, abbreviated DIBAL-H, has two bulky isobutyl groups which makes this reagent less reactive than $LiAlH_4$.
- DIBAL-H reduces acid chlorides, anhydrides and esters to aldehydes.



DIBAL-H



REDUCTION OF CARBOXYLIC ACIDS AND THEIR DERIVATIVES

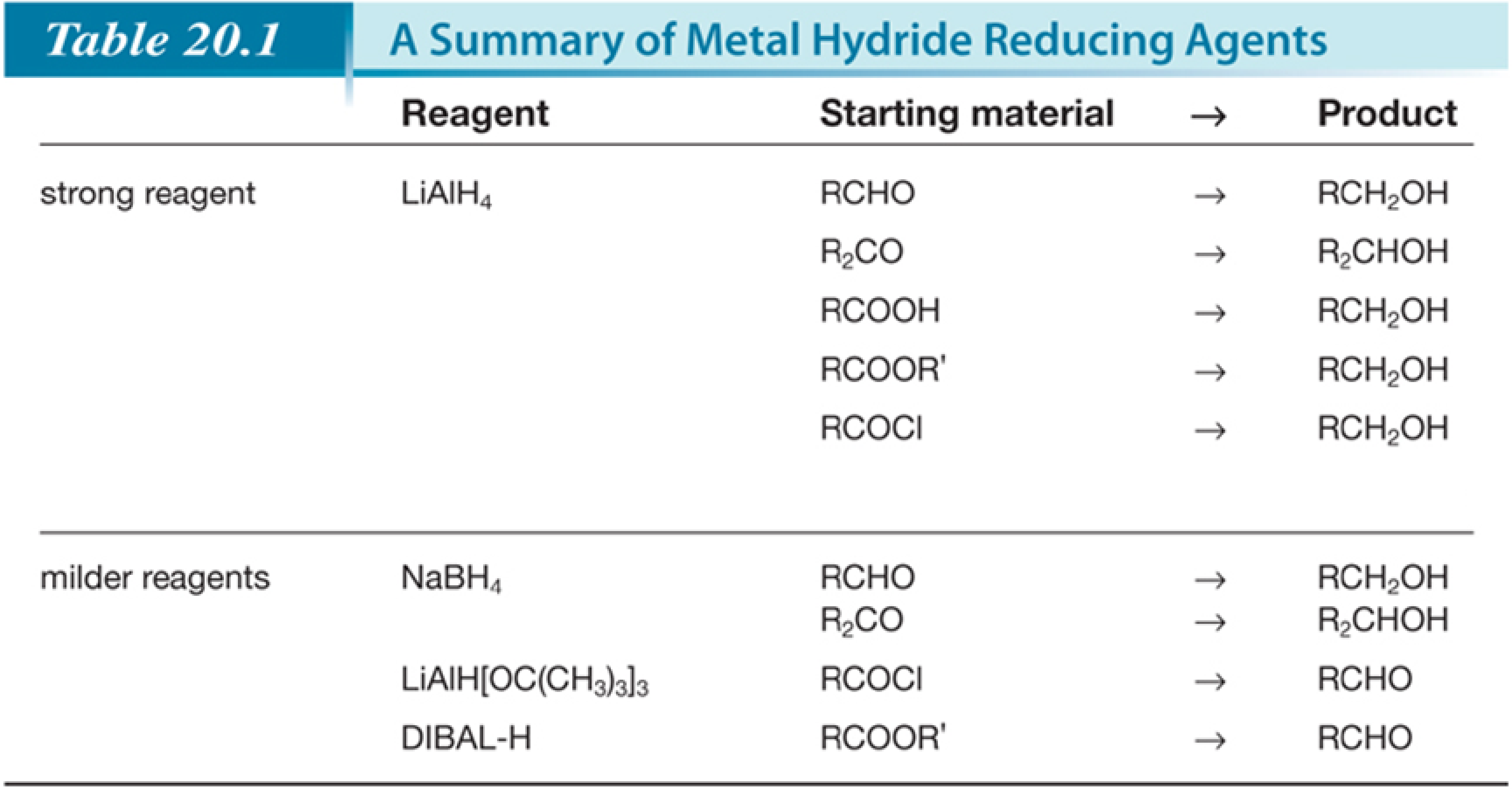


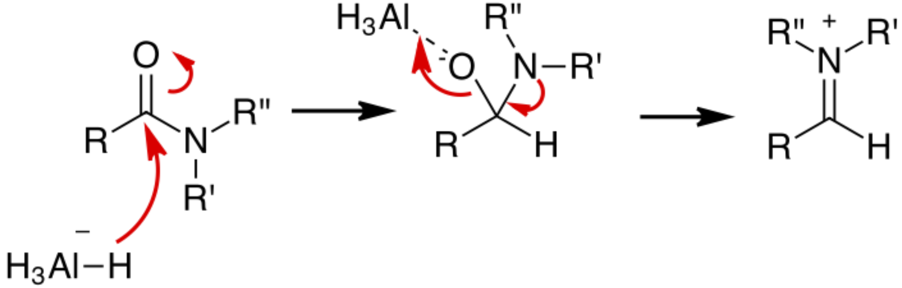
Table 20.1 A Summary of Metal Hydride Reducing Agents

	Reagent	Starting material	→	Product
strong reagent	$LiAlH_4$	RCHO	→	RCH_2OH
		R_2CO	→	R_2CHOH
		RCOOH	→	RCH_2OH
		RCOOR'	→	RCH_2OH
		RCOCl	→	RCH_2OH
milder reagents	$NaBH_4$	RCHO	→	RCH_2OH
		R_2CO	→	R_2CHOH
	$LiAlH[OC(CH_3)_3]_3$	RCOCl	→	RCHO
	DIBAL-H	RCOOR'	→	RCHO

REDUCTION OF AMIDES

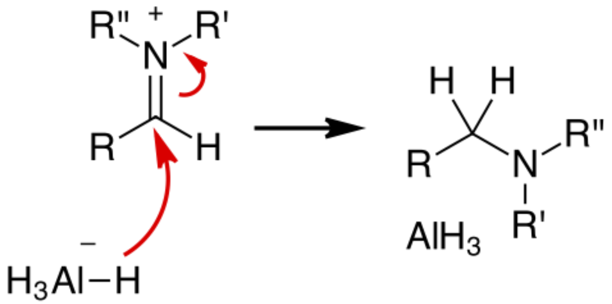
- Amides are reduced to amines by Al hydrides, e.g. $LiAlH_4$
- A two-step reaction:

Nucleophilic addition-elimination



imminium ion

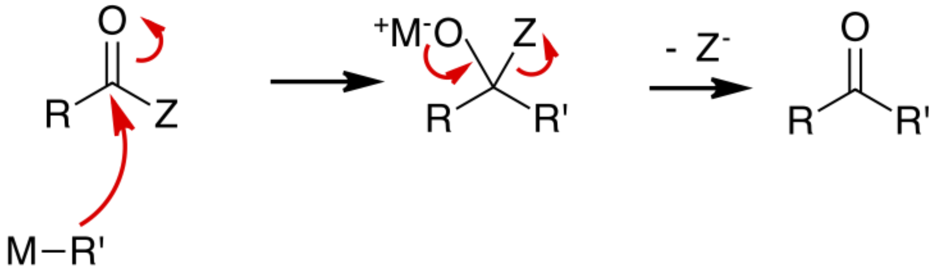
Nucleophilic addition



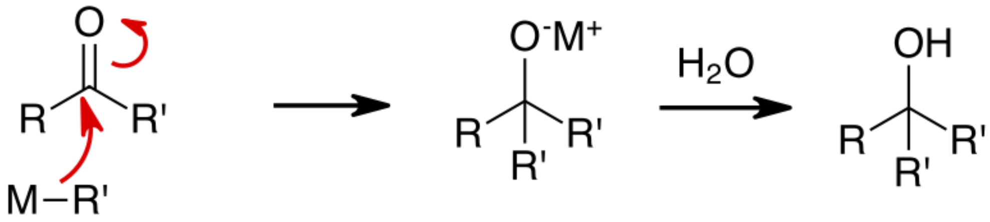
REACTION OF ORGANOMETALLIC REAGENTS WITH CARBOXYLIC ACID DERIVATIVES.

- Both esters and acid chlorides form 3° alcohols when treated with two equivalents of either Grignard or organolithium reagents.
- A two-step reaction:

1. Nucleophilic acyl substitution

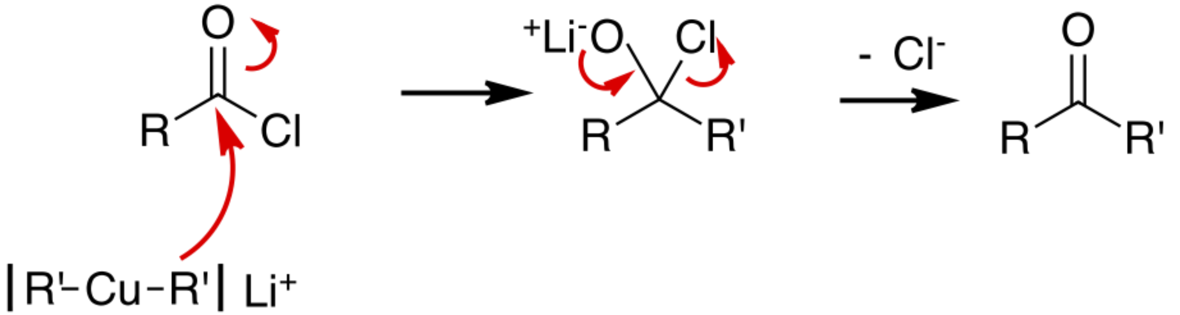


2. Nucleophilic addition

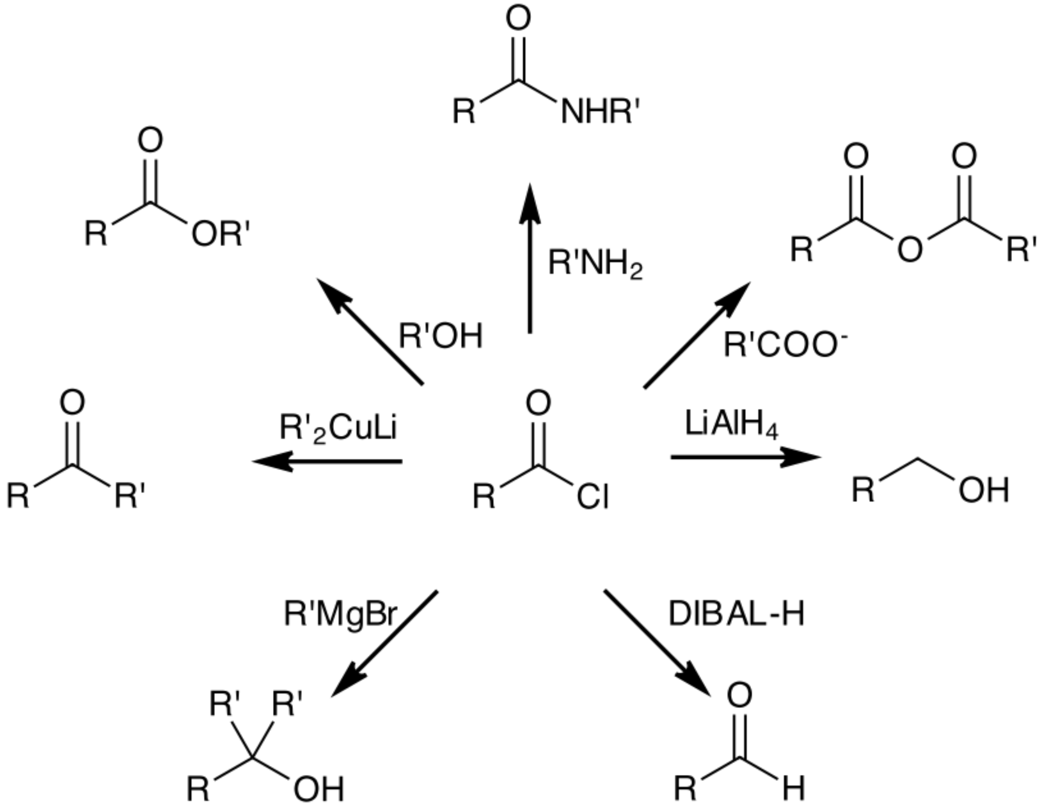


REACTION OF ORGANOMETALLIC REAGENTS WITH CARBOXYLIC ACID DERIVATIVES.

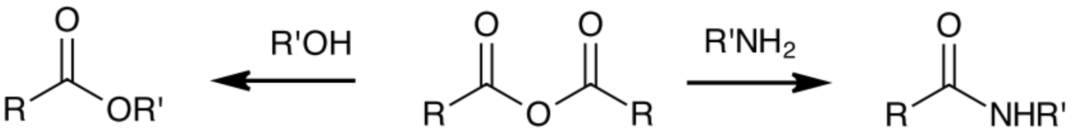
- Organocuprates (R'_2CuLi) are less reactive than organolithium and organomagnesium compounds.
- R'_2CuLi react only with acid chlorides, which are the more reactive among carboxylic acid derivatives, to give a ketone as the product.
- Esters do not react with R'_2CuLi.



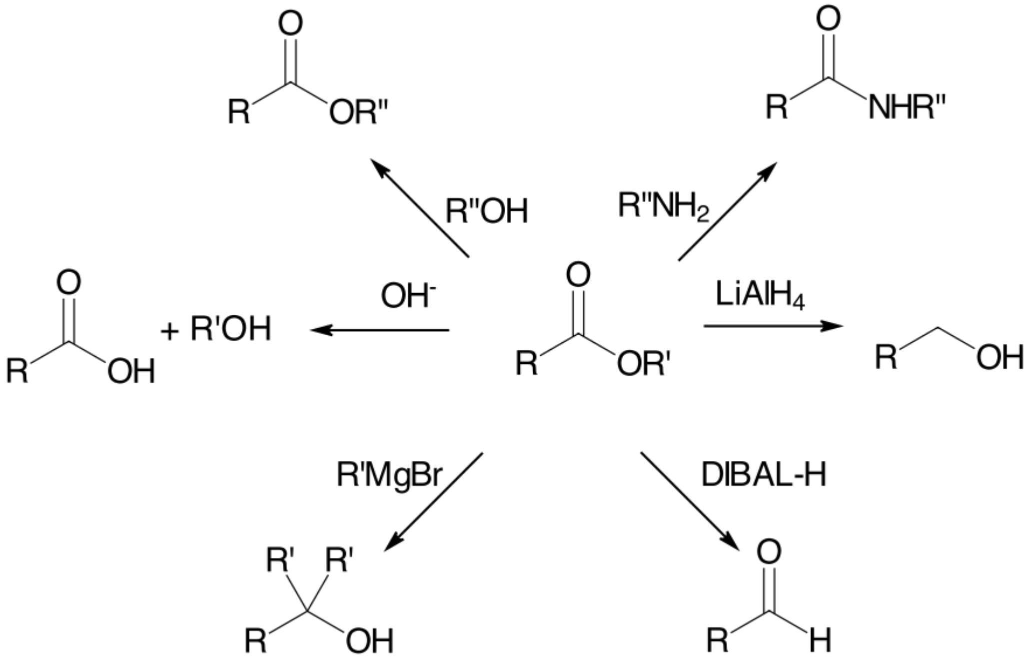
SUMMARY: IMPORTANT REACTIONS OF ACID CHLORIDES.



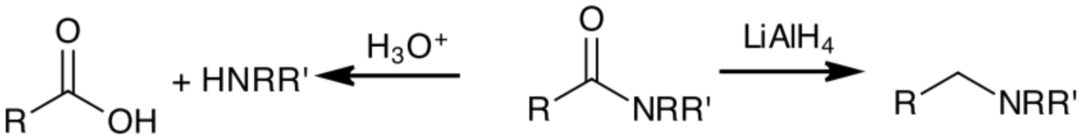
SUMMARY: IMPORTANT REACTIONS OF ANHYDRIDES.



SUMMARY: IMPORTANT REACTIONS OF ESTERS.



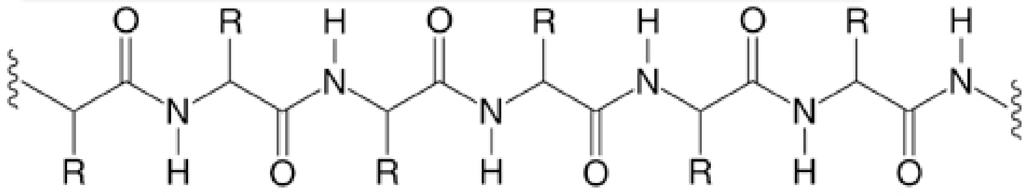
SUMMARY: IMPORTANT REACTIONS OF AMIDES.



NATURAL AND SYNTHETIC FIBERS

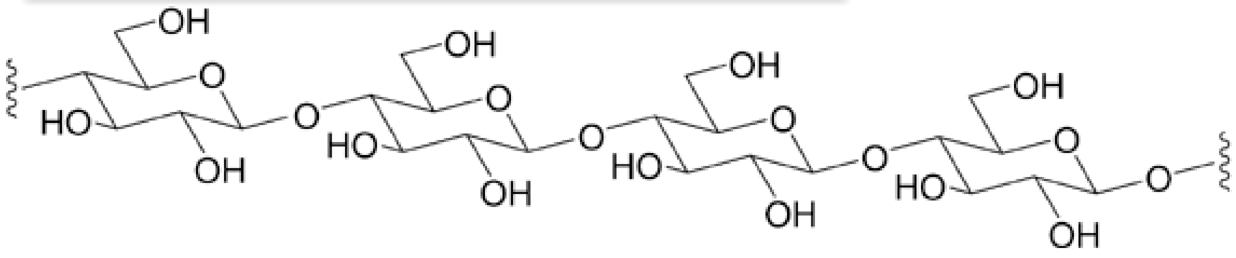
- Fibers like wool and silk are proteins obtained from animals.
- Cotton and linen are derived from carbohydrates having the general structure of cellulose.

Wool and silk—Proteins with many amide bonds



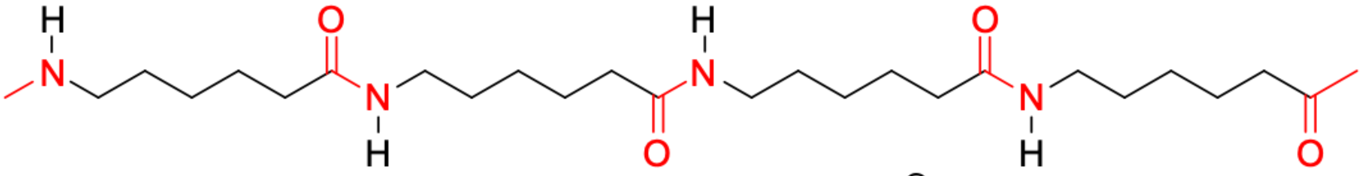
R groups contain C, H, and functional groups like NH_2, COOH, OH, and SH.

Cotton and linen—Carbohydrates like cellulose

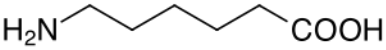


NATURAL AND SYNTHETIC FIBERS: NYLON—A POLYAMIDE

Nylon 6

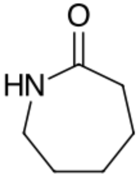


monomers:



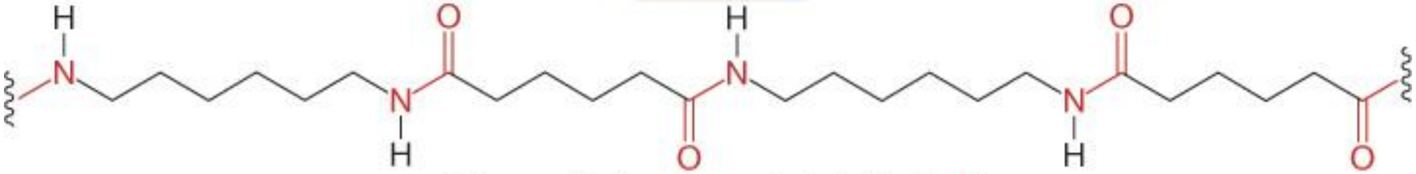
6-aminohexanoic acid

or



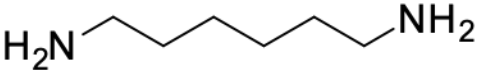
ε-caprolactam

Nylon 6,6

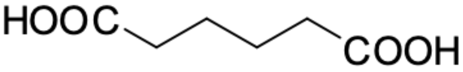


[The amide bonds are labeled in red.]

monomers:



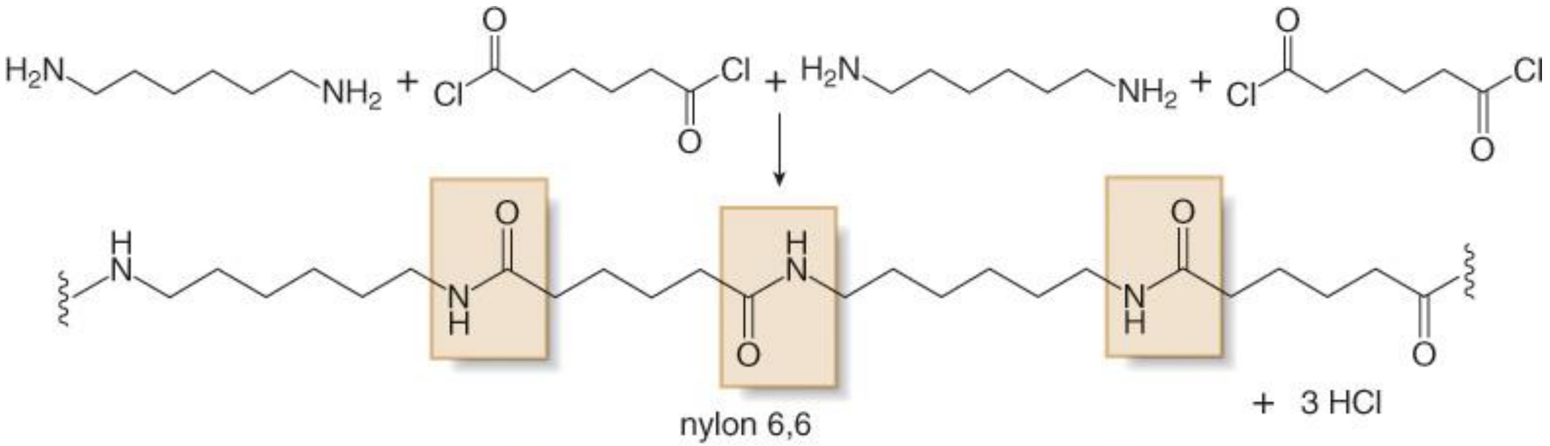
hexamethylenediamine



adipic acid

NATURAL AND SYNTHETIC FIBERS: NYLON—A POLYAMIDE

- Nylon is a condensation polymer

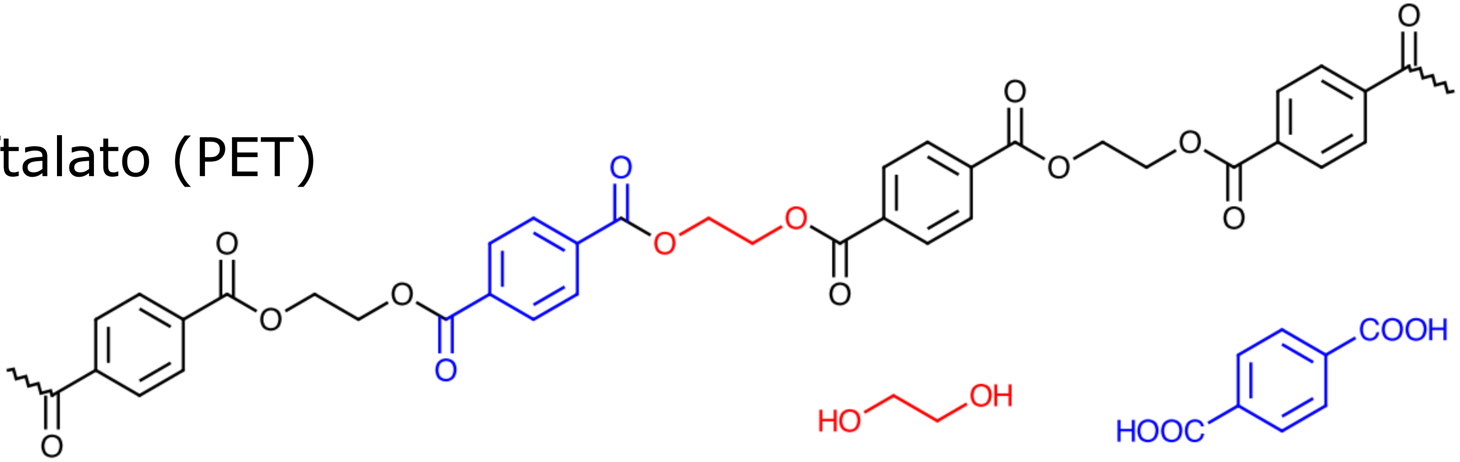


Three new amide bonds are shown.

POLIESTERI

Polietilentereftalato (PET)

bottiglie di plastica;
filati (Terital)

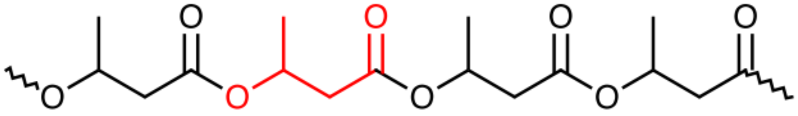


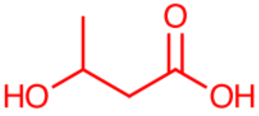
etilenglicol

acido tereftalico

Poliidrossibutirrato (PHB)

sacchetti
biodegradabili



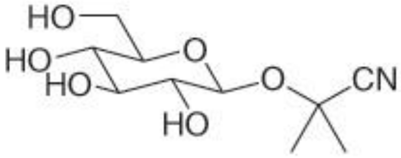


ac. 3-idrossibenzoico

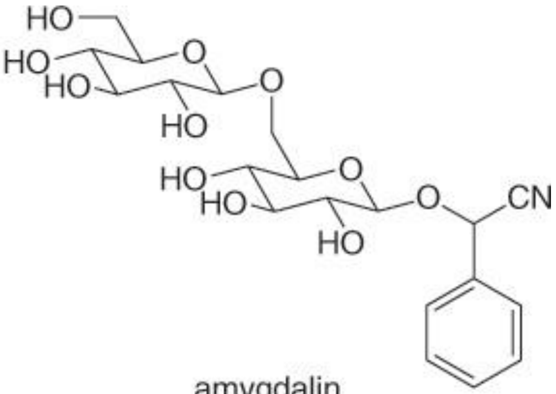
NITRILES

- Nitriles are not common in nature.

- Cyanohydrins are the most common natural nitriles.

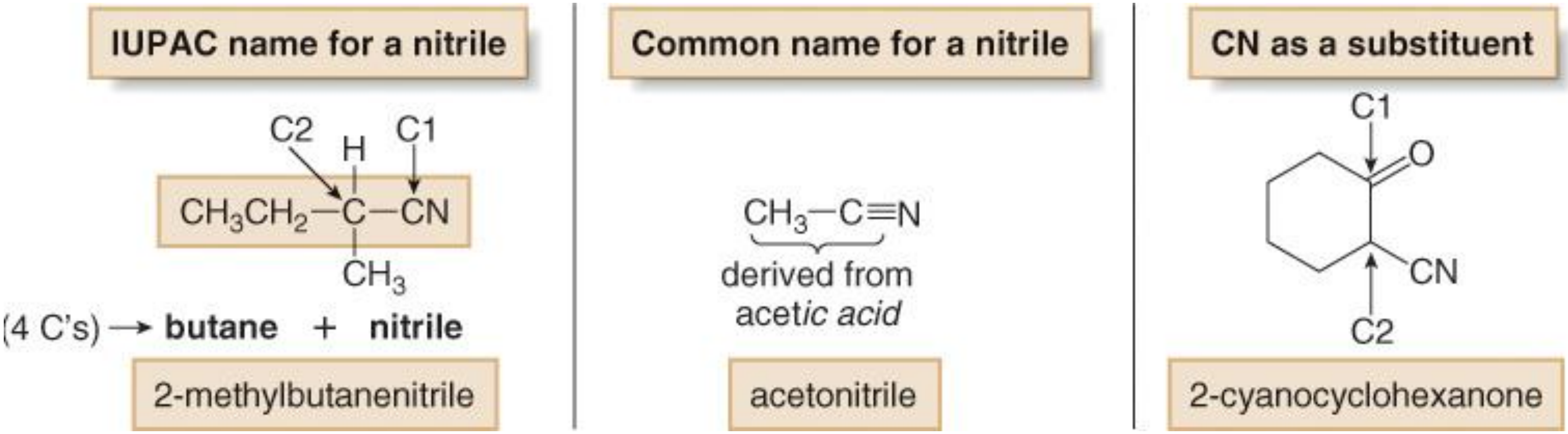


linamarin
(found in cassava root)



amygdalin
(commonly called laetrile)

NOMENCLATURE — NITRILES



IUPAC name for a nitrile

2-methylbutanenitrile

Common name for a nitrile

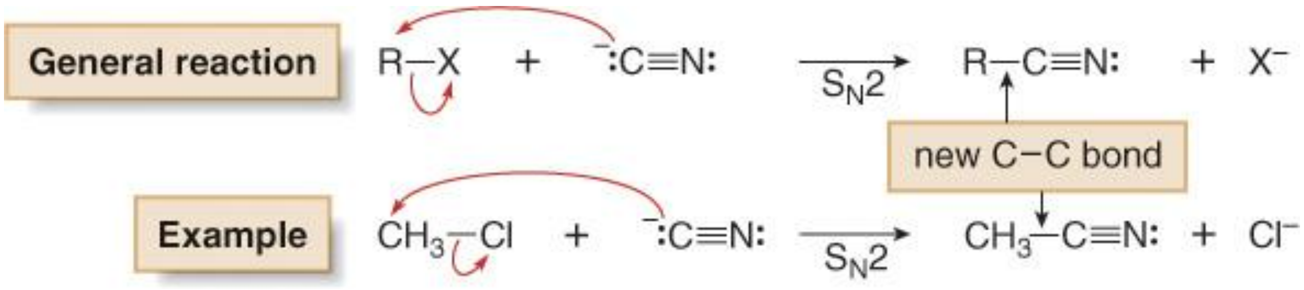
acetonitrile

CN as a substituent

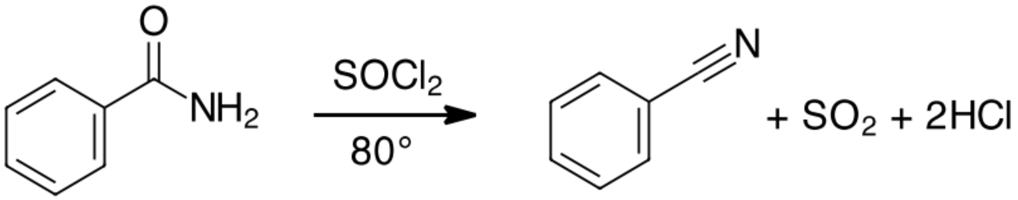
2-cyanocyclohexanone

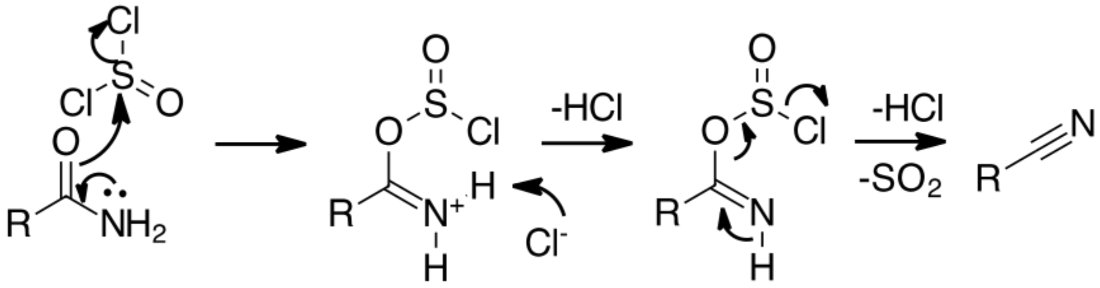
NITRILES

- Nitriles are prepared by S_N2 reactions of unhindered methyl and 1° alkyl halides with ^{-}CN.

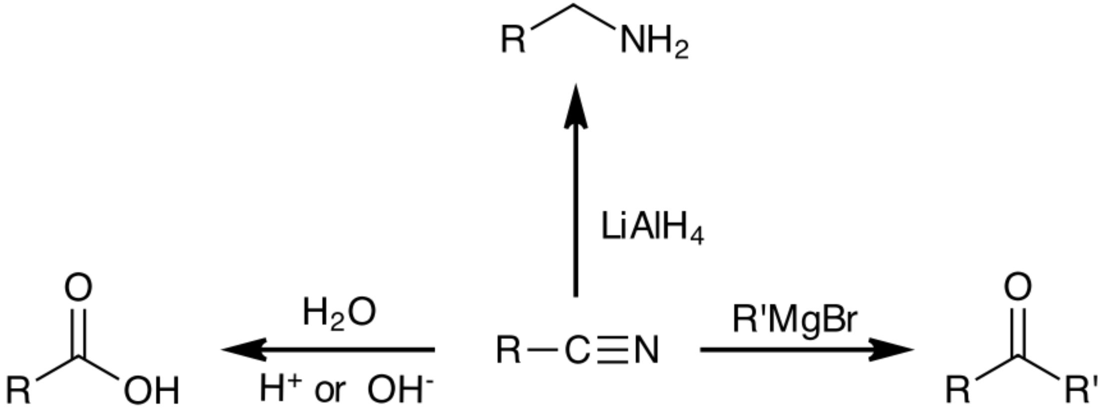


- Nitriles are prepared by dehydration of amides (more general).





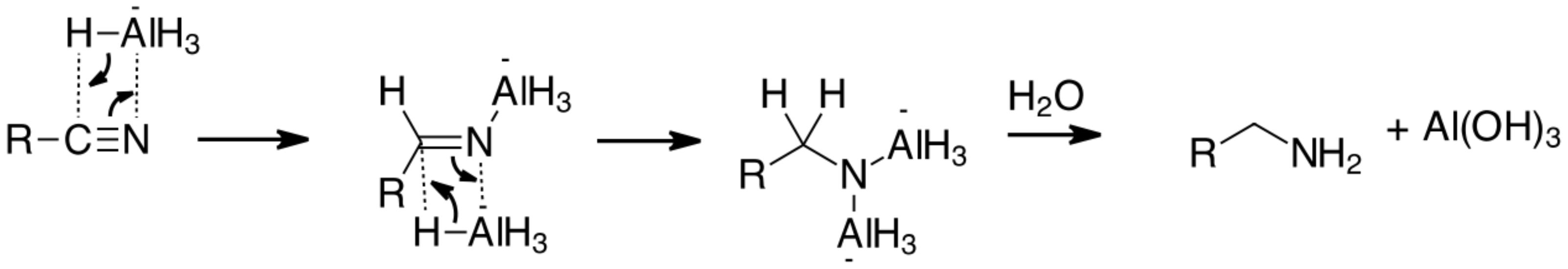
SUMMARY: IMPORTANT REACTIONS OF NITRILES.



REACTIONS OF NITRILES — REDUCTION

$LiAlH_4$ (more reactive)

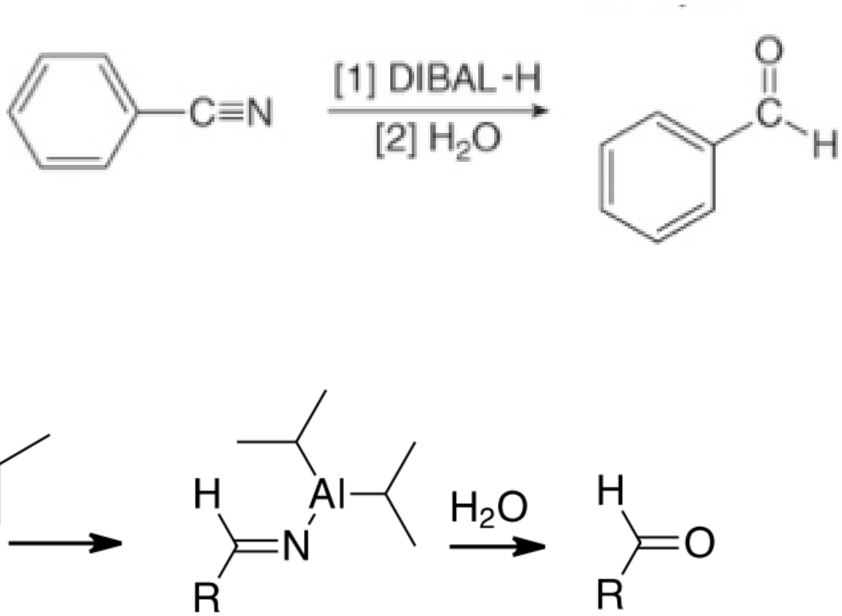
Example $(CH_3)_3C{-}C{\equiv}N \xrightarrow[\text{[2] } H_2O]{\text{[1] } LiAlH_4} (CH_3)_3C{-}CH_2NH_2$



REACTIONS OF NITRILES — REDUCTION

DIBAL-H (less reactive)

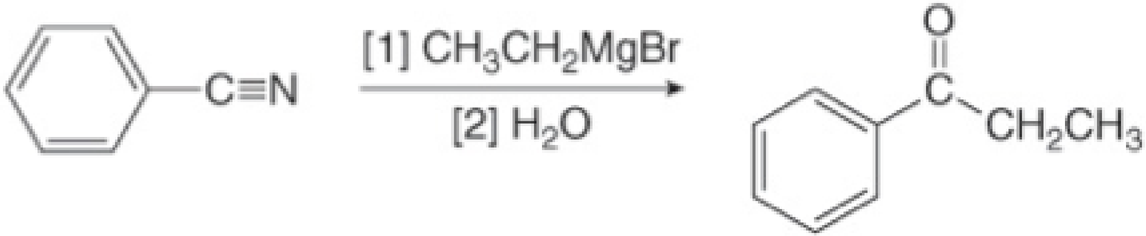
Example

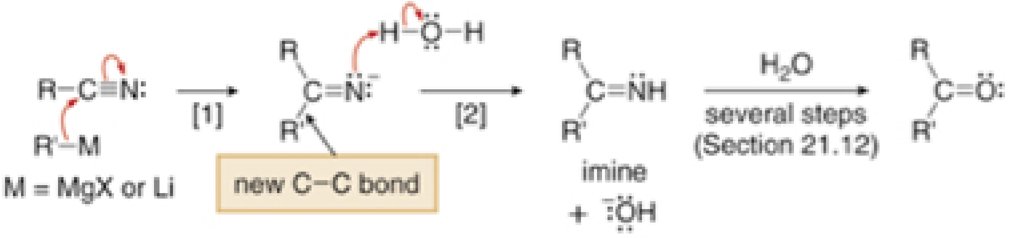


ADDITION OF ORGANOMETALLIC REAGENTS

Both Grignard and organolithium reagents react with nitriles to form ketones with a new C—C bond.

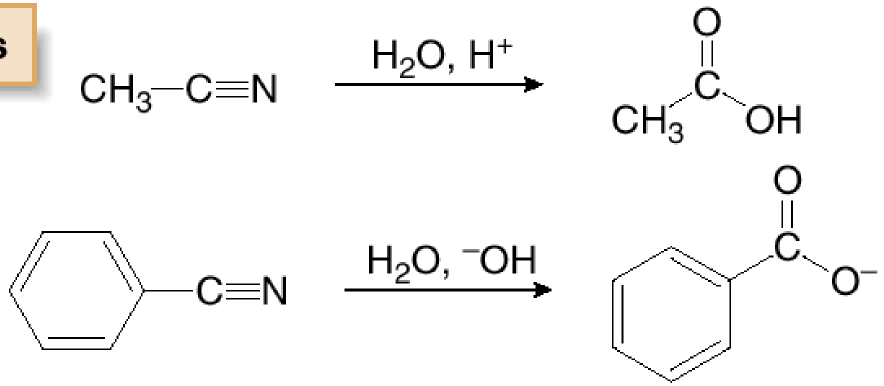
Example



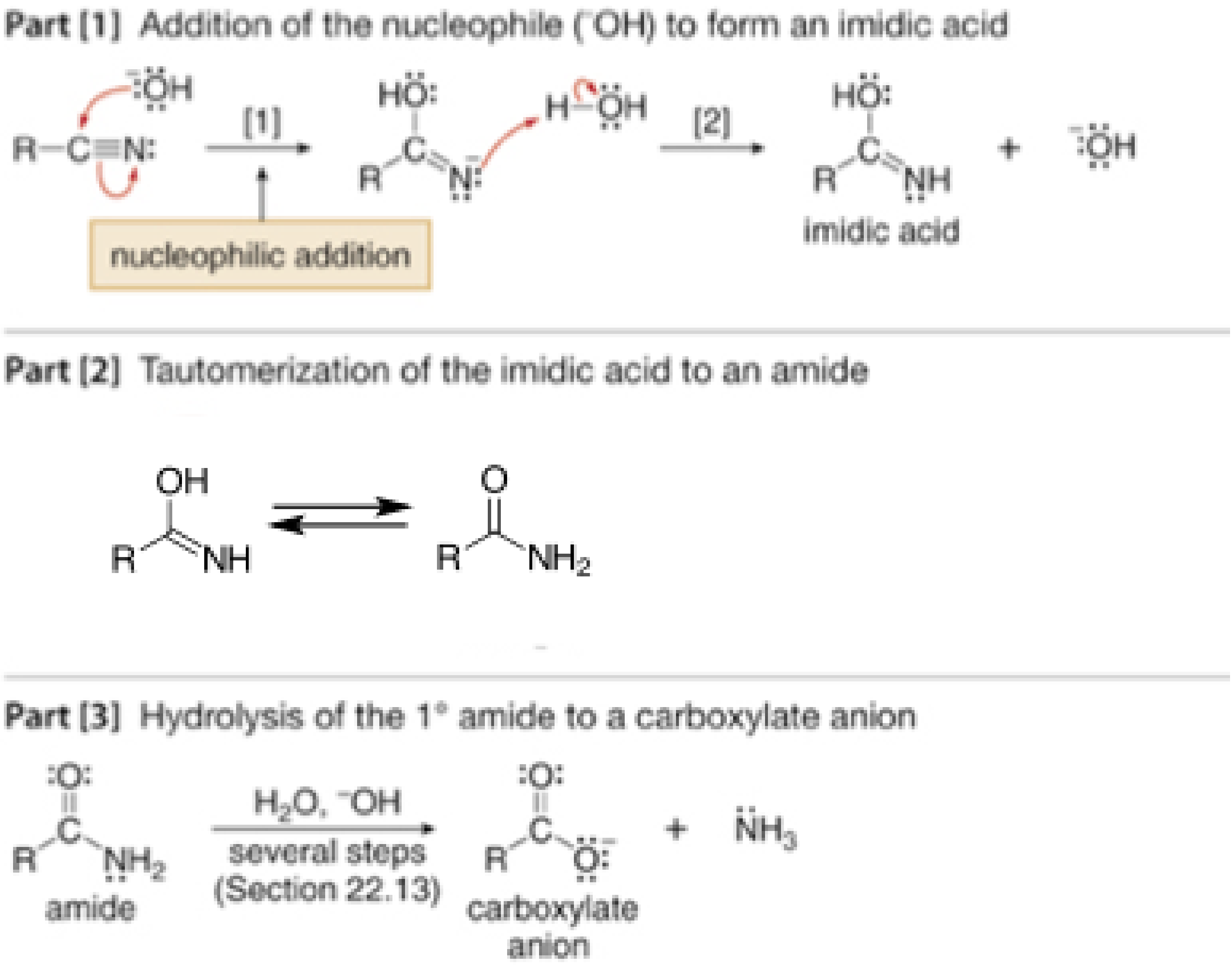


REACTIONS OF NITRILES—HYDROLYSIS

Examples



REACTIONS OF NITRILES — HYDROLYSIS



Part [1] Addition of the nucleophile (⁻OH) to form an imidic acid

Part [2] Tautomerization of the imidic acid to an amide

Part [3] Hydrolysis of the 1° amide to a carboxylate anion