

Chapter 22. Substitution of Carboxylic Acids and Derivatives.

1. Carboxylic acids.
 - a) Nomenclature (briefly).
 - b) Acidity.
 - i) More acidic than alcohols (16), not as acidic as mineral acids like HCl (-7).
 - ii) Inductive withdrawing groups make more acidic. $\text{CF}_3\text{CO}_2\text{H}$ (0), $\text{CH}_3\text{CO}_2\text{H}$ (4.7). Range rather narrow.
2. Carboxylic acid analogs. All but nitriles have in common a leaving group attached to the carbonyl C.
 - a) Esters, amides, acyl halides, acyl anhydrides, nitriles (honorary members of carboxylic acid class).
 - b) Nomenclature of esters: ethyl acetate, 2-methylphenyl 2-hydroxyhexanoate, *t*-butyl cyclohexanecarboxylate.
 - c) Nomenclature of other derivatives: read book.
3. Biological and real-life examples.
 - a) Fatty acids are carboxylic acids.
 - b) Peptides are amides.
 - c) Di- and triglycerides and lipopeptides (through serine and threonine) are esters.
 - d) Nucleoside di- and triphosphates are phosphoric acid analogs of acyl anhydrides.
 - e) Nylon, polyester.
4. Thermodynamic and kinetic stability.
 - a) Carboxylates (lowest energy) > amides > nitriles > esters/ acids > ketones > aldehydes > anhydrides > acyl chlorides (highest energy).
 - b) Corresponds to stability of $\overset{+}{\text{C}}-\overset{-}{\text{O}}$ resonance structure.
 - c) Acyl chlorides don't exist in nature; anhydrides are rare. Instead, nature uses thioesters instead of acyl chlorides.
5. Acidity.
 - a) Carboxylic acids and their derivatives are acidic at the α -carbon.
 - b) Acidity corresponds to stability of $\overset{+}{\text{C}}-\overset{-}{\text{O}}$ resonance structure.
 - c) $\text{p}K_{\text{a}}$: Carboxylates (least acidic) > amides > nitriles > esters > ketones > aldehydes > anhydrides > acyl chlorides (most acidic).
 - d) Carboxylic acids are much more acidic at O than at the α -carbon (4 vs. 25). 1° and 2° amides are also more acidic at N than at the α -carbon (18 vs. 29).
6. Electrophilic reactivity.
 - a) Carboxylic acids and their analogs are electrophilic at the carbonyl C, just like aldehydes and ketones.
 - b) Nucleophiles add to carbonyl C under acidic or basic conditions to give a *tetrahedral intermediate*.

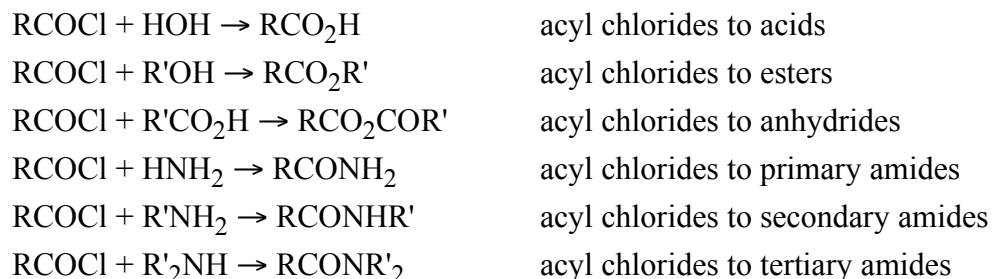
- c) After nucleophile adds, though, loss of a leaving group can occur to *re-form the carbonyl!* This is how carboxylic acid derivatives differ from ketones and aldehydes. Overall mechanism is called *addition–elimination*.
- d) Under acidic conditions, protonations and deprotonations occur in between the addition and elimination steps. *Electrophiles such as H^+ always react with the carbonyl C, not the leaving group!*
- e) Nitriles are different, as no leaving group is attached to electrophilic C. Nitriles do addition reactions that are analogous to the addition reactions of aldehydes and ketones. After protonation, an imine is obtained. This initial product is usually converted to other compounds by tautomerization or hydrolysis.

7. Syntheses of carboxylic acids covered previously.

- a) Oxidation of $ArR \rightarrow ArCO_2H$
- b) Oxidation of 1° alcohols and aldehydes.
- c) $CO_2 + RMgBr \rightarrow$ carboxylic acid.

8. Interconversions of carboxylic acids and derivatives.

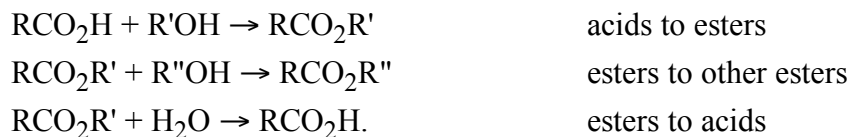
- a) Anything (esters, amides, acyl chlorides, and nitriles) can be converted into a carboxylic acid by aqueous base or aqueous acid.
 - i) Mechanisms are addition–elimination; for nitrile, it is addition to give an amide, then addition–elimination.
 - ii) Under basic conditions, driving force is formation of carboxylate ion.
 - iii) Under acidic conditions, reaction is driven by equilibrium.
 - iv) Equilibrium can be driven by thermodynamics (acyl chlorides), excess of H_2O (esters), or prevention of reverse reaction by protonation of leaving group (amides).
- b) Acids to anything.
 - i) An acid can be converted into an acyl chloride with $SOCl_2$. Mechanism involves an addition–elimination step. Acidic conditions.
 - ii) Acyl chlorides can be converted into anything:



A weak base such as Et_3N is usually used also, so conditions are basic. In case of amide formation, amine can be used in two-fold excess, with one equivalent acting as nucleophile and one as base. Mechanisms are addition–elimination.

- c) Esters and acids are interconvertible.

i) Under *acidic* conditions:



Equilibrium reaction driven by excess of R''OH. Most useful for converting acids to simple esters such as Et and Me esters.

ii) Under *basic* conditions, esters can be converted into acids or other esters, but acids cannot be converted into esters.

iii) Lactones are cyclic esters and can be made by Fischer esterification also.

d) Amides can be made from esters or acids.

i) Esters + amine. Reaction proceeds because of greater stability of amides and good nucleophilicity of RNH₂.

ii) Acids + amines doesn't work because amines are also bases.

iii) Acids + amines + DCC. Proceeds through *O*-acylisourea that is analog of acyl halide. Can be used to make peptides.

e) 1° Amides are converted to nitriles by dehydration with SOCl₂.

Interconversions of carboxylic acid derivatives.

