

Carboxylic Acid Derivatives

Reading: Wade chapter 21, sections 21-1- 21-16

Study Problems: 21-45, 21-46, 21-48, 21-49, 21-50, 21-53, 21-56, 21-58, 21-63

Key Concepts and Skills:

- Interpret the spectra of acid derivatives; show how the carbonyl stretching frequency in the IR depends on the structure of the acid
- Show how acid derivatives are interconverted by nucleophilic acyl substitution from more reactive to less reactive derivatives. Show how acid chlorides serve as activated intermediates to convert acids to acid derivatives
- Show how acid catalysis is used to synthesize acid derivatives, and show how acid derivatives hydrolyze to carboxylic acids under acidic or basic conditions.
- Show the products of the reaction of acid derivatives with reducing agents and Grignard reagents

Lecture Topics:

I. Structures and reactivity of carboxylic acid derivatives

Acid chlorides are the most reactive of the carboxylic acid derivatives, and they can be converted to all other derivatives by nucleophilic acyl substitution. Anhydrides are slightly less reactive than acid chlorides. Esters are less reactive than anhydrides; amides and nitriles are less reactive than esters. Hydrolysis of any carboxylic acid derivative gives a carboxylic acid, which can be converted to any other carboxylic acid via the acid chloride. Note that it is impossible to directly prepare an ester, acid chloride, or anhydride from an amide; it is impossible to prepare an anhydride or acid chloride from an ester, and so on.

II. Spectroscopy of Acid Derivatives

A. Infrared spectra

The carbonyl stretching frequencies are an indication of the bond order and mirror the importance of the minor resonance contributor in the structure of each acid derivative. Note that acid chlorides have relatively little resonance overlap between the chlorine lone pairs and the carbonyl, resulting in a very strong and stiff C=O. Amides, on the other hand, have excellent lone-pair overlap of the nitrogen lone pair with the carbonyl group, and we see a low stretching frequency indicative of partial single bond character

B. NMR

Alpha protons to the carbonyl of acid derivatives resonate at 2.0-2.5 ppm. Protons adjacent to the heteroatom (N,O) resonate at 3-4 ppm. Formate and formamide protons directly attached to the carbonyl resonate at 8 ppm. The carbonyl carbons resonate at 170 ppm in ^{13}C spectra, while carbons neighboring heteroatoms resonate at 50-60 ppm. For N,N-dimethyl amides, restricted bond rotation about C-N (because of partial N-lone pair overlap with the carbonyl) results in two separate methyl resonances in the ^1H NMR.

c. Diazomethane for preparation of methyl esters:

d. Transesterification (see reactions of esters below)

Reactions of esters. Esters are more stable to nucleophilic acyl substitution than acid chlorides or anhydrides; they are more reactive than amides

- a. *Unstabilized nucleophiles:* LiAlH_4 and Grignard reagents successively add two equivalents of nucleophile to esters to yield 1° alcohols and 3° alcohols, respectively. This is the case because in reduction, the intermediate aldehyde is more reactive than the starting ester, and for Grignard reactions, the intermediate ketone is more reactive than the starting ester.

B. Reactions with weak nucleophiles

1. amines

Synthesis of amides by reaction of esters with amines; amines are good nucleophiles. Note that alkoxides are better leaving groups from the tetrahedral intermediate than amide ions because the negative charge resides on the more electronegative element oxygen rather than nitrogen. The transition state for the rate-determining step resembles the tetrahedral intermediate, and thus the stability of the expelled ion is not reflected in the transition state energy.

2. Alcohols

Acid-catalyzed transesterification (the interconversion of two esters bearing different alkoxy groups) occurs by a mechanism very similar to the Fischer esterification. There is also a base-promoted variant of this reaction. In all cases, transesterification is an equilibrium process that must be shifted toward product by either using an excess of reactants or by removing the by-product alcohol (by distillation)

3. Water as a weak nucleophile

Hydrolysis of esters to acids occurs under acidic or basic conditions. The acid-catalyzed process is simply the reverse of the Fischer esterification. The base promoted process is not a reversible equilibrium since the base deprotonates the product acid quantitatively, thus removing it from the equilibrium process.

IV. Amides and Lactams

An amide is a composite of a carboxylic acid and ammonia or an amine.

Amides protonate on the carbonyl oxygen, not on nitrogen, as can be seen from the second best resonance form of the amide:

Examples:

Lactams are cyclic amides formed by heating amino acids , effecting dehydration.

Synthesis of Amides. *Remember: amides are the least reactive carboxylic acid derivatives*

Reactions of Amides: Since amides are the most stable of the carboxylic acid derivatives, there are relatively few reactions they undergo

- a. unstabilized nucleophiles: Reduction. Hydride reduction proceeds by two sequential hydride transfers; first to the amide, and then to an intermediate imine.

b. Stabilized Nucleophiles: H₂O

Hydrolysis of amides occurs under acidic or basic conditions to yield acids. The reaction usually requires prolonged heating in concentrated acid or base. Again, each step is an equilibrium except for the last step which is fast and irreversible.

Note: lactams are quite resistant toward hydrolysis with one exception: four-membered lactams known as β -lactams are susceptible to nucleophilic attack at the carbonyl carbon due to excessive ring strain:

c. Dehydration of amides to nitriles

Treatment of a primary amide with POCl_3 or P_2O_5 effects dehydration to give the nitrile: