Lecture 6:   Hydrolysis Reactions of Esters and Amides

Objectives:

By the end of this lecture you will be able to:

- draw the mechanism of ester hydrolysis under acidic and basic reaction conditions;
- account for the irreversibility of the hydrolysis reaction under basic conditions;
- form new esters by base- or acid-catalysed transesterification mechanisms;
- draw the mechanism for cleaving *tert*-butyl esters and understand why the mechanism is different from that for methyl esters;
- understand why protonation of an amide occurs on oxygen and not on nitrogen;
- draw the mechanism of hydrolysis of amides under acidic and basic reaction conditions.

Introduction

We have seen that carboxylic acid derivatives usually react through nucleophilic addition-elimination mechanisms. The parent carboxylic acid can be obtained from all its derivatives by this mechanism through a hydrolysis process. We shall just consider the mechanism of hydrolysis of esters and amides although similar reaction pathways are followed with other carboxylic acid derivatives.

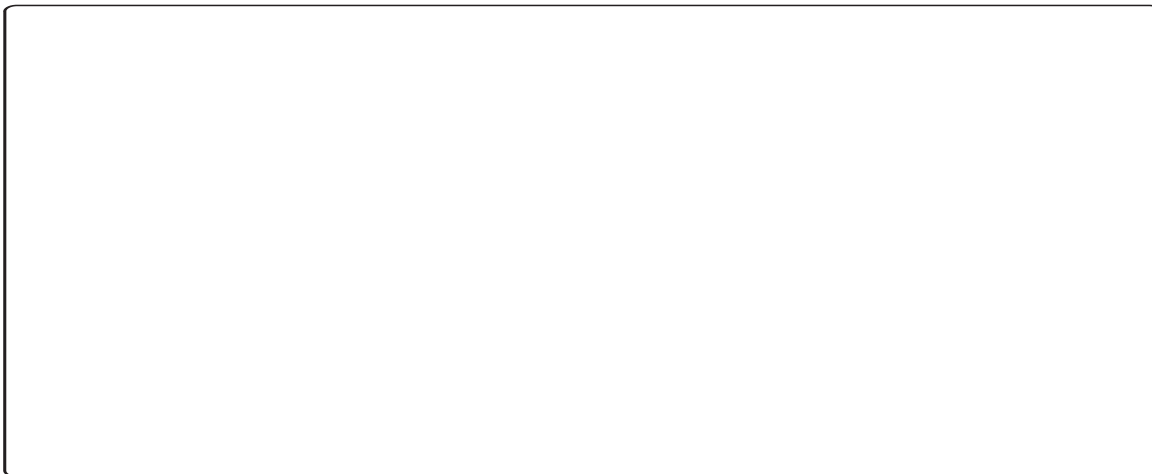## Hydrolysis of Methyl Esters

Unlike acid chlorides, which are strong electrophiles and react readily with mild nucleophiles such as water, esters are much less electrophilic and do not react with water at pH 7 to any appreciable extent. However, the rate of ester hydrolysis can be substantially increased by carrying out the reaction under acidic or basic conditions.

Acid-Catalysed Hydrolysis of Methyl Esters

Since water is such a poor nucleophile, one method for increasing the rate of nucleophilic addition with an ester is to increase the electrophilicity of the ester. This can be achieved in a number of ways. The most common is to use a Lewis acid or Brønsted acid to form a positively charged intermediate that is far more reactive and with which even mild nucleophiles such as water will react.

Notes:

- the reaction is catalytic in acid.
- the reaction is an equilibrium process; thus the reverse reaction can be used to form esters from carboxylic acids. When carrying out hydrolysis reactions, a large excess of water (often used as a co-solvent), is used to drive the reaction over to the carboxylic acid product.
- to form an ester from a carboxylic acid under these conditions (*i.e.* the reverse reaction), carry out the reaction in an alcoholic solvent:
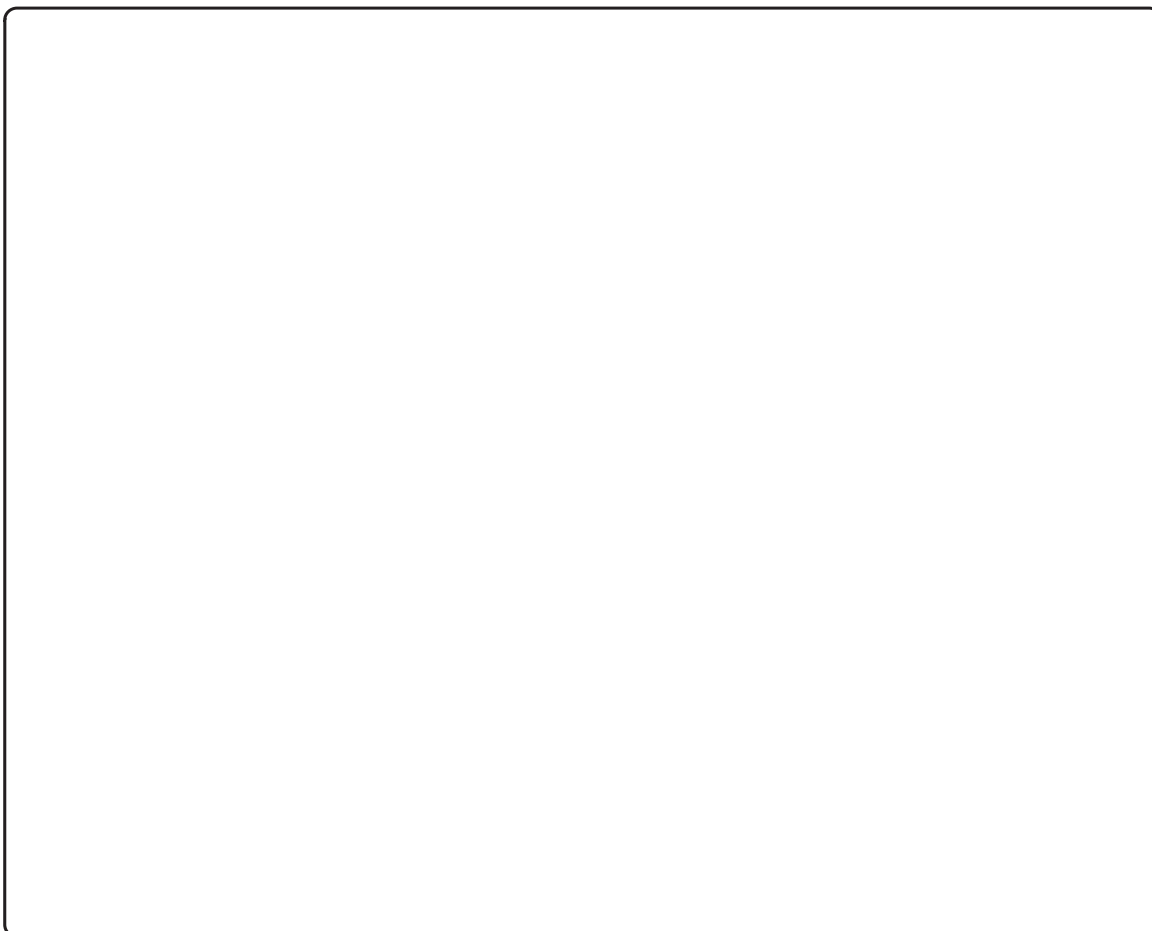
A related reaction is acid-catalysed transesterification, which also proceeds under similar conditions. The reaction is again an equilibrium process so to drive the forward reaction, an excess of the alcohol (often used as the solvent) that will provide the new ester is used:

Base-Mediated Hydrolysis of Methyl Esters

An alternative method for increasing the rate of ester hydrolysis is to increase the reactivity of the nucleophile. Negatively charged species are generally more nucleophilic than electronically neutral species (they are also more basic). On these grounds hydroxide should be, and is, a better nucleophile than water.
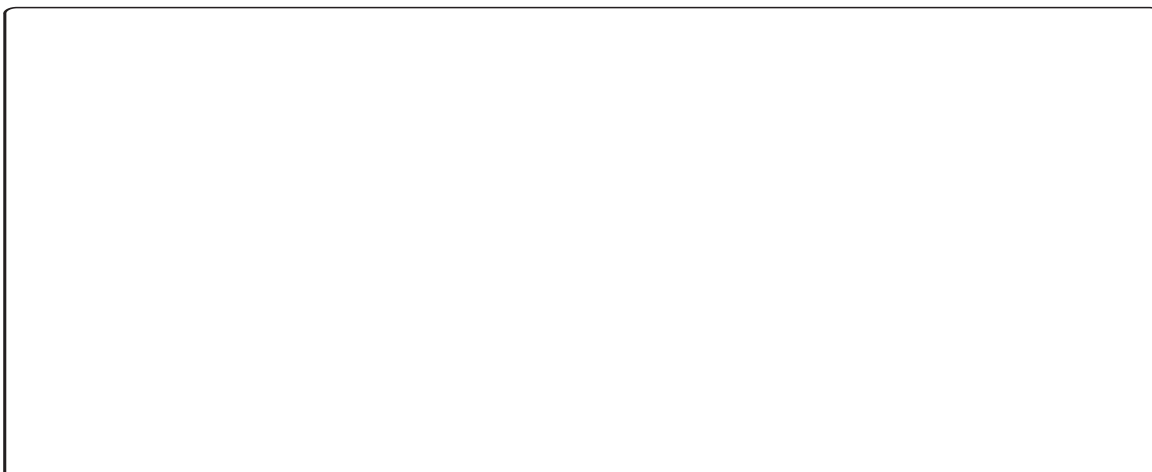
Mechanism

Notes:

- The first step involves nucleophilic attack of hydroxide on the ester in the standard fashion to afford a tetrahedral intermediate. This step is reversible.
- Collapse of the tetrahedral intermediate back to a carbonyl compound can proceed either by expulsion of the hydroxyl (return to starting material) or the methoxy group. Both will occur at a similar rate as both methanol and water have similar pK_a values (~15) *i.e.* they exhibit similar leaving group capacities.
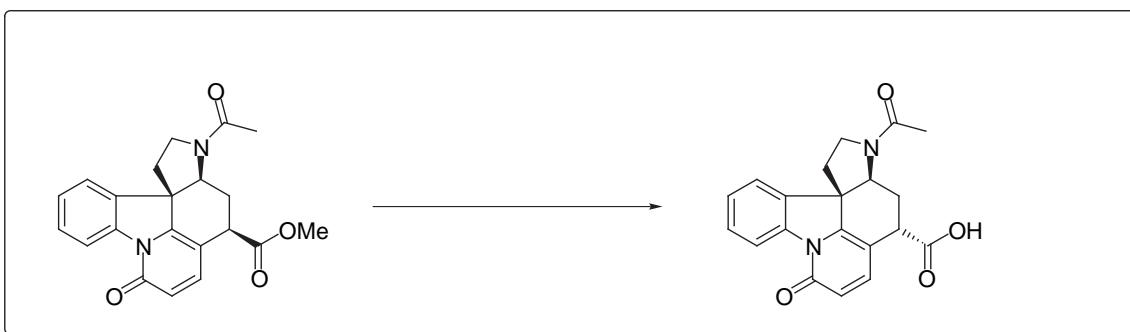
- So what is it that drives the reaction forward to product?

  If we consider the loss of methoxide, the carbonyl-containing product is a carboxylic acid. Methoxide is a relatively good base and can abstract the proton of the carboxylic acid in an acid-base process. The large difference in pK_a values between an alcohol and a carboxylic acid (>10 pK_a units) ensures that ionisation of the carboxylic acid is essentially complete:

- Since the carboxylate product is negatively charged it is no longer electrophilic; the net result is that the reverse reaction is effectively completely suppressed. As a result of this, the base-mediated hydrolysis reaction is a more efficient method for forming a carboxylic acid from an ester than the corresponding acid-catalysed process.
- Since one mole of hydroxide is consumed for every ester that is hydrolysed, the reaction is NOT catalytic in base.

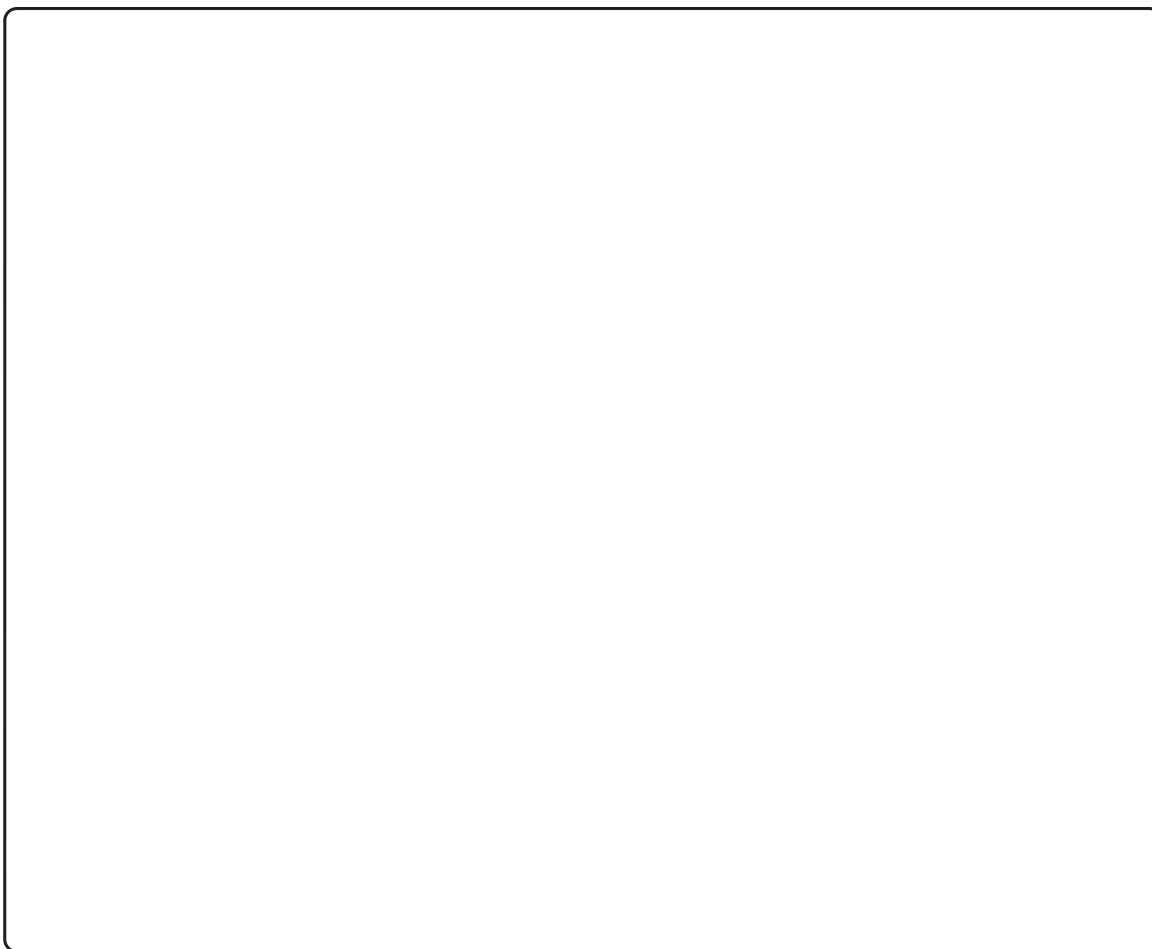Example from R. B. Woodward's synthesis of strychnine:

Acid-Catalysed Hydrolysis of *tert*-Butyl Esters

Simple alkyl esters, such as methyl and ethyl esters, are hydrolysed under acidic conditions in a reaction mechanism that is described as an **A$_{AC}$2** reaction: the reaction is _acid-catalysed_, the _acyl–oxygen_ bond is cleaved and there are two molecules involved in the rate-determining step, *i.e.* it is a _bimolecular process._

Other types of alkyl esters undergo hydrolysis *via* different reaction mechanisms. For example when the alkyl group can form a relatively stable carbocation, the hydrolysis proceeds *via* a so-called **A$_{AL}$1** reaction mechanism. The reaction is again _acid-catalysed_, only this time the _alkyl–oxygen_ bond is cleaved in a _unimolecular_ dissociative rate-determining step.

Hydrolysis of *tert*-butyl esters proceeds *via* this type of mechanistic pathway:
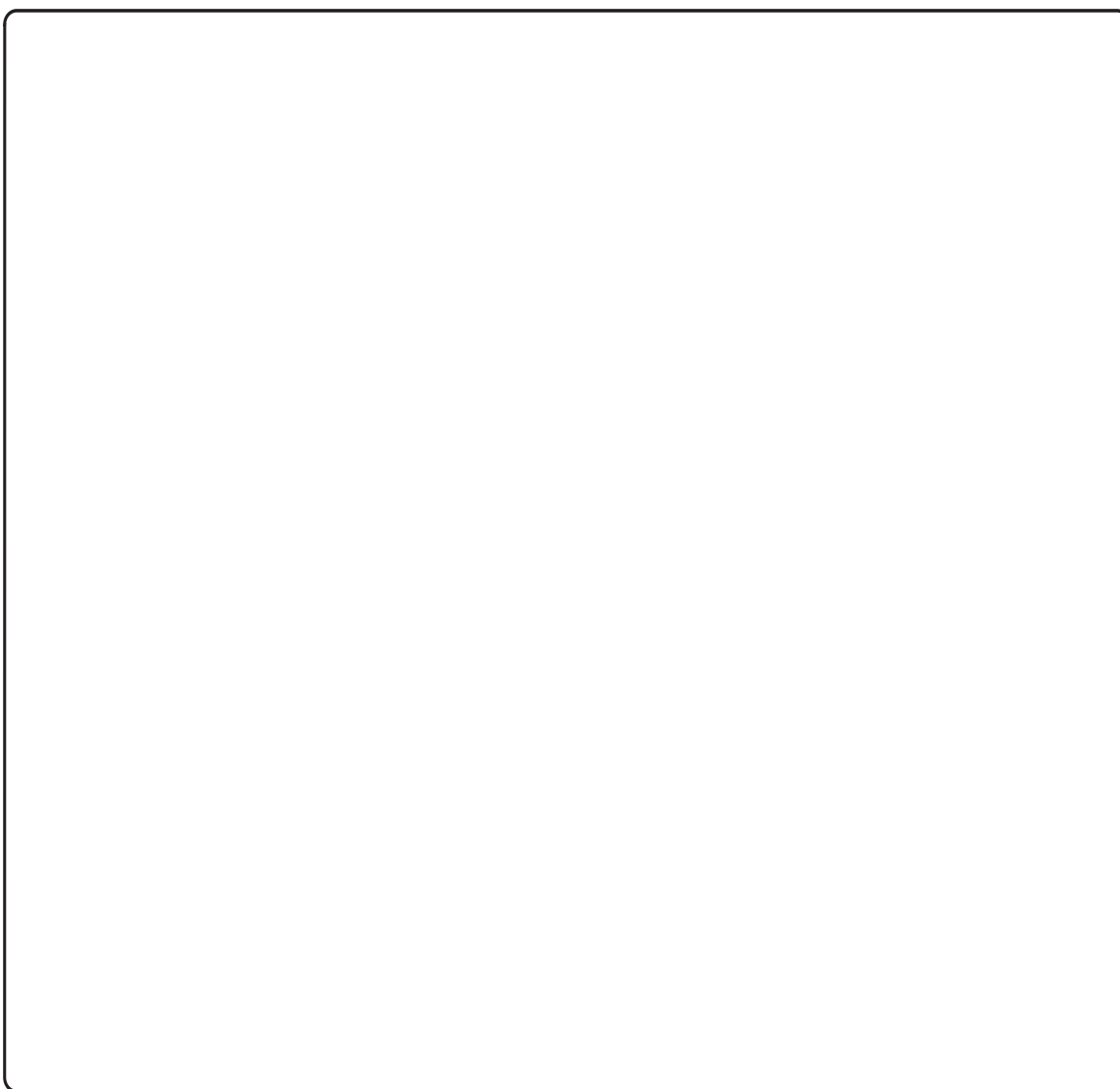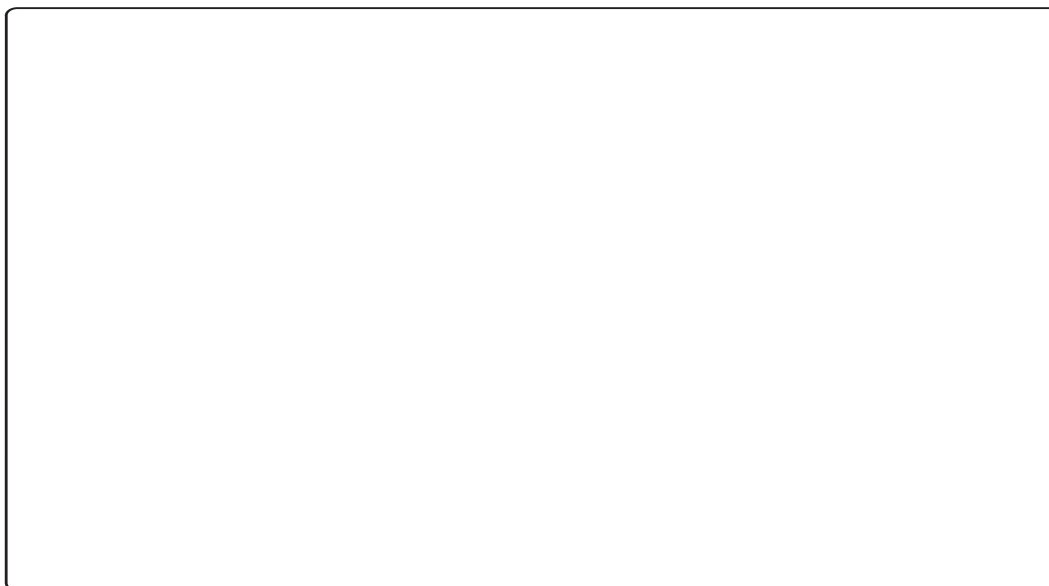
Hydrolysis of Amides

Owing to resonance stabilisation effects, amides are one of the least electrophilic carboxylic acid derivatives. Hydrolysis of an amide to the carboxylic acid therefore requires quite forcing reaction conditions.

Acid-Mediated Hydrolysis of Amides.

This reaction mechanism closely resembles the acid-catalysed hydrolysis of methyl esters. Proton transfer steps again increase the electrophilicity of the amide carbonyl group, and also generate a better leaving group (an amine instead of an amide):
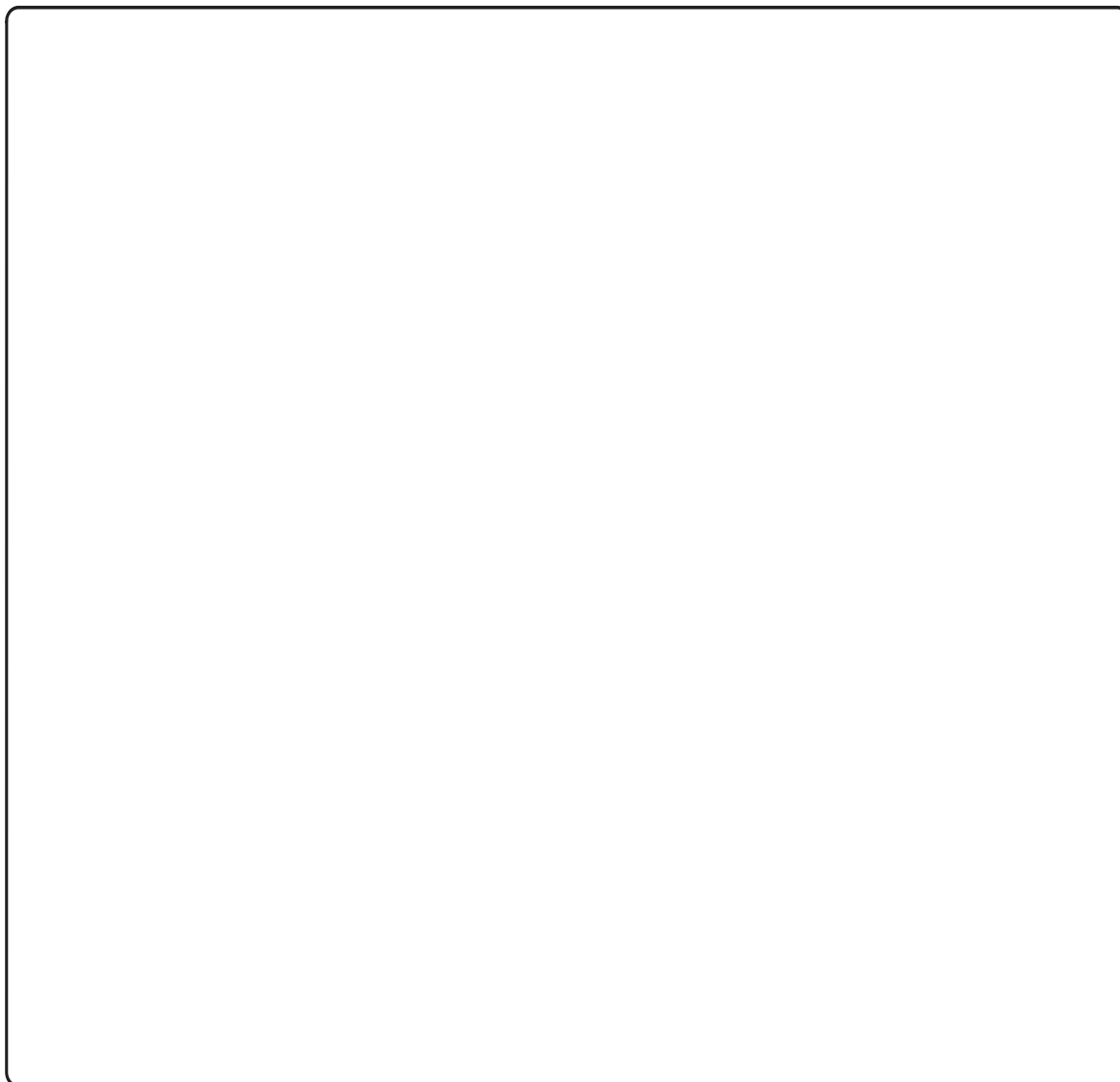
Although protonation on an amide can conceivably occur either on the oxygen or on the nitrogen centre, in reality it *always* occurs on oxygen: unusually oxygen is more basic than nitrogen. This observation can be readily rationalised by considering the relative stability of the two protonated species:

Base-Mediated Amide Hydrolysis

Amides can also be hydrolysed under basic conditions. Since an amide (R_2N^-) is such a poor leaving group, a protonation step is required before the tetrahedral intermediate can collapse to a carboxylic acid. For the same reason as base-mediated hydrolysis of esters, the product from the reaction is the carboxylate salt.

The rate-determining step for this reaction is highly dependent on the reaction conditions and substrate. At high base concentrations, formation of the tetrahedral intermediate is rate-determining. At lower concentrations of base, collapse of this intermediate can become the RDS.

Summary

Esters and amides are two of the least reactive carboxylic acid derivatives. Both groups benefit from a resonance stabilisation effect that is lost when a nucleophile attacks to form a tetrahedral intermediate. The greater is the resonance stabilisation, the lower is the energy of the starting material and therefore the larger is the barrier to forming the tetrahedral intermediate (usually rate-determining). This accounts for the observation that amides are less electrophilic than esters.

Nevertheless both esters and amides can be hydrolysed to the parent carboxylic acid. Reaction is very sluggish at pH7; however by using acidic conditions to increase the electrophilicity of the carbonyl centre, or using a base to generate a more reactive nucleophile (hydroxide), the hydrolysis can be made to proceed at reasonable rates.

The precise mechanism of acid-catalysed hydrolysis of esters depends on the structure of the alkyl group in the ester. A mechanism involving cleavage of the acyl–oxygen bond is most common and is observed for all simple esters. *tert*-Butyl esters, however, react through a different mechanism involving scission of the alkyl–oxygen bond in the rate-determining step.

Acid-catalysed hydrolysis reactions are reversible. The forward reaction is driven over to product by using an excess of water, usually as the solvent. Base-mediated hydrolyses, however are essentially irreversible because the product is a non-electrophilic carboxylate salt.

Transesterification reactions proceed *via* similar mechanisms and are also catalysed by either acid or base.

Protonation of amides occurs on oxygen and not on nitrogen.