

## Lecture 5: Nucleophilic Addition Reactions of Carboxylic Acid Derivatives

### Objectives:

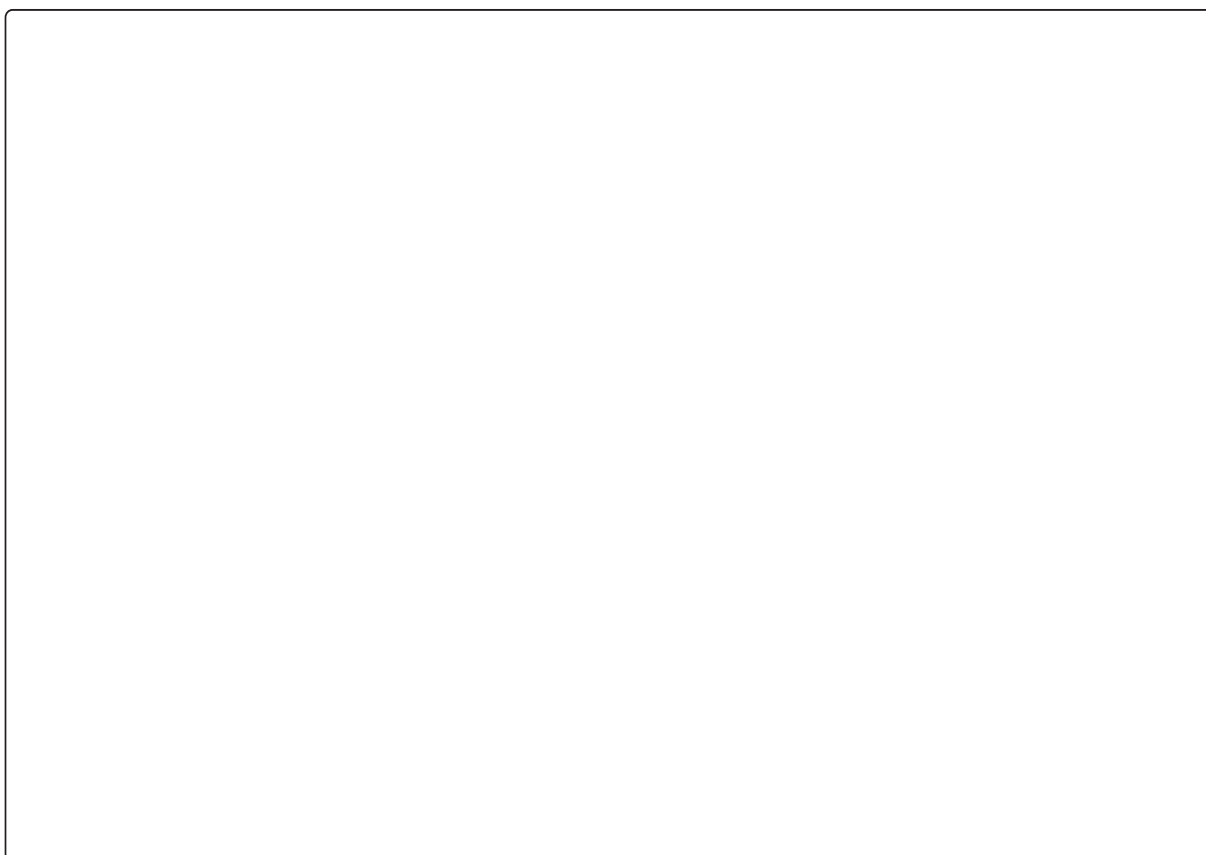
By the end of this lecture you will be able to:

- draw the mechanism of a nucleophilic addition-elimination reaction with a carboxylic acid derivative;
- rationalise the relative reactivity of carboxylic acid derivatives towards nucleophilic attack;
- use  $pK_a$  values to predict leaving group ability.

### Introduction

The most important reaction for aldehydes and ketones is nucleophilic addition. Carboxylic acid derivatives are also electrophilic in nature and not surprisingly also react with a wide range of nucleophiles. However the presence of a *leaving group* in the tetrahedral intermediate means that the mechanism has to be modified slightly.

Compare the reaction of a simple Grignard reagent, MeMgBr, with an aldehyde, benzaldehyde and with a carboxylic acid derivative, benzoyl chloride:



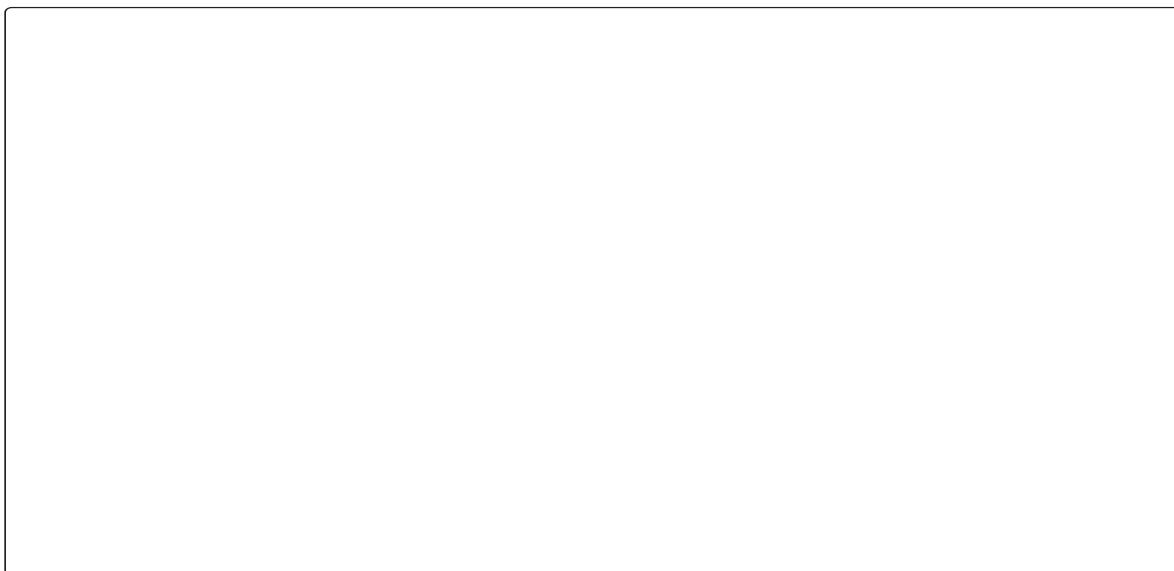
- Benzaldehyde reacts with the Grignard reagent to provide a secondary alcohol.
- The product from the reaction with the acid chloride and one equivalent of Grignard reagent is a ketone.

In both cases the first step is addition of the nucleophile to the electrophilic carbonyl carbon to form a *tetrahedral intermediate*.

In the case of benzaldehyde, this intermediate cannot react further and is quenched on work-up to provide an alcohol product.

In the case of benzoyl chloride, the tetrahedral intermediate collapses to a ketone by expelling a chloride anion. It can do this because chloride is a good *leaving group*. Since C=O groups are strong bonds, the re-formation of this bond provides a strong thermodynamic driving force. The reaction that most closely resembles this process with aldehydes and ketones is reversible addition of a nucleophile such as water or cyanide; in these cases, the nucleophile is also a good leaving group, which renders the addition process reversible.

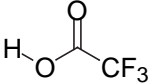
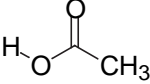
Carboxylic acid derivatives react with nucleophiles through a nucleophilic addition-elimination sequence. The general mechanism is as follows:



Clearly if the nucleophile is also a good leaving group then this can be expelled from the tetrahedral intermediate returning to the starting material. Thus *to proceed to product, X must be a better leaving group than Nu<sup>-</sup>*.

## What makes a Good Leaving Group?

Acid chlorides are more reactive than esters partly because the chloride anion is a weaker conjugate base than an alkoxide, or in other words, H-Cl is a stronger acid than MeO-H. Once again we see the importance of  $pK_a$  values; this time we are using them to determine the relative leaving group ability of substituents.

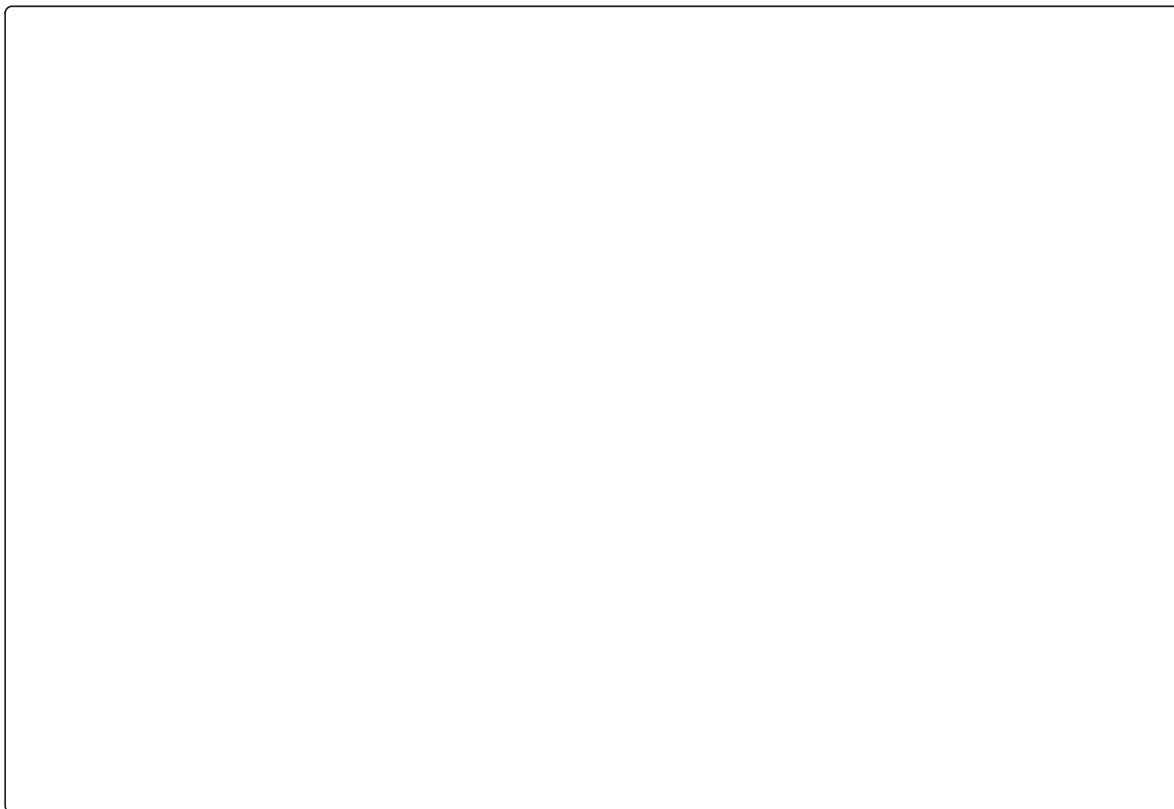
$H-A \rightleftharpoons A^- + H^+$	$pK_a$ value
H-Br	
H-Cl	
	
	
MeO-H	
H-NMe <sub>2</sub>	

From the table of  $pK_a$  values, it is now obvious why acid chlorides are one of the most reactive carboxylic acid derivatives. Chloride is a very stable anion as indicated by the low  $pK_a$  value of H-Cl (the acid is essentially completely ionised in water).

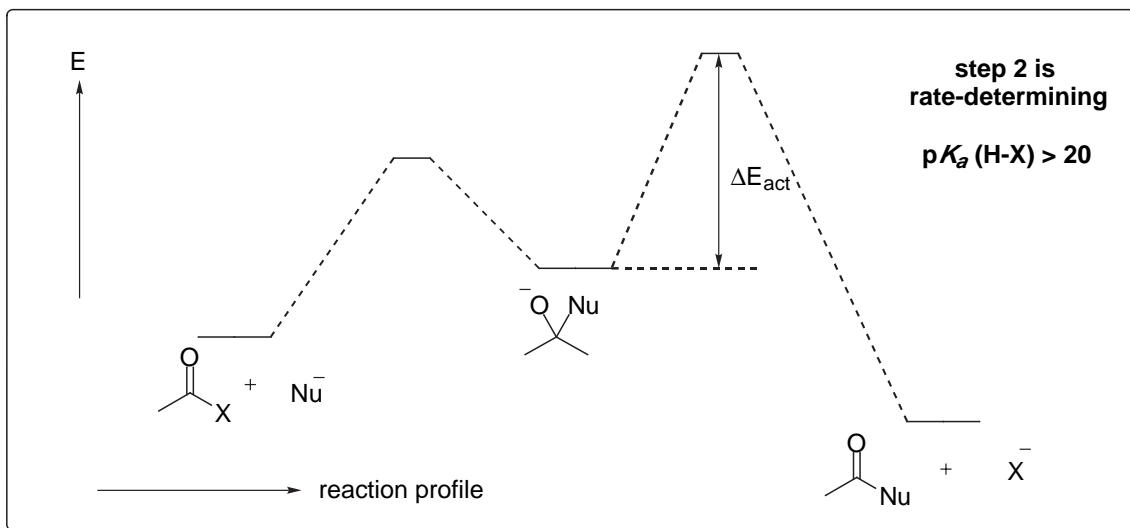
Acid anhydrides are less reactive than acid halides although by changing the substituents on the acyl leaving group it is possible to influence the leaving group ability of the carboxylate.

### Which Step is Rate-Determining?

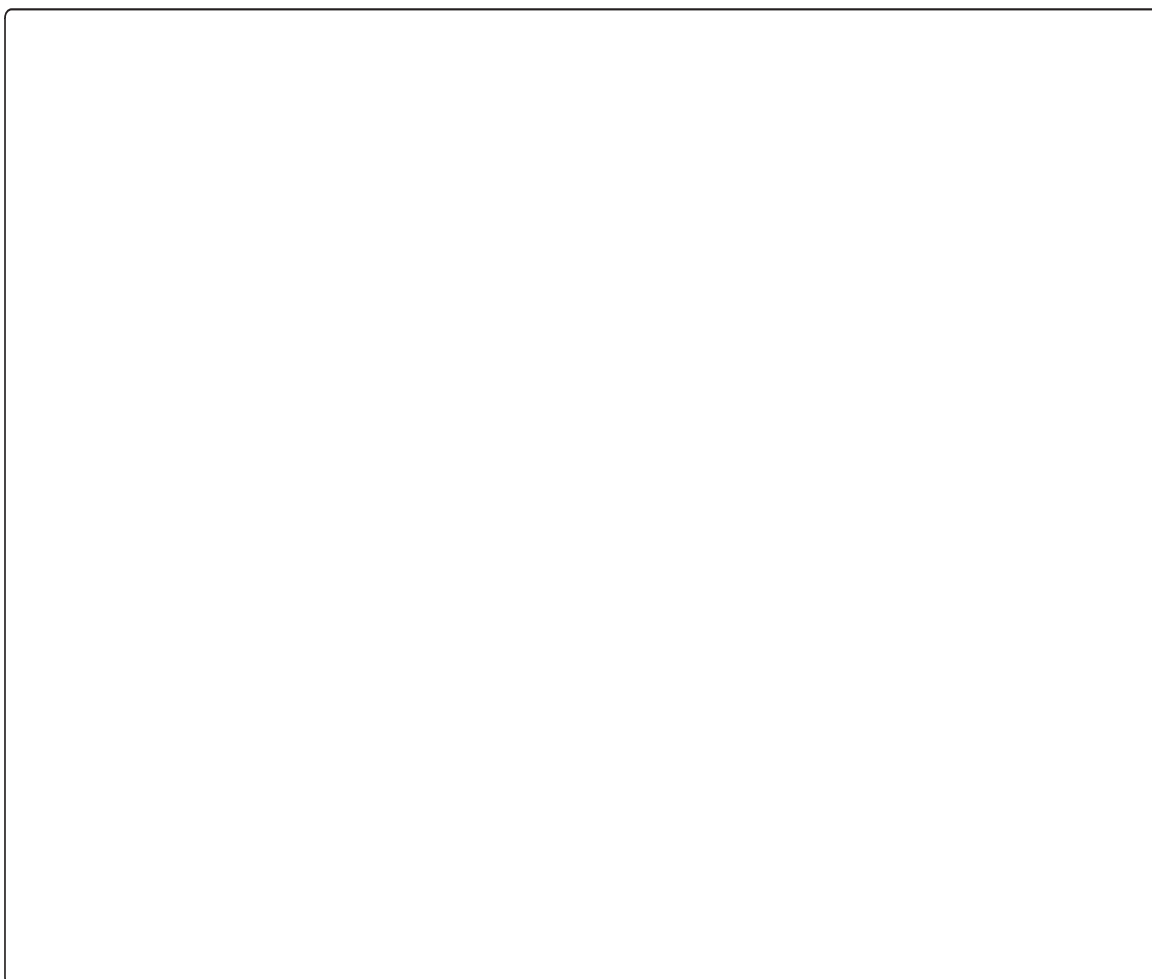
The ability of the heteroatom substituent to behave as a leaving group can govern which step is rate-determining. For a general carboxylic acid derivative  $RC(O)X$ , if the  $pK_a$  of  $H-X < 20$  then the rate-determining step is formation of the tetrahedral intermediate. This kinetic profile is therefore observed for acid halides, anhydrides and esters:-



We can see from the  $pK_a$  table earlier that the dialkylamide anion will be a very very poor leaving group; in fact it is so poor that it almost never behaves as such. For this type of carboxylic acid derivative, nucleophilic addition and formation of a tetrahedral intermediate is still possible. However now this intermediate is *relatively* stable and does NOT break down until the work-up where the dialkylamide leaving group can be modified; thus for carboxylic acid derivatives,  $RC(O)X$ , if the  $pK_a$  of  $H-X > 20$  then the rate-determining step is breakdown of the tetrahedral intermediate. This kinetic profile is therefore observed for amides and carboxylates.

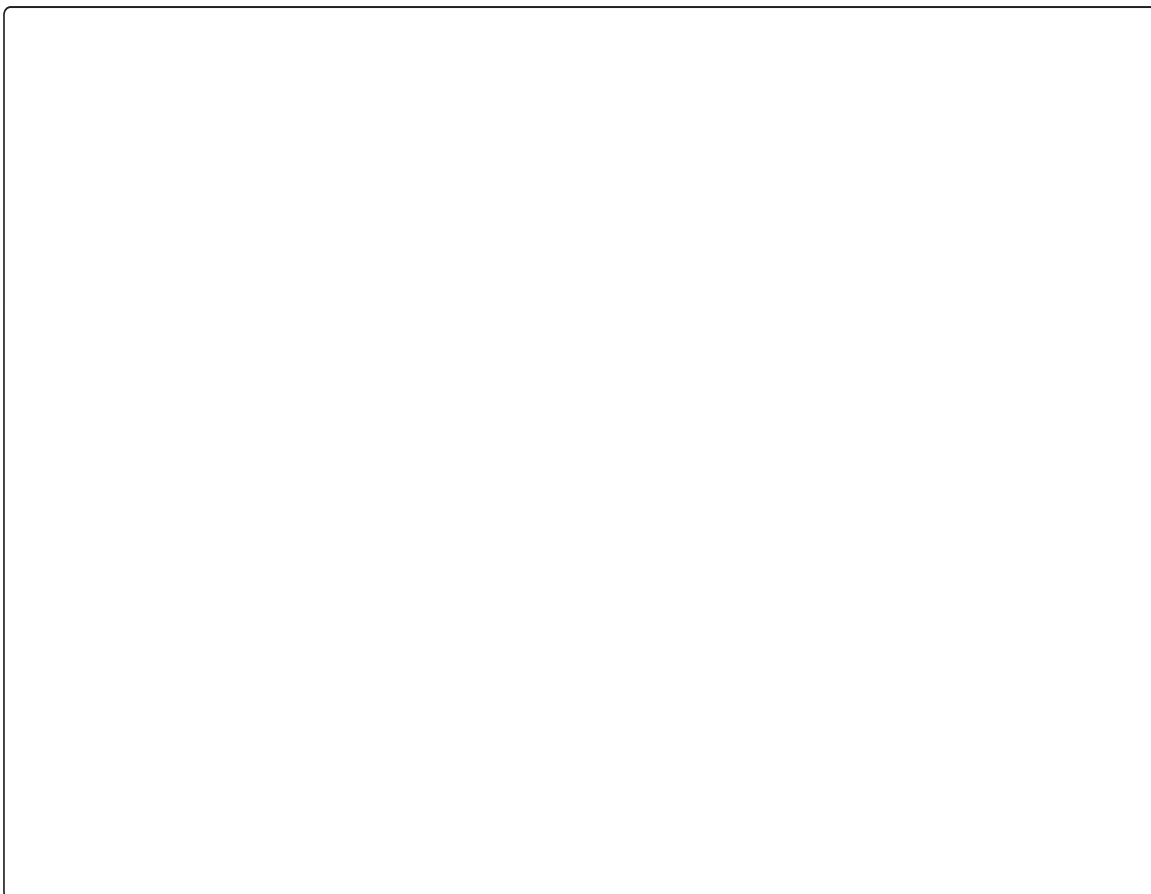


Consider the reaction of an ester with 2 equivalents of a Grignard reagent.



Collapse of the first tetrahedral intermediate generates a ketone, which is *even more electrophilic* than an ester and therefore reacts again with the second equivalent of Grignard reagent to provide a tertiary alcohol on work-up.

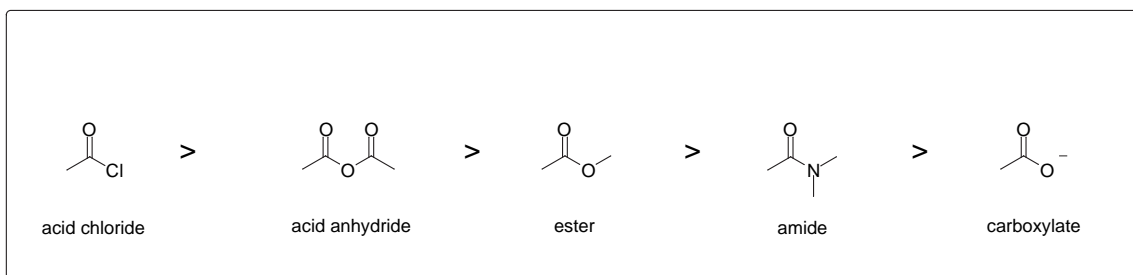
Now consider the reaction of a tertiary amide with 2 equivalents of a Grignard reagent.



Reaction of the first equivalent of Grignard reagent provides a tetrahedral intermediate that does not collapse until the work-up when protonation of the nitrogen group generates a much better leaving group (an amine). At the same time, the second equivalent of Grignard reagent is destroyed. The net result is that the intermediate ketone can be isolated.

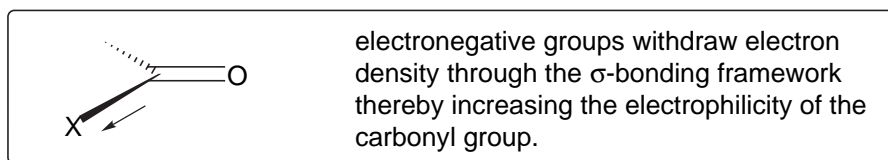
### Relative Reactivity of Carboxylic Acid Derivatives Towards Nucleophilic Attack.

There are many types of carboxylic acid derivatives. The order of reactivity towards nucleophilic addition-elimination of a few is as follows:

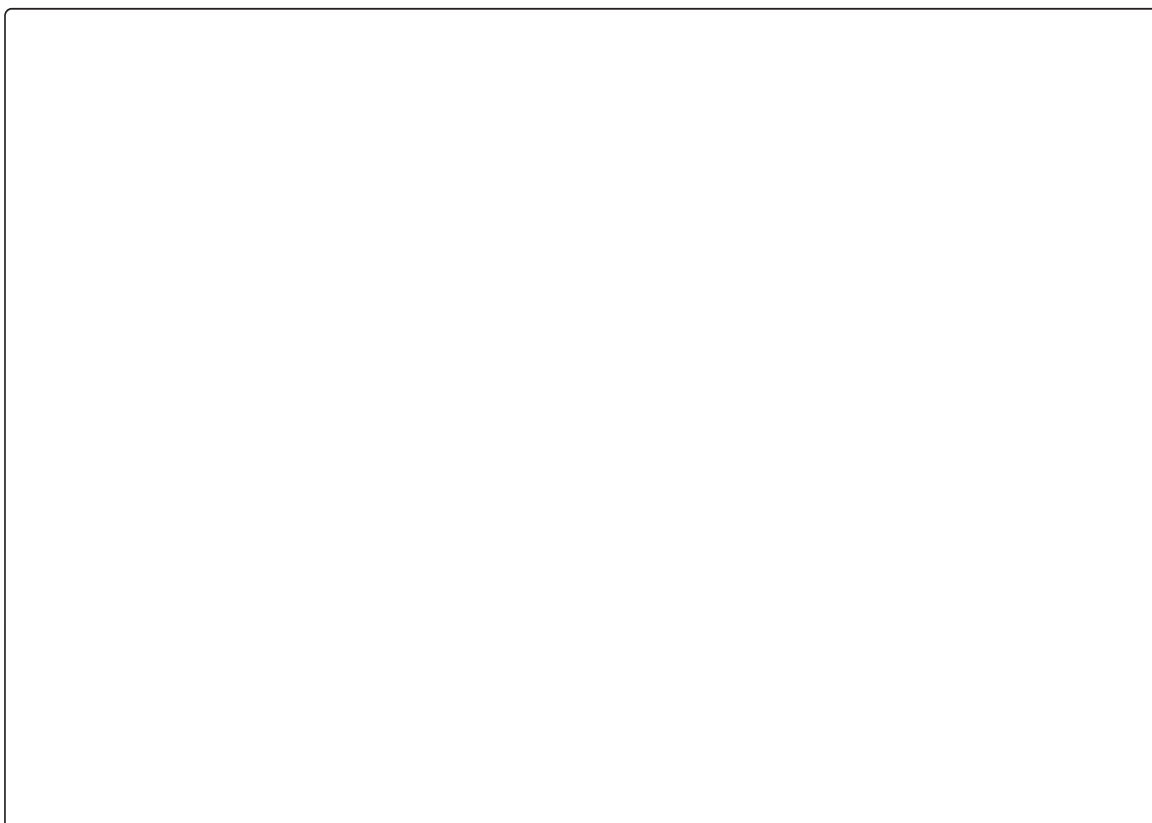


We need to be able to rationalise this order of reactivity. In essence the more  $\delta^+$  charge on the carbonyl carbon, the more electrophilic is the group and more reactive it is towards nucleophilic addition. Substituents modulate the degree of  $\delta^+$  charge on the carbonyl group by *resonance* and *inductive* effects.

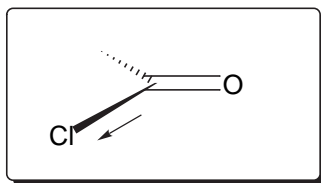
**Inductive effects** can withdraw or push electron density away or towards the carbonyl carbon. The effect operates through the  $\sigma$ -bonding framework. Strongly electronegative elements such as chlorine exert a powerful  $-I$  inductive effect which increases the  $\delta^+$  charge on the carbonyl carbon thereby increasing its electrophilicity and susceptibility towards nucleophilic attack.



**Resonance effects** operate through the  $\pi$ -bonding framework. They tend to push electron density on to the carbonyl group rendering it less electrophilic. For resonance stabilisation to be able to operate, the substituent must have available electrons (lone pair) in an orbital that can overlap with the  $\pi$ -bond (this accounts for the planarity of amides and esters - the C-O/N bond has double bond character).



### Acid Chlorides:

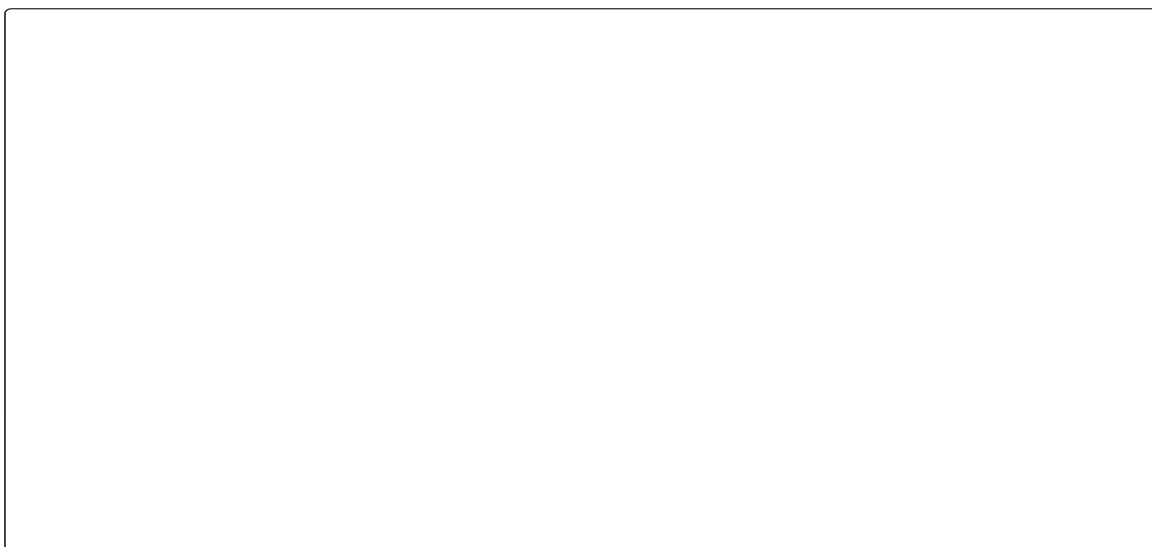


Chlorine is a very electronegative element and therefore exerts a strong  $-I$  inductive effect that increases the  $\delta+$  charge on the carbonyl carbon rendering it highly electrophilic. Although it has lone pairs which can take part in resonance stabilisation, these are in a 3p AO and therefore do not overlap efficiently with the  $\pi$ -MOs in the C=O group that are derived from overlapping 2p AOs.

**Net result:** Acid chlorides are one of the most electrophilic carboxylic acid derivatives and react readily even with relatively weak nucleophiles.

### Acid Anhydrides

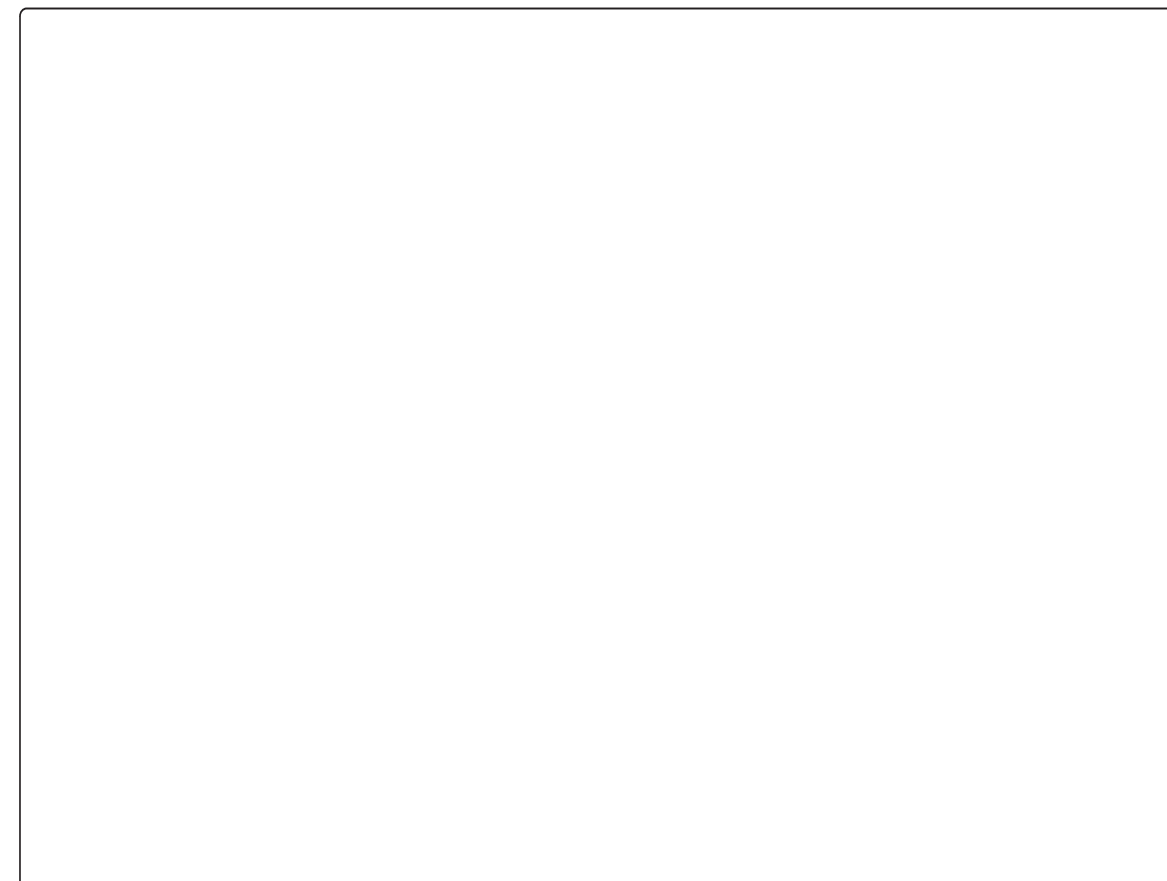
Acetates are better electron-withdrawing groups than alkoxy groups and therefore acid anhydrides are more electrophilic than esters. They are less reactive than acid chlorides.



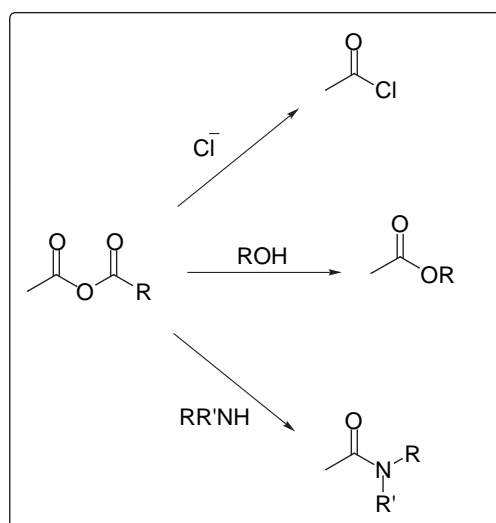
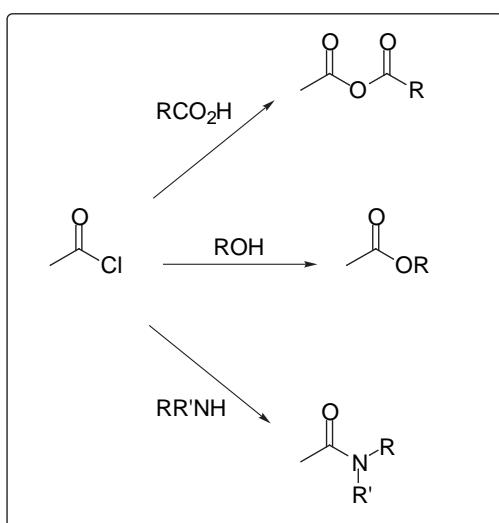
### Esters and Amides

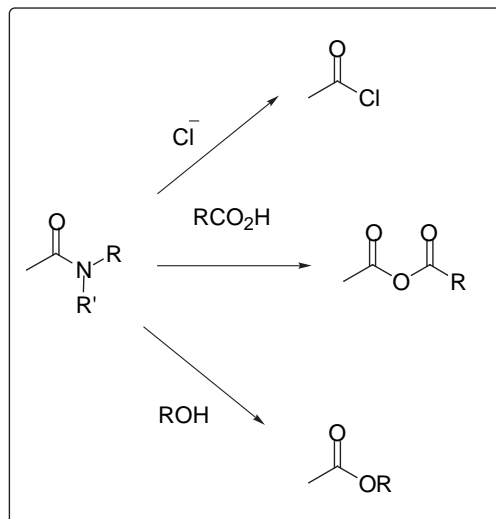
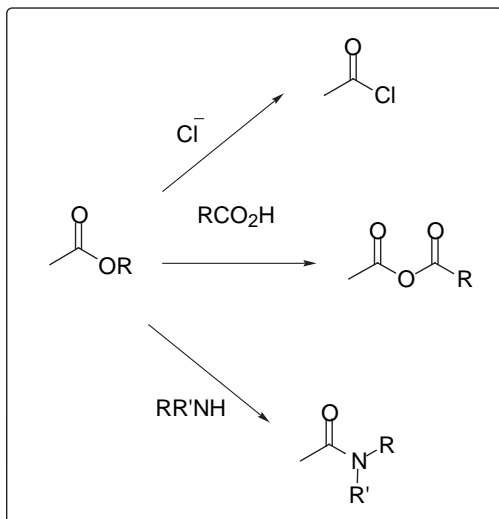
Resonance stabilisation overrides electron withdrawal through inductive effects in esters and amides rendering them less electrophilic than acid chlorides and acid anhydrides. Nitrogen is also less electronegative than oxygen which makes resonance stabilisation more important in amides. As a result amides are not very electrophilic at all.





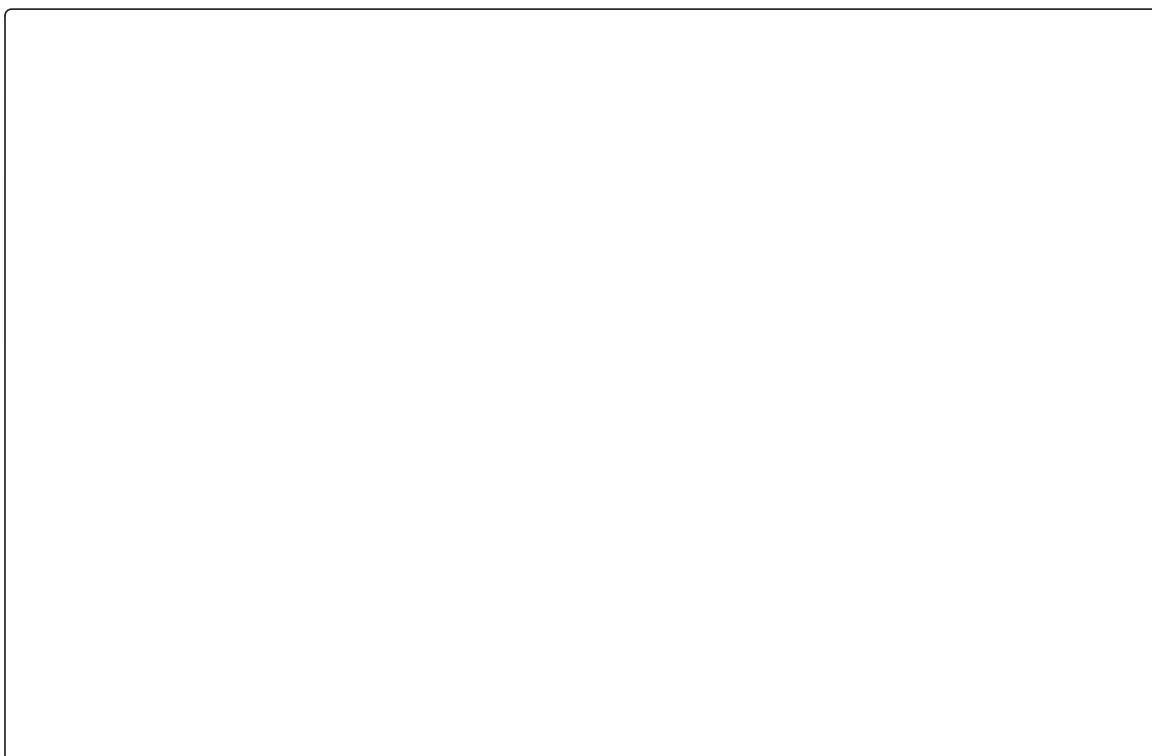
As a consequence of the differing electrophilicities of carboxylic acid derivatives, acid chlorides can be used to form acid anhydrides, esters and amides. Acid anhydrides readily react with alcohols and amines to form esters and amides respectively but they do not react with chloride to form acid chlorides; chloride is a better leaving group than acetate making the addition reaction reversible. Amides being the least electrophilic and possessing the worst leaving group, cannot be used to form esters, anhydrides or acid chlorides.





### Why are carboxylic acids such poor electrophiles?

Carboxylic acids possess an acidic proton ( $\text{p}K_a(\text{AcOH}) = 4.74$ ). As nucleophiles are also capable of behaving as bases, exposure of a carboxylic acid to a nucleophile invariably results in an *acid-base reaction* to form the negatively charged carboxylate salt.



Since the carboxylate salt is now negatively charged, it is no longer electrophilic and therefore not reactive towards further attack by electron-rich nucleophiles.

## Summary

The presence of a potential leaving group in the tetrahedral intermediate resulting from nucleophilic attack on a carboxylic acid derivative allows the formation of a new carbonyl functional group by expulsion of this leaving group. The reaction of nucleophiles with carboxylic acid derivatives is therefore characterised by an addition-elimination reaction mechanism.

The rate-determining step of this reaction for  $RC(O)X$  depends strongly on the leaving group ability of X. For leaving groups where  $pK_a(H-X) < 20$  (esters, acid anhydrides and acid halides), formation of the tetrahedral intermediate is rate-determining. For leaving groups where  $pK_a(H-X) > 20$  (amides and carboxylates), breakdown of the tetrahedral intermediate is rate-determining.

Resonance and inductive effects affect the electrophilicity of the carbonyl carbon: when  $-I$  inductive effects are dominant, as in acid chlorides, we obtain highly reactive electrophiles; when resonance effects dominate, as in amides, weak electrophiles are obtained.

Carboxylic acids are not good electrophiles because the first reaction with a nucleophile is not addition to form a tetrahedral intermediate, rather an acid-base process that forms a negatively charged carboxylate salt, which is no longer electrophilic owing to its negative charge.