Carboxylic acid derivatives: Acyl Chlorides and Acid Anhydrides

Acyl Chlorides

Acyl chlorides are much more reactive than carboxylic acids

\[
\text{Acyl Chloride} \quad \begin{array}{c} \text{CH}_3\text{C} \\text{O} \end{array} \quad \begin{array}{c} \text{Cl} \end{array}
\]

Acid Anhydrides

Acid anhydrides have a similar reactivity to acyl chlorides and therefore bring about the same changes in functional groups.

\[
\text{Acid Anhydride} \quad \begin{array}{c} \text{CH}_3\text{C} \\text{O} \end{array} \quad \begin{array}{c} \text{O} \qquad \text{O} \end{array} \quad \begin{array}{c} \text{CH}_3\text{C} \\text{O} \end{array}
\]

The main difference is the by-products. Acyl chlorides mostly give off HCl. Acid anhydrides give off RCOOH.

Explaining reactivity

Many of the reactions of the carboxylic acid derivatives follow the pattern below with an attack by an nucleophile.

\[
\begin{array}{c} \text{CH}_3\text{C} \\text{O} \end{array} \quad + \quad \begin{array}{c} :W \end{array} \quad \rightarrow \quad \begin{array}{c} \text{CH}_3\text{C} \\text{O} \end{array} \quad + \quad \begin{array}{c} :W \end{array}
\]

Where −W: and :W can be −Cl and Cl−

or −OCH₃ and OCH₃−

or −NH₂ and NH₂−

(acyl chlorides)

(esters)

(esters)

On a simplistic level, the stronger the electron attracting power of "W", the more positive the carbon, and the more attractive the carbon is to nucleophiles.

The relative attractive powers of the −W: are

−Cl > −OH > −OCH₃ > −NH₂

Therefore in the case of hydrolysis reactions, acyl chlorides are highly reactive and will be hydrolysed by weak nucleophiles such as water.

Amides and Esters contain only weak electron attracting W groups and need strong nucleophiles such as hydroxide ions in NaOH to hydrolyse.

This difference in reactivity is caused by a combination of two factors

1. the electronegativity of the Cl’s, N’s and O’s causing electron density to be withdrawn from the carbon making the carbon more positive and more attractive to nucleophiles—This factor makes them more reactive.

2. delocalisation of the lone pairs on these atoms into the carbonyl system which reduces the reactivity.

Comparing the reactivity of Acyl chlorides to amides

Acyl Chloride

\[
\begin{array}{c} \text{CH}_3\text{C} \\text{O} \end{array} \quad \begin{array}{c} \text{Cl} \end{array}
\]

Amide

\[
\begin{array}{c} \text{CH}_3\text{C} \\text{O} \end{array} \quad \begin{array}{c} \text{NH}_2 \end{array}
\]

Acyl chloride are more reactive than amides

Cl and N have similar electronegativities and so should attract electron density from the carbon by similar amounts, making the carbons equally positive.

However, the lone pair on the nitrogen delocalises with the π bond in the carbonyl group which decreases its reactivity.

The Cl is too big (3p orbital rather than 2p orbital in N) to be able to delocalise. This difference in the ability to delocalise explains the difference in reactivity.
**Reaction with water**

<table>
<thead>
<tr>
<th>Change in functional group: acyl chloride → carboxylic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reagent: water</td>
</tr>
<tr>
<td>Conditions: room temp.</td>
</tr>
</tbody>
</table>

\[
\text{RCOCl} (l) + \text{H}_2\text{O} \rightarrow \text{RCO}_2\text{H} + \text{HCl} (g)
\]

\[
\text{CH}_3\text{C}=\text{O} + \text{H}_2\text{O} \rightarrow \text{CH}_3\text{C}=\text{O} + \text{HCl} (g)
\]

Observation: Steamy white fumes of HCl are given off

<table>
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</tr>
</tbody>
</table>

\[
\text{(RCO)}_2\text{O} + \text{H}_2\text{O} \rightarrow 2\text{RCO}_2\text{H}
\]

\[
\text{CH}_3\text{C}=\text{O} + \text{H}_2\text{O} \rightarrow 2\text{CH}_3\text{C}=\text{O}
\]

**Nucleophilic Addition Elimination Mechanism**

**Reaction with alcohol**

<table>
<thead>
<tr>
<th>Change in functional group: acyl chloride → ester</th>
</tr>
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</tr>
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</tr>
</tbody>
</table>

\[
\text{RCOCl} (l) + \text{CH}_3\text{CH}_2\text{OH} \rightarrow \text{RCO}_2\text{CH}_2\text{CH}_3 + \text{HCl} (g)
\]

\[
\text{CH}_3\text{C}=\text{O} + \text{CH}_3\text{CH}_2\text{OH} \rightarrow \text{H}_2\text{C}=\text{O} + \text{H}_2\text{C}=\text{O} + \text{HCl}
\]

Observation: Steamy white fumes of HCl are given off

<table>
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<tr>
<th>Change in functional group: acid anhydride → ester</th>
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<tr>
<td>Conditions: room temp.</td>
</tr>
</tbody>
</table>

\[
\text{(RCO)}_2\text{O} + \text{CH}_3\text{CH}_2\text{OH} \rightarrow \text{RCO}_2\text{CH}_2\text{CH}_3 + \text{RCO}_2\text{H}
\]

\[
\text{CH}_3\text{C}=\text{O} + \text{CH}_3\text{CH}_2\text{OH} \rightarrow \text{H}_2\text{C}=\text{O} + \text{H}_2\text{C}=\text{O} + \text{CH}_3\text{CO}_2\text{H}
\]

**Nucleophilic Addition Elimination Mechanism**

This reaction for making esters is much better than using carboxylic acids as the reaction is much quicker and it is not a reversible reaction.
**Reaction with ammonia**

Change in functional group: **acyl chloride** → **primary amide**  
Reagent: ammonia  
Conditions: room temp.

\[
\text{RCOCl (l) } + 2\text{NH}_3 \rightarrow \text{RCONH}_2 + \text{NH}_4\text{Cl (s)}
\]

Observation: white smoke of NH\(_4\)Cl is given off

Change in functional group: **acid anhydride** → **primary amide**  
Reagent: ammonia  
Conditions: room temp.

\[
\text{(RCO)}_2\text{O } + 2\text{NH}_3 \rightarrow \text{RCONH}_2 + \text{RCO}_2\text{NH}_4^+
\]

**Nucleophilic Addition Elimination Mechanism**

**Reaction with primary amines**

Change in functional group: **acyl chloride** → **secondary amide**  
Reagent: primary amine  
Conditions: room temp.

\[
\text{RCOCI +2CH}_3\text{NH}_2 \rightarrow \text{RCONHCH}_3 + \text{CH}_3\text{NH}_2\text{Cl}^{-}
\]

N-methylethanamide

Change in functional group: **acid anhydride** → **secondary amide**  
Reagent: primary amine  
Conditions: room temp.

\[
\text{(RCO)}_2\text{O } + 2\text{CH}_3\text{NH}_2 \rightarrow \text{RCONHCH}_3 + \text{RCO}_2\text{CH}_3\text{NH}_3^+
\]

N-methylethanamide

**Nucleophilic Addition Elimination Mechanism**
Making Aspirin

Aspirin is made from 2-hydroxybenzoic acid which contains a phenol group. In the reaction the phenol group is turned into an ester by reacting it with the reactive ethanoic anhydride.

Ethanoic anhydride is used instead of acid chlorides because it is cheaper, less corrosive, less vulnerable to hydrolysis, and less dangerous to use.

Making Paracetamol

Paracetamol is made by the reaction of an aromatic amine with an acyl chloride to produce an amide.
Add to a 50 cm$^3$ pear-shaped flask 2.0 g of 2-hydroxybenzoic acid and 4 cm$^3$ of ethanoic anhydride.

To this mixture add 5 drops of 85% phosphoric(v) acid and swirl to mix. Fit the flask with a reflux condenser and heat the mixture on a boiling water bath for about 5 minutes. Without cooling the mixture, carefully add 2 cm$^3$ of water in one portion down the condenser.

When the vigorous reaction has ended, pour the mixture into 40 cm$^3$ of cold water in a 100 cm$^3$ beaker, stir and rub the sides of the beaker with a stirring rod necessary to induce crystallisation and, finally, allow the mixture to stand in ice bath to complete crystallisation. Collect the product by suction filtration and wash it with a little water.

**Purification stage: recrystallisation**

Using a measuring cylinder, measure out 15 cm$^3$ of ethanol into a boiling tube.

Prepare a beaker half-filled with hot water from a kettle at a temperature of approximately 75 °C.

Use a spatula to add the crude aspirin to the boiling tube with ethanol and place the tube in the beaker of hot water.

Stir the contents of the boiling tube until all of the aspirin dissolves into the ethanol.

Pour the hot solution containing dissolved aspirin through a warmed filter funnel and fluted filter paper to hot filter.

Then pour filtrate into 40 cm$^3$ of water in a conical flask.

Allow the conical flask to cool slowly and white needles of aspirin should separate.

Cool the whole mixture in an ice bath.

Filter off the purified solid under reduced pressure and allow it to dry on filter paper.

Record the mass of the dry purified solid.

Aspirin is made from 2-hydroxybenzoic acid which contains a phenol group. In the reaction the phenol group is turned into an ester by reacting it with the reactive ethanoic anhydride.

Ethanoic anhydride is used instead of acid chlorides because it is cheaper, less corrosive, less vulnerable to hydrolysis, and less dangerous to use.

The excess ethanoic anhydride will hydrolyse and the contents of the flask will boil.

Avoid naked flames due to flammability of ethanol.

This step will remove any insoluble impurities and heat will prevent crystals reforming during filtration.

Soluble impurities will remain in solution form because they are present in small quantities so solution is not saturated. Ice will increase the yield of crystals.