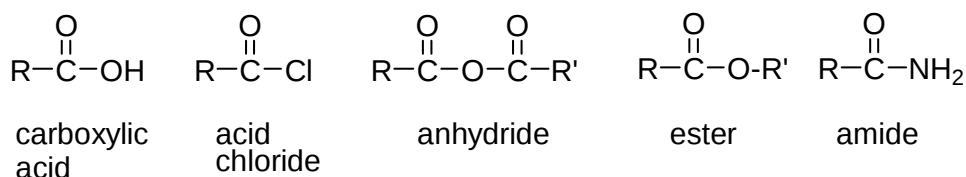


DERIVATIVES OF CARBOXYLIC ACIDS

AMIDES, ACID ANHYDRIDES AND NITRILES

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Medical University of Varna*

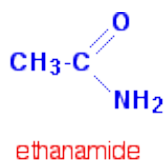


AMIDES

Amides are derived from carboxylic acids. A carboxylic acid contains the -COOH group, and in an amide the -OH part of that group is replaced by an -NH₂ group.

Some simple amides

The most commonly discussed amide is ethanamide, CH₃CONH₂ (old name: acetamide).



Physical properties

Melting points

Methanamide is a liquid at room temperature (melting point: 3°C), but the other amides are solid.

The melting points of the amides are high for the size of the molecules because they can form hydrogen bonds. The hydrogen atoms in the -NH₂ group are sufficiently positive to form a hydrogen bond with a lone pair on the oxygen atom of another molecule.

Solubility in water

The small amides are soluble in water because they have the ability to hydrogen bond with the water molecules.

It needs energy to break the hydrogen bonds between amide molecules and between water molecules before they can mix - but enough energy is released again when the new hydrogen bonds are set up to allow this to happen.

MAKING AMIDES

Making amides from carboxylic acids

The carboxylic acid is first converted into an ammonium salt which then produces an amide on heating.

The ammonium salt is formed by adding solid ammonium carbonate to an excess of the acid.

HYDROLYSING AMIDES

What is hydrolysis?

Technically, hydrolysis is a reaction with water. That is exactly what happens when amides are hydrolysed in the presence of dilute acids such as dilute hydrochloric acid. The acid acts as a catalyst for the reaction between the amide and water.

The alkaline hydrolysis of amides actually involves reaction with hydroxide ions, but the result is similar enough that it is still classed as hydrolysis.

Hydrolysis under acidic conditions

Taking ethanamide as a typical amide:

If ethanamide is heated with a dilute acid (such as dilute hydrochloric acid), ethanoic acid is formed together with ammonium ions. So, if you were using hydrochloric acid, the final solution would contain ammonium chloride and ethanoic acid.



OTHER REACTIONS OF AMIDES

The lack of base character in amides

Unusually for compounds containing the $-\text{NH}_2$ group, amides are neutral. This section explains why $-\text{NH}_2$ groups are usually basic and why amides are different.

The usual basic character of the $-\text{NH}_2$ group

Simple compounds containing an $-\text{NH}_2$ group such as ammonia, NH_3 , or a primary amine like methylamine, CH_3NH_2 , are weak bases. A primary amine is a compound where the $-\text{NH}_2$ group is attached to a hydrocarbon group.

The active lone pair of electrons on the nitrogen atom in ammonia can combine with a hydrogen ion (a proton) from some other source - in other words it acts as a base.

With a compound like methylamine, all that has happened is that one of the hydrogen atoms attached to the nitrogen has been replaced by a methyl group. It doesn't make a huge amount of difference to the lone pair and so ammonia and methylamine behave similarly.

For example, if you dissolve these compounds in water, the nitrogen lone pair takes a hydrogen ion from a water molecule - and equilibria like these are set up:



Notice that the reactions are reversible. In both cases the positions of equilibrium lie well to the left. These compounds are *weak* bases because they don't hang on to the incoming hydrogen ion very well.

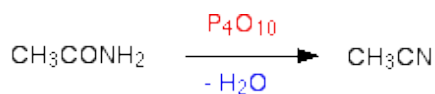
Both ammonia and the amines are alkaline in solution because of the presence of the hydroxide ions, and both of them turn red litmus blue.

The dehydration of amides

Amides are dehydrated by heating a solid mixture of the amide and phosphorus(V) oxide, P₄O₁₀.

Water is removed from the amide group to leave a nitrile group, -CN. The liquid nitrile is collected by simple distillation.

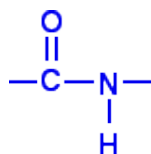
For example, with ethanamide, you will get ethanenitrile.



POLYAMIDES

Polyamides are polymers where the repeating units are held together by amide links.

An amide *group* has the formula - CONH₂. An amide *link* has this structure:



In an amide itself, of course, the bond on the right is attached to a hydrogen atom.

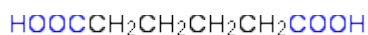
Nylon

In nylon, the repeating units contain chains of carbon atoms. There are various different types of nylon depending on the nature of those chains.

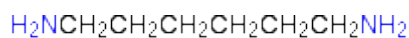
Nylon-6,6

Nylon-6,6 is made from two monomers each of which contain 6 carbon atoms - hence its name.

One of the monomers is a 6 carbon acid with a -COOH group at each end - hexanedioic acid.



The other monomer is a 6 carbon chain with an amino group, -NH₂, at each end. This is 1,6-diaminohexane (also known as hexane-1,6-diamine).



When these two compounds polymerise, the amine and acid groups combine, each time with the loss of a molecule of water. This is known as **condensation polymerisation**.

Nylon-6

Nylon-6 is made from a monomer called caprolactam.

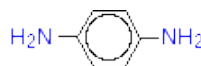
Kevlar

Kevlar is similar in structure to nylon-6,6 except that instead of the amide links joining chains of carbon atoms together, they join benzene rings.

The two monomers are benzene-1,4-dicarboxylic acid and 1,4-diaminobenzene.



benzene-1,4-dicarboxylic acid

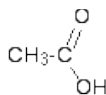


1,4-diaminobenzene

ACID ANHYDRIDES

The structure of acid anhydrides

A carboxylic acid such as ethanoic acid has the structure:



ethanoic acid

Naming acid anhydrides

This is really easy. You just take the name of the parent acid, and replace the word "acid" by "anhydride". "Anhydride" simply means "without water".

Physical properties of acid anhydrides

We will take ethanoic anhydride as typical.

Appearance

Ethanoic anhydride is a colourless liquid, smelling strongly of vinegar (ethanoic acid).

The smell is because ethanoic anhydride reacts with water vapour in the air (and moisture in your nose) to produce ethanoic acid again.

Solubility in water

Ethanoic anhydride can't be said to dissolve in water because it reacts with it to give ethanoic acid. There is no such thing as an aqueous solution of ethanoic anhydride.

Boiling point

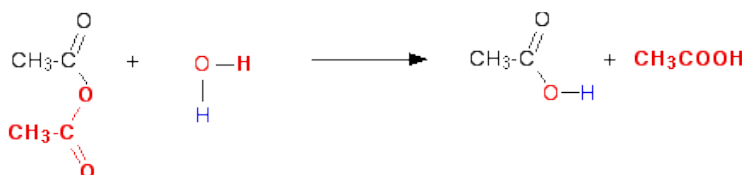
Ethanoic anhydride boils at 140°C. This is because it is a fairly big polar molecule and so has both van der Waals dispersion forces and dipole-dipole attractions.

It doesn't, however, form hydrogen bonds. That means that its boiling point isn't as high as a carboxylic acid of similar size. For example, pentanoic acid (the most similarly sized acid) boils at 186°C.

THE REACTION OF ACID ANHYDRIDES WITH WATER, ALCOHOLS AND PHENOL

The reaction with water

Modifying the general equation we've just looked at, you will see that you just get two molecules of ethanoic acid produced.

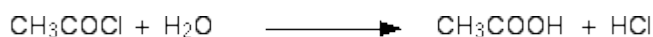


This is more usually (and more easily!) written as:



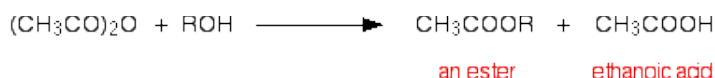
The reaction happens slowly at room temperature (faster on gentle warming) without a great deal exciting to observe - unlike in the acyl chloride case where hydrogen chloride fumes are produced. You mix two colourless liquids and get another colourless liquid!

The equivalent acyl chloride reaction is:

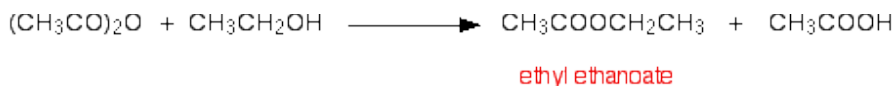


The reaction with alcohols

We'll start by taking the general case of any alcohol reacting with ethanoic anhydride. The equation would be:

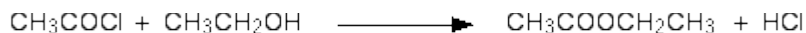


The product this time (apart from the ethanoic acid always produced) is an ester. For example, with ethanol you would get the ester ethyl ethanoate:



This reaction also needs gentle heating for it to happen at a reasonable rate, and again there isn't anything visually dramatic.

The equivalent acyl chloride reaction is:

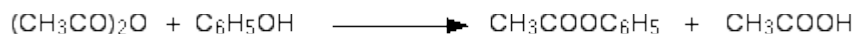


The reaction with phenols

The reaction with phenol itself

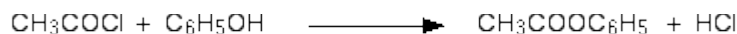
Phenols have an -OH group attached directly to a benzene ring. In the substance normally called "phenol", there isn't anything else attached to the ring as well. We'll look at that first.

The reaction between phenol and ethanoic anhydride isn't particularly important, but you would get an ester just as you do with an alcohol.



Especially if you write the equation in this second way, it is obvious that you have just produced another ester - in this case, called phenyl ethanoate.

The equivalent acyl chloride reaction is:



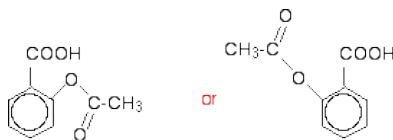
Using a similar reaction to make aspirin

The reaction with phenol itself isn't very important, but you can make aspirin by a very similar reaction.

The molecule below is 2-hydroxybenzoic acid (also known as 2-hydroxybenzenecarboxylic acid). The old name for this is salicylic acid.

You might also find it with the -OH group at the top and the -COOH group next door and either to the left or right of it. Life can get very confusing!

When this reacts with ethanoic anhydride, it is ethanoylated (or acylated, if you want to use the more general term) to give:



You might find all sorts of other variants on drawing this as well.

This molecule is **aspirin**.

Although this reaction can also be done with ethanoyl chloride, aspirin is *manufactured* by reacting 2-hydroxybenzoic acid with ethanoic anhydride at 90°C.

The reasons for using ethanoic anhydride rather than ethanoyl chloride include:

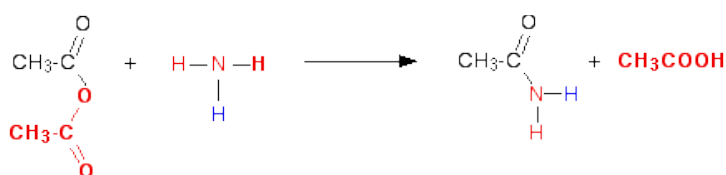
- Ethanoic anhydride is cheaper than ethanoyl chloride.
- Ethanoic anhydride is safer to use than ethanoyl chloride. It is less corrosive and not so readily hydrolysed (its reaction with water is slower).

- Ethanoic anhydride doesn't produce dangerous (corrosive and poisonous) fumes of hydrogen chloride.

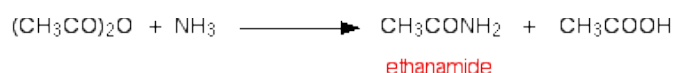
The reaction with ammonia

In this case, the "X" in the equations above is a hydrogen atom. So in the first instance you get ethanoic acid and an organic compound called an **amide**.

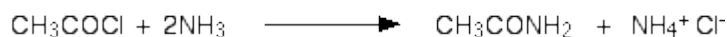
Amides contain the group -CONH₂. In the reaction between ethanoic anhydride and ammonia, the amide formed is called ethanamide.



This is more usually (and more easily!) written as:



The corresponding reaction with an acyl chloride is:



NITRILES

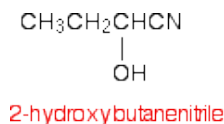
What are nitriles?

Nitriles contain the -CN group, and used to be known as cyanides.

Some simple nitriles

The smallest organic nitrile is ethanenitrile, CH₃CN, (old name: methyl cyanide or acetonitrile - and sometimes now called ethanonitrile). Hydrogen cyanide, HCN, doesn't usually count as organic, even though it contains a carbon atom.

Notice the triple bond between the carbon and nitrogen in the -CN group.



Physical properties

Boiling points

The small nitriles are liquids at room temperature.

These boiling points are very high for the size of the molecules - similar to what you would expect if they were capable of forming hydrogen bonds.

Solubility in water

Ethanenitrile is completely soluble in water, and the solubility then falls as chain length increases.

The reason for the solubility is that although nitriles can't hydrogen bond with themselves,

MAKING NITRILES

Making nitriles from halogenoalkanes

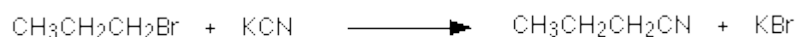
The halogenoalkane is heated under reflux with a solution of sodium or potassium cyanide in ethanol. The halogen is replaced by a -CN group and a nitrile is produced. Heating under reflux means heating with a condenser placed vertically in the flask to prevent loss of volatile substances from the mixture.

The solvent is important. If water is present you tend to get substitution by -OH instead of -CN.

For example, using 1-bromopropane as a typical halogenoalkane:



You could write the full equation rather than the ionic one, but it slightly obscures what's going on:



The bromine (or other halogen) in the halogenoalkane is simply replaced by a -CN group - hence a substitution reaction. In this example, butanenitrile is formed.

Making a nitrile by this method is a useful way of increasing the length of a carbon chain. Having made the nitrile, the -CN group can easily be modified to make other things.

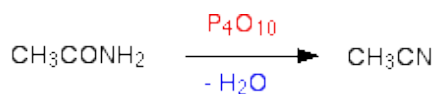
Making nitriles from amides

Nitriles can be made by dehydrating amides.

Amides are dehydrated by heating a solid mixture of the amide and phosphorus(V) oxide, P₄O₁₀.

Water is removed from the amide group to leave a nitrile group, -CN. The liquid nitrile is collected by simple distillation.

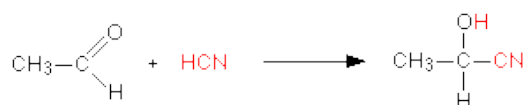
For example, you will get ethanenitrile by dehydrating ethanamide.



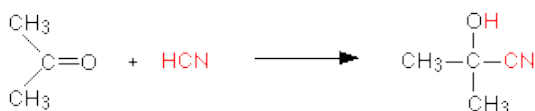
Making nitriles from aldehydes and ketones

Aldehydes and ketones undergo an addition reaction with hydrogen cyanide. The hydrogen cyanide adds across the carbon-oxygen double bond in the aldehyde or ketone to produce a hydroxynitrile. Hydroxynitriles used to be known as cyanohydrins.

For example, with ethanal (an aldehyde) you get 2-hydroxypropanenitrile:



With propanone (a ketone) you get 2-hydroxy-2-methylpropanenitrile:



In every example of this kind, the -OH group will be on the number 2 carbon atom - the one next to the -CN group.

The reaction isn't normally done using hydrogen cyanide itself, because this is an extremely poisonous gas. Instead, the aldehyde or ketone is mixed with a solution of sodium or potassium cyanide in water to which a little sulphuric acid has been added. The pH of the solution is adjusted to about 4 - 5, because this gives the fastest reaction. The reaction happens at room temperature.

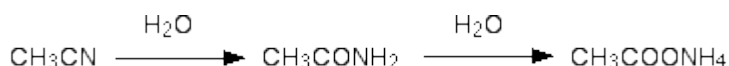
The solution will contain hydrogen cyanide (from the reaction between the sodium or potassium cyanide and the sulphuric acid), but still contains some free cyanide ions. This is important for the mechanism.

HYDROLYSING NITRILES

The hydrolysis of nitriles

When nitriles are hydrolysed you can think of them reacting with water in two stages - first to produce an amide, and then the ammonium salt of a carboxylic acid.

For example, ethanenitrile would end up as ammonium ethanoate going via ethanamide.



In practice, the reaction between nitriles and water would be so slow as to be completely negligible. The nitrile is instead heated with either a dilute acid such as dilute hydrochloric acid, or with an alkali such as sodium hydroxide solution.

The end result is similar in all the cases, but the *exact* nature of the final product varies depending on the conditions you use for the reaction.

REDUCING NITRILES TO PRIMARY AMINES

The reduction of nitriles using LiAlH_4

The reducing agent

Despite its name, the structure of the reducing agent is very simple. There are four hydrogens ("tetrahydido") around the aluminium in a negative ion (shown by the "ate" ending). In the negative ion, one of the bonds is a co-ordinate covalent (dative covalent) bond using the lone pair on a hydride ion (H^-) to form a bond with an empty orbital on the aluminium.

The overall reaction

The nitrile reacts with the lithium tetrahydridoaluminate in solution in ethoxyethane (diethyl ether, or just "ether") followed by treatment of the product of that reaction with a dilute acid.

Overall, the carbon-nitrogen triple bond is reduced to give a primary amine. Primary amines contain the $-\text{NH}_2$ group.

For example, with ethanenitrile you get ethylamine:



Notice that this is a simplified equation - perfectly acceptable to UK A level examiners. $[\text{H}]$ means "hydrogen from a reducing agent".

The reduction of nitriles using hydrogen and a metal catalyst

The carbon-nitrogen triple bond in a nitrile can also be reduced by reaction with hydrogen gas in the presence of a variety of metal catalysts.

Commonly quoted catalysts are palladium, platinum or nickel.

The reaction will take place at a raised temperature and pressure. It is impossible to give exact details because it will vary from catalyst to catalyst.

For example, ethanenitrile can be reduced to ethylamine by reaction with hydrogen in the presence of a palladium catalyst.

