Conversion of Acids to Esters

The following reaction occurs in bad wine (wine containing acetic acid).



Would an ester be formed under basic conditions?



There is no ester formation from a carboxylic acid with a base. A salt is obtained instead. In water, a carboxylic acid is usually acidic enough to catalyze the reaction though.

Reactions at the α Carbon

Compare the pKa's of the alpha hydrogens of an ester and a ketone:



The ketone is more acidic. This can be explained by the resonance structures of the enolate (2 major forms and one minor form):



To abstract an alpha hydrogen a base is needed that will not act like a nucleophile and attack the carbonyl. This may be achieved by using sterically hindered bases:



Electrophiles reacting with enolates (exactly analogous to ketone and aldehydes):





Examples:

<u>Halogenation</u>



Alkylation





 $S_N 2$ substitution

What else could be used (instead of ICH₃)?



No, $S_{\ensuremath{N}\ensuremath{2}}^{\ensuremath{N}\ensuremath{2}}$ reactions won't go with this reagent



Yes, in the above reaction the product would be

Benzyl iodide



Aldol



Mechanism



Acylation



Mechanism



Acylating Agents:



Amines

Nomenclature:



For simple amines, name the alkyl group (R), and add amine at the end of the nomenclature. Secondary and tertiary amines in which R groups are all the same are simpled named as di- or trialkylamines. Amines bearing different R groups are named by ordering the groups alphabetically.

Examples:

H₃C -----NH₂

Methylamine





Triethylamine

Allylbenzylamine

You should know the three structures below:



Methyl 2-aminobenzoate. It has the flavour of grapes, and also repels geese. Benzoic acid numbering used on aromatic ring

Note that the ester group takes priority as parent structure, rather than the amine. Then you count around the ring to give the lowest substitution number. In this case, C2 is where the amine is substituted.



Trimethylamine



The structure shown above is an α -amino acid, named L-alanine. It is a major constituent of spider silk.

The systematic name for alanine is (S)-2-aminopropanoic acid.

Properties of Amines

Amines are polar, and therefore have higher boiling points than hydrocarbons of similar molecular weight. Small amines tend to be water soluble, while larger amines containing more carbons are usually soluble in acid.

Amines have a lone pair and are both nucleophiles and bases, so they will react with acids such as a hydrogen halide to form salts.

$$NR_3 + H^{\bigoplus}X^{\bigoplus} \longrightarrow NHR_3X^{\bigoplus}$$

The pKa for ammonia is about 36.

$$NH_3 \longrightarrow NH_2 + H^{\oplus}$$

amide
anion

$$K_a = [NH_2][H+]/[NH_3] = 10^{-36}$$

The pKa for an ammonium ion is about 9.4.

$$\stackrel{\bigoplus}{\mathrm{NH}_4} \xrightarrow{} \mathrm{NH}_3 + \mathrm{H}^{\bigoplus}$$

$$\mathrm{K}_a = [\mathrm{NH}_3][\mathrm{H}_4]/[\mathrm{NH}_4] = 10^{-9.4}$$

In biology, the acidity of pKa of an amine may be mentioned, but usually they are referring to the ammonium ion and not the amine itself.

Example:



spermidine

Spermidine is a polyamine isolated from seminal fluid in males, but occurs in all cells. It reacts with acetic acid that is present in females.

Which amine is protonated first?

The secondary amine in the middle, since it is the most basic nitrogen (2 alkyl groups donate negative charge through the inductive effect to nitrogen).

Example of diamines:



Some of these diamines occur in rotting meat, warning you not to eat it.

Reactions of amines

Alkylation

Amines are good nucleophiles and can displace leaving groups in S_N2 reactions.



For the reaction of ammonia with an alkyl halide, at least two equivalents of ammonia are needed. One to do the alkylation, and the other one to react with the acidic proton that is produced from the first S_N2 reaction (here it is shown as an ammonium salt, it could also occur as an HX acid)

For reactions of primary alkyl halides with substituted amines, the alkylation is difficult to stop after the first alkylation because the product amine is also nucleophilic, and usually more so than the starting material. The result is generally a mixture of alkylated products. Depending on how many hydrogens the starting amine has, the alkylation will continue until all protons are removed, or even further to make an ammonium salts. This is usually undesirable as mixtures are often formed.



Example:



In this example, the nitrogen of amine has alkylated 3 times, whereas the oxygen is not alkylated at all. Alcohols are much less reactive than amines. Oxygen is more electronegative than nitrogen and is less nucleophilic. The oxygen can be alkylated by making an alkoxide anion and then adding yet more methyl iodide.

Choline can react with acetyl chloride to form acetylcholine, a neurotransmitter. An enzyme called acetylcholinesterase removes the acetyl group in vivo. Parathion and sarin are inhibitors of this enzyme. Parathion is used as an insecticide (which is also toxic to humans), while sarin has been used as a chemical weapon.



Amides are more stable than esters, and an amine is more reactive than an alcohol (oxygen is more electronegative than nitrogen):

Halogenation

 $NH_3 + I_2 \longrightarrow NI_3$

This kind of reaction was shown in the demo in a previous class. (Explosive product)

Acylation

Amines can be acylated by the following:



Aminal and Imine Formation from Ketones and Aldehydes (review – see below also)



Reductive Amination (via imine formation with ketone or aldehyde)

When the carbon-nitrogen double bond (an imine) is reduced to give primary or secondary amine, this process is called reductive amination.



Alkaloids

Nicotine is found naturally in tobacco and is shown below. It constitutes 0.3 to 5% of the tobacco plant by dry weight. It is a potent nerve poison and is included in many insecticides. The body converts nicotine into nicotinic acid or better known as niacin. Niacin, also known as vitamin B3, is a water-soluble vitamin whose derivatives such as NADH, NAD, NAD+, and NADP play essential roles in energy metabolism in the living cell and DNA repair. Severe lack of niacin causes the deficiency disease pellagra, whereas a mild deficiency slows down the metabolism, which in turn decreases cold tolerance and is a potential contributing factor towards obesity.



Nicotine

Nicotinic acid

Solanine is a glycoalkaloid (contains a steroidal alkaloid linked to a sugar) poison found primarily in the green parts of potato (stems, leaves) and greening potatoes. It is very toxic even in small quantities. Studies suggest that 2-5 mg/kg body weight can cause toxic symptoms and a dosage of 3-6 mg/kg body weight can be fatal. Solanine has both fungicidal and pesticide properties, and it is one of the plant's natural defenses against insects, disease, and predators.



Solanine

Atropine is a tropane alkaloid extracted from the deadly nightshade (*Atropa belladonna*) and other plants of the family Solanaceae. It is a secondary metabolite of these plants and serves as a drug with a wide variety of effects. Being potentially deadly, it derives its name from Atropos, one of the three Fates who, according to Greek mythology, cut the thread of life. In the Renaissance times, women used the juice of the berries of *Atropa belladonna* to enlarge the pupils of their eyes, for cosmetic reasons; "belladonna" is Italian for "beautiful lady".



Atropine

Cocaine is a crystalline tropane alkaloid that is obtained from the leaves of the coca plant (*Erythroxylum coca*). This is not in the *Solanaceae* family, but rather is in family *Erythroxylaceae*. It is a stimulant of the central nervous system and an appetite suppressant, creating what has been described as a euphoric sense of happiness and increased energy. Though most often used recreationally for this effect, cocaine is also a topical anesthetic that was used in eye and throat surgery in the 19th and early 20th centuries. Cocaine is addictive, especially in free base form (e.g. Crack). Shown below are two representations of cocaine:



Cocaine

The addictive properties of cocaine hindered its use as an anesthetic. Derivatives were synthesized to isolate the anesthetic properties from the addictive properties. Novocain and Benzocaine are non-addictive, local anesthetics commonly used in dentistry and as a topical pain reliever respectively.

NH₂

NH₂

Novocaine

Benzocaine