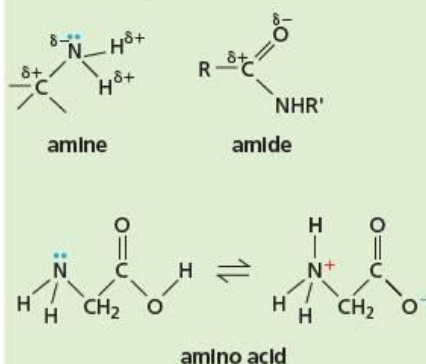


27 Amines, amides and amino acids

Functional groups:



Amines are organic bases. They react with acids to form salts, and amines that are soluble in water form alkaline solutions. The reaction of aryl amines with nitrous acid is the first step in making dyes.

Amides are neutral compounds formed when ammonia or an amine reacts with an acyl chloride.

Amino acids contain both the basic —NH_2 group and the acidic $\text{—CO}_2\text{H}$ group; they are therefore amphoteric, reacting with both acids and bases. Amino acids are the building blocks of the important class of biological polymers known as the polypeptides, or proteins.

The topic concludes with a look at synthetic polyamides, including the various types of nylon.

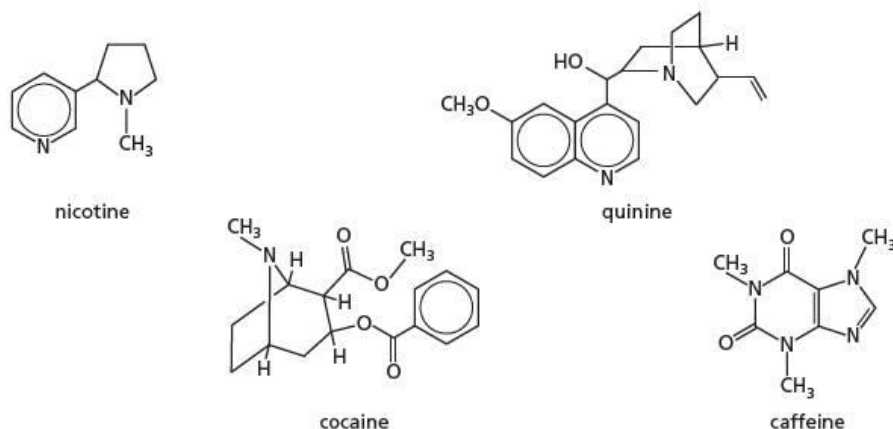
Learning outcomes

By the end of this topic you should be able to:

- 14.1a)** interpret and use the general, structural, displayed and skeletal formulae of the amides and amino acids
- 20.1a)** describe the formation of alkyl amines such as ethylamine (by the reaction of ammonia with halogenoalkanes; the reduction of amides with LiAlH_4 ; the reduction of nitriles with LiAlH_4 or H_2/Ni) and of phenylamine (by the reduction of nitrobenzene with tin/concentrated HCl)
- 20.1b)** describe and explain the basicity of amines
- 20.1c)** explain the relative basicities of ammonia, ethylamine and phenylamine in terms of their structures
- 20.1d)** describe the reaction of phenylamine with aqueous bromine, and with nitrous acid to give the diazonium salt and phenol
- 20.1e)** describe the coupling of benzenediazonium chloride and phenol
- 20.2a)** describe the formation of amides from the reaction between NH_3 or RNH_2 and $\text{R}'\text{COCl}$
- 20.2b)** recognise that amides are neutral
- 20.2c)** describe amide hydrolysis on treatment with aqueous alkali or acid, and describe the reduction of amides with LiAlH_4
- 20.3a)** describe the acid/base properties of amino acids and the formation of zwitterions
- 20.3b)** describe the formation of peptide bonds between amino acids to give di- and tri-peptides
- 20.3c)** describe simply the process of electrophoresis and the effect of pH, using peptides and amino acids as examples.

27.1 Introduction

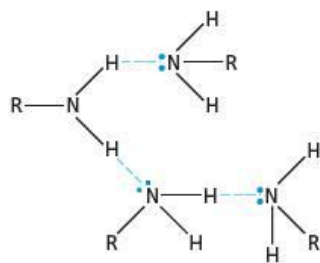
From prehistoric times, people have been aware that the leaves or seeds of certain plants were pharmacologically active, in alleviating pain, reducing fever or causing euphoria. In the early days of organic chemistry, when chemists were extracting, purifying and attempting to identify the hundreds of compounds that occur in natural organisms, they discovered that many of these compounds were insoluble in water, but dissolved in dilute acids. They called these the **alkaloids** ('alkali-like'). Many of the alkaloids extracted from plants were found to have strong physiological and psychological effects on humans and other animals. These included hypnotics such as morphine, narcotics such as cocaine, and cardiac poisons such as strychnine. All alkaloids contained at least one nitrogen atom, and all belonged to the class of compounds we now call **amines**. Figure 27.1 illustrates some of their structures.

Figure 27.1 The structures of some naturally occurring alkaloids**Now try this**

- 1 Apart from the nitrogen atoms, what functional groups are contained in
 - a the quinine molecule
 - b the cocaine molecule?
- 2 Work out the molecular formula of:
 - a quinine
 - b caffeine
- 3 The molecule of nicotine is chiral. Draw out the structure, showing which atom is the chiral one.

Most alkaloids have a bitter taste, but are too involatile (that is, they produce too little vapour) to have an odour. Those amines that are volatile have distinctive smells. The short-chain amines have an astringent ammonia-like smell, but this is replaced by a strong fishy odour in butylamine and longer-chain amines. Aryl amines such as phenylamine have a more 'oily' smell.

The amines can be derived from ammonia by replacing one or more of the hydrogen atoms in NH_3 by organic groups; replacing the amine hydrogen atoms can often be carried out in the laboratory.

**Figure 27.2** Intermolecular hydrogen bonding in amines

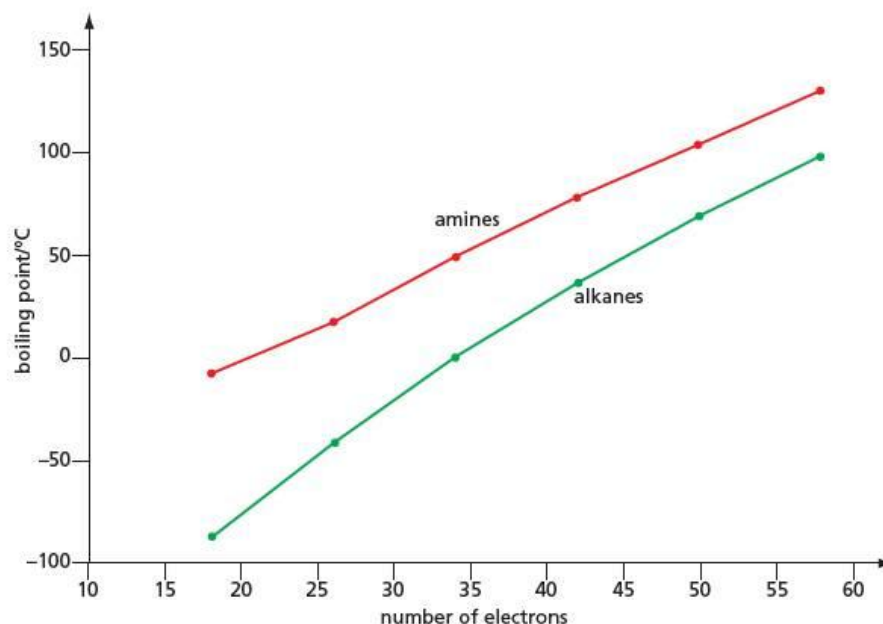
The carbon–nitrogen bond, although quite strongly polarised, is fairly inert and it is not so easily broken as the C–O bond in alcohols (see Topic 16, page 282). There are few reactions in which the $\text{C}^{\delta+}$ atom takes part. The key point of reactivity in the amines is the lone pair of electrons on the nitrogen atom, which is more readily donated than a lone pair on oxygen. This lone pair is nucleophilic towards $\text{C}^{\delta+}$ and basic towards $\text{H}^{\delta+}$. Amines form strong hydrogen bonds to hydrogen-donor molecules such as water. Those amines that contain N–H bonds also form strong intermolecular hydrogen bonds (see Figure 27.2).

The short-chain amines are therefore water soluble and their boiling points are higher than those of the corresponding alkanes (see Table 27.1 and Figure 27.3). The effect of hydrogen bonding on boiling point is not so pronounced as it is in the alcohols, however (compare Table 27.1 with Table 16.1, page 282).

Table 27.1 Boiling points of some alkanes and corresponding amines

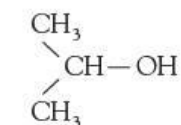
Number of electrons in the molecule	Alkane		Amine		Increase in boiling point/ $^{\circ}\text{C}$
	Formula	Boiling point/ $^{\circ}\text{C}$	Formula	Boiling point/ $^{\circ}\text{C}$	
18	C_2H_6	–88	CH_3NH_2	–8	80
26	C_3H_8	–42	$\text{C}_2\text{H}_5\text{NH}_2$	17	59
34	C_4H_{10}	0	$\text{C}_3\text{H}_7\text{NH}_2$	49	49
42	C_5H_{12}	36	$\text{C}_4\text{H}_9\text{NH}_2$	78	42
50	C_6H_{14}	69	$\text{C}_5\text{H}_{11}\text{NH}_2$	104	35
58	C_7H_{16}	98	$\text{C}_6\text{H}_{13}\text{NH}_2$	130	32

Figure 27.3 Boiling points of some alkanes and corresponding amines

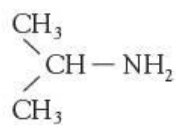


27.2 Isomerism and nomenclature

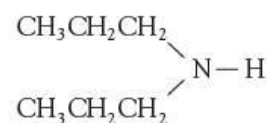
The most important feature of the amine molecule is the nitrogen atom. This is reflected in the nomenclature of amines. The simpler ones, such as dimethylamine and phenylamine shown opposite, are named as though they are derived from ammonia. Up to three hydrogen atoms in ammonia can be replaced by organic groups. Successive replacement forms **primary**, **secondary** and **tertiary amines** (see Table 27.2). Note that it is the branching that takes place at the nitrogen atom, rather than at the carbon atom attached to it, that determines whether an amine is primary, secondary or tertiary. This is not the same as in the case of the alcohols:



propan-2-ol
a secondary alcohol


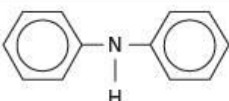
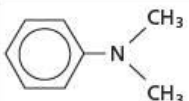
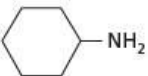
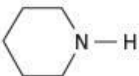
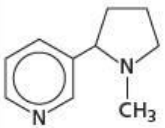


2-aminopropane
a primary amine

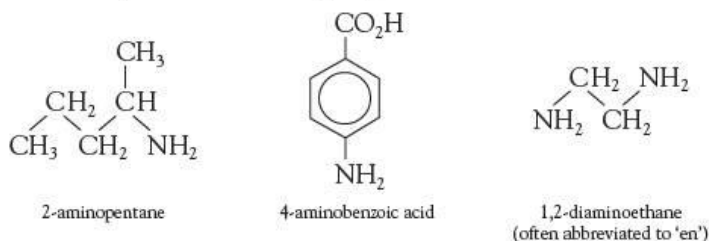


dipropylamine
a secondary amine

Table 27.2 Some primary, secondary and tertiary amines

Primary amines	Secondary amines	Tertiary amines
$\text{CH}_3\text{CH}_2\text{NH}_2$ ethylamine	$(\text{CH}_3\text{CH}_2)_2\text{NH}$ diethylamine	$(\text{CH}_3\text{CH}_2)_3\text{N}$ triethylamine
 4-methylphenylamine	 diphenylamine	 <i>N,N</i> -dimethylphenylamine
 cyclohexylamine	 piperidine	 nicotine

An alternative way of naming amines is used when the chain becomes more branched, or when other functional groups are present. This views the —NH_2 group as a substituent, called an **amino group**:



Apart from the usual structural or positional isomerism that can occur in the carbon chain, amines also demonstrate structural isomerism around the nitrogen atom, through the formation of secondary and tertiary amines as well as primary amines.

Worked example

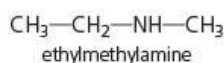
How many isomers are there with the formula $\text{C}_3\text{H}_9\text{N}$?

Answer

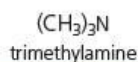
There are four isomers. Structural isomerism in the propyl group allows two primary amines:



In addition to these, we can split the three-carbon chain into two or three chains, to form a secondary amine:



and a tertiary amine:



Now try this

Fourteen of the isomers with the formula $\text{C}_8\text{H}_{11}\text{N}$ contain a nitrogen atom directly bonded to a benzene ring. Draw their structures, and state which are primary, secondary and tertiary amines.

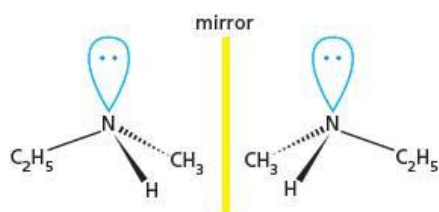


Figure 27.4 Theoretical enantiomers of ethylmethanamine

The nitrogen atom in amines is pyramidal, as it is in ammonia. Although the secondary amine ethylmethanamine could exist as a mirror-image pair of compounds (see Figure 27.4), in practice the nitrogen atom undergoes a rapid inversion, like an umbrella turning inside out, causing a 50:50 mixture of the two forms to exist at room temperature (see Figure 27.5).

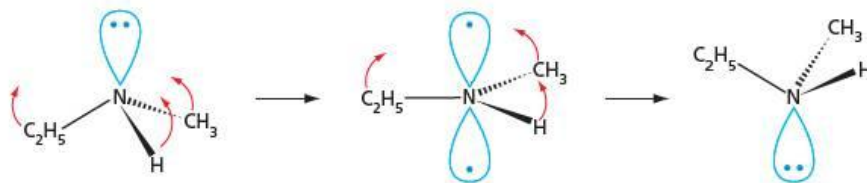
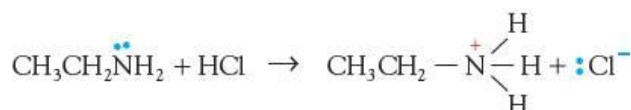


Figure 27.5 Inversion at the nitrogen atom produces a racemic mixture.

27.3 Reactions of amines

Basicity

Amines are basic. They react with acids to form salts:



The alkylammonium chlorides, sulfates and nitrates are white crystalline solids, soluble in water, but insoluble in organic solvents.

Those amines that are soluble in water form weakly alkaline solutions, just as ammonia does, due to partial reaction with the solvent, producing OH^- ions:

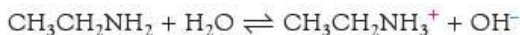


Table 27.3 The basicity of some amines

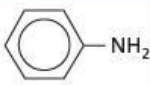
Amine	Formula	K_b /mol dm ⁻³
phenylamine		4.2×10^{-10}
ammonia	NH_3	1.8×10^{-5}
ethylamine	$\text{CH}_3\text{CH}_2\text{NH}_2$	5.1×10^{-4}
diethylamine	$(\text{CH}_3\text{CH}_2)_2\text{NH}$	1.0×10^{-3}

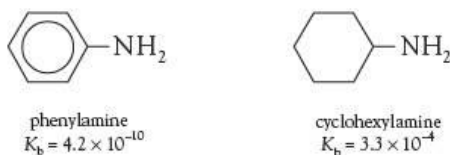
Figure 27.6 When an amine acts as a base, the nitrogen lone pair forms a dative bond with a proton.



The larger K_b is, the stronger is the base. Ammonia is included for comparison.

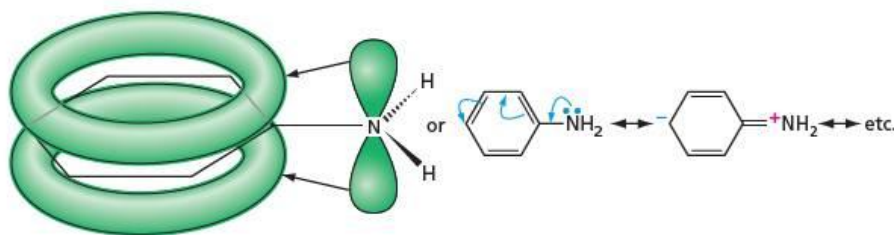
From Table 27.3 we can see that electron-donating alkyl groups attached to the nitrogen atom increase the basicity of amines. This is expected, since the basicity depends on the availability of the lone pair of electrons on nitrogen to form a dative bond with a proton (see Figure 27.6). Electron donation from an alkyl group will encourage dative bond formation.

The most dramatic difference in basicities to be seen in Table 27.3 is between that of phenylamine ($K_b \approx 10^{-10}$) and the alkyl amines ($K_b \approx 10^{-3}$). Taking two compounds of about the same relative molecular mass and shape, we see that phenylamine is about a million times less basic than cyclohexylamine:



This is because in phenylamine, the lone pair of electrons on the nitrogen atom is delocalised over the benzene ring. The bonds around the nitrogen atom can take up a planar arrangement, with the nitrogen's lone pair in a p orbital, so that extra stability can be gained by overlapping this p orbital with the delocalised π bond of the benzene ring (see Figure 27.7).

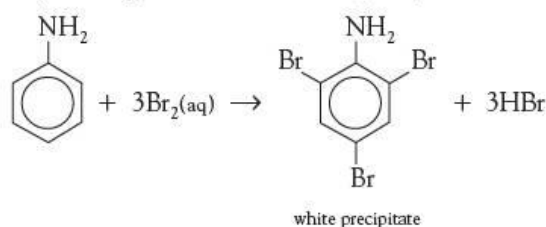
Figure 27.7 Delocalisation of the nitrogen lone pair in phenylamine



This overlap, causing a drift of electron density from nitrogen to the ring, has two effects on the reactivity of phenylamine.

- It causes the lone pair to be much less basic (see above) and also much less nucleophilic.
- It causes the ring to be more electron rich, and so to undergo electrophilic substitution reactions much more readily than benzene. The enhanced reactivity of phenylamine in this regard is similar to that of phenol (see Topic 25, page 434), an

example being the ease with which phenylamine decolorises bromine water:



We shall see a similar drift of electron density from nitrogen when we look at amides in section 27.5.

Only the shorter-chained amines (with five or fewer carbon atoms) are soluble in water, but the ionic nature of their salts allows *all* amines to dissolve in dilute aqueous acids. This is a very useful way of purifying amines from a mixture with non-basic compounds. The amines can be regenerated by adding an excess of aqueous sodium hydroxide to the solution, after the non-basic impurity has been extracted with an organic solvent (see the experiment below).

Experiment

The separation of codeine and paracetamol from a medicine tablet

This separation makes use of the fact that codeine is basic, forming water-soluble salts with acids, but paracetamol is slightly acidic, and is insoluble in water (see Figures 27.8 and 27.9).

Figure 27.8 Flow chart for the experimental procedure to be followed

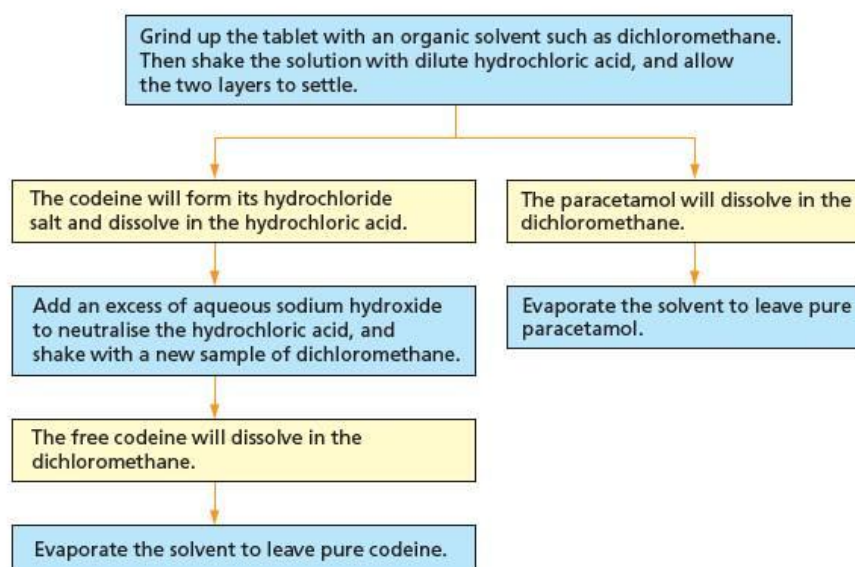
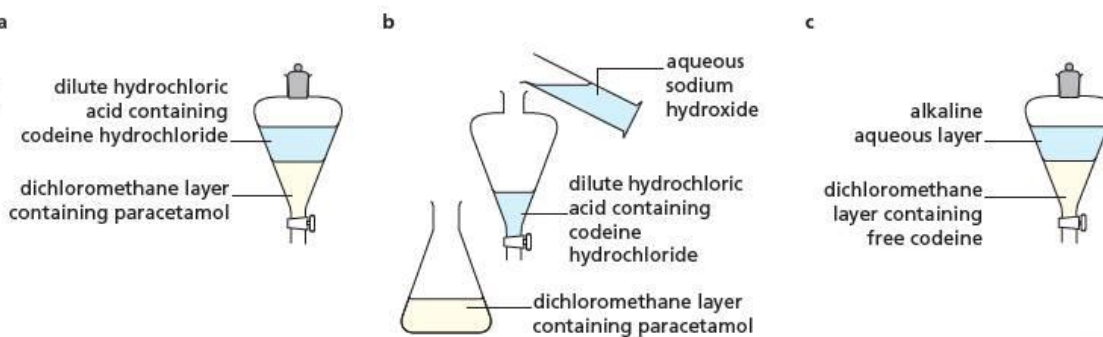
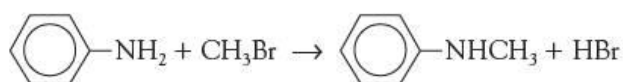
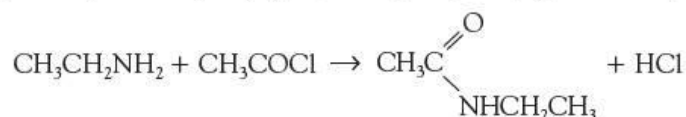


Figure 27.9 Stages in the separation: **a** the first separation removes the paracetamol in the organic layer, **b** sodium hydroxide neutralises the aqueous layer, and **c** the un-ionised codeine is re-formed and dissolves in the organic layer.

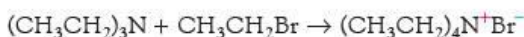
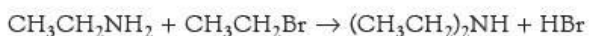


Reactions as nucleophiles

Another similarity between amines and ammonia is their nucleophilicity. The lone pair on the nitrogen atom of amines makes them good nucleophiles. They react with alkyl and acyl halides (see page 274 in Topic 15 and page 444 in Topic 26).



In the presence of an excess of a bromoalkane, amines can be successively alkylated, first to secondary and then to tertiary amines. These are still strongly nucleophilic, and are readily alkylated to quaternary ammonium salts:



Quaternary ammonium salts are water-soluble solids, with no basic character at all, because there is no lone pair of electrons on the nitrogen atom. An important naturally occurring ammonium salt is choline. Phosphatidylcholine is a key phospholipid component of cell membranes. Acetylcholine is an important neurotransmitter, allowing a nerve impulse to pass from the end of one nerve to the start of the next one (see Figures 27.10 and 27.11).

Figure 27.10 Some important naturally occurring quaternary ammonium salts

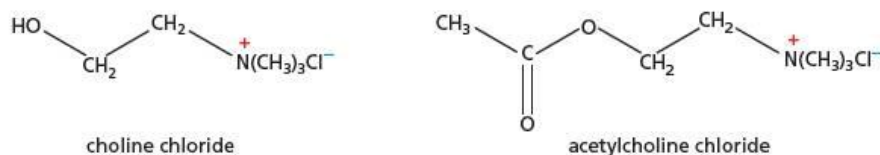
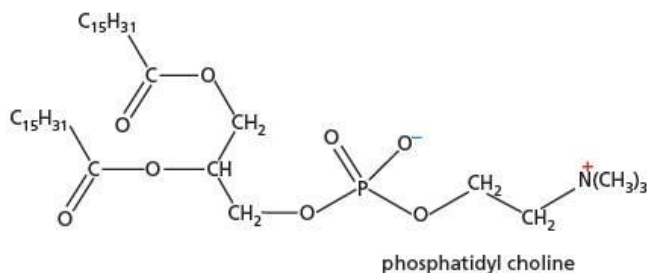
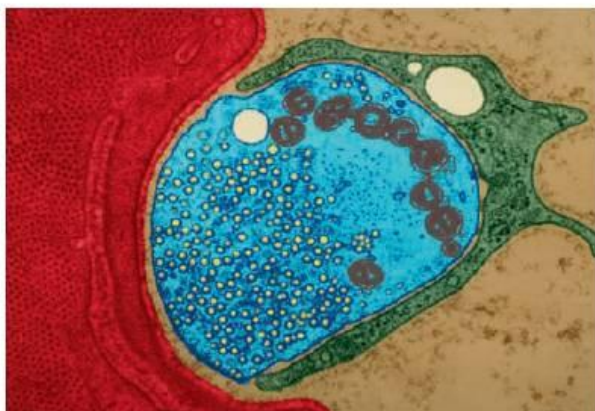


Figure 27.11 a Acetylcholine transmits a nerve impulse from one end of a nerve to another at a synapse or to a muscle at a motor end plate. **b** Curare, a deadly poison used by South American Indians on their arrow tips, blocks the action of acetylcholine.



a

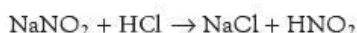


b



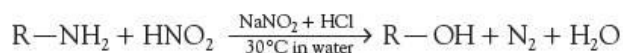
Reaction with nitrous acid (nitric(III) acid)

Nitrous acid, HNO_2 , is unstable, and has to be made as required by reacting together sodium nitrite and hydrochloric acid:

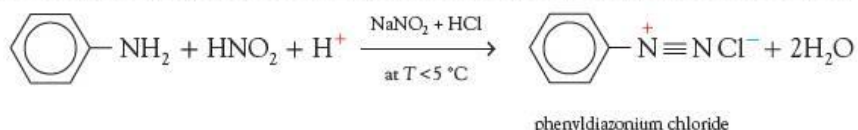


Aromatic and aliphatic amines differ markedly in their reactions with nitrous acid.

Primary aliphatic amines react in warm aqueous acidic solution to give nitrogen gas and alcohols:



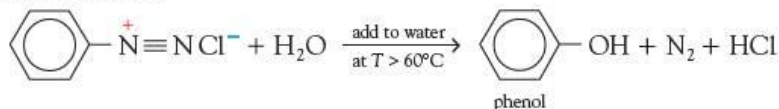
Aryl amines, however, form fairly stable diazonium salts at low temperatures. Under these conditions nitrogen is not evolved, but a solution of the diazonium salt is formed:



Aryl diazonium salts are unstable and explosive when dry, but can be kept for several days in solution in a refrigerator.

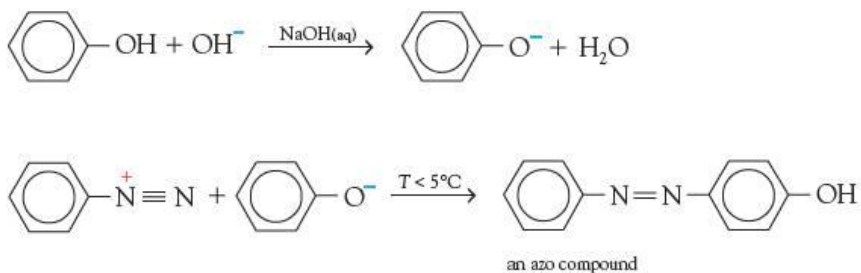
Reactions of diazonium salts

- 1 Adding a solution of a diazonium salt to hot water causes decomposition, and produces phenol:



This is the analogous product to the alcohol produced when an aliphatic primary amine reacts with nitrous acid.

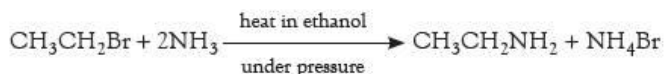
- 2 The most important reactions of diazonium salts are their use in the formation of **azo dyes** (see panel opposite). When a solution of a diazonium salt is added to an alkaline solution of a phenol, an electrophilic substitution reaction (known as a **coupling reaction**) takes place:



27.4 Preparing amines

The two main methods of preparing alkyl amines both start with halogenoalkanes.

- By nucleophilic substitution with ammonia (see Topic 15, page 273):



As long as an excess of ammonia is used, further substitutions giving secondary and tertiary amines can be avoided (see page 444).

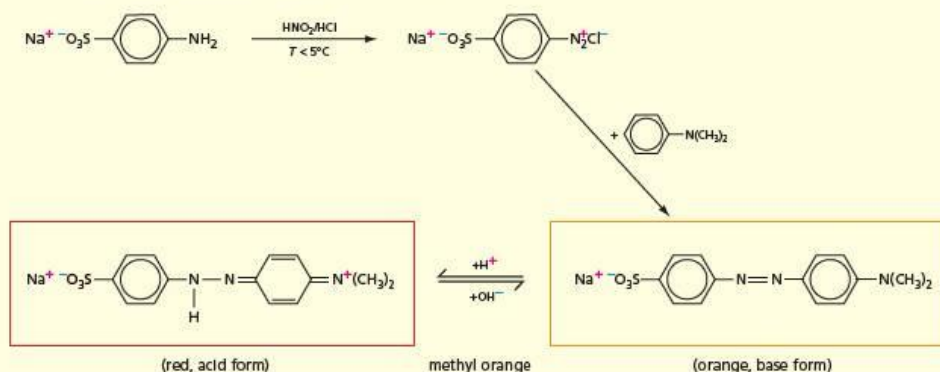
Azo dyes

A **chromophore** is a group which, especially when joined to other unsaturated groups, causes a compound to absorb visible light, and so become coloured.

The azo group, $-\text{N}=\text{N}-$, is called a **chromophore**. Compounds containing this group are highly coloured. Their colours range from yellow and orange to red, blue and green, depending on what other groups are attached to the benzene rings.

The common acid-base indicator methyl orange is an azo compound, made by the coupling reaction shown in Figure 27.12.

Figure 27.12 Methyl orange is an azo compound formed by a coupling reaction.

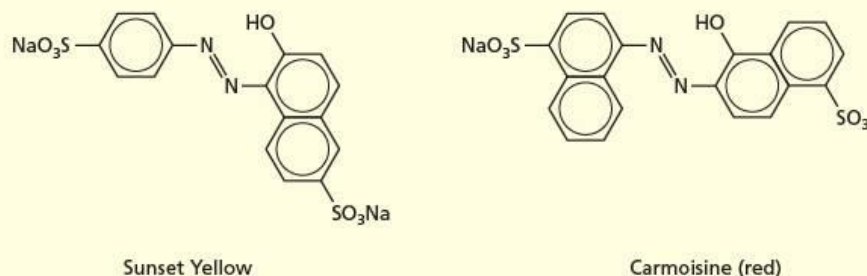


Many dye molecules used for dyeing clothes do not easily stick to the fibres of the material by themselves. This is especially the case if their main method of intermolecular bonding (for example, van der Waals', hydrogen bonding, ionic forces) does not match that of the molecules that make up the material. Mordants are often used to help the dye molecules stick. A **mordant** is a polyvalent metal ion, such as Al^{3+} or Fe^{3+} , which can form co-ordination complexes both with the dye molecule and with $-\text{OH}$, $-\text{CO}$ or $-\text{NH}$ groups on the molecules that make up the fibres of the material. By this means the dye molecule and the fibre molecule are permanently held together by the metal ion. A great number of dyes for clothes, colour printing and food colouring (Figure 27.13) are azo dyes. Figure 27.14 shows two examples.

Figure 27.13 Food colours often contain azo dyes.



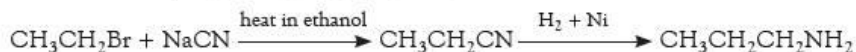
Figure 27.14 Some azo dyes used commercially



Now try this

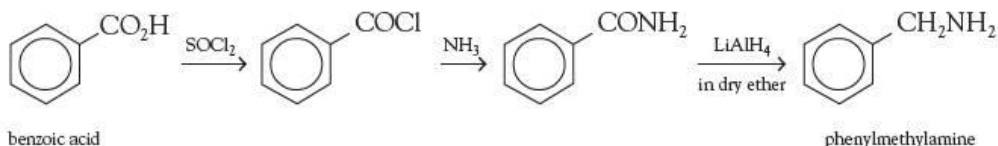
- 1 Draw the structures of the two compounds from which Sunset Yellow can be made by a coupling reaction.
- 2 What are the structures of the two compounds that couple to form Carmoisine?

- By nucleophilic substitution with sodium cyanide, followed by reduction using either lithium tetrahydridoaluminate(III) (lithium aluminium hydride) or hydrogen over a nickel catalyst (see Topic 15, page 274):

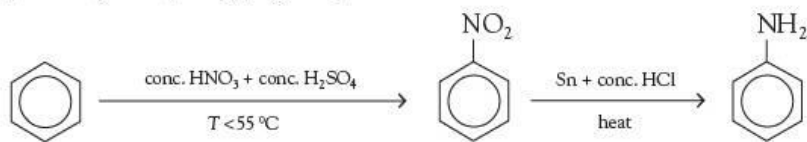


Notice that during this reaction the carbon chain length has been extended by one carbon atom.

Amines are also produced when amides are reduced by lithium tetrahydridoaluminate(III) (catalytic hydrogenation only succeeds under conditions of high pressure and temperature). This allows amines to be synthesised from carboxylic acids:



Aryl amines are most commonly prepared by the reduction of aromatic nitro compounds (see Topic 25, page 424):



To produce the free amine, excess sodium hydroxide must be added after the reduction is completed.

Now try this

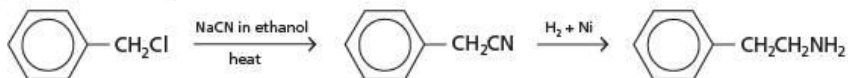
Suggest **two** ways of making butylamine ($\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{NH}_2$), each method starting from a compound containing a different number of carbon atoms.

Worked example

The 'good feeling' factor in chocolate has been identified as 2-phenylethylamine, $\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{NH}_2$. Suggest a synthesis of this compound from chloromethylbenzene, $\text{C}_6\text{H}_5\text{CH}_2\text{Cl}$.

Answer

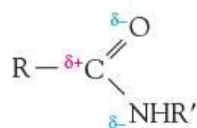
The target amine has one more carbon atom than the suggested starting material, so the cyanide route is required:



27.5 Amides

Properties of amides

Amides have the functional group:



R and R' can be alkyl, aryl or hydrogen.

Amides are extensively hydrogen bonded, having both $\text{H}^{\delta+}$ atoms (on nitrogen) and lone pairs of electrons (on oxygen and nitrogen). Most amides are solids at room temperature, and quite a number are soluble in water.

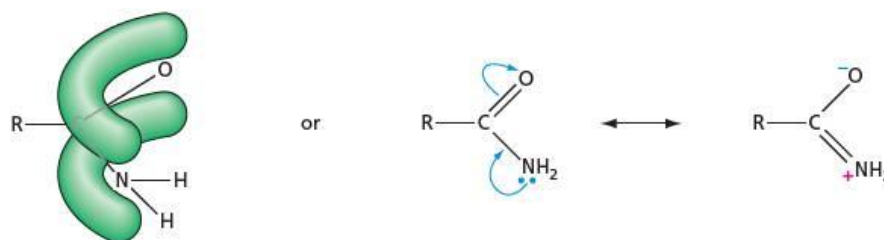
Unlike amines, amides form neutral solutions in water, and can be protonated only by strong acids. The site of protonation is unusual, and explains why amides are such weak bases.

Now try this

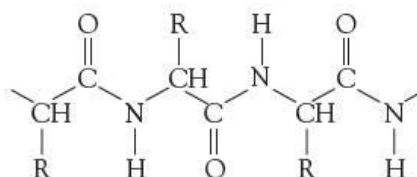
Draw diagrams to show the hydrogen bonding between

- two molecules of ethanamide, CH_3CONH_2
- a molecule of ethanamide and two molecules of water.

Figure 27.15 Delocalisation of the nitrogen lone pair in the amide group

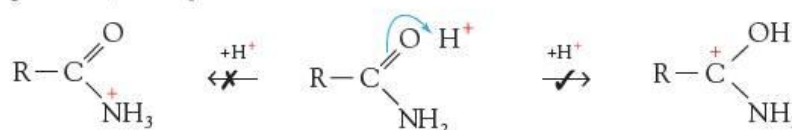


The lone pair on the nitrogen atom in amides is in a p orbital, and can overlap with the π orbital of the adjacent carbonyl group; the electrons are attracted to the electronegative oxygen atom (see Figure 27.15). This confers considerable double-bond characteristics to the C—N bond, including restricted rotation about it (compare with the alkenes, see Topic 14 page 252). This has great significance for the stereochemistry of polypeptide chains in proteins, which we shall meet later in Topic 28. Polypeptide chains contain secondary amide groups:

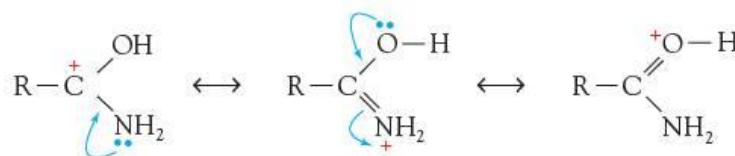


The properties of synthetic polyamides such as nylon are covered in section 28.2.

When amides react with strong acids, it is the oxygen atom, rather than the nitrogen atom, that is protonated:



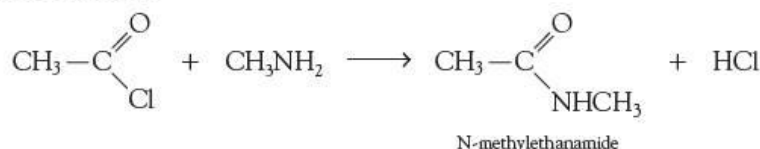
Protonation of the nitrogen atom would result in a positively charged nitrogen adjacent to the δ^+ carbon of the carbonyl group – an unfavourable situation. On the other hand, protonation of the oxygen atom allows the positive charge on the cation to be delocalised over three atoms – an energetically favourable situation:



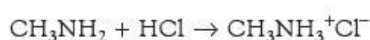
So, although amides are more basic (through their oxygen atom) than other carbonyl compounds (because of the electron donation from nitrogen), they are still much less basic than conventional nitrogen bases such as amines.

Preparation and hydrolysis of amides

Amides are most readily prepared by reacting acyl chlorides (see section 26.3) with ammonia or amines.



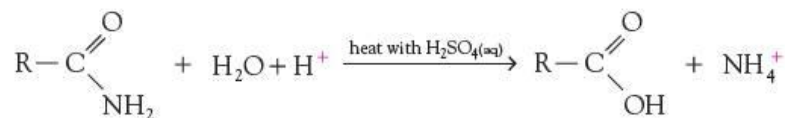
The HCl formed reacts with an excess of amine to produce a salt.



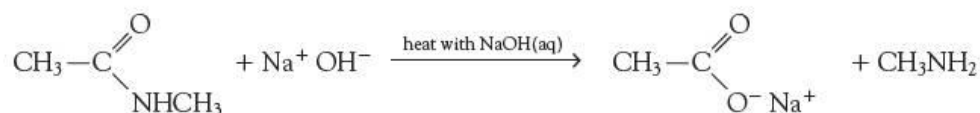
Reactions of amides

With water

Because of the high degree of positive charge on the carbon atom in protonated amides, they are susceptible to nucleophilic attack. Hydrolysis is usually carried out in dilute sulfuric acid. It is still quite a slow reaction, however – heating under reflux for several hours is usually required:



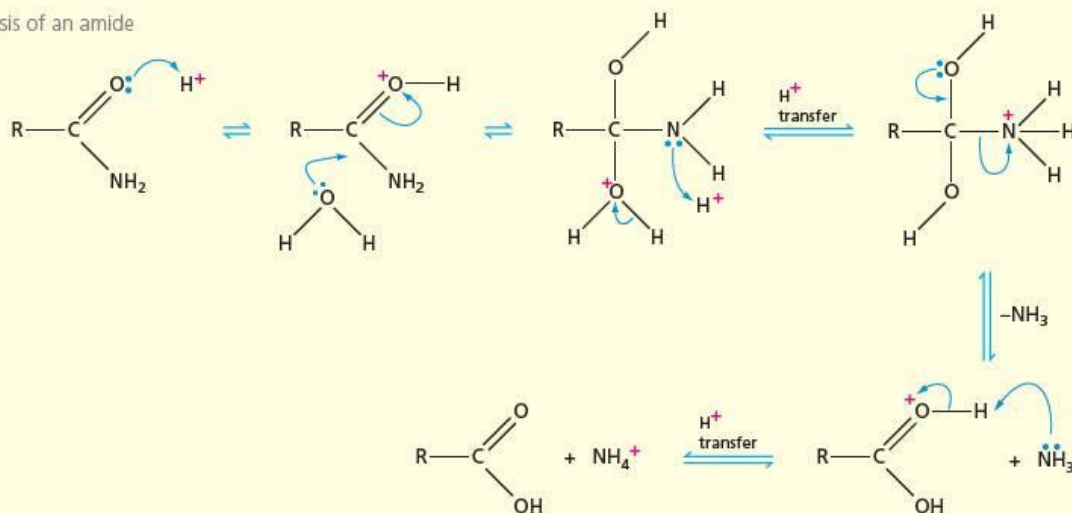
Amides can also be hydrolysed under basic conditions, by heating with NaOH(aq).



The mechanism of the hydrolysis of amides

The mechanism is very similar to that of the hydrolysis of esters, described in section 18.3. The initial reaction is the protonation of the amide by the mineral acid (this occurs on the oxygen atom, as described above). The protonated amide is then attacked nucleophilically by a water molecule. Protons rearrange themselves amongst the oxygen and nitrogen atoms, and eventually the C–N bond cleaves, and a proton is then transferred to NH_3 (see Figure 27.16).

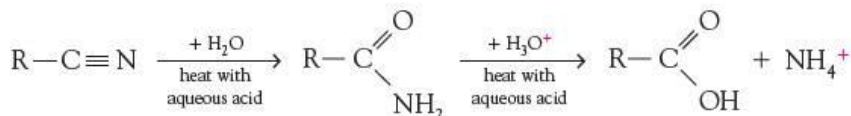
Figure 27.16 The hydrolysis of an amide



Now try this

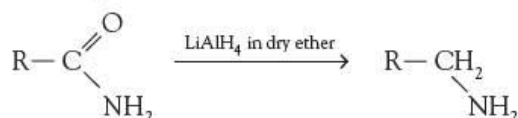
- Write a balanced equation for the conversion of ethanenitrile, CH_3CN , into ethanoic acid by heating with hydrochloric acid.
- (Difficult!) Draw out the mechanism of the hydrolysis of a nitrile to an amide. (Hint: the nitrogen atom has to be protonated twice, in two separate steps of the mechanism.)

Amides are intermediates in the hydrolysis of nitriles to carboxylic acids:



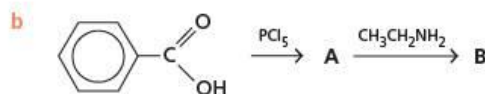
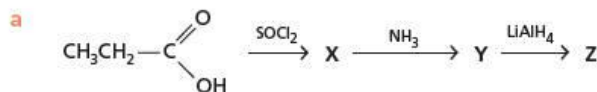
Reduction to amines

Amides can be reduced to amines by lithium tetrahydridoaluminate(III) (lithium aluminium hydride):



Worked example

Suggest products of the following reactions.



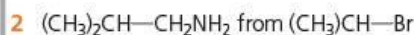
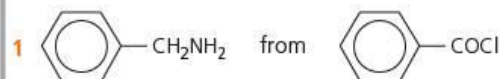
Answer

a X is $\text{CH}_3\text{CH}_2\text{COCl}$ Y is $\text{CH}_3\text{CH}_2\text{CONH}_2$ Z is $\text{CH}_3\text{CH}_2\text{CH}_2\text{NH}_2$



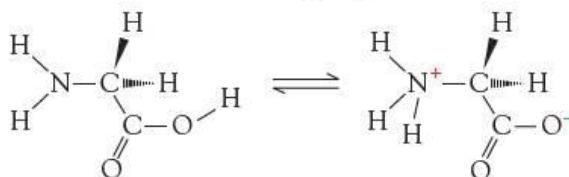
Now try this

Suggest two-stage syntheses of the following compounds, from the stated starting materials.



27.6 Amino acids

Amino acids have two functional groups:



The 2-amino acids (α -amino acids) form an interesting class of compounds, apart from their great importance as the building blocks of proteins. In many compounds containing two or more functional groups, the reactions of one group can be considered independently of those of the other group. They are often widely separated, and dissimilar to each other. In 2-amino acids, however, the two groups are near to each other. What is more, they are of opposite chemical types: the $-\text{NH}_2$ group is basic, whilst the $-\text{CO}_2\text{H}$ group is acidic. Interaction between the two is inevitable.

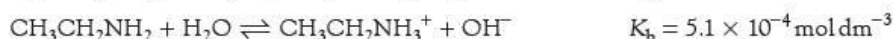
Physical and chemical properties

Whilst alkyl amines and the small-chain aliphatic carboxylic acids are liquids, the amino acids are all solids. They have high melting points (often decomposing before they can be heated to a sufficiently high temperature to melt them), and are soluble in water. In another contrast to amines and carboxylic acids, they are insoluble in organic solvents such as methylbenzene.

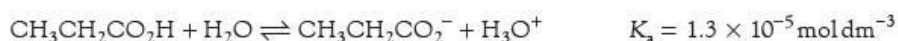
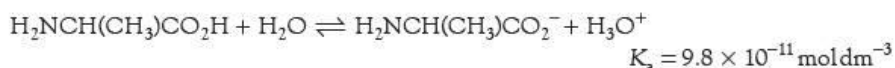
Table 27.4 A comparison of some properties of simple amino acids (glycine and alanine) with those of a simple amine and a simple carboxylic acid

Compound	Formula	Melting point/°C	$K_a/\text{mol dm}^{-3}$	$K_b/\text{mol dm}^{-3}$
glycine	$\text{H}_2\text{NCH}_2\text{CO}_2\text{H}$	233	1.4×10^{-10}	2.4×10^{-12}
alanine	$\text{H}_2\text{NCH}(\text{CH}_3)\text{CO}_2\text{H}$	297	9.8×10^{-11}	2.2×10^{-12}
ethylamine	$\text{H}_2\text{NCH}_2\text{CH}_3$	-81	—	5.1×10^{-4}
propanoic acid	$\text{CH}_3\text{CH}_2\text{CO}_2\text{H}$	-21	1.3×10^{-5}	—

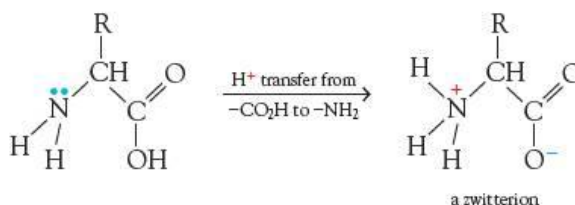
Table 27.4 compares the properties of the two simplest amino acids with those of a simple amine and a simple carboxylic acid. Apart from their extremely high melting points, another clear difference between the amino acids and their mono-functional counterparts is their much reduced basicity and acidity. Glycine is 200 million times less basic than ethylamine:



Likewise, alanine is over 100 000 times less acidic than propanoic acid:



This large reduction in basicity and acidity is readily explained by the idea that the acidic and basic groups within an amino acid molecule have already reacted with each other:



The product is an 'internal salt', called a **zwitterion** (from the German word *Zwitter*, meaning 'hybrid' – zwitterionic structures were first proposed by the German chemist Küster in 1897).

A **zwitterion** is a molecule that contains both a cationic group and an anionic group.

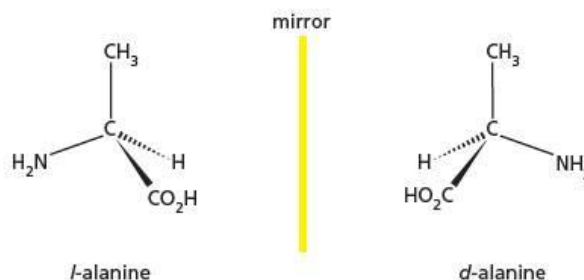
The salt-like nature of zwitterions also explains the high melting points and the solubility characteristics of amino acids. It is thought that all amino acids exist as zwitterions (or dipolar ions) in solution and in the solid lattice. Their low acidity is therefore due to proton donation from the ammonium group rather than from the carboxylic acid group:



This value is directly comparable with the ionisation of other ammonium salts:



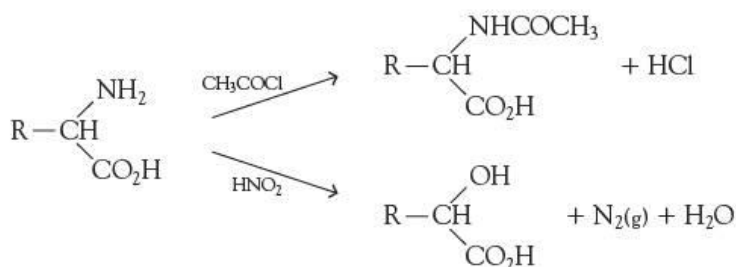
One further characteristic property of 2-amino acids is their optical activity. All except glycine possess a chiral carbon atom, having four different atoms or groups attached to it. There are two distinct and different ways in which these four groups can arrange themselves around the central carbon atom, as shown in Figure 27.17 (see also page 224). All amino acids derived from the hydrolysis of proteins have the '*l*' configuration.

Figure 27.17 *l*- and *d*-alanine

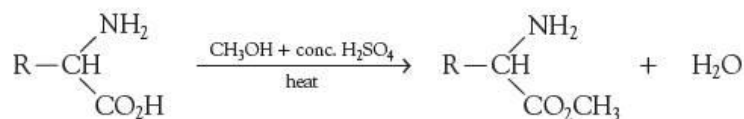
Reactions of amino acids

Because the dipolar form of amino acids is in equilibrium with a small amount of the un-ionised form, amino acids show many of the typical reactions of amines and carboxylic acids.

- 1 The amino group can be acylated (see page 455) and reacts with nitrous acid (see page 456):



- 2 The carboxylic acid group can be esterified:

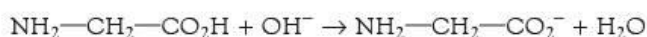


- 3 Amino acids act as buffers, stabilising the pH of a solution if excess acid or alkali is added (see section 22.3).

On adding acid:



On adding alkali:



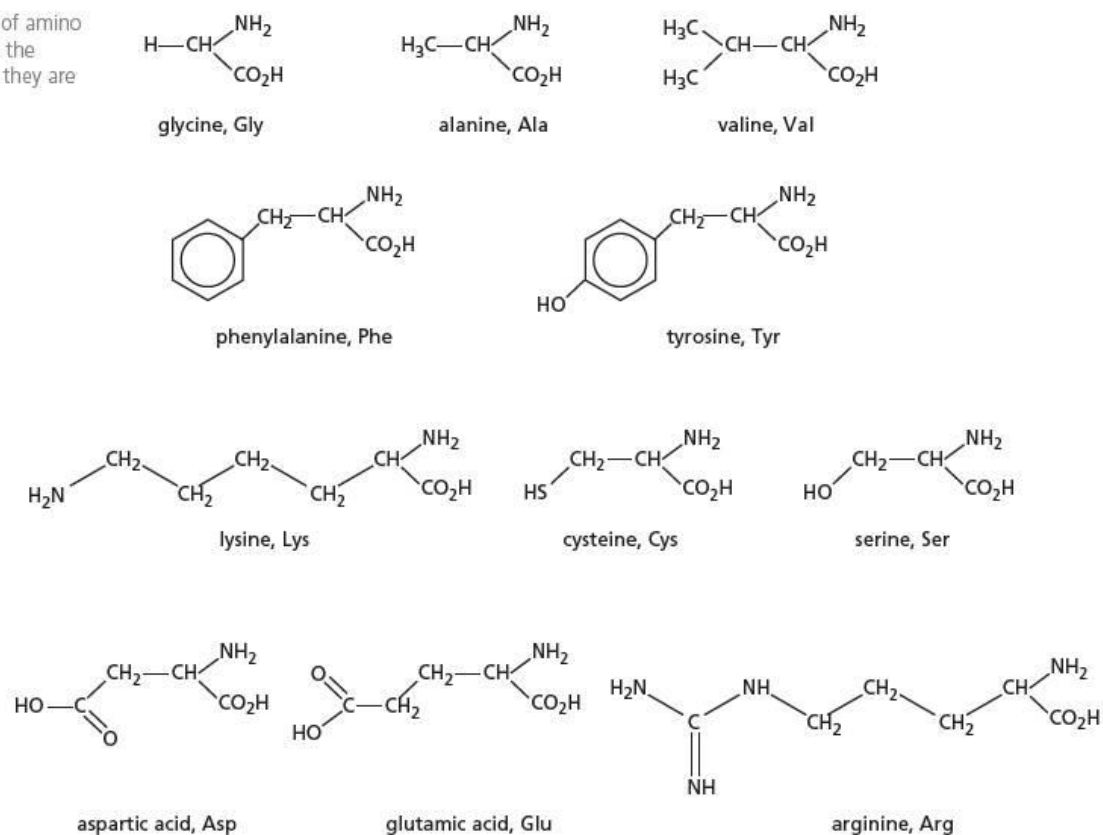
- 4 In addition to the reactions of the $-\text{NH}_2$ and the $-\text{CO}_2\text{H}$ groups, amino acids with side chains that contain functional groups also show the reactions of that group. Figure 27.18 shows the side chains of some amino acids. For example, serine reacts with phosphorus(V) chloride to form a chloroalkyl side chain, and tyrosine reacts with bromine water just as phenol does (see Topic 25, page 435).

Now try this

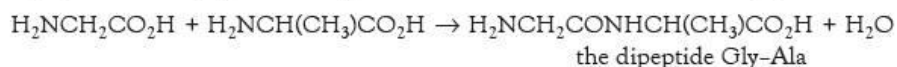
Draw the structure of the product of each of the following reactions (see Figure 27.18).

- Tyr with $\text{Br}_2(\text{aq})$
- Lys with an excess of hydrochloric acid
- Glu when heated with an excess of CH_3OH and a trace of concentrated H_2SO_4
- Ser with an excess of CH_3COCl

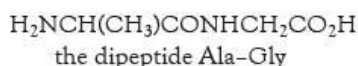
Figure 27.18 A selection of amino acids, with their names and the three-letter codes by which they are known



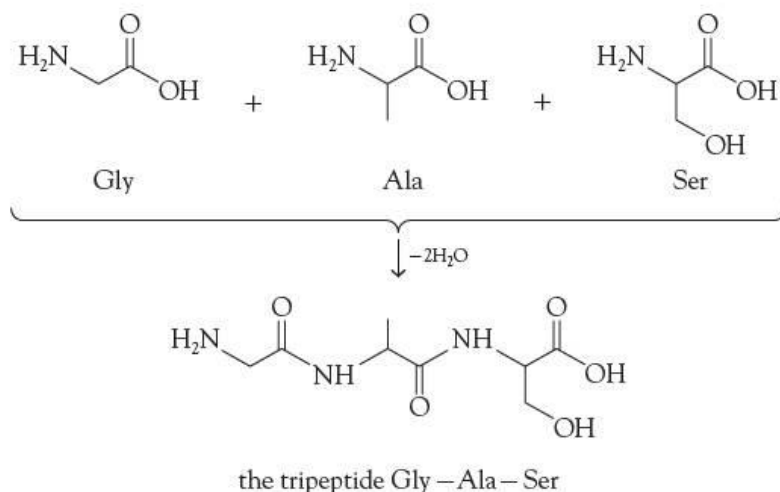
5 Peptide bond formation—two or more amino acids can undergo condensation reactions between themselves to form amides, which, if formed from amino acids, are called **peptides**. If the peptide is composed of two amino acids it is called a dipeptide.



Notice that the dipeptide Ala-Gly is not the same as Gly-Ala: it is a structural isomer of it.



If three amino acids join together, a tripeptide is formed.



Notice that the prefixes *di-* and *tri-* refer to the number of amino acids in the peptide, and not the number of peptide bonds.

Worked example

How many possible tripeptides can be formed from the three amino acids Gly, Ala and Ser, if each tripeptide contains all three amino acids?

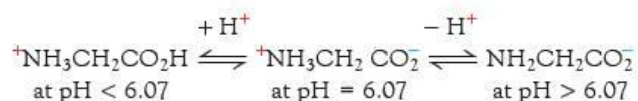
Answer

There are six isomeric tripeptides: Gly-Ala-Ser, Gly-Ser-Ala, Ala-Ser-Gly, Ala-Gly-Ser, Ser-Gly-Ala and Ser-Ala-Gly.

We shall meet peptides again in Topic 28, in the description of proteins.

27.7 Electrophoresis of amino acids and peptides

The principle of electrophoresis is best explained by looking first at how the simple amino acid, glycine, behaves at different pH values. This is because of the amphoteric properties of amino acids. If we have a solution of an amino acid in water, the average charge on the many molecules of amino acid in the solution depends on the pH of the solution. The pH at which the net overall charge is zero is called the **isoelectric point** of that amino acid. For glycine, this is pH 6.07.



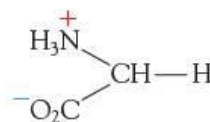
In solution at pH < 6.07, the average charge on glycine molecules becomes positive. At pH > 6.07, the molecules become negatively charged.

Depending on the side groups, different amino acids have different tendencies to form cations or anions in solution, and so their isoelectric points will occur at different pH values. The more basic ones such as lysine, which have a tendency to form cations if dissolved in water, will have their isoelectric points at a more alkaline pH than most. On the other hand, the acidic amino acids such as aspartic acid will have their isoelectric points at a more acidic pH than most (see Table 27.5).

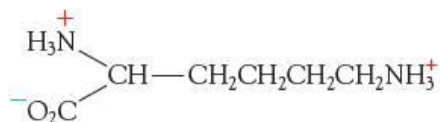
Table 27.5 The isoelectric points of some amino acids

Amino acid	R group in R—CH(NH ₂)CO ₂ H	Isoelectric point (IEP)
glycine	—H	6.07
lysine	—(CH ₂) ₄ NH ₂	9.74
aspartic acid	—CH ₂ CO ₂ H	2.98

If all three of these amino acids were dissolved together in the same buffer solution kept at pH 6.07, on average, the molecules of glycine would be electrically neutral,



the molecules of lysine would be positively charged,



and the molecules of aspartic acid would be negatively charged.

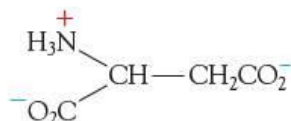
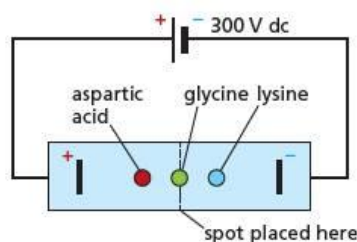


Figure 27.19 Electrophoresis separates lysine, aspartic acid and glycine.



If a drop of the buffer solution at pH 6.07 containing these three amino acids was spotted onto a gel-coated plate, immersed in a conducting liquid, and a potential difference applied, the lysine would move to the cathode, the aspartic acid would move to the anode, and the glycine, having no overall electrical charge, would not move at all (see Figure 27.19).

This separation of a mixture in an electric field is called **electrophoresis**. The electrophoretic mobility depends not only on average charge but also on the size and shape of a molecule:

$$v = \frac{EZ}{F}$$

where v = velocity, E = electric field (voltage applied), Z = average charge and F = frictional resistance.

The frictional resistance is composed of various factors:

- the size of the pores in the gel support (the smaller the pores, the slower the sample moves)
- the shape of the molecule (large, spiky molecules travel slower than small, spherical ones)
- the size/molecular mass of the molecule (larger molecules travel slower than smaller ones).

Other factors that can affect the speed at which the components of a sample move during electrophoresis are:

- the pH of the buffer solution (the average number of charged groups on an amphoteric molecule depends on pH; as the pH increases, the average charge becomes more negative/less positive)
- the temperature of the apparatus (the speed of movement increases with temperature).

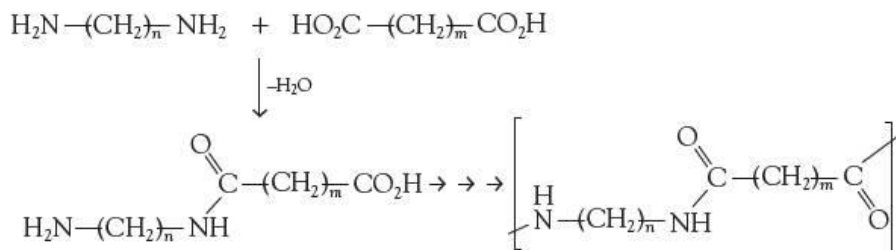
Electrophoresis is used regularly to separate and identify not only mixtures of amino acids, but mixtures of peptides obtained from proteins, and even mixtures of proteins themselves (see Figure 27.20). By this means, abnormal proteins can be identified in patients suffering from genetic disorders, and possible treatments monitored.



Figure 27.20 Electrophoresis of proteins

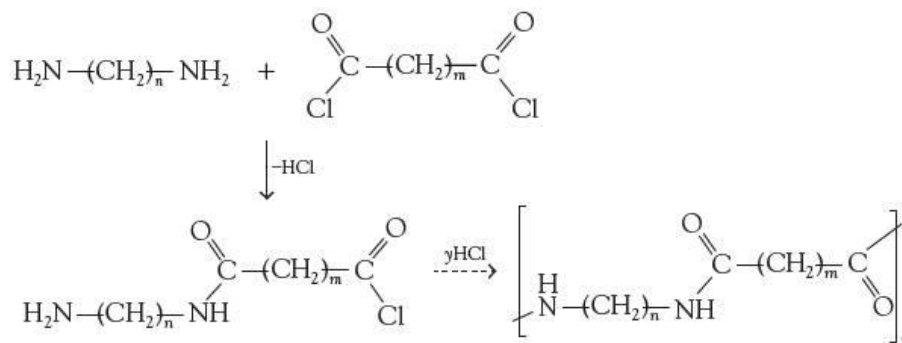
27.8 Synthetic polyamides (nylons)

Synthetic polyamides (nylons) are an important class of manufactured polymer. They are condensation polymers (see section 28.2), usually formed by the reaction between a diamine and a dicarboxylic acid:



Values of n and m vary from 4 to 10.

Diacyl chlorides can also be used, in a reaction similar to the preparation of simple amides (see section 26.3).



Further information about polyamides can be found in Topic 28.

Summary

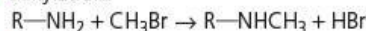
- **Amines** are weak organic bases, reacting with acids to form salts, and dissolving in water to give alkaline solutions.
- There are three types of amine – **primary**, RNH_2 , **secondary**, R_2NH , and **tertiary**, R_3N .
- Aryl amines react with nitric(III) acid (nitrous acid) to form **diazonium salts**, from which many useful **azo dyes** are manufactured.
- **Amino acids** contain the $-\text{NH}_2$ and $-\text{CO}_2\text{H}$ functional groups adjacent to each other. In solution and in the solid they exist as **zwitterions**, $^+\text{NH}_3\text{CHRCO}_2^-$.
- Most amino acids are chiral. Those isolated from natural proteins have the '*l*' configuration.
- Electrophoresis can be used to separate amino acids and peptides.
- **Synthetic polyamides** such as nylon are made by condensing diamines with dicarboxylic acids.

Key reactions you should know

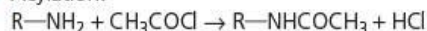
(R = alkyl or aryl unless otherwise stated.)

• Amines:

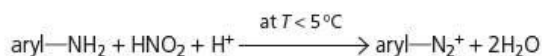
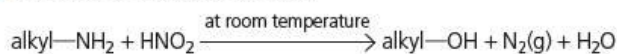
• Alkylation:



• Acylation:

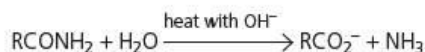
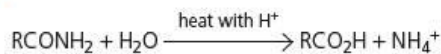


• With nitrous acid (nitric(III) acid):

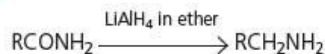


• Amides:

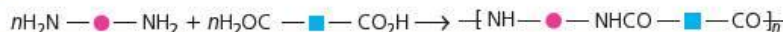
• Hydrolysis:



• Reduction:



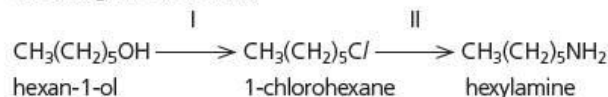
• Polymerisation:



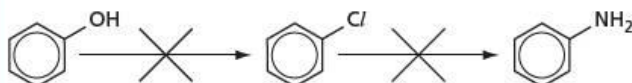
Examination practice questions

Please see the data section of the CD for any A_r values you may need.

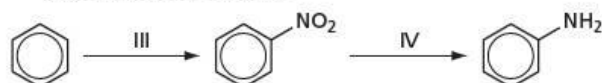
- 1 Phenol and chlorobenzene are less reactive towards certain reagents than similar non-aromatic compounds. Thus hexan-1-ol can be converted into hexylamine by the following two reactions,



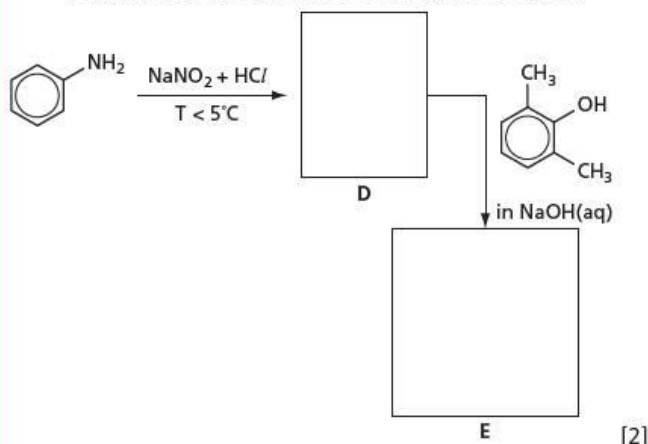
whereas neither of the following two reactions takes place.



- a i Suggest reagents and conditions for reaction I
reaction II
 - ii What type of reaction is reaction II?
 - iii Suggest a reason why chlorobenzene is much less reactive than 1-chlorohexane. [4]
- b Phenylamine can be made from benzene by the following two reactions.



- i Suggest reagents and conditions for reaction III
reaction IV
 - ii State the type of reaction for reaction III
reaction IV [5]
- c Suggest a reagent that could be used to distinguish phenylamine from hexylamine.
reagent and conditions
observation with phenylamine
observation with hexylamine [2]
- d Phenylamine is used to make azo dyes. Draw the structural formula of the intermediate **D** and of the azo dye **E**.

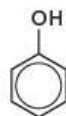


[Cambridge International AS & A Level Chemistry 9701, Paper 4 Q6 June 2009]

- 2 a Describe the reagents and conditions required to form a nitro compound from the following.
- i methylbenzene

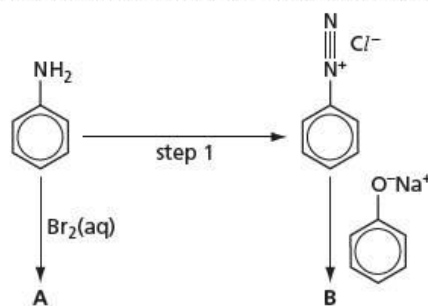


- ii phenol



[3]

- b Draw the structure of the intermediate organic ion formed during the nitration of benzene. [1]
- c Write the reagents needed to convert nitrobenzene into phenylamine. [1]
- d Phenylamine can be converted into the organic compounds **A** and **B**.
i Suggest the structural formulae of **A** and **B**.
ii Suggest suitable reagents and conditions for step 1.



[3]

- e When phenylamine is treated with propanoyl chloride a white crystalline compound, **C**, $\text{C}_9\text{H}_{11}\text{NO}$, is formed.
i Name the functional group formed in this reaction.
ii Calculate the percentage by mass of nitrogen in **C**.
iii Draw the structural formula of **C**. [3]

[Cambridge International AS & A Level Chemistry 9701, Paper 42 Q3 June 2013]