1

Chemistry of acids and bases

Chemistry is the defining science of pharmacy. To understand *anything* about a drug – the synthesis, the determination of its purity, the formulation into a medicine, the dose given, the absorption and distribution around the body, the molecular interaction of drug with its receptor, the metabolism of the drug and, finally, the elimination of drug from the body – requires a thorough and comprehensive understanding of the chemical structure of the drug and how this chemical structure influences the properties and behaviour of the drug in the body. For these reasons, chemistry is the most important of all the scientific disciplines contributing to the understanding of drugs and their actions in the body. A good understanding of the chemistry of drugs will allow the study of advanced topics such as drug design and medicinal chemistry, molecular pharmacology and novel drug delivery systems that are usually encountered in the later stages of a pharmacy or pharmaceutical science degree.

As stated in the preface, most drugs are small organic molecules that behave in solution as either weak acids or weak bases. In order to understand and appreciate these compounds a study must be made of simple acid–base theory.

In 1887, the Swedish chemist Svante August Arrhenius suggested that solutions that conduct electricity (so-called electrolytes) do so because they dissociate into charged species called ions. Positively charged ions (or *cations*) migrate towards the negative terminal, or cathode, while negatively charged ions (or *anions*) migrate towards the positive terminal, or anode. It is this movement of ions that allows the passage of electric current through the solution.

Compounds of this type may be classified as strong electrolytes, which dissociate almost completely into ions in solution, or as weak electrolytes, which only dissociate to a small extent in solution. Since strong electrolytes are almost completely dissociated in solution, measurement of the equilibrium constant for their dissociation is very difficult. For weak electrolytes, however, the dissociation can be expressed by the law of mass action in terms of the equilibrium constant.

Considering the reaction

$$A + B \rightleftharpoons C + D$$

the equilibrium constant (K) for the reaction is given by the product of the concentrations of the reaction products divided by the product of the concentrations of the reactants, or

$$K = \frac{[C] \times [D]}{[A] \times [B]}$$

Clearly, if the equilibrium lies to the right-hand (or products) side, the numerator in the above expression will be greater than the denominator, and K will be greater than 1. Conversely, if the reaction does not proceed very far and the equilibrium lies closer to the left-hand side, [A] × [B] will be larger than [C] × [D] and K will be less than 1.

Strictly speaking, the law of mass action states that 'the rate of a chemical reaction is proportional to the active masses of the reacting substances', but for dilute solutions active mass may be replaced by concentration, which is much easier to measure.

The law of mass action can be applied to the dissociation of water, a weak electrolyte widely used as a solvent in biological and pharmaceutical systems:

$$H_2O \rightleftharpoons H^+ + OH^-$$

The equilibrium constant for this reaction is given by

$$K = \frac{[H^+] \times [OH^-]}{[H_2O]}$$

In pure water, and in dilute aqueous solutions, the concentration of molecular water, $[H_2O]$ is so large as to be considered constant (approximately 55.5 M), so the above expression simplifies to

$$K_w = [H^+] \times [OH^-] \tag{1.1}$$

and K_w is called the *ionic product* or *autoprotolysis constant* of water. The value of this equilibrium varies with temperature but is usually quoted as 1×10^{-14} at 25°C. The units of K_w are mole litre^{-1} × mole litre^{-1}, or mole^2 litre^{-2} (also sometimes written as mole^2 dm^{-6} where 1 dm^3 = 1 litre).

Since, in pure water, $[H^+] = [OH^-]$, the hydrogen ion concentration in water is given by the square root of K_w, which is 1×10^{-7} mole litre^{-1}.

Solutions in which the hydrogen ion concentration is greater than 10^{-7} mole litre^{-1} are called acidic, while solutions with a concentration of hydrogen ions less than 10^{-7} mole litre^{-1} are referred to as alkaline.

The range of hydrogen ion concentrations encountered in chemistry is very large, so it is convenient to adopt the pH notation first developed by another Scandinavian chemist (Danish this time), Søren Peder Lauritz Sørensen. He defined pH as 'the negative logarithm (to the base 10) of the hydrogen ion concentration', or

$$\mathbf{pH} = -\log_{10}[\mathbf{H}^+] = \log_{10}\frac{\mathbf{1}}{[\mathbf{H}^+]}$$

Use of the pH notation allows all degrees of acidity and alkalinity normally encountered in chemistry to be expressed on a scale from 0 to 14, corresponding to the concentrations of H^+ ions contained in the solution. Solutions with a pH < 7 are considered acidic, solutions with a pH > 7 are alkaline, while a solution with a pH $= 7$ is neutral.

It should be noted that a sample of water will often give a pH reading of less than 7, particularly if the sample has been left in an open beaker. This is due to carbon dioxide present in the atmosphere dissolving in the water to give carbonic acid (H_2CO_3), which dissociates to release H^+ ions.

Dissociation of weak acids and bases

Acids are compounds that ionise to release hydrogen ions, or protons, to their surroundings. Bases are compounds that can accept hydrogen ions. This is called the Brønsted–Lowry definition of acids and bases (named after yet another Scandinavian chemist, Johannes Nicolaus Brønsted, and Thomas Martin Lowry, who was British). There are other ways of explaining acidity and basicity, but the Brønsted–Lowry theory works most of the time, and will be used throughout this book.

The dissociation of a weak acid is usually represented as follows:

$$HA \rightleftharpoons H^+ + A^-$$

However, this suggests that protons exist free in solution like little tennis balls bouncing around chemical reactions. The reality is that protons are solvated in solution, that is they go around attached to a solvent molecule. Since the most common solvent in pharmaceutical and biological systems is water, the ionisation of a weak acid is better represented as

$$HA + H_2O \rightleftharpoons H_3O^+ + A^-$$

where H_3O^+ is a *hydroxonium* ion, and the ionisation of a base can be represented as

$$B + H_2O \rightleftharpoons BH^+ + OH^-$$

It is important to notice that water appears in these equations as both a proton acceptor and a proton donor. This is an example of the amphoteric (sometimes termed the amphiprotic) nature of water. Although the ionisation of acids and bases in water is best described using the equations above, it is convenient to disregard the water when deriving useful expressions and relationships.

Consider any weak acid, HA, which dissociates as shown below:

$$HA \rightleftharpoons H^+ + A^-$$

The equilibrium constant for this reaction is given, as before, by

$$K = \frac{[H^+] \times [A^-]}{[HA]}$$

In the case of an acid dissociation, the equilibrium constant for the reaction is termed K_a, and is called the ionisation constant, the dissociation constant or, sometimes, the acidity constant. The above equation can now be rewritten as

$$K_a = \frac{[H^+] \times [A^-]}{[HA]}$$

For exact work, the concentration term must be replaced by the thermodynamic activity of the ion, but for dilute solutions concentration may be used.

K_a is a constant for a given compound at a given temperature. Clearly, the farther the above equilibrium lies to the right-hand side, the more completely the acid will ionise and the greater will be the value of K_a.

To put it more simply, the greater the value of K_a, the stronger is the acid. Using the equation above, it is possible to derive an expression for the strength of acid solutions. If the acid, HA, ionises to a moles of H^+ ions and a moles of OH^- ions, where a is the fraction of the acid that is ionised, then the number of moles of undissociated acid is given by $(1 - a)$. This acid solution can now be prepared with c moles of acid in 1 litre (or 1 dm^3), which will yield ac moles of H^+ and ac moles of A^-. Hence,

$$\begin{array}{ccc} HA & \rightleftharpoons & H^+ + A^- \\ (1-a)c & & ac + ac \end{array}$$

$$K_a = \frac{ac \times ac}{(1-a)c}$$

$$K_a = \frac{\alpha^2 c^2}{(1 - \alpha)c}$$

$$K_a = \frac{\alpha^2 c}{(1 - \alpha)}$$

For weak electrolytes, α is very small and may be neglected so $(1 - \alpha)$ is approximately = 1. The simplified expression may now be written as

$$K_a = \alpha^2 c$$

where c is the concentration, in moles per litre, and α is the degree of ionisation of the acid. Then

$$\alpha = \sqrt{\left(\frac{K_a}{c}\right)}$$

The pH of the solution can now be determined:

$$[H^+] = \alpha c$$

Therefore,

$$[H^+] = c\sqrt{\left(\frac{K_a}{c}\right)} = \sqrt{(K_a c)}$$

Taking logarithms,

$$\log[H^+] = \tfrac{1}{2} \log K_a + \tfrac{1}{2} \log c$$

Multiplying throughout by -1 gives

$$-\log[H^+] = -\tfrac{1}{2} \log K_a - \tfrac{1}{2} \log c$$

Therefore,

$$\mathbf{pH = \tfrac{1}{2}\, pK_a - \tfrac{1}{2} \log c} \qquad (1.2)$$

Equation (1.2) applies to the ionisation of weak acids, but a similar expression can be derived for weak bases. The equation for the ionisation of a weak base may be expressed as

$$\begin{array}{lccc} B + H_2O & \rightleftharpoons & BH^+ + OH^- \\ (1 - \alpha)c & & \alpha c \quad + \quad \alpha c \end{array}$$

where B is the base and BH^+ is termed the *conjugate acid* of the base.
The equilibrium constant for this reaction is written as

$$K_b = \frac{[BH^+] \times [OH^-]}{[B]}$$

where K_b is termed the base dissociation constant or basicity constant.

$$K_b = \frac{a^2 c}{(1 - a)}$$

As before a is very small and can be neglected, so $(1 - a)$ is approximately $= 1$.

$$a^2 = \frac{K_b}{c}$$

$$a = \sqrt{\left(\frac{K_b}{c}\right)}$$

From above,

$$[OH^-] = ca$$

Therefore,

$$[OH^-] = c\sqrt{\left(\frac{K_b}{c}\right)} = \sqrt{(K_b c)}$$

However,

$$[OH^-] = \frac{K_w}{[H^+]}$$

Therefore,

$$\frac{K_w}{[H^+]} = \sqrt{(K_b c)}$$

and

$$[H^+] = \frac{K_w}{\sqrt{(K_b c)}}$$

Taking logarithms,

$$\log[H^+] = \log K_w - \tfrac{1}{2} \log K_b - \tfrac{1}{2} \log c$$

or

$$\mathbf{pH = pK_w - \tfrac{1}{2}\, pK_b + \tfrac{1}{2} \log c} \qquad (1.3)$$

Equations (1.2) and (1.3) are extremely useful because they allow the pH of solutions of weak acids and bases to be calculated if the concentrations and dissociation constant are known.

How strong an acid is depends on how many hydrogen ions are released when the acid ionises, and this depends on the degree of ionisation, a, for any given concentration. As stated above, K_a, the equilibrium constant for the dissociation of the acid, gives a measure of how far the ionisation equilibrium lies to the right-hand, or products, side. As can be seen from equation (1.3), the similar expression K_b gives a measure of basic strength and, as with K_a, the higher the numerical value of K_b, the stronger is the base.

It is often useful and convenient to express the strengths of acids and bases using the same term, pK_a, and this can be done by considering the equilibria that exist between an acid and its conjugate base. A weak acid (HA) and its conjugate base (A^-) are related as follows:

$$HA \rightleftharpoons H^+ + A^-$$

$$A^- + H_2O \rightleftharpoons HA + OH^-$$

From the equations above,

$$K_a = \frac{[H^+] \times [A^-]}{[HA]}$$

and

$$K_b = \frac{[HA] \times [OH^-]}{[A^-]}$$

Then

$$K_a \times K_b = \frac{[H^+] \times [A^-]}{[HA]} \times \frac{[HA] \times [OH^-]}{[A^-]}$$

Cancelling similar terms gives

$$K_a \times K_b = [H^+] \times [OH^-]$$

which can be rewritten as

$$\boldsymbol{K_a \times K_b = K_w = 1 \times 10^{-14}} \qquad (1.4)$$

That is, the acid dissociation constant and the base dissociation constant are related through the ionic product of water.

Equation (1.4) is a very important relationship since it allows the calculation of K_b or K_a if the other is known. It also follows that the strengths of acids and their conjugate bases are related through K_w. This means that a strong acid must have a weak conjugate base and, similarly, a weak acid must have a strong conjugate base. A moment's thought will confirm that this must, indeed, be true. Acids and their conjugate bases are related by equilibria, which can be thought of as giant seesaws. If one partner of the pair is very strong and heavy, the other will be weak and light. The same relationship applies to acid–conjugate base equilibria.

This relationship also allows chemists to be lazy and express the strengths of acids and bases in terms of the dissociation constant for the acid. This is particularly true when we consider the term pK_a.

In a similar manner to pH, the pK_a of an acid is defined as the negative logarithm (to the base 10) of the dissociation constant, K_a; i.e.

$$pK_a = -\log_{10} K_a$$

This terminology allows chemists to talk loosely about the pK_a of acids and bases, when what they really mean is the pK_a of acids and the conjugate acids of bases. It is incorrect to say 'the pK_a of a primary amine is between 9 and 10', although the usage is widespread. It is more accurate to say 'the pK_a of the conjugate acid of a primary amine is between 9 and 10'. This is just another example of lecturers saying one thing and meaning another.

Another source of confusion concerning strengths of acids arises with K_a and pK_a. The term K_a is the dissociation constant for the ionisation of an acid, and hence the larger the value of K_a, the stronger is the acid (since the equilibrium constant lies farther to the right-hand side).

pK_a is the negative logarithm of K_a, and is used commonly because K_a values for organic acids are very small and hard to remember (typically 10^{-5}). It follows that since pK_a is the *negative* logarithm of K_a, the smaller the value of pK_a the stronger is the acid.

Consider the two carboxylic acids below:

Acetic acid, CH_3COOH, $pK_a = 4.7$

Chloroacetic acid, $ClCH_2COOH$, $pK_a = 2.7$

In answer to the question 'which acid is the stronger?', clearly it is chloroacetic acid, since its pK_a is smaller. A student of organic chemistry could even suggest that the reason is due to increased stabilisation of the anion formed on ionisation by the electronegative chlorine atom. If the question is asked 'how much stronger is chloroacetic than acetic?', then all sorts of interesting answers appear, ranging from 'twice as strong' to a

'million times as strong'. The answer, obvious to anyone who is familiar with logarithms, is that chloroacetic is 100 times stronger than acetic acid. This is because the difference in pK_a is two units on a log scale, and the antilog of 2 to the base 10 is 100. It is important for students (and graduates!) to appreciate that pH and pK_a are *logarithmic* relationships and that a K value corresponding to a pK_a of 2.7 is not really close to a K value corresponding to a pK_a of 4.7.

Equation (1.4) can be rewritten in a logarithmic form by taking the negative logarithm of both sides, to give

$$\mathbf{p}K_a + \mathbf{p}K_b = \mathbf{p}K_w = \mathbf{14} \qquad (1.5)$$

In addition, since pK_b may be rewritten as $pK_w - pK_a$, this allows equation (1.3) to be rewritten omitting any reference to pK_b as

$$\mathbf{pH} = \tfrac{1}{2}\,\mathbf{p}K_w + \tfrac{1}{2}\,\mathbf{p}K_a + \tfrac{1}{2}\,\mathbf{log}\,c$$

or alternatively

$$\mathbf{pH} = \tfrac{1}{2}(\mathbf{p}K_w + \mathbf{p}K_a + \mathbf{log}\,c)$$

Hydrolysis of salts

When a salt is dissolved in water, the compound dissociates completely to give solvated anions and cations. This breaking of bonds by the action of water is called *hydrolysis* and the salt is said to be *hydrolysed*.

The pH of the resulting solution depends on whether the salt was formed from reaction of strong or weak acids and bases and there are four possible combinations.

For example, if the salt results from reaction between a strong acid and a strong base (e.g. NaCl), then the resulting solution will be neutral, and NaCl is termed a neutral salt. Of the two ions produced, Na^+ and Cl^-, only the Cl^- reacts with water:

$$Cl^- + H_2O \rightleftharpoons HCl + OH^-$$

This reaction does not occur to any great extent since the Cl^- is the conjugate base of a strong acid, namely HCl. The Cl^- is therefore a very weak conjugate base and its reaction with water can be neglected.

If the salt results from reaction between a strong acid and a weak base (e.g. the reaction of ammonia and hydrogen chloride to give ammonium chloride),

$$HCl + NH_3 \rightleftharpoons NH_4^+ + Cl^-$$

then the resulting salt solution will be acidic by hydrolysis and the pH of an aqueous solution of the salt will be less than 7.

This can be demonstrated by considering the reactions that occur when ammonium chloride is hydrolysed. The salt dissociates completely to give hydrated ammonium ions and hydrated chloride ions. The Cl^- ion is not very reactive towards water, but the ammonium ions react with water to give ammonium hydroxide. This is because NH_4^+ is the conjugate acid of the weak base NH_3, and must therefore be quite strong. The NH_4^+ reacts with water as follows to produce H_3O^+ ions:

$$NH_4^+Cl^- \rightleftharpoons NH_4^+Cl^-$$

$$NH_4^+ + H_2O \rightleftharpoons NH_3 + H_3O^+$$

An increase in the concentration of H_3O^+ ions results in a fall in pH, and an acidic solution.

The pH of this solution can be calculated by using the equation derived for a weak acid, equation (1.2) above:

$$\mathbf{pH} = \tfrac{1}{2}\,\mathbf{p}K_a - \tfrac{1}{2}\log c$$

If the salt results from the reaction of a strong base and weak acid (e.g. sodium acetate from reaction of sodium hydroxide and acetic acid), then the solution formed on hydrolysis will be basic, i.e.

$$NaOH + CH_3COOH \rightleftharpoons CH_3COO^-Na^+ + H_2O$$

$$CH_3COO^-Na^+ + H_2O \rightleftharpoons CH_3COOH + OH^- + Na^+$$

Na^+ does not react with water to any great extent, but CH_3COO^- is the conjugate base of the weak acid CH_3COOH and is therefore strong enough to react with water to produce OH^- ions.

The increase in concentration of OH^- gives a basic solution, the pH of which can be calculated from the equation for the pH of weak bases, equation (1.3).

$$\mathbf{pH} = \mathbf{p}K_w - \tfrac{1}{2}\,\mathbf{p}K_b + \tfrac{1}{2}\log c$$

or, if pK_b is replaced by the expression $pK_w - pK_a$,

$$\mathbf{pH} = \tfrac{1}{2}\,\mathbf{p}K_w + \tfrac{1}{2}\,\mathbf{p}K_a + \tfrac{1}{2}\log c$$

which is probably the easiest form to remember.

The final scenario involves a salt formed between a weak acid and a weak base (e.g. ammonium acetate, $NH_4^+CH_3COO^-$). The H^+ and OH^- ions formed by hydrolysis of ammonium acetate occur in roughly equal concentrations, which will yield a neutral salt.

These relationships can be summarised as follows:

Strong acid + Strong base ⟶ *Neutral salt*
Strong acid + Weak base ⟶ *Acidic salt*
Weak acid + Strong base ⟶ *Basic salt*
Weak acid + Weak base ⟶ *Neutral salt*

and do seem to follow a type of logic. Using the seesaw analogy for equilibria again, if both partners are strong or both are weak, then the seesaw balances, and the solution formed by hydrolysis is neutral. If either partner is strong then the seesaw tilts to that side to give an acidic or basic solution. This analogy is not precise, but it may help the desperate student to remember the pH values of hydrolysed salt solutions.

Amphiprotic salts

The reactions of salts in water become more complicated if the salt in question is *amphiprotic*, i.e. can function both as an acid and a base. Examples of amphiprotic anions are bicarbonate (sometimes called hydrogencarbonate), HCO_3^-, and bisulfite (or hydrogensulfite), HSO_3^-. These species can donate or accept H^+ ions in solution.

The pH of a solution of an amphiprotic salt (e.g. sodium bicarbonate, $Na^+HCO_3^-$) is given by the equation

$$\text{pH} = \tfrac{1}{2}(\text{p}K_{\text{a1}} + \text{p}K_{\text{a2}}) \qquad (1.6)$$

where $\text{p}K_{\text{a1}}$ and $\text{p}K_{\text{a2}}$ refer to the ionisation constants for the acid and base reactions, respectively. In the case of sodium bicarbonate, these values are 6.37 and 10.25 which means the pH of *any concentration* of sodium bicarbonate will be 8.31 and the solution will be slightly basic.

Buffer solutions

A buffer solution is a solution that resists changes in pH. If acid is added then, within reason, the pH does not fall; if base is added, the pH does not rise. Buffers are usually composed of a mixture of weak acids or weak bases and their salts and function best at a pH equal to the $\text{p}K_{\text{a}}$ of the acid or base involved in the buffer. The equation that predicts the behaviour of buffers is known as the Henderson–Hasselbalch equation (named after chemists Lawrence Joseph Henderson and Karl Albert Hasselbalch), and is another vitally important equation worth committing to memory. It is derived as follows, by considering a weak acid that ionises in solution:

$$HA \rightleftharpoons H^+ + A^-$$

The equilibrium constant for this ionisation is given by

$$K_a = \frac{[H^+] \times [A^-]}{[HA]}$$

Taking logarithms of both sides and separating the hydrogen ion term gives

$$\log K_a = \log[H^+] + \log \frac{[A^-]}{[HA]}$$

Multiplication throughout by -1 gives

$$-\log K_a = -\log[H^+] - \log \frac{[A^-]}{[HA]}$$

or

$$pK_a = pH - \log \frac{[A^-]}{[HA]}$$

which rearranges to give

$$pH = pK_a + \log \frac{[A^-]}{[HA]}$$

Since the acid in question is weak, the number of A^- ions derived from dissociation of the acid itself is very small compared with the number derived from the fully ionised salt. This means that $[A^-]$ is approximately equal to total concentration [SALT]; and similarly [HA], since the acid is weak and predominantly unionised, is approximately equal to the total acid concentration [ACID]. The equation can now be rewritten as

$$\mathbf{pH = pK_a + \log \frac{[SALT]}{[ACID]}} \tag{1.7}$$

The Henderson–Hasselbalch equation can also be derived from consideration of the ionisation of a weak base, B, which ionises in aqueous solution as follows:

$$B + H_2O \rightleftharpoons BH^+ + OH^-$$

In this case the [SALT] term can be replaced by the concentration of the conjugate acid of the weak base, $[BH^+]$, which, in effect, yields the same equation.

An example of a buffer is a mixture of acetic acid and sodium acetate, which will ionise as follows:

$$\mathbf{CH_3COOH} \rightleftharpoons CH_3COO^- + H^+$$

$$CH_3COO^-Na^+ \rightleftharpoons \mathbf{CH_3COO^-} + \mathbf{Na^+}$$

Since the acetic acid only ionises to a small extent, there will be a high concentration of undissociated acid (shown in bold) or, to put it another way, the equilibrium for the reaction will lie predominantly to the left-hand side. Sodium acetate is a salt and will ionise completely to give high concentrations of CH_3COO^- and Na^+ (shown in bold).

If H^+ ions are now added to the buffer solution, they will react with the high concentration of CH_3COO^- present to give undissociated acetic acid. Acetic acid is a weak acid and only dissociates to a small extent, so the pH of the solution does not decrease. In effect, a strong acid such as H^+ is mopped up by the buffer to produce a weak acid, acetic acid, which is not sufficiently acidic to lower the pH.

$$H^+ + CH_3COO^- \rightleftharpoons CH_3COOH$$

Similarly, if OH^- ions are added to the buffer system, the OH^- will react with the high concentration of free acetic acid present to give water and acetate ions:

$$OH^- + CH_3COOH \rightleftharpoons H_2O + CH_3COO^-$$

Neither water nor acetate is sufficiently basic to make the solution alkaline, so the pH of the buffer solution will not increase.

The high concentration of sodium ions has little or no effect on the pH of the solution since when these ions react with water they do so to produce equal numbers of H^+ and OH^- ions as shown below:

$$Na^+ + H_2O \rightleftharpoons Na^+OH^- + H^+$$

and

$$Na^+OH^- \rightleftharpoons Na^+ + OH^-$$

Buffers can also be composed of weak bases and their salts; examples include ammonia buffer, used to control the pH of complexiметric titrations (see Chapter 6) and the common biological buffer TRIS (or tris(hydroxymethylaminomethane), $C_4H_{11}NO_3$), used to control the pH of protein solutions.

Buffer capacity

Buffer solutions work best at controlling pH at pH values roughly equal to the pK_a of the component acid or base, i.e. when the [SALT] is equal to the [ACID]. This can be shown by calculating the ability of the buffer to resist changes in pH, which is the *buffer capacity*.

The buffer capacity is defined as the number of moles per litre of strong monobasic acid or base required to produce an increase or decrease of one pH unit in the solution. When the concentrations of salt and acid are equal, the log term in the Henderson–Hasselbalch equation becomes the logarithm of 1, which equals 0. To move the pH of the buffer solution by one unit of pH will require the Henderson–Hasselbalch equation to become

$$\text{pH} = pK_a + \log \frac{10}{1}$$

It will require addition of more acid or base to move the pH by one unit from the point where $\text{pH} = pK_a$ than at any other given value of the ratio. This can be neatly illustrated by the following example.

Suppose one litre of buffer consists of 0.1 M CH_3COOH and 0.1 M $CH_3COO^-Na^+$; the pH of this buffer solution will be 4.7 (since the log term in the Henderson–Hasselbalch equation cancels). Now, if 10 mL of 1 M NaOH is added to this buffer, what will be the new pH?

Clearly, the 10 mL of NaOH will ionise completely (strong alkali) and some of the 0.1 M acetic acid will have to convert to acetate anion to compensate. The new pH will be

$$\text{pH} = pK_a + \log \frac{[\text{SALT}]}{[\text{ACID}]}$$

$$\text{pH} = 4.7 + \log \frac{(0.1 + 0.01)}{(0.1 - 0.01)}$$

$$\text{pH} = 4.7 + \log \frac{0.11}{0.09}$$

$$\text{pH} = 4.79$$

The addition of 10 mL of 1 M alkali has only increased the pH of the buffer by a small amount. By way of comparison, if 10 mL of 1 M NaOH were added to 1 litre of pure water, the pH of the solution would increase from a pH of 7 to a value of approximately 12. This can be easily shown by using the term, pOH, which is defined as the negative logarithm of the OH^-

concentration in a similar way to pH = $-\log [H^+]$. The term pOH is used much less frequently in the literature than pH but it follows that if pOH for 0.01 M NaOH = 2 and pH + pOH = 14, the pH of the solution in the example above = 12.

The buffer capacity (β) for this buffer can now be calculated as

$$\beta = \frac{\text{No. of moles of NaOH added}}{\text{Change in pH observed}}$$

$$\beta = \frac{0.01}{(4.79 - 4.7)}$$

$$\beta = \frac{0.01}{0.09}$$

$$\beta = 0.11$$

Since buffer solutions work best at a pH equal to the pK_a of the acid or base of which they are composed, consideration of the pK_a will determine choice of buffer for a given situation. The pK_a of acetic acid is 4.7, and therefore an acetic acid–acetate buffer would be useful for buffering a solution to a pH of approximately 5. Similarly, an alkaline buffer can be obtained by using ammonia solution, which will buffer to a pH of approximately 10 (pK_a of ammonia = 9.25).

If a buffer is required to control the pH of a neutral solution, use is made of the second ionisation of phosphoric acid. Phosphoric acid is a triprotic acid, which requires three equivalents of NaOH as follows:

$$H_3PO_4 + NaOH \rightleftharpoons Na^+H_2PO_4^- + H_2O \qquad pK_a = 2.12$$

$$Na^+H_2PO_4^- + NaOH \rightleftharpoons (Na^+)_2HPO_4^{2-} + H_2O \qquad pK_a = 7.21$$

$$(Na^+)_2HPO_4^{2-} + NaOH \rightleftharpoons (Na^+)_3PO_4^{3-} + H_2O \qquad pK_a = 12.67$$

A mixture of sodium dihydrogenphosphate, $Na^+H_2PO^-$ and disodium hydrogenphosphate, $(Na^+)_2HPO_4^{2-}$, will function as a buffer and control the pH to a value of approximately 7.0. In this example, the species with the greater number of available hydrogen atoms functions as the acid, i.e. $Na^+H_2PO_4^-$, while the $(Na^+)_2HPO_4^{2-}$ functions as the salt.

The choice of buffer to use in a given situation therefore depends on the pK_a of the acid or base involved. As a general rule, buffer solutions work well within plus or minus one pH unit of the pK_a. Beyond these values, the buffer capacity is too small to allow effective buffer action.

Biological buffers

The human body contains many buffer systems, which control the pH of body compartments and fluids very effectively. Blood plasma is maintained at a pH of 7.4 by the action of three main buffer systems: first, dissolved carbon dioxide, which gives carbonic acid (H_2CO_3) in solution, and its sodium salt (usually sodium bicarbonate, $NaHCO_3$). This is responsible for most of the buffering capacity. The other two buffers are dihydrogenphosphate ($H_2PO_4^-$), also with its sodium salt, and protein macromolecules. Proteins are polymers composed of repeating units called amino acids. These amino acids (as their name suggests) are compounds containing NH_2 and COOH groups in the same molecule and have the general formula shown in Figure 1.1.

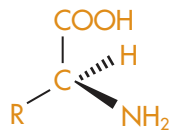

Figure 1.1 The general formula of amino acids.

Proteins are composed of about 20 different amino acids, which are connected to each other by *peptide bonds* formed between one amino acid and its neighbour. The side-chain of the amino acid may be acidic (as in the case of glutamic and aspartic acids), basic (as in the case of arginine and lysine) or neutral (as in alanine). A protein, which may be composed of hundreds of amino acids, is therefore a polyelectrolyte whose properties depend on the balance of acidic and basic groups on the side-chains. Generally, most proteins act as weak acids and form buffers with their sodium salts. Compounds like amino acids, which are capable of acting as both acids and bases, are known as *amphoteric*, or sometimes, *amphiprotic*. In solution, free amino acids usually do not exist in the molecular form shown in Figure 1.1, but instead both the amino and carboxyl groups ionise to form an internal salt as shown in Figure 1.2.

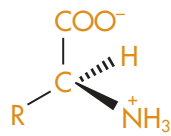

Figure 1.2 The structure of a zwitterion.

These internal salts are known by the German word *zwitterion* (German for 'dipolar ion'), and formation of the zwitterion makes the amino acid very polar and therefore very soluble in water. If acid is added to the zwitterion, the ionised COO^- group will accept a proton to give undissociated COOH. The overall charge on the amino acid will now be positive, due to the NH_3^+. Similarly, if base is added to the zwitterion, the NH_3^+ (which is really the conjugate acid of NH_2) will function as an acid and donate its proton to the base. The overall charge on the amino acid will now be negative, due to the ionised COO^-. Amino acids are, therefore, ionised at all values of pH. They are positively charged at low pH, negatively charged at high pH and zwitterionic at neutral pH. The fact that amino acids are ionised at all values of pH and are zwitterionic at neutral pH has profound implications for the oral absorption and bioavailability of amino acids from the diet. The body has to resort to specialised uptake mechanisms to ensure that sufficient levels of these essential nutrients are absorbed (see Chapter 2). The ionisation of the simplest amino acid, glycine, is represented in Figure 1.3.

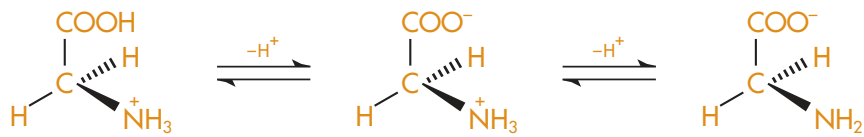

Figure 1.3 The ionisation of glycine.

If the pH of the protein or amino acid solution is adjusted so that the number of ionised COO^- groups is equal to the number of ionised NH_3^+ groups, then that value of pH equals pI, the *isoelectric point* of the protein or amino acid. This point corresponds to the minimum solubility of the protein, and the point at which migration of the protein in an electric field is slowest (as in the technique of *electrophoresis*, which is used to separate mixtures of proteins according to their overall electrical charge). The isoelectric point for an amino acid may be easily calculated if the pK_a values for the NH_3^+ and COO^- are known (e.g. by titration). For a simple amino acid, such as glycine, the pI is simply the average of the two pK_a values. For more complex amino acids, such as glutamic acid or arginine which have ionisable groups in the side-chains, the pI is given by averaging the two pK_a values that lie on either side of the zwitterion. This is true no matter how many times an amino acid or peptide ionises. For an amino acid with one acidic group on the side-chain, there are three distinct ionisations and hence

three distinct pK_a values. Fully protonated aspartic acid ionises as shown in Figure 1.4.

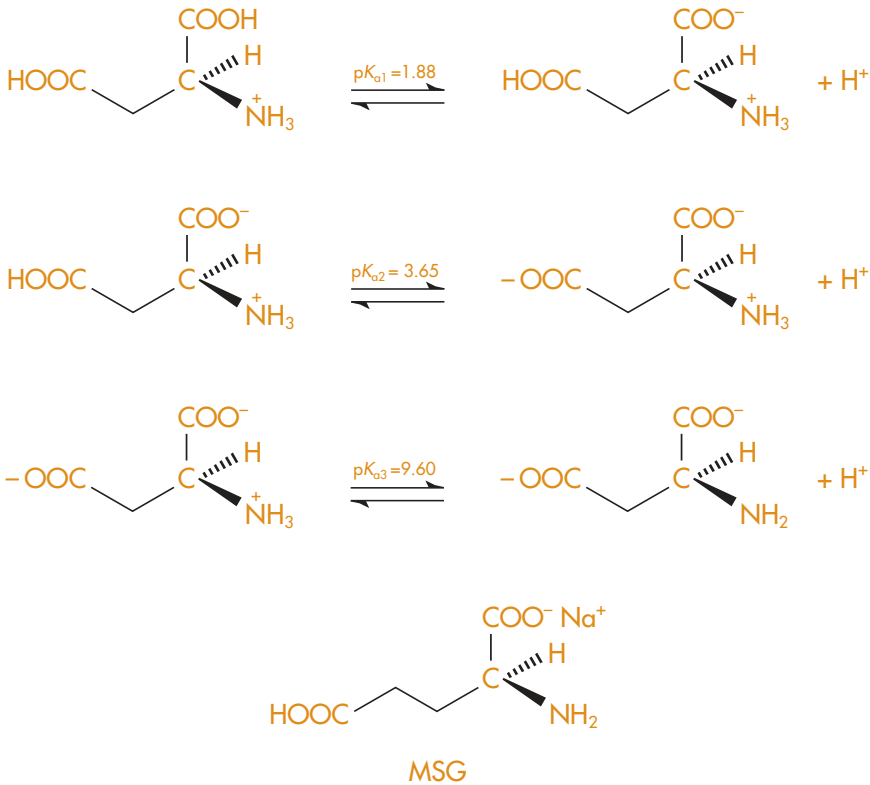

Figure 1.4 The ionisation of aspartic acid and structure of MSG.

The first group to ionise (and hence the strongest acid) is the COOH group on the α carbon. This gives pK_{a1}. The second proton is lost from the side-chain COOH to give pK_{a2}. Finally, the NH_3^+ on the α carbon ionises to give pK_{a3}. There is, of course, only one pI, which is given by the average of the two pK_a values on either side of the zwitterion, i.e. $\frac{1}{2}$(pK_{a1} + pK_{a2}).

The other commonly occurring amino acid with an acidic side-chain is glutamic acid. This compound is probably best known as its monosodium salt (monosodium glutamate or MSG). This salt is added to foods (especially oriental food) to enhance the flavour and impart a 'meat-like' taste to the food. Interestingly, both the D enantiomer of glutamic acid and the naturally occurring L form are used as food additives. Use of the non-natural D isomer may account for some of the adverse reactions experienced by consumers of MSG in food.

Ionisation of drugs

When a weakly acidic or basic drug is administered to the body, the drug will ionise to a greater or lesser extent depending on its pK_a and the pH of the body fluid in which it is dissolved. The pH of the body varies widely, but the most important biological solution is the blood, which, as stated above, normally has a pH of 7.4. An equation can be derived that will predict the extent to which the drug ionises, and, as is often the case, the starting point for the derivation is the Henderson–Hasselbalch equation (1.7).

$$\text{pH} = \text{p}K_a + \log \frac{[\text{SALT}]}{[\text{ACID}]}$$

$$\text{pH} = \text{p}K_a + \log \frac{[\text{A}^-]}{[\text{HA}]}$$

Rearranging,

$$\text{p}K_a - \text{pH} = \log \frac{[\text{HA}]}{[\text{A}^-]}$$

and, therefore,

$$[\text{HA}] = [\text{A}^-] \times \text{antilog}(\text{p}K_a - \text{pH})$$

The fraction of the total drug that is ionised is given by

$$\frac{[\text{A}^-]}{[\text{HA}] + [\text{A}^-]}$$

so that the fraction ionised is

$$\frac{[\text{A}^-]}{[\text{A}^-] \times \text{antilog}(\text{p}K_a - \text{pH}) + [\text{A}^-]}$$

which simplifies to

$$\textbf{Fraction ionised} = \frac{\mathbf{1}}{\mathbf{1} + \textbf{antilog}(\mathbf{p}K_a - \mathbf{pH})} \qquad (1.8)$$

Equation (1.8) applies to drugs that are weak acids and allows the fraction of the total dose that is ionised to be calculated for any pH if the pK_a of the drug is known. The equation is sometimes written as the percentage ionised, which is simply given by

$$\% \text{ Ionised} = \frac{100}{1 + \text{antilog}(pK_a - \text{pH})} \quad (1.9)$$

A similar expression can be derived for drugs that are weak bases, to give equations (1.10) and (1.11) below.

$$\text{Fraction ionised for basic drug} = \frac{1}{1 + \text{antilog}(\text{pH} - pK_a)} \quad (1.10)$$

and

$$\% \text{ Ionised for basic drug} = \frac{100}{1 + \text{antilog}(pK_a - \text{pH})} \quad (1.11)$$

pK_a values of drug molecules

Most compounds used in medicine are either weak acids or weak bases (and quite a few are both!). This means that the range of possible pK_a values encountered in drug molecules is huge. It is important to remember that the value of the pK_a for a drug tells you absolutely nothing about whether the compound is an acid or a base. The pK_a value is simply the negative logarithm of the dissociation constant and can, within reason, have any value. This contrasts with the pH notation, where a pH value <7 means that the solution is acidic and a pH value >7 means that it is alkaline.

It would be quite wrong to say that because one particular acid has a pK_a of 3, then all compounds with a pK_a of 3 must be acids. Many weak bases have pK_a values of 2 to 4. Similarly, while a basic drug like cocaine has a pK_a of 8.5, this does not mean that all compounds with a pK_a greater than 7 are bases. Indeed, phenols, which are weak acids, mostly have pK_a value of approximately 10. *Only a thorough understanding of chemical structure and a knowledge of the functional groups that confer acidity or basicity on a molecule will allow the correct prediction of the acidic or basic nature of a molecule*. To illustrate this, Table 1.1 lists some common acidic and basic drugs with their pK_a values.

pH indicators

In Chapter 6, the long-suffering reader will encounter volumetric analyses. This technique involves the accurate addition of volumes of solution in order to determine the purity of drugs and raw materials. The end point of

Table 1.1 pK_a values of some common drugs

Drug	pK_a value
Acidic drugs	
Aspirin	3.5
Paracetamol	9.5
Phenobarbital	7.4 (first ionisation)
Basic drugs	
Cocaine	8.6
Diazepam	3.3
Diphenhydramine	9.0
Amphoteric drugs	
Morphine	8.0 (amine), 9.9 (phenol)
Adrenaline (epinephrine)	8.7 (amine), 10.2, 12.0 (phenols)

many of these titrations can be determined by the colour change of an indicator. The indicators used in pH titrations are themselves weak acids or bases that change colour depending on whether they are ionised or not. The best indicators change colour sharply at a given pH, and tables of indicators and their pH ranges are available. The ionisation of indicators is determined by the Henderson–Hasselbalch equation, where pK_a refers to the negative logarithm of the acid dissociation constant of the indicator, and [SALT] and [ACID] refer to the concentrations of the ionised and unionised forms of the indicator, respectively. If the indicator is a weak base, the Henderson–Hasselbalch equation has to be rewritten as

$$\text{pH} = \text{p}K_a + \log\frac{[\text{BASE}]}{[\text{ACID}]}$$

since the salt term is really the conjugate acid of the weak base. The choice of an indicator for a titration can be made by predicting the pH at the end point of the titration. This is done accurately by working out the proportion of each species at the end of the titration, using the equations above, and determining also the pH due to hydrolysis of any salts present; it may be estimated (and a lot of miserable algebra avoided) as follows.

If the pH of the end point solution is equal to the pK_a of the acid or conjugate acid involved, then there will be equal concentrations of the ionised and unionised forms of the compound present. This is because if pH = pK_a then the log term in the Henderson–Hasselbalch equation is 1 and [unionised] = [ionised]. If the pH of the solution is increased to one unit above the pK_a of the acid (or one unit below the pK_a of the conjugate

acid), then the percentage of the compound ionised increases to about 90%. If the pH increases to two units above the pK_a (or two units below for a base), the percentage ionised increases to 99%, since both pH and pK_a are logarithmic relationships, and so on to 99.9%, 99.99% etc. This approximate 'rule of thumb' is summarised below.

For weak acids:

$pH = pK_a$	**compound is approximately 50% ionised**
$pH = pK_a + 1$	**compound is approximately 90% ionised**
$pH = pK_a + 2$	**compound is approximately 99% ionised**
$pH = pK_a + 3$	**compound is approximately 99.9% ionised**
$pH = pK_a + 4$	**compound is approximately 99.99% ionised**

For weak bases:

$pH = pK_a$	**compound is approximately 50% ionised**
$pH = pK_a - 1$	**compound is approximately 90% ionised**
$pH = pK_a - 2$	**compound is approximately 99% ionised**
$pH = pK_a - 3$	**compound is approximately 99.9% ionised**
$pH = pK_a - 4$	**compound is approximately 99.99% ionised**

This relationship is hugely important and well worth committing to memory. It will reappear many times in this book, in many different guises, and will allow the readers to impress colleagues (particularly medical colleagues) with their uncanny understanding of pH and ionisation of drugs.

In the case of predicting the pH at the end point of titrations, most acid–base reactions are considered over when the ratio of ionised form to unionised form is 1000 to 1, i.e. when

$$pH = pK_a + \log \frac{99.9}{0.1}$$

From the rules above, this point is reached when the pH of the solution is three units above the pK_a of the acid (or three units below the pK_a of the conjugate acid of the base), and this allows an appropriate indicator to be chosen.

For example, if the acid being titrated has a pK_a of 4.7, then the end point pH will be $4.7 + 3 = 7.7$, and an indicator that changes colour between pH 7.0 and 8.0 should be chosen. Similarly, for a base with a pK_a of 8.5, the end point pH will be $8.5 - 3 = 5.5$, and an indicator with a pH range of 5.0 to 6.0 should be used. The pH ranges of many common indicators are shown in Chapter 6 (p. 144).

Tutorial examples

Q *1 Ephedrine is a naturally occurring drug useful in the treatment of asthma. Its structure is shown in Figure 1.5.*
(a) Classify ephedrine as acidic, basic or neutral.
(b) Using your answer to part (a) as a guide suggest a simple way in which the water solubility of the drug could be increased.

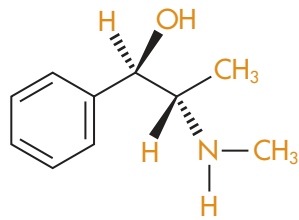

Figure 1.5 The structure of ephedrine, $pK_a = 9.6$.

A 1(a) Ephedrine is an alkaloid produced by Ephedra (the *Ma huang* plant). It was widely used for the relief of bronchospasm associated with an attack of asthma. The drug has been superseded in recent years by safer, more effective bronchodilators such as salbutamol and terbutaline. The diastereoisomer of ephedrine, pseudoephedrine, is widely used in cough mixtures as a decongestant. Ephedrine is a secondary amine and, because the lone pair of electrons on the nitrogen can react with H^+ ions, is basic in solution (Figure 1.6).

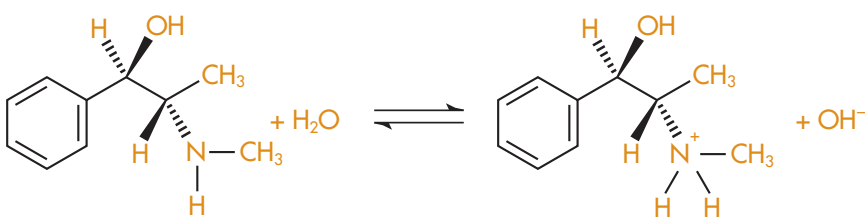

Figure 1.6 Reaction of ephedrine with water.

(b) The water solubility of the drug could be increased by forming a salt with a mineral acid such as hydrochloric acid to give ephedrine hydrochloride (Figure 1.7).

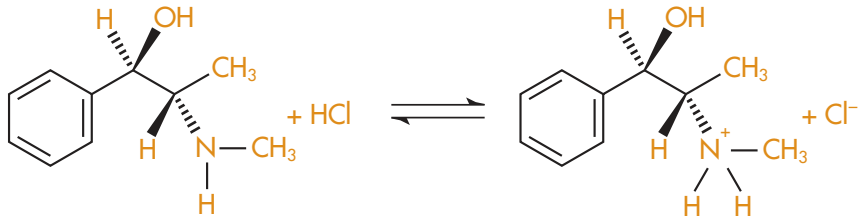

Figure 1.7 Reaction of ephedrine with hydrochloric acid.

This salt will be acidic by partial hydrolysis (salt of a weak base and a strong acid). The pH of the salt solution is given by equation (1.2).

$$\text{pH} = \tfrac{1}{2}\,\text{p}K_a - \tfrac{1}{2}\log c$$

If 1 M HCl is reacted with 1 M ephedrine, the resulting concentration of ephedrine hydrochloride will be 0.5 M; therefore,

$$\begin{aligned}\text{pH} &= \tfrac{1}{2}\,\text{p}K_a - \tfrac{1}{2}\log c\\ &= \tfrac{1}{2}\,(9.6) - \tfrac{1}{2}\log(0.5)\\ &= 4.8 - (-0.15)\\ \text{pH} &= 4.95\end{aligned}$$

which, as predicted, is on the acidic side of neutral. Incidentally, note that the concentration of ephedrine hydrochloride formed above is not 1 M, which might be supposed initially. One mole of ephedrine does give one mole of salt, but the volume of the solution will double when the HCl is added, so the concentration will be halved.

Q *2 Calculate the pH of 0.05 M sodium acetate, given that the pK_a of acetic acid is 4.66.*

A 2 Since sodium acetate is the salt of a strong base and a weak acid, it will be basic by partial hydrolysis. We can therefore use equation (1.3) for weak bases to calculate the answer.

$$\text{pH} = \text{p}K_\text{w} - \tfrac{1}{2}(\text{p}K_\text{b} - \log c)$$

$$= 14 - \tfrac{1}{2}(14 - 4.66) + \tfrac{1}{2}\log(0.05)$$

$$= 14 - 4.67 + (-0.65)$$

$$\text{pH} = 8.68$$

Q *3 Calculate the concentration of acetic acid to be added to a 0.1 M solution of sodium acetate to give a buffer of pH 5 ($p\text{K}_a$ of acetic acid = 4.66).*

A 3 Acetic acid is a weak acid, so its degree of ionisation is very small and the contribution to the total concentration of acetate anions from ionisation of the acid can be ignored. The total salt concentration is therefore 0.1 M from the fully ionised sodium acetate.

Using the Henderson–Hasselbalch equation (1.7),

$$\text{pH} = \text{p}K_\text{a} + \log\frac{[\text{SALT}]}{[\text{ACID}]}$$

$$5.0 = 4.66 + \log\frac{0.1}{[\text{ACID}]}$$

$$0.34 = \log\frac{0.1}{[\text{ACID}]}$$

$$2.188 = \frac{0.1}{[\text{ACID}]}$$

$$[\text{ACID}] = 0.046 \text{ M}$$

4 Weak acids and bases are often formulated as their salts to make them more water soluble. The ionised salts, however, do not cross biological membranes very well. Calculate the percentage of a dose of pentobarbital that will be ionised at plasma pH (7.4). The structure of pentobarbital is shown in Figure 1.8.

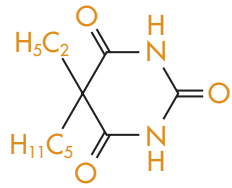

Figure 1.8 The structure of pentobarbital, pK_a = 8.0.

A 4 Pentobarbital is a barbiturate and is a weak acid. Normally, compounds that contain a nitrogen atom are basic (ammonia, amines, some heterocycles, etc.), but these compounds are only basic if the lone pair of electrons on the nitrogen is available for reaction with H^+ ions to form salts. In the case of pentobarbital (and other barbiturates such as phenobarbital, butobarbital, etc.), the lone pair on the ring nitrogens is unavailable for reaction due to resonance with the adjacent carbonyl groups. Instead, the hydrogen on the nitrogen can be lost as a proton, and the resulting negative charge delocalised around the molecule as shown in Figure 1.9.

This *resonance-stabilised anion* allows barbiturates to function as weak acids, and sodium salts may be formed to increase the water solubility of the drug and allow parenteral administration.

To calculate the percentage ionised, use can be made of equations of the type

$$\%\ \text{Ionised for basic drug} = \frac{100}{1 + \text{antilog}(pK_a - \text{pH})}$$

which is easily derived from the Henderson–Hasselbalch equation and will work for weak acids if the pK_a is known. However, in this case an expression can easily be derived from first principles. If we let x = % ionised,

$$\text{pH} = pK_a + \log\frac{[\text{SALT}]}{[\text{ACID}]}$$

$$7.4 = 8.0 + \log\frac{x}{(100 - x)}$$

$$-0.6 = \log\frac{x}{(100 - x)}$$

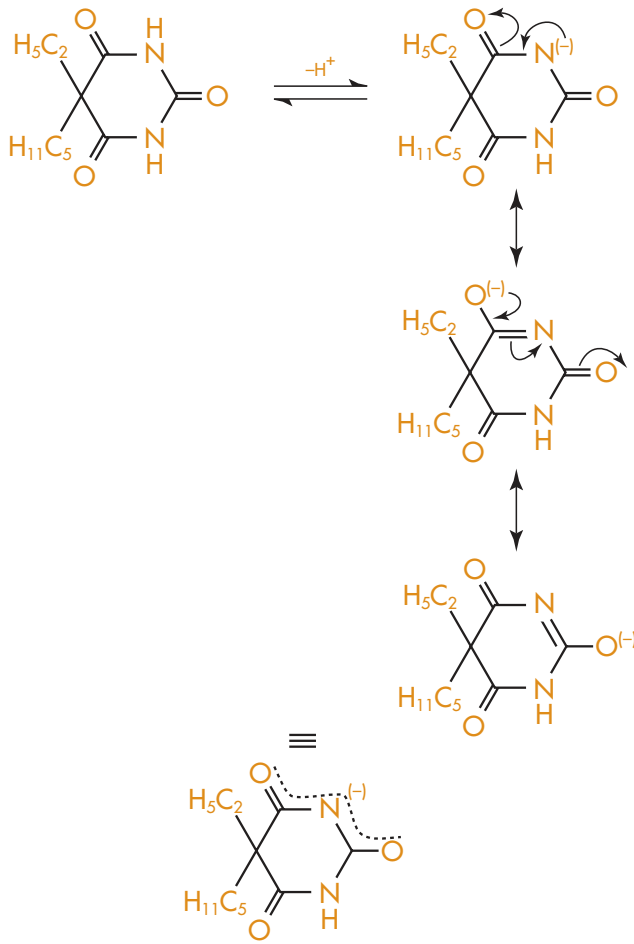

Figure 1.9 Resonance forms of the pentobarbital anion.

$$\frac{x}{(100 - x)} = \text{antilog}(-0.6) = 0.251$$

$$x = 0.251(100 - x)$$

$$x = 25.1 - 0.251x$$

$$x = \frac{25.1}{1.251} = 20.1$$

% Ionised at pH 7.4 = 20.1%

% Unionised at pH 7.4 = 79.9%

Problems

Q1.1 (a) Ethanolamine ($HOCH_2CH_2NH_2$, relative molecular mass = 61.08) has a pK_a of 9.4. Explain what this term means.

(b) Explain why ethanolamine is freely soluble in water, and why the resulting solution is basic.

(c) Calculate the pH of a 1% w/v solution of ethanolamine.

(d) A solution of pH 9.0 is required that will resist changes in pH on the addition of small amounts of strong acid or strong base. Indicate briefly a possible composition of such a solution, and show how pH changes are resisted.

Q1.2 (a) What do you understand by the term pK_a? Explain how this value can be used to indicate the strength of a base.

(b) The base ephedrine has a pK_a value of 9.6. Calculate the theoretical end point pH when a 0.1 M solution of ephedrine is titrated with 0.1 M HCl.

(c) Acetic acid (CH_3COOH) has a pK_a value of 4.76. How might you prepare an acetate buffer with a pH of 5.0, containing 0.1 mol L^{-1} of the acid?

(d) Calculate the buffer capacity of the solution described above.

Q1.3 Describe the ionisation or ionisations that occur when fully protonated lysine (Figure 1.10) is subjected to increasing pH. What is the dominant structure present at the isoelectric point?

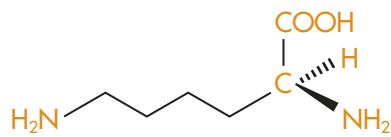

Figure 1.10 The structure of lysine.

(Answers to problems can be found on pp. 251–253.)