1

Introduction: Basic Concepts

Learning objectives

This chapter was written for those unfamiliar with certain aspects of pharmacology and chemistry, including physical chemistry, and for those who feel a little revision would be helpful. By the end of the chapter the reader should be able to:

• use the Henderson–Hasselbalch equation to calculate the ionization of weak acids and bases
• plot concentration–time data to determine first-order and zero-order rate constants
• explain the effect of ionization on the partitioning of weak electrolytes between buffers and octanol.

1.1 Introduction

Pharmacology can be divided into two major areas, pharmacodynamics (PD) – the study of what a drug does to the body – and pharmacokinetics (PK) – the study of what the body does to the drug; hardly rigorous definitions but they suffice. Drug disposition is a collective term used to describe drug absorption, distribution, metabolism and excretion whilst pharmacokinetics is the study of the rates of these processes. By subjecting the observed changes, for example in plasma concentrations as a function of time, to mathematical
equations (models) pharmacokinetic parameters such as elimination half-life ($t_{1/2}$), volume of distribution ($V$) and plasma clearance ($CL$) can be derived. Pharmacokinetic modelling is important for the:

- selection of the right drug for pharmaceutical development
- evaluation of drug delivery systems
- design of drug dosage regimens
- appropriate choice and use of drugs in the clinic.

A detailed knowledge of mathematics is not required to understand pharmacokinetics and it is certainly not necessary to be able to differentiate or integrate complex equations. The few examples in this book are standard differentials or integrals that can be quickly learnt if they are not known already. To understand the equations in this book requires little more than a basic knowledge of algebra, laws of indices and logarithms, a brief explanation of which can be found in Appendix 1. Furthermore, the astute reader will quickly realize that, although seemingly different, many equations take the same form, making learning easier. For example, drug binding to macromolecules, whether they be receptors, plasma proteins, transporters or enzymes, can be described using the same basic equation. Similarly, the equation describing the time course of formation and excretion of a drug metabolite is very much like that describing the plasma concentrations during the absorption and elimination of a drug.

The role of pharmacokinetics is illustrated in Figure 1.1. There is an optimum range of concentrations over which a drug has beneficial effects, but little or no toxicity – this range is the therapeutic range, sometimes referred to as the therapeutic window. There is a threshold concentration below which the drug is ineffective and a higher threshold above which adverse effects become problematic. If a single dose of a drug, for example aspirin taken to relieve a headache, is consumed, the concentration in the plasma will rise until the aspirin becomes effective. After a period of time the processes which remove aspirin from the body will reduce the concentration until the drug is no longer effective (Figure 1.1, curve (a)).

![Figure 1.1](image.png)

**Figure 1.1** Typical concentration–time curves after oral administration of a drug: (a) single dose of drug; (b) a single dose twice the size of the previous one; (c) the same drug given as divided doses. The dose and frequency of dosing for (c) were calculated to ensure the concentrations remained in the therapeutic window.
The short duration of action may be fine for treating a headache but if the aspirin is to treat rheumatoid arthritis a much longer duration of action is required. Simply increasing the size of the dose is not the answer because eventually the plasma concentrations will enter the toxic region (Figure 1.1, curve (b)). However, by giving the aspirin as smaller divided doses at regular intervals the plasma concentrations can be maintained within the therapeutic window (Figure 1.1, curve (c)). The three curves depicted in Figure 1.1 were produced using relatively simple pharmacokinetic equations which will be explained later.

1.2 Drugs and drug nomenclature

A drug is a substance that is taken, or administered, to produce an effect, usually a desirable one. These effects are assessed as physiological, biochemical or behavioural changes. There are two major groups of chemicals studied and used as drugs. First, there is a group of pharmacologically interesting endogenous substances, for example epinephrine, insulin and oxytocin. Second, there are the non-endogenous or ‘foreign’ chemicals (xenobiotics), which are mostly products of the laboratories of the pharmaceutical industry. Early medicines, some of which have been used for at least 5000 years, relied heavily on a variety of mixtures prepared from botanical and inorganic materials. Amongst the plant materials, the alkaloids, morphine from opium, cocaine from coca leaves and atropine from the deadly nightshade (belladonna) are still used today. Insulin, once obtained from pigs (porcine insulin), is more usually genetically engineered using a laboratory strain of Escherichia coli bacteria to produce human insulin. A few inorganic chemicals are used as drugs, including lithium carbonate (Li₂CO₃) and sodium hydrogen carbonate (sodium bicarbonate, NaHCO₃).

1.2.1 Drug nomenclature

Wherever possible specific drug examples are given throughout this book, but unfortunately drug names can lead to confusion. Generally a drug will have at least three names: a full chemical name, a proprietary name, i.e. a trade name registered to a pharmaceutical company, and a non-proprietary name (INN) and/or an approved or adopted name. Names that may be encountered include the British Approved Name (BAN), the European Pharmacopoeia (EuP) name, the United States Adopted Name (USAN), the United States Pharmacopoeia (USP) name and the Japanese Approved Name (JAN). The World Health Organization (WHO) is introducing a system of recommended INNs and it is hoped that this will become the norm for naming drugs, replacing alternative systems (http://www.who.int/medicines/services/inn/inguidance/en/, accessed 17 February 2016). For example, lidocaine is classed as a rINN, USAN and JAN, replacing the name lignocaine that was once a BAN. Generally, the alternatives obviously refer to the same drug, e.g. ciclosporin, cyclosporin and cyclosporine. There are some notable exceptions, for example pethidine is known as meperidine in the US and paracetamol as acetaminophen. Even a simple molecule like paracetamol may have several chemical names but the number of proprietary names or products containing paracetamol is even greater, including Panadol, Calpol, Tylenol and Anadin Extra. It is therefore necessary to use an unequivocal approved name whenever possible, but alternative names and spellings are likely to be encountered, some examples of which are given in Table 1.1. Useful sites for checking, names, synonyms,

### 1.3 Law of mass action

The reversible binding of drugs to macromolecules such as receptors and plasma proteins is described by the law of mass action: ‘The rate at which a chemical reaction proceeds is proportional to the active masses (usually molar concentrations) of the reacting substances’. This concept is easily understood if the assumption is made that for the reaction to occur, collision between the reacting molecules must take place. It follows that the rate of reaction will be proportional to the number of collisions and the number of collisions will be proportional to the molar concentrations of the reacting molecules. If a substance X is transformed into substance Y,

\[ X \rightarrow Y \]

the rate of reaction = \( k[X] \), where \( k \) is the rate constant and \([X]\) represents the molar concentration of X at that time. If two substances A and B are reacting to form two other substances C and D, and if the concentrations of the reactants at any particular moment are \([A]\) and \([B]\) then:

\[ A + B \rightarrow C + D \]

and the rate of reaction = \( k[A][B] \).
1.3.1 Reversible reactions and equilibrium constants

Consider the reaction:

\[ A + B \rightleftharpoons C + D \]

The rate of the forward reaction is:

\[ \text{forward rate} = k_1 [A][B] \quad (1.1) \]

whilst the backward rate is:

\[ \text{backward rate} = k_{-1} [C][D] \quad (1.2) \]

where \( k_1 \) and \( k_{-1} \) are the rate constants of the forward and backward reactions, respectively. When equilibrium is reached the forward and backward rates are equal, so:

\[ k_1 [A][B] = k_{-1} [C][D] \quad (1.3) \]

The equilibrium constant \( K \) is the ratio of the forward and backward rate constants, and rearranging Equation 1.3 gives:

\[ K = \frac{k_1}{k_{-1}} = \frac{[C][D]}{[A][B]} \quad (1.4) \]

The term dissociation constant is used when describing the equilibrium of a substance which dissociates into smaller units, as in the case, for example, of an acid (Section 1.4). The term is also applied to the binding of a drug, D, to a macromolecule such as a receptor, R, or plasma protein (Sections 2.5 and 8.2). The complex DR dissociates:

\[ DR \rightleftharpoons D + R \]

so:

\[ K = \frac{[D][R]}{[DR]} \quad (1.5) \]

An association constant is the inverse of a dissociation constant.

1.3.1.1 Sequential reactions

When a product D arises as a result of several sequential reactions (Figure 1.2), it cannot be formed any faster than the rate of at which its precursor C is formed, which in turn cannot be formed any faster than its precursor B. The rates of each of these steps are determined by the rate constants \( k_1, k_2 \) and \( k_3 \), therefore, the rate at which D is formed will be the rate of the slowest step, i.e. the reaction with the lowest value of rate constant. Say, for example, \( k_2 \) is the lowest rate constant, then the rate of formation of D is determined by \( k_2 \) and the reaction B \( \rightarrow \) C is said to be the rate-limiting or rate-determining step. This concept is fundamental to understanding sustained-release preparations (Chapter 4) and also drug metabolism when it occurs in more than one step (Chapter 6).
1.3.2 Reaction order and molecularity

The order of a reaction is the number, \( n \), of concentration terms affecting the rate of the reaction, whereas molecularity is the number of molecules taking part in the reaction. The order of a reaction is measured experimentally and because it is often close to an integer, 0, 1, or 2, reactions may be referred to as zero-, first- or second-order, respectively. The reaction \( X \rightarrow Y \) is clearly monomolecular, and may be either zero- or first-order depending on whether the rate is proportional to \([X]^0\) or \([X]^1\). The reactions

\[ 2X \rightarrow Y \]

and

\[ A + B \rightarrow C + D \]

are both bimolecular and second-order providing the rate is proportional to \([X]^2\) in the first case and to \([A][B]\) in the second. Note how the total reaction order is the sum of the indices of each reactant: rate \( \propto [A]^1[B]^1 \), so \( n = 2 \). However, if one of the reactants, say \( A \), is present in such a large excess that there is no detectable change in its concentration, then the rate will be dependent only on the concentration of the other reactant, \( B \). Thus, the rate is proportional to \([A]^0[B]^1\). The reaction is first-order (rate \( \propto [B]\)) but it is still bimolecular. Hydrolysis of an ester in dilute aqueous solution is a commonly encountered example of a bimolecular reaction which is first-order with respect to the concentration of ester and zero-order with respect to the concentration of water, giving an overall reaction order of unity.

Enzyme-catalysed reactions have reaction orders between 1 and 0 with respect to the drug concentration. This is because the Michaelis–Menten equation (Section 4.7) limits to zero-order when the substrate is in excess and the enzyme is saturated so that increasing the drug concentration will have no further effect on the reaction rate. When the concentration of enzyme is in vast excess compared to the substrate concentration, the enzyme concentration is not rate determining and the reaction is first order. Thus, the reaction order of an enzyme-catalysed reaction changes as the reaction proceeds and substrate is consumed.
1.3.3 Decay curves and half-lives

As discussed above, the rate of a chemical reaction is determined by the concentrations of the reactants and from the foregoing it is clear that a general equation relating the rate of decline in concentration ($-\frac{dC}{dt}$), rate constant ($\lambda$) and concentration ($C$) can be written:

$$\frac{-dC}{dt} = \lambda C^n$$

Note the use of $\lambda$ to denote the rate constant when it refers to decay; the symbol is used for radioactive decay, when it is known as the decay constant. Use of $\lambda$ to denote elimination rate constants is becoming more prevalent in pharmacokinetic publications.

1.3.3.1 First-order decay

Because first-order kinetics are of prime importance in pharmacokinetics, we shall deal with these first. For a first-order reaction, $n = 1$ and

$$\frac{-dC}{dt} = \lambda C$$

Thus, the rate of the reaction is directly proportional to the concentration of substance present. As the reaction proceeds and the concentration of the substance falls, the rate of the reaction decreases. This is exponential decay, analogous to radioactive decay, where the probability of a disintegration is proportional to the number of unstable nuclei present. The first-order rate constant has units of reciprocal time (e.g. h$^{-1}$). Integrating Equation 1.7 gives:

$$C = C_0 \exp(-\lambda t)$$

which is the equation of a curve that asymptotes to 0 from the initial concentration, $C_0$ (Figure 1.3(a)). Taking natural logarithms of Equation 1.8 gives:

$$\ln C = \ln C_0 - \lambda t$$

which is the equation of a straight line of slope, $-\lambda$ (Figure 1.3(b)). Before the advent of inexpensive calculators and the availability of spreadsheets, common logarithms were often used to plot log $C$ against $t$ when the slope was $-\lambda/2.303$. Another way of presenting the data is to plot $C$ on a logarithmic scale. This approach was often used when computers were not readily available. The half-life can be read easily from such graphs and $\lambda$ can be calculated via Equation 1.10.

The half-life ($t_{1/2}$) is the time for the initial concentration ($C_0$) to fall to $C_0/2$, and substitution in Equation 1.9 gives:

$$t_{1/2} = \frac{\ln 2}{\lambda} = \frac{0.693}{\lambda}$$

because $\ln 2 = 0.693$. This important relationship, where $t_{1/2}$ is constant (independent of the initial concentration) and inversely proportional to $\lambda$, is unique to first-order reactions.
Because $t_{1/2}$ is constant, 50% is eliminated in $1 \times t_{1/2}$, 75% in $2 \times t_{1/2}$ and so on. Thus, when five half-lives have elapsed less than 5% of the substance remains, and after seven half-lives less than 1% remains.

### 1.3.3.2 Zero-order decay

For a zero-order reaction, $n=0$ and:

$$-\frac{dC}{dt} = \lambda C^0 = \lambda \tag{1.11}$$

Because $C^0=1$, it is clear that a zero-order reaction proceeds at a constant rate, and the zero-order rate constant must have units of rate (e.g. g L$^{-1}$ h$^{-1}$). Integrating Equation 1.11:

$$C = C_0 - \lambda t \tag{1.12}$$

gives the equation of a straight line of slope, $-\lambda$, when concentration is plotted against time (Figure 1.4(a)). The ln $C$ plot is a convex curve because initially the proportion of drug eliminated is less when the concentration is higher (Figure 1.4(b)). The half-life can be obtained as before, and substituting $t=t_{1/2}$ and $C=C_0$ gives:

$$t_{1/2} = \frac{C_0}{2\lambda} \tag{1.13}$$

The zero-order half-life is inversely proportional to $\lambda$, as would be expected, but $t_{1/2}$ is also directly proportional to the initial concentration. In other words, the greater the amount of drug present initially, the longer the time taken to reduce the amount present by 50%, as would be expected. The term ‘concentration-dependent half-life’ has been applied to this situation.

Equations such as Equations 1.8 and 1.12 are referred to as linear equations. Note that in this context it is important not to confuse ‘linear’ with ‘straight-line’. While it is true
that the equation of a straight-line is a linear equation, exponential equations are also linear. On the other hand, non-linear equations are those where the variable to be solved cannot be written as a linear combination of independent variables. The Michaelis–Menten equation is such an example.

1.3.3.3 Importance of half-life in pharmacokinetics

Half-life is a very useful parameter in pharmacokinetics. It is much easier to compare the duration of action of drugs in terms of their relative half-lives rather than rate constants, and the rate of attainment of steady-state concentrations during multiple dosing and the fluctuations in peak and trough levels is a function of \( t_{1/2} \) (Figure 4.16). However, it is important to recognize at the outset that the half-life of a drug is, in fact, dependent on two other pharmacokinetic parameters, apparent volume of distribution (\( V \)) and clearance (\( CL \)). The apparent volume of distribution, as its name implies, is a quantitative measure of the extent to which a drug is distributed in the body (Section 2.4.1.1) whilst clearance can be thought of as an indicator of how efficiently the body’s eliminating organs remove the drug, therefore the larger the value of \( CL \), the shorter will be \( t_{1/2} \), and any change in half-life will be as a result of changes in either \( V \) or \( CL \), or both (Section 4.2.1).

1.4 Ionization

The degree of ionization of a molecule can have a major influence on its disposition and pharmacokinetics. The term strength when applied to an acid or base refers to its tendency to ionize. The term should not be confused with concentrated. Strong acids and bases can be considered to be 100% ionized at any practical pH value. Weak electrolytes, such as amines and carboxylic acids, are only partially ionized in aqueous solutions:
The degree of ionization is determined by the $pK_a$ of the ionizing group and the pH of the aqueous environment. The $pK_a$ of the compound, a measure of its inherent acidity or basicity, is numerically equal to the pH at which the compound is 50% ionized.

For an acid, $AH$, dissolved in water:

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

The acid dissociation constant is:

$$K_a = \frac{[H^+][A^-]}{[AH]} \quad (1.14)$$

Clearly the more the equilibrium is to the right, the greater is the hydrogen ion concentration, with a subsequent reduction in the concentration of unionized acid, so the larger will be the value of $K_a$. Note that because $pK_a$ is the negative logarithm of $K_a$ (analogous to pH), strong acids have low values of $pK_a$. Taking logarithms (see Appendix 1 for details) of Equation 1.14 gives:

$$\log K_a = \log[H^+] + \log[A^-] - \log[AH] \quad (1.15)$$

and on rearrangement:

$$-\log[H^+] = -\log K_a + \log \frac{[A^-]}{[AH]} \quad (1.16)$$

Because $-\log[H^+]$ is the pH of the solution:

$$\text{pH} = pK_a + \log \frac{[A^-]}{[AH]} = pK_a + \log \frac{[\text{base}]}{[\text{acid}]} \quad (1.17)$$

where $pK_a = -\log K_a$, by analogy with pH. Note that when $[A^-]=[AH]$ the ratio is 1 and because $\log(1)=0$, the $pK_a=pH$, as stated earlier.

The range of $pK_a$ values extends below 1 and above 14, but for the majority of drugs values are between 2 and 13. Benzylpenicillin ($pK_a=2.3$) is an example of a relatively strong acid and metformin ($pK_a=12.4$) is an example of a relatively strong base (Figure 1.5). It should be noted that it is not possible from a knowledge of the $pK_a$ alone to say whether a substance is an acid or a base. It is necessary to know how the molecule ionizes. Pentobarbital, $pK_a=8.0$, forms sodium salts and so must be an acid, albeit a rather weak one. The electron‐withdrawing oxygen atoms result in the hydrogen atom being acidic. Diazepam, $pK_a=3.3$, must be a base because it can be extracted from organic solvents into hydrochloric acid. Imines are weak bases because of delocalization of the nitrogen lone pair of electrons around the C=N double bond. In oxazepam, the
electron‐withdrawing effect of the oxygen in the hydroxyl group reduces the pKₐ (=1.7) of the imine compared to that in diazepam. Molecules can have more than one ionizable group, for example salicylic acid has a carboxylic acid (pKₐ =3.0) and a weaker acidic phenol group (pKₐ =13.4). The amide in oxazepam is very weakly acidic (pKₐ =11.6), making this compound amphoteric, that is, both acidic and basic. Sulfonamides are usually more acidic than amides and if the primary aromatic amine is not acetylated they are amphoteric, as illustrated by sulfadimidine. Similarly, morphine is amphoteric, having a tertiary amine group (pKₐ =8.0) and an acidic phenol (pKₐ =9.9) (Figure 1.5).

Not all drugs ionize. The volatile and gaseous anaesthetics are usually neutral compounds, for example enflurane (CHClF₂-CF₂-C-O-CF₂-H), which is an ether. Alcohols such as ethanol and chloral hydrate (CCl₃CH(OH)₂) are usually referred to as being neutral as they do not ionize at physiological pH values.

![Chemical structures](image_url)

**Figure 1.5** Examples of ionizable groups in selected drug examples. Note how the pKₐ values range (strong to weak) from 2.3 to 11.6 for the acids and 12.4 to 1.7 for the basic groups. Acidic hydrogen atoms are shown in red and basic nitrogen atoms in blue.
1.4.1 Henderson–Hasselbalch equation

Equation 1.17 is a form of the Henderson–Hasselbalch equation, which is important in determining the degree of ionization of weak electrolytes and calculating the pH of buffer solutions. If the degree of ionization is \( \alpha \), then the degree non-ionized is \((1 - \alpha)\) and, for an acid:

\[
pH = pK_a + \log \frac{\alpha}{1 - \alpha} \quad (1.18)
\]

Taking antilogarithms and rearranging allows the degree of ionization to be calculated:

\[
\alpha = \frac{10^{[pH - pK_a]}}{1 + 10^{[pH - pK_a]}} \quad (1.19)
\]

The equivalent equation for a base is:

\[
\alpha = \frac{10^{[pK_a - pH]}}{1 + 10^{[pK_a - pH]}} \quad (1.20)
\]

Although Equations 1.19 and 1.20 may look complex, they are easy to use. Using the ionization of aspirin as an example, the \( pK_a \) of aspirin is \( \sim 3.4 \), so at the pH of plasma (pH 7.4)

\[
pH - pK_a = 7.4 - 3.4 = 4
\]

\[
\alpha = \frac{10^4}{1 + 10^4} = \frac{10000}{10001} = 0.9999
\]

In other words aspirin is 99.99% ionized at the pH of plasma, or the ratio of ionized to non-ionized is 10,000:1. In gastric contents, pH 1.4, aspirin will be largely non-ionized; 1.4 – 3.4 = –2, so the ratio of ionized to non-ionized is \(1:10^{-2}\), that is, there are 100 non-ionized molecules for every ionized one.

1.5 Partition coefficients

The ability of a drug to dissolve in, and so cross, lipid cell membranes can be a major factor in its disposition. This ability can be assessed from its partition coefficient. When an aqueous solution of a substance is shaken with an immiscible solvent (e.g. diethyl ether) the substance is extracted into the solvent until equilibrium between the concentration in the organic phase and the aqueous phase is established. For dilute solutions the ratio of concentrations is known as the distribution, or partition coefficient, \( P \):

\[
P = \frac{\text{concentration in organic phase}}{\text{concentration in aqueous phase}} \quad (1.21)
\]

Organic molecules with large numbers of paraffin chains, aromatic rings and halogens tend to have large values of \( P \), whilst the introduction of polar groups such as hydroxyl or carbonyl groups generally reduces the partition coefficient. Drugs with high partition
coefficients are lipophilic or hydrophobic, whereas those that are very water soluble and are poorly extracted by organic solvents are hydrophilic. Lipophilicity can have a major influence on how a drug is distributed in the body, its tendency to bind to macromolecules such as proteins and, as a consequence, drug activity. A relationship between partition coefficient and pharmacological activity was demonstrated as early as 1901, but it was in the 1960s that Corwin Hansch used regression analysis to correlate biological activity with partition coefficient. He chose n-octanol as the organic phase and this has become the standard for such studies (Figure 1.6). Because \( P \) can vary between \(<1\) (poorly extracted by the organic phase) to several hundred thousand, values are usually converted to \( \log P \), to encompass the large range (Appendix 1).

1.5.1 Effect of ionization on partitioning

Generally, ionized molecules cannot be extracted into organic solvents, or at least not appreciably. Thus, for weak electrolytes the amount extracted will be dependent on the degree of ionization, which of course is a function of the pH of the aqueous solution and the \( pK_a \) of the ionizing group, as discussed above (Section 1.4), and the partition coefficient. If the total concentration (ionized + non-ionized) of solute in the aqueous phase is measured and used to calculate an apparent partition coefficient \( D \), then the partition coefficient \( P \), can be calculated. For an acid:

\[
P = D \left[ 1 + 10^{(pH - pK_a)} \right] \tag{1.22}
\]

**Figure 1.6** (a) Partitioning of chloral hydrate is unaffected by buffer pH. (b) Partitioning of non-ionized amfetamine remains constant, 63:1. However, the ratio of ionized to non-ionized is affected by buffer pH and as a consequence affects the apparent partition coefficient (APC) and the proportion extracted (inset). Note how when \( pH = pK_a, x = 1 \) and there are equal concentrations of ionized and non-ionized amfetamine in the aqueous phase.
and for a base:

\[ P = D \left[ 1 + 10^{(pK_a - \text{pH})} \right] \]  

(1.23)

When \( \text{pH} = pK_a \), then, because \( 10^0 = 1 \), \( P = 2D \). When the \( \text{pH} \) is very much less than the \( pK_a \), in the case of acids, or very much larger than the \( pK_a \), in the case of bases, there will be no appreciable ionization and then \( D \) will be a good estimate of \( P \) (Figure 1.6(b)).

Unless stated otherwise, \( \log P \) is taken to represent the logarithm of the true partition coefficient, that is, when there is no ionization of the drug. However, for some weak electrolytes, biological activity may correlate better with the partition coefficient between octanol and \( \text{pH} 7.4 \) buffer solution. These values are referred to as \( \log D \) or \( \log D_{7.4} \).

Differences in the \( \text{pH} \) of different physiological environments, for example plasma and gastric contents, can have a major influence on the way drugs are absorbed and distributed (Chapter 2).

Summary

This chapter has introduced rates, rate constants and half-lives, all crucially important to understanding the pharmacokinetics described in Chapters 4 and 5, and elsewhere in this book. Rate-determining reactions will be encountered when considering sustained-release formulations (Chapter 4) and the kinetics of metabolism (Chapter 6). The influence of the degree of ionization on partitioning of weak electrolytes will be helpful in understanding Chapters 2 and 3.

1.6 Further reading