

7 Ionic Equilibria

Chapter Objectives

At the conclusion of this chapter the student should be able to:

1. Describe the Brønsted–Lowry and Lewis electronic theories.
2. Identify and define the four classifications of solvents.
3. Understand the concepts of acid–base equilibria and the ionization of weak acids and weak bases.
4. Calculate dissociation constants K_a and K_b and understand the relationship between K_a and K_b .
5. Understand the concepts of pH, pK, and pOH and the relationship between hydrogen ion concentration and pH.
6. Calculate pH.
7. Define strong acid and strong base.
8. Define and calculate acidity constants.

Introduction

Arrhenius defined an acid as a substance that liberates hydrogen ions and a base as a substance that supplies hydroxyl ions on dissociation. Because of a need for a broader concept, Brønsted in Copenhagen and Lowry in London independently proposed parallel theories in 1923.¹ The *Brønsted–Lowry theory*, as it has come to be known, is more useful than the Arrhenius theory for the representation of ionization in both aqueous and nonaqueous systems.

Brønsted–Lowry Theory

According to the Brønsted–Lowry theory, an acid is a substance, charged or uncharged, that is capable of donating a proton, and a base is a substance, charged or uncharged, that is capable of accepting a proton from an acid. The relative strengths of acids and bases are measured by the tendencies of these substances to give up and take on protons. Hydrochloric acid is a strong acid in water because it gives up its proton readily, whereas acetic acid is a weak acid because it gives up its proton only to a small extent. The strength of an acid or a base varies with the solvent. Hydrochloric acid is a weak acid in glacial acetic acid and acetic acid is a strong acid in liquid ammonia. Consequently, the strength of an acid depends not only on its ability to give up a proton but also on the ability of the solvent to accept the proton from the acid. This is called the *basic strength* of the solvent.

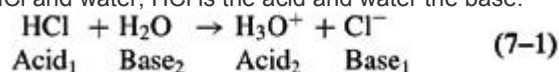
Key Concept

Classification of Solvents

Solvents can be classified as protophilic, protogenic, amphiprotic, and aprotic. A *protophilic* or basic solvent is one that is capable of accepting protons from the solute. Such solvents as acetone, ether, and liquid ammonia fall into this group. A *protophonic* solvent is a proton-donating compound and is represented by acids such as formic acid, acetic acid, sulfuric acid, liquid HCl, and liquid HF. *Amphiprotic* solvents act as both proton acceptors and proton donors, and this class includes water and the alcohols. *Aprotic* solvents, such as the hydrocarbons, neither accept nor donate protons, and, being neutral in this sense, they are useful for studying the reactions of acids and bases free of solvent effects.

In the Brønsted–Lowry classification, acids and bases may be anions such as HSO_4^- and CH_3COO^- , cations such as NH_4^+ and H_3O^+ , or neutral molecules such as HCl and NH_3 . Water can act as either an acid or a base and thus is amphiprotic. Acid–base reactions occur when an acid reacts with a base to form a new acid and a new base. Because the reactions involve a transfer of a proton, they are known as *protolytic reactions* or *protolysis*.

In the reaction between HCl and water, HCl is the acid and water the base:



Acid₁ and Base₁ stand for an *acid–base pair* or *conjugate pair*, as do Acid₂ and Base₂. Because the bare proton, H⁺, is practically nonexistent in aqueous solution, what is normally referred to as the hydrogen ion consists of the hydrated proton, H₃O⁺, known as the *hydronium ion*. Higher solvated forms can also exist in solution.* In an ethanolic solution, the “hydrogen ion” is the proton attached to a molecule of solvent, represented as C₂H₅OH₂⁺. In equation (7-1), hydrogen chloride, the acid, has donated a proton to water, the base, to form the corresponding acid, H₃O⁺, and the base, Cl⁻.

The reaction of HCl with water is one of ionization. Neutralization and hydrolysis are also considered as acid–base reactions or proteolysis following the broad definitions of the Brønsted–Lowry concept. Several examples illustrate these types of reactions, as shown in Table 7-1. The displacement reaction, a special type of neutralization, involves the displacement of a weaker acid, such as acetic acid, from its salt as in the reaction shown later.

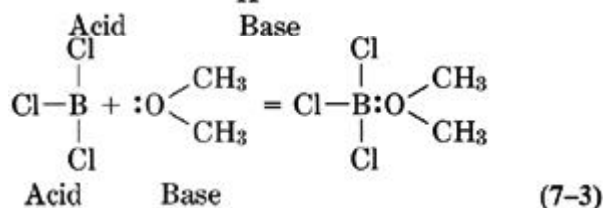
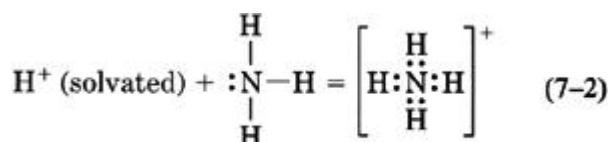
P.147

	Acid₁		Base₂		Acid₂		Base₁
Neutralization	NH ₄ ⁺	+	OH ⁻	=	H ₂ O	+	NH ₃
Neutralization	H ₃ O ⁺	+	OH ⁻	=	H ₂ O	+	H ₂ O
Neutralization	HCl	+	NH ₃	=	NH ₄ ⁺	+	Cl ⁻
Hydrolysis	H ₂ O	+	CH ₃ COO ⁻	=	CH ₃ COOH	+	OH ⁻
Hydrolysis	NH ₄ ⁺	+	H ₂ O	=	H ₃ O ⁺	+	NH ₃
Displacement	HCl	+	CH ₃ COO ⁻	=	CH ₃ COOH	+	Cl ⁻

Lewis Electronic Theory

Other theories have been suggested for describing acid–base reactions, the most familiar of which is the *electronic theory* of Lewis.³

According to the Lewis theory, an acid is a molecule or an ion that accepts an electron pair to form a covalent bond. A base is a substance that provides the pair of unshared electrons by which the base coordinates with an acid. Certain compounds, such as boron trifluoride and aluminum chloride, although not containing hydrogen and consequently not serving as proton donors, are nevertheless acids in this scheme. Many substances that do not contain hydroxyl ions, including amines, ethers, and carboxylic acid anhydrides, are classified as bases according to the Lewis definition. Two Lewis acid–base reactions are



The Lewis system is probably too broad for convenient application to ordinary acid–base reactions, and those processes that are most conveniently expressed in terms of this electronic classification should be referred to simply as a form of electron sharing rather than as acid–base reactions.⁴ The Lewis theory is finding increasing use for describing the mechanism of many organic and inorganic reactions. It will be mentioned again in the chapters on solubility and complexation. The Brønsted–Lowry nomenclature is particularly useful for describing ionic equilibria and is used extensively in this chapter.

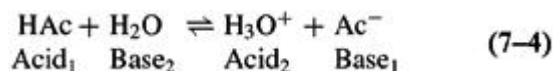
Key Concept

Equilibrium

Equilibrium can be defined as a balance between two opposing forces or actions. This statement does not imply cessation of the opposing reactions, suggesting rather a dynamic equality between the velocities of the two. Chemical equilibrium maintains the concentrations of the reactants and products constant. Most chemical reactions proceed in both a forward and a reverse direction if the products of the reaction are not removed as they form. Some reactions, however, proceed nearly to completion and, for practical purposes, may be regarded as irreversible. The topic of chemical equilibria is concerned with truly reversible systems and includes reactions such as the ionization of weak electrolytes.

Acid–Base Equilibria

The ionization or proteolysis of a weak electrolyte, acetic acid, in water can be written in the Brønsted–Lowry manner as



The arrows pointing in the forward and reverse directions indicate that the reaction is proceeding to the right and left simultaneously. According to the law of mass action, the velocity or rate of the forward reaction, R_f , is proportional to the concentration of the reactants:

$$R_f = k_1 \times [\text{HAc}]^1 \times [\text{H}_2\text{O}]^1 \quad (7-5)$$

The speed of the reaction is usually expressed in terms of the decrease in the concentration of either the reactants per unit time. The terms rate, speed, and velocity have the same meaning here. The reverse reaction

$$R_r = k_2 \times [\text{H}_3\text{O}^+]^1 \times [\text{Ac}^-]^1 \quad (7-6)$$

expresses the rate, R_r , of re-formation of un-ionized acetic acid. Because only 1 mole of each constituent appears in the

P.148

reaction, each term is raised to the first power, and the exponents need not appear in subsequent expressions for the dissociation of acetic acid and similar acids and bases. The symbols k_1 and k_2 are proportionality constants commonly known as *specific reaction rates* for the forward and the reverse reactions, respectively, and the brackets indicate concentrations. A better representation of the facts would be had by replacing concentrations with activities, but for the present discussion, the approximate equations are adequate.

Ionization of Weak Acids

According to the concept of equilibrium, the rate of the forward reaction decreases with time as acetic acid is depleted, whereas the rate of the reverse reaction begins at zero and increases as larger quantities of hydrogen ions and acetate ions are formed. Finally, a balance is attained when the two rates are equal, that is, when

$$R_f = R_r \quad (7-7)$$

The *concentrations* of products and reactants are not necessarily equal at equilibrium; the *speeds* of the forward and reverse reactions are what are the same. Because equation (7-7) applies at equilibrium, equations (7-5) and (7-6) may be set equal:

$$k_1 \times [\text{HAc}] \times [\text{H}_2\text{O}] = k_2 \times [\text{H}_3\text{O}^+] \times [\text{Ac}^-] \quad (7-8)$$

and solving for the ratio k_1/k_2 , one obtains

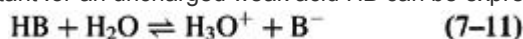
$$k = \frac{k_1}{k_2} = \frac{[\text{H}_3\text{O}^+][\text{Ac}^-]}{[\text{HAc}][\text{H}_2\text{O}]} \quad (7-9)$$

In dilute solutions of acetic acid, water is in sufficient excess to be regarded as constant at about 55.3 moles/liter (1 liter H_2O at 25°C weighs 997.07 g, and $997.07/18.02 = 55.3$). It is thus combined with k_1/k_2 to yield a new constant K_a , the *ionization constant* or the *dissociation constant* of acetic acid.

$$K_a = 55.3k = \frac{[\text{H}_3\text{O}^+][\text{Ac}^-]}{[\text{HAc}]} \quad (7-10)$$

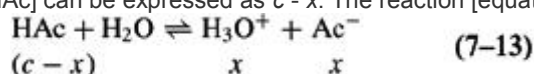
Equation (7-10) is the equilibrium expression for the dissociation of acetic acid, and the dissociation constant K_a is an equilibrium constant in which the essentially constant concentration of the solvent is incorporated. In the discussion of equilibria involving charged as well as uncharged acids, according to the Brønsted–Lowry nomenclature, the term *ionization constant*, K_a , is not satisfactory and is replaced by the name *acidity constant*. Similarly, for charged and uncharged bases, the term *basicity constant* is now often used for K_b , to be discussed in the next section.

In general, the acidity constant for an uncharged weak acid HB can be expressed by



$$K_a = \frac{[\text{H}_3\text{O}^+][\text{B}^-]}{[\text{HB}]} \quad (7-12)$$

Equation (7-10) can be presented in a more general form, using the symbol c to represent the initial molar concentration of acetic acid and x to represent the concentration $[\text{H}_3\text{O}^+]$. The latter quantity is also equal to $[\text{Ac}^-]$ because both ions are formed in equimolar concentration. The concentration of acetic acid remaining at equilibrium $[\text{HAc}]$ can be expressed as $c - x$. The reaction [equation (7-4)] is



and the equilibrium expression (7-10) becomes

$$K_a = \frac{x^2}{c - x} \quad (7-14)$$

where c is large in comparison with x . The term $c - x$ can be replaced by c without appreciable error, giving the equation

$$K_a \cong \frac{x^2}{c} \quad (7-15)$$

which can be rearranged as follows for the calculation of the hydrogen ion concentration of weak acids:

$$\begin{aligned} x^2 &= K_a c \\ x &= [\text{H}_3\text{O}^+] = \sqrt{K_a c} \end{aligned} \quad (7-16)$$

Example 7-1

In a liter of a 0.1 M solution, acetic acid was found by conductivity analysis to dissociate into 1.32×10^{-3} g ions (“moles”) each of hydrogen and acetate ion at 25°C . What is the acidity or dissociation constant K_a for acetic acid?

According to equation (7-4), at equilibrium, 1 mole of acetic acid has dissociated into 1 mole each of hydrogen ion and acetate ion. The concentration of ions is expressed as moles/liter and less frequently as molality. A solution containing 1.0078 g of hydrogen ions in 1 liter represents 1 g ion or 1 mole of hydrogen ions. The molar concentration of each of these ions

is expressed as x . If the original amount of acetic acid was 0.1 mole/liter, then at equilibrium the undissociated acid would equal $0.1 - x$ because x is the amount of acid that has dissociated. The calculation according to equation (7-12) is

$$K_a = \frac{(1.32 \times 10^{-3})^2}{0.1 - (1.32 \times 10^{-3})}$$

It is of little significance to retain the small number, 1.32×10^{-3} , in the denominator, and the calculations give

$$K_a = \frac{(1.32 \times 10^{-3})^2}{0.1}$$

$$K_a = \frac{1.74 \times 10^{-6}}{1 \times 10^{-1}} = 1.74 \times 10^{-5}$$

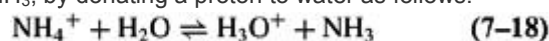
The value of K_a in Example 7-1 means that, at equilibrium, the ratio of the product of the ionic concentrations to that of the undissociated acid is 1.74×10^{-5} ; that is, the dissociation of acetic acid into its ions is small, and acetic acid may be considered as a weak electrolyte.

P.149

When a salt formed from a strong acid and a weak base, such as ammonium chloride, is dissolved in water, it dissociates completely as follows:

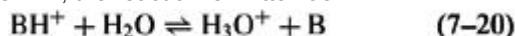


The Cl^- is the conjugate base of a strong acid, HCl, which is 100% ionized in water. Thus, the Cl^- cannot react any further. In the Brønsted–Lowry system, NH_4^+ is considered to be a cationic acid, which can form its conjugate base, NH_3 , by donating a proton to water as follows:



$$K_a = \frac{[\text{H}_3\text{O}^+][\text{NH}_3]}{[\text{NH}_4^+]} \quad (7-19)$$

In general, for charged acids BH^+ , the reaction is written as

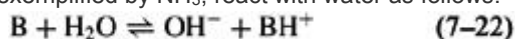


and the acidity constant is

$$K_a = \frac{[\text{H}_3\text{O}^+][\text{B}]}{[\text{BH}^+]} \quad (7-21)$$

Ionization of Weak Bases

Nonionized weak bases B, exemplified by NH_3 , react with water as follows:



$$K_b = \frac{[\text{OH}^-][\text{BH}^+]}{[\text{B}]} \quad (7-23)$$

which, by a procedure like that used to obtain equation (7-16), leads to

$$[\text{OH}^-] = \sqrt{K_b c} \quad (7-24)$$

Example 7-2

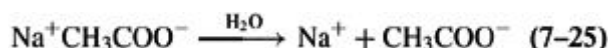
The basicity or ionization constant K_b for morphine base is 7.4×10^{-7} at 25°C . What is the hydroxyl ion concentration of a 0.0005 M aqueous solution of morphine? We have

$$[\text{OH}^-] = \sqrt{7.4 \times 10^{-7} \times 5.0 \times 10^{-4}}$$

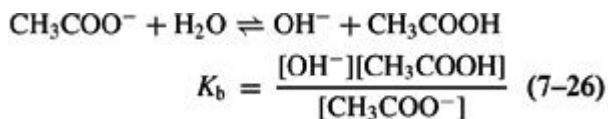
$$[\text{OH}^-] = \sqrt{37.0 \times 10^{-11}} = \sqrt{3.7 \times 10^{-10}}$$

$$x = [\text{OH}^-] = 1.92 \times 10^{-5} \text{ mole/liter}$$

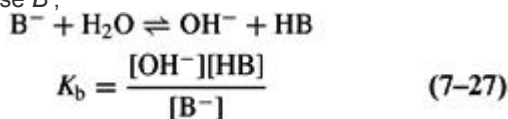
Salts of strong bases and weak acids, such as sodium acetate, dissociate completely in aqueous solution to given ions:



The sodium ion cannot react with water, because it would form NaOH, which is a strong electrolyte and would dissociate completely into its ions. The acetate anion is a Brønsted–Lowry weak base, and



In general, for an anionic base B^- ,



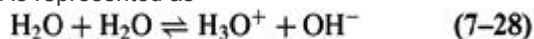
The Ionization of Water

The concentration of hydrogen or hydroxyl ions in solutions of acids or bases may be expressed as gram ions/liter or as moles/liter. A solution containing 17.008 g of hydroxyl ions or 1.008 g of hydrogen ions per liter is said to contain 1 g ion or 1 mole of hydroxyl or hydrogen ions per liter. Owing to the ionization of water, it is possible to establish a quantitative relationship between the hydrogen and hydroxyl ion concentrations of any aqueous solution.

The concentration of either the hydrogen or the hydroxyl ion in acidic, neutral, or basic solutions is usually expressed in terms of the hydrogen ion concentration or, more conveniently, in pH units.

In a manner corresponding to the dissociation of weak acids and bases, water ionizes slightly to yield hydrogen and hydroxyl ions. As previously observed, a weak electrolyte requires the presence of water or some other polar solvent for ionization. Accordingly, one molecule of water can be thought of as a weak electrolytic solute that reacts with another molecule of water as the solvent.

This *autoprotolytic* reaction is represented as



The law of mass action is then applied to give the equilibrium expression

$$\frac{[\text{H}_3\text{O}^+][\text{OH}^-]}{[\text{H}_2\text{O}]^2} = k \quad (7-29)$$

The term for molecular water in the denominator is squared because the reactant is raised to a power equal to the number of molecules appearing in the equation, as required by the law of mass action.

Because molecular water exists in great excess relative to the concentrations of hydrogen and hydroxyl ions, $[\text{H}_2\text{O}]^2$ is considered as a constant and is combined with k to give a new constant, K_w , known as the *dissociation constant*, the *autoprotolysis constant*, or the *ion product* of water:

$$K_w = k \times [\text{H}_2\text{O}]^2 \quad (7-30)$$

The value of the ion product is approximately 1×10^{-14} at 25°C; it depends strongly on temperature, as shown in Table 7-2. In any calculations involving the ion product, one must be certain to use the proper value of K_w for the temperature at which the data are obtained.

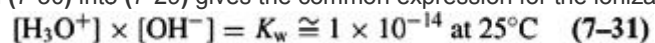
P.150

Table 7-2 Ion Product of Water at Various Temperatures*
--

Temperature (°C)	$K_w \times 10^{14}$	pK_w
0	0.1139	14.944
10	0.2920	14.535
20	0.6809	14.167
24	1.000	14.000
25	1.008	13.997
30	1.469	13.833
37	2.57	13.59
40	2.919	13.535
50	5.474	13.262
60	9.614	13.017
70	15.1	12.82
80	23.4	12.63
90	35.5	12.45
100	51.3	12.29
300	400	11.40

*From H. S. Harned and R. A. Robinson, Trans. Faraday Soc. **36**, 973, 1940.

Substituting equation (7-30) into (7-29) gives the common expression for the ionization of water:



In pure water, the hydrogen and hydroxyl ion concentrations are equal, and each has the value of approximately 1×10^{-7} mole/liter at 25°C.*

$$\begin{aligned} [\text{H}_3\text{O}^+] &= [\text{OH}^-] \cong \sqrt{1 \times 10^{-14}} \\ &\cong 1 \times 10^{-7} \end{aligned} \quad (7-32)$$

When an acid is added to pure water, some hydroxyl ions, provided by the ionization of water, must always remain. The increase in hydrogen ions is offset by a decrease in the hydroxyl ions so that K_w remains constant at about 1×10^{-14} at 25°C.

Example 7-3

Calculate [OH⁻]

A quantity of HCl (1.5×10^{-3} M) is added to water at 25°C to increase the hydrogen ion concentration from 1×10^{-7} to 1.5×10^{-3} mole/liter. What is the new hydroxyl ion concentration?

From equation (7-31),

$$\begin{aligned} [\text{OH}^-] &= \frac{1 \times 10^{-14}}{1.5 \times 10^{-3}} \\ &= 6.7 \times 10^{-12} \text{ mole/liter} \end{aligned}$$

Relationship Between K_a and K_b

A simple relationship exists between the dissociation constant of a weak acid HB and that of its conjugate base B⁻, or between BH⁺ and B, when the solvent is amphiprotic. This can be obtained by multiplying equation (7-12) by equation (7-27):

$$\begin{aligned} K_a K_b &= \frac{[\text{H}_3\text{O}^+][\text{B}^-]}{[\text{HB}]} \cdot \frac{[\text{OH}^-][\text{HB}]}{[\text{B}^-]} \\ &= [\text{H}_3\text{O}^+][\text{OH}^-] = K_w \end{aligned} \quad (7-33)$$

and

$$K_b = \frac{K_w}{K_a} \quad (7-34)$$

or

$$K_a = \frac{K_w}{K_b} \quad (7-35)$$

Example 7-4

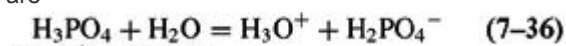
Calculate K_a

Ammonia has a K_b of 1.74×10^{-5} at 25°. Calculate K_a for its conjugate acid, NH₄⁺. We have

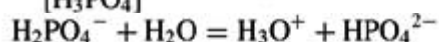
$$\begin{aligned} K_a &= \frac{K_w}{K_b} = \frac{1.00 \times 10^{-14}}{1.74 \times 10^{-5}} \\ &= 5.75 \times 10^{-10} \end{aligned}$$

Ionization of Polyprotic Electrolytes

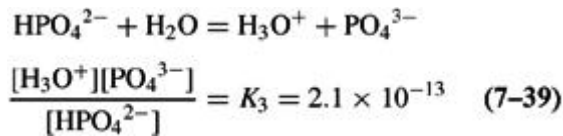
Acids that donate a single proton and bases that accept a single proton are called *monoprotic electrolytes*. A polyprotic (polybasic) acid is one that is capable of donating two or more protons, and a polyprotic base is capable of accepting two or more protons. A diprotic (dibasic) acid, such as carbonic acid, ionizes in two stages, and a triprotic (tribasic) acid, such as phosphoric acid, ionizes in three stages. The equilibria involved in the protolysis or ionization of phosphoric acid, together with the equilibrium expressions, are



$$\frac{[\text{H}_3\text{O}^+][\text{H}_2\text{PO}_4^-]}{[\text{H}_3\text{PO}_4]} = K_1 = 7.5 \times 10^{-3} \quad (7-37)$$



$$\frac{[\text{H}_3\text{O}^+][\text{HPO}_4^{2-}]}{[\text{H}_2\text{PO}_4^-]} = K_2 = 6.2 \times 10^{-8} \quad (7-38)$$

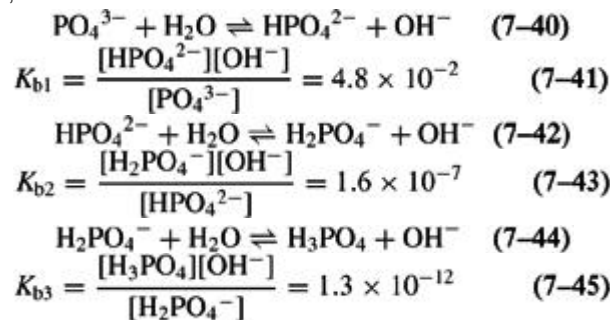


In any polyprotic electrolyte, the primary protolysis is greatest, and succeeding stages become less complete at any given acid concentration.

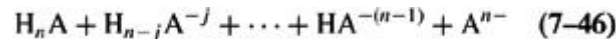
The negative charges on the ion HPO_4^{2-} make it difficult for water to remove the proton from the phosphate ion, as reflected in the small value of K_3 . Thus, phosphoric acid is weak in the third stage of ionization, and a solution of this acid contains practically no PO_4^{3-} ions.

P.151

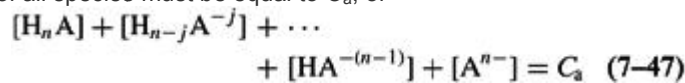
Each of the species formed by the ionization of a polyprotic acid can also act as a base. Thus, for the phosphoric acid system,



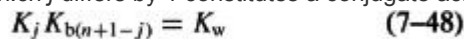
In general, for a polyprotic acid system for which the parent acid is H_nA , there are $n + 1$ possible species in solution:



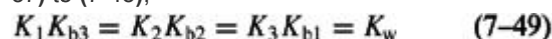
where j represents the number of protons dissociated from the parent acid and goes from 0 to n . The total concentration of all species must be equal to C_a , or



Each of the species pairs in which j differs by 1 constitutes a conjugate acid–base pair, and in general



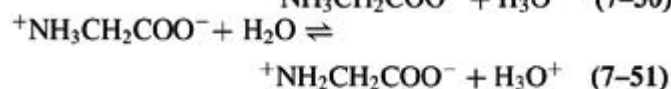
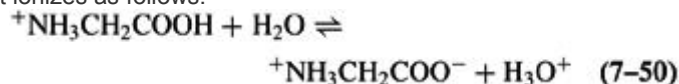
where K_j represents the various acidity constants for the system. Thus, for the phosphoric acid system described by equations (7-37) to (7-45),



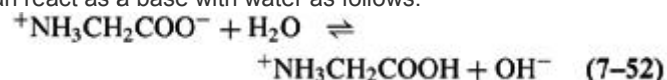
Ampholytes

In the preceding section, equations (7-37), (7-38), (7-41), and (7-43) demonstrated that in the phosphoric acid system, the species H_2PO_4^- and HPO_4^{2-} can function either as an acid or a base. A species that can function either as an acid or as a base is called an *ampholyte* and is said to be *amphoteric* in nature. In general, for a polyprotic acid system, all the species, with the exception of H_nA and A^{n-} , are ampholytic.

Amino acids and proteins are ampholytes of particular interest in pharmacy. If glycine hydrochloride is dissolved in water, it ionizes as follows:



The species $^+\text{NH}_3\text{CH}_2\text{COO}^-$ is ampholytic in that, in addition to reacting as an acid as shown in equation (7-51), it can react as a base with water as follows:



The amphoteric species $^+\text{NH}_3\text{CH}_2\text{COO}^-$ is called a *zwitterion* and differs from the amphoteric species formed from phosphoric acid in that it carries both a positive and a negative charge, and the whole molecule is electrically neutral. The pH at which the zwitterion concentration is a maximum is known as the *isoelectric point*. At the isoelectric point the net movement of the solute molecules in an electric field is negligible.

Sørensen's pH

The hydrogen ion concentration of a solution varies from approximately 1 in a 1 M solution of a strong acid to about 1×10^{-14} in a 1 M solution of a strong base, and the calculations often become unwieldy. To alleviate this difficulty, Sørensen⁵ suggested a simplified method of expressing hydrogen ion concentration. He established the term *pH*, which was originally written as p_{H^+} , to represent the hydrogen ion potential, and he defined it as the common logarithm of the reciprocal of the hydrogen ion concentration:

$$\text{pH} = \log \frac{1}{[\text{H}_3\text{O}^+]} \quad (7-53)$$

According to the rules of logarithms, this equation can be written as

$$\text{pH} = \log 1 - \log[\text{H}_3\text{O}^+] \quad (7-54)$$

and because the logarithm of 1 is zero,

$$\text{pH} = -\log[\text{H}_3\text{O}^+] \quad (7-55)$$

Equations (7-53) and (7-55) are identical; they are acceptable for approximate calculations involving pH. The pH of a solution can be considered in terms of a numeric scale having values from 0 to 14, which expresses in a quantitative way the degree of acidity (7 to 0) and alkalinity (7-14). The value 7 at which the hydrogen and hydroxyl ion concentrations are about equal at room temperature is referred to as the *neutral point*, or neutrality. The neutral pH at 0°C is 7.47, and at 100°C it is 6.15 (Table 7-2). The scale relating pH to the hydrogen and hydroxyl ion concentrations of a solution is given in Table 7-3.

Conversion of Hydrogen Ion Concentration to pH

The student should practice converting from hydrogen ion concentration to pH and vice versa until he or she is proficient in these logarithmic operations. The following examples are given to afford a review of the mathematical operations

P.152

involving logarithms. Equation (7-55) is more convenient for these calculations than equation (7-53).

Table 7-3 The pH Scale and Corresponding Hydrogen and Hydroxyl Ion Concentrations

pH	$[\text{H}_3\text{O}^+]$ (moles/liter)	$[\text{OH}^-]$ (moles/liter)	
0	$10^0 = 1$	10^{-14}	
1	10^{-1}	10^{-13}	
2	10^{-2}	10^{-12}	
3	10^{-3}	10^{-11}	Acidic
4	10^{-4}	10^{-10}	

5	10^{-5}	10^{-9}	
6	10^{-6}	10^{-8}	
7	10^{-7}	10^{-7}	Neutral
8	10^{-8}	10^{-6}	
9	10^{-9}	10^{-5}	
10	10^{-10}	10^{-4}	
11	10^{-11}	10^{-3}	Basic
12	10^{-12}	10^{-2}	
13	10^{-13}	10^{-1}	
14	10^{-14}	$10^0 = 1$	

Example 7-5 pH Calculation

The hydronium ion concentration of a 0.05 M solution of HCl is 0.05 M. What is the pH of this solution? We write

$$\begin{aligned} \text{pH} &= -\log(5.0 \times 10^{-2}) = -\log 10^{-2} - \log 5.0 \\ &= 2 - 0.70 = 1.30 \end{aligned}$$

A handheld calculator permits one to obtain pH simply by use of the log function followed by a change of sign.

A better definition of pH involves the activity rather than the concentration of the ions:

$$\text{pH} = -\log a_{\text{H}^+} \quad (7-56)$$

and because the activity of an ion is equal to the activity coefficient multiplied by the molal or molar concentration [equation (7-42)],

$$\begin{aligned} \text{Hydronium ion concentration} \times \text{Activity coefficient} \\ = \text{Hydronium ion activity} \end{aligned}$$

the pH may be computed more accurately from the formula

$$\text{pH} = -\log(\gamma_{\pm} \times c) \quad (7-57)$$

Example 7-6 Solution pH

The mean molar ionic activity coefficient of a 0.05 M solution of HCl is 0.83 at 25°C. What is the pH of the solution? We write

$$\text{pH} = -\log(0.83 \times 0.05) = 1.38$$

If sufficient NaCl is added to the HCl solution to produce a total ionic strength of 0.5 for this mixture of uni-univalent electrolytes, the activity coefficient is 0.77. What is the pH of this solution? We write

$$\text{pH} = -\log(0.77 \times 0.05) = 1.41$$

Hence, the addition of a neutral salt affects the hydrogen ion activity of a solution, and activity coefficients should be used for the accurate calculation of pH.

Example 7-7

Solution pH

The hydronium ion concentration of a 0.1 M solution of barbituric acid was found to be 3.24×10^{-3} M. What is the pH of the solution? We write

$$\text{pH} = -\log(3.24 \times 10^{-3})$$

$$\text{pH} = 3 - \log 3.24 = 2.49$$

For practical purposes, activities and concentrations are equal in solutions of weak electrolytes to which no salts are added, because the ionic strength is small.

Conversion of pH to Hydrogen Ion Concentration

The following example illustrates the method of converting pH to $[\text{H}_3\text{O}^+]$.

Example 7-8

Hydronium Ion Concentration

If the pH of a solution is 4.72, what is the hydronium ion concentration? We have

$$\text{pH} = -\log[\text{H}_3\text{O}^+] = 4.72$$

$$\log[\text{H}_3\text{O}^+] = -4.72 = -5 + 0.28$$

$$[\text{H}_3\text{O}^+] = \text{antilog } 0.28 \times \text{antilog } (-5)$$

$$[\text{H}_3\text{O}^+] = 1.91 \times 10^{-5} \text{ mole/liter}$$

The use of a handheld calculator bypasses this two-step procedure. One simply enters -4.72 into the calculator and presses the key for antilog or 10^x to obtain $[\text{H}_3\text{O}^+]$.

pK and pOH

The use of pH to designate the negative logarithm of hydronium ion concentration has proved to be so convenient that expressing numbers less than unity in "p" notation has become a standard procedure. The mathematician would say that "p" is a *mathematical operator* that acts on the quantity $[\text{H}^+]$, K_a , K_b , K_w , and so on to convert the value into the negative of its common logarithm. In other words, the term "p" is used to express the negative logarithm of the term following the "p." For example, pOH expresses $-\log[\text{OH}^-]$, $\text{p}K_a$ is used for $-\log K_a$, and $\text{p}K_w$ is $-\log K_w$. Thus, equations (7-31) and (7-33) can be expressed as

$$\text{pH} + \text{pOH} = \text{p}K_w \quad (7-58)$$

$$\text{p}K_a + \text{p}K_b = \text{p}K_w \quad (7-59)$$

where pK is often called the *dissociation exponent*.

P.153

The pK values of weak acidic and basic drugs are ordinarily determined by ultraviolet spectrophotometry (95) and potentiometric titration (202). They can also be obtained by solubility analysis^{6,7,8} (254) and by a partition coefficient method.⁸

Species Concentration as a Function of pH

As shown in the preceding sections, polyprotic acids, H_nA , can ionize in successive stages to yield $n + 1$ possible species in solution. In many studies of pharmaceutical interest, it is important to be able to calculate the concentration of all acidic and basic species in solution.

The concentrations of all species involved in successive acid-base equilibria change with pH and can be represented solely in terms of equilibrium constants and the hydronium ion concentration. These

relationships can be obtained by defining all species in solution as fractions α of total acid, C_a , added to the system [see equation (7-47) for C_a]:

$$\alpha_0 = [\text{H}_n\text{A}]/C_a \quad (7-60)$$

$$\alpha_1 = [\text{H}_{n-1}\text{A}^{-1}]/C_a \quad (7-61)$$

and in general

$$\alpha_j = [\text{H}_{n-j}\text{A}^{-j}]/C_a \quad (7-62)$$

and

$$\alpha_n = [\text{A}^{-n}]/C_a \quad (7-63)$$

where j represents the number of protons that have ionized from the parent acid. Thus, dividing equation (7-47) by C_a and using equations (7-60) to (7-63) gives

$$\alpha_0 + \alpha_j + \dots + \alpha_{n-1} + \alpha_n = 1 \quad (7-64)$$

All of the α values can be defined in terms of equilibrium constants α_0 and $[\text{H}_3\text{O}^+]$ as follows:

$$K_1 = \frac{[\text{H}_{n-1}\text{A}^{-1}][\text{H}_3\text{O}^+]}{[\text{H}_n\text{A}]} = \frac{\alpha_1 C_a [\text{H}_3\text{O}^+]}{\alpha_0 C_a} \quad (7-65)$$

Therefore,

$$K_2 = \frac{\alpha_1 = K_1 \alpha_0 / [\text{H}_3\text{O}^+]}{[\text{H}_{n-2}\text{A}^{2-}][\text{H}_3\text{O}^+]} = \frac{[\text{H}_{n-2}\text{A}^{2-}][\text{H}_3\text{O}^+]^2}{K_1 [\text{H}_n\text{A}]} \quad (7-66)$$

$$= \frac{\alpha_2 C_a [\text{H}_3\text{O}^+]^2}{\alpha_0 C_a K_1} \quad (7-67)$$

or

$$\alpha_2 = \frac{K_1 K_2 \alpha_0}{[\text{H}_3\text{O}^+]^2} \quad (7-68)$$

and, in general,

$$\alpha_j = (K_1 K_2 \dots K_j) \alpha_0 / [\text{H}_3\text{O}^+]^j \quad (7-69)$$

Inserting the appropriate forms of equation (7-69) into equation (7-64) gives

$$\alpha_0 + \frac{K_1 \alpha_0}{[\text{H}_3\text{O}^+]} + \frac{K_1 K_2 \alpha_0}{[\text{H}_3\text{O}^+]^2} + \dots + \frac{K_1 K_2 \dots K_n \alpha_0}{[\text{H}_3\text{O}^+]^n} = 1 \quad (7-70)$$

Solving for α_0 yields

$$\alpha_0 = \frac{[\text{H}_3\text{O}^+]^n}{\{[\text{H}_3\text{O}^+]^n + K_1 [\text{H}_3\text{O}^+]^{n-1} + K_1 K_2 [\text{H}_3\text{O}^+]^{n-2} + \dots + K_1 K_2 \dots K_n\}} \quad (7-71)$$

or

$$\alpha_0 = \frac{[\text{H}_3\text{O}^+]^n}{D} \quad (7-72)$$

where D represents the denominator of equation (7-71). Thus, the concentration of H_nA as a function of $[\text{H}_3\text{O}^+]$ can be obtained by substituting equation (7-60) into equation (7-72) to give

$$[\text{H}_n\text{A}] = \frac{[\text{H}_3\text{O}^+]^n C_a}{D} \quad (7-73)$$

Substituting equation (7-61) into equation (7-66) and the resulting equation into equation (7-72) gives

$$[\text{H}_{n-1}\text{A}^{-1}] = \frac{K_1 [\text{H}_3\text{O}^+]^{n-1} C_a}{D} \quad (7-74)$$

In general,

$$[\text{H}_{n-j}\text{A}^{-j}] = \frac{K_1 \dots K_j [\text{H}_3\text{O}^+]^{n-j} C_a}{D} \quad (7-75)$$

and

$$[\text{A}^{-n}] = \frac{K_1 K_2 \dots K_n C_a}{D} \quad (7-76)$$

Although these equations appear complicated, they are in reality quite simple. The term D in equations (7-72) to (7-76) is a power series in $[\text{H}_3\text{O}^+]$, each term multiplied by equilibrium constants. The series starts with $[\text{H}_3\text{O}^+]$ raised to the power representing n , the total number of dissociable hydrogens in the parent acid, H_nA . The last term is the product of all the acidity constants. The intermediate terms can

be obtained from the last term by substituting $[\text{H}_3\text{O}^+]$ for K_n to obtain the next to last term, then substituting $[\text{H}_3\text{O}^+]$ for K_{n-1} to obtain the next term, and so on, until the first term is reached. The following equations show the denominators D to be used in equations (7-72) to (7-76) for various types of polyprotic acids:

$$\text{H}_4\text{A}: D = [\text{H}_3\text{O}^+]^4 + K_1[\text{H}_3\text{O}^+]^3 + K_1K_2[\text{H}_3\text{O}^+]^2 + K_1K_2K_3[\text{H}_3\text{O}^+] + K_1K_2K_3K_4 \quad (7-77)$$

$$\text{H}_3\text{A}: D = [\text{H}_3\text{O}^+]^3 + K_1[\text{H}_3\text{O}^+]^2 + K_1K_2[\text{H}_3\text{O}^+] + K_1K_2K_3 \quad (7-78)$$

$$\text{H}_2\text{A}: D = [\text{H}_3\text{O}^+]^2 + K_1[\text{H}_3\text{O}^+] + K_1K_2 \quad (7-79)$$

$$\text{HA}: D = [\text{H}_3\text{O}^+] + K_a \quad (7-80)$$

P.154

In all instances, for a species in which j protons have ionized, the numerator in equations (7-72) to (7-76) is C_a multiplied by the term from the denominator D that has $[\text{H}_3\text{O}^+]$ raised to the $n - j$ power. Thus, for the parent acid H_2A , the appropriate equation for D is equation (7-79). The molar concentrations of the species H_nA ($j = 0$), HA^- ($j = 1$), and A^{2-} ($j = 2$) can be given as

$$[\text{H}_2\text{A}] = \frac{[\text{H}_3\text{O}^+]^2 C_a}{[\text{H}_3\text{O}^+]^2 + K_1[\text{H}_3\text{O}^+] + K_1K_2} \quad (7-81)$$

$$[\text{HA}^-] = \frac{K_1[\text{H}_3\text{O}^+] C_a}{[\text{H}_3\text{O}^+]^2 + K_1[\text{H}_3\text{O}^+] + K_1K_2} \quad (7-82)$$

$$[\text{A}^{2-}] = \frac{K_1K_2 C_a}{[\text{H}_3\text{O}^+]^2 + K_1[\text{H}_3\text{O}^+] + K_1K_2} \quad (7-83)$$

These equations can be used directly to solve for molar concentrations. It should be obvious, however, that lengthy calculations are needed for substances such as citric acid or ethylenediaminetetraacetic acid, requiring the use of a digital computer to obtain solutions in a reasonable time. Graphic methods have been used to simplify the procedure.⁹

Calculation of pH

Proton Balance Equations

According to the Brønsted–Lowry theory, every proton donated by an acid must be accepted by a base. Thus, an equation accounting for the total proton transfers occurring in a system is of fundamental importance in describing any acid–base equilibria in that system. This can be accomplished by establishing a proton balance equation (PBE) for each system. In the PBE, the sum of the concentration terms for species that form by proton consumption is equated to the sum of the concentration terms for species that are formed by the release of a proton.

For example, when HCl is added to water, it dissociates completely into H_3O^+ and Cl^- ions. The H_3O^+ is a species that is formed by the consumption of a proton (by water acting as a base), and the Cl^- is formed by the release of a proton from HCl. In all aqueous solutions, H_3O^+ and OH^- result from the dissociation of two water molecules according to equation (7-28). Thus, OH^- is a species formed from the release of a proton. The PBE for the system of HCl in water is

$$[\text{H}_3\text{O}^+] = [\text{OH}^-] + [\text{Cl}^-]$$

Although H_3O^+ is formed from two reactions, it is included only once in the PBE. The same would be true for OH^- if it came from more than one source.

The general method for obtaining the PBE is as follows:

- Always start with the species added to water.
- On the left side of the equation, place all species that can form when protons are consumed by the starting species.
- On the right side of the equation, place all species that can form when protons are released from the starting species.

- d. Each species in the PBE should be multiplied by the number of protons lost or gained when it is formed from the starting species.
- e. Add $[\text{H}_3\text{O}^+]$ to the left side of the equation and $[\text{OH}^-]$ to the right side of the equation. These result from the interaction of two molecules of water, as shown previously.

Example 7-9

Proton Balance Equations

What is the PBE when H_3PO_4 is added to water?

The species H_2PO_4^- forms with the release of one proton.

The species HPO_4^{2-} forms with the release of two protons.

The species PO_4^{3-} forms with the release of three protons. We thus have

$$[\text{H}_3\text{O}^+] = [\text{OH}^-] + [\text{H}_2\text{PO}_4^-] + 2[\text{HPO}_4^{2-}] + 3[\text{PO}_4^{3-}]$$

Example 7-10

Proton Balance Equations

What is the PBE when Na_2HPO_4 is added to water?

The salt dissociates into two Na^+ and one HPO_4^{2-} ; Na^+ is neglected in the PBE because it is not formed from the release or consumption of a proton; HPO_4^{2-} , however, does react with water and is considered to be the starting species.

The species H_2PO_4^- results with the consumption of one proton.

The species of H_3PO_4 can form with the consumption of two protons.

The species PO_4^{3-} can form with the release of one proton.

Thus, we have

$$[\text{H}_3\text{O}^+] + [\text{H}_2\text{PO}_4^-] + 2[\text{H}_3\text{PO}_4] = [\text{OH}^-] + [\text{PO}_4^{3-}]$$

Example 7-11

Proton Balance Equations

What is the PBE when sodium acetate is added to water?

The salt dissociates into one Na^+ and one CH_3COO^- ion. The CH_3COO^- is considered to be the starting species. The CH_3COOH can form when CH_3COO^- consumes one proton. Thus,

$$[\text{H}_3\text{O}^+] + [\text{CH}_3\text{COOH}] = [\text{OH}^-]$$

The PBE allows the pH of any solution to be calculated readily, as follows:

- a. Obtain the PBE for the solution in question.
- b. Express the concentration of all species as a function of equilibrium constants and $[\text{H}_3\text{O}^+]$ using equations (7-73) to (7-76).
- c. Solve the resulting expression for $[\text{H}_3\text{O}^+]$ using any assumptions that appear valid for the system.
- d. Check all assumptions.
- e. If all assumptions prove valid, convert $[\text{H}_3\text{O}^+]$ to pH.

If the solution contains a base, it is sometimes more convenient to solve the expression obtained in part (b) for $[\text{OH}^-]$, then convert this to pOH, and finally to pH by use of equation (7-58).

Solutions of Strong Acids and Bases

Strong acids and bases are those that have acidity or basicity constants greater than about 10^{-2} . Thus, they are considered

P.155

to ionize 100% when placed in water. When HCl is placed in water, the PBE for the system is given by

$$[\text{H}_3\text{O}^+] = [\text{OH}^-] + [\text{Cl}^-] = \frac{K_w}{[\text{H}_3\text{O}^+]} + C_a \quad (7-84)$$

which can be rearranged to give

$$[\text{H}_3\text{O}^+]^2 - C_a[\text{H}_3\text{O}^+] - K_w = 0 \quad (7-85)$$

where C_a is the total acid concentration. This is a quadratic equation of the general form

$$aX^2 + bX + c = 0 \quad (7-86)$$

which has the solution

$$X = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a} \quad (7-87)$$

Thus, equation (7-85) becomes

$$[\text{H}_3\text{O}^+] = \frac{C_a + \sqrt{C_a^2 + 4K_w}}{2} \quad (7-88)$$

where only the positive root is used because $[\text{H}_3\text{O}^+]$ can never be negative.

When the concentration of acid is 1×10^{-6} M or greater, $[\text{Cl}^-]$ becomes much greater than $[\text{OH}^-]$ in equation (7-84) and C_a^2 becomes much greater than $4K_w$ in equation (7-88). Thus, both equations simplify to

$$[\text{H}_3\text{O}^+] \cong C_a \quad (7-89)$$

A similar treatment for a solution of a strong base such as NaOH gives

$$[\text{OH}^-] = \frac{C_b + \sqrt{C_b^2 + 4K_w}}{2} \quad (7-90)$$

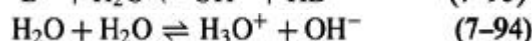
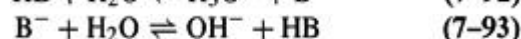
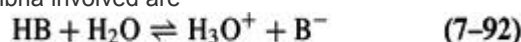
and

$$[\text{OH}^-] \cong C_b \quad (7-91)$$

if the concentration of base is 1×10^{-6} M or greater.

Conjugate Acid–Base Pairs

Use of the PBE enables us to develop one master equation that can be used to solve for the pH of solutions composed of weak acids, weak bases, or a mixture of a conjugate acid–base pair. To do this, consider a solution made by dissolving both a weak acid, HB, and a salt of its conjugate base, B^- , in water. The acid–base equilibria involved are



The PBE for this system is

$$[\text{H}_3\text{O}^+] + [\text{HB}] = [\text{OH}^-] + [\text{B}^-] \quad (7-95)$$

The concentrations of the acid and the conjugate base can be expressed as

$$[\text{HB}] = \frac{[\text{H}_3\text{O}^+]C_b}{[\text{H}_3\text{O}^+] + K_a} \quad (7-96)$$

$$[\text{B}^-] = \frac{K_a C_a}{[\text{H}_3\text{O}^+] + K_a} \quad (7-97)$$

Equation (7-96) contains C_b (concentration of base added as the salt) rather than C_a because in terms of the PBE, the species HB was generated from the species B^- added in the form of the salt.

Equation (7-97) contains C_a (concentration of HB added) because the species B^- in the PBE came from the HB added. Inserting equations (7-96) and (7-97) into equation (7-95) gives

$$\begin{aligned} [\text{H}_3\text{O}^+] + \frac{[\text{H}_3\text{O}^+]C_b}{[\text{H}_3\text{O}^+] + K_a} \\ = [\text{OH}^-] + \frac{K_a C_a}{[\text{H}_3\text{O}^+] + K_a} \end{aligned} \quad (7-98)$$

which can be rearranged to yield

$$[\text{H}_3\text{O}^+] = K_a \frac{(C_a - [\text{H}_3\text{O}^+] + [\text{OH}^-])}{(C_b + [\text{H}_3\text{O}^+] - [\text{OH}^-])} \quad (7-99)$$

This equation is exact and was developed using no assumptions.* It is, however, quite difficult to solve. Fortunately, for real systems, the equation can be simplified.

Solutions Containing Only a Weak Acid

If the solution contains only a weak acid, C_b is zero, and $[\text{H}_3\text{O}^+]$ is generally much greater than $[\text{OH}^-]$. Thus, equation (7-99) simplifies to

$$[\text{H}_3\text{O}^+]^2 + K_a[\text{H}_3\text{O}^+] - K_a C_a = 0 \quad (7-100)$$

which is a quadratic equation with the solution

$$[\text{H}_3\text{O}^+] = \frac{-K_a + \sqrt{K_a^2 + 4K_a C_a}}{2} \quad (7-101)$$

In many instances, C_a is much greater than $[\text{H}_3\text{O}^+]$, and equation (7-100) simplifies to

$$[\text{H}_3\text{O}^+] = \sqrt{K_a C_a} \quad (7-102)$$

Example 7-12

Calculate pH

Calculate the pH of a 0.01 M solution of salicylic acid, which has a $K_a = 1.06 \times 10^{-3}$ at 25°C.

- a. Using equation (7-102), we find

$$\begin{aligned} [\text{H}_3\text{O}^+] &= \sqrt{(1.06 \times 10^{-3}) \times (1.0 \times 10^{-2})} \\ &= 3.26 \times 10^{-3} \text{ M} \end{aligned}$$

The approximation that $C_a \gg \text{H}_3\text{O}^+$ is not valid.

- b. Using equation (7-101), we find

$$\begin{aligned} [\text{H}_3\text{O}^+] &= \frac{-(1.06 \times 10^{-3})}{2} \\ &\quad + \frac{\sqrt{(1.06 \times 10^{-3})^2 + 4(1.06 \times 10^{-3})(1.0 \times 10^{-2})}}{2} \\ &= 2.77 \times 10^{-3} \text{ M} \\ \text{pH} &= -\log(2.77 \times 10^{-3}) = 2.56 \end{aligned}$$

P.156

The example just given illustrates the importance of checking the validity of all assumptions made in deriving the equation used for calculating $[\text{H}_3\text{O}^+]$. The simplified equation (7-102) gives an answer for $[\text{H}_3\text{O}^+]$ with a relative error of 18% as compared with the correct answer given by equation (7-101).

Example 7-13

Calculate pH

Calculate the pH of a 1-g/100 mL solution of ephedrine sulfate. The molecular weight of the salt is 428.5, and K_b for ephedrine base is 2.3×10^{-5} .

- a. The ephedrine sulfate, $(\text{BH}^+)_2\text{SO}_4$, dissociates completely into two BH^+ cations and one SO_4^{2-} anion. Thus, the concentration of the weak acid (ephedrine cation) is twice the concentration, C_s , of the salt added.

$$C_a = 2C_s = \frac{2 \times 10 \text{ g/liter}}{428.5 \text{ g/mole}} = 4.67 \times 10^{-2} \text{ M}$$

$$\begin{aligned} \text{b. } K_a &= \frac{1.00 \times 10^{-14}}{2.3 \times 10^{-5}} = 4.35 \times 10^{-10} \\ [\text{H}_3\text{O}^+] &= \sqrt{(4.35 \times 10^{-10}) \times (4.67 \times 10^{-2})} \\ \text{c. } &= 4.51 \times 10^{-6} \text{ M} \end{aligned}$$

All assumptions are valid. We have

$$\text{pH} = -\log(4.51 \times 10^{-6}) = 5.35$$

Solutions Containing Only a Weak Base

If the solution contains only a weak base, C_a is zero, and $[\text{OH}^-]$ is generally much greater than $[\text{H}_3\text{O}^+]$. Thus, equation (7-99) simplifies to

$$[\text{H}_3\text{O}^+] = \frac{K_a[\text{OH}^-]}{C_b - [\text{OH}^-]} = \frac{K_a K_w}{[\text{H}_3\text{O}^+]C_b - K_w} \quad (7-103)$$

This equation can be solved for either $[\text{H}_3\text{O}^+]$ or $[\text{OH}^-]$. Solving for $[\text{H}_3\text{O}^+]$ using the left and rightmost parts of equation (7-103) gives

$$C_b[\text{H}_3\text{O}^+]^2 - K_w[\text{H}_3\text{O}^+] - K_a K_w = 0 \quad (7-104)$$

which has the solution

$$[\text{H}_3\text{O}^+] = \frac{K_w + \sqrt{K_w^2 + 4C_b K_a K_w}}{2C_b} \quad (7-105)$$

If K_a is much greater than $[\text{H}_3\text{O}^+]$, which is generally true for solutions of weak bases, equation (7-100) gives

$$[\text{H}_3\text{O}^+] = \sqrt{\frac{K_a K_w}{C_b}} \quad (7-106)$$

Equation (7-103) can be solved for $[\text{OH}^-]$ by using the left and middle portions and converting K_a to K_b to give

$$[\text{OH}^-] = \frac{-K_b + \sqrt{K_b^2 + 4K_b C_b}}{2} \quad (7-107)$$

and if C_b is much greater than $[\text{OH}^-]$, which generally obtains for solutions of weak bases,

$$[\text{OH}^-] = \sqrt{K_b C_b} \quad (7-108)$$

A good exercise for the student would be to prove that equation (7-106) is equal to equation (7-108).

The applicability of both these equations will be shown in the following examples.

Example 7-14

Calculate pH

What is the pH of a 0.0033 M solution of cocaine base, which has a basicity constant of 2.6×10^{-6} ? We have

$$[\text{OH}^-] = \sqrt{(2.6 \times 10^{-6}) \times (3.3 \times 10^{-3})} \\ = 9.26 \times 10^{-5} \text{ M}$$

All assumptions are valid. Thus,

$$\text{pOH} = -\log(9.26 \times 10^{-5}) = 4.03 \\ \text{pH} = 14.00 - 4.03 = 9.97$$

Example 7-15

Calculate pH

Calculate the pH of a 0.165 M solution of sodium sulfathiazole. The acidity constant for sulfathiazole is 7.6×10^{-8} .

(a) The salt Na^+B^- dissociates into one Na^+ and one B^- as described by equations (7-24) to (7-27). Thus, $C_b = C_s = 0.165$ M. Because K_a for a weak acid such as sulfathiazole is usually given rather than K_b for its conjugate base, equation (7-106) is preferred over equation (7-108):

$$[\text{H}_3\text{O}^+] = \sqrt{\frac{(7.6 \times 10^{-8}) \times (1.00 \times 10^{-14})}{0.165}} \\ = 6.79 \times 10^{-11} \text{ M}$$

All assumptions are valid. Thus,

$$\text{pH} = -\log(6.79 \times 10^{-11}) = 10.17$$

Solutions Containing a Single Conjugate Acid–Base Pair

In a solution composed of a weak acid and a salt of that acid (e.g., acetic acid and sodium acetate) or a weak base and a salt of that base (e.g., ephedrine and ephedrine hydrochloride), C_a and C_b are generally much greater than either $[H_3O^+]$ or $[OH^-]$. Thus, equation (7-99) simplifies to

$$[H_3O^+] = \frac{K_a C_a}{C_b} \quad (7-109)$$

P.157

Example 7-16

Calculate pH

What is the pH of a solution containing acetic acid 0.3 M and sodium acetate 0.05 M? We write

$$[H_3O^+] = \frac{(1.75 \times 10^{-5}) \times (0.3)}{5.0 \times 10^{-2}} = 1.05 \times 10^{-4} \text{ M}$$

All assumptions are valid. Thus,

$$\text{pH} = -\log(1.05 \times 10^{-4}) = 3.98$$

Example 7-17

Calculate pH

What is the pH of a solution containing ephedrine 0.1 M and ephedrine hydrochloride 0.01 M? Ephedrine has a basicity constant of 2.3×10^{-5} ; thus, the acidity constant for its conjugate acid is 4.35×10^{-10} .

$$[H_3O^+] = \frac{(4.35 \times 10^{-10}) \times (1.0 \times 10^{-2})}{1.0 \times 10^{-1}} = 4.35 \times 10^{-11} \text{ M}$$

All assumptions are valid. Thus,

$$\text{pH} = -\log(4.35 \times 10^{-11}) = 10.36$$

Solutions made by dissolving in water both an acid and its conjugate base, or a base and its conjugate acid, are examples of buffer solutions. These solutions are of great importance in pharmacy and are covered in greater detail in the next two chapters.

Two Conjugate Acid–Base Pairs

The Brønsted–Lowry theory and the PBE enable a single equation to be developed that is valid for solutions containing an ampholyte, which forms a part of two dependent acid–base pairs. An amphoteric species can be added directly to water or it can be formed by the reaction of a diprotic weak acid, H_2A , or a diprotic weak base, A^{2-} . Thus, it is convenient to consider a solution containing a diprotic weak acid, H_2A , a salt of its ampholyte, HA^- , and a salt of its diprotic base, A^{2-} , in concentrations C_a , C_{ab} , and C_b , respectively. The total PBE for this system is

$$\begin{aligned} [H_3O^+] + [H_2A]_{ab} + [HA^-]_b + 2[H_2A]_b \\ = [OH^-] + [HA^-]_a + 2[A^{2-}]_a \\ + [A^{2-}]_{ab} \end{aligned} \quad (7-110)$$

where the subscripts refer to the source of the species in the PBE, that is, $[H_2A]_{ab}$ refers to H_2A generated from the ampholyte and $[H_2A]_b$ refers to the H_2A generated from the diprotic base. Replacing these species concentrations as a function of $[H_3O^+]$ gives

$$\begin{aligned} + \frac{K_1 [H_3O^+] C_a}{D} + \frac{2K_1 K_2 C_a}{D} \\ + \frac{K_1 K_2 C_{ab}}{D} \end{aligned} \quad (7-111)$$

Multiplying through by $[H_3O^+]$ and D , which is given by equation (7-79), gives

$$\begin{aligned}
& [\text{H}_3\text{O}^+]^4 + [\text{H}_3\text{O}^+]^3(K_1 + 2C_b + C_{ab}) \\
& + [\text{H}_3\text{O}^+]^2[K_1(C_b - C_a) + K_1K_2 - K_w] \\
& - [\text{H}_3\text{O}^+][K_1K_2(2C_a + C_{ab}) + K_1K_w] \\
& - K_1K_2K_w = 0 \qquad (7-112)
\end{aligned}$$

This is a general equation that has been developed using no assumptions and that can be used for solutions made by adding a diprotic acid to water, adding an ampholyte to water, adding a diprotic base to water, and by adding combinations of these substances to water. It is also useful for tri- and quadriprotic acid systems because K_3 and K_4 are much smaller than K_1 and K_2 for all acids of pharmaceutical interest. Thus, these polyprotic acid systems can be handled in the same manner as a diprotic acid system.

Solutions Containing Only a Diprotic Acid

If a solution is made by adding a diprotic acid, H_2A , to water to give a concentration C_a , the terms C_{ab} and C_b in equation (7-112) are zero. In almost all instances, the terms containing K_w can be dropped, and after dividing through by $[\text{H}_3\text{O}^+]$, we obtain from equation (7-112)

$$\begin{aligned}
& [\text{H}_3\text{O}^+]^3 + [\text{H}_3\text{O}^+]^2K_1 - [\text{H}_3\text{O}^+](K_1C_a - K_1K_2) \\
& - 2K_1K_2C_a = 0 \qquad (7-113)
\end{aligned}$$

If $C_a \gg K_2$, as is usually true,

$$\begin{aligned}
& [\text{H}_3\text{O}^+]^3 + [\text{H}_3\text{O}^+]^2K_1 - [\text{H}_3\text{O}^+]K_1C_a \\
& - 2K_1K_2C_a = 0 \qquad (7-114)
\end{aligned}$$

If $[\text{H}_3\text{O}^+]$ is much greater than $2K_2$, the term $2K_1K_2C_a$ can be dropped, and dividing through by $[\text{H}_3\text{O}^+]$ yields the quadratic equation

$$[\text{H}_3\text{O}^+]^2 + [\text{H}_3\text{O}^+]K_1 - KC_a = 0 \qquad (7-115)$$

The assumptions C_a is much greater than K_2 and $[\text{H}_3\text{O}^+]$ is much greater than $2K_2$ will be valid whenever K_2 is much less than K_1 . Equation (7-115) is identical to equation (7-100), which was obtained for a solution containing a monoprotic weak acid. Thus, if C_a is much greater than $[\text{H}_3\text{O}^+]$, equation (7-115) simplifies to equation (7-100).

Example 7-18

Calculate pH

Calculate the pH of a 1.0×10^{-3} M solution of succinic acid. $K_1 = 6.4 \times 10^{-5}$ and $K_2 = 2.3 \times 10^{-6}$.

- a. Use equation (7-102) because K_1 is approximately 30 times K_2 :

$$\begin{aligned}
[\text{H}_3\text{O}^+] &= \sqrt{(6.4 \times 10^{-5}) \times (1.0 \times 10^{-3})} \\
&= 2.53 \times 10^{-4} \text{ M}
\end{aligned}$$

The assumption that C_a is much greater than $[\text{H}_3\text{O}^+]$ is not valid.

- b. Use the quadratic equation (7-115):

$$\begin{aligned}
[\text{H}_3\text{O}^+] &= - (6.4 \times 10^{-5})/2 \\
&+ \frac{\sqrt{(6.4 \times 10^{-5})^2 + 4(6.4 \times 10^{-5})(1.0 \times 10^{-3})}}{2} \\
&= 2.23 \times 10^{-4} \text{ M}
\end{aligned}$$

Note that C_a is much greater than K_2 , and $[\text{H}_3\text{O}^+]$ is much greater than $2K_2$. Thus, we have $\text{pH} = -\log(2.23 \times 10^{-4}) = 3.65$

Solutions Containing Only an Ampholyte

If an ampholyte, HA^- , is dissolved in water to give a solution with concentration C_{ab} , the terms C_a and C_b in equation (7-112) are zero. For most systems of practical importance, the first, third, and fifth terms of equation (7-112) are negligible when compared with the second and fourth terms, and the equation becomes

$$[\text{H}_3\text{O}^+] = \sqrt{\frac{K_1 K_2 C_{ab} + K_1 K_w}{K_1 + C_{ab}}} \quad (7-116)$$

The term $K_2 C_{ab}$ is generally much greater than K_w , and

$$[\text{H}_3\text{O}^+] = \sqrt{\frac{K_1 K_2 C_{ab}}{K_1 + C_{ab}}} \quad (7-117)$$

If the solution is concentrated enough that C_{ab} is much greater than K_1 ,

$$[\text{H}_3\text{O}^+] = \sqrt{K_1 K_2} \quad (7-118)$$

Example 7-19

Calculate pH

Calculate the pH of a 5.0×10^{-3} M solution of sodium bicarbonate at 25°C . The acidity constants for carbonic acid are $K_1 = 4.3 \times 10^{-7}$ and $K_2 = 4.7 \times 10^{-11}$.

Because $K_2 C_{ab}$ (23.5×10^{-14}) is much greater than K_w and C_{ab} is much greater than K_1 , equation (7-118) can be used. We have

$$\begin{aligned} [\text{H}_3\text{O}^+] &= \sqrt{(4.3 \times 10^{-7}) \times (4.7 \times 10^{-11})} \\ &= 4.5 \times 10^{-9} \text{ M} \\ \text{pH} &= -\log(4.5 \times 10^{-9}) = 8.35 \end{aligned}$$

Solutions Containing Only a Diacidic Base

In general, the calculations for solutions containing weak bases are easier to handle by solving for $[\text{OH}^-]$ rather than $[\text{H}_3\text{O}^+]$. Any equation in terms of $[\text{H}_3\text{O}^+]$ and acidity constants can be converted into terms of $[\text{OH}^-]$ and basicity constants by substituting $[\text{OH}^-]$ for $[\text{H}_3\text{O}^+]$, K_{b1} for K_1 , K_{b2} for K_2 , and C_b for C_a . These substitutions are made into equation (7-112). Furthermore, for a solution containing only a diacidic base, C_a and C_{ab} are zero; all terms containing K_w can be dropped; C_b is much greater than K_{b2} ; and $[\text{OH}^-]$ is much greater than $2K_{b2}$. The following expression results:

$$[\text{OH}^-]^2 + [\text{OH}^-]K_{b1} - K_{b1}C_b = 0 \quad (7-119)$$

If C_b is much greater than $[\text{OH}^-]$, the equation simplifies to

$$[\text{OH}^-] = \sqrt{K_{b1}C_b} \quad (7-120)$$

Example 7-20

Calculate pH

Calculate the pH of a 1.0×10^{-3} M solution of Na_2CO_3 . The acidity constants for carbonic acid are $K_1 = 4.31 \times 10^{-7}$ and $K_2 = 4.7 \times 10^{-11}$.

a. Using equation (7-48), we obtain

$$\begin{aligned} K_{b1} &= \frac{K_w}{K_2} = \frac{1.00 \times 10^{-14}}{4.7 \times 10^{-11}} = 2.1 \times 10^{-4} \\ K_{b2} &= \frac{K_w}{K_1} = \frac{1.00 \times 10^{-14}}{4.31 \times 10^{-7}} = 2.32 \times 10^{-8} \end{aligned}$$

b. Because K_{b2} is much greater than K_{b2} , one uses equation (7-120):

$$\begin{aligned} [\text{OH}^-] &= \sqrt{(2.1 \times 10^{-4}) \times (1.0 \times 10^{-3})} \\ &= 4.6 \times 10^{-4} \text{ M} \end{aligned}$$

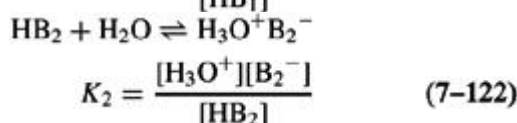
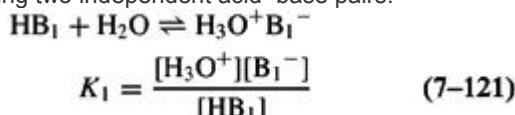
The assumption that C_b is much greater than $[\text{OH}^-]$ is not valid, and equation (7-119) must be used. [See equations (7-86) and (7-87) for the solution of a quadratic equation.] We obtain

$$\begin{aligned}
[\text{OH}^-] &= -(2.1 \times 10^{-4})/2 \\
&+ \frac{\sqrt{(2.1 \times 10^{-4})^2 + 4(2.1 \times 10^{-4})(1.0 \times 10^{-3})}}{2} \\
&= 3.7 \times 10^{-4} \text{ M} \\
\text{pOH} &= -\log(3.7 \times 10^{-4}) = -3.4 \\
\text{pH} &= 14.00 - 3.4 = 10.6
\end{aligned}$$

Use of the simplified equation (7-120) gives an answer for $[\text{OH}^-]$ that has a relative error of 24% as compared with the correct answer given by equation (7-119). It is absolutely essential that all assumptions made in the calculation of $[\text{H}_3\text{O}^+]$ or $[\text{OH}^-]$ be verified!

Two Independent Acid–Base Pairs

Consider a solution containing two independent acid–base pairs:



A general equation for calculating the pH of this type of solution can be developed by considering a solution made by adding to water the acids HB_1 and HB_2 in concentrations C_{a1}

P.159

and C_{a2} and the bases B_1^- and B_2^- in concentrations C_{b1} and C_{b2} . The PBE for this system is

$$\begin{aligned}
[\text{H}_3\text{O}^+] + [\text{HB}_1]_{B1} + [\text{HB}_2]_{B2} \\
= [\text{OH}^-] + [\text{B}_1^-]_{A1} + [\text{B}_2^-]_{A2} \quad (7-123)
\end{aligned}$$

where the subscripts refer to the sources of the species in the PBE. Replacing these species concentrations as a function of $[\text{H}_3\text{O}^+]$ gives

$$\begin{aligned}
[\text{H}_3\text{O}^+] + \frac{[\text{H}_3\text{O}^+]C_{b1}}{[\text{H}_3\text{O}^+] + K_1} + \frac{[\text{H}_3\text{O}^+]C_{b2}}{[\text{H}_3\text{O}^+] + K_2} \\
= \frac{K_w}{[\text{H}_3\text{O}^+]} + \frac{K_1 C_{a1}}{[\text{H}_3\text{O}^+] + K_1} \\
+ \frac{K_2 C_{a2}}{[\text{H}_3\text{O}^+] + K_2} \quad (7-124)
\end{aligned}$$

which can be rearranged to

$$\begin{aligned}
[\text{H}_3\text{O}^+]^4 + [\text{H}_3\text{O}^+]^3(K_1 + K_2 + C_{b1} + C_{b2}) + [\text{H}_3\text{O}^+]^2 \\
\times [K_1(C_{b2} - C_{a1}) + K_2(C_{b1} - C_{a2}) + K_1 K_2 - K_w] \\
- [\text{H}_3\text{O}^+][K_1 K_2(C_{a1} + C_{a2}) + K_w(K_1 + K_2)] \\
- K_1 K_2 K_w = 0 \quad (7-125)
\end{aligned}$$

Although this equation is extremely complex, it simplifies readily when applied to specific systems.

Solutions Containing Two Weak Acids

In systems containing two weak acids, C_{b1} and C_{b2} are zero, and all terms in K_w can be ignored in equation (7-125). For all systems of practical importance, C_{a1} and C_{a2} are much greater than K_1 and K_2 , so the equation simplifies to

$$\begin{aligned}
[\text{H}_3\text{O}^+]^2 + [\text{H}_3\text{O}^+](K_1 + K_2) \\
- (K_1 C_{a1} + K_2 C_{a2}) = 0 \quad (7-126)
\end{aligned}$$

If C_{a1} and C_{a2} are both greater than $[\text{H}_3\text{O}^+]$, the equation simplifies to

$$[\text{H}_3\text{O}^+] = \sqrt{K_1 C_{a1} + K_2 C_{a2}} \quad (7-127)$$

Example 7-21
Calculate pH

What is the pH of a solution containing acetic acid, 0.01 mole/liter, and formic acid, 0.001 mole/liter? We have

$$\begin{aligned} [\text{H}_3\text{O}^+] &= \sqrt{(1.75 \times 10^{-5})(1.0 \times 10^{-2}) + (1.77 \times 10^{-4})(1.0 \times 10^{-3})} \\ &= 5.93 \times 10^{-4} \text{ M} \\ \text{pH} &= -\log(5.93 \times 10^{-4}) = 3.23 \end{aligned}$$

Solutions Containing a Salt of a Weak Acid and a Weak Base

The salt of a weak acid and a weak base, such as ammonium acetate, dissociates almost completely in aqueous solution to yield NH_4^+ and Ac^- , the NH_4^+ is an acid and can be designated as HB_1 , and the base Ac^- can be designated as B_2^- in equations (7-121) and (7-122). Because only a single acid, HB_1 , and a single base, B_2^- , were added to water in concentrations C_{a1} and C_{b2} , respectively, all other stoichiometric concentration terms in equation (7-115) are zero. In addition, all terms containing K_w are negligibly small and may be dropped, simplifying the equation to

$$\begin{aligned} &[\text{H}_3\text{O}^+]^2 (K_1 + K_2 + C_{b2}) \\ &+ [\text{H}_3\text{O}^+][K_1(C_{b2} - C_{a1}) + K_1 K_2] \\ &- K_1 K_2 C_{a1} = 0 \end{aligned} \quad (7-128)$$

In solutions containing a salt such as ammonium acetate, $C_{a1} = C_{b2} = C_s$, where C_s is the concentration of salt added. In all systems of practical importance, C_s is much greater than K_1 or K_2 , and equation (7-128) simplifies to

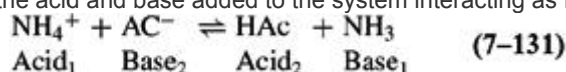
$$[\text{H}_3\text{O}^+]^2 C_s + [\text{H}_3\text{O}^+] K_1 K_2 - K_1 K_2 C_s = 0 \quad (7-129)$$

which is a quadratic equation that can be solved in the usual manner. In most instances, however, C_s is much greater than $[\text{H}_3\text{O}^+]$, and the quadratic equation reduces to

$$[\text{H}_3\text{O}^+] = \sqrt{K_1 K_2} \quad (7-130)$$

Equations (7-121) and (7-122) illustrate the fact that K_1 and K_2 are not the successive acidity constants for a single diprotic acid system, and equation (7-130) is not the same as equation (7-118);

instead, K_1 is the acidity constant for HB_1 (Acid_1) and K_2 is the acidity constant for the conjugate acid, HB_2 (Acid_2), of the base B_2^- . The determination of Acid_1 and Acid_2 can be illustrated using ammonium acetate and considering the acid and base added to the system interacting as follows:



Thus, for this system, K_1 is the acidity constant for the ammonium ion and K_2 is the acidity constant for acetic acid.

Example 7-22

Calculate pH

Calculate the pH of a 0.01 M solution of ammonium acetate. The acidity constant for acetic acid is $K_2 = K_a = 1.75 \times 10^{-5}$, and the basicity constant for ammonia is $K_b = 1.74 \times 10^{-5}$.

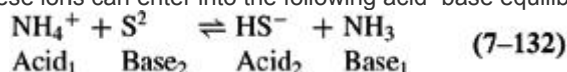
(a) K_1 can be found by dividing K_b for ammonia into K_w :

$$\begin{aligned} K_1 &= \frac{1.00 \times 10^{-14}}{1.74 \times 10^{-5}} = 5.75 \times 10^{-10} \\ [\text{H}_3\text{O}^+] &= \sqrt{(5.75 \times 10^{-10}) \times (1.75 \times 10^{-5})} \\ &= 1.00 \times 10^{-7} \text{ M} \end{aligned}$$

Note that all of the assumptions are valid. We have

$$\text{pH} = -\log(1.00 \times 10^{-7}) = 7.00$$

When ammonium succinate is dissolved in water, it dissociates to yield two NH_4^+ cations and one succinate (S^{2-}) anion. These ions can enter into the following acid-base equilibrium:



In this system, $C_{b2} = C_s$ and $C_{a1} = 2C_s$, the concentration of salt added. If C_s is much greater than either K_1 or K_2 , equation (7-125) simplifies to

$$[\text{H}_3\text{O}^+]^2 - [\text{H}_3\text{O}^+]K_1 - 2K_1K_2 = 0 \quad (7-133)$$

and if $2K_2$ is much greater than $[\text{H}_3\text{O}^+]$,

$$[\text{H}_3\text{O}^+] = \sqrt{2K_1K_2} \quad (7-134)$$

In this example, equation (7-132) shows that K_1 is the acidity constant for the ammonium cation and K_2 , referring to Acid_2 , must be the acidity constant for the bisuccinate species HS^- or the second acidity constant for succinic acid.

In general, when Acid_2 comes from a polyprotic acid H_nA , equation (7-128) simplifies to

$$[\text{H}_3\text{O}^+]^2 - [\text{H}_3\text{O}^+]K_1(n-1) - nK_1K_2 = 0 \quad (7-135)$$

and

$$[\text{H}_3\text{O}^+] = \sqrt{nK_1K_2} \quad (7-136)$$

using the same assumptions that were used in developing equations (7-132) and (7-133).

It should be pointed out that in deriving equations (7-132) to (7-136), the base was assumed to be monoprotic. Thus, it would appear that these equations should not be valid for salts such as ammonium succinate or ammonium phosphate. For all systems of practical importance, however, the solution to these equations yields a pH value above the final $\text{p}K_a$ for the system. Therefore, the concentrations of all species formed by the addition of more than one proton to a polyacidic base will be negligibly small, and the assumption of only a one-proton addition becomes quite valid.

Example 7-23

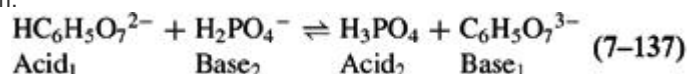
Calculate pH

Calculate the pH of a 0.01 M solution of ammonium succinate. As shown in equation (7-132), K_1 is the acidity constant for the ammonium cation, which was found in the previous example to be 5.75×10^{-10} , and K_2 refers to the acid succinate (HS^-) or the second acidity constant for the succinic acid system. Thus, $K_2 = 2.3 \times 10^{-6}$. We have

$$\begin{aligned} [\text{H}_3\text{O}^+] &= \sqrt{2(5.75 \times 10^{-10}) \times (2.3 \times 10^{-6})} \\ &= 5.14 \times 10^{-8} \\ \text{pH} &= -\log(5.14 \times 10^{-8}) = 7.29 \end{aligned}$$

Solutions Containing a Weak Acid and a Weak Base

In the preceding section, the acid and base were added in the form of a single salt. They can be added as two separate salts or an acid and a salt, however, forming buffer solutions whose pH is given by equation (7-130). For example, consider a solution made by dissolving equimolar amounts of sodium acid phosphate, NaH_2PO_4 , and disodium citrate, $\text{Na}_2\text{HC}_6\text{H}_5\text{O}_7$, in water. Both salts dissociate to give the amphoteric species H_2PO_4^- and $\text{HC}_6\text{H}_5\text{O}_7^{2-}$, causing a problem in deciding which species to designate as HB_1 and which to designate as B_2^- in equations (7-121) and (7-122). This problem can be resolved by considering the acidity constants for the two species in question. The acidity constant for H_2PO_4^- is 7.2 and that for the species $\text{HC}_6\text{H}_5\text{O}_7^{2-}$ is 6.4. The citrate species, being more acidic, acts as the acid in the following equilibrium:



Thus, K_1 in equation (7-130) is K_3 for the citric acid system, and K_2 in equation (7-130) is K_1 for the phosphoric acid system.

Example 7-24

Calculate pH

What is the pH of a solution containing NaH_2PO_4 and disodium citrate (disodium hydrogen citrate) $\text{Na}_2\text{HC}_6\text{H}_5\text{O}_7$, both in a concentration of 0.01 M? The third acidity constant for $\text{HC}_6\text{H}_5\text{O}_7^{2-}$ is 4.0×10^{-7} , whereas the first acidity constant for phosphoric acid is 7.5×10^{-3} . We have

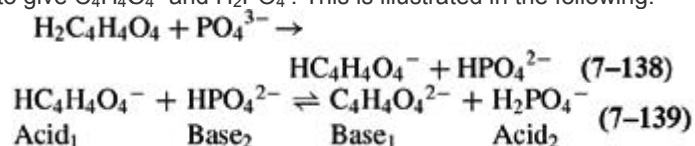
$$\begin{aligned} [\text{H}_3\text{O}^+] &= \sqrt{(4.0 \times 10^{-7}) \times (7.5 \times 10^{-3})} \\ &= 5.48 \times 10^{-5} \text{ M} \end{aligned}$$

All assumptions are valid. We find

$$\text{pH} = -\log(5.48 \times 10^{-5}) = 4.26$$

The equilibrium shown in equation (7-137) illustrates the fact that the system made by dissolving NaH_2PO_4 and $\text{Na}_2\text{HC}_6\text{H}_5\text{O}_7$ in water is identical to that made by dissolving H_3PO_4 and $\text{Na}_3\text{C}_6\text{H}_5\text{O}_7$ in water. In the latter case, H_3PO_4 is HB_1 and the tricitrate is B_2^- , and if the two substances are dissolved in equimolar amounts, equation (7-130) is valid for the system.

A slightly different situation arises for equimolar combinations of substances such as succinic acid, $\text{H}_2\text{C}_4\text{H}_4\text{O}_4$, and tribasic sodium phosphate, Na_3PO_4 . In this case, it is obvious that succinic acid is the acid, which can protonate the base to yield the species $\text{HC}_4\text{H}_4\text{O}_4^-$ and HPO_4^{2-} . The acid succinate ($\text{p}K_a$ 5.63) is a stronger acid than HPO_4^{2-} ($\text{p}K_a$ 12.0), however, and an equilibrium cannot be established between these species and the species originally added to water. Instead, the HPO_4^{2-} is protonated by the acid succinate to give $\text{C}_4\text{H}_4\text{O}_4^{2-}$ and H_2PO_4^- . This is illustrated in the following:



Thus, K_1 in equation (7-139) is K_2 for the succinic acid system, and K_2 in equation (7-130) is actually K_2 from the phosphoric acid system.

P.161

Example 7-25

Calculate pH

Calculate the pH of a solution containing succinic acid and tribasic sodium phosphate, each at a concentration of 0.01 M. The second acidity constant for the succinic acid system is 2.3×10^{-6} . The second acidity constant for the phosphoric acid system is 6.2×10^{-8} . Write

$$\text{a.} \quad [\text{H}_3\text{O}^+] = \sqrt{(2.3 \times 10^{-6})(6.2 \times 10^{-8})} = 3.78 \times 10^{-7} \text{ M}$$

All assumptions are valid. We have

$$\text{pH} = -\log(3.78 \times 10^{-7}) = 6.42$$

b. Equation (7-130) can also be solved by taking logarithms of both sides to yield

$$\begin{aligned} \text{pH} &= \frac{1}{2}(\text{p}K_1 + \text{p}K_2) \\ &= \frac{1}{2}(5.63 + 7.21) = 6.42 \quad (7-140) \end{aligned}$$

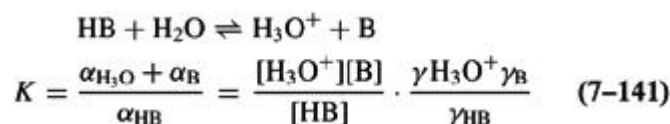
Equations (7-138) and (7-139) illustrate the fact that solutions made by dissolving equimolar amounts of $\text{H}_2\text{C}_4\text{H}_4\text{O}_4$ and Na_3PO_4 , $\text{NaHC}_4\text{H}_4\text{O}_4$ and Na_2HPO_4 , or $\text{Na}_2\text{C}_4\text{H}_4\text{O}_4$ and NaH_2PO_4 in water all equilibrate to the same pH and are identical.

Acidity Constants

One of the most important properties of a drug molecule is its acidity constant, which for many drugs can be related to physiologic and pharmacologic activity,¹⁰ solubility,¹¹ rate of solution,¹² extent of binding,¹⁴ and rate of absorption.¹⁵

Effect of Ionic Strength on Acidity Constants

In the preceding sections, the solutions were considered dilute enough that the effect of ionic strength on the acid–base equilibria could be ignored. A more exact treatment for the ionization of a weak acid, for example, would be



where K is the thermodynamic acidity constant, and the charges on the species have been omitted to make the equations more general. Equation (7-141) illustrates the fact that in solving equations involving acidity constants, both the concentration and the activity coefficient of each species must be considered. One way to simplify the problem would be to define the acidity constant as an apparent constant in terms of the hydronium ion activity and species concentrations and activity coefficients, as follows:

$$K = \alpha_{\text{H}_3\text{O}^+} \frac{[\text{B}]}{[\text{HB}]} \frac{\gamma_{\text{B}}}{\gamma_{\text{HB}}} = K' \frac{\gamma_{\text{B}}}{\gamma_{\text{HB}}} \quad (7-142)$$

and

$$\text{p}K' = \text{p}K + \log \frac{\gamma_{\text{B}}}{\gamma_{\text{HB}}} \quad (7-143)$$

The following form of the Debye–Hückel equation¹⁶ can be used for ionic strengths up to about 0.3 M:

$$-\log \gamma_i = \frac{0.51 Z_i^2 \sqrt{\mu}}{1 + \alpha B \sqrt{\mu}} - K_s \mu \quad (7-144)$$

where Z_i is the charge on the species i . The value of the constant αB can be taken to be approximately 1 at 25°C, and K_s is a “salting-out” constant. At moderate ionic strengths, K_s can be assumed to be approximately the same for both the acid and its conjugate base.¹⁶ Thus, for an acid with charge Z going to a base with charge $Z - 1$,

$$\text{p}K' = \text{p}K + \frac{0.51(2Z - 1)\sqrt{\mu}}{1 + \sqrt{\mu}} \quad (7-145)$$

Example 7-26

Calculate $\text{p}K'_2$

Calculate $\text{p}K'_2$ for citric acid at an ionic strength of 0.01 M. Assume that $\text{p}K_2 = 4.78$. The charge on the acidic species is -1. We have

$$\begin{aligned} \text{p}K'_2 &= 4.78 + \frac{0.51(-3)\sqrt{0.01}}{1 + \sqrt{0.01}} \\ &= 4.78 - 1.53(0.091) = 4.64 \end{aligned}$$

If either the acid or its conjugate base is a zwitterion, it will have a large dipole moment, and the expression for its activity coefficient must contain a term K_r , the “salting-in” constant.¹⁷ Thus, for the zwitterion $[+ -]$,

$$-\log \gamma_{+-} = (K_r - K_s)\mu \quad (7-146)$$

The first ionization of an amino acid such as glycine hydrochloride involves an acid with a charge of +1 going to the zwitterion, $[+ -]$. Combining equations (7-146) and (7-144) with equation (7-143) gives

$$\text{p}K'_1 = \text{p}K_1 + \frac{0.51\sqrt{\mu}}{1 + \sqrt{\mu}} - K_r \mu \quad (7-147)$$

The second ionization step involves the zwitterion going to a species with a charge of -1. Thus, using equations (7-146), (7-144), and (7-143) gives

$$\text{p}K'_2 = \text{p}K_2 - \frac{0.51\sqrt{\mu}}{1 + \sqrt{\mu}} + K_r \mu \quad (7-148)$$

The “salting-in” constant, K_r , is approximately 0.32 for alpha-amino acids in water and approximately 0.6 for dipeptides.¹⁷ Use of these values for K_r enables equations (7-147) and (7-148) to be used for solutions with ionic strengths up to about 0.3 M.

The procedure to be used in solving pH problems in which the ionic strength of the solution must be considered is as follows:

- Convert all $\text{p}K$ values needed for the problem into $\text{p}K'$ values.
- Solve the appropriate equation in the usual manner.

Example 7-27**Calculate pH**

Calculate the pH of a 0.01 M solution of acetic acid to which enough KCl had been added to give an ionic strength of 0.01 M at 25°C. The pK_a for acetic acid is 4.76.

$$\begin{aligned} (a) \quad pK'_a &= 4.76 - \frac{0.51\sqrt{0.10}}{1 + \sqrt{0.10}} \\ a. \quad &= 4.76 - 0.12 = 4.64 \\ b. \quad &\text{Taking logarithms of equation (7-99) gives} \end{aligned}$$

$$pH = \frac{1}{2}(pK'_a - \log C_a)$$

in which we now write pK_a as pK'_a :

$$pH = \frac{1}{2}(4.64 + 2.00) = 3.32$$

Example 7-28**Calculate pH**

Calculate the pH of a 10^{-3} M solution of glycine at an ionic strength of 0.10 at 25°C. The pK_a values for glycine are $pK_1 = 2.35$ and $pK_2 = 9.78$.

$$\begin{aligned} (a) \quad pK'_1 &= 2.35 + \frac{0.51\sqrt{0.10}}{1 + \sqrt{0.10}} - 0.32(0.10) \\ &= 2.35 + 0.12 - 0.03 = 2.44 \\ (b) \quad pK'_2 &= 9.78 - \frac{0.51\sqrt{0.10}}{1 + \sqrt{0.10}} + 0.32(0.10) \\ &= 9.78 - 0.12 + 0.03 = 9.69 \\ (c) \quad &\text{Taking logarithms of equation (7-118) gives} \\ pH &= \frac{1}{2}(pK_1 + pK_2) \\ &= \frac{1}{2}(2.44 + 9.69) = 6.07 \end{aligned}$$

Chapter Summary

In this chapter, the student is introduced to ionic equilibria in the pharmaceutical sciences. The Brønsted–Lowry and Lewis electronic theories are introduced. The four classes of solvents (protophilic, protogenic, amphiprotic, and aprotic) are described as well. The student should understand the concepts of acid–base equilibria and the ionization of weak acids and weak bases. Further, you should be able to use this theory in your practice. In other words, you should be able to calculate dissociation constants K_a and K_b and understand the relationship between K_a and K_b . It is also very important to understand the concepts of pH, pK, and pOH and the relationship between hydrogen ion concentration and pH. Of course, you should be able to calculate pH. Finally, strong acids and strong bases were defined and described. You should strive for a working understanding of acidity constants. Practice problems for this chapter can be found at thePoint.lww.com/Sinko6e.

References

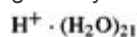
1. J. N. Brønsted, *Rec. Trav. Chim.* **42**, 718, 1923; *Chem. Rev.* **5**, 231, 1928; T. M. Lowry, *J. Chem. Soc.* **123**, 848, 1923.
2. A. W. Castleman Jr, *J. Chem. Phys.* **94**, 3268, 1991; *Chem. Eng. News* **69**, 47, 1991.

3. W. F. Luder and S. Zuffanti, *Electronic Theory of Acids and Bases*, Wiley, New York, 1947; G. N. Lewis, *Valency and the Structure of Atoms and Molecules*, Reinhold, New York, 1923.
4. R. P. Bell, *Acids and Bases*, Methuen, London, 1952, Chapter 7.
5. S. P. L. Sørensen, *Biochem. Z.* **21**, 201, 1909.
6. S. F. Kramer and G. L. Flynn, *J. Pharm. Sci.* **61**, 1896, 1972.
7. P. A. Schwartz, C. T. Rhodes and J. W. Cooper Jr, *J. Pharm. Sci.* **66**, 994, 1977.
8. J. Blanchard, J. O. Boyle and S. Van Wagenen, *J. Pharm. Sci.* **77**, 548, 1988.
9. T. S. Lee and L. Gunnar Sillen, *Chemical Equilibrium in Analytical Chemistry*, Interscience, New York, 1959; J. N. Butler, *Solubility and pH Calculations*, Addison–Wesley, Reading, Mass., 1964; A. J. Bard, *Chemical Equilibrium*, Harper & Row, New York, 1966.
10. P. B. Marshall, *Br. J. Pharmacol.* **10**, 270, 1955.
11. P. Bell and R. O. Roblin, *J. Am. Chem. Soc.* **64**, 2905, 1942.
12. I. M. Klotz, *J. Am. Chem. Soc.* **66**, 459, 1944.
13. W. E. Hamlin and W. I. Higuchi, *J. Pharm. Sci.* **55**, 205, 1966.
14. M. C. Meyer and D. E. Guttman, *J. Pharm. Sci.* **57**, 245, 1968.
15. B. B. Brodie, in T. B. Binns (Ed.), *Absorption and Distribution of Drugs*, Williams & Wilkins, Baltimore, 1964, pp. 16–48.
16. J. T. Edsall and J. Wyman, *Biophysical Chemistry*, Vol. 1, Academic Press, New York, 1958, p. 442.
17. J. T. Edsall and J. Wyman, *Biophysical Chemistry*, Vol. 1, Academic Press, New York, 1958, p. 443.

Recommended Reading

J. N. Butler, *Ionic Equilibrium: Solubility and pH Calculations*, Wiley Interscience, Hoboken, NJ, 1998.

*Reports have appeared in the literature² describing the discovery of a polymer of the hydrogen ion consisting of 21 molecules of water surrounding one hydrogen ion, namely,



*Under laboratory conditions, distilled water in equilibrium with air contains about 0.03% by volume of CO₂, corresponding to a hydrogen ion concentration of about 2×10^{-6} (pH [congruent] 5.7).

*To adopt a definite and consistent method of making approximations throughout this chapter, the expression “much greater than” means that the larger term is at least 20 times greater than the smaller term.

*Except that, in this and all subsequent developments for pH equations, it is assumed that concentration may be used in place of activity.

Chapter Legacy

Fifth Edition: published as Chapter 7 (Ionic Equilibria). Updated by Patrick Sinko.

Sixth Edition: published as Chapter 7 (Ionic Equilibria). Updated by Patrick Sinko.