7

Ionic Equilibria

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MODERN THEORIES OF ACIDS, BASES, AND SALTS

As pointed out in the previous chapter, 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, Brönsted in Copenhagen and Lowry in London independently proposed parallel theories in 1923.[1] The *Brönsted–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.

Brönsted–Lowry Theory. According to the Brönsted–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 since 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 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.

Solvents may 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 *protogenic* 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 Brönsted–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. Since 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.

$$\underset{\text{Acid}_1}{\text{HCl}} + \underset{\text{Base}_2}{H_2O} \rightarrow \underset{\text{Acid}_2}{H_3O^+} + \underset{\text{Base}_1}{Cl^-} \qquad (7\text{–}1)$$

Acid$_1$ and base$_1$ stand for an *acid–base pair* or *conjugate pair,* as do acid$_2$ and base$_2$. Since the bare proton, H^+, is practically nonexistent in aqueous solution, what is normally referred to as the hydrogen ion consists of the hydrated proton, H_3O^+, known as the *hydronium ion.* Higher solvated forms may also exist in solution.* In an ethanolic solution, the "hydrogen ion" is the proton attached to a molecule of solvent, represented as $C_2H_5OH_2^+$. In equation (7–1), hydrogen chloride, the acid, has donated a proton to water, the base, to form the corresponding acid, H_3O^+, and the base, Cl^-.

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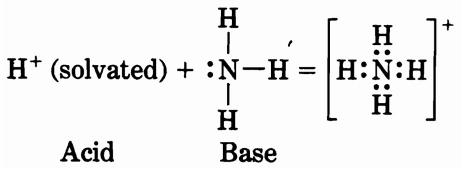
*Reports have appeared in the literature[2] describing the discovery of a polymer of the hydrogen ion consisting of 21 molecules of water surrounding one hydrogen ion, namely

$$H^+ \cdot (H_2O)_{21}$$

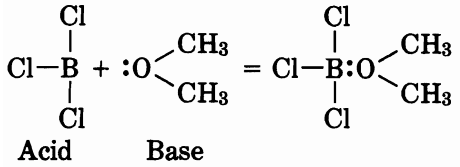
The reaction of HCl with water is one of ionization. Neutralization and hydrolysis are also considered as acid–base reactions or protolysis following the broad definitions of the Brönsted–Lowry concept. Several examples illustrate these types of reactions, as shown in Table 7–1. The displacement reaction,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

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 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 follow:



$$\mathrm{H^+\ (solvated)} + :\overset{\displaystyle H}{\underset{\displaystyle H}{N}}-H = \left[H:\overset{\displaystyle H}{\underset{\displaystyle H}{\ddot{N}}}:H\right]^+ \qquad (7\text{–}2)$$



$$Cl-\overset{\displaystyle Cl}{\underset{\displaystyle Cl}{B}} + :O\genfrac{}{}{0pt}{}{CH_3}{CH_3} = Cl-\overset{\displaystyle Cl}{\underset{\displaystyle Cl}{B}}:O\genfrac{}{}{0pt}{}{CH_3}{CH_3} \qquad (7\text{–}3)$$

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 Brönsted–Lowry nomenclature is particularly useful for describing ionic equilibria and is used extensively in this chapter.

TABLE 7–1. ***Examples of Acid–Base Reactions***

	Acid_1		Base_2		Acid_2		Base_1
Neutralization	NH_4^+	+	OH^-	=	H_2O	+	NH_3
Neutralization	H_3O^+	+	OH^-	=	H_2O	+	H_2O
Neutralization	HCl	+	NH_3	=	NH_4^+	+	Cl^-
Hydrolysis	H_2O	+	CH_3COO^-	=	CH_3COOH	+	OH^-
Hydrolysis	NH_4^+	+	H_2O	=	H_3O^+	+	NH_3
Displacement	HCl	+	CH_3COO^-	=	CH_3COOH	+	Cl^-

ACID–BASE EQUILIBRIA

Equilibrium may be defined as a balance between two opposing forces or actions. This statement does not imply cesssation 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 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, chemical equilibria, is concerned with truly reversible systems and includes reactions such as the ionization of weak electrolytes.

The ionization or protolysis of a weak electrolyte, acetic acid, in water may be written in the Brönsted–Lowry manner as

$$\underset{\text{Acid}_1}{HAc} + \underset{\text{Base}_2}{H_2O} \rightleftharpoons \underset{\text{Acid}_2}{H_3O^+} + \underset{\text{Base}_1}{Ac^-} \qquad (7\text{–}4)$$

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 proportion to the concentration of the reactants:

$$R_f = k_1 \times [\mathrm{HAc}]^1 \times [\mathrm{H_2O}]^1 \qquad (7\text{–}5)$$

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

$$R_r = k_2 \times [\mathrm{H_3O^+}]^1 \times [\mathrm{Ac^-}]^1 \qquad (7\text{–}6)$$

expresses the rate R_r of reformation of un-ionized acetic acid. Since only one mole of each constituent appears in the 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

$$R_f = R_r \qquad (7\text{–}7)$$

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

$$k_1 \times [\mathrm{HAc}] \times [\mathrm{H_2O}] = k_2 \times [\mathrm{H_3O^+}] \times [\mathrm{Ac^-}] \qquad (7\text{–}8)$$

and solving for the ratio, k_1/k_1, one obtains

$$k = \frac{k_1}{k_2} = \frac{[\mathrm{H_3O^+}][\mathrm{Ac^-}]}{[\mathrm{HAc}][\mathrm{H_2O}]} \qquad (7\text{–}9)$$

In dilute solutions of acetic acid, water is in sufficient excess to be regarded as constant at about 55.3 moles per liter (1 liter H_2O at 25° C weights 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.

$$K_a = 55.3\,k = \frac{[\mathrm{H_3O^+}][\mathrm{Ac^-}]}{[\mathrm{HAc}]} \qquad (7\text{–}10)$$

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 Brönsted–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, may be expressed by the following:

$$\mathrm{HB} + \mathrm{H_2O} \rightleftharpoons \mathrm{H_3O^+} + \mathrm{B^-} \qquad (7\text{–}11)$$

$$K_a = \frac{[\mathrm{H_3O^+}][\mathrm{B^-}]}{[\mathrm{HB}]} \qquad (7\text{–}12)$$

Equation (7–10) may 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 $[H_3O^+]$. The latter quantity is also equal to $[Ac^-]$ since both ions are formed in equimolar concentration. The concentration of acetic acid remaining at equilibrium [HAc] can be expressed as $c - x$. The reaction, equation (7–4), is

$$\begin{array}{ccccccc} \mathrm{HAc} & + & \mathrm{H_2O} & \rightleftharpoons & \mathrm{H_3O^+} & + & \mathrm{Ac^-} \\ (c-x) & & & & x & & x \end{array} \qquad (7\text{–}13)$$

and the equilibrium expression (7–10) becomes

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

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

$$K_a \cong \frac{x^2}{c} \qquad (7\text{–}15)$$

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

$$x^2 = K_a c$$

$$x = [\mathrm{H_3O^+}] = \sqrt{K_a c} \qquad (7\text{–}16)$$

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} gram 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 per liter and less frequently as molality. A solution containing 1.0078 g of hydrogen ions in a liter represents 1 gram 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 per liter, then at equilibrium the undissociated acid would equal $0.1 - x$, since x is the amount of acid that has dissociated. The calculations according to equation (7–12) are:

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

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

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

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

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 to say, the dissociation of acetic acid into its ions is small, and acetic acid may be considered as a weak electrolyte.

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

$$\mathrm{NH_4^+Cl^-} \xrightarrow{\mathrm{H_2O}} \mathrm{NH_4^+} + \mathrm{Cl^-} \qquad (7\text{–}17)$$

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 Brönsted–Lowry system, NH_4^+ is considered to be a cationic acid that can form its conjugate base, NH_3, by donating a proton to water as follows:

$$\mathrm{NH_4^+} + \mathrm{H_2O} \rightleftharpoons \mathrm{H_3O^+} + \mathrm{NH_3} \qquad (7\text{–}18)$$

$$K_a = \frac{[\mathrm{H_3O^+}][\mathrm{NH_3}]}{[\mathrm{NH_4^+}]} \qquad (7\text{–}19)$$

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

$$\mathrm{BH^+} + \mathrm{H_2O} \rightleftharpoons \mathrm{H_3O^+} + \mathrm{B} \qquad (7\text{–}20)$$

and the acidity constant is

$$K_a = \frac{[\mathrm{H_3O^+}][\mathrm{B}]}{[\mathrm{BH^+}]} \qquad (7\text{–}21)$$

Ionization of Weak Bases. Nonionized weak bases, B, exemplified by NH_3, react with water as follows:

$$\mathrm{B} + \mathrm{H_2O} \rightleftharpoons \mathrm{OH^-} + \mathrm{BH^+} \qquad (7\text{–}22)$$

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

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

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

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?

$$[OH^-] = \sqrt{7.4 \times 10^{-7} \times 5.0 \times 10^{-4}}$$
$$[OH^-] = \sqrt{37.0 \times 10^{-11}} = \sqrt{3.7 \times 10^{-10}}$$
$$x = [OH^-] = 1.92 \times 10^{-5} \text{ moles/liter}$$

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

$$Na^+CH_3COO^- \xrightarrow{H_2O} Na^+ + CH_3COO^- \qquad (7-25)$$

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

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

$$K_b = \frac{[OH^-][CH_3COOH]}{[CH_3COO^-]} \qquad (7-26)$$

In general, for an anionic base, B^-

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

$$K_b = \frac{[OH^-][HB]}{[B^-]} \qquad (7-27)$$

The acidity and basicity constants for a number of pharmaceutically important acids and bases are listed in Tables 7-2 and 7-3. The last column gives the *dissociation exponent* or p*K* value, which is discussed on pages 152 and 162.

The Ionization of Water. The concentration of hydrogen or hydroxyl ions in solutions of acids or bases may be expressed as gram ions per liter or as moles per liter. A solution containing 17.008 g of hydroxyl ions or 1.008 g of hydrogen ions per liter is said to contain 1 gram 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 concentration 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 may be thought of as a weak electrolytic solute that reacts with another molecule of water as the solvent. This *autoprotolytic* reaction is represented as

$$H_2O + H_2O \rightleftharpoons H_3O^+ + OH^- \qquad (7-28)$$

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

$$\frac{[H_3O^+][OH^-]}{[H_2O]^2} = k \qquad (7-29)$$

The term for molecular water in the denominator is squared since 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, $[H_2O]^2$ 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:

$$K_w = k \times [H_2O]^2 \qquad (7-30)$$

The value of the ion product is approximately 1×10^{-14} at 25° C; it depends strongly upon temperature, as shown in Table 7-4. 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.

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

$$[H_3O^+] \times [OH^-] = K_w \cong 1 \times 10^{-14} \text{ at } 25^\circ\text{ C} \qquad (7-31)$$

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

$$[H_3O^+] = [OH^-] \cong \sqrt{1 \times 10^{-14}} \qquad (7-32)$$
$$\cong 1 \times 10^{-7}$$

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. 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} moles per liter. What is the new hydroxyl ion concentration?

From equation (7-31),

$$[OH^-] = \frac{1 \times 10^{-14}}{1.5 \times 10^{-3}}$$
$$= 6.7 \times 10^{-12} \text{ moles/liter}$$

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

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[*] Under laboratory conditions, distilled water in equilibrium with air contains about 0.03% by volume of CO_2, corresponding to a hydrogen ion concentration of about 2×10^{-6} (pH ≅ 5.7).

TABLE 7–2. ***Ionization or Acidity Constants for Weak Acids at 25° C***

Weak Acids	MW	K_a	pK_a
Acetaminophen	151.16	1.20×10^{-10}	9.92
Acetic	60.05	1.75×10^{-5}	4.76
Acetylsalicylic	180.15	3.27×10^{-4}	3.49
p-Aminobenzoic acid	137.13	$K_1\ 2.24 \times 10^{-5}$	4.65
		$K_2\ 1.58 \times 10^{-5}$	4.80
Amobarbital	226.27	1.15×10^{-8}	7.94
Ascorbic	176.12	$K_1\ 5.0 \times 10^{-5}$	4.3
		$K_2\ 1.6 \times 10^{-12}$	11.8
Barbital	184.19	1.23×10^{-8}	7.91
Barbituric	128.09	1.05×10^{-4}	3.98
Benzoic	122.12	6.30×10^{-5}	4.20
Benzyl penicillin	334.38	1.74×10^{-3}	2.76
Boric	61.84	$K_1\ 5.8 \times 10^{-10}$	9.24
Butylparaben	194.22	4.0×10^{-9}	8.4
Caffeine	194.19	1×10^{-14}	14.0
Carbonic	44.01	$K_1\ 4.31 \times 10^{-7}$	6.37
		$K_2\ 4.7 \times 10^{-11}$	10.33
Citric (1 H_2O)	210.14	$K_1\ 7.0 \times 10^{-4}$	3.15
		$K_2\ 1.66 \times 10^{-5}$	4.78
		$K_3\ 4.0 \times 10^{-7}$	6.40
Dichloroacetic	128.95	5×10^{-2}	1.3
Formic	48.02	1.77×10^{-4}	3.75
Fumaric	116.07	$K_1\ 9.3 \times 10^{-4}$	3.03
		$K_2\ 4.2 \times 10^{-5}$	4.38
Gallic	170.1	4×10^{-5}	4.4
α-D-Glucose	180.16	8.6×10^{-13}	12.1
Glycerophosphoric	172.08	$K_1\ 3.4 \times 10^{-2}$	1.47
		$K_2\ 6.4 \times 10^{-7}$	6.19
Glycine (protonated cation)	75.07	$K_1\ 4.5 \times 10^{-3}$	2.35
		$K_2\ 1.7 \times 10^{-10}$	9.78
Hydroquinone	110.11	1.1×10^{-10} (18°)	9.96
Lactic	90.08	1.39×10^{-4}	3.86
Maleic	116.07	$K_1\ 1.0 \times 10^{-2}$	2.00
		$K_2\ 5.5 \times 10^{-7}$	6.26
Malic	134.09	$K_1\ 4 \times 10^{-4}$	3.4
		$K_3\ 9 \times 10^{-6}$	5.1
Malonic	104.06	$K_1\ 1.40 \times 10^{-3}$	2.85
		$K_2\ 2.0 \times 10^{-6}$	5.70
Mandelic	152.14	4.29×10^{-4}	3.37
Methylparaben	152.14	4.0×10^{-9}	8.4
Monochloroacetic	94.50	1.40×10^{-3}	2.86
Oxalic (2 H_2O)	126.07	$K_1\ 5.5 \times 10^{-2}$	1.26
		$K_2\ 5.3 \times 10^{-5}$	4.28
Penicillin V	350.38	1.86×10^{-3}	2.73
Pentobarbital	226.28	1.0×10^{-8}	8.0
Phenobarbital	232.23	3.9×10^{-8}	7.41
Phenol	95.12	1×10^{-10}	10.0
Phenytoin (Dilantin)	252.26	7.9×10^{-9}	8.1
Phosphoric	98.00	$K_1\ 7.5 \times 10^{-3}$	2.12
		$K_2\ 6.2 \times 10^{-8}$	7.21
		$K_3\ 2.1 \times 10^{-13}$	12.67
Picric	229.11	4.2×10^{-1}	0.38
Propionic	74.08	1.34×10^{-5}	4.87
Propylparaben	180.20	4.0×10^{-9}	8.4
Saccharin	183.18	2.1×10^{-12}	11.7
Salicylic	138.12	1.06×10^{-3}	2.97
Succinic	118.09	$K_1\ 6.4 \times 10^{-5}$	4.19
		$K_2\ 2.3 \times 10^{-6}$	5.63
Sucrose	342.30	2.4×10^{-13} (19° C)	12.62
Sulfacetamide	214.24	1.35×10^{-6}	5.87
Sulfadiazine	250.28	3.3×10^{-7}	6.48
Sulfamerazine	264.30	8.7×10^{-8}	7.06
Sulfapyridine	249.29	3.6×10^{-9}	8.44
Sulfathiazole	255.32	7.6×10^{-8}	7.12
Sulfisomidine	278.34	3.4×10^{-8}	7.47
Sulfisoxazole	267.30	1.0×10^{-5}	5.0
Tartaric	150.09	$K_1\ 9.6 \times 10^{-4}$	3.02
		$K_2\ 4.4 \times 10^{-5}$	4.36
Tetracycline	444.43	$K_1\ 5.01 \times 10^{-4}$	3.30
		$K_2\ 2.09 \times 10^{-8}$	7.68
		$K_3\ 2.04 \times 10^{-10}$	9.69
Trichloroacetic	163.40	1.3×10^{-1}	0.89
Valeric	102.13	1.56×10^{-5}	4.81

TABLE 7–3. *Ionization or Basicity Constants for Weak Bases at 25° C**

Weak Bases	MW	K_b	pK_b	pK_a (conjugate acid)
Acetanilide	135.16	4.1×10^{-14} (40°)	13.39	0.61
Ammonia	35.05	1.74×10^{-5}	4.76	9.24
Apomorphine	267.31	1.0×10^{-7}	7.00	7.00
Atropine	289.4	4.5×10^{-5}	4.35	9.65
Benzocaine	165.19	6.0×10^{-12}	11.22	2.78
Caffeine	194.19	K_1 3.98×10^{-11}	10.4	3.6
		K_2 4.07×10^{-14}	13.4	0.6
Cocaine	303.35	2.6×10^{-6}	5.59	8.41
Codeine	299.36	1.6×10^{-6}	5.8	8.2
Ephedrine	165.23	2.3×10^{-5}	4.64	9.36
Epinephrine	183.20	K_1 7.9×10^{-5}	4.1	9.9
		K_2 3.2×10^{-6}	5.5	8.5
Erythromycin	733.92	6.3×10^{-6}	5.2	8.8
Ethylenediamine	60.10	7.1×10^{-8}	7.15	6.85
Glycine	75.07	2.3×10^{-12}	11.65	2.35
Hydroquinone	110.11	4.7×10^{-6}	5.33	8.67
Morphine	285.33	7.4×10^{-7}	6.13	7.87
Nalorphine	311.37	6.3×10^{-7}	6.2	7.8
Papaverine	339.39	8×10^{-9}	8.1	5.9
Physostigmine	275.34	K_1 7.6×10^{-7}	6.12	7.88
		K_2 5.7×10^{-13}	12.24	1.76
Pilocarpine	208.25	K_1 7×10^{-8}	7.2	6.8
		K_2 2×10^{-13}	12.7	1.3
Procaine	236.30	7×10^{-6}	5.2	8.8
Pyridine	79.10	1.4×10^{-9}	8.85	5.15
Quinacrine (dihydrochloride)	472.88	1.0×10^{-6}	6.0	8.0
Quinine	324.41	K_1 1.0×10^{-6}	6.00	8.00
		K_2 1.3×10^{-10}	9.89	4.11
Reserpine	608	4×10^{-8}	7.4	6.6
Scopolamine	303.35	1.6×10^{-6}	5.8	8.2
Strychnine	334.40	K_1 1×10^{-6}	6.0	8.0
		K_2 2×10^{-12}	11.7	2.3
Theobromine	180.17	K_1 7.76×10^{-7}	6.11	7.89
		K_2 4.8×10^{-14}	13.3	0.7
Theophylline	180.17	K_1 1.58×10^{-9}	8.80	5.20
		K_2 5.0×10^{-14}	13.3	0.7
Thiourea	76.12	1.25×10^{-12}	11.90	2.1
Tolbutamide	270.34	2.0×10^{-9}	8.7	5.3
Urea	60.06	1.5×10^{-14}	13.82	0.18

*Additional pKs for acids and bases of pharmaceutical interest are found in R. F. Doerge, Ed., *Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry*, 8th Ed., Lippincott, Philadelphia, 1982, pp. 841–847; D. W. Newton and R. B. Kluza. Drug Intel. Clin. Pharm. **12**, 546, 1978.

TABLE 7–4. *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 Harned and Robinson, Trans. Far. Soc. **36**, 973, 1940, and other sources.

BH^+ and B, when the solvent is amphiprotic. This can be obtained by multiplying equation (7–12) by equation (7–27):

$$K_aK_b = \frac{[H_3O^+][B^-]}{[HB]} \cdot \frac{[OH^-][HB]}{[B^-]} \tag{7-33}$$

$$= [H_3O^+][OH^-] = K_w$$

and

$$K_b = \frac{K_w}{K_a} \tag{7-34}$$

or

$$K_a = \frac{K_w}{K_b} \tag{7-35}$$

Example 7–4. Ammonia has a K_b of 1.74×10^{-5} at 25° C. Calculate K_a for its conjugate acid, NH_4^+.

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

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

$$H_3PO_4 + H_2O = H_3O^+ + H_2PO_4^- \qquad (7\text{–}36)$$

$$\frac{[H_3O^+][H_2PO_4^-]}{[H_3PO_4]} = K_1 = 7.5 \times 10^{-3} \qquad (7\text{–}37)$$

$$H_2PO_4^- + H_2O = H_3O^+ + HPO_4^{2-}$$

$$\frac{[H_3O^+][HPO_4^{2-}]}{[H_2PO_4^-]} = K_2 = 6.2 \times 10^{-8} \qquad (7\text{–}38)$$

$$HPO_4^{2-} + H_2O = H_3O^+ + PO_4^{3-}$$

$$\frac{[H_3O^+][PO_4^{3-}]}{[HPO_4^{2-}]} = K_3 = 2.1 \times 10^{-13} \qquad (7\text{–}39)$$

In any polyprotic electrolyte, the primary protolysis is greatest, and suceeding 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.

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

$$PO_4^{3-} + H_2O \rightleftharpoons HPO_4^{2-} + OH^- \qquad (7\text{–}40)$$

$$K_{b1} = \frac{[HPO_4^{2-}][OH^-]}{[PO_4^{3-}]} = 4.8 \times 10^{-2} \qquad (7\text{–}41)$$

$$HPO_4^{2-} + H_2O \rightleftharpoons H_2PO_4^- + OH^- \qquad (7\text{–}42)$$

$$K_{b2} = \frac{[H_2PO_4^-][OH^-]}{[HPO_4^{2-}]} = 1.6 \times 10^{-7} \qquad (7\text{–}43)$$

$$H_2PO_4^- + H_2O \rightleftharpoons H_3PO_4 + OH^- \qquad (7\text{–}44)$$

$$K_{b3} = \frac{[H_3PO_4][OH^-]}{[H_2PO_4^-]} = 1.3 \times 10^{-12} \qquad (7\text{–}45)$$

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

$$H_nA + H_{n-j}A^{-j} + \cdots + HA^{-(n-1)} + A^{n-} \qquad (7\text{–}46)$$

in which 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

$$[H_nA] + [H_{n-j}A^{-j}] + \cdots$$
$$+ [HA^{-(n-1)}] + [A^{n-}] = C_a \qquad (7\text{–}47)$$

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

$$K_jK_{b(n+1-j)} = K_w \qquad (7\text{–}48)$$

in which K_j represents the various acidity constants for the system. Thus, for the phosphoric acid system described by equations (7–37) to (7–45):

$$K_1K_{b3} = K_2K_{b2} = K_3K_{b1} = K_w \qquad (7\text{–}45)$$

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 acids or bases. 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 amphoteric.

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

$$^+NH_3CH_2COOH + H_2O \rightleftharpoons$$
$$^+NH_3CH_2COO^- + H_3O^+ \qquad (7\text{–}50)$$

$$^+NH_3CH_2COO^- + H_2O \rightleftharpoons$$
$$NH_2CH_2COO^- + H_3O^+ \qquad (7\text{–}51)$$

The species $^+NH_3CH_2COO^-$ is amphoteric 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:

$$^+NH_3CH_2COO^- + H_2O \rightleftharpoons$$
$$^+NH_3CH_2COOH + OH^- \qquad (7\text{–}52)$$

The amphoteric species $^+NH_3CH_2COO^-$ 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.

SÖRENSEN'S pH SCALE

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 unwieldly. To alleviate this difficulty, Sörensen[5] 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 logarithm of the reciprocal of the hydrogen ion concentration:

$$pH = \log \frac{1}{[H_3O^+]} \qquad (7-53)$$

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

$$pH = \log 1 - \log [H_3O^+] \qquad (7-54)$$

and since the logarithm of 1 is zero,

$$pH = -\log [H_3O^+] \qquad (7-55)$$

equations (7–53) and (7–55) are identical; they are acceptable for approximate calculations involving pH.

The pH of a solution may 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 to 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 (cf. Table 7–4). The scale relating pH to the hydrogen and hydroxyl ion concentration of a solution is given in Table 7–5, and the pH of a number of pharmaceutical vehicles and solutions frequently used as vehicles are found in Table 7–6.

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

Example 7–5. The hydronium ion concentration of a 0.05-*M* solution of HCl is 0.05 *M*. What is the pH of this solution?

$$pH = -\log (5.0 \times 10^{-2}) = -\log 10^{-2} - \log 5.0$$
$$= 2 - 0.70 = 1.30$$

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

TABLE 7–5. *The pH Scale and Corresponding Hydrogen and Hydroxyl Ion Concentrations*

pH	$[H^3O^+]$ (moles/liter)	$[OH^-]$ (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}	$10^0 = 1$	↓

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

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

and since the activity of an ion is equal to the activity coefficient multiplied by the molal or molar concentration (equation (7–41),

hydronium ion concentration × activity coefficient

= hydronium ion activity

the pH may be computed more accurately from the formula

$$pH = -\log (\gamma_\pm \times c) \qquad (7-57)$$

Example 7–6. 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?

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

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?

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

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

Example 7–6 dealt with the pH of a strong acid. For a weak electrolyte (*Example 7–7*), pH is calculated in the same manner from the hydrogen ion concentration.

Example 7–7. 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?

$$pH = -\log (3.24 \times 10^{-3})$$
$$pH = 3 - \log 3.24 = 2.49$$

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

Conversion of pH to Hydrogen Ion Concentration. The following example illustrates the method of converting pH to $[H_3O^+]$.

Example 7–8. If the pH of a solution is 4.72, what is the hydronium ion concentration?

$$pH = -\log [H_3O^+] = 4.72$$
$$\log [H_3O^+] = -4.72 = -5 + 0.28$$
$$[H_3O^+] = \text{antilog } 0.28 \times \text{antilog } (-5)$$
$$[H_3O^+] = 1.91 \times 10^{-5} \text{ moles/liter}$$

The use of a hand calculator bypasses this two-step procedure. One simply enters −4.72 into the calculator and presses the key for antilog or 10^x in order to obtain $[H_3O^+]$.

***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

TABLE 7–6. ***Approximate pH Numbers of Some Pharmaceutical Specialties and Vehicles****

Product	pH	Manufacturer
Acacia syrup	5.0	
Acromycin-V syrup	4.0–5.0	Lederle
Actifed syrup	5.0–7.2	Burroughs Wellcome
Ambenyl	5.5–6.0	Marion
Anspor for oral suspension	3.5–6.0	SmithKline Beecham
Antepar syrup	5.7–6.3	Burroughs Wellcome
Aromatic Eriodictyon syrup	7.0–8.0	
Artane	2.0–3.0	Lederle
Aventyl liquid	2.5–4.0	Lilly
Bactrium suspension	5.0–6.0	Roche
Benadryl elixir	7.0	Parke–Davis
Bentyl HCl	5.0–5.5	Merrell–National
Benzaldehyde compound elixir	6.0	
Bromides syrup	4.5	
Butisol sodium elixir	9.7	Wallace Laboratories
Calcidrin syrup	4.0–5.0	Abbott
Catnip and fennel elixir	8.0	
Cerose	5.0–5.2	Ives
Cerose-DM	5.0–5.2	Ives
Cetro-Cirose	5.3	Ives
Cheracol	4.0	Upjohn
Cherry syrup	3.5–4.0	
Chlor-Trimeton maleate syrup	4.4–5.6	Schering
Cibalith-S	4.0–5.0	Ciba
Compound cardamom elixir	7.5	
Comtrex Cough Formula	4.5–5.5	Bristol–Meyers
Comtrex Multi-Symptom Liquid	4.3	Bristol–Meyers
Contac Cough and Congestion Formula	4.3	SmithKline Beecham
Contac Cough, Chest Congestion and Sore Throat Formula	4.5	SmithKline Beecham
Contac Jr. Nondrowsy Cold Liquid	4.5	SmithKline Beecham
Contac Nighttime Cold Medicine	5.6	SmithKline Beecham
Cosanyl	3.0	Health Care Industries
Darvon-N suspension	4.0–6.0	Lilly
Decadron elixir	3.0–3.4	Merck Sharp & Dohme
Demazin syrup	4.5–6.0	Schering
Dimetapp elixir	2.2–3.2	Robins
Diuril oral suspension	3.5–4.0	Merck Sharp & Dohme
Donnagel suspension	4.0–5.5	Robins
Donnatal elixir	4.0–5.5	Robins
Elixir Alurate Verdum	2.5	Hoffmann–La Roche
Excedrin PM liquid	4.6	Bristol–Myers
Feosol elixir	2.0–2.4	SmithKline Beecham
Gantanol suspension	4.7–5.0	Roche
Gantrisin syrup	4.5–5.0	Roche
Glycyrrhiza syrup	6.0–6.5	
Haldol	2.8–3.8	McNeil
Homicebrin	3.5–4.0	Lilly
Hydriodic acid syrup	1.0	Lilly
Ilosone suspension	4.5–6.0	Lilly
Iso-alcoholic elixir	5.0	
Kaopectate	4.2	Upjohn
Lanoxin pediatric elixir	6.8–7.2	Burroughs Wellcome
Lipo Gantrisin	4.3–4.8	Roche
Lipomul oral	5.0	Upjohn
Mestinon syrup	4.2–4.8	Roche
Naldecon adult syrup	4.0–5.0	Bristol Laboratories
Naldecon CX solution	4.5–5.5	Bristol Laboratories
Naldecon DX adult liquid	4.5–5.5	Bristol Laboratories
Naldecon DX pediatric drops	3.7–4.7	Bristol Laboratories
Naldecon DX pediatric syrup	2.7–3.7	Bristol Laboratories
Naldecon EX pediatric Drops	3.5–4.5	Bristol Laboratories
Naldecon EX pediatric syrup	3.0–4.0	Bristol Laboratories
Naldecon pediatric drops	4.0–5.0	Bristol Laboratories
Naldecon pediatric syrup	4.0–5.0	Bristol Laboratories
Naldecon senior DX syrup	4.5–5.5	Bristol Laboratories
Neldecon senior EX syrup	4.5–5.5	Bristol Laboratories
Naprosyn (naproxin) suspension	2.2–3.7	Syntex
Nasalide (flunisolidate) nasal solution	4.5–6.0	Syntex
Nembutal elixir	3.2–4.0	Abbott
Noctec	4.8–5.2	Squibb
Novafed liquid	2.5–4.5	Dow
Novahistine DH	2.5–4.0	Dow
Novahistine elixir	2.5–4.0	Dow
Novahistine expectorant	2.5–4.0	Dow
Orange syrup	2.5–3.0	
Orthoxicol	2.5–3.0	Upjohn
Pepsin, lactated	4.0–5.0	
Periactin syrup	3.5–4.5	Merck Sharp & Dohme

TABLE 7–6. ***(continued)***

Phenobarbital elixir	6.0	
Prolixin elixir	5.3–5.8	Squibb
Pyribenzamine elixir	4.5	Ciba
Raspberry syrup	3.0	
Robitussin	2.3–3.0	Robins
Romilar CF	4.9	Block
Roniacol elixir	4.0–5.0	Roche
Sarsaparilla, compound syrup	5.0	
Stelazine concentrate	2.2–3.2	SmithKline Beecham
Sudafed syrup	2.5–3.5	Burroughs Wellcome
Sudafed Plus syrup	2.5–4.0	Burroughs Wellcome
Sumycin syrup	3.5–6.0	Squibb
Suptra suspension	5.0–6.0	Burroughs Wellcome
Surbex	3.7–3.9	Abbott
Synarel (nafarelin acetate) nasal solution	5.2±0.5	Syntex
Syrup	6.5–7.0	
Tagamet liquid	5.0–6.5	SmithKline Beecham
Taka-Diastase	6.0	Parke–Davis
Taractan concentrate	3.5–4.5	Roche
Tegretol suspension	3.0–5.0	Geigy
Terpin hydrate elixir	6.0	
Terpin hydrate elixir and codeine	8.0	
Theragran liquid	4.7–5.2	Squibb
Thiamine HCl elixir	4.0–5.0	
Thorazine concentrate, 30 mg	3.0–4.0	SmithKline Beecham
Thorazine concentrate, 100 mg	2.4–3.4	SmithKline Beecham
Thorazine syrup	4.0–5.0	SmithKline Beecham
Toradol IM (ketorolac tromethamine) injection	7.4±0.5	Syntex
Tuss-Ornade liquid	4.0–4.4	SmithKline Beecham
Tussend expectorant	2.5–4.5	Dow
Tussend liquid	2.0–4.0	Dow
Tylenol with codeine elixir	4.0–6.1	McNeil
Valadol liquid	3.8–6.1	Squibb
Vitamin B complex elixir	4.0–5.0	
White Pine compound syrup	6.5	
Wild Cherry syrup	4.5	

*Results are correct to about ±0.3 pH unit. Some of the products are suspensions, whereas others contain nonaqueous vehicles. The pH values in the table therefore are not necessarily the same as those obtained in aqueous systems and are accordingly called pH numbers (p. 201). These pH ranges are used by the pharmaceutical manufacturers as quality control specifications and are kindly supplied by the companies.

unity in "p" notation has become a standard procedure. The mathematician would say that "p" is a *mathematical operator* that acts on the quantity, $[H^+]$, K_a, K_b, K_w, etc., 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 $-\log [OH^-]$, pK_a is used for $-\log K_a$, and pK_w is $-\log K_w$. Thus, equations (7–31) and (7–33) can be expressed as

$$pH + pOH = pK_w \qquad (7\text{–}58)$$

$$pK_a + pK_b = pK_w \qquad (7\text{–}59)$$

in which pK is often called the *dissociation exponent.*

The pK of weak acidic and basic drugs are ordinarily determined by ultraviolet spectrophotometry (p. 81) and potentiometric titration (p. 204). They may also be obtained by solubility analysis[6–8] (p. 233) and by a partition coefficient method.[8]

SPECIES CONCENTRATION AS A FUNCTION OF pH

As was 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).

$$\alpha_0 = [H_nA]/C_a \qquad (7\text{–}60a)$$

$$\alpha_1 = [H_{n-1}A^{-1}]/C_a \qquad (7\text{–}60b)$$

and in general.

$$\alpha_j = [H_{n-j}A^{-j}]/C_a \qquad (7\text{–}61a)$$

and

$$\alpha_n = [A^{-n}]/C_a \qquad (7\text{–}61b)$$

in which j represents the number of protons that have ionized from the parent acid. Thus, dividing equation (7–47) by C_a and using equations (7–60a) to (7–61b) gives

$$\alpha_0 + \alpha_j + \cdots + \alpha_{n-1} + \alpha_n = 1 \qquad (7\text{–}62)$$

All of the α values can be defined in terms of equilibrium constants, α_0, and H_3O^+ as follows:

$$K_1 = \frac{[H_{n-1}A^-][H_3O^+]}{[H_nA]} = \frac{\alpha_1 C_a[H_3O^+]}{\alpha_0 C_a} \quad (7\text{-}63)$$

therefore

$$\alpha_1 = K_1\alpha_0/[H_3O^+] \quad (7\text{-}64)$$

$$K_2 = \frac{[H_{n-2}A^{2-}][H_3O^+]}{[H_{n-1}A^-]} = \frac{[H_{n-2}A^{2-}][H_3O^+]^2}{K_1[H_nA]}$$

$$= \frac{\alpha_2 C_a[H_3O^+]^2}{\alpha_0 C_a K_1} \quad (7\text{-}65)$$

or

$$\alpha_2 = \frac{K_1K_2\alpha_0}{[H_3O^+]^2} \quad (7\text{-}66)$$

and, in general

$$\alpha_j = (K_1K_2 \ldots K_j)\alpha_0/[H_3O^+]^j \quad (7\text{-}67)$$

Inserting the appropriate forms of equation (7–67) into equation (7–62) gives

$$\alpha_0 + \frac{K_1\alpha_0}{[H_3O^+]} + \frac{K_1K_2\alpha_0}{[H_3O^+]^2} + \cdots + \frac{K_1K_2 \ldots K_n\alpha_0}{[H_3O^+]^n} = 1 \quad (7\text{-}68)$$

Solving for α_0 yields

$$\alpha_0 = [H_3O^+]^n/\{[H_3O^+]^n + K_1[H_3O]^{n-1} + K_1K_2[H_3O^+]^{n-2} + \cdots + K_1K_2 \ldots K_n\} \quad (7\text{-}69)$$

or

$$\alpha_0 = \frac{[H_3O^+]^n}{D} \quad (7\text{-}70)$$

in which D represents the denominator of equation (7–69). Thus, the concentration of H_nA as a function of $[H_3O^+]$ can be obtained by substituting equation (7–60*a*) into equation (7–70) to give

$$[H_nA] = \frac{[H_3O^+]^nC_a}{D} \quad (7\text{-}71)$$

Substituting equation (7–60*b*) into equation (7–64) and the resulting equation into equation (7–70) gives

$$[H_{n-1}A^{-1}] = \frac{K_1[H_3O^+]^{n-1}C_a}{D} \quad (7\text{-}72)$$

In general,

$$[H_{n-j}A^{-j}] = \frac{K_1 \ldots K_j[H_3O^+]^{n-j}C_a}{D} \quad (7\text{-}73)$$

and

$$[A^{-n}] = \frac{K_1K_2 \ldots K_nC_a}{D} \quad (7\text{-}74)$$

Although these equations appear complicated, they are in reality quite simple. The term D in equations (7–70) to (7–74) is a power series in $[H_3O^+]$, each term multiplied by equilibrium constants. The series starts with $[H_3O^+]$ 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 $[H_3O^+]$ for K_n to obtain the next-to-last term, then substituting $[H_3O^+]$ 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 equation (7–70) to (7–74) for various types of polyprotic acids:

$$H_4A{:}\quad D = [H_3O^+]^4 + K_1[H_3O^+]^3 + K_1K_2[H_3O^+]^2 + K_1K_2K_3[H_3O^+] + K_1K_2K_3K_4 \quad (7\text{-}75)$$

$$H_3A{:}\quad D = [H_3O^+]^3 + K_1[H_3O^+]^2 + K_1K_2[H_3O^+] + K_1K_2K_3 \quad (7\text{-}76)$$

$$H_2A{:}\quad D = [H_3O^+]^2 + K_1[H_3O^+] + K_1K_2 \quad (7\text{-}77)$$

$$HA{:}\quad D = [H_3O^+] + K_a \quad (7\text{-}78)$$

In all instances, for a species in which j protons have ionized, the numerator in equations (7–70) to (7–74) is C_a multiplied by the term from the denominator D that has $[H_3O^+]$ raised to the $n - j$ power. Thus, for the parent acid H_2A, the appropriate equation for D would be equation (7–77). The molar concentrations of the species $H_nA(j = 0)$, $HA^-(j = 1)$, and $A^{2-}(j = 2)$ can be given as

$$[H_2A] = \frac{[H_3O^+]^2C_a}{[H_3O^+]^2 + K_1[H_3O^+] + K_1K_2} \quad (7\text{-}79)$$

$$[HA^-] = \frac{K_1[H_3O^+]C_a}{[H_3O^+]^2 + K_1[H_3O^+] + K_1K_2} \quad (7\text{-}80)$$

$$[A^{2-}] = \frac{K_1K_2C_a}{[H_3O^+]^2 + K_1[H_3O^+] + K_1K_2} \quad (7\text{-}81)$$

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 Brönsted–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 should be 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

$$[H_3O^+] = [OH^-] + [Cl^-]$$

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:

(a) Always start with the species added to water.

(b) On the left side of the equation, place all species that can form when protons are consumed by the starting species.

(c) 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 $[H_3O^+]$ to the left side of the equation, and $[OH^-]$ to the right side of the equation. These result from the interaction of two molecules of water, as shown previously.

Example 7–9. 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.

$$[H_3O^+] = [OH^-] + [H_2PO_4^-] + 2[HPO_4^{2-}] + 3[PO_4^{3-}]$$

Example 7–10. What is the PBE when Na_2HPO_4 is added to water?
The salt dissociates into $2Na^+$ and $1\ HPO_4^{2-}$; Na^+ is neglected in the PBE since 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.

$$[H_3O^+] + [H_2PO_4^-] + 2[H_3PO_4] = [OH^-] + [PO_4^{3-}]$$

Example 7–11. 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.

$$[H_3O^+] + [CH_3COOH] = [OH^-]$$

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 $[H_3O^+]$ using equations (7–71) to (7–74).

(c) Solve the resulting expression for $[H_3O^+]$ using any assumptions that appear valid for the system.

(d) Check all assumptions.

(e) If all assumptions prove valid, convert $[H_3O^+]$ to pH.

If the solution contains a base, it is sometimes more convenient to solve the expression obtained in part *(b)* for $[OH^-]$, 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 to ionize 100% when placed in water. When HCl is placed in water, the PBE for the system is given by

$$[H_3O^+] = [OH^-] + [Cl^-] = \frac{K_w}{[H_3O^+]} + C_a \qquad (7\text{–}82a)$$

which can be rearranged to give

$$[H_3O^+]^2 - C_a[H_3O^+] - K_w = 0 \qquad (7\text{–}82b)$$

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

$$aX^2 + bX + c = 0 \qquad (7\text{–}83)$$

which has the solution

$$X = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a} \qquad (7\text{–}84)$$

Thus, equation (7–82*b*) becomes

$$[H_3O^+] = \frac{C_a + \sqrt{C_a^2 + 4K_w}}{2} \qquad (7\text{–}85)$$

in which only the positive root is used, since $[H_3O^+]$ can never be negative.

When the concentration of acid is 1×10^{-6} *M* or greater, $[Cl^-]$ becomes much greater than* $[OH^-]$ in equation (7–82*a*), and C_a^2 becomes much greater than $4K_w$ in equation (7–85). Thus, both equations simplify to

$$[H_3O^+] \cong C_a \qquad (7\text{–}86)$$

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

$$[OH^-] = \frac{C_b + \sqrt{C_b^2 + 4K_w}}{2} \qquad (7\text{–}87)$$

and

$$[OH^-] \cong C_b \qquad (7\text{–}88)$$

if the concentration of base is 1×10^6 molar 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,

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*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.

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

$$HB + H_2O \rightleftharpoons H_3O^+ + B^- \qquad (7\text{–}89)$$

$$B^- + H_2O \rightleftharpoons OH^- + HB \qquad (7\text{–}90)$$

$$H_2O + H_2O \rightleftharpoons H_3O^+ + OH^- \qquad (7\text{–}91)$$

The PBE for this system is

$$[H_3O^+] + [HB] = [OH^-] + [B^-] \qquad (7\text{–}92)$$

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

$$[HB] = \frac{[H_3O^+]C_b}{[H_3O^+] + K_a} \qquad (7\text{–}93)$$

$$[B^-] = \frac{K_aC_a}{[H_3O^+] + K_a} \qquad (7\text{–}94)$$

Equation (7–93) contains C_b (concentration of base added as the salt) rather than C_a, since in terms of the PBE, the species HB was generated from the species B^- added in the form of the salt. Equation (7–94) contains C_a (concentration of HB added), since the species B^- in the PBE came from the HB added. Inserting equations (7–93) and (7–94) into equation (7–92) gives

$$[H_3O^+] + \frac{[H_3O^+]C_b}{[H_3O^+] + K_a} = [OH^-] + \frac{K_aC_a}{[H_3O^+] + K_a} \qquad (7\text{–}95)$$

which can be rearranged to yield

$$[H_3O^+] = K_a\frac{(C_a - [H_3O^+] + [OH^-])}{(C_b + [H_3O^+] - [OH^-])} \qquad (7\text{–}96)$$

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

Solutions Containing Only a Weak Acid. If the solution contains only a weak acid, C_b is zero, and $[H_3O^+]$ is generally much greater than $[OH^-]$. Thus, equation (7–96) simplifies to

$$[H_3O^+]^2 + K_a[H_3O^+] - K_aC_a = 0 \qquad (7\text{–}97)$$

which is a quadratic equation with the solution

$$[H_3O^+] = \frac{-K_a + \sqrt{K_a^2 + 4K_aC_a}}{2} \qquad (7\text{–}98)$$

In many instances, $C_a \gg [H_3O^+]$, and equation (7–97) simplifies to (p. 145)

$$[H_3O^+] = \sqrt{K_aC_a} \qquad (7\text{–}99)$$

Example 7–12. 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 (7–99),

$$[H_3O^+] = \sqrt{(1.06 \times 10^{-3}) \times (1.0 \times 10^{-2})}$$
$$= 3.26 \times 10^{-3}\ M$$

The approximation that $C_a \gg H_3O^+$ is not valid.

(*b*) Using equation (7–98),

$$[H_3O^+] = -\frac{(1.06 \times 10^{-3})}{2} + \frac{\sqrt{(1.06 \times 10^{-3})^2 + 4(1.06 \times 10^{-3})(1.0 \times 10^{-2})}}{2}$$
$$= 2.77 \times 10^{-3}\ M$$

$$pH = -\log(2.77 \times 10^{-3}) = 2.56$$

The example just given illustrates the importance of checking the validity of all assumptions made in deriving the equation used for calculating $[H_3O^+]$. The simplified equation (7–99) gives an answer for $[H_3O^+]$ with a relative error of 18% as compared with the correct answer given by equation (7–98).

Example 7–13. 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, $(BH^+)_2SO_4$, 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.

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

(*b*)

$$K_a = \frac{1.00 \times 10^{-14}}{2.3 \times 10^{-5}} = 4.35 \times 10^{-10}$$

(*c*)

$$[H_3O^+] = \sqrt{(4.35 \times 10^{-10}) \times (4.67 \times 10^{-2})}$$
$$= 4.51 \times 10^{-6}\ M$$

All assumptions are valid.

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

Solutions Containing Only a Weak Base. If the solution contains only a weak base, C_a is zero, and $[OH^-]$ is generally much greater than $[H_3O^+]$. Thus, equation (7–96) simplifies to

$$[H_3O^+] = \frac{K_a[OH^-]}{C_b - [OH^-]} = \frac{K_aK_w}{[H_3O^+]C_b - K_w} \qquad (7\text{–}100)$$

This equation can be solved for either $[H_3O^+]$ or $[OH^-]$. Solving for $[H_3O^+]$ using the left and far-right parts of equation (7–100) gives

$$C_b[H_3O^+]^2 - K_w[H_3O^+] - K_aK_w = 0 \qquad (7\text{–}101)$$

which has the solution

$$[H_3O^+] = \frac{K_w + \sqrt{K_w^2 + 4C_bK_aK_w}}{2C_b} \qquad (7\text{–}102)$$

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

If $K_a \gg [H_3O^+]$, which is generally true for solutions of weak bases, equation (7–100) gives

$$[H_3O^+] = \sqrt{\frac{K_aK_w}{C_b}} \qquad (7\text{–}103)$$

Equation (7–100) can be solved for $[OH^-]$ by using the left and middle portions and converting K_a to K_b to give

$$[OH^-] = \frac{-K_b + \sqrt{K_b^2 + 4K_bC_b}}{2} \qquad (7\text{–}104)$$

and if $C_b \gg [OH^-]$, which generally obtains for solutions of weak bases,

$$[OH^-] = \sqrt{K_bC_b} \qquad (7\text{–}105)$$

A good exercise for the student would be to prove that equation (7–103) is equal to equation (7–105). The applicability of both these equations will be shown in the following examples.

Example 7–14. What is the pH of a 0.0033-*M* solution of cocaine base, which has a basicity constant of 2.6×10^{-6}?

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

All assumptions are valid.

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

Example 7–15. 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, $C_b = C_s = 0.165\ M$. Since K_a for a weak acid such as sulfathiazole is usually given, rather than K_b for its conjugate base, equation (7–103) is preferred over equation (7–105).

$$[H_3O^+] = \sqrt{\frac{(7.6 \times 10^{-8}) \times (1.00 \times 10^{-14})}{0.165}}$$
$$= 6.79 \times 10^{-11}\ M$$

All assumptions are valid.

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

Solutions Containing a Single Conjugate Acid–Base Pair. In a solution composed of a weak acid and a salt of that acid, for example, acetic acid and sodium acetate; or a weak base and a salt of that base, for example, ephedrine and ephedrine hydrochloride, C_a and C_b are generally much greater than either $[H_3O^+]$ or $[OH^-]$. Thus, equation (7–96) simplifies to

$$[H_3O^+] = \frac{K_aC_a}{C_b} \qquad (7\text{–}106)$$

Example 7–16. What is the pH of a solution containing acetic acid 0.3 *M* and sodium acetate 0.05 *M*?

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

All assumptions are valid.

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

Example 7–17. 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}.

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

All assumptions are valid.

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

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 Brönsted–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

$$[H_3O^+] + [H_2A]_{ab} + [HA^-]_b + 2[H_2A]_b$$
$$= [OH^-] + [HA^-]_a + 2[A^{2-}]_a$$
$$+ [A^{2-}]_{ab} \qquad (7\text{–}107)$$

in which 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

$$[H_3O^+] + \frac{[H_3O^+]^2C_{ab}}{D} + \frac{K_1[H_3O^+]C_b}{D}$$
$$+ \frac{2[H_3O^+]^2C_b}{D} = \frac{K_w}{[H_3O^+]}$$
$$+ \frac{K_1[H_3O^+]C_a}{D} + \frac{2K_1K_2C_a}{D}$$
$$+ \frac{K_1K_2C_{ab}}{D} \qquad (7\text{–}108)$$

Multiplying through by $[H_3O^+]$ and D, which is given by equation (7–77), gives

$$[H_3O^+]^4 + [H_3O^+]^3(K_1 + 2C_b + C_{ab})$$
$$+ [H_3O^+]^2[K_1(C_b - C_a) + K_1K_2 - K_w]$$
$$- [H_3O^+][K_1K_2(2C_a + C_{ab}) + K_1K_w]$$
$$- K_1K_2K_w = 0 \qquad (7\text{–}109)$$

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 combinations of these substances added 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 may 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 (7–109) are zero. In almost all instances, the terms containing K_w can be dropped, and after dividing through by $[H_3O^+]$, equation (7–109) becomes

$$[H_3O^+]^3 + [H_3O^+]^2K_1 - [H_3O^+](K_1C_a - K_1K_2) - 2K_1K_2C_a = 0 \quad (7\text{–}110)$$

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

$$[H_3O^+]^3 + [H_3O^+]^2K_1 - [H_3O^+]K_1C_a - 2K_1K_2C_a = 0 \quad (7\text{–}111)$$

If $[H_3O^+] \gg 2K_2$, the term $2K_1K_2C_a$ can be dropped, and dividing through by $[H_3O^+]$ yields the quadratic equation

$$[H_3O^+]^2 + [H_3O^+]K_1 - KC_a = 0 \quad (7\text{–}112)$$

The assumptions $C_a \gg K_2$ and $[H_3O^+] \gg 2K_2$ will be valid whenever $K_2 \ll K_1$. Equation (7–112) is identical to equation (7–97), which was obtained for a solution containing a monoprotic weak acid. Thus, if $C_a \gg [H_3O^+]$, equation (7–112) simplifies to equation (7–99).

Example 7–18. 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 (7–99), since K_1 is approximately 30 times K_2.

$$[H_3O^+] = \sqrt{(6.4 \times 10^{-5}) \times (1.0 \times 10^{-3})}$$
$$= 2.53 \times 10^{-4}\ M$$

The assumption that $C_a \gg [H_3O^+]$ is not valid.

(*b*) Use the quadratic equation (7–112):

$$[H_3O^+] = -(6.4 \times 10^{-5})/2 + \frac{\sqrt{(6.4 \times 10^{-5})^2 + 4(6.4 \times 10^{-5})(1.0 \times 10^{-3})}}{2}$$
$$= 2.23 \times 10^{-4}\ M$$

Note that C_a is much greater than K_2, and $[H_3O^+]$ is much greater than $2K_2$.

$$\text{pH} = -\log (2.23 \times 10^{-4}) = 3.65$$

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 (7–109) are zero. For most systems of practical importance, the first, third, and fifth terms of equation (7–109) are negligible when compared with the second and fourth terms, and the equation becomes

$$[H_3O^+] = \sqrt{\frac{K_1K_2C_{ab} + K_1K_w}{K_1 + C_{ab}}} \quad (7\text{–}113)$$

The term K_2C_{ab} is generally much greater than K_w, and

$$[H_3O^+] = \sqrt{\frac{K_1K_2C_{ab}}{K_1 + C_{ab}}} \quad (7\text{–}114)$$

If the solution is concentrated enough that $C_{ab} \gg K_1$,

$$[H_3O^+] = \sqrt{K_1K_2} \quad (7\text{–}115)$$

Example 7–19. 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 $K_2 = 4.7 \times 10^{-11}$.

Since $K_2C_{ab}(23.5 \times 10^{-14})$ is much greater than K_w, and $C_{ab} \gg K_1$, equation (7–115) can be used.

$$[H_3O^+] = \sqrt{(4.3 \times 10^{-7}) \times (4.7 \times 10^{-11})}$$
$$= 4.5 \times 10^{-9}\ M$$
$$\text{pH} = -\log (4.5 \times 10^{-9}) = 8.35$$

Solutions Containing Only a Diacidic Base. In general, the calculations for solutions containing weak bases are easier to handle by solving for $[OH^-]$ rather than $[H_3O^+]$. Any equation in terms of $[H_3O^+]$ and acidity constants can be converted into terms of $[OH^-]$ and basicity constants by substituting $[OH^-]$ for $[H_3O^+]$, K_{b1} for K_1, K_{b2} for K_2, and C_b for C_a. These substitutions are made into equation (7–109). Furthermore, for a solution containing only a diacidic base, C_a and C_{ab} are zero; all terms containing K_w can be dropped; $C_b \gg K_{b2}$; and $[OH^-] \gg 2K_{b2}$. The following expression results:

$$[OH^-]^2 + [OH^-]K_{b1} - K_{b1}C_b = 0 \quad (7\text{–}116)$$

If $C_b \gg [OH^-]$, the equation simplifies to

$$[OH^-] = \sqrt{K_{b1}C_b} \quad (7\text{–}117)$$

Example 7–20. 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),

$$K_{b1} = \frac{K_w}{K_2} = \frac{1.00 \times 10^{-14}}{4.7 \times 10^{-11}} = 2.1 \times 10^{-4}$$

$$K_{b2} = \frac{K_w}{K_1} = \frac{1.00 \times 10^{-14}}{4.31 \times 10^{-7}} = 2.32 \times 10^{-8}$$

(*b*) Since $K_{b2} \ll K_{b1}$, one uses equation (7–117):

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

The assumption that $C_b \gg [OH^-]$ is not valid, and equation (7–116) must be used. (See equations (7–83) and (7–84) for the solution of a quadratic equation.)

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

Use of the simplified equation (7–117) gives an answer for $[OH^-]$ that has a relative error of 24% as compared with the correct answer given by equation (7–116). It is absolutely essential that all assumptions made in the calculation of $[H_3O^+]$ or $[OH^-]$ be verified!

Two Independent Acid–Base Pairs. Consider a solution containing two independent acid–base pairs:

$$HB_1 + H_2O \rightleftharpoons H_3O^+ + B_1^-$$

$$K_1 = \frac{[H_3O^+][B_1^-]}{[HB_1]} \tag{7–118}$$

$$HB_2 + H_2O \rightleftharpoons H_3O^+ + B_2^-$$

$$K_2 = \frac{[H_3O^+][B_2^-]}{[HB_2]} \tag{7–119}$$

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

$$[H_3O^+] + [HB_1]_{B1} + [HB_2]_{B2} = [OH^-] + [B_1^-]_{A1} + [B_2^-]_{A2} \tag{7–105}$$

in which the subscripts refer to the source of the species in the PBE. Replacing these species concentrations as a function of $[H_3O^+]$ gives

$$[H_3O^+] + \frac{[H_3O^+]C_{b1}}{[H_3O^+] + K_1} + \frac{[H_3O^+]C_{b2}}{[H_3O^+] + K_2} = \frac{K_w}{[H_3O^+]} + \frac{K_1C_{a1}}{[H_3O^+] + K_1} + \frac{K_2C_{a2}}{[H_3O^+] + K_2} \tag{7–121}$$

which can be rearranged to:

$$[H_3O^+]^4 + [H_3O^+]^3(K_1 + K_2 + C_{b1} + C_{b2}) + [H_3O^+]^2[K_1(C_{b2} - C_{a1}) + K_2(C_{b1} - C_{a2}) + K_1K_2 - K_w] - [H_3O^+][K_1K_2(C_{a1} + C_{a2}) + K_w(K_1 + K_2)] - K_1K_2K_w = 0 \tag{7–122}$$

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 (7–122). 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

$$[H_3O^+]^2 + [H_3O^+](K_1 + K_2) - (K_1C_{a1} + K_2C_{a2}) = 0 \tag{7–123}$$

If C_{a1} and C_{a2} are both greater than $[H_3O^+]$, the equation simplifies to

$$[H_3O^+] = \sqrt{K_1C_{a1} + K_2C_{a2}} \tag{7–124}$$

Example 7–21. What is the pH of a solution containing acetic acid, 0.01 mole/liter, and formic acid, 0.001 mole/liter?

$$[H_3O^+] = \sqrt{(1.75 \times 10^{-5})(1.0 \times 10^{-2}) + (1.77 \times 10^{-4})(1.0 \times 10^{-3})} = 5.93 \times 10^{-4}\ M$$

$$pH = -\log (5.93 \times 10^{-4}) = 3.23$$

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 (7–118) and (7–119). Since 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 (7–112) are zero. In addition, all terms containing K_w are negligibly small and may be dropped, simplifying the equation to

$$[H_3O^+]^2(K_1 + K_2 + C_{b2}) + [H_3O^+][K_1(C_{b2} - C_{a1}) + K_1K_2] - K_1K_2C_{a1} = 0 \tag{7–125}$$

In solutions containing a salt such as ammonium acetate, $C_{a1} = C_{b2} = C_s$. C_s is the concentration of salt added. In all systems of practical importance, $C_s \gg K_1$ or K_2, and equation (7–125) simplifies to:

$$[H_3O^+]^2C_s + [H_3O^+]K_1K_2 - K_1K_2C_s = 0 \tag{7–126}$$

which is a quadratic equation that can be solved in the usual manner. In most instances, however, $C_s \gg [H_3O^+]$, and the quadratic equation reduces to

$$[H_3O^+] = \sqrt{K_1K_2} \tag{7–127}$$

Equations (7–118) and (7–119) illustrate the fact that K_1 and K_2 are not the successive acidity constants for a single diprotic acid system, and equation (7–127) is not the same as equation (7–115); 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:

$$\underset{Acid_1}{NH_4^+} + \underset{Base_2}{Ac^-} \rightleftharpoons \underset{Acid_2}{HAc} + \underset{Base_1}{NH_3} \tag{7–128}$$

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 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:

$$K_1 = \frac{1.00 \times 10^{-14}}{1.74 \times 10^{-5}} = 5.75 \times 10^{-10}$$

$$[H_3O^+] = \sqrt{(5.75 \times 10^{-10}) \times (1.75 \times 10^{-5})}$$
$$= 1.00 \times 10^{-7}\ M$$

Note that all of the assumptions are valid.

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

When ammonium succinate is dissolved in water, it dissociates to yield two NH_4^+ cations and 1 succinate (S^2-) anion. These ions can enter into the following acid-base equilibrium:

$$\begin{array}{cccc} NH_4^+ \; + & S^{2-} \; \rightleftharpoons & HS^- \; + & NH_3 \\ \text{Acid}_1 & \text{Base}_2 & \text{Acid}_2 & \text{Base}_1 \end{array} \tag{7-129}$$

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

$$[H_3O^+]^2 - [H_3O^+]K_1 - 2K_1K_2 = 0 \tag{7-130}$$

and if $2K_2 \gg [H_3O^+]$,

$$[H_3O^+] = \sqrt{2K_1K_2} \tag{7-131}$$

In this example, equation (7-129) 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 (7-125) simplifies to

$$[H_3O^+]^2 - [H_3O^+]K_1(n-1) - nK_1K_2 = 0 \tag{7-132}$$

and

$$[H_3O^+] = \sqrt{nK_1K_2} \tag{7-133}$$

using the same assumptions that were used in developing equations (7-129) and (7-130).

It should be pointed out that in deriving equations (7-129) to (7-133), 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 pK_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 the pH of a 0.01-M solution of ammonium succinate. As shown in equation (7-129), 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, $K_2 = 2.3 \times 10^{-6}$

$$[H_3O^+] = \sqrt{2(5.75 \times 10^{-10}) \times (2.3 \times 10^{-6})}$$
$$= 5.14 \times 10^{-8}$$
$$\text{pH} = -\log(5.14 \times 10^{-8}) = 7.29$$

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 (see Chapter 8) whose pH is given by equation (7-127). For example, consider a solution made by dissolving equimolar amounts of sodium acid phosphate, NaH_2PO_4, and disodium citrate, $Na_2HC_6H_5O_7$, in water. Both salts dissociate to give the amphoteric species $H_2PO_4^-$ and $HC_6H_5O_7^{2-}$, causing a problem in deciding which species to designate as HB_1 and which to designate as B_2^- in equations (7-118) and (7-119). 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 $HC_6H_5O_7^{2-}$ is 6.4. The citrate species, being more acidic, acts as the acid in the following equilibrium:

$$\begin{array}{cc} HC_6H_5O_7^{2-} \; + & H_2PO_4^- \; \rightleftharpoons \\ \text{Acid}_1 & \text{Base}_2 \end{array}$$
$$\begin{array}{cc} H_3PO_4 \; + & C_6H_5O_7^{3-} \\ \text{Acid}_2 & \text{Base}_1 \end{array} \tag{7-134}$$

Thus, K_1 in equation (7-127) is K_3 for the citric acid system, and K_2 in equation (7-127) is K_1 for the phosphoric acid system.

Example 7-24. What is the pH of a solution containing NaH_2PO_4 and disodium citrate (disodium hydrogen citrate) $Na_2HC_6H_5O_7$, both in a concentration of 0.01 M? The third acidity constant for $HC_6H_5O_7^{2-}$ is 4.0×10^{-7}, while the first acidity constant for phosphoric acid is 7.5×10^{-3}.

$$[H_3O^+] = \sqrt{(4.0 \times 10^{-7}) \times (7.5 \times 10^{-3})}$$
$$= 5.48 \times 10^{-5}\ M$$

All assumptions are valid.

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

The equilibrium shown in equation (7-134) illustrates the fact that the system made by dissolving NaH_2PO_4 and $Na_2HC_6H_5O_7$ in water is identical to that made by dissolving H_3PO_4 and $Na_3C_6H_5O_7$ 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 (7-127) is valid for the system.

A slightly different situation arises for equimolar combinations of substances such as succinic acid, $H_2C_4H_4O_4$, and tribasic sodium phosphate, Na_3PO_4. In this case it is obvious that succinic acid is the acid that can protonate the base to yield the species $HC_4H_4O_4^-$ and HPO_4^{2-}. The acid succinate (pK_a 5.63) is a stronger acid than HPO_4^{2-} (pK_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 $C_4H_4O_4^{2-}$ and $H_2PO_4^-$. This is illustrated in the following:

$$H_2C_4H_4O_4 + PO_4^{3-} \rightarrow$$
$$HC_4H_4O_4^- + HPO_4^{2-} \tag{7-135}$$

$$\underset{\text{Acid}_1}{HC_4H_4O_4^-} + \underset{\text{Base}_2}{HPO_4^{2-}} \rightleftharpoons \underset{\text{Base}_1}{C_4H_4O_4^{2-}} + \underset{\text{Acid}_2}{H_2PO_4^-} \qquad (7-136)$$

Thus, K_1 in equation (7–136) is K_2 for the succinic acid system, and K_2 in equation (7–127) is actually K_2 from the phosphoric acid system.

Example 7–25. 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}.

(*a*)

$$[H_3O^+] = \sqrt{(2.3 \times 10^{-6})(6.2 \times 10^{-8})} = 3.78 \times 10^{-7}\ M$$

All assumptions are valid.

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

(*b*) Equation (7–127) can also be solved by taking logarithms of both sides to yield

$$pH = \tfrac{1}{2}(pK_1 + pK_2) = \tfrac{1}{2}(5.63 + 7.21) = 6.42 \qquad (7-137)$$

Equations (7–135) and (7–136) illustrate the fact that solutions made by dissolving equimolar amounts of $H_2C_4H_4O_4$ and Na_3PO_4, $NaHC_4H_4O_4$ and Na_2HPO_4, or $Na_2C_4H_4O_4$ 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,[10-12] solubility (see Chapter 10), rate of solution,[13] extent of binding,[14] and rate of absorption.[15]

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

$$HB + H_2O \rightleftharpoons H_3O^+ + B$$

$$K = \frac{a_{H_3O^+}a_B}{a_{HB}} = \frac{[H_3O^+][B]}{[HB]} \cdot \frac{\gamma_{H_3O^+}\gamma_B}{\gamma_{HB}} \qquad (7-138)$$

in which K is the thermodynamic acidity constant, and the charges on the species have been omitted to make the equations more general. Equation (7–138) illustrates the fact that in solving equations involving acidity constants, both the concentration and 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:

$$K = a_{H_3O^+}\frac{[B]}{[HB]}\frac{\gamma_B}{\gamma_{HB}} = K'\frac{\gamma_B}{\gamma_{HB}} \qquad (7-139)$$

and

$$pK' = pK + \log\frac{\gamma_B}{\gamma_{HB}} \qquad (7-140)$$

The following form of the Debye–Hückel equation[16] can be used for ionic strengths up to about 0.3 *M*:

$$-\log \gamma_i = \frac{0.51Z_i^2\sqrt{\mu}}{1 + aB\sqrt{\mu}} - K_s\mu \qquad (7-141)$$

in which Z_i is the charge on the species i. The value of the constants $a \cdot B$ 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 $Z - 1$:

$$pK' = pK + \frac{0.51(2Z - 1)\sqrt{\mu}}{1 + \sqrt{\mu}} \qquad (7-142)$$

Example 7–26. Calculate pK_2' for citric acid at an ionic strength of 0.01 *M*. Assume that $pK_2 = 4.78$. The charge on the acidic species is −1.

$$pK_2' = 4.78 + \frac{0.51(-3)\sqrt{0.01}}{1 + \sqrt{0.01}} = 4.78 - 1.53(0.091) = 4.64$$

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 [+ −]:

$$-\log \gamma_{+-} = (K_r - K_s)\mu \qquad (7-143)$$

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 (7–143) and (7–141) with equation (7–140) gives

$$pK_1' = pK_1 + \frac{0.51\sqrt{\mu}}{1 + \sqrt{\mu}} - K_r\mu \qquad (7-144)$$

The second ionization step involves the zwitterion going to a species with a charge of −1. Thus, using equations (7–143), (7–141), and (7–140) gives

$$pK_2' = pK_2 - \frac{0.51\sqrt{\mu}}{1 + \sqrt{\mu}} + K_r\mu \qquad (7-145)$$

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 (7–144) and (7–145) 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 would be as follows:

(*a*) Convert all p*K* values needed for the problem into p*K*′ values.

(*b*) Solve the appropriate equation in the usual manner.

Example 7–27. Calculate the pH of 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.

(*a*)

$$pK'_a = 4.76 - \frac{0.51\sqrt{0.10}}{1 + \sqrt{0.10}}$$
$$= 4.76 - 0.12 = 4.64$$

(*b*) Taking logarithms of equation (7–99) gives

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

in which we now write pK_a as pK'_a

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

Example 7–28. Calculate the pH of 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 $pK_2 = 9.78$.

(*a*)

$$pK'_1 = 2.35 + \frac{0.51\sqrt{0.10}}{1 + \sqrt{0.10}} - 0.32(0.10)$$
$$= 2.35 + 0.12 - 0.03 = 2.44$$

(*b*)

$$pK'_2 = 9.78 - \frac{0.51\sqrt{0.10}}{1 + \sqrt{0.10}} + 0.32(0.10)$$
$$= 9.78 - 0.12 + 0.03 = 9.69$$

(*c*) Taking logarithms of equation (7–115) gives

$$pH = \tfrac{1}{2}(pK_1 + pK_2)$$
$$= \tfrac{1}{2}(2.44 + 9.69) = 6.07$$

The pH value that is calculated using the apparent acidity constants, designated *K*′, in place of the thermodynamic acidity constants *K*, is defined as the negative logarithm of the *hydronium ion activity.* Taking antilogarithms, therefore, would give the hydronium ion activity, *not* the hydronium ion *concentration.* If the hydronium ion concentration is desired, it can be obtained by dividing the hydronium ion activity by the mean ionic activity coefficient for the electrolyte (p. 150).

Free Energy of Ionization and the Effect of Temperature Upon Ionic Equilibria. Recall from Chapter 3 that the standard free energy change $\Delta G°$ of a reaction is related to the equilibrium constant. Therefore, the standard free energy change of an ionization reaction can be computed from the ionization constant, K_a:

$$\Delta G° = -RT \ln K_a \qquad (7–146)$$

Using the pK_a, equation (7–146) can be written as

$$\Delta G° = 2.303\ RT\ pK_a \qquad (7–147)$$

Example 7–29. The pK_a value for the weak acid amobarbital at 25° C is 7.96 (Table 7–7). Compute the standard free energy change for the ionization of this barbituric acid derivative.

$$\Delta G° = 2.303 \times 1.9872 \times 298 \times 7.96$$
$$= 10{,}855.9 \text{ cal/mole}$$
$$= 10.86 \text{ kcal/mole}$$

Notice that although $\Delta G°$ is positive, it is not $\Delta G°$ but rather ΔG that determines whether or not a process is spontaneous, according to Chapter 3, equation (3–117)

$$\Delta G = \Delta G° + RT \ln Q \qquad (7–148)$$

Example 7–30. An organic acid dissociates according to the reaction

$$HA + H_2O = H_3O^+ + A^-$$

The dissociation exponent pK_a of the acid at 25° C is 5.0. Assume that the reaction proceeds at a rate slow enough that the concentration of the products may be determined at any time. Disregard the difference between activities and concentrations. Compute (*a*) the standard free energy $\Delta G°$ and (*b*) the free energy change ΔG accompanying the reaction when 0.1 mole per liter of the acid has dissociated sufficiently to form 10^{-4} mole per liter of ions. (*c*) In terms of the sign of $\Delta G°$ state whether or not the reaction is spontaneous.

(*a*)

$$\Delta G° = 2.303 \times 1.987 \times 298 \times 5.0$$
$$= 6818 \text{ cal/mole}$$

(*b*) The reaction quotient *Q*, expressed in concentrations, is

$$Q = \frac{[H_3O^+][A]}{[HA]} = \frac{10^{-4} \times 10^{-4}}{10^{-1} - 10^{-4}} \cong 10^{-7}$$

The concentration of water, being great, is not altered significantly by the reaction and thus does not appear in the quotient. Alternatively, it may be stated that the $[H_2O]$ term does not appear because water is present essentially at unit activity, pure water at 1 atm and 25° C being taken as the standard state of H_2O. *Q* must not be confused with the equilibrium constant *K*, the latter being the ratio of the concentrations of the reactant and products as the forward and reverse reactions proceed under the conditions of dynamic equilibrium.

$$\Delta G = \Delta G° + 2.303\ RT \log \frac{a_{prod}}{a_{react}} = 2.303\ RTpK + 2.303\ RT \log Q$$

$$\Delta G = 6818 + (2.303 \times 1.987 \times 298 \times \log 10^{-7})$$
$$= 6818 - 9546 = -2728 \text{ cal/mole}$$

(*c*) The conversion of 0.1 mole per liter of acid into 10^{-4} mole per liter of its ions is a spontaneous reaction since ΔG is negative at constant pressure and temperature.

By writing equation (7–148) as

$$\Delta G = RT \ln \frac{Q}{K}$$

it can be seen that the sign and hence the spontaneity of the reaction depends on the relative values of the quantities *Q* and *K*. If *Q* is smaller than *K*, signifying that the concentrations (activities) of the products are yet below the values at equilibrium, ΔG will have a negative sign, and the process will move spontaneously toward a state of equilibrium. If *Q* is larger than *K*, the concentrations of the products are greater than the equilibrium values, ΔG will have a positive sign, and the process will be nonspontaneous. If $K = Q$, then $\Delta G = 0$, and the system is at equilibrium.

The positive value of $\Delta G°$ signifies that the electrolyte in its standard state of unit activity cannot dissociate spontaneously into ions of unit activity. Ionization does occur, nevertheless, its possibility being shown by the sign of ΔG and not by the sign of $\Delta G°$. This fact was brought out in *Example 7–30,* in which neither the reactant nor the products were in their standard states.

The *CRC Handbook of Physics and Chemistry*, 63rd ed., p. D-62 gives the following standard thermodynamic values, where *f* stands for free energy or enthalpy of *formation* (see p. 59 for an explanation of the standard enthalpy [heat] of formation; standard free energy of formation is defined in an analogous way). $S°$ is a standard thermodynamic property, as designated by the superscript "o." It is not a *difference* in entropies, ΔS, as in the case of enthalpy and free energy, but is rather absolute entropy of a substance based on its entropy value above zero degrees Kelvin.

Now, the change in enthalpy, entropy, or free energy in a reaction may be characterized by the standard enthalpy, entropy, and free energy changes, $\Delta H°$, $\Delta S°$, and $\Delta G°$. These are obtained by taking the differences between the $\Delta H_f°$, $S°$, and $\Delta G_f°$ of the product and reactant.

Example 7–31. In the case of the ionization of acetic acid in aqueous solution at 25° C (298.15° K), we can use these thermodynamic properties to calculate the dissociation (ionization) constant, K_a, and the dissociation exponent, pK_a.

Standard Thermodynamic Values For Ionization Of Acetic Acid*

	CH_3COOH	$\longrightarrow$	CH_3COO^-	$\longrightarrow$	H^+
$\Delta H_f°$ (kcal/mole)	−116.10		−116.16		0
$\Delta G_f°$ (kcal/mole)	− 94.8		− 88.29		0
$S°$ (cal/deg mole)	42.7		20.7		0

*Standard thermodynamic values vary somewhat from one literature source to another.

In its standard state of 1 molar aqueous solution, the value of the hydrogen ion for these thermodynamic properties is zero, as seen in the table.

The standard enthalpy and standard entropy changes, $\Delta H°$ and $\Delta S°$, for the ionization reaction are the values for the product, CH_3COO^-, minus the values for the reactant at 25° C:

$$\Delta H° = (-116.16) - (-116.10) = -0.060 \text{ kcal/mole}$$
$$= -60.0 \text{ cal/mole}$$
$$\Delta S° = \quad 20.7 \; - \quad 42.7 \quad = -22.0 \text{ cal/deg mole}$$

Now, from equation (7–147),

$$pK_a = +\Delta G°/(2.303\ RT) \tag{7–149}$$

Since

$$\Delta G° = \Delta H° - T\Delta S° \tag{7–150}$$

we also have

$$2.303 \cdot \log K_a = \frac{\Delta S°}{R} - \frac{\Delta H°}{RT} \tag{7–151}$$

Therefore, knowing $\Delta H_f°$ and $S°$ or simply having $\Delta G_f°$ (as found in *Problem 3–20*) for both reactants and products, we can obtain K_a and pK_a for the ionization of weak acids and weak bases. This procedure may also be used to calculate equilibria constants for nonionic chemical reactions *(Problem 3–22)*.

Continuing with the case of acetic acid and using equation (7–151),

$$2.303 \log K_a = \frac{-22.0}{1.9872} - \frac{-60.0}{(1.9872)(298.15)} = -10.96958$$
$$\log K_a = 4.763;\ K_a = 1.73 \times 10^{-5}$$
$$pK_a = 4.76$$

Example 7–32. Calculate the K_a and pK_a for the first and second ionization stages of H_2CO_3 at 25° C in aqueous solution. The data are as follows*:

	$\Delta H_f°$	$S°$	$\Delta G_f°$
H_2CO_3 aq	−167.22	44.8	−148.94
HCO_3^- aq	−165.39	21.8	−140.26
CO_3^{2-} aq	−161.84	−13.6	−126.17

**CRC Handbook of Chemistry and Physics*, 63rd ed. CRC Press, Boca Raton, Fla., p. D–60.

$\Delta H_f°$ and $\Delta G_f°$ are the heat and free energy of formation at 25° C (298.15° K), respectively. $S°$ is the absolute entropy at 25° C. The "o" indicates that these thermodynamic quantities are for each species in its standard state of 1 molal aqueous solution at 1 atmosphere pressure and ordinary temperature.

The reaction for the first stage is

$$H_2CO_3 \rightarrow HCO_3^- + H^+$$

and the standard enthalpy, entropy, and free energies are

$$\Delta H° = \Delta H_f°(HCO_3^-\ \text{aq}) - \Delta H_f°(H_2CO_3)$$
$$-(165.39) \quad - (-167.22) = 1.830 \text{ kcal/mole}$$
$$= 1830 \text{ cal/mole}$$
$$\Delta S° = S°(HCO_3^-\ \text{aq}) - S°(H_2CO_3)$$
$$(21.8) \quad - \quad (44.8) \quad = -23.0 \text{ cal/deg mole}$$
$$\Delta G° = \Delta G_f°(HCO_3^-\ \text{aq}) - \Delta G_f°(H_2CO_3)$$
$$(-140.26) \quad - \quad (-148.94) \quad = 8.680 \text{ kcal/mole}$$
$$= 8680 \text{ cal/mole}$$

The ionization constant for the first stage of ionization of H_2CO_3 is obtained from the equation, $\Delta G° = \Delta H° - T\Delta S° = -RT \ln K_1$, or

$$\ln K_1 = \frac{\Delta S_{12}°}{R} - \frac{\Delta H_{12}°}{RT} = -\frac{\Delta G_{12}°}{RT}$$

TABLE 7–7. pK_a and $\Delta G°$ Values for Substituted Barbituric Acids, 25° C*

Compound	pK_a	$\Delta G°$ (kcal/mol)
5-Allyl-5-isopropylbarbituric acid (Aprobarbital)‡	8.02	10.96
5-5-Diallylbarbituric acid (Dial)	7.81	10.66
5,5-Dibromobarbituric acid‡	5.68	7.75
5,5-Dichlorobarbituric acid‡	5.55	7.57
5,5-Diethylbarbituric acid (Barbital)†,‡	7.98	10.89
5,5-Dimethylbarbituric acid‡	8.51	11.61
5-Ethyl-5-butylbarbituric acid (Butethal)§	7.98	10.89
5-Ethyl-5-isopropylbarbituric acid (Probarbital)‡	8.14	11.11
5-Ethyl-5-(l-methylbutyl)barbituric acid (Pentobarbital)§, ‖	8.13	11.09
5-Ethyl-5-(3-methylbutyl)barbituric acid (Amobarbital)§	7.96	10.86
5-Ethyl-5-phenylbarbituric acid (Phenobarbital)¶	7.48	10.20
5-Methyl-5-phenylbarbituric acid (Rutonal)‡	7.78	10.61

*This table was provided by R. J. Prankerd, College of Pharmacy, University of Florida, Gainesville, Fla.

†From G. G. Manov, K. E. Schuette and F. S. Kirk, J. Res. Nat. Bur. Stand. **48**, 84–91, 1952.

‡From R. H. McKeown, J. Chem. Soc., Perk. II, 506–514, 1980.

§From A. I. Biggs, J. Chem. Soc. 2485–2488, 1956.

‖From R. J. Prankerd, Ph.D. Thesis, University of Otago, New Zealand, 1985.

¶From D. R. Baird, R. H. McKeown and R. J. Prankerd, School of Pharmacy, University of Otago, New Zealand. Unpublished data.

TABLE 7–8. ***Thermodynamic Constants of Ionization****

Electrolyte	A	C	D	$T_{\max}$° K	$pK_{T\max}$	$\Delta G°_{25°C}$ cal/mole	$\Delta H°_{25°C}$ cal/mole	$\Delta S°_{25°C}$ cal/deg mole
Formic acid	1342.85	0.015168	5.2743	297.5	3.7519	5117	−23	−17.6
Acetic acid	1170.48	0.013399	3.1649	295.6	4.7555	6486	−92	−22.1
Propionic acid	1213.26	0.014055	3.3860	293.8	4.8729	6647	−163	−22.8
Boric acid	2193.55	0.016499	3.0395	364.6	8.9923	12596	3328	−31.1
Barbital	2324.47	0.011856	3.3491	†	†	†	†	†
Lactic acid	1304.72	0.014926	4.9639	‡	‡	‡	‡	‡

*From H. S. Harned and B. B. Owen, *Physical Chemistry of Electrolytic Solutions*, Reinhold, New York, 1958.

†See *Problem 7–42* on page 168.

‡See *Problem 7–43* on page 168.

Substituting the values from the table for the first stage, $H_2CO_3 \rightarrow HCO_3^- + H^+$, we obtain

$$\ln K_1 = \frac{-23.0}{1.9872} - \frac{1830}{(1.9872)(298.15)} = -14.663; \ \log K_1 = \ln K_1/2.303$$

$$-\log K_1 = pK_1 = 6.37$$

(The value in Table 7–1 is 6.37.)

One can also obtain the dissociation constant using $\Delta G_{12}°$, where $_{1,2}$ refers to the values for the species H_2CO_3 and HCO_3^-, respectively. From the table we obtain $\Delta G_{12}° = 8.68$ kcal/mole or 868.0 cal/mole:

$$\ln K_1 = -\frac{8680}{(1.9872)(298.15)} = -14.650; \ \log K_1 = \ln K_1/2.303$$

$$pK_1 = -\log K_1 = 6.36$$

As an exercise, the student should calculate K_2 and pK_2, the values for the second stages of the ionization of H_2CO_3. Compare your values with those found in Table 7–1. The pK_a and $\Delta G°$ values for some substituted barbituric acids at 25° C are found in Table 7–7.

Harned and Owen[18] suggest the following empiric equation by which to relate the ionization constants and temperature:

$$\log K = -\frac{A}{T} - CT + D \qquad (7\text{–}152)$$

in which A, C, and D are constants obtained by careful experimentation. Ionization constants of many of the weak electrolytes pass through a maximum value between 0° and 60° C, and the temperature at which maximum ionization occurs is given by the expression

$$T_{\max} = \sqrt{\frac{A}{C}} \qquad (7\text{–}153)$$

The dissociation exponent at this temperature is

$$pK_{T\max} = 2\sqrt{AC} - D \qquad (7\text{–}154)$$

The thermodynamic quantities for ionization are also obtained by use of the constants A, C, and D.

$$\Delta G° = 2.3026R(A - DT + CT^2) \qquad (7\text{–}155)$$

$$\Delta H° = 2.3026R(A - CT^2) \qquad (7\text{–}156)$$

$$\Delta S° = 2.3026R(D - 2CT) \qquad (7\text{–}157)$$

The results of Harned and Owen[18] for some representative weak electrolytes are listed in Table 7–8.

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Problems

7–1. Practice calculations involving pH, pOH, and ionic concentration in aqueous solutions.

(a) Convert pH = 2.54 to hydrogen ion concentration, $[H^+]$.

(b) What is the pH of a 7.93×10^{-4} molar solution of a strong acid?

(c) If the pH of a solution of a strong base is 8.75, what is its hydroxyl ion concentration? What is its hydrogen ion concentration?

(d) What is the pH of a 0.00379-M solution of HNO_3? What is its pOH?

(e) Convert the hydroxyl ion concentration, 0.00915 M to pH.

(f) Calculate the pH of a 2.37×10^{-3} M solution of sulfuric acid. H_2SO_4 dissociates completely as a strong electrolyte in a dilute solution, as found in the present problem.

(g) A 0.017-M solution of HCl is mixed with a 0.017-M solution of NaOH. What is the pH of the final mixture?

(h) What is the pH of a 0.034-M solution of NaCl?

(i) The solubility of phenobarbital in water at 25° C is 0.14% (w/v). What is the pH of the saturated solution?

(j) If 15 mL of 0.02 M NaOH is added to 15 mL of 0.02 M acetic acid, what is the pH of the solution? Convert the pH to hydrogen ion concentration.

(k) The pOH of a drug solution is 6.82; what is the pH of the solution? What is the hydroxyl ion concentration if the solution is a strong base?

(l) What is the pH and pOH of a 5×10^{-8} M solution of HCl at 25° C?

(m) Calculate the pH of a 0.06-M solution of formic acid.

Answers: **(a)** $[H_3O^+] = 2.88 \times 10^{-3}$; **(b)** pH = 3.10; **(c)** $[OH^-] = 5.62 \times 10^{-6}$, $[H_3O^+] = 1.78 \times 10^{-9}$; **(d)** pH = 2.42, pOH = 11.58; **(e)** pH = 11.96; **(f)** pH = 2.32; **(g)** pH = 7.07; **(h)** pH = 7.08; **(i)** pH = 4.81; **(j)** pH = 8.53, $[H_3O^+] = 2.95 \times 10^{-9}$; **(k)** pH = 7.18, $[OH^-] = 1.51 \times 10^{-7}$; **(l)** pH = 6.89, pOH = 7.11; **(m)** pH = 2.49

7–2. If 100 mL of 0.005 M sulfathiazole is mixed with 57 mL of 0.003 M sodium hydroxide, what is the pH of the mixture? What is the pOH of the solution? Sulfathiazole reacts in part with NaOH to give sodium sulfathiazole. *Hint:* Use the Henderson–Hasselbalch equation (8–8) in the form

$$\text{pH} = \text{p}K_a + \log \frac{[\text{sodium sulfathiazole}]}{[\text{sulfathiazole}]}$$

The $\text{p}K_a$ of sulfathiazole is 7.12.

Answer: pH = 6.84, pOH = 7.16

7–3.(a) What is the mole percent of free phenobarbital in solution at pH 8.00? **(b)** What is the mole percent of free cocaine in solution at pH 8.00? (The fraction of nonionized drug in the form of a weak acid is obtained using equation (13–95), and as a weak base, equation (13–96)). (Also see equations (13–77) and (13–78) for the ionized rather than the nonionized case.)

Answers: **(a)** 23%; **(b)** 28%

7–4. (a) What is the pH of a 5 g per 100 mL solution of phenol? **(b)** What is the hydroxyl ion concentration of the solution?

Answers: **(a)** pH = 5.14; **(b)** $[OH^-] = 1.38 \times 10^{-9}$

7–5. Compute the hydronium ion concentration and pH of a 0.001-M solution of acetic acid using both the approximate and the more exact quadratic equations.

Answer: approximate $[H_3O^+] = 1.32 \times 10^{-4}$ M, pH = 3.88; exact $[H_3O^+] = 1.24 \times 10^{-4}$ M, pH = 3.91

7–6. Calculate the pH of a 1% (w/v) solution of morphine sulfate. The molecular weight of this salt is 668.76.

Answer: pH = 4.70

7–7. What is the pH of a 1:200 aqueous solution of ephedrine at 25°?

Answer: pH = 10.92

7–8. Calculate the pH of a 0.01-M solution of tartaric acid.

Answer: pH = 2.58

7–9. Calculate the pH of a 0.01-M solution of physostigmine at 25° C.

Answer: pH = 9.94

7–10. Calculate the pH of a solution containing 0.1 M acetic acid and 0.1 M formic acid.

Answer: pH = 2.36

7–11. What is the hydronium ion concentration and the pH of a solution at 25° C containing 0.01 mole/liter of sulfadiazine and 0.05 mole/liter of sulfisoxazole? The necessary data are found in Table 7–1.

Answer: $[H_3O^+] = 7.094 \times 10^{-4}$ mole/liter; pH = 3.15

7–12. (a) What is the PBE for a solution of ammonium chloride? **(b)** What is the PBE for a solution containing equimolecular amounts of Na_2HPO_4 and ammonium chloride?

Answers: **(a)** $[H_3O^+] = [OH^-] + [NH_3]$; **(b)** $[H_3O^+] + 2[H_3PO_4] + [H_2PO_4^-] = [OH^-] + [NH_3] + [PO_4^{3-}]$

7–13. What is the isoionic pH of the ampholyte *p*-aminobenzoic acid ($^+NH_3C_6H_4COO^-$), which has the two acidity constants, $\text{p}K_1$ = 2.3 and $\text{p}K_2$ = 4.9?

Answer: pH = 3.6

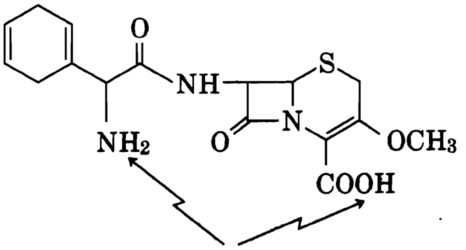
7–14. The sulfonamides can exist in the form of an ampholyte $^+NH_3C_6H_4SO_2NR^-$ in aqueous solution. The two acidity constants of sulfadiazine are $\text{p}K_1$ = 2.1 and $\text{p}K_2$ = 6.5. Calculate the isoionic point for this drug.

Answer: pH = 4.3

7–15. Cefroxadine, a β-lactam antibiotic, has two ionizable groups, –COOH and NH_2 (Nieto et al.[19]). The equilibrium for this ampholyte may be represented as

$$^+NH_3—R—COOH \underset{K_1}{\overset{-H^+}{\rightleftarrows}} {}^+NH_3—R—COO^- \underset{K_2}{\overset{-H^+}{\rightleftarrows}} NH_2—R—COO^-$$

Calculate the pH of a 4.7×10^{-3} M solution of cefroxadine at 25° C. The dissociation constants are $K_1 = 6.92 \times 10^{-4}$ M and $K_2 = 1.17 \times 10^{-7}$ M. Use equation (7–115) and the more exact equation (7–114) to obtain the pH of this ampholyte.



These points of ionization become NH_3^+ and COO^-

Cefroxadine

Answer: More exact result, pH = 5.08; less exact result, pH = 5.05. At this pH the zwitterionic form of cefroxadine, $^+NH_3$–R–COO^-, predominates.

7–16. What is the pH of a solution containing acetic acid 0.1 M and sodium acetate 0.02 M?

Answer: pH = 4.06

7–17.(a) Calculate the pH of a 0.1-M solution of ammonium borate. **(b)** Calculate the pH of a 0.1-M solution of ammonium propionate.

Answers: **(a)** pH = 9.24; **(b)** pH = 7.06

7–18. What is the pH of a 0.01-M solution of $(NH_4)_3PO_4$?

Answer: pH = 10.72

7–19. What is the pH of a solution containing equimolar amounts of succinic acid and tribasic sodium citrate?

Answer: pH = 5.20

7–20. Aminophylline is a complex of theophylline ($C_7H_8N_4O_2$) and ethylenediamine $C_2H_4(NH_2)_2 \cdot 2H_2O$ and belongs to the therapeutic category of smooth muscle relaxant. It behaves as a weak base with a $\text{p}K_b$ = 5.0.

(a) Compute the concentration in mole/liter of ionized aminophylline (BH^+) in aqueous solution at 25° C when the reaction, $B + H_2O \rightleftarrows BH^+ + OH^-$, is at equilibrium. The total concentration of aminophylline is 0.003 mole/liter.

(b) What is the pH of the solution at 25° C?

Answers: **(a)** The concentration of the conjugate acid species (BH^+) at equilibrium is 1.68×10^{-4} mole/liter; **(b)** pH = 10.23

7–21. What is the pH of a sulfadiazine sodium solution containing 0.5 mole of drug in 1000 mL of solution?

Answer: pH = 10.09

7–22.* An aspirin tablet (acetylsalicylic acid, pK_a 3.49, molecular weight 180.15 g/mole), was taken orally with cold water to make a solution of aspirin in the stomach fluids of 0.00167 mole/liter. The cold water produced a temperature in the stomach temporarily of 25° C.

(a) What is the percentage of aspirin in the ionic form, $C_6H_4(OOCCH_3)COO^-$, in the stomach in which the pH of the fluid is 3.20? See equation (13–77).

(b) Determine $\Delta G°$ for the ionization of aspirin at 25° C.

(c) compute ΔG for the ionization of aspirin at a molar concentration of 0.00167 in the stomach, assuming that the fluids are at a temperature of 25° C. Is the ionization of aspirin under these conditions a spontaneous process?

Answers: (a) % of ionization = 33.9; (b) $\Delta G° = 4762$ cal/mole; (c) $\Delta G = -65$ cal/mole. ΔG being negative, the reaction is spontaneous.

7–23.* (a) Calculate K_a and pK_a for the ionization of formic acid.

Data for *Problem 7–23*

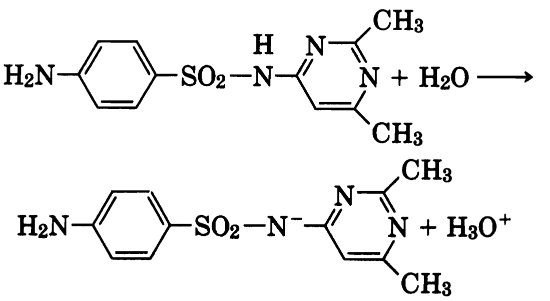
	HCOOH	→ $HCOO^-$	+ H^+
$\Delta H_f°$ (kcal/mole)	−101.68	−101.71	0
$S°$ (cal/deg mole)	39.0	22.0	0

Source: Data from CRC *Handbook of Chemistry and Physics*, 63rd ed. p. D-60

(b) Calculate K_a and pK_a for formic acid using the free energies of formation, in which $\Delta G°_f(HCOO^-)$ is −83.9 kcal/mole and $\Delta G°_f$(HCOOH) is −89.0 kcal/mole.

Answers: (a) $K_a = 2.03 \times 10^{-4}$, p$K_a$ = 3.69; (b) $K_a = 1.83 \times 10^{-4}$; p$K_a$ = 3.74. Compare your results with the K_a and pK_a values found in Table 7–2.

7–24. The ionization of sulfisomidine, pK_a = 7.47, is shown as



When taken orally the drug exists as a 0.073-M aqueous solution in the upper intestinal tract where the pH is 5.83.

(a) Calculate the percent of sulfisomidine in the ionic form in the solution in the intestinal tract (use equation (13–77)).

(b) Obtain the standard free energy change, $\Delta G°$, for the ionization reaction at 25° C, and explain the meaning of this result.

(c) What is the value of ΔG for the ionization in the intestinal tract, and what is the interpretation of this result?

Answers: (a) the percent ionization, 2.24%, is small in the intestinal tract where the pH of the environment is 5.83. (b) The standard free energy change is $\Delta G°$ = 10,191 cal/mole. This large positive value for $\Delta G°$ suggests that the ionization reaction does not proceed far to the right in the above equation. Sulfisomidine is therefore a weak acid, which corroborates the ionization constant of 3.39×10^{-8}, the pK_a of 7.47, and the percentage ionization of 2.24%. (c) The free energy change, ΔG, for the reaction is 4156 cal/mole. Because of the positive value of ΔG the ionization reaction is not spontaneous. This predominantly nonionic antibacterial compound will probably be well absorbed through the intestinal mucosa. If the pH is raised, the drug will not be 50% ionized until the pH becomes 7.47 in the GI tract.

If the pK_a of the drug were, say, 3.0, it would be largely ionized (99.9%) at pH 5.83 in the GI tract. It would then not be significantly absorbed by passive diffusion, except at special places along the gut where ionic species are absorbed by facilitated transport mechanisms.

7–25. Phosphoric acid ionizes in three stages, as shown on page 149, and the species $H_2PO_4^-$ and HPO_4^{2-} in the body help to maintain the pH at a value of about 7.4. Calculate the K_a and pK_a for the first, second, and third stages of ionization of phosphoric acid. The required data, $\Delta H°_f$ and $S°$, are given in the table.[20]

Data for *Problem 7–25*

	$\Delta H°_f$ kcal/mole	$S°$ cal/deg mole
H_3PO_4(aq)	−308.2	42.1
$H_2PO_4^-$(aq)	−311.3	21.3
HPO_4^{2-}(aq)	−310.4	−8.6
PO_4^{3-}(aq)	−306.9	−52.0
H^+(aq)	0	0

The ionization for the first stage is often written for thermodynamic calculations as

$$H_3PO_4(aq) \rightleftarrows H_2PO_4^-(aq) + H^+(aq)$$

It is shown on page 149 as

$$H_3PO_4 + H_2O = H_2PO_4^- + [H_3O^+]$$

Liquid water is written H_2O(liq) and the hydronium ion, $[H_3O^+]$, in aqueous solution as $[H_3O^+]$(aq). The $\Delta H°_f$ and $S°$ values for H_2O(liq) and $[H_3O^+]$(aq) are identical (Bent[21]) and may be eliminated. The values for H^+(aq) are by convention set equal to zero and may also be dropped.

Partial Answer: $K_1 = 5.3 \times 10^{-3}$, pK_1 = 2.27

7–26. The equation for the first stage of ionization of phosphoric acid and the standard free energies of formation $\Delta G°_f$ of the reactants and products are

	H_3PO_4(aq) +	H_2O(liq) ⇄	$H_2PO_4^-$(aq) +	H_3O^+(aq)
$\Delta G°_f$(kcal/mole)	−274.2	−52.69	−271.3	−56.69

(a) Compute the first ionization constant K_1 from standard free energies of formation (Bent[21]). Compare your result with the K_1 in Table 7–2 and with the value obtained in *Problem 7–25*, using $\Delta H°_f$ and $S°$.

(b) Compute the standard free energy of formation of HPO_4^{2-}, knowing that pK_2, the "dissociation exponent" for the second stage of ionization of phosphoric acid, is 7.21.

Answers: (a) $K_1 = 7.49 \times 10^{-3}$, p$K_1$ = 2.13; (b) $\Delta G°$ = +9.84 kcal/mole

7–27. Magnesium carbonate is the active ingredient in some over-the-counter antacid products. It reacts with HCl in the stomach, neutralizing some of the acid and releasing CO_2 according to the reaction

	$MgCO_3(s)$ +	2HCl(aq) $\overset{K}{\rightleftarrows}$	$MgCl_2$(aq) +	CO_2(g) +	H_2O(liq)
$\Delta G_f°$ (25° C) (kcal/mole)	−241.9	2(−31.372)	−171.444	−94.254	−56.687

In the equation s stands for solid, g for gas, liq for liquid, and aq for aqueous solution. Below each term of the equation is given the standard free energy of formation.

You have just ingested a newly formulated 100-mg magnesium carbonate tablet. (a) If you follow this with a second tablet, how will

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*Problems 7–22 and 7–23 are modified from J. W. Moncrief and W. H. Jones *Elements of Physical Chemistry*, Addison-Wesley, Reading, MA., 1977, p. 123.

it affect the equilibrium established following the first tablet, as shown in the equation? **(b)** How will the equilibrium be affected if instead of taking another tablet you burp and expel some of the CO_2 formed in the reaction? **(c)** Compute the standard free energy change $\Delta G°$ of this reaction, and use $\Delta G°$ to obtain the equilibrium constant for the reaction.

Answers: **(a)** The reaction proceeds to the right, maintaining the value of the equilibrium constant, *K*. **(b)** Following a burp, the reaction also proceeds to the right so as to maintain the value of *K*. **(c)** $\Delta G° = -17.741$ kcal/mole, $K = 1.01 \times 10^{13}$

7–28. Some nonprescription antacid tablets contain magnesium oxide as the active ingredient to react with HCl of the stomach. The equation for the reaction, together with the standard heat of formation, standard free energy of formation, and the standard absolute entropy, is

	$MgO(s)$	$+\ 2HCl(aq)$	$\rightleftharpoons MgCl_2(aq)$	$+\ H_2O(liq)$
$\Delta H_f°\left(\frac{\text{kcal}}{\text{mole}}\right)$	−143.81	2(-39.952)	−191.48	−68.315
$\Delta G_f°\left(\frac{\text{kcal}}{\text{mole}}\right)$	−136.10	2(−31.372)	−171.444	−56.687
$S°\left(\frac{\text{cal}}{\text{deg} \cdot \text{mole}}\right)$	6.380	2(13)	−6.117	16.71

Notice that the standard thermodynamic values for HCl(aq) have each been shown multiplied by 2 since 2 molecules of HCl appear in the equation. Tables of the standard thermodynamic properties are obtained from the National Bureau of Standards and are found in the appendixes of some thermodynamic books. The CRC *Handbook of Chemistry and Physics* contains a number of these values.

(a) Using the $\Delta G°_f$ values of the magnesium oxide reaction, calculate the standard free energy change $\Delta G°$ accompanying the reaction when an MgO antacid tablet interacts with the acid in the stomach.

(b) Having obtained $\Delta G°$ for the reaction, and assuming a temperature of 25° C, determine the constant, *K*, for the reaction.

(c) Use $\Delta H°_f$ and $S°$ values to obtain $\Delta G°$ and *K* for the reaction. Do you get the same results as under (a) and (b)?

(d) In terms of the chemical species in the reaction, describe what occurs when the first magnesium oxide antacid tablet is followed by a second or third tablet. In what way are $\Delta G°$ and *K* changed? What happens to the pH of the stomach fluid?

Partial Answer: **(a)** $\Delta G° = -29.287$ kcal/mole; **(b)** $K = 2.93 \times 10^{21}$. the large value for *K* demonstrates that the reaction goes essentially to completion (from left to right in the equation).

7–29. pK_a values of sulfacetamide have been determined by Agrawal et al.[22] in mixtures of dioxane and water at 25° C as given in the table.

Data (a) for *Problem 7–29*

Mole fraction of dioxane:	0.083	0.123	0.147	0.175
Temp (°C)	pK_a			
25	6.75	7.24	7.46	7.75
35	6.50	7.00	7.23	7.51

(a) Compute the standard free energy, standard enthalpy, and standard entropy for the ionization reaction $HA \rightleftharpoons H^+ + A^-$ in the four mixtures of dioxane and water at the two temperatures. Prepare a table of results as shown in data table (b). From the thermodynamic result obtained, is it possible to decide whether or not the reaction is a spontaneous process? If not spontaneous, would it be impossible for this reaction to occur? (*Hint:* The value of $\Delta H°$ may be obtained using the van't Hoff equation (equation 3–124, p. 71). Once $\Delta G°$ and $\Delta H°$ are known, $\Delta S°$ is readily calculated.

(b) Plot the pK_a values (vertical axis) against the mole fraction of dioxane and extrapolate the lines to zero concentration of dioxane (100% water, 0% dioxane). Read off the pK_a values in water at 25° C and 35° C.

(c) Using least-squares regression analysis, regress pK_a versus mole fraction of dioxane both at 25° C and 35° C. Compare these results with pK_a (25° C) and pK_a (35° C) obtained by extrapolation in (b).

Answers: **(a)** The values of $\Delta G°$, $\Delta H°$, and $\Delta S°$ for 0.175 mole fraction of dioxane have been given you in data table (b). Complete the table. **(b)** By extrapolation: pK_a = 5.87 at 25° C and 5.58 at 35° C in 100% water. **(c)** By least-squares regression analysis: pK_a = 5.87 at 25° C and 5.61 at 35° C in 100% water.

Data (b) for *Problem 7–29*

Mole fraction of dioxane:	0.083		0.123		0.147		0.175	
Temperature (°C)	25°	35°	25°	35°	25°	35°	25°	35°
$\Delta G°\ \frac{\text{kcal}}{\text{mole}}$							10.6	10.6
$\Delta H°\ \frac{\text{kcal}}{\text{mole}}$							10.1	
$\Delta S°\ \frac{\text{cal}}{\text{deg} \cdot \text{mole}}$							−1.61	

7–30. **(a)** The pK_a of amobarbital at 20° C is 8.06. What is the standard free energy change for the dissociation of this barbiturate at 20° C? **(b)** If the standard entropy change $\Delta S°$ for this reaction is −3.1 cal/(deg mole), what is the enthalpy change $\Delta H°$ at this temperature?

Answers: **(a)** 10,813 cal/mole; **(b)** 9904 cal/mole

7–31. From the dissociation constant K_a of acetic acid at 25° C, compute the standard free energy change using the equation $\Delta G° = -RT \ln K$. If $\Delta H°$ for this dissociation at 25° C is −92 cal/mole, what is the value for $\Delta S°$? (*Hint:* $\Delta G° = \Delta H° - T\,\Delta S°$.)

Answer: $\Delta G°$ = 6490 cal/mole; $\Delta S°$ = −22 cal/(deg mole)

7–32. Mercurous chloride (calomel) is a white powder, used in the past as an antiseptic and a cathartic. Mercurous chloride, mixed with mercuric chloride, is permitted by the Environmental Protection Agency as a fungicide to prevent fungus infections in certain trees, grasses, grains, and textiles.

The formation of mercurous chloride from its elements—liquid mercury and gaseous chlorine—is written, together with the standard enthalpy and free energy of formation and the standard absolute entropy, as

	$Hg(liq)$	$+\ \frac{1}{2}Cl_2(g)$	$= \frac{1}{2}Hg_2Cl_2(s)$
$\Delta H°_f$ values (kcal/mole)	0.0	0.0	$\frac{1}{2}(-63.32)$
$\Delta G°_f$ values (kcal/mole)	0.0	0.0.	$\frac{1}{2}(-50.35)$
$S°$ values (cal/[deg mole])	18.5	$\frac{1}{2}(53.286)$	$\frac{1}{2}(46.8)$

(a) Calculate $\Delta G°$ from the $\Delta G°_f$ values for the reaction of mercury and chlorine to form calomel. (Notice that the heat and free energy of formation of the elements Hg(liq) and $Cl_2(g)$ are zero, therefore the value for the formation of Hg_2Cl_2 (−63.32 kcal/mole) is the *heat of formation* and −50.35 kcal/mole is the free energy of formation obtained by calorimetry. These are values for the heat and the free energy of formation found in a table of $\Delta H°_f$ and $\Delta G°_f$. The superscript ° indicates that the values are for the elements in their standard states.

(b) Using the $\Delta H°_f$ and $S°$ values, calculate $\Delta G°$ for the reaction and compare its value with that obtained in (a).

(c) Using $\Delta G°$ from (a) or (b), calculate the equilibrium constant for the reaction at 25° C.

Data for *Problem 7–33*

	CH_3COOH(liq)	+	C_2H_5OH(liq)	=	$CH_3COOC_2H_5$(liq)	+	H_2O(liq)
ΔH°_f (kcal/mole	−116.4		−66.20*		−114.49*		−68.317
ΔG°_f (kcal/mole)	−93.8		−41.77		−79.70**		−56.690
S° (cal/[deg mole])	38.2		38.4		62.0		16.716

(Below the equation are listed the standard heat of formation, the standard free energy of formation, and the standard absolute entropy.

Source: The values not designated with asterisks are from H. A. Bent, *The Second Law*, Oxford University Press, Oxford, 1965, pp. 398, 402.

*From J. A. Dean, Editor, *Lange's Handbook of Chemistry*, McGraw-Hill, New York, 1979, Table 9–2.

**Modified from the Lange Handbook value.

(d) Does the value obtained for ΔG° allow one to determine whether this process is spontaneous or not?

Answers: **(a)** $\Delta G^\circ = -25.175$ kcal/mole; **(b)** ΔG° (from ΔH° and ΔS°) = −25.177 kcal/mole; **(c)** $K_{(298^\circ\text{ K})} = 2.84 \times 10^{18}$; **(d)** refer to page 161 for the relationship of ΔG° to spontaneity of a reaction.

7–33. In order to prepare the ester, ethyl acetate, acetic acid is reacted with ethyl alcohol at 25° C as shown in the table above.

(a) Using the ΔG°_f values, calculate ΔG° for the reaction at 25° C and the equilibrium constant, K.

(b) Using the ΔH°_f, and S° values, calculate ΔG° and K at 25° C and compare the results with those obtained in (a).

(c) According to the equation, if the reaction proceeded completely to the right, 1 mole each of acetic acid and ethyl alcohol would yield 1 mole each of ethyl acetate and water. However, the equilibrium constant K found in (a) or (b) shows that the reaction does not proceed completely to the right, for if that were the case, K would have the value of infinity. Let us suppose that 0.0027 M each of acetic acid and ethyl alcohol react together at 25° C to form the products, ethyl acetate and water. The amounts of acetic acid and ethyl alcohol are of course used up at the same rate to form ethyl acetate and water in equal amounts. What will be the concentration of the ester, ethyl acetate, at equilibrium? The following procedure is suggested. Having calculated the value of K in (a) and (b), and assigning x as the concentration of both ethyl acetate and water, one obtains the expression

$$\frac{x \cdot x}{(0.0027 - x)(0.0027 - x)} = K \cong 4.0$$

Note that at equilibrium, the original concentration 0.0027 M each for acetic acid and ethyl alcohol is reduced by the equilibrium concentration, x, for both ethyl acetate and water.

The equation for the reaction and the associated thermodynamic quantities are found in the table above. The value designated with a double asterisk was modified from the *Lange's Handbook* value of −79.52 to −79.70 to bring the ΔG° values into agreement by the two methods of calculation required for answers (a) and (b).

Answers: **(a)** $K = 3.99$ (if −79.52 kcal/mole had been used for ΔG°_f of ethyl acetate, as mentioned above, K would have been obtained as 2.95). **(b)** Using ΔH°_f and S° values, $\Delta G^\circ = -837.9$ cal/mole; $K = 4.11$. The value of K obtained experimentally from the concentrations of the reactants and the products at equilibrium, rather than the thermodynamic approach used here, is $K = 4.00$. **(c)** The concentration of ethyl acetate at equilibrium by experimentation is 0.0018 mole/liter. An equal concentration, 0.0018 M of water is formed. The concentration of acetic acid and ethyl alcohol is therefore each 0.0027 − 0.0018, or 0.0009 M, and the equilibrium expression appears as

$$K = \frac{(0.0018)(0.0018)}{(0.0027 - 0.0018)(0.0027 - 0.0018)} = 4.00$$

7–34. Once ΔH°, the standard heat of reaction, is found at 25° C and the constant K for the reaction is known, also at 25° C, the van't Hoff equation (equation 3–124), may be employed to obtain K, the reaction constant for ionization over a range of temperatures from roughly 0° C to 50° C. The ionization of acetic acid and the standard heat of formation for the species involved in the reaction are:

	$CH_3COOH(aq) \rightarrow$	$CH_3COO^-(aq)$ +	H^+
ΔH°_f (kcal/mole)	-116.743^{23}	−116.843	0

(a) Calculate ΔH° at 25° C and using K_a for acetic acid at 25° C, substitute these values into the van't Hoff equation to obtain K_a at 0° C and 37° C. **(b)** If a curved line of K_a versus temperature occurs for an acid such as acetic, is it possible to obtain K_a values at say, 0° and 37° C, knowing the K_a value at 25° C? *Hint:* Plot on the same graph the values of ln K_a against 1/T given in CRC, p. D-174, and the values of ln K_a against 1/T you obtained under (a) and compare the results.

Partial Answer: **(a)** The ionization constant K_a for acetic acid at 0° C is 1.777×10^{-5}. The CRC *Handbook of Chemistry and Physics*, 63rd ed., p. D-174 gives K_a (acetic acid) as 1.657×10^{-5} at 0° C, 1.754×10^{-5} at 25° C; by extrapolation we obtain $K_a = 1.739 \times 10^{-5}$ at 37° C. The K_a value for acetic acid is greater at 25° C than at 0° C or 37° C (CRC, p. D-174). This is not true for all acids in water.

7–35. The standard free energy ΔG° is 10.26 kcal/mole and the standard heat content or enthalpy ΔH° is 19.32 kcal/mole for the dissociation of sulfathiazole at 35° C. (The term *standard* in thermodynamics refers to the value of the thermodynamic property, ΔG°, ΔH°, or ΔS° at ordinary temperatures [usually 25° C] and at 1 atm pressure).

(a) Compute the dissociation exponent, pK_a, at 35° C.

(b) The ΔG° and ΔS° values at a temperature T_1, say 35° C, can be used to compute pK_a at another temperature T_2, say 20° C, according to the equation

$$\text{p}K_a = \frac{\Delta G^\circ_{T_1} - \Delta S^\circ_{T_1}(T_2 - T_1)}{2.303RT_2}$$

where ΔS° at the temperature T_1 (35° C) is calculated from the ΔG° and ΔH° values given above at 35° C. Compute the pK_a of sulfathiazole at 20° C.

Answers: **(a)** pK_a (35° C) = 7.28; **(b)** pK_a (20° C) = 7.32

7–36. The pH of a 1:500 aqueous solution of ephedrine was determined with a pH meter and was found to be 10.70. Calculate the pK_b for ephedrine.

Answer: pK_b = 4.68 (cf. Table 7–3, p. 148)

7–37. Calculate α, the degree of dissociation of 0.01 molar physostigmine, disregarding the secondary ionization. α is the concentration of the ionized form, [physostigmine$^+$] = $[OH^-]/C_b$, where C_b is the concentration of the compound. The student may use the relationship, $[OH^-]/C_b$ or equation (13–78), p. 342.

Answer: 0.0087 or 0.87%

7–38. The weak acid, corresponding to the salt benzylpenicillin sodium, molecular weight 356.38, has a pK_a of 2.76. the drug is dissolved in isotonic sodium chloride solution (0.9 g NaCl per 100 mL) to make a 3% w/v solution of the antibiotic. **(a)** What is the pH of this solution, disregarding activity coefficients? **(b)** What is the result using ionic activity coefficients? (Use the Debye–Hückel equation.)

Answer: **(a)** pH = 7.84; **(b)** pH = 7.68

7–39. What is the hydroxyl ion concentration of an aqueous solution containing 0.1 g per 1000 mL of reserpine and 9 g per 1000 mL of sodium chloride? The molecular weight of reserpine is 608. Calculate the results **(a)** without activity coefficients and **(b)** with activity coefficients, using the Debye–Hückel equation.

Answer: **(a)** $[OH^-] = 2.56 \times 10^{-6}$ M; **(b)** $[OH^-] = 1.84 \times 10^{-6}$ M

7-40. In a study of insecticidal oximes ($R_2C{=}NOH$) Kurtz and D'Silva[24] postulated a relationship between the pK_a value of an oxime and its proton chemical shift, δ_{OH} (see pp. 92 and 93 for a description of chemical shift). To learn whether pK_a values could be obtained from NMR data, the authors determined chemical shifts of the hydroxyl proton, δ_{OH}, of selected oximes with known pK_a values. pK_a and δ_{OH} values are listed in the table.

(a) Plot pK_a on the vertical axis versus the experimentally determined δ_{OH} values on the horizontal axis.

(b) Use least-squares linear regression analysis, regressing pK_a versus δ_{OH} to obtain an equation relating these two variables. How well do the coefficients of your equation correspond to those of Kurtz and D'Silva?

(c) Use your equation of the least-squares regression line to calculate the pK_a from $\delta_{OH} = 11.15$ for acetophenone oxime. Compare your calculated pK_a with the literature value, $pK_a = 11.41$, for acetophenone oxime.

Data for *Problem 7-40*

Known pK_a and Experimental δ_{OH} Values		
Compound	δ_{OH}	pK_a
2-Propanone oxime	10.12	12.42
2-Butanone oxime	10.14	12.45
3-Pentanone oxime	10.18	12.60
Acetophenone oxime	11.15	11.41
Benzaldehyde oxime	11.19	10.78
4-Nitrobenzaldehyde oxime	11.84	9.88
2,3-Butanedione monooxime	12.27	9.34
3-Oximinopentane-2,4-dione	12.92	7.35
2-Oximino-1,3-dithiolane	11.15	10.70

Partial Answer: **(b)** The equation obtained using the nine oximes from the work of Kurtz and D'Silva is

$$pK_a = 29.92 - 1.71\ \delta_{OH};\ r^2 = 0.967,\ n = 9$$

(n stands for the number of compounds involved in the regression as independent variables)

(c) The pK_a of acetophenone oxime calculated from the equation under (b) above is 10.85. The literature value is 11.41.

7-41. Kurtz and D'Silva[24] used NMR chemical shift data to obtain the pK_a of a number of oximes, as described in *Problem 7-40*. Furthermore, these workers observed that the sensitivity of phenol pK_a values was similar to that of oxime pK_a values for changes in proton chemical shift, δ_{OH}. That is, the slope of the plot of pK_a versus δ_{OH} for oximes was nearly the same as that for phenols. Thus, it should be possible to use a single equation to express the pK_a vs. δ_{OH} values for both oximes and phenols. To test this possibility the authors used 20 oxime pK_a values and 51 phenol pK_a values and regressed these against measured δ_{OH} values. Kurtz and D'Silva added an *indicator variable*[*] to account for the difference in these two classes of chemicals. The indicator variable I is taken as equal to unity for each phenol in the equation and as zero for each compound which is an oxime, giving the expression

$$pK_a = a + b(\delta_{OH}) + c(I)$$

The 20 pK_a and δ_{OH} values for the oximes and the 51 pK_a and δ_{OH} values for the phenols are entered into a computer program designed to handle linear regression with indicator variables. As the oxime and phenol data are entered, I is given a value of 0 for each oxime and a value of 1 for each phenol. The computer-generated results (see the statistical package, SPSS, 1975, pp. 373–375) provide values for a, b, and c in the above equation.

In essence, the indicator variable produces different intercepts and thus divides the results into two separate lines having the same slope. The lines in this case represent the two classes of compounds, oximes and phenols; and the single equation relating pK_a and δ_{OH} for these two classes is, according to Kurtz and D'Silva,

$$pK_a = 28.15 - 1.55\ \delta_{OH} - 3.96I,\ r^2 = 0.97$$

Plot the two lines on a graph of pK_a against δ_{OH}. Locate the points for benzaldehyde oxime and 2-3 butanedione monooxime on the one line, and phenol and 2-nitrophenol on the other line. Use the observed (measured) δ_{OH} values for these four compounds:

Data for *Problem 7-41*

Compound	Measured δ_{OH}
Benzaldehyde oxime	11.19
2,3-Butanedione monooxime	12.27
Phenol	9.23*
2-Nitrophenol	10.82*

*From G. Socrates, Trans. Faraday Soc. **66**, 1052, 1966.

and the above equation, to calculate the pK_a values.

Answer:

	pK_a	
Compound	Calculated	Literature
Benzaldehyde oxime	10.81	10.78
2,3-Butanedione monooxime	9.13	9.34
Phenol	9.88	9.97
2-Nitrophenol	7.42	7.14

7-42. The constants, A, C, and D for barbital found in Table 7-8 were obtained from a precision e.m.f. study of the pK_a–temperature dependence. Compute T_{max}, $pK_{T_{max}}$, $\Delta G°$, $\Delta H°$, and $\Delta S°$ at physiologic temperature using equation (7-152) through (7-157) on page 163, and introduce them into the squares[†] of Table 7-8.

Partial Answer: $T_{max} = 443°\ C$; $\Delta G° = 11.1$ kcal/mole

7-43. The constants A, C, and D for lactic acid in Table 7-8 are obtained using equations (7-152) through (7-157) on page 163. Calculate the values for T_{max}, $pK_{T_{max}}$, $\Delta G°$, $\Delta H°$, and $S°$ at 25° C and introduce them into the squares, ‡, of Table 7-8.

Partial Answer: $pK_{T_{max}} = 3.86$; $\Delta H° = -101$ cal/mole

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[*] Indicator variables, also called *dummy variables*, are described in SPSS, McGraw-Hill, 1975, p. 373