PHYSICAL PHARMACY

ALFRED MARTIN

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Physical Pharmacy

PHYSICAL CHEMICAL PRINCIPLES IN THE PHARMACEUTICAL SCIENCES

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6
Solutions of Electrolytes

Properties of Solutions of Electrolytes
Arrhenius Theory of Electrolytic Dissociation
Theory of Strong Electrolytes
Coefficients for Expressing Colligative Properties

The first satisfactory theory of ionic solutions was that proposed by Arrhenius in 1887. The theory was based largely on studies of electric conductance by Kohlrausch, colligative properties by van't Hoff, and chemical properties such as heats of neutralization by Thomsen. Arrhenius[1] was able to bring together the results of these diverse investigations into a broad generalization known as the theory of electrolytic dissociation.

Although the theory proved quite useful for describing weak electrolytes, it was soon found unsatisfactory for strong and moderately strong electrolytes. Accordingly, many attempts were made to modify or replace Arrhenius's ideas with better ones, and finally, in 1923, Debye and Hückel put forth a new theory. It is based on the principles that *strong electrolytes* are completely dissociated into ions in solutions of moderate concentration and that any deviation from complete dissociation is due to interionic attractions. Debye and Hückel expressed the deviations in terms of activities, activity coefficients, and ionic strengths of electrolytic solutions. These quantities, which had been introduced earlier by Lewis, are discussed in this chapter together with the theory of interionic attraction. Other aspects of modern ionic theory and the relationships between electricity and chemical phenomena are considered in following chapters.

We begin with a discussion of some of the properties of ionic solutions that led to Arrhenius theory of electrolytic dissociation.

PROPERTIES OF SOLUTIONS OF ELECTROLYTES

Electrolysis. When, under a potential of several volts, a direct electric current (dc) flows through an electrolytic cell (Figure 6–1), a chemical reaction occurs. The process is known as *electrolysis*. Electrons enter the cell from the battery or generator at the *cathode* (road down); they combine with positive ions or *cations*, in the solution, and the cations are accordingly reduced. The negative ions, or *anions*, carry electrons through the solution and discharge them at the *anode* (road up), and the anions are accordingly oxidized. *Reduction* is the addition of electrons to a chemical species, and *oxidation* is removal of electrons from a species. The current in a solution consists of a flow of positive and negative ions toward the electrodes, whereas the current in a metallic conductor consists of a flow of free electrons migrating through a crystal lattice of fixed positive ions. Reduction occurs at the cathode, where electrons enter from the external circuit and are added to a chemical species in solution. Oxidation occurs at the anode where the electrons are removed from a chemical species in solution and go into the external circuit.

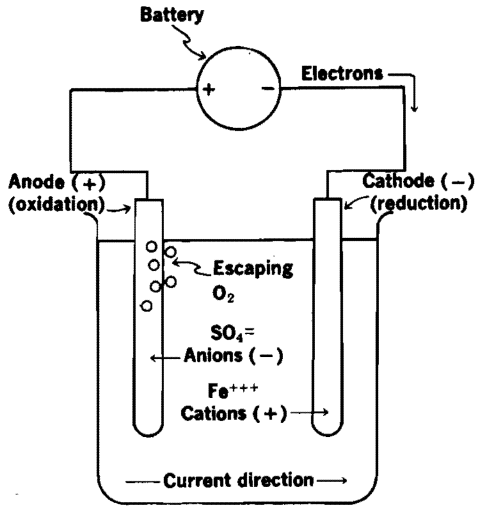

Fig. 6–1. Electrolysis in an electrolytic cell.

In the electrolysis of a solution of ferric sulfate in a cell containing platinum electrodes, a ferric ion migrates to the cathode where it picks up an electron and is reduced:

$$Fe^{3+} + e = Fe^{2+} \qquad (6-1)$$

The sulfate ion carries the current through the solution to the anode, but it is not easily oxidized; therefore, hydroxyl ions of the water are converted into molecular oxygen, which escapes at the anode, and sulfuric acid is found in the solution around the electrode. The oxidation reaction at the anode is

$$OH^- = \tfrac{1}{4}O_2 + \tfrac{1}{2}H_2O + e \qquad (6-2)$$

Platinum electrodes are used here since they do not pass into solution to any extent. When *attackable* metals, such as copper or zinc, are used as the anode, their atoms tend to lose electrons, and the metal passes into solution as the positively charged ion.

In the electrolysis of cupric chloride between platinum electrodes, the reaction at the cathode is

$$\tfrac{1}{2}Cu^{2+} + e = \tfrac{1}{2}Cu \qquad (6-3)$$

while at the anode, chloride and hydroxyl ions are converted respectively into gaseous molecules of chlorine and oxygen, which then escape. In each of these two examples, the net result is the transfer of one electron from the cathode to the anode.

Transference Numbers. It should be noted that the flow of electrons through the solution from right to left in Figure 6–1 is accomplished by the movement of cations to the right as well as anions to the left. The fraction
of total current carried by the cations or by the anions is known as the *transport* or *transference number* t_+ or t_-.

$$t_+ = \frac{\text{current carried by cations}}{\text{total current}} \qquad (6-4)$$

$$t_- = \frac{\text{current carried by anions}}{\text{total current}} \qquad (6-5)$$

The sum of the two transference numbers is obviously equal to unity:

$$t_+ + t_- = 1 \qquad (6-6)$$

The transference numbers are related to the velocities of the ions, the faster-moving ion carrying the greater fraction of current. The velocities of the ions in turn depend on hydration as well as ion size and charge. Hence, the speed and the transference numbers are not necessarily the same for positive and for negative ions. For example, the transference number of the sodium ion in a 0.10-*M* solution of NaCl is 0.385. Because it is greatly hydrated, the lithium ion in a 0.10-*M* solution of LiCl moves slower than the sodium ion and hence has a lower transference number, viz., 0.317.

Electrical Units. According to Ohm's law, the strength of an electric current I in amperes flowing through a metallic conductor is related to the difference in applied potential or voltage E and the resistance R in ohms, as follows:

$$I = \frac{E}{R} \qquad (6-7)$$

The current strength I is the rate of flow of current or the quantity Q of electricity (electronic charge) in coulombs flowing per unit time:

$$I = \frac{Q}{t} \qquad (6-8)$$

and

$$\text{Quantity of electric charge, } Q = \text{current, } I \times \text{time, } t \qquad (6-9)$$

The quantity of electric charge is expressed in coulombs (1 coul = 3×10^9 electrostatic units of charge, or esu), the current in amperes, and the electric potential in volts.

Electric energy consists of an intensity factor, electromotive force or voltage, and a quantity factor, coulombs.

$$\text{Electric energy} = E \times Q \qquad (6-10)$$

Faraday's Laws. In 1833 and 1834, Michael Faraday announced his famous laws of electricity, which may be summarized in the statement, *the passage of 96,500 coulombs of electricity through a conductivity cell produces a chemical change of 1 gram equivalent weight of any substance.* The quantity 96,500 is known as the faraday, F. The best estimate of the value today is 9.648456×10^4 coulombs per gram equivalent.

A univalent negative ion is an atom to which a valence electron has been added; a univalent positive ion is an atom from which an electron has been removed. Each gram equivalent of ions of any electrolyte carries Avogadro's number (6.02×10^{23}) of positive or negative charges. Hence, from Faraday's laws, the passage of 96,500 coulombs of electricity results in the transport of 6.02×10^{23} electrons in the cell. A faraday is an Avogadro's number of electrons, corresponding to the mole, which is an Avogadro's number of molecules. The passage of 1 faraday of electricity causes the electrolytic deposition of the following number of gram atoms or "moles" of various ions: $1Ag^+$, $1Cu^+$, $\frac{1}{2}Cu^{2+}$, $\frac{1}{2}Fe^{2+}$, $\frac{1}{3}Fe^{3+}$. Thus, the number of positive charges carried by 1 gram equivalent of Fe^{3+} is 6.02×10^{23}, but the number of positive charges carried by 1 gram atom or 1 mole of ferric ions is $3 \times 6.02 \times 10^{23}$.

Faraday's laws can be used to compute the charge on an electron in the following way. Since 6.02×10^{23} electrons are associated with 96,500 coulombs of electricity, each electron has a charge e of

$$e = \frac{96{,}500 \text{ coulombs}}{6.02 \times 10^{23} \text{ electrons}}$$

$$= 1.6 \times 10^{-19} \text{ coulombs/electron} \qquad (6-11)$$

and since 1 coulomb = 3×10^9 esu

$e = 4.8 \times 10^{-10}$ electrostatic units of charge/electron (6–12)

Electrolytic Conductance. The resistance $\boldsymbol{R}$ in ohms of any uniform metallic or electrolytic conductor is directly proportional to its length l in cm and inversely proportional to its cross-sectional area A in cm^2,

$$\boldsymbol{R} = \rho \frac{l}{A} \tag{6–13}$$

in which ρ is the resistance between opposite faces of a 1-cm cube of the conductor and is known as the *specific resistance.*

The *conductance* $\boldsymbol{C}$ is the reciprocal of resistance,

$$\boldsymbol{C} = \frac{1}{\boldsymbol{R}} \tag{6–14}$$

and hence can be considered as a measure of the ease with which current can pass through the conductor. It is expressed in reciprocal ohms or *mhos*. From equation (6–13),

$$\boldsymbol{C} = \frac{1}{\boldsymbol{R}} = \frac{1}{\rho}\frac{A}{l} \tag{6–15}$$

The *specific conductance* κ is the reciprocal of specific resistance and is expressed in mhos/cm.

$$\kappa = \frac{1}{\rho} \tag{6–16}$$

It is the conductance of a solution confined in a cube 1 cm on an edge as seen in Figure 6–2. The relationship between specific conductance and conductance or resistance is obtained by combining equations (6–15) and (6–16).

$$\kappa = \boldsymbol{C}\frac{l}{A} = \frac{1}{\boldsymbol{R}}\frac{l}{A} \tag{6–17}$$

Measuring the Conductance of Solutions. The Wheatstone bridge assembly for measuring the conductance of a solution is shown in Figure 6–3. The solution of unknown resistance $\boldsymbol{R_x}$ is placed in the cell and

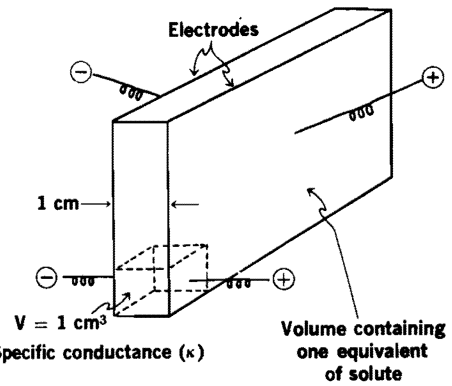

Fig. 6–2. Relationship between specific conductance and equivalent conductance.

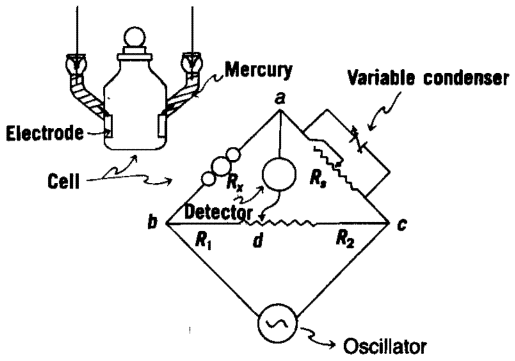

Fig. 6–3. Wheatstone bridge for conductance measurements.

connected in the circuit. The contact point is moved along the slide wire *bc* until at some point, say *d*, no current from the source of alternating current (oscillator) flows through the detector (earphones or oscilloscope). When the bridge is balanced the potential at *a* is equal to that at *d*, the sound in the earphones or the oscillating pattern on the oscilloscope is at a minimum, and the resistances $\boldsymbol{R_s}$, $\boldsymbol{R_1}$, and $\boldsymbol{R_2}$ are read. In the balanced state, the resistance of the solution $\boldsymbol{R_x}$ is obtained from the equation

$$\boldsymbol{R_x} = \boldsymbol{R_s}\frac{\boldsymbol{R_1}}{\boldsymbol{R_2}} \tag{6–18}$$

The variable condenser across resistance $\boldsymbol{R_s}$ is used to produce a sharper balance. Some conductivity bridges are calibrated in conductance as well as resistance values. The electrodes in the cell are platinized with platinum black by electrolytic deposition so that catalysis of the reaction will occur at the platinum surfaces, and formation of a nonconducting gaseous film will not occur on the electrodes.

Water that is carefully purified by redistillation in the presence of a little permanganate is used to prepare the solutions. Conductivity water, as it is called, has a specific conductance of about 0.05×10^{-6} mho/cm at 18° C, whereas ordinary distilled water has a value somewhat over 1×10^{-6} mho/cm. For most conductivity studies, "equilibrium water" containing CO_2 from the atmosphere is satisfactory. It has a specific conductance of about 0.8×10^{-6} mho/cm.

The specific conductance κ is computed from the resistance $\boldsymbol{R_x}$ or conductance C by use of equation (6–17). The quantity l/A, the ratio of distance between electrodes to the area of the electrode, has a definite value for each conductance cell; it is known as the *cell constant, K.* Equation (6–17) thus can be written

$$\kappa = \boldsymbol{KC} = \boldsymbol{K/R} \tag{6–19}$$

(The subscript x is no longer needed on $\boldsymbol{R}$ and is therefore dropped.) It would be difficult to measure l and A, but it is a simple matter to determine the cell constant experimentally. The specific conductance of several standard solutions has been determined in carefully calibrated cells. For example, a solution

containing 7.45263 g of potassium chloride in 1000 g of water has a specific conductance of 0.012856 mho/cm at 25° C. A solution of this concentration contains 0.1 mole of salt per cubic decimeter (100 cm^3) of water and is known as a 0.1 *demal* solution. When such a solution is placed in a cell and the resistance is measured, the cell constant can be determined by use of equation (6–19).

Example 6–1. A 0.1-demal solution of KCl was placed in a cell whose constant K was desired. The resistance R was found to be 34.69 ohms at 25° C.

$$K = \kappa R = 0.012856 \text{ mho/cm} \times 34.69 \text{ ohms}$$
$$= 0.4460 \text{ cm}^{-1}$$

Example 6–2. When the cell described in *Example 6–1* was filled with a 0.01-N Na_2SO_4 solution, it had a resistance of 397 ohms. What is the specific conductance?

$$\kappa = \frac{K}{R} = \frac{0.4460}{397} = 1.1234 \times 10^{-3} \text{ mho/cm}$$

Equivalent Conductance. To study the dissociation of molecules into ions, independent of the concentration of the electrolyte, it is convenient to use equivalent conductance rather than specific conductance. All solutes of equal normality produce the same number of ions when completely dissociated, and equivalent conductance measures the current-carrying capacity of this given number of ions. Specific conductance, on the other hand, measures the current-carrying capacity of all ions in a unit volume of solution and accordingly varies with concentration.

Equivalent conductance Λ is defined as the conductance of a solution of sufficient volume to contain 1 gram equivalent of the solute when measured in a cell in which the electrodes are spaced 1 cm apart. The equivalent conductance Λ_c at a concentration of c gram equivalents per liter is calculated from the product of the specific conductance κ and the volume V in cm^3 that contains 1 gram equivalent of solute. The cell may be imagined as having electrodes 1 cm apart and to be of sufficient area so that it can contain the solution. The cell is shown in Figure 6–2.

$$V = \frac{1000 \text{ cm}^3/\text{liter}}{c \text{ Eq/liter}} = \frac{1000}{c} \text{ cm}^3/\text{Eq} \qquad (6\text{–}20)$$

The equivalent conductance is obtained when κ, the conductance per cm^3 of solution (i.e., the specific conductance), is multiplied by V, the volume in cm^3 that contains 1 gram equivalent weight of solute. Hence, the equivalent conductance Λ_c, expressed in units of mho cm^2/Eq, is given by the expression

$$\Lambda_c = \kappa \times V \qquad (6\text{–}21)$$
$$= \frac{1000\,\kappa}{c} \text{ mho cm}^2/\text{Eq}$$

If the solution is 0.1 N in concentration, then the volume containing 1 gram equivalent of the solute will be 10,000 cm^3, and, according to equation (6–21), the equivalent conductance will be 10,000 times as great as the specific conductance. This is seen in *Example 6–3.*

Example 6–3. The measured conductance of a 0.1-N solution of a drug is 0.0563 mho at 25° C. The cell constant at 25° C is 0.520 cm^{-1}. What is the specific conductance and what is the equivalent conductance of the solution at this concentration?

$$\kappa = 0.0563 \times 0.520 = 0.0293 \text{ mho/cm}$$
$$\Lambda_c = 0.0293 \times 1000/0.1$$
$$= 293 \text{ mho cm}^2/\text{Eq}$$

Equivalent Conductance of Strong and Weak Electrolytes. As the solution of a strong electrolyte is diluted, the *specific conductance* κ *decreases* because the number of ions per unit volume of solution is reduced. (It sometimes goes through a maximum before decreasing.) Conversely, the *equivalent conductance* Λ of a solution of a strong electrolyte steadily *increases* on dilution. The increase in Λ with dilution is explained as follows. The quantity of electrolyte remains constant at 1 gram equivalent according to the definition of equivalent conductance; however, the ions are hindered less by their neighbors in the more dilute solution and hence can move faster. The equivalent conductance of a weak electrolyte also increases on dilution, but not as rapidly at first.

Kohlrausch was one of the first investigators to study this phenomenon. He found that the equivalent conductance was a linear function of the square root of the concentration for strong electrolytes in dilute solutions, as illustrated in Figure 6–4. The expression for Λ_c, the equivalent conductance at a concentration c (Eq/L), is

$$\Lambda_c = \Lambda_0 - b\sqrt{c} \qquad (6\text{–}22)$$

in which Λ_0 is the intercept on the vertical axis and is known as the *equivalent conductance at infinite dilution.* The constant b is the slope of the line for the strong electrolytes shown in Figure 6–4.

When the equivalent conductance of a weak electrolyte is plotted against the square root of the concentra-

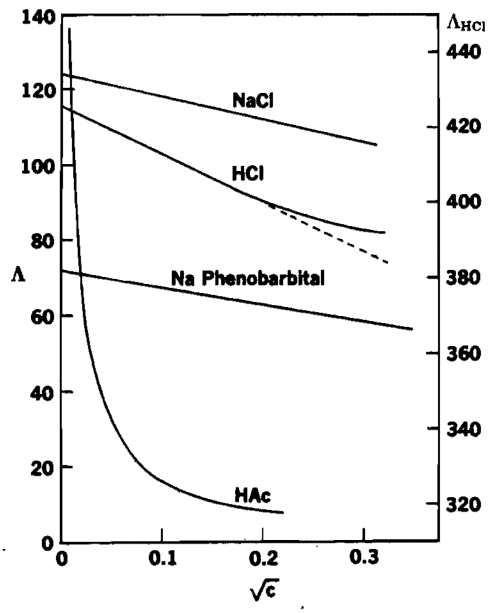

Fig. 6–4. Equivalent conductance of strong and weak electrolytes.

tion, as shown for acetic acid in Figure 6–4, the curve cannot be extrapolated to a limiting value, and Λ_o must be obtained by a method such as is described in the following paragraph. The steeply rising curve for acetic acid results from the fact that the dissociation of weak electrolytes increases on dilution, with a large increase in the number of ions capable of carrying the current.

Kohlrausch concluded that the ions of all electrolytes begin to migrate independently as the solution is diluted; the ions in dilute solutions are so far apart that they do not interact in any way. Under these conditions, Λ_o is the sum of the equivalent conductances of the cations l_c° and the anions l_a° at infinite dilution

$$\Lambda_o = l_c^\circ + l_a^\circ \qquad (6\text{–}23)$$

Based on this law, the known Λ_o values for certain electrolytes can be added and subtracted to yield Λ_o for the desired weak electrolyte. The method is illustrated in the following example.

Example 6–4. What is the equivalent conductance at infinite dilution of the weak acid phenobarbital? The Λ_o of the strong electrolytes, HCl, sodium phenobarbital (NaP), and NaCl are obtained from the experimental results shown in Figure 6–4. The values are $\Lambda_{oHCl} = 426.2$, $\Lambda_{oNaP} = 73.5$, and $\Lambda_{oNaCl} = 126.5$ mho cm^2/Eq.

Now, by Kohlrausch's law of the independent migration of ions,

$$\Lambda_{oHP} = l^\circ_{H+} + l^\circ_{P-}$$

and

$$\Lambda_{oHCl} + \Lambda_{oNaP} - \Lambda_{oNaCl} = l^\circ_{H+} + l^\circ_{Cl-} + l^\circ_{Na+} + l^\circ_{P-} - l^\circ_{Na+} - l^\circ_{Cl-}$$

which, on simplifying the right-hand side of the equation, becomes

$$\Lambda_{oHCl} + \Lambda_{oNaP} - \Lambda_{oNaCl} = l^\circ_{H+} + l^\circ_{P-}$$

Therefore,

$$\Lambda_{oHP} = \Lambda_{oHCl} + \Lambda_{oNaP} - \Lambda_{oNaCl}$$

and

$$\Lambda_{oHP} = 426.2 + 73.5 - 126.5$$
$$= 373.2 \text{ mho cm}^2\text{/Eq}$$

Colligative Properties of Electrolytic Solutions and Concentrated Solutions of Nonelectrolytes. As stated in the previous chapter, van't Hoff observed that the osmotic pressure of dilute solutions of nonelectrolytes, such as sucrose and urea, could be expressed satisfactorily by the equation, $\pi = RTc$, equation (5–34), page 118, in which R is the gas constant, T is the absolute temperature, and c is the concentration in moles per liter. Van't Hoff found, however, that solutions of electrolytes gave osmotic pressures approximately two, three, and more times larger than expected from this equation, depending on the electrolyte investigated. By introducing a correction factor i to account for the irrational behavior of ionic solutions, he wrote

$$\pi = iRTc \qquad (6\text{–}24)$$

By the use of this equation, van't Hoff was able to obtain calculated values that compared favorably with the experimental results of osmotic pressure. Van't Hoff recognized that i approached the number of ions into which the molecule dissociated as the solution was made increasingly dilute.

The factor i may also be considered to express the departure of concentrated solutions of nonelectrolytes from the laws of ideal solutions. The deviations of concentrated solutions of nonelectrolytes can be explained on the same basis as deviations of real solutions from Raoult's law, considered in the preceding chapter. They included differences of internal pressures of the solute and solvent, polarity, compound formation or complexation, and association of either the solute or solvent. The departure of electrolytic solutions from the colligative effects in ideal solutions of nonelectrolytes may be attributed—in addition to the factors just enumerated—to dissociation of weak electrolytes and to interaction of the ions of strong electrolytes. Hence, the van't Hoff factor i accounts for the deviations of real solutions of nonelectrolytes and electrolytes, regardless of the reason for the discrepancies.

The i factor is plotted against the molal concentration of both electrolytes and nonelectrolytes in Figure 6–5. For nonelectrolytes, it is seen to approach unity, and for strong electrolytes, it tends toward a value equal to the number of ions formed upon dissociation. For example, i approaches the value of 2 for solutes such as NaCl and $CaSO_4$, 3 for K_2SO_4 and $CaCl_2$, and 4 for $K_3Fe(C)_6$ and $FeCl_3$.

The van't Hoff factor can also be expressed as the ratio of any colligative property of a real solution to that of an ideal solution of a nonelectrolyte, since i represents the number of times greater that the colligative effect is for a real solution (electrolyte or nonelectrolyte) than for an ideal nonelectrolyte.

The colligative properties in dilute solutions of electrolytes are expressed on the molal scale by the equations

$$\Delta p = 0.018ip_1^\circ m \qquad (6\text{–}25)$$

$$\pi = iRTm \qquad (6\text{–}26)$$

$$\Delta T_f = iK_f m \qquad (6\text{–}27)$$

$$\Delta T_b = iK_b m \qquad (6\text{–}28)$$

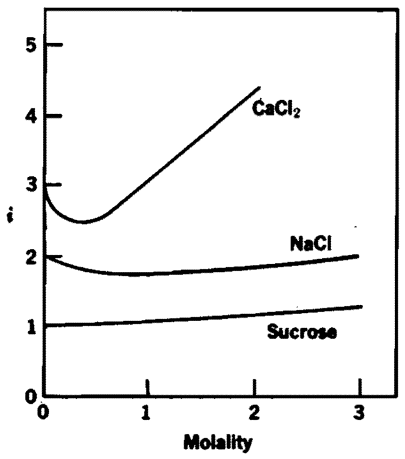

Fig. 6–5. Van't Hoff i factor of representative compounds.

Equation (6–25) applies only to aqueous solutions, whereas (6–26), (6–27), and (6–28) are independent of the solvent used.

Example 6–5. What is the osmotic pressure of a 2.0-*m* solution of sodium chloride at 20° C?

The *i* factor for a 2.0-*m* solution of sodium chloride as observed in Figure 6–5 is about 1.9.

$$\pi = 1.9 \times 0.082 \times 293 \times 2.0 = 91.3 \text{ atm}$$

ARRHENIUS THEORY OF ELECTROLYTIC DISSOCIATION

During the period in which van't Hoff was developing the solution laws, the Swedish chemist Svante Arrhenius was preparing his doctoral thesis on the properties of electrolytes at the University of Uppsala in Sweden. In 1887, he published the results of his investigations and proposed the now classic theory of dissociation.[1] The new theory resolved many of the anomalies encountered in the earlier interpretations of electrolytic solutions. Although the theory was viewed with disfavor by some influential scientists of the nineteenth century, Arrhenius's basic principles of electrolytic dissociation were gradually accepted and are still considered valid today. The theory of the existence of ions in solutions of electrolytes even at ordinary temperatures remains intact, aside from some modifications and elaborations that have been made through the years to bring it into line with certain stubborn experimental facts.

The original Arrhenius theory, together with the alterations that have come about as a result of the intensive research on electrolytes, is summarized as follows. When electrolytes are dissolved in water, the solute exists in the form of ions in the solution, as seen in the following equations

$$\underset{\text{[Ionic compound]}}{H_2O + Na^+Cl^-} \rightarrow \underset{\text{[Strong electrolyte]}}{Na^+ + Cl^- + H_2O} \qquad (6\text{–}29)$$

$$\underset{\text{[Covalent compound]}}{H_2O + HCl} \rightarrow \underset{\text{[Strong electrolyte]}}{H_3O^+ + Cl^-} \qquad (6\text{–}30)$$

$$\underset{\text{[Covalent compound]}}{H_2O + CH_3COOH} \rightleftharpoons \underset{\text{[Weak electrolyte]}}{H_3O^+ + CH_3COO^-} \qquad (6\text{–}31)$$

The solid form of sodium chloride is marked with + and − signs in reaction (6–29) to indicate that sodium chloride exists as ions even in the crystalline state. If electrodes are connected to a source of current and are placed in a mass of fused sodium chloride, the molten compound will conduct the electric current, since the crystal lattice of the pure salt consists of ions. The addition of water to the solid dissolves the crystal and separates the ions in solution.

Hydrogen chloride exists essentially as neutral molecules rather than as ions in the pure form, and does not conduct electricity. When it reacts with water, however, it ionizes according to reaction (6–30). H_3O^+ is the modern representation of the hydrogen ion in water and is known as the *hydronium* or *oxonium* ion. In addition to H_3O^+, other hydrated species of the proton probably exist in solution, but they need not be considered here.[2]

Sodium chloride and hydrochloric acid are *strong electrolytes* because they exist almost completely in the ionic form in moderately concentrated aqueous solutions. Inorganic acids such as HCl, HNO_3, H_2SO_4, and HI; inorganic bases as NaOH and KOH of the alkali metal family and $Ba(OH)_2$ and $Ca(OH)_2$ of the alkaline earth group; and most inorganic and organic salts are highly ionized and belong to the class of strong electrolytes.

Acetic acid is a *weak electrolyte*, the oppositely directed arrows in equation (6–31) indicating that an equilibrium between the molecules and ions is established. Most organic acids and bases and some inorganic compounds, such as H_3BO_3, H_2CO_3, and NH_4OH, belong to the class of weak electrolytes. Even some salts (lead acetate, $HgCl_2$, HgI, and HgBr) and the complex ions $Hg(NH_3)_2^{+}$, $Cu(NH_3)_4^{2+}$, and $Fe(CN)_6^{3-}$ are weak electrolytes.

Faraday applied the term *ion* (Greek: wanderer) to these species of electrolytes and recognized that the cations (positively charged ions) and anions (negatively charged ions) were responsible for conducting the electric current. Before the time of Arrhenius's publications, it was believed that a solute was not spontaneously decomposed in water, but rather dissociated appreciably into ions only when an electric current was passed through the solution.

Drugs and Ionization. Some drugs, such as anionic and cationic antibacterial and antiprotozoal agents, are more active when in the ionic state. Other compounds, such as the hydroxybenzoate esters (parabens) and many general anesthetics, bring about their biologic effects as nonelectrolytes. Still other compounds, such as the sulfonamides, are thought to exert their drug action both as ions and as neutral molecules.[3]

Degree of Dissociation. Arrhenius did not originally consider strong electrolytes to be ionized completely except in extremely dilute solutions. He differentiated between strong and weak electrolytes by the fraction of the molecules ionized: the *degree of dissociation* α. A strong electrolyte was one that dissociated into ions to a high degree and a weak electrolyte one that dissociated into ions to a low degree.

Arrhenius determined the degree of dissociation directly from conductance measurements. He recognized that the equivalent conductance at infinite dilution Λ_o was a measure of the complete dissociation of the solute into its ions and that Λ_c represented the number of solute particles present as ions at a concentration c. Hence, the fraction of solute molecules

ionized, or the degree of dissociation, was expressed by the equation[4]

$$\alpha = \frac{\Lambda_c}{\Lambda_o} \qquad (6\text{–}32)$$

in which Λ_c/Λ_o is known as the *conductance ratio.*

Example 6–6. The equivalent conductance of acetic acid at 25° C and at infinite dilution is 390.7 mho cm²/Eq. The equivalent conductance of a 5.9×10^{-3} *M* solution of acetic acid is 14.4 mho cm²/Eq. What is the degree of dissociation of acetic acid at this concentration?

$$\alpha = \frac{14.4}{390.7} = 0.037 \text{ or } 3.7\%$$

The van't Hoff factor i can be connected with the degree of dissociation α in the following way. The i factor equals unity for an ideal solution of a nonelectrolyte; however, a term must be added to account for the particles produced when a molecule of an electrolyte dissociates. For 1 mole of calcium chloride, which yields 3 ions per molecule, the van't Hoff factor is given by

$$i = 1 + \alpha(3 - 1) \qquad (6\text{–}33)$$

or, in general, for an electrolyte yielding v ions,

$$i = 1 + \alpha(v - 1) \qquad (6\text{–}34)$$

from which is obtained an expression for the degree of dissociation,

$$\alpha = \frac{i - 1}{v - 1} \qquad (6\text{–}35)$$

The cryoscopic method is used to determine i from the expression

$$\Delta T_f = iK_f m \qquad (6\text{–}36)$$

or

$$i = \frac{\Delta T_f}{K_f m} \qquad (6\text{–}37)$$

Example 6–7. The freezing point of a 0.10-*m* solution of acetic acid is −0.188° C. Calculate the degree of ionization of acetic acid at this concentration. Acetic acid dissociates into two ions, that is, $v = 2$.

$$i = \frac{0.188}{1.86 \times 0.10} = 1.011$$

$$\alpha = \frac{i - 1}{v - 1} = \frac{1.011 - 1}{2 - 1} = 0.011$$

In other words, according to the result of *Example 6–7* the fraction of acetic acid present as free ions in a 0.10-*m* solution is 0.011. Stated in percentage terms, acetic acid in 0.1 *m* concentration is ionized to the extent of about 1%.

THEORY OF STRONG ELECTROLYTES

Arrhenius used α to express the degree of dissociation of both strong and weak electrolytes, and van't Hoff introduced the factor i to account for the deviation of strong and weak electrolytes and nonelectrolytes from the ideal laws of the colligative properties, regardless of the nature of these discrepancies. According to the early ionic theory, the degree of dissociation of ammonium chloride, a strong electrolyte, was calculated in the same manner as that of a weak electrolyte.

Example 6–8. The freezing point depression for a 0.01-*m* solution of ammonium chloride is 0.0367° C. Calculate the "degree of dissociation" of this electrolyte.

$$i = \frac{\Delta T_f}{K_f m} = \frac{0.0367°}{1.86 \times 0.010} = 1.97$$

$$\alpha = \frac{1.97 - 1}{2 - 1} = 0.97$$

The Arrhenius theory is now accepted for describing the behavior only of weak electrolytes. The degree of dissociation of a weak electrolyte can be calculated satisfactorily from the conductance ratio Λ_c/Λ_o or obtained from the van't Hoff i factor.

Many inconsistencies arise, however, when an attempt is made to apply the theory to solutions of strong electrolytes. In dilute and moderately concentrated solutions, they dissociate almost completely into ions, and it is not satisfactory to write an equilibrium expression relating the concentration of the ions and the minute amount of undissociated molecules, as is done for weak electrolytes (Chapter 7). Moreover, a discrepancy exists between α calculated from the i value and α calculated from the conductivity ratio for strong electrolytes in aqueous solutions having concentrations greater than about 0.5 *M*.

For these reasons, one does not account for the deviation of a strong electrolyte from ideal nonelectrolyte behavior by calculating a degree of dissociation. It is more convenient to consider a strong electrolyte as completely ionized and to introduce a factor that expresses the deviation of the solute from 100% ionization. The *activity* and *osmotic coefficient*, discussed in subsequent paragraphs, are used for this purpose.

Activity and Activity Coefficients. An approach that conforms well to the facts and that has evolved from a large number of studies on solutions of strong electrolytes ascribes the behavior of strong electrolytes to an electrostatic attraction between the ions.

The large number of oppositely charged ions in solutions of electrolytes influence one another through *interionic attractive forces.* Although this interference is negligible in dilute solutions, it becomes appreciable at moderate concentrations. In solutions of weak electrolytes, regardless of concentration, the number of ions is small and the interionic attraction correspondingly insignificant. Hence, the Arrhenius theory and the concept of the degree of dissociation are valid for solutions of weak electrolytes but not for strong electrolytes.

Not only are the ions interfered with in their movement by the "atmosphere" of oppositely charged ions surrounding them; they also can associate at high concentration into groups known as *ion pairs*, for example, Na^+Cl^-, and ion triplets, $Na^+Cl^-Na^+$. Asso-

ciations of still higher orders may exist in solvents of low dielectric constant, in which the force of attraction of oppositely charged ions is large.

Because of the electrostatic attraction and ion association in moderately concentrated solutions of strong electrolytes, the values of the freezing point depression and the other colligative properties are less than expected for solutions of unhindered ions. Consequently, a strong electrolyte may be *completely ionized*, yet *incompletely dissociated* into free ions.

One may think of the solution as having an "effective concentration'" or, as it is called, an *activity*. The activity, in general, is less than the actual or stoichiometric concentration of the solute, not because the strong electrolyte is only partly ionized, but rather because some of the ions are effectively "taken out of play" by the electrostatic forces of interaction.

At infinite dilution in which the ions are so widely separated that they do not interact with one another, the activity a of an ion is equal to its concentration, expressed as molality or molarity. It is written on a molal basis at infinite dilution as

$$a = m \tag{6-38}$$

or

$$\frac{a}{m} = 1 \tag{6-39}$$

As the concentration of the solution is increased, the ratio becomes less than unity because the effective concentration or activity of the ions becomes less than the stoichiometric or molal concentration. This ratio is known as the *practical activity coefficient* γ_m on the molal scale, and the formula is written, for a particular ionic species, as

$$\frac{a}{m} = \gamma_m \tag{6-40}$$

or

$$a = \gamma_m m \tag{6-41}$$

On the molarity scale, another *practical activity coefficient* γ_c is defined as

$$a = \gamma_c c \tag{6-42}$$

and on the mole fraction scale, a *rational activity coefficient* is defined as

$$a = \gamma_x X \tag{6-43}$$

One sees from equations (6–41), (6–42), and (6–43) that these coefficients are proportionality constants relating activity to molality, molarity, and mole fraction, respectively, for an ion. The activity coefficients take on a value of unity and are thus identical in infinitely dilute solutions. The three coefficients usually decrease and assume different values as the concentration is increased; however, the differences among the three activity coefficients may be disregarded in dilute solutions in which $c \cong m < 0.01$. The concept of activity and activity coefficient was first introduced by Lewis and Randall[5] and may be applied to solutions of nonelectrolytes and weak electrolytes as well as to the ions of strong electrolytes.

A cation and an anion in an aqueous solution may each have a different ionic activity. This is recognized by using the symbol a_+ when speaking of the activity of a cation and the symbol a_- when speaking of the activity of an anion. An electrolyte in solution contains each of these ions, however, so it is convenient to define a relationship between the activity of the electrolyte $a_\pm$ and the activities of the individual ions. The activity of an electrolyte is defined by its *mean ionic activity*, which is given by the relation

$$a_\pm = (a_+{}^m a_-{}^n)^{1/(m+n)} \tag{6-44}$$

in which the exponents m and n give the stoichiometric number of given ions that are in solution. Thus, an NaCl solution has a mean ionic activity of

$$a_\pm = (a_{Na^+} a_{Cl^-})^{1/2}$$

whereas an $FeCl_3$ solution has a mean ionic activity of

$$a_\pm = (a_{Fe^{+3}} a_{Cl^-}{}^3)^{1/4}$$

The ionic activities of equation (6–44) may be expressed in terms of concentrations using any of equations (6–41) to (6–43). Using equation (6–42) one obtains from equation (6–44) the expression

$$a_\pm = [(\gamma_+ c_+)^m (\gamma_- c_-)^n]^{1/(m+n)} \tag{6-45}$$

or

$$a_\pm = (\gamma_+{}^m \gamma_-{}^n)^{1/(m+n)} (c_+{}^m c_-{}^n)^{1/(m+n)} \tag{6-46}$$

The *mean ionic activity coefficient* for the electrolyte can be defined by

$$\gamma_\pm = (\gamma_+{}^m \gamma_-{}^n)^{1/(m+n)} \tag{6-47}$$

and

$$\gamma_\pm^{m+n} = \gamma_+{}^m \gamma_-{}^n \tag{6-48}$$

Substitution of equation (6–47) into equation (6–46) yields

$$a_\pm = \gamma_\pm (c_+{}^m c_-{}^n)^{1/(m+n)} \tag{6-49}$$

In using equation (6–49), it should be noted that the concentration of the electrolyte c is related to the concentration of its ions by

$$c_+ = mc \tag{6-50}$$

and

$$c_- = nc \tag{6-51}$$

Example 6–9. What is the mean ionic activity of a 0.01 *M* solution of $FeCl_3$?

$$a_\pm = \gamma_\pm (c_+ c_-{}^3)^{1/4} = \gamma_\pm [(0.01)(3 \times 0.01)^3]^{1/4}$$
$$= 2.3 \times 10^{-2} \gamma_\pm$$

It is possible to obtain the *mean ionic activity coefficient* $\gamma_{\pm}$ of an electrolyte by several experimental methods as well as by a theoretic approach. The experimental methods include distribution coefficient studies, electromotive force measurement, colligative property methods, and solubility determinations. (These results may then be used to obtain approximate activity coefficients for individual ions, where this is desired.[6])

Debye and Hückel have developed a theoretic method by which it is possible to calculate the activity coefficient of a single ion as well as the mean ionic activity coefficient of a solute without recourse to experimental data. Although the theoretic equation agrees with experimental findings only in dilute solutions (so dilute, in fact, that some chemists have referred jokingly to such solutions as "slightly contaminated water"), it has certain practical value in solution calculations. Furthermore, the Debye-Hückel equation provides a remarkable confirmation of modern solution theory.

The mean ionic activity coefficients of a number of strong electrolytes are found in Table 6–1. The results of various investigators vary in the third decimal place; therefore, most of the entries in the table have been recorded only to two places, providing sufficient precision for the calculations in this book. Although the values in the table are given at various molalities, we may accept these activity coefficients for problems involving molar concentrations (in which $m < 0.1$) since, in dilute solutions, the difference between molality and molarity is not great.

The mean values of Table 6–1 for NaCl, $CaCl_2$, and $ZnSO_4$ are plotted in Figure 6–6 against the square root of the molality. The reason for plotting the square root of the concentration is due to the form that the Debye–Hückel equation takes (p. 135). The activity coefficient approaches unity with increasing dilution. As the concentrations of some of the electrolytes are increased, their curves pass through minima and rise again to values greater than unity. Although the curves for different electrolytes of the same ionic class coincide at lower concentrations, they differ widely at higher values. The initial decrease in the activity coefficient

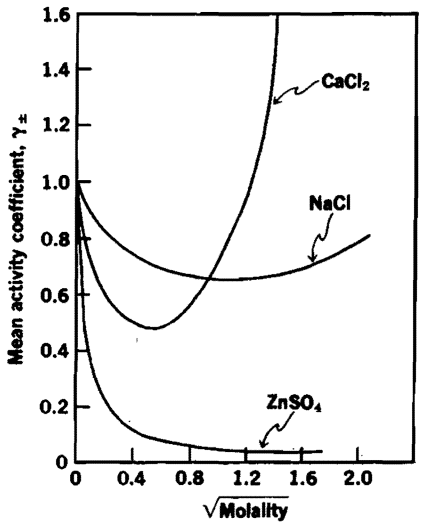

Fig. 6–6. Mean ionic activity coefficients of representative electrolytes plotted against the square root of concentration.

with increasing concentration is due to the interionic attraction, which causes the activity to be less than the stoichiometric concentration. The rise in the activity coefficient following the minimum in the curve of an electrolyte, such as HCl and $CaCl_2$, can be attributed to the attraction of the water molecules for the ions in concentrated aqueous solution. This *solvation* reduces the interionic attractions and increases the activity coefficient of the solute. It is the same effect that results in the salting out of nonelectrolytes from aqueous solutions to which electrolytes have been added.

Activity of the Solvent. Thus far, the discussion of activity and activity coefficients has centered on the solute and particularly on electrolytes. It is customary to define the activity of the solvent on the mole fraction scale. When a solution is made infinitely dilute, it can be considered to consist essentially of pure solvent. Therefore, $X_1 \cong 1$, and the solvent behaves ideally in conformity with Raoult's law. Under this condition, the mole fraction can be set equal to the activity of the solvent, or

$$a = X_1 = 1 \qquad (6\text{–}52)$$

TABLE 6–1. ***Mean Ionic Activity Coefficients of Some Strong Electrolytes at 25° C on the Molal Scale***

Molality (m)	HCl	NaCl	KCl	NaOH	$CaCl_2$	H_2SO_4	Na_2SO_4	$CuSO_4$	$ZnSO_4$
0.000	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
0.005	0.93	0.93	0.93	—	0.79	0.64	0.78	0.53	0.48
0.01	0.91	0.90	0.90	0.90	0.72	0.55	0.72	0.40	0.39
0.05	0.83	0.82	0.82	0.81	0.58	0.34	0.51	0.21	0.20
0.10	0.80	0.79	0.77	0.76	0.52	0.27	0.44	0.15	0.15
0.50	0.77	0.68	0.65	0.68	0.51	0.16	0.27	0.067	0.063
1.00	0.81	0.66	0.61	0.67	0.73	0.13	0.21	0.042	0.044
2.00	1.01	0.67	0.58	0.69	1.55	0.13	0.15	—	0.035
4.00	1.74	0.79	0.58	0.90	2.93	0.17	0.14	—	—

As the solution becomes more concentrated in solute, the activity of the solvent ordinarily becomes less than the mole fraction concentration, and the ratio can be given, as for the solute, by the rational activity coefficient

$$\frac{a}{X_1} = \gamma_x \tag{6-53}$$

or

$$a = \gamma_x X_1 \tag{6-54}$$

The activity of a volatile solvent can be determined rather simply. The ratio of the vapor pressure p_1 of the solvent in a solution to the vapor pressure of pure solvent p_1° is approximately equal to the *activity* of the solvent at ordinary pressures: $a_1 = p_1/p^\circ$.

Example 6–10. The vapor pressure of water in a solution containing 0.5 mole of sucrose in 1000 g of water is 17.38 mm, and the vapor pressure of pure water at 20° C is 17.54 mm. What is the activity (or escaping tendency) of water in the solution?

$$a = \frac{17.38}{17.54} = 0.991$$

Reference State. The assignment of activities to the components of solutions provides a measure of the extent of departure from ideal solution behavior. For this purpose, a *reference state* must be established in which each component behaves ideally. The reference state may be defined as the solution in which the concentration (mole fraction, molal or molar) of the component is equal to the activity:

$$\text{activity} = \text{concentration}$$

or, what amounts to the same thing, the activity coefficient is unity,

$$\gamma_i = \frac{\text{activity}}{\text{concentration}} = 1$$

The reference state for a solvent on the mole fraction scale was shown in equation (6–52) to be the pure solvent.

The reference state for the solute may be chosen from one of several possibilities. If a liquid solute is miscible with the solvent (e.g., in a solution of alcohol in water), the concentration may be expressed in mole fraction, and the pure liquid may be taken as the reference state, as was done for the solvent. For a liquid or solid solute having a limited solubility in the solvent, the reference state is ordinarily taken as the infinitely dilute solution in which the concentration of the solute and the ionic strength (see the following) of the solution are small. Under these conditions, the activity is equal to the concentration, and the activity coefficient is unity.

Standard State. The activities ordinarily used in chemistry are relative activities. It is not possible to know the absolute value of the activity of a component; therefore, a standard must be established just as was done in Chapter 1 for the fundamental measurable properties.

The *standard state* of a component in a solution is the state of the component at unit activity. The relative activity in any solution is then the ratio of the activity in that state relative to the value in the standard state. When defined in these terms, activity is a dimensionless number.

The pure liquid at 1 atm and at a definite temperature is chosen as the standard state of a solvent or of a liquid solute miscible with the solvent, since, for the pure liquid, $a = 1$. Because the mole fraction of a pure solvent is also unity, mole fraction is equal to activity, and the reference state is identical with the standard state.

The standard state of the solvent in a solid solution is the pure solid at 1 atm and at a definite temperature. The assignment of $a = 1$ to pure liquids and pure solids will be found to be convenient in later discussions on equilibria and electromotive force.

The standard state for a solute of limited solubility is more difficult to define. The activity of the solute in an infinitely dilute solution, although equal to the concentration, is not unity, and the standard state is thus not the same as the reference state. The standard state of the solute is defined as a hypothetic solution of unit concentration (mole fraction, molal or molar) having, at the same time, the characteristics of an infinitely dilute or ideal solution. For complete understanding, this definition requires careful development, as carried out by Klotz and Rosenberg.[7]

Ionic Strength. In dilute solutions of nonelectrolytes, activities and concentrations are considered to be practically identical, since electrostatic forces do not bring about deviations from ideal behavior in these solutions. Likewise, for weak electrolytes that are present alone in solution, the differences between the ionic concentration terms and activities are usually disregarded in ordinary calculations, since the number of ions present is small, and the electrostatic forces are negligible.

However, for strong electrolytes and for solutions of weak electrolytes together with salts and other electrolytes, such as exist in buffer systems, it is important to use activities instead of concentrations. The activity coefficient, and hence the activity, may be obtained by using one of the forms of the Debye–Hückel equation (considered below) if one knows the ionic strength of the solution. Lewis and Randall[8] introduced the concept of *ionic strength* μ to relate interionic attractions and activity coefficients. The ionic strength is defined on the molar scale as

$$\mu = \tfrac{1}{2}(c_1 z_1^2 + c_2 z_2^2 + c_3 z_3^2 + \cdots + c_j z_j^2) \tag{6-55}$$

or, in abbreviated notation

$$\mu = \tfrac{1}{2} \sum_1^j c_i z_i^2 \tag{6-56}$$

in which the summation symbol $\sum_{1}^{j}$ indicates that the product of cz^2 terms for all the ionic species in the solution, from the first one to the j^{th} species, are to be added together. The term c_i is the concentration in moles per liter of any of the ions and z_i is its valence. Ionic strength represents the contribution to the electrostatic forces of the ions of all types. It depends on the total number of ionic charges and not on the specific properties of the salts present in the solution. It was found that bivalent ions are equivalent not to two but to four univalent ions; hence, by introducing the square of the valence, proper weight is given to the ions of higher charge. The sum is divided by two because positive ion–negative ion pairs contribute to the total electrostatic interaction, whereas we are interested in the effect of each ion separately.

Example 6–11. What is the ionic strength of (*a*) 0.010 *M* KCl, (*b*) 0.010 *M* $BaSO_4$, and (*c*) 0.010 *M* Na_2SO_4, and (*d*) what is the ionic strength of a solution containing all three electrolytes together with salicylic acid in 0.010 *M* concentration in aqueous solution?

(*a*) KCl

$$\mu = \tfrac{1}{2}[(0.01 \times 1^2) + (0.01 \times 1^2)]$$
$$= 0.010$$

(*b*) $BaSO_4$

$$\mu = \tfrac{1}{2}[(0.01 \times 2^2) + (0.01 \times 2^2)]$$
$$= 0.040$$

(*c*) Na_2SO_4

$$\mu = \tfrac{1}{2}[(0.02 \times 1^2) + (0.01 \times 2^2)]$$
$$= 0.030$$

(*d*) The ionic strength of a 0.010-*M* solution of salicylic acid is 0.003 as calculated from a knowledge of the ionization of the acid at this concentration (using the equation $[H_3O^+] = \sqrt{K_a c}$ of pp. 145, 155). Unionized salicyclic acid does not contribute to the ionic strength.

The ionic strength of the mixture of electrolytes is the sum of the ionic strengths of the individual salts. Thus,

$$\mu_{total} = \mu_{KCl} + \mu_{BaSO_4} + \mu_{Na_2SO_4} + \mu_{HSal}$$
$$= 0.010 + 0.040 + 0.030 + 0.003$$
$$= 0.083$$

Example 6–12. A buffer contains 0.3 mole of K_2HPO_4 and 0.1 mole of KH_2PO_4 per liter of solution. Calculate the ionic strength of the solution.

The concentrations of the ions of K_2HPO_4 are $[K^+] = 0.3 \times 2$ and $[HPO_4^{2-}] = 0.3$. The values for KH_2PO_4 are $[K^+] = 0.1$ and $[H_2PO_4^-] = 0.1$. Any contributions to μ by further dissociation of $[HPO_4^{2-}]$ and $[H_2PO_4^-]$ are neglected.

$$\mu = \tfrac{1}{2}[(0.3 \times 2 \times 1^2) + (0.3 \times 2^2) + (0.1 \times 1^2) + (0.1 \times 1^2)]$$
$$\mu = 1.0$$

It will be observed in *Example 6–11* that the ionic strength of a 1:1 electrolyte such as KCl is the same as the molar concentration; μ of a 1:2 electrolyte such as Na_2SO_4 is three times the concentration; and μ for a 2:2 electrolyte is four times the concentration.

The mean ionic activity coefficients of electrolytes should be expressed at various ionic strengths instead of concentrations. Lewis has shown the uniformity in activity coefficients when they are related to ionic strength:

(*a*) The activity coefficient of a strong electrolyte is roughly constant in all dilute solutions of the same ionic strength, irrespective of the type of salts that are used to provide the additional ionic strength.

(*b*) The activity coefficients of all strong electrolytes of a single class, for example, all uni-univalent electrolytes, are approximately the same at a definite ionic strength, provided the solutions are dilute.

The results in Table 6–1 illustrate the similarity of the mean ionic activity coefficients for 1:1 electrolytes at low concentrations (below 0.1 *m*) and the differences that become marked at higher concentrations.

Bull[9] pointed out the importance of the principle of ionic strength in biochemistry. In the study of the influence of pH on biologic action, the effect of the variable salt concentration in the buffer may obscure the results unless the buffer is adjusted to a constant ionic strength in each experiment. If the biochemical action is affected by the specific salts used, however, even this precaution may fail to yield satisfactory results. Further use will be made of ionic strength in the chapters on ionic equilibria, solubility, and kinetics.

The Debye–Hückel Theory. Debye and Hückel derived an equation based on the principles that strong electrolytes are completely ionized in dilute solution and that the deviations of electrolytic solutions from ideal behavior are due to the electrostatic effects of the oppositely charged ions. The equation relates the activity coefficient of a particular ion or the mean ionic activity coefficient of an electrolyte to the valence of the ions, the ionic strength of the solution, and the characteristics of the solvent. The mathematical derivation of the equation is not attempted here but can be found in Lewis and Randall's *Thermodynamics* as revised by Pitzer and Brewer.[10] The equation may be used to calculate the activity coefficients of drugs, the values of which have not been obtained experimentally and are not available in the literature.

According to the theory of Debye and Hückel, the activity coefficient γ_i of an ion of valence z_i is given by the expression

$$\log \gamma_i = -Az_i^2\sqrt{\mu} \qquad (6\text{–}57)$$

Equation (6–57) yields a satisfactory measure of the activity coefficient of an ion species up to an ionic strength μ of about 0.02. For water at 25° C, A, a factor that depends only on the temperature and the dielectric constant of the medium, is approximately equal to 0.51. The values of A for various solvents of pharmaceutical importance are found in Table 6–2.

The form of the Debye–Hückel equation for a binary electrolyte, consisting of ions with valences of z_+ and z_- and present in a dilute solution ($\mu < 0.02$), is

$$\log \gamma_\pm = -Az_+z_-\sqrt{\mu} \qquad (6\text{–}58)$$

TABLE 6–2. *Values of A for Solvents at 25° C*

Solvent	Dielectric Constant ϵ	A^*_{calc}
Acetone	20.70	3.76
Ethanol	24.30	2.96
Water	78.54	0.509

*$A_{(calc)} = \dfrac{1.824 \times 10^6}{(\epsilon \times T)^{3/2}}$ in which ϵ is the dielectric constant and T is the absolute temperature on the Kelvin scale.

The symbols z_+ and z_- stand for the valences or charges, ignoring algebraic signs, on the ions of the electrolyte whose mean ionic activity coefficient is sought. The coefficient in equation (6–58) is γ_x, the rational activity coefficient (i.e., $\gamma_\pm$ on the mole fraction scale), but in dilute solutions for which the Debye–Hückel equation is applicable, γ_x can be assumed without serious error to be equal also to the practical coefficients, γ_m and γ_c, on the molal and molar scales.

Example 6–13. Calculate the mean ionic activity coefficient for 0.005 *M* atropine sulfate (1:2 electrolyte) in an aqueous solution containing 0.01 *M* NaCl at 25° C. Since the drug is a uni-bivalent electrolyte, $z_1z_2 = 1 \times 2 = 2$. *A* for water at 25° C is 0.51.

μ for atropine sulfate $= \frac{1}{2}[(0.005 \times 2 \times 1^2) + (0.005 \times 2^2)] = 0.015$

μ for NaCl $= \frac{1}{2}[(0.01 \times 1^2) + (0.01 \times 1^2)] = 0.01$

Total μ $= 0.025$

$$\log \gamma_\pm = -0.51 \times 2 \times \sqrt{0.025}$$

$$\log \gamma_\pm = -1.00 + 0.839 = -0.161$$

$$\gamma_\pm = 0.690$$

With the present-day accessibility of the hand calculator, the intermediate step in this calculation (needed only when log tables are used) may be deleted.

Thus one observes that the activity coefficient of a strong electrolyte in dilute solution depends on the total ionic strength of the solution, the valence of the ions of the drug involved, the nature of the solvent, and the temperature of the solution. Notice that although the ionic strength term results from the contribution of all ionic species in solution, the z_1z_2 terms apply only to the drug, the activity coefficient of which is being determined.

Extension of the Debye–Hückel Equation to Higher Concentrations. The limiting expressions, equations (6–57) and (6–58), are not satisfactory above an ionic strength of about 0.02, and (6–58) is not completely satisfactory for use in *Example 6–13*. A formula that applies up to an ionic strength of perhaps 0.1 is

$$\log \gamma_\pm = -\frac{Az_+z_-\sqrt{\mu}}{1 + a_iB\sqrt{\mu}} \qquad (6\text{–}59)$$

The term a_i is the mean distance of approach of the ions and is called the *mean effective ionic diameter* or the *ion size parameter*. Its exact significance is not known; however, it is somewhat analogous to the b term in the van der Waals gas equation. The term B, like A, is a constant influenced only by the nature of the solvent and the temperature. The values of a_i for several electrolytes at 25° C are given in Table 6–3, and the values of B and A for water at various temperatures are shown in Table 6–4. The values of A for various solvents, as previously mentioned, are listed in Table 6–2.

Since a_i for most electrolytes equals 3 to 4×10^{-8} and B for water at 25° C equals 0.33×10^8, the product of a_i and B is approximately unity. Equation (6–59) then simplifies to

$$\log \gamma_\pm = -\frac{Az_+z_-\sqrt{\mu}}{1 + \sqrt{\mu}} \qquad (6\text{–}60)$$

Example 6–14. Calculate the activity coefficient of a 0.004*M* aqueous solution of sodium phenobarbital at 25° C, which has been brought to an ionic strength of 0.09 by the addition of sodium chloride. Use equations (6–58), (6–59), and (6–60) and compare the results.

Equation (6–58): $\log \gamma_\pm = -0.51\sqrt{0.09}$; $\gamma_\pm = 0.70$

Equation (6–59): $\log \gamma_\pm = -\dfrac{0.51\sqrt{0.09}}{1 + [(2 \times 10^{-8}) \times (0.33 \times 10^8) \times \sqrt{0.09}]}$; $\gamma_\pm = 0.75$

Equation (6–60): $\log \gamma_\pm = -\dfrac{0.51\sqrt{0.09}}{1 + \sqrt{0.09}}$; $\gamma_\pm = 0.76$

These results may be compared with the experimental values for some uni-univalent electrolytes in Table 6–1 at a molal concentration of about 0.1.

For still higher concentrations, that is, at ionic strengths above 0.1, the observed activity coefficients for some electrolytes pass through minima and then

TABLE 6–3. *Mean Effective Ionic Diameter for Some Electrolytes at 25° C*

Electrolyte	a_i (cm)
HCl	5.3×10^{-8}
NaCl	4.4×10^{-8}
KCl	4.1×10^{-8}
Methapyrilene HCl	3.9×10^{-8}
$MgSO_4$	3.4×10^{-8}
K_2SO_4	3.0×10^{-8}
$AgNO_3$	2.3×10^{-8}
Sodium phenobarbital	2.0×10^{-8}

TABLE 6–4. *Values of A and B for Water at Various Temperatures*

Temperature (°C)	*A*	*B*
0	0.488	0.325×10^8
15	0.500	0.328×10^8
25	0.509	0.330×10^8
40	0.524	0.333×10^8
70	0.560	0.339×10^8
100	0.606	0.348×10^8

increase with concentration; in some cases they become greater than unity, as seen in Figure 6–6. To account for the increase in $\gamma_\pm$ at higher concentrations, an empirical term $C\mu$ can be added to the Debye–Hückel equation, resulting in the expression

$$\log \gamma_\pm = -\frac{Az_+z_-\sqrt{\mu}}{1 + a_iB\sqrt{\mu}} + C\,\mu \qquad (6\text{–}61)$$

This equation gives satisfactory results in solutions of concentrations as high as 1 M. The mean ionic activity coefficient obtained from equation (6–61) is γ_x; however, it is not significantly different from γ_m *and* γ_c even at this concentration. Zografi et al.[11] have used the extended Debye–Hückel equation (equation (6–61)) in a study of the interaction between the dye orange II and quarternary ammonium salts.

Investigations have resulted in equations that extend the concentration to about 5 moles/liter.[12]

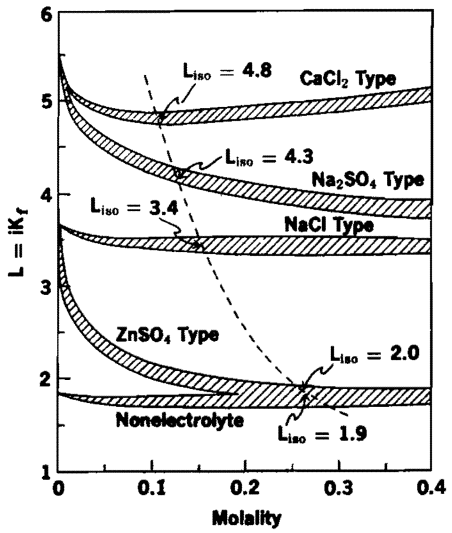

Fig. 6–7. L_{iso} values of various ionic classes.

COEFFICIENTS FOR EXPRESSING COLLIGATIVE PROPERTIES

Although activities may be used to bring the colligative properties of strong electrolytes into line with experimental results, the equations are complicated and are not treated in this book. Activities are more valuable in connection with equilibria expressions and electrochemical calculations. The use of activities for calculating the colligative properties of weak electrolytes is particularly inconvenient, for it also requires a knowledge of the degree of dissociation.

The *L* Value. The van't Hoff expression $\Delta T_f = iK_f m$ probably provides the best single equation for computing the colligative properties of nonelectrolytes, weak electrolytes, and strong electrolytes. It can be modified slightly for convenience in dilute solutions by substituting molar concentration c and by writing iK_f as L, so that

$$\Delta T_f = Lc \qquad (6\text{–}62)$$

L has been computed from experimental data for a number of drugs by Goyan et al.[13] It varies with the concentration of the solution. At a concentrtion of drug that is isotonic with body fluids, $L = iK_f$ is designated here as L_{iso}. It has a value equal to about 1.9 (actually 1.86) for nonelectrolytes, 2.0 for weak electrolytes, 3.4 for uni-univalent electrolytes, and larger values for electrolytes of high valences. A plot of iK_f against the concentration of some drugs is presented in Figure 6–7, in which each curve is represented as a band to show the variability of the L values within each ionic class. The approximate L_{iso} for each of the ionic classes may be obtained from the dashed line running vertically through the figure. The application of L_{iso} to the preparation of isotonic drug solutions is described in Chapter 8.

Osmotic Coefficient. Other methods of correcting for the deviations of electrolytes from ideal colligative behavior have been suggested. One of these is based on the fact that as the solution becomes more dilute, i approaches ν, the number of ions into which an electrolyte dissociates, and at infinite dilution, $i = \nu$, or $i/\nu = 1$. Proceeding in the direction of more concentrated solutions, i/ν becomes less (and sometimes greater) than unity.

The ratio i/ν is designated as g and is known as the *practical osmotic coefficient* when expressed on a molal basis. In the case of a weak electrolyte, it provides a measure of the degree of dissociation. For strong electrolytes g is equal to unity for complete dissociation, and the depature of g from unity, that is, $1 - g$, in moderately concentrated solutions is an indication of the interionic attraction. Osmotic coefficients, g, for electrolytes and nonelectrolytes are plotted against ionic concentration, νm, in Figure 6–8. Since $g = 1/\nu$ or $i = g\nu$ in a dilute solution, the cryoscopic equation may be written

$$\Delta T_f = g\nu K_f m \qquad (6\text{–}63)$$

The molal osmotic coefficients of some salts are listed in Table 6–5.

Example 6–15. The osmotic coefficient of LiBr at 0.2 m is 0.944 and the L_{iso} value is 3.4. Compute ΔT_f for this compound using g and L_{iso}. Disregard the difference between molality and molarity.

$$\Delta T_f = g\nu K_f m = 0.944 \times 2 \times 1.86 \times 0.2$$
$$= 0.70°$$
$$\Delta T_f = L_{iso}c = 3.4 \times 0.2 = 0.68°$$

Osmolality. Although osmotic pressure (pp. 117–119) classically is given in atmospheres, in clinical practice it is expressed in terms of osmols (Osm) or milliosmols (mOsm). A solution containing 1 mole (1 gram molecular weight) of a nonionizable substance in 1 kg of water (a

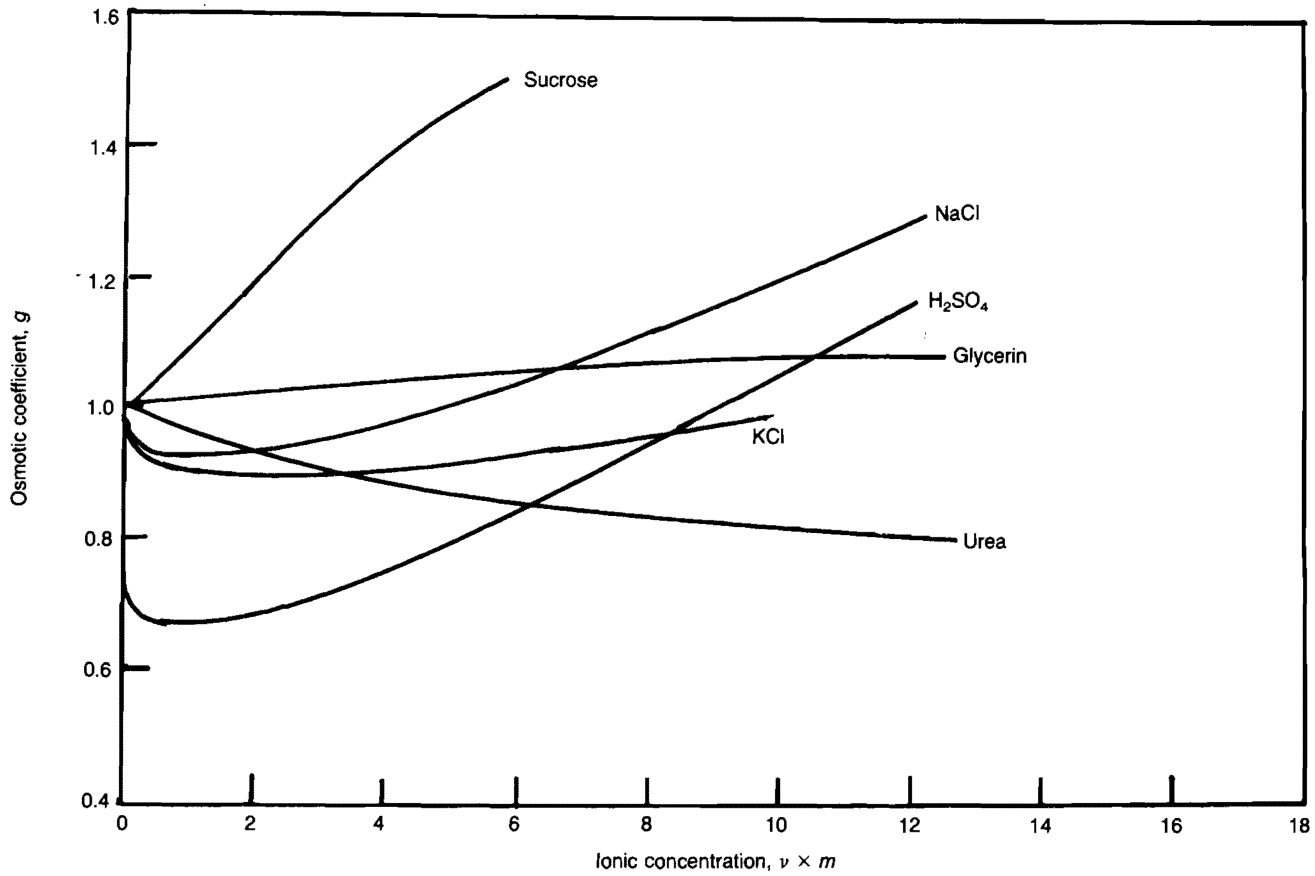

Fig. 6–8. Osmotic coefficient, g, for some common solutes. (From G. Scatchard, W. Hamer and S. Wood, J. Am. Chem. Soc. **60**, 3061, 1938. Reproduced with permission of the copyright owner.)

1-m solution) is referred to as a 1-osmolal solution. It contains 1 osmol (Osm) or 1000 milliosmols (mOsm) of solute per kilogram of solvent. Osmolality measures the total number of particles dissolved in a kilogram of water, that is, the osmols per kilogram of water, and depends on the electrolytic nature of the solute. An ionic species dissolved in water will dissociate to form ions or "particles." These ions tend to associate somewhat, however, owing to their ionic interactions. The apparent number of "particles" in solution, as measured by osmometry or one of the other colligtive methods, will depend on the extent of these interactions. An un-ionized material (i.e., a nonelectrolyte) is used as the reference solute for osmolality measurements, ionic interactions being insignificant for a nonelectrolyte. For an electrolyte that dissociates into ions in a dilute solution, osmolality or milliosmolality can be calculated from

$$\text{Milliosmolality (mOsm/kg)} = i \cdot mm \quad (6\text{–}64)$$

TABLE 6–5. ***Osmotic Coefficients, g, at 25° C****

m	NaCl	KCl	H_2SO_4	Sucrose	Urea	Glycerin
0.1	0.9342	0.9264	0.6784	1.0073	0.9959	1.0014
0.2	0.9255	0.9131	0.6675	1.0151	0.9918	1.0028
0.4	0.9217	0.9023	0.6723	1.0319	0.9841	1.0055
0.6	0.9242	0.8987	0.6824	1.0497	0.9768	1.0081
0.8	0.9295	0.8980	0.6980	1.0684	0.9698	1.0105
1.0	0.9363	0.8985	0.7176	1.0878	0.9631	1.0128
1.6	0.9589	0.9024	0.7888	1.1484	0.9496	1.0192
2.0	0.9786	0.9081	0.8431	1.1884	0.9346	1.0230
3.0	1.0421	0.9330	0.9922	1.2817	0.9087	1.0316
4.0	1.1168	0.9635	1.1606	1.3691	0.8877	1.0393
5.0	1.2000	0.9900	—	1.4477	0.8700	1.0462

*From G. Scatchard, W. G. Hamer and S. E. Wood, J. Am. Chem. Soc. **60**, 3061, 1938. Reproduced with permission of the copyright owner.

in which i (see p. 129) is approximately the number of ions formed per molecule and mm is the millimolal concentration. If no ionic interactions occurred in a solution of sodium chloride, i would equal 2.0. In a typical case, for a 1:1 electrolyte in dilute solution, i is approximately 1.86 rather than 2.0, owing to ionic interaction between the positively and negatively charged ions.

Example 6–16. What is the milliosmolality of a 0.120-m solution of potassium bromide? What is its osmotic pressure in atmospheres?

For a 120 millimolal solution of KBr:

$$\text{Milliosmolality} = 1.86 \times 120 = 223 \text{ mOsm/kg}$$

A 1-osmolal solution raises the boiling point 0.52° C, lowers the freezing point 1.86° C, and produces an osmotic pressure of 24.4 atm at 25° C. Therefore, a 0.223 Osm/kg solution yields an osmotic pressure of $24.4 \times 0.223 = 5.44$ atm.

Refer to the reports by Streng et al.[14] and Murty et al.[15] for discussions on the use of osmolality and osmolarity in clinical pharmacy. Molarity (moles of solute per liter of solution) is used in clinical practice more frequently than molality (moles of solute per kilogram of solvent). Also, osmolarity is used more frequently than osmolality in labeling parenteral solutions in the hospital. Yet osmolarity cannot be measured and must be calculated from the experimentally determined osmolality of a solution. As shown by Murty et al.,[15] the conversion is made using the relation:

$$\begin{aligned}\text{Osmolarity} = {} & (\text{measured osmolality}) \\ & \times (\text{solution density in g/mL} \\ & - \text{anhydrous solute concentration in g/mL})\end{aligned} \quad (6\text{–}65)$$

According to Streng et al.,[14] osmolality is converted to osmolarity using the equation

$$\text{mOsm/liter solution} = \text{mOsm/(kg } H_2O) \times [d_1^\circ(1 - 0.001\,\bar{v}_2^\circ)] \quad (6\text{–}66)$$

where d_1° is the density of the solvent and $\bar{v}_2^\circ$ is the partial molal volume of the solute at infinite dilution.

Example 6–17. A 30-g/L solution of sodium bicarbonate contains 0.030 g/mL of anhydrous sodium bicarbonate. The density of this solution was found to be 1.0192 g/mL at 20° C, and its measured milliosmolality was 614.9 mOsm/kg. Convert milliosmolality to milliosmolarity.

$$\text{Milliosmolarity} = 614.9 \text{ mOsm/kg } H_2O \times (1.0192 \text{ g/mL} - 0.030 \text{ g/mL})$$
$$= 608.3 \text{ mOsm/L solution}$$

Example 6–18. A 0.154-molal sodium chloride solution has a milliosmolality of 286.4 mOsm/kg (see *Example* (6–19)). Calculate the milliosmolarity, mOsm/L solution, using equation (6–66). The density of the solvent—water—at 25° C is $d_1^\circ = 0.9971$ g/cm^3, and the partial molal volume of the solute—sodium chloride— is $\bar{v}_2^\circ = 16.63$ mL/mole.

$$\text{Milliosmolality} = (286.4 \text{ mOsm/kg } H_2O) \times [0.9971(1 - 0.001(16.63))]$$
$$= 280.8 \text{ mOsm/L solution}$$

As noted here, osmolarity differs from osmolality by only 1 or 2%. However, in more concentrated solutions of polyvalent electrolytes together with buffers, preservatives, and other ions, the difference may become significant. For accuracy in the preparation and labeling of parenteral solutions, osmolality should be measured carefully with a vapor pressure or freezing point osmometer (rather than calculated) and the results converted to osmolarity using equation (6–65) or (6–66). UIC, Inc., of Joliet, Ill. manufactures a cryoscopic osmometer for automatic osmolality determinations.

Whole blood, plasma, and serum are complex liquids consisting of proteins, glucose, nonprotein nitrogenous materials, sodium, potassium, calcium, magnesium, chloride, and bicarbonate ions. The serum electrolytes, constituting less than 1% of the blood's weight, determine the osmolality of the blood. Sodium chloride contributes a milliosmolality of 275, while glucose and the other constituents together provide about 10 mOsm/kg to the blood.

Colligative properties such as freezing point depression are related to osmolality through equations (6–27) and (6–63).

$$\Delta T_f \cong K_f im \quad (6\text{–}67)$$

in which $i = g\nu$ and $im = g\nu m$ is osmolality.

Example 6–19. Calculate the freezing point depression of *(a)* a 0.154-m solution of NaCl and *(b)* a 0.154-m solution of glucose. What are the milliosmolalities of these two solutions?

(*a*) From Table 6–5, g for NaCl at 25° C is about 0.93, and since NaCl ionizes into two ions, $i = \nu \cdot g = 2 \times 0.93 = 1.86$. From equation (6–64), the osmolality of a 0.154-m solution is $i \cdot m = 1.86 \times 0.154 = 0.2864$. The milliosmolality of this solution is therefore 286.4 mOsm/kg. Using equation (6–67), with K_f also equal to 1.86, we obtain for the freezing point depression of a 0.154-m solution—or its equivalent, a 0.2864-Osm/kg solution—of NaCl

$$\Delta T_f = (1.86)(1.86)(0.154)$$
$$= (1.86)(0.2864) = 0.53^\circ \text{ C}$$

(*b*) Glucose is a nonelectrolyte, producing only one particle for each of its molecules in solution, and for a nonelectrolyte, $i = \nu = 1$ and $g = i/\nu = 1$. Therefore, the freezing point depression of a 0.154-m solution of glucose is approximately

$$\Delta T_f = K_f im = (1.86)(1.00)(0.154)$$
$$= 0.286^\circ \text{ C}$$

which is nearly one half of the freezing point depression provided by sodium chloride, a 1:1 electrolyte that provides two particles rather than one particle in solution.

The osmolality of a nonelectrolyte such as glucose is identical to its molal concentration since osmolality = $i \times$ molality, and i for a nonelectrolyte is 1.00. The milliosmolality of a solution is 1000 times its osmolality or, in this case, 154 mOsm/kg.

Ohwaki et al.[16] studied the effect of osmolality on the nasal absorption of secretin, a hormone used in the treatment of duodenal ulcers. They found that maximum absorption through the nasal mucosa occurred at a sodium chloride milliosmolarity of about 860 mOsm/L (0.462 M), possibly owing to structural changes in the epithelial cells of the nasal mucosa at this high mOsm/L value.

Although the osmolality of blood and other body fluids is contributed mainly by the content of sodium chloride, the osmolality and milliosmolality of these complex solutions by convention are calculated based on i or nonelectrolytes, that is, i is taken as unity, and osmolality becomes equal to molality. This principle is best described by an example.

Example 6–20. Freezing points were determined using the blood of 20 normal subjects and were averaged to −0.5712° C. This value of course is equivalent to a freezing point depression of +0.5712° C below the freezing point of water because the freezing point of water is taken as 0.000° C at atmospheric pressure. What is the average milliosmolality, x, of the blood of these subjects?

Using equation (6–67) with the arbitrary choice of $i = 1$ for body fluids, we obtain

$$0.5712 = (1.86)(1.00)\,x$$
$$x = 0.3071 \text{ Osm/kg}$$
$$= 307.1 \text{ mOsm/kg}$$

It is noted in *Example 20* that although the osmolality of blood and its freezing point depression are contributed mainly by NaCl, an i value of 1 was used for blood rather than $gv = 1.86$ for an NaCl solution.

The milliosmolality for blood obtained by various workers using osmometry, vapor pressure, and freezing point depression apparatus (Chapter 5) ranges from about 250 to 350 mOsm/kg.[17] The normal osmolality of body fluids is given in medical handbooks[18] as 275 to 295 mOsm/kg, but normal values are likely to fall in an even narrower range of 286 ± 4 mOsm/kg.[19] Freezing point and vapor pressure osmometers are now used routinely in the hospital. A difference of 50 mOsm/kg or more from the accepted values of a body fluid suggests an abnormality such as liver failure, hemorrhagic shock, uremia, or other toxic manifestations. Body water and electrolyte balance are also monitored by measurement of milliosmolality. Colligative property measurements and apparatus are describe in Chapter 5.

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Problems

6–1. The equivalent conductance Λ_0 of the sodium salt of a sulfonamide at infinite dilution was found by experiment to be 100.3 mho cm²/Eq. The Λ_0 for HCl is 426.16; for NaCl, 126.45. What is Λ_0 for the free acid (the free sulfonamide)?

Answer: 400 mho cm²/Eq

6–2. The equivalent conductance at infinite dilution for the following strong electrolytes are given: Λ_0(HCl) = 426.16, Λ_0(NaAc) = 91.0, and Λ_0 (NaCl) = 126.45 mho cm²/Eq. Compute the equivalent conductance at infinite dilution for acetic acid.

Answer: 390.7 mho cm²/Eq

6–3. The equivalent conductances Λ_c (mho cm²/Eq) of NaCl at several molar concentrations, c, are

Data for *Problem 6–3*

c	0.09	0.04	0.01
Λ_c	113.34	117.70	122.08

(a) Plot Λ_c against $\sqrt{c}$ as in Figure 6–4. Compute Λ_0 and the equation of the line (use least squares).

(b) The transference number, t_c, of Na^+ at infinite dilution is 0.396. Compute the ionic equivalent conductance of Na^+, Cl^-, and the transference number of Cl^- at infinite dilution.

Answers: **(a)** The equation of the line is $\Lambda_c = 126.45 - 43.70\sqrt{c}$; $r^2 = 0.9999$. The intercept $\Lambda_0 = 126.45$ ohm^{-1} cm²/Eq.

(b) From the definition of transference number and the Kohlrausch law, equation 6–23, we can use the transference numbers to calculate the ionic equivalent conductances ℓ_a° and ℓ_a° in which $\ell_a^\circ = \Lambda_0 t_{a-}^\circ$; $\ell_c^\circ = \Lambda_0 t_{c+}^\circ$; and $\Lambda_0 = \ell_a^\circ + \ell_c^\circ$; $t_{a-}^\circ = 0.604$.

In the literature we find $\ell_a^\circ = 76.34$, $\ell_c^\circ = 50.07$ mho cm²/Eq.

6–4. Chloral hydrate is one of the oldest hypnotic drugs. It was synthesized in 1832 and is still of some importance in general anesthesia and in some types of neurosis. The conductance Λ_c of a 1-molar solution of NaCl in water at 25° C decreases with the addition of increasing amounts of chloral hydrate. The measured conductances Λ_c of the 1-M aqueous solution of NaCl in the presence of various amounts of chloral hydrate are

Data for *Problem 6–4*

Chloral hydrate, c (molar conc., M)	0.2	0.4	0.6	0.8
Λ_c (mho cm²/Eq)	78.92	74.30	69.68	65.06

Barcza and Lenner[20] found a direct relationship between Λ_c and the chloral hydrate concentration, c.

(a) Plot c on he x-axis against Λ_c and extrapolate to zero concentration of chloral hydrate to get Λ_c for the 1-M aqueous solution of NaCl.

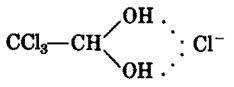
(b) Compute Λ_c for the 1-M aqueous solution of NaCl using the equation obtained in *Problem 6–3*. Do your results correlate with those obtained in *Problem 6–3*?

(c) Why does the conductivity of the 1-M aqueous solution of NaCl decrease as chloral hydrate is added?

Answers: (a) Extrapolating by eye, using a ruler, one obtains Λ_c = 83 mho cm²/Eq. By least-squares regression we obtain the linear equation, $\Lambda_c = 83.54 - 23.1c$; $r^2 = 1.000$. The intercept, 83.54 mho cm²/Eq, is the value of Λ_c for 1-M NaCl in the absence of chloral hydrate.

(b) From the equation obtained in *Problem 6–3*, $\Lambda_c(1\text{ M}) = 126.45 - 43.70\sqrt{1.0} = 82.75$ mho cm²/Eq. That value compares well with the intercept value found above in (a).

(c) *Hint:* Consider the size and therefore the velocity of the large anionic complex relative to the small Cl^- ion,



6–5. A 1.0 m solution of sucrose had an observed osmotic pressure of 24.8 atm at 0° C. Calculate the van't Hoff i factor for sucrose at this concentration.

Answer: i = 1.11 (a dimensionless number).

6–6.* Calcium chloride may be used to melt the ice from sidewalks. How many pounds (avoirdupois) of $CaCl_2$ are required to melt a layer of ice 0.5 inch thick on a sidewalk 50 ft long and 4 ft wide if the temperature of ice is 10° F? The molecular weight of $CaCl_2$ is 110.99 g/mole. The density of the ice at 10° F is 0.9923 g/mL, and the degree of ionization α of $CaCl_2$ is 0.8.

Answer: 145 lb (66 kg). Some ice will sublime and pass directly from the solid into the vapor state. This and other factors such as heating by the sun will render the answer given here a rough approximation. However, the calculation will give the city winter emergency crews an estimate of the amount of $CaCl_2$ needed for clearing sidewalks and streets. (*Note:* Some cities are no longer using "salt" on streets and sidewalks because of its pollution problems.)

6–7. Some cooks add salt to a kettle of water in which they are boiling peeled corn or unpeeled potatoes. In addition to improving the flavor, this practice is reputed to cook and soften the food better. (a) Is there any scientific justification for this? Explain. (b) What is the concentration of NaCl in grams of salt per kg of water needed to obtain a significant rise in the boiling point, say 5° C? (c) Would this concentration of NaCl render the food too salty to the taste?

Partial Answer: (b) Concentration of NaCl solution = 4.9 molal or 286 g salt/kg water. (c) Check with a good cook about the saltiness of the food in this concentration of salt solution.

6–8. The data for an isotonic solution of aureomycin hydrochloride is found in Table 8–4, page 183. The freezing point depression ΔT_f for a 1% solution (1 g/dL) is listed as 0.06°. (a) What is the van't Hoff factor i and the degree of dissociation α for this antibiotic in the 1% w/v solution? At this low concentration, one may assume molarity is approximately equal to molality. (b) Repeat the calculation for atropine sulfate and physostigmine salicylate, and find the i and α values for these additional two solutions.

Answers: (a) $i = 1.753$; $\alpha = 0.753$. Aureomycin is dissociated to the extent of 75.3%. (b) For the salt, $(\text{atropine})_2\,SO_4$, $i = 2.614$; $\alpha = 0.807$. For physostigmine salicylate, $i = 1.999$; $\alpha = 0.999$. Atropine sulfate is 81% dissociated and physostigmine salicylate is 99.9% dissociated.

6–9. Using the data and the value of Λ_0 given in *Problem* 6–3, compute the degree of ionization α of a 0.09-m solution of NaCl, the i value, and the freezing point depression.

Answer: You will need equation (6–27), page 129, and equations (6–32) and (6–34), page 131. $\alpha = 0.896$; $i = 1.896$; $\Delta T_f = 0.32$ deg

6–10. The equivalent conductance of a sulfonamide at 0.01 M concentration was found by experiment to be 1.104. The equivalent conductance of the drug at infinite dilution is 400.0. What is the degree of dissociation of the weak electrolyte at this concentration?

Answer: 0.00276 or 0.28%

6–11. (a) The vapor pressure of water over an aqueous solution of a drug is 721 mm Hg at 100° C. What is the activity of water in this solution? (b) Methanol has a boiling point of 64.7° C. The vapor pressure of methanol in a methanolic solution of a sulfonamide is 703 mm Hg. What is the activity of methanol in this solution at 64.7° C? (c) Chlorine has a vapor pressure of 10.0 atm at 35.6° C. In a mixture of chlorine and carbon tetrachloride the vapor pressure of chlorine is 9.30 atm at 35.6° C. What is the activity of chlorine in the mixture?

(d) Formic acid has a vapor pressure of 40.0 mm Hg at 24° C. In a mixture of formic acid and acetic acid, formic acid has a vapor pressure of 32.2 mm at 24° C. What is the activity of formic acid in the mixture?

Answer: (a) $a = 0.949$; (b) $a = 0.925$; (c) $a = 0.930$; (d) $a = 0.805$.

6–12.* The vapor pressure p_1° of water at 25° C is 23.8 torr. (a) Compute the lowering of the vapor pressure of water when 25 g of $CaCl_2$ is added to 100 g of water. The molecular weight of $CaCl_2$ is 110.99 g/mole. (b) Compute the activity and the activity coefficient of water in the solution.

Answers: (a) The vapor pressure is lowered from 23.8 torr to 20.91 torr or $\Delta p_1 = 2.89$ torr. (b) $a_1 = 0.879$; $\gamma_1 = 0.915$ (you will need to calculate X_1 the mole fraction of water, to obtain this activity coefficient, 0.915, for water).

6–13. If 15 g of a strong electrolyte, NaOH, molecular weight 40.01 g/mole, is added to 100 g of water at 25° C, the vapor pressure of pure water, viz. 23.8 mm Hg, is lowered. (a) Calculate the vapor pressure of the solution. (b) The activity coefficient γ_1 of the water in the solution is given using the equation $\gamma_1 = p_1/X_1 p_1$°. This we are assured of because $\gamma_1 X_1 = a_1 = p_1/p_1$°, which we know to be the equation to obtain activities for gases and vapors. Calculate the activity coefficient and the activity of water in this solution.

Answers: (a) 20.59 torr; (b) $\gamma_1 = 0.934$; $a_1 = 0.865$

6–14. The vapor pressure of pure water (23.8 torr) at 25° C is lowered when 100 g of the nonelectrolyte, glucose, is added to 1000 g of the water. The molecular weight of glucose is 180.16 g/mole. What is the activity and the activity coefficient of water at this temperature and concentration of glucose?

Answer: $a_1 = 0.990$; $\gamma_1 = 1.000$. Thus in a 100-g/kg H_2O solution of glucose (fairly concentrated, 0.56 molal), both the activity and the activity coefficient of water may be taken as approximately equal to 1.0. This is not so for a solution of an electrolyte, as seen in *Problems 6–12* and *6–13*.

6–15. Compute the mean ionic activity coefficient of a 0.01-M aqueous solution of diphenylhydantoin sodium containing 0.01 M KCl at 25° C. Use the limiting Debye-Hückel equation.

Answer: $\gamma_\pm = 0.85$

6–16. Using the extended Debye–Hückel equation, compute the mean ionic activity coefficient of a 0.05-M solution of epinephrine hydrochloride containing a 0.05 M potassium chloride.

Answer: $\gamma_\pm = 0.75$

6–17. (a) What amount of $CaCl_2$ (in moles/liter) should be added to a 0.02-M solution of neomycin sulfate to produce an ionic strength of 0.09?

(b) Calculate the mean ionic activity and the mean ionic activity coefficient for the 0.02-M solution of neomycin sulfate at an ionic strength of 0.09 and 25° C. Use both equations (6–58) and (6–60) (pp. 135, 136) and compare the results.

*Problems 6–6 and 6–12 are modified from J. W. Moncrief and W. H. Jones, ***Elements of Physical Chemistry***, Addison-Wesley, Reading, Mass., 1977, pp. 146 and 124, respectively.

Answers: (a) 0.01 M $CaCl_2$. (b) From equation (6–58), $\gamma_\pm = 0.494$ and $a_\pm = 0.0157$. From equation (6–60), $\gamma_\pm = 0.582$ and $a_\pm = 0.0185$. The results from the two equations are different. The ionic strength of the solution is 0.02 M, so equation (6–60) is required.

6–18. King and associates[21] investigated the properties of a new anticancer agent, brequinar sodium. The solubility in water at room temperature (≈23° C) was found to be 0.274 M. The compound is a 1:1 electrolyte.

(a) Compute the mean ionic activity and the mean ionic activity coefficient in the saturated solution (0.274 M) at 23° C.

(b) After adding a 0.01-M solution of NaCl the solubility decreased because of the common ion effect, Na^+ being the common ion (see p. 231). The new solubility value was 0.245 M. Compute new values for the mean ionic activity and the mean ionic activity coefficient. Choose the proper equation to obtain the most accurate value for $\gamma_\pm$.

Answers: (a) The ionic strength is 0.274; $\gamma_\pm = 0.668$ (equation 6–60) and $a_\pm = 0.183$. (b) The ionic strength is 0.245 for the drug and 0.01 for NaCl; $\gamma_\pm = 0.674$ and $a_\pm = 0.165$.

6–19. A solution contains 0.003 M of sodium phenobarbital together with a buffer consisting of 0.20 M sodium acetate and 0.30 M acetic acid. Acetic acid is a weak electrolyte; its degree, or fraction, of dissociation α at this concentration is 0.008 and the undissociated species do not contribute to the ionic strength. What is the ionic strength of the solution?

Answer: $\mu = 0.205$

6–20. A solution contains 0.05 M $AlCl_3$ and 0.2 M Na_2HPO_4. What is the ionic strength of this solution?

Answer: 0.90

6–21. Ringer's solution USP has been designed to have approximately the same ionic strength as that of normal blood. Calculate the ionic strength of blood from the concentration of the constituents of Ringer's solution.

Answer: $\mu = 0.16$

6–22. The freezing point depression of a solution containing 4 g of methapyrilene hydrochloride in 100 mL of solution was 0.423°. Methapyrilene hydrochloride dissociates into two ions and has a molecular weight of 297.85. Calculate (a) the van't Hoff factor i, (b) the osmotic coefficient g, and (c) the L value for the drug at this concentration.

Answer: (a) $i = 1.69$; (b) $g = 0.85$; (c) $L = 3.16$

6–23. The equivalent conductance of acetic acid is 48.15 mho cm^2/Eq at a concentration of 1×10^{-3} mole/liter. The value at infinite dilution as calculated in *Problem 6–2* is 390.7. Compute α, i, and L at this concentration.

Answer: $\alpha = 0.12$; $i = 1.12$; $L = 2.1$

6–24. The L_{iso} value of an aqueous solution of ascorbic is 1.90 and its osmotic pressure at 37° is $\pi = 1182$ mm Hg. Compute i, ΔT_f, and the degree of dissociation α.

Answer: $i = 1.02$; $\Delta T_f = 0.11°$; $\alpha = 0.02$ or 2% dissociated

6–25. Calculate the freezing point depression and the milliosmolality of 0.25-M solutions of sodium iodide, sodium bicarbonate, and calcium chloride, and of 340 millimolal solutions of griseofulvin and pentobarbital. What is the osmotic pressure in atmospheres of the sodium bicarbonate solution; of the pentobarbital solution at 25° C? (*Hint:* Sodium bicarbonate, like sodium iodide, provides two particles in solution. Pentobarbital and grisseofulvin can be assumed to be nonelectrolytes, and the i value for their solutions is taken as unity. For $CaCl_2$, $i = 2.6$.)

Partial Answer: Milliosmolality of sodium iodide is 465 mOsm/kg and its freezing point depression is 0.86° C. The osmotic pressure of the pentobarbital solution is 8.3 atm.

6–26. A 0.120-molal solution of potassium bromide has a milliosmolality of 1.86 × 120 millimolal = 223 mOsm/kg (see *Example 6–16*, p. 139). The density of water at 25° C is 0.997 g/cm^3, and the partial molar volume of KBr is $\bar{v}_2^\circ = 33.97$ cm^3/mole. Calculate the milliosmolarity, mOsm/(liter solution), of this KBr solution using equation (6–66).

Answer: 214.8 mOsm/(liter solution).

6–27. Partial pressures (in mm Hg), p_1, of acetone at various mole fractions, X_1, are given in the following table for a mixture of acetone and chloroform.

Data for *Problem 6–27*

X_1	1.000	0.950	0.925	0.878	0.710	0.575
p_1(mm)	344.5	327.5*	317.0*	299.7	230.7	173.7

*These points have been added to the data.

Source: Data from J. von Zawidzki as reported by I. M. Klotz and R. M. Rosenberg, *Chemical Thermodynamics*, W. A. Benjamin, Menlo Park, Cal., 1972, pp. 355, 356. Some points are omitted and two points have been added near $X_1 = 1.000$.

(a) Compute the activity and activity coefficient for acetone at various X_1 values in these solutions.

(b) Plot both the experimental p_1 values and the Raoult law pressures versus X_1. Discuss the deviations from Raoult's law and its implications regarding possible intermolecular interaction between chloroform and acetone.

Partial Answer: (a)

X_1	1.0	0.878	0.575
a_1	1.0	0.870	0.504
γ_1	1.0	0.991	0.877

This tabular answer states that when $X_1 = 1.0$, $a_1 = 1.0$ and $\gamma_1 = 1.0$, and so on

6–28. The mole fraction concentrations and vapor pressures in mm Hg (torr) for a new general anesthetic, theasotrate, in ethanol at 45° C are given in the table below. Calculate the activities and activity coefficients for the new drug.

Data for *Problem 6–28*

X_1	1.000	0.942	0.740	0.497
p_1(mm)	402	377	277	174

Partial Answer: For $X_1 = 0.942$, $a_1 = 0.938$, $\gamma_1 = 0.996$

8

Buffered and Isotonic Solutions

Buffers are compounds or mixtures of compounds that, by their presence in solution, resist changes in pH upon the addition of small quantities of acid or alkali. The resistance to a change in pH is known as *buffer action*. According to Roos and Borm,[1] Koppel and Spiro published the first paper on buffer action in 1914 and suggested a number of applications, which were later elaborated by Van Slyke.[2]

If, to water or a solution of sodium chloride, a small amount of a strong acid or base is added, the pH is altered considerably; such systems have no buffer action.

A combination of a weak acid and its conjugate base (i.e., its salt), or a weak base and its conjugate acid act as buffers. If 1 mL of a 0.1-*N* HCl solution is added to 100 mL of pure water, the pH is reduced from 7 to 3. If the strong acid is added to a 0.01-*M* solution containing equal quantities of acetic acid and sodium acetate, the pH is changed only 0.09 pH units, because the base Ac^- ties up the hydrogen ions according to the reaction

$$Ac^- + H_3O^+ \rightleftharpoons HAc + H_2O \qquad (8\text{–}1)$$

If a strong base, sodium hydroxide, is added to the buffer mixture, acetic acid neutralizes the hydroxyl ions as follows:

$$HAc + OH^- \rightleftharpoons H_2O + Ac^- \qquad (8\text{–}2)$$

THE BUFFER EQUATION

Common Ion Effect and the Buffer Equation for a Weak Acid and Its Salt. The pH of a buffer solution and the change in pH upon the addition of an acid or base may be calculated by use of the *buffer equation*. This expression is developed by considering the effect of a salt on the ionization of a weak acid when the salt and the acid have an ion in common.

For example, when sodium acetate is added to acetic acid, the dissociation constant for the weak acid,

$$K_a = \frac{[H_3O^+][Ac^-]}{[HAc]} = 1.75 \times 10^{-5} \qquad (8\text{–}3)$$

is momentarily disturbed since the acetate ion supplied by the salt increases the $[Ac^-]$ term in the numerator. To reestablish the constant K_a at 1.75×10^{-5}, the hydrogen ion term in the numerator $[H_3O^+]$ is instantaneously decreased, with a corresponding increase in [HAc]. Therefore, the constant K_a remains unaltered, and the equilibrium is shifted in the direction of the reactants. Consequently, the ionization of acetic acid,

$$HAc + H_2O \rightleftharpoons H_3O^+ + Ac^- \qquad (8\text{–}4)$$

is *repressed* upon the addition of the common ion $[Ac^-]$. This is an example of the *common ion effect*. The pH of the final solution is obtained by rearranging the equilibrium expression for acetic acid:

$$[H_3O^+] = K_a \frac{[HAc]}{[Ac^-]} \qquad (8\text{–}5)$$

If the acid is weak and ionizes only slightly, the expression [HAc] may be considered to represent the total concentration of acid, and it is written simply as [acid]. In the slightly ionized acidic solution, the acetate concentration $[Ac^-]$ may be considered as having come entirely from the salt, sodium acetate. Since 1 mole of sodium acetate yields 1 mole of acetate ion, $[Ac^-]$ is equal to the total salt concentration and is replaced by the term [salt]. Hence, equation (8–5) is written,

$$[H_3O^+] = K_a \frac{[acid]}{[salt]} \qquad (8\text{–}6)$$

Equation (8–6) may be expressed in logarithmic form, with the signs reversed, as

$$-\log [H_3O^+] = -\log K_a - \log [\text{acid}] + \log [\text{salt}] \quad (8-7)$$

from which is obtained an expression, known as the *buffer equation* or the *Henderson–Hasselbalch equation*, for a weak acid and its salt:

$$\text{pH} = \text{p}K_a + \log \frac{[\text{salt}]}{[\text{acid}]} \quad (8-8)$$

The ratio [acid]/[salt] in equation (8–6) has been inverted by undergoing the logarithmic operations in (8–7) and it appears in (8–8) as [salt]/[acid]. pK_a, the negative logarithm of K_a, is called the *dissociation exponent* (p. 152).

The buffer equation is important in the preparation of buffered pharmaceutical solutions; it is satisfactory for calculations within the pH range of 4 to 10.

Example 8–1. What is the pH of 0.1-*M* acetic acid solution, pK_a = 4.76? What is the pH after enough sodium acetate has been added to make the solution 0.1 *M* with respect to this salt?

The pH of the acetic acid solution is calculated by use of the logarithmic form of equation (7–99) on p. 155.

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

$$\text{pH} = 2.38 + 0.50 = 2.88$$

The pH of the buffer solution containing acetic acid and sodium acetate is determined by use of the buffer equation (8–8):

$$\text{pH} = 4.76 + \log \frac{0.1}{0.1} = 4.76$$

It is seen from *Example 8–1* that the pH of the acetic acid solution has been *increased* almost 2 pH units; that is, the acidity has been *reduced* to about one hundredth of its original value by the addition of an equal concentration of a salt with a common ion. This example bears out the statement regarding the repression of ionization upon the addition of a common ion.

Sometimes it is desired to know the ratio of salt to acid in order to prepare a buffer of a definite pH. *Example 8–2* demonstrates the calculation involved in such a problem.

Example 8–2. What is the molar ratio, [salt]/[acid], required to prepare an acetate buffer of pH 5.0? Also express the result in mole percent.

$$5.0 = 4.76 + \log \frac{[\text{salt}]}{[\text{acid}]}$$

$$\log \frac{[\text{salt}]}{[\text{acid}]} = 5.0 - 4.76 = 0.24$$

$$\frac{[\text{salt}]}{[\text{acid}]} = \text{antilog } 0.24 = 1.74$$

Therefore, the mole ratio of salt to acid is 1.74/1. Mole percent is mole fraction multiplied by 100. The mole fraction of salt in the salt–acid mixture is 1.74/(1 + 1.74) = 0.635, and in mole percent, the result is 63.5%.

The Buffer Equation for a Weak Base and Its Salt. Buffer solutions are not ordinarily prepared from weak bases and their salts because of the volatility and instability of the bases and because of the dependence of their pH on pK_w, which is often affected by temperature changes. Pharmaceutical solutions—for example, a solution of ephedrine base and ephedrine hydrochloride—however, often contain combinations of weak bases and their salts.

The buffer equation for solutions of weak bases and the corresponding salts may be derived in a manner analogous to that for the weak acid buffers. Accordingly,

$$[OH^-] = K_b \frac{[\text{base}]}{[\text{salt}]} \quad (8-9)$$

and using the relationship, $[OH^-] = K_w/[H_3O^+]$, the buffer equation becomes

$$\text{pH} = \text{p}K_w - \text{p}K_b + \log \frac{[\text{base}]}{[\text{salt}]} \quad (8-10)$$

Example 8–3. What is the pH of a solution containing 0.10 mole of ephedrine and 0.01 mole of ephedrine hydrochloride per liter of solution? The pK_b of ephedrine is 4.64.

$$\text{pH} = 14.00 - 4.64 + \log \frac{0.10}{0.01}$$

$$\text{pH} = 9.36 + \log 10 = 10.36$$

Activity Coefficients and the Buffer Equation. A more exact treatment of buffers begins with the replacement of concentrations by activities in the equilibrium of a weak acid:

$$K_a = \frac{a_{H_3O^+}a_{Ac^-}}{a_{HAc}} = \frac{(\gamma_{H_3O^+}c_{H_3O^+}) \times (\gamma_{Ac^-}c_{Ac^-})}{\gamma_{HAc}c_{HAc}} \quad (8-11)$$

The activity of each species is written as the activity coefficient multiplied by the molar concentration. The activity coefficient of the undissociated acid γ_{HAc} is essentially 1 and may be dropped. Solving for the hydrogen ion activity and pH, defined as $-\log a_{H_3O^+}$, yields the equations

$$a_{H_3O^+} = \gamma_{H_3O^+} \times c_{H_3O^+} = K_a \frac{c_{HAc}}{\gamma_{Ac^-}c_{Ac^-}} \quad (8-12)$$

$$\text{pH} = \text{p}K_a + \log \frac{[\text{salt}]}{[\text{acid}]} + \log \gamma_{Ac^-} \quad (8-13)$$

From the Debye–Hückel expression (equation (6–59), p. 136) for an aqueous solution of a univalent ion at 25° C having an ionic strength not greater than about 0.1 or 0.2, we write

$$\log \gamma_{Ac^-} = \frac{-0.5\sqrt{\mu}}{1 + \sqrt{\mu}}$$

and equation (8–13) then becomes

$$\text{pH} = \text{p}K_a + \log \frac{[\text{salt}]}{[\text{acid}]} - \frac{0.5\sqrt{\mu}}{1 + \sqrt{\mu}} \quad (8-14)$$

The general equation for buffers of polybasic acids is

$$\text{pH} = \text{p}K_n + \log \frac{[\text{salt}]}{[\text{acid}]} - \frac{A(2n-1)\sqrt{\mu}}{1 + \sqrt{\mu}} \quad (8-15)$$

in which n is the stage of the ionization. (See *Problem 8–3*, p. 187).

Example 8–4. A buffer contains 0.05 mole per liter of formic acid and 0.10 mole per liter of sodium formate. The pK_a of formic acid is 3.75. The ionic strength of the solution is 0.10. Compute the pH (*a*) with and (*b*) without consideration of the activity coefficient correction.

(*a*)

$$\text{pH} = 3.75 + \log \frac{0.10}{0.05} - \frac{0.5\sqrt{0.10}}{1 + \sqrt{0.10}}$$

$$= 3.93$$

(*b*)

$$\text{pH} = 3.75 + \log \frac{0.10}{0.05} = 4.05$$

Some Factors Influencing the pH of Buffer Solutions. The addition of neutral salts to buffers changes the pH of the solution by altering the ionic strength, as shown in equation (8–13). Changes in ionic strength and hence in the pH of a buffer solution may also be brought about by dilution. The addition of water in moderate amounts, while not changing the pH, may cause a small positive or negative deviation because it alters activity coefficients and because water itself can act as a weak acid or base. Bates[3a] has expressed this quantitatively in terms of a *dilution value*, which is the change in pH on diluting the buffer solution to one half its original strength. Some dilution values for National Bureau of Standards buffers are found in Table 9–2, p. 199. A positive dilution value signifies that the pH rises with dilution, and a negative value signifies that the pH decreases with dilution of the buffer.

Temperature also influences buffers. Kolthoff and Tekelenburg[4] determined the *temperature coefficient of* pH, that is, the change in pH with temperature, for a large number of buffers. The pH of acetate buffers was found to increase with temperature, whereas the pH of boric acid–sodium borate buffers decreased with temperature. Although the temperature coefficient of acid buffers was relatively small, the pH of most basic buffers was found to change more markedly with temperature, owing to K_w, which appears in the equation of basic buffers and which changes significantly with temperature. Bates[3] refers to several basic buffers that show only a small change of pH with temperature and can be used in the pH range of 7 to 9. The temperature coefficients for the calomel electrode are given in Bates,[3b] Table 10–10.

Drugs as Buffers. It is important to recognize that solutions of drugs that are weak electrolytes also manifest buffer action. Salicylic acid solution in a soft glass bottle is influenced by the alkalinity of the glass. It might be thought at first that the reaction would result in an appreciable increase in pH; however, the sodium ions of the soft glass combine with the salicylate ions to form sodium salicylate. Thus, there arises a solution of salicylic acid and sodium salicylate—a buffer solution that resists the change in pH. Similarly, a solution of ephedrine base manifests a natural buffer protection against reductions in pH. Should hydrochloric acid be added to the solution, ephedrine hydrochloride is formed, and the buffer system—ephedrine plus ephedrine hydrochloride—will resist large changes in pH until the ephedrine is depleted by reaction with the acid. Therefore, a drug in solution may often act as its own buffer over a definite pH range. Such buffer action, however, is often too weak to counteract pH changes brought about by the carbon dioxide of the air and the alkalinity of the bottle. Additional buffers are therefore frequently added to drug solutions to maintain the system within a certain pH range. A quantitative measure of the efficiency or capacity of a buffer to resist pH changes will be discussed in a later section.

pH Indicators. Indicators may be considered as weak acids or weak bases that act like buffers and also exhibit color changes as their degree of dissociation varies with pH. For example, methyl red shows its full alkaline color, yellow, at a pH of about 6 and its full acid color, red, at about pH 4. Indicators therefore offer a convenient alternative method to electrometric techniques (Chapter 9) for determining the pH of a solution.

The dissociation of an acid indicator is given here in simplified form:

$$\underset{\substack{\text{Acid}_1\\(\text{acid color})}}{\text{HIn}} + \underset{\text{Base}_2}{H_2O} \rightleftharpoons \underset{\text{Acid}_2}{H_3O^+} + \underset{\substack{\text{Base}_1\\(\text{alkaline color})}}{In^-} \qquad (8\text{–}16)$$

The equilibrium expression is

$$\frac{[H_3O^+][In^-]}{[HIn]} = K_{In} \qquad (8\text{–}17)$$

HIn is the un-ionized form of the indicator, which gives the acid color, and In^- is the ionized form, which produces the basic color. K_{In} is referred to as the *indicator constant*. If an acid is added to a solution of the indicator, the hydrogen ion concentration term on the right-hand side of equation (8–16) is increased, and the ionization is repressed by the common ion effect. The indicator is then predominantly in the form of HIn, the acid color. If base is added, $[H_3O^+]$ is reduced by reaction of the acid with the base, reaction (8–16) proceeds to the right, yielding more ionized indicator In^-, and the base color predominates. Thus, the color of an indicator is a function of the pH of the solution. A number of indicators with their useful pH ranges are listed in Table 8–1.

The equilibrium expression (8–16) may be treated in a manner similar to that for a buffer consisting of a weak acid and its salt or conjugate base. Hence

$$[H_3O^+] = K_{In} \frac{[HIn]}{[In^-]} \qquad (8\text{–}18)$$

and since [HIn] represents the acid color of the indicator and the conjugate base $[In^-]$ represents the

TABLE 8–1. *Color, pH and pK_{In}, the Indicator Constant, of Some Common Indicators*

Indicator	Color		pH Range	pK_{In}
	Acid	Base		
Thymol blue (acid range)	red	yellow	1.2– 2.8	1.5
Methyl violet	blue	violet	1.5– 3.2	—
Methyl orange	red	yellow	3.1– 4.4	3.7
Bromcresol green	yellow	blue	3.8– 5.4	4.7
Methyl red	red	yellow	4.2– 6.2	5.1
Bromcresol purple	yellow	purple	5.2– 6.8	6.3
Bromthymol blue	yellow	blue	6.0– 7.6	7.0
Phenol red	yellow	red	6.8– 8.4	7.9
Cresol red	yellow	red	7.2– 8.8	8.3
Thymol blue (alkaline range)	yellow	blue	8.0– 9.6	8.9
Phenolphthalein	colorless	red	8.3–10.0	9.4
Alizarin yellow	yellow	lilac	10.0–12.0	—
Indigo carmine	blue	yellow	11.6–14	—

basic color, these terms may be replaced by the concentration expressions, [acid] and [base]. The formula for pH as derived from equation (8–18) becomes

$$\text{pH} = \text{p}K_{\text{In}} + \log \frac{[\text{base}]}{[\text{acid}]} \qquad (8\text{–}19)$$

Example 8–5.* An indicator, methyl red, is present in its ionic form In^-, in a concentration of 3.20×10^{-3} M and in its molecular form, *HIn*, in an aqueous solution at 25° C in a concentration of 6.78×10^{-3} M. From Table 8–1 we observe a pK_{In} of 5.1 for methyl red. What is the pH of this solution?

$$\text{pH} = 5.1 + \log \frac{3.20 \times 10^{-3}}{6.78 \times 10^{-3}} = 4.77$$

Just as a buffer shows its greatest efficiency when $\text{pH} = \text{p}K_a$, an indicator exhibits its *middle tint* when [base]/[acid] = 1 and $\text{pH} = \text{p}K_{\text{In}}$. The most efficient indicator range, corresponding to the effective buffer interval, is about 2 pH units, that is, $\text{p}K_{\text{In}} \pm 1$. The reason for the width of this color range may be explained as follows. It is known from experience that one cannot discern a change from the acid color to the salt or conjugate base color until the ratio of [base] to [acid] is about 1 to 10. That is, there must be at least 1 part of the basic color to 10 parts of the acid color before the eye can discern a change in color from acid to alkaline. The pH value at which this change is perceived is given by the equation

$$\text{pH} = \text{p}K_{\text{In}} + \log \frac{1}{10} = \text{p}K_{\text{In}} - 1 \qquad (8\text{–}20)$$

Conversely, the eye cannot discern a change from the alkaline to the acid color until the ratio of [base] to [acid] is about 10 to 1, or

$$\text{pH} = \text{p}K_{\text{In}} + \log \frac{10}{1} = \text{p}K_{\text{In}} + 1 \qquad (8\text{–}21)$$

Therefore, when base is added to a solution of a buffer in its acid form, the eye first visualizes a change in color at $\text{p}K_{\text{In}} - 1$, and the color ceases to change any further at $\text{p}K_{\text{In}} + 1$. The effective range of the indicator between its full acid and full basic color may thus be expressed as

$$\text{pH} = \text{p}K_{\text{In}} \pm 1 \qquad (8\text{–}22)$$

As buffers may be mixed to cover a wide pH range, so also can several indicators be combined to yield so-called *universal indicators*. The *Merck Index* suggests one such universal indicator consisting of a mixture of methyl yellow, methyl red, bromthymol blue, thymol blue, and phenolphthalein, which covers the range from pH 1 to 11.

The colorimetric method for the determination of pH is probably less accurate and less convenient but also less expensive than the electrometric method. It may be used in the determination of the pH of aqueous solutions that are not colored or turbid, and it is particularly useful for the study of acid–base reactions in nonaqueous solutions. The details of the method are given in the treatise of Kolthoff and Rosenblum.[5] Wyss[6] has discussed the determination of the pH of solutions in the prescription laboratory. In general, the colorimetric determination of pH involves the following steps.

(*a*) Determine the approximate pH of the solution by the addition of several drops of a universal indicator. Wide-range pH papers, prepared by applying a universal indicator solution to paper strips, may be used.

(*b*) A series of Clark–Lubs buffer solutions as modified by Bower and Bates,[7] differing by 0.2 pH unit and within the pH range of the unknown solution, are chosen. Several drops of an indicator solution, having a pK_{In} approximately equal to the pH of the unknown solution so that it changes color within the pH range

*In dealing with indicators, one is concerned only with the color changes and not with the concentrations of the colored species of the indicator. Example (8–5) simply shows that if the concentrations of the colored species were known, the same equation could be used in principle for indicator solutions as for buffer systems to calculate the pH of a solution.

under consideration, are added to each buffer sample and to the unknown solution contained in suitable test tubes.

(*c*) The colors of the buffers of known pH are matched with the color of the unknown solution; accordingly, the pH of the unknown solution can be determined to within 0.1 pH unit.

Narrow-range pH papers may be used in the same way as the indicator solution by comparing the color when a drop of buffer and a drop of the unknown solution are applied to adjacent strips.

Goyan and Coutsouris[8] concluded that it was possible to cover the pH range from 4 to 8 by the use of only three indicators, bromcresol green, bromthymol blue, and thymol blue. For details of this method, refer to the original article.

A final note of caution should be added regarding the colorimetric method. Since indicators themselves are acids (or bases), their addition to unbuffered solutions whose pH is to be determined will change the pH of the solution. The colorimetric method is therefore not applicable to the determination of the pH of sodium chloride solution or similar unbuffered pharmaceutical preparations unless special precautions are taken in the measurement. Some medicinal solutions and pharmaceutical vehicles, however, to which no buffers have been added, are buffered by the presence of the drug itself (p. 171) and can withstand the addition of an indicator without a significant change in pH. Errors in the result may also be introduced by the presence of salts and proteins, and these errors must be determined for each indicator over the range involved.

BUFFER CAPACITY

Thus far it has been stated that a buffer counteracts the change in pH of a solution upon the addition of a strong acid, a strong base, or other agents that tend to alter the hydrogen ion concentration. Furthermore, it has been shown in a rather qualitative manner how this buffer action is manifested by combinations of weak acids and weak bases together with their salts. The resistance to changes of pH now remains to be discussed in a more quantitative way.

The magnitude of the resistance of a buffer to pH changes is referred to as the buffer capacity β. It is also known as *buffer efficiency*, *buffer index*, and *buffer value*. Koppel and Spiro[1] and Van Slyke[2] introduced the concept of buffer capacity and defined it as the ratio of the increment of strong base (or acid) to the small change in pH brought about by this addition. For the present discussion, the approximate formula,

$$\beta = \frac{\Delta B}{\Delta \text{pH}} \qquad (8\text{–}23)$$

may be used, in which delta, Δ, has its usual meaning, a *finite change*, and ΔB is the small increment in gram equivalents per liter of strong base added to the buffer solution to produce a pH change of ΔpH. According to equation (8–23), the buffer capacity of a solution has a value of 1 when the addition of 1 gram Eq of strong base (or acid) to 1 liter of the buffer solution results in a change of 1 pH unit. The significance of this index will be appreciated better when it is applied to the calculation of the capacity of a buffer solution.

Approximate Calculation of Buffer Capacity. Consider an acetate buffer containing 0.1 mole each of acetic acid and sodium acetate in 1 liter of solution. To this are added 0.01-mole portions of sodium hydroxide. When the first increment of sodium hydroxide is added, the concentration of sodium acetate, the [salt] term in the buffer equation, increases by 0.01 mole/liter, and the acetic acid concentration [acid] decreases proportionately, because each increment of base converts 0.01 mole of acetic acid into 0.01 mole of sodium acetate according to the reaction

$$\underset{(0.1\,-\,0.01)}{\text{HAc}} + \underset{(0.01)}{\text{NaOH}} \rightleftharpoons \underset{(0.1\,+\,0.01)}{\text{NaAc}} + \text{H}_2\text{O} \qquad (8\text{–}24)$$

The changes in concentration of the salt and the acid by the addition of a base are represented in the buffer equation (8–8) by using the modified form:

$$\text{pH} = \text{p}K_a + \log \frac{[\text{salt}] + [\text{base}]}{[\text{acid}] - [\text{base}]} \qquad (8\text{–}25)$$

Before the addition of the first portion of sodium hydroxide, the pH of the buffer solution is

$$\text{pH} = 4.76 + \log \frac{(0.1 + 0)}{(0.1 - 0)} = 4.76 \qquad (8\text{–}26)$$

The results of the continual addition of sodium hydroxide are shown in Table 8–2. The student should verify the pH values and buffer capacities by the use of equations (8–25) and (8–23) respectively.

As may be seen from Table 8–2, the buffer capacity is not a fixed value for a given buffer system, but rather depends on the amount of base added. The buffer capacity changes as the ratio log [salt]/[acid] increases with added base. With the addition of more sodium hydroxide, the buffer capacity decreases rapidly, and,

TABLE 8–2. *Buffer Capacity of Solutions Containing Equimolar Amounts (0.1 M) of Acetic Acid and Sodium Acetate*

Moles of NaOH Added	pH of Solution	Buffer Capacity, β
0	4.76	
0.01	4.85	0.11
0.02	4.94	0.11
0.03	5.03	0.11
0.04	5.13	0.10
0.05	5.24	0.09
0.06	5.36	0.08

when sufficient base has been added to convert the acid completely into sodium ions and acetate ions, the solution no longer possesses an acid reserve. The buffer has its greatest capacity before any base is added where [salt]/[acid] = 1, and, therefore, according to equation (8–8), pH = pK_a. The buffer capacity is also influenced by an increase in the total concentration of the buffer constituents since, obviously, a great concentration of salt and acid provides a greater alkaline and acid reserve. The influence of concentration on buffer capacity is treated following the discussion of Van Slyke's equation.

A More Exact Equation for Buffer Capacity. The buffer capacity calculated from equation (8–23) is only approximate. It gives the average buffer capacity over the increment of base added. Koppel and Spiro[1] and Van Slyke[2] developed a more exact equation,

$$\beta = 2.3C \frac{K_a[H_3O^+]}{(K_a + [H_3O^+])^2} \qquad (8–27)$$

where C is the total buffer concentration, that is, the sum of the molar concentrations of the acid and the salt. Equation (8–27) permits one to compute the buffer capacity at any hydrogen ion concentration—for example, at the point where no acid or base has been added to the buffer.

Example 8–6. At a hydrogen ion concentration of 1.75×10^{-5} (pH = 4.76), what is the capacity of a buffer containing 0.10 mole each of acetic acid and sodium acetate per liter of solution? The total concentration, C = [acid] + [salt], is 0.20 mole per liter, and the dissociation constant is 1.75×10^{-5}.

$$\beta = \frac{2.3 \times 0.20 \times (1.75 \times 10^{-5}) \times (1.75 \times 10^{-5})}{[(1.75 \times 10^{-5}) + (1.75 \times 10^{-5})]^2}$$
$$= 0.115$$

Example 8–7. Prepare a buffer solution of pH 5.00 having a capacity of 0.02. The steps in the solution of the problem are:

(*a*) One chooses a weak acid having a pK_a close to the pH desired. Acetic acid, pK_a = 4.76, is suitable in this case.

(*b*) The ratio of salt and acid required to produce a pH of 5.00 was found in *Example 8–2* to be [salt]/[acid] = 1.74/1.

(*c*) The buffer capacity equation (8–27) is used to obtain the total buffer concentration, C = [salt] + [acid]

$$0.02 = 2.3C \frac{(1.75 \times 10^{-5}) \times (1 \times 10^{-5})}{[(1.75 \times 10^{-5}) + (1 \times 10^{-5})]^2}$$
$$C = 3.75 \times 10^{-2} \text{ mole/liter}$$

(*d*) Finally from (*b*), [salt] = 1.74 × [acid], and from (*c*):

$$C = (1.74 \times [\text{acid}]) + [\text{acid}]$$
$$= 3.75 \times 10^{-2} \text{ mole/liter}$$

Therefore

$$[\text{acid}] = 1.37 \times 10^{-2} \text{ mole/liter}$$

and

$$[\text{salt}] = 1.74 \times [\text{acid}]$$
$$= 2.38 \times 10^{-2} \text{ mole/liter}$$

The Influence of Concentration on Buffer Capacity. The buffer capacity is affected not only by the [salt]/[acid] ratio but also by the total concentrations of acid and salt. As shown in Table 8–2, when 0.01 mole of base was added to a 0.1 molar acetate buffer, the pH increased from 4.76 to 4.85 or a ΔpH of 0.09.

If the concentration of acetic acid and sodium acetate is raised to 1 molar, the pH of the original buffer solution remains at about 4.76, but now, upon the addition of 0.01 mole of base, it becomes 4.77, a ΔpH of only 0.01. The calculation, disregarding activity coefficients, is

$$\text{pH} = 4.76 + \log \frac{(1.0 + 0.01)}{(1.0 - 0.01)} = 4.77 \qquad (8–28)$$

Therefore, an increase in the concentration of the buffer components results in a greater buffer capacity or efficiency. This conclusion is also evident in equation (8–27), where an increase in the total buffer concentration, C = [salt] + [acid], obviously results in a greater value of β.

In summary, the buffer capacity depends on (*a*) the value of the ratio [salt]/[acid], increasing as the ratio approaches unity; and (*b*) the magnitude of the individual concentrations of the buffer components, the buffer becoming more efficient as the salt and acid concentrations are increased.

Maximum Buffer Capacity. An equation expressing the maximum buffer capacity may be derived from the buffer capacity formula of Koppel and Spiro[1] and Van Slyke[2] (equation (8–27)). The maximum buffer capacity occurs where pH = pK_a, or, in equivalent terms, where $[H_3O^+] = K_a$. Substituting $[H_3O^+]$ for K_a in both the numerator and denominator of equation (8–27) gives

$$\beta_{max} = 2.303C \frac{[H_3O^+]^2}{(2[H_3O^+])^2} = \frac{2.303}{4} C$$

$$\beta_{max} = 0.576C \qquad (8–29)$$

in which C is the total buffer concentration.

Example 8–8. What is the maximum buffer capacity of an acetate buffer with a total concentration of 0.020 mole per liter?

$$\beta_{max} = 0.576 \times 0.020$$
$$= 0.01152 \text{ or } 0.012$$

Neutralization Curves and Buffer Capacity. A further understanding of buffer capacity can be obtained by considering the titration curves of strong and weak acids when they are mixed with increasing quantities of alkali. The reaction of an equivalent of an acid with an equivalent of a base is called neutralization; it may be expressed according to the method of Brönsted and Lowry. The neutralization of a strong acid by a strong base and weak acid by a strong base are written, as explained on pp. 143–145, in the form

Acid_1	Base_2	Acid_2	Base_1
$H_3O^+(Cl^-)$ +	$(Na^+)OH^-$ =	H_2O	+ H_2O + Na^+ + Cl^-
HAc +	$(Na^+)OH^-$ =	H_2O	+ $(Na^+)Ac^-$

in which $(H_3O^+)(Cl^-)$ is the hydrated form of HCl in water. The neutralization of a strong acid by a strong base simply involves a reaction between hydronium and hydroxyl ions and is usually written

$$H_3O^+ + OH^- = 2H_2O \qquad (8-30)$$

Since (Cl^-) and (Na^+) appear on both sides of the equation just given, they may be disregarded without influencing the result. The reaction between the strong acid and strong base proceeds almost to completion; however, the weak acid–strong base reaction is incomplete, since Ac^- reacts in part with water, that is, it hydrolyzes to regenerate the free acid.

The neutralization of 10 mL of 0.1 *N* HCl (curve I) and 10 mL of 0.1 *N* acetic acid (curve II) by 0.1 *N* NaOH is shown in Figure 8–1. The plot of pH versus milliliters of NaOH added produces the titration curve. It is computed as follows for HCl. Before the first increment of NaOH is added, the hydrogen ion concentration of the 0.1-*N* solution of HCl is 10^{-1} mole/liter and the pH = 1, disregarding activities and assuming HCl to be completely ionized. The addition of 5 mL of 0.1 *N* NaOH neutralizes 5 mL of 0.1 *N* HCl, leaving 5 mL of the original HCl in 10 + 5 = 15 mL of solution, or $[H_3O^+] = \frac{5}{15} \times 0.1 = 3.3 \times 10^{-2}$ mole per liter and pH = 1.48. When 10 mL of base has been added, all the HCl is converted to NaCl, and the pH, disregarding the difference between activity and concentration resulting from the ionic strength of the NaCl solution, is 7. This is known as the equivalence point of the titration. Curve I in Figure 8–1 results from plotting such data. It is seen that the pH does not change markedly until nearly all the HCl is neutralized. Hence, a solution of a strong acid has a high buffer capacity below a pH of 2. Likewise, a strong base has a high buffer capacity above a pH of 12.

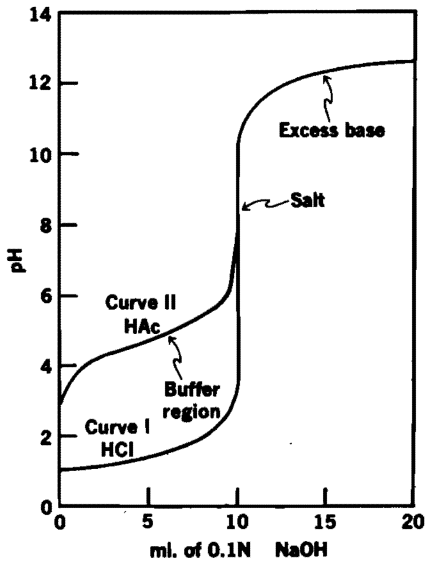


Fig. 8–1. Neutralization of a strong acid and a weak acid by a strong base.

The buffer capacity equations considered thus far have pertained exclusively to mixtures of weak electrolytes and their salts. The buffer capacity of a solution of a strong acid was shown by Van Slyke to be directly proportional to the hydrogen ion concentration, or

$$\beta = 2.303\,[H_3O^+] \qquad (8-31)$$

The buffer capacity of a solution of a strong base is similarly proportional to the hydroxyl ion concentration,

$$\beta = 2.303\,[OH^-] \qquad (8-32)$$

The total buffer capacity of a water solution of a strong acid or base at any pH is the sum of the separate capacities just given, equations (8–31) and (8–32), or

$$\beta = 2.303([H_3O^+] + [OH^-]) \qquad (8-33)$$

Example 8–9. What is the buffer capacity of a solution of hydrochloric acid having a hydrogen ion concentration of 10^{-2} mole per liter?

The hydroxyl ion concentration of such a solution is 10^{-12}, and the total buffer capacity is

$$\beta = 2.303(10^{-2} + 10^{-12})$$
$$\beta = 0.023$$

The OH^- concentration is obviously so low in this case that it may be neglected in the calculation.

Three equations are normally used to obtain the data for the titration curve of a weak acid (curve II of Figure 8–1), although a single equation that is somewhat complicated can be used. Suppose that increments of 0.1 *N* NaOH are added to 10 mL of a 0.1-*N* HAc solution.

(*a*) The pH of the solution, before any NaOH has been added, is obtained from the equation for a weak acid (p. 155, equation (7–99)).

$$\text{pH} = \tfrac{1}{2}pK_a - \tfrac{1}{2}\log c$$
$$= 2.38 - \tfrac{1}{2}\log 10^{-1} = 2.88$$

(b) At the equivalence point, where the acid has been converted completely into sodium ions and acetate ions, the pH is computed from the equation for a salt of a weak acid and strong base (p. 156, equation (7–103)) in log form:

$$\text{pH} = \tfrac{1}{2}\,pK_w + \tfrac{1}{2}\,pK_a + \tfrac{1}{2}\log c$$
$$= 7.00 + 2.38 + \tfrac{1}{2}\log (5 \times 10^{-2})$$
$$= 8.73$$

The concentration of the acid is given in the last term of this equation as 0.05, because the solution has been reduced to half its original value by mixing it with an equal volume of base at the equivalence point.

(*c*) Between these points on the neutralization curve, the increments of NaOH convert some of the acid to its conjugate base Ac^- to form a buffer mixture, and the

pH of the system is calculated from the buffer equation. When 5 mL of base is added, the equivalent of 5 mL of 0.1 *N* acid remains and 5 mL of 0.1 *N* Ac^- is formed, and using the Henderson–Hasselbalch equation,

$$pH = pK_a + \log \frac{[salt]}{[acid]}$$

$$= 4.76 + \log \frac{5}{5} = 4.76$$

The slope of the curve is a minimum and the buffer capacity is greatest at this point, where the solution shows the smallest pH change per gram equivalent of base added. The buffer capacity of a solution is the reciprocal of the slope of the curve at a point corresponding to the composition of the buffer solution. As seen in Figure 8–1, the slope of the line is a minimum, and the buffer capacity is greatest at half-neutralization, where $pH = pK_a$.

The titration curve for a tribasic acid such as H_3PO_4 consists of three stages, as shown in Figure 8–2. These may be considered as being produced by three separate acids (H_3PO_4, $pK_1 = 2.21$; $H_2PO_4^-$, $pK_2 = 7.21$; and HPO_4^{2-}, $pK_3 = 12.67$) whose strengths are sufficiently different so that their curves do not overlap. The curves may be plotted by using the buffer equation and their ends joined by smooth lines to produce the continuous curve of Figure 8–2.

A mixture of weak acids, whose pK_a values are sufficiently alike (differing by no more than about 2 pH units) so that their buffer regions overlap, can be used as a *universal buffer* over a wide range of pH values. A buffer of this type was introduced by Britton and Robinson.[9] The three stages of citric acid—$pK_1 = 3.15$, $pK_2 = 4.78$, $pK_3 = 6.40$—are sufficiently close to provide overlapping of neutralization curves and efficient buffering over this range. Adding Na_2HPO_4, whose conjugate acid $H_2PO_4^-$ has a pK_2 of 7.2,

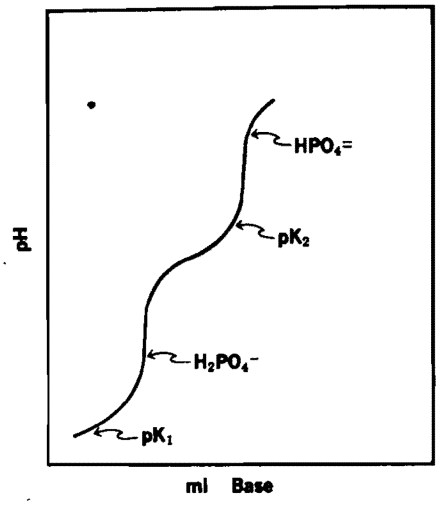


Fig. 8–2. Neutralization of a tribasic acid.

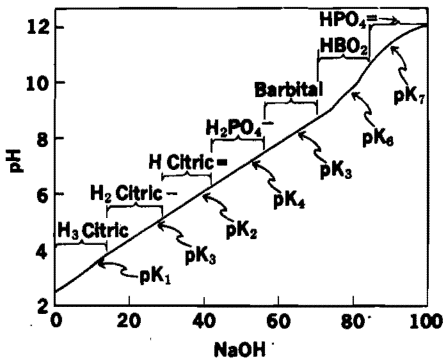


Fig. 8–3. Neutralization curve for a universal buffer. The horizontal axis is marked off in milliliters of 0.2 *N* NaOH. (After H. T. Britton, *Hydrogen Ions*, Vol. I, D. Van Nostrand, New York, 1956, p. 368.)

diethylbarbituric acid, $pK_1 = 7.91$, and boric acid, $pK_1 = 9.24$, provides a universal buffer that covers the pH range of about 2.4 to 12. The neutralization curve for the universal buffer mixture is linear between pH 4 and 8, as seen in Figure 8–3, because the successive dissociation constants differ by only a small value.

A titration curve depends on the ratio of the successive dissociation constants. Theoretically, when one *K* is equal to or less than 16 times the previous *K*, that is, when successive p*K*s do not differ by greater than 1.2 units, the second ionization begins well before the first is completed, and the titration curve is a straight line with no inflection points. Actually the inflection is not noticeable until one *K* is about 50 to 100 times that of the previous *K* value.

The buffer capacity of several acid–salt mixtures is plotted against pH in Figure 8–4. A buffer solution is useful within a range of about ±1 pH unit about the pK_a of its acid, where the buffer capacity is roughly greater than 0.01 or 0.02, as observed in Figure 8–4. Accordingly, the acetate buffer should be effective over a pH range of about 3.8 to 5.8, and the borate buffer should be effective over a range of 8.2 to 10.2. In each case, the greatest capacity occurs where [salt]/[acid] = 1 and $pH = pK_a$. Because of interionic effects, buffer capacities do not in general exceed a value of 0.2. The buf-

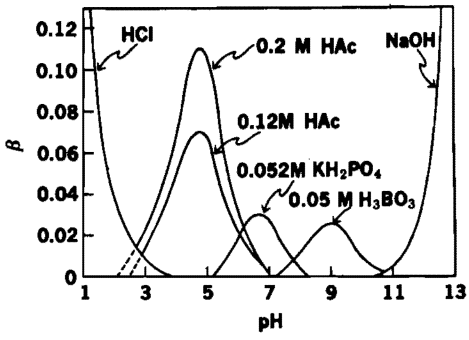


Fig. 8–4. The buffer capacity of several buffer systems as a function of pH. (Modified from R. G. Bates, *Electrometric pH Determinations*, Wiley, New York, 1954.)

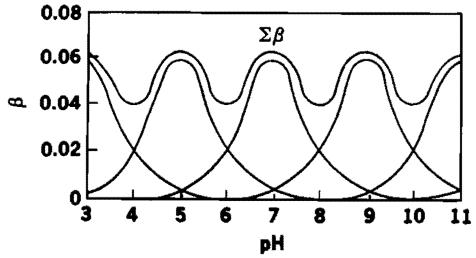


Fig. 8–5. The total buffer capacity of a universal buffer as a function of pH. From I. M. Kolthoff and C. Rosenblum, *Acid–Base Indicators*, Macmillan, New York, 1937, p. 29.)

fer capacity of a solution of the strong acid HCl becomes marked below a pH of 2, and the buffer capacity of a strong base NaOH becomes significant above a pH of 12.

The buffer capacity of a combination of buffers, the pK_a values of which overlap to produce a universal buffer, is plotted in Figure 8–5. It is seen that the total buffer capacity $\Sigma\beta$ is the sum of the β values of the individual buffers. In this figure, it is assumed that the maximum β's of all buffers in the series are identical.

BUFFERS IN PHARMACEUTICAL AND BIOLOGIC SYSTEMS

In Vivo Biologic Buffer Systems. *Blood* is maintained at a pH of about 7.4 by the so-called primary buffers in the plasma and the secondary buffers in the erythrocytes. The plasma contains carbonic acid/bicarbonate and acid/alkali sodium salts of phosphoric acid as buffers. Plasma proteins, which behave as acids in blood, can combine with bases and so act as buffers. In the erythrocytes, the two buffer systems consist of hemoglobin/oxyhemoglobin and acid/alkali potassium salts of phosphoric acid.

The dissociation exponent pK_1 for the first ionization stage of carbonic acid in the plasma at body temperature and an ionic strength of 0.16 is about 6.1. The buffer equation for the carbonic acid/bicarbonate buffer of the blood is

$$\text{pH} = 6.1 + \log \frac{[HCO_3^-]}{[H_2CO_3]} \qquad (8\text{–}34)$$

in which $[H_2CO_3]$ represents the concentration of CO_2 present as H_2CO_3 dissolved in the blood. At a pH of 7.4, the ratio of bicarbonate to carbonic acid in normal blood plasma is

$$\log \frac{[HCO_3^-]}{[H_2CO_3]} = 7.4 - 6.1 = 1.3$$

or

$$[HCO_3^-]/[H_2CO_3] = 20/1 \qquad (8\text{–}35)$$

This result checks with experimental findings, since the actual concentrations of bicarbonate and carbonic acid in the plasma are about 0.025 *M* and 0.00125 *M* respectively.

The buffer capacity of the blood in the physiologic range pH 7.0 to 7.8 is obtained as follows. According to Peters and Van Slyke,[10] the buffer capacity of the blood owing to hemoglobin and other constituents, exclusive of bicarbonate, is about 0.025 gram equivalents per liter per pH unit. The pH of the bicarbonate buffer in the blood (i.e. pH 7.4) is rather far removed from the pH (6.1) where it exhibits maximum buffer capacity; therefore, the bicarbonate's buffer action is relatively small with respect to that of the other blood constituents. According to the calculation just given, the ratio $[NaHCO_3]/[H_2CO_3]$ is 20:1 at pH 7.4. Using equation (8–27), the buffer capacity for the bicarbonate system ($K_1 = 4 \times 10^{-7}$) at a pH of 7.4 ($[H_3O^+] = 4 \times 10^{-8}$) is found to be roughly 0.003. Therefore, the total buffer capacity of the blood in the physiologic range, the sum of the capacities of the various constituents, is 0.025 + 0.003 = 0.028. Salenius[11] reported a value of 0.0318 ± 0.0035 for whole blood, whereas Ellison et al.[12] obtained a buffer capacity of about 0.039 gram equivalents per liter per pH unit for whole blood, of which 0.031 was contributed by the cells and 0.008 by the plasma.

Usually when the pH of the blood goes below 6.9 or above 7.8, life is in serious danger. The pH of the blood in diabetic coma is alleged to drop as low as about 6.8.

Lacrimal fluid, or tears, have been found to have a great degree of buffer capacity, allowing a dilution of 1:15 with neutral distilled water before an alteration of pH is noticed.[13] In the terminology of Bates,[14] this would be referred to today as *dilution value* rather than buffer capacity (p. 171). The pH of tears is about 7.4, with a range of 7 to 8 or slightly higher. Pure conjunctival fluid is probably more acidic than the tear fluid commonly used in pH measurements. This is because pH increases rapidly when the sample is removed for analysis because of the loss of CO_2 from the tear fluid.

Urine. The 24-hour urine collection of a normal adult has a pH averaging about 6.0 units; it may be as low as 4.5 or as high as 7.8. When the pH of the urine is below normal values, hydrogen ions are excreted by the kidneys. Conversely, when the urine is above pH 7.4, hydrogen ions are retained by action of the kidneys in order to return the pH to its normal range of values.

Pharmaceutical Buffers. Buffer solutions are used frequently in pharmaceutical practice, particularly in the formulation of ophthalmic solutions. They also find application in the colorimetric determination of pH and for those research studies in which pH must be held constant.

Gifford[15] suggested two stock solutions, one containing boric acid and the other monohydrated sodium carbonate, which, when mixed in various proportions, yield buffer solutions with pH values from about 5 to 9.

Sörensen[16] proposed a mixture of the salts of sodium phosphate for buffer solutions of pH 6 to 8. Sodium

chloride is added to each buffer mixture to make it isotonic with body fluids.

A buffer system suggested by Palitzsch[17] and modified by Hind and Goyan[18] consists of boric acid, sodium borate, and sufficient sodium chloride to make the mixtures isotonic. It is used for ophthalmic solutions in the pH range of 7 to 9.

The buffers of Clark and Lubs,[19] based on the original pH scale of Sörensen, have been redetermined at 25° C by Bower and Bates[7] so as to conform to the present definition of pH (p. 200). Between pH 3 and 11, the older values were about 0.04 unit lower than the values now assigned, and at the ends of the scale, the differences were greater. The original values were determined at 20° C, whereas most experiments today are performed at 25° C.

The Clark–Lubs mixtures and their corresponding pH ranges are:

(*a*) HCl and KCl, pH 1.2 to 2.2

(*b*) HCl and potassium hydrogen phthalate, pH 2.2 to 4.0

(*c*) NaOH and potassium hydrogen phthalate, pH 4.2 to 5.8

(*d*) NaOH and KH_2PO_4, pH 5.8 to 8.0

(*e*) H_3BO_3, NaOH and KCl, pH 8.0 to 10.0

With regard to mixture (*a*), consisting of HCl and KCl and used for the pH range from 1.0 to 2.2, it will be recalled from the discussion of the neutralization curve (I), Figure 8–1, that HCl alone has considerable buffer efficiency below pH 2. KCl is a neutral salt and is added to adjust the ionic strength of the buffer solutions to a constant value of 0.10; the pH calculated from the equation, $-\log a_{H^+} = -\log (\gamma_{\pm} c)$, corresponds closely to the experimentally determined pH. The role of the KCl in the Clark–Lubs buffer is sometimes erroneously interpreted as that of a salt of the buffer acid, HCl, corresponding to the part played by sodium acetate as the salt of the weak buffer acid, HAc. Potassium chloride is added to (*e*), the borate buffer, to produce an ionic strength comparable to that of (*d*), the phosphate buffer, where the pH of the two buffer series overlap.

Buffer solutions are discussed in the USP XXII on pp. 1598, 1599, 1784, and 1785. A buffer commonly used in biologic research (pH 7 to 9) and reported in the *Merck Index* is TRIS, aminohydroxymethyl propanediol.

Preparation of Pharmaceutical Buffer Solutions. The pharmacist may be called upon at times to prepare buffer systems, the formulas for which do not appear in the literature. The following steps should be helpful in the development of a new buffer.

(*a*) Select a weak acid having a pK_a approximately equal to the pH at which the buffer is to be used. This will ensure maximum buffer capacity.

(*b*) From the buffer equation, calculate the ratio of salt and weak acid required to obtain the desired pH. The buffer equation is satisfactory for approximate calculations within the pH range of 4 to 10.

(*c*) Consider the individual concentrations of the buffer salt and acid needed to obtain a suitable buffer capacity. A *concentration* of 0.05 to 0.5 *M* is usually sufficient; and a *buffer capacity* of 0.01 to 0.1 is generally adequate.

(*d*) Other factors of some importance in the choice of a pharmaceutical buffer include availability of chemicals, sterility of the final solution, stability of the drug and buffer on aging, cost of materials, and freedom from toxicity. For example, a borate buffer, because of its toxic effects, certainly cannot be used to stabilize a solution to be administered orally or parenterally.

(*e*) Finally, one should determine the pH and buffer capacity of the completed buffered solution using a reliable pH meter. In some cases, sufficient accuracy is obtained by the use of pH papers. Particularly when the electrolyte concentration is high, it may be found that the pH calculated by use of the buffer equation is somewhat different from the experimental value. This is to be expected when activity coefficients are not taken into account, and it emphasizes the necessity for carrying out the actual determination.

Influence of Buffer Capacity and pH on Tissue Irritation. Solutions to be applied to tissues or administered parenterally are liable to cause irritation if their pH is greatly removed from the normal pH of the relevant body fluid. Consequently, the pharmacist must consider this point when formulating ophthalmic solutions, parenteral products, and fluids to be applied to abraded surfaces. Of possible greater significance than the actual pH of the solution is its buffer capacity and the volume to be used in relation to the volume of body fluid with which the buffered solution will come in contact. The buffer, capacity of the body fluid should also be considered. Tissue irritation, due to large pH differences between the solution being administered and the physiologic environment in which it is used, will be minimal (*a*) the lower the buffer capacity of the solution, (*b*) the smaller the volume used, for a given concentration, and (*c*) the larger the volume and buffer capacity of the physiologic fluid.

Friedenwald et al.[20] claimed that the pH of solutions for introduction into the eye may vary from 4.5 to 11.5 without marked pain or damage. This statement evidently would be true only if the buffer capacity were kept low. Martin and Mims[21] found that Sörensen's phosphate buffer produced irritation in the eyes of a number of subjects when used outside the narrow pH range of 6.5 to 8, whereas a boric acid solution of pH 5 produced no discomfort in the eyes of the same subjects. Martin and Mims concluded that a pH range of nonirritation cannot be established absolutely but rather depends upon the buffer employed. In light of the previous discussion, this apparent anomaly can be explained partly in terms of the low buffer capacity of boric acid as compared with that of the phosphate buffer (cf. *Problems 8–12* and *8–13*, p. 188) and partly

to the difference of the physiologic response to various ion species.

Riegelman and Vaughn[22] assumed that the acid-neutralizing power of the tears when 0.1 mL of a 1% solution of a drug is instilled into the eye is roughly equivalent to 10 microliters of a 0.01-*N* strong base. They point out that while in a few cases irritation of the eye may result from the presence of the free base form of a drug at the physiologic pH, it is more often due to the acidity of the eye solution. For example, since only one carboxyl group of tartaric acid is neutralized by epinephrine base in epinephrine bitartrate, a 0.06-*M* solution of the drug has a pH of about 3.5. The prolonged pain resulting from instilling two drops of this solution into the eye is presumably due to the unneutralized acid of the bitartrate, which requires ten times the amount of tears to restore the normal pH of the eye as compared with the result following two drops of epinephrine hydrochloride. Solutions of pilocarpine salts also possess sufficient buffer capacity to cause pain or irritation owing to their acid reaction when instilled into the eye.

Parenteral solutions for injection into the blood are usually not buffered, or they are buffered to a low capacity so that the buffers of the blood may readily bring them within the physiologic pH range. If the drugs are to be injected only in small quantities and at a slow rate, their solutions can be buffered weakly to maintain approximate neutrality.

Following oral administration, aspirin is absorbed more rapidly in systems buffered at low buffer capacity than in systems containing no buffer or in highly buffered preparations, according to Mason.[23] Thus, the buffer capacity of the buffer should be optimized to produce rapid absorption and minimal gastric irritation of orally administered aspirin.

In addition to the adjustment of tonicity and pH for ophthalmic preparations, similar requirements are demanded for nasal delivery of drugs. This has become all the more important in recent years since the nasal passage is now used for the administration of systemic drugs (see pp. 525–527 for nasal dosage forms). Insulin, for example, is more effective by nasal administration than by other nonparenteral routes.[24]

Stability vs. Optimum Therapeutic Response. For the sake of completeness, some mention must be made at this point of the effect of buffer capacity and pH on the stability and therapeutic response of the drug being used in solution.

As will be discussed later (Chapter 10), the undissociated form of a weakly acidic or basic drug often has a higher therapeutic activity than the dissociated salt form. This is because the former is lipid soluble and can penetrate body membranes readily, whereas the ionic form, not being lipid soluble, can penetrate membranes only with greater difficulty. Thus Swan and White[25] and Cogan and Kinsey[26] observed an increase in therapeutic response of weakly basic alkaloids (used as ophthalmic drugs) as the pH of the solution, and hence concentration of the undissociated base, was increased. At a pH of about 4, these drugs are predominantly in the ionic form, and penetration is slow or insignificant. When the tears bring the pH to about 7.4, the drugs may exist to a significant degree in the form of the free base, depending on the dissociation constant of the drug.

Example 8–10. The pK_b of pilocarpine is 7.15 at 25° C. Compute the mole percent of free base present on 25° C and at a pH of 7.4.

$$\underset{\text{Pilocarpine base}}{C_{11}H_{16}N_2O_2} + H_2O \rightleftharpoons \underset{\text{Pilocarpine ion}}{C_{11}H_{16}N_2O_2H^+} + OH^-$$

$$pH = pK_w - pK_b + \log \frac{[\text{base}]}{[\text{salt}]}$$

$$7.4 = 14.00 - 7.15 + \log \frac{[\text{base}]}{[\text{salt}]}$$

$$\log \frac{[\text{base}]}{[\text{salt}]} = 7.40 - 14.00 + 7.15 = 0.55$$

$$\frac{[\text{base}]}{[\text{salt}]} = \frac{3.56}{1}$$

$$\text{mole percent of base} = \frac{[\text{base}]}{[\text{salt}] + [\text{base}]} \times 100$$

$$= [3.56/(1 + 3.56)] \times 100 = 78\%$$

Hind and Goyan[27] pointed out that the pH for maximum stability of a drug for ophthalmic use may be far below that of the optimum physiologic effect. Under such conditions, the solution of the drug can be buffered at a low buffer capacity and at a pH that is a compromise between that of optimum stability and the pH for maximum therapeutic action. The buffer is adequate to prevent changes in pH due to the alkalinity of the glass or acidity of CO_2 from dissolved air. Yet, when the solution is instilled in the eye, the tears participate in the gradual neutralization of the solution; conversion of the drug occurs from the physiologically inactive form to the undissociated base. The base can then readily penetrate the lipoidal membrane. As the base is absorbed at the pH of the eye, more of the salt is converted into base to preserve the constancy of pK_b; hence, the alkaloidal drug is gradually absorbed.

pH and Solubility. The relationship of pH and the solubility of weak electrolytes will be treated in some detail in Chapter 10. At this point it is necessary only to point out briefly the influence of buffering on the solubility of an alkaloidal base. At a low pH, a base is predominantly in the ionic form, which is usually very soluble in aqueous media. As the pH is raised, more undissociated base is formed as calculated by the method illustrated in *Example 8–10*. When the amount of base exceeds the limited water solubility of this form, free base precipitates from solution. Therefore, the solution should be buffered at a sufficiently low pH so that the concentration of alkaloidal base in equilibrium with its salt is calculated to be less than the solubility of

the free base at the storage temperature. Stabilization against precipitation can thus be maintained.

BUFFERED ISOTONIC SOLUTIONS

Reference has already been made to the in vivo buffer systems, such as blood and lacrimal fluid, and the desirability for buffering pharmaceutical solutions under certain conditions. In addition to carrying out pH adjustment, pharmaceutical solutions that are meant for application to delicate membranes of the body should also be adjusted to approximately the same osmotic pressure (Chapter 5) as that of the body fluids. Isotonic solutions cause no swelling or contraction of the tissues with which they come in contact, and produce no discomfort when instilled in the eye, nasal tract, blood, or other body tissues. Isotonic sodium chloride is a familiar pharmaceutical example of such a preparation.

The need to achieve isotonic conditions with solutions to be applied to delicate membranes is dramatically illustrated by mixing a small quantity of blood with aqueous sodium chloride solutions of varying tonicity. For example, if a small quantity of blood, defibrinated to prevent clotting, is mixed with a solution containing 0.9 g NaCl per 100 mL, the cells retain their normal size. The solution has essentially the same salt concentration and hence the same osmotic pressure as the red blood cell contents, and is said to be *isotonic* with blood. If the red blood cells are suspended in a 2.0% NaCl solution, the water within the cells passes through the cell membrane in an attempt to dilute the surrounding salt solution until the salt concentrations on both sides of the erythrocyte membrane are identical. This outward passage of water causes the cells to shrink and become wrinkled or *crenated*. The salt solution in this instance is said to be *hypertonic* with respect to the blood cell contents. Finally, if the blood is mixed with 0.2% NaCl solution or with distilled water, water enters the blood cells, causing them to swell and finally burst, with the liberation of hemoglobin. This phenomenon is known as *hemolysis*, and the weak salt solution or water is said to be *hypotonic* with respect to the blood.

The student should appreciate that the red blood cell membrane is not impermeable to all drugs; that is, it is not a perfect semipermeable membrane. Thus, it will permit the passage of not only water molecules, but also solutes such as urea, ammonium chloride, alcohol, and boric acid.[28] A 2.0% solution of boric acid has the same osmotic pressure as the blood cell contents when determined by the freezing point method and is therefore said to be *isosmotic* with blood. The molecules of boric acid pass freely through the erythrocyte membrane, however, regardless of concentration. As a result, this solution acts essentially as water when in contact with blood cells. Being extremely hypotonic with respect to the blood, boric acid solution brings about rapid hemolysis. Therefore, a solution containing a quantity of drug calculated to be isosmotic with blood is isotonic *only* when the blood cells are impermeable to the solute molecules and permeable to the solvent, water. It is interesting to note that the mucous lining of the eye acts as a true semipermeable membrane to boric acid in solution. Accordingly, a 2.0% boric acid solution serves as an isotonic ophthalmic preparation.

To overcome this difficulty, Husa[29] has suggested that the term *isotonic* should be restricted to solutions having equal osmotic pressures with respect to a particular membrane. Goyan and Reck[30] felt that, rather than restricting the use of the term in this manner, a new term should be introduced that is defined on the basis of the sodium chloride concentration. These workers defined the term *isotonicity value* as the concentration of an aqueous NaCl solution having the same colligative properties as the solution in question. Although all solutions having an isotonicity value of 0.9 g NaCl per 100 mL of solution need not *necessarily* be isotonic with respect to the living membranes concerned. Nevertheless, many of them are roughly isotonic in this sense, and all may be considered isotonic across an ideal membrane. Accordingly, the term *isotonic* is used with this meaning throughout the present chapter. Only a few substances—those that penetrate animal membranes at a sufficient rate—will show exception to this classification.

The remainder of this chapter is concerned with a discussion of isotonic solutions and the means by which they may be buffered.

Measurement of Tonicity. The tonicity of solutions may be determined by one of two methods. First, in the *hemolytic* method, the effect of various solutions of the drug is observed on the appearance of red blood cells suspended in the solutions. The various effects produced have been described in the previous section. Husa and his associates[29] have used this method. In their later work, a quantitative method developed by Hunter[31] was used based on the fact that a hypotonic solution liberates oxyhemoglobin in direct proportion to the number of cells hemolyzed. By such means, the van't Hoff i factor (p. 129) can be determined and the value compared with that computed from cryoscopic data, osmotic coefficient, and activity coefficient.[32]

Husa has found that a drug having the proper i value as measured by freezing point depression or computed from theoretic equations nevertheless may hemolyze human red blood cells; it was on this basis that he suggested restriction of the term *isotonic* to solutions having equal osmotic pressures with respect to a particular membrane.

The second approach used to measure tonicity is based on any of the methods that determine colligative properties, as discussed in Chapter 5. Goyan and Reck[30] investigated various modifications of the Hill–Baldes technique[33] (p. 111) for measuring tonicity. This

method is based on a measurement of the slight temperature differences arising from differences in the vapor pressure of thermally insulated samples contained in constant-humidity chambers.

One of the first references to the determination of the freezing point of blood and tears (as was necessary to make solutions isotonic with these fluids) was that of Lumiere and Chevrotier,[34] in which the values of −0.56° and −0.80° C were given respectively for the two fluids. Following work by Pedersen-Bjergaard and co-workers,[35,36] however, it is now well established that −0.52° is the freezing point of both human blood and lacrimal fluid. This temperature corresponds to the freezing point of a 0.90% NaCl solution, which is therefore considered to be isotonic with both blood and lacrimal fluid.

Calculating Tonicity Using L_{iso} Values. Since the freezing point depressions for solutions of electrolytes of both the weak and strong types are always greater than those calculated from the equation, $\Delta T_f = K_f c$, a new factor, $L = iK_f$, is introduced to overcome this difficulty.[37] The equation already discussed in Chapter 6, p. 137, is

$$\Delta T_f = Lc \qquad (8\text{–}36)$$

The L value may be obtained from the freezing point lowering of solutions of representative compounds of a given ionic type at a concentration c that is isotonic with body fluids. This specific value of L is symbolized as L_{iso} (p. 137).

The L_{iso} value for a 0.90% (0.154-M) solution of sodium chloride, which has a freezing point depression of 0.52° and is thus isotonic with body fluids, is 3.4:

$$L_{iso} = \frac{\Delta T_f}{c} \qquad (8\text{–}37)$$

$$L_{iso} = \frac{0.52°}{0.154} = 3.4$$

The interionic attraction in solutions that are not too concentrated is roughly the same for all uni-univalent electrolytes regardless of the chemical nature of the various compounds of this class, and all have about the same value for L_{iso}, namely 3.4. As a result of this similarity between compounds of a given ionic type, a table can be arranged listing the L value for each class of electrolytes at a concentration that is isotonic with body fluids. The L_{iso} values obtained in this way are found in Table 8–3.

It will be observed that for dilute solutions of nonelectrolytes, L_{iso} is approximately equal to K_f. Table 8–3 is used to obtain the approximate ΔT_f for a solution of a drug, if the ionic type can be correctly ascertained. A plot of iK_f against molar concentration of various types of electrolytes, from which the values of L_{iso} can be read, is shown in Figure 6–7, p. 137.

Example 8–11. What is the freezing point lowering of a 1% solution of sodium propionate (molecular weight 96)? Since sodium propionate is a uni-univalent electrolyte, its L_{iso} value is 3.4. The molar concentration of a 1% solution of this compound is 0.104.

$$\Delta T_f = 3.4 \times 0.104 = 0.35° \qquad (8\text{–}38)$$

Although 1 g per 100 mL of sodium propionate is not the isotonic concentration, it is still proper to use L_{iso} as a simple average that agrees with the concentration range expected for the finished solution. The selection of L values in this concentration region is not sensitive to minor changes in concentration; no pretense to an accuracy greater than about 10% is implied or needed in these calculations.

The calculation of *Example 8–11* may be simplified by expressing molarity c as grams of drug contained in a definite volume of solution. Thus

$$\text{Molarity} = \frac{\text{moles}}{\text{liter}}$$

$$= \frac{\text{weight in grams}}{\text{molecular weight in g/mole}} \div \frac{\text{volume in mL}}{1000 \text{ mL/liter}} \qquad (8\text{–}39)$$

or

$$c = \frac{w}{MW} \times \frac{1000}{v} \qquad (8\text{–}40)$$

in which w is the grams of solute, MW is the molecular weight of the solute, and v is the volume of solution in milliliters. Substituting in equation (8–36)

TABLE 8–3. *Average L_{iso} Values for Various Ionic Types

Type	L_{iso}	Examples
Nonelectrolytes	1.9	Sucrose, glycerin, urea, camphor
Weak electrolytes	2.0	Boric acid, cocaine, phenobarbital
Di-divalent electrolytes	2.0	Magnesium sulfate, zinc sulfate
Uni-univalent electrolytes	3.4	Sodium chloride, cocaine hydrochloride, sodium phenobarbital
Uni-divalent electrolytes	4.3	Sodium sulfate, atropine sulfate
Di-univalent electrolytes	4.8	Zinc chloride, calcium bromide
Uni-trivalent electrolytes	5.2	Sodium citrate, sodium phosphate
Tri-univalent electrolytes	6.0	Aluminum chloride, ferric iodide
Tetraborate electrolytes	7.6	Sodium borate, potassium borate

*From J. M. Wells, J. Am. Pharm. Assoc., Pract. Ed. 5, 99, 1944.

$$\Delta T_f = L_{iso} \times \frac{w \times 1000}{MW \times v} \qquad (8-41)$$

The problem in *Example (8–11)* can be solved in one operation by the use of equation (8–41) without the added calculation needed to obtain the molar concentration.

$$\Delta T_f = 3.4 \times \frac{1 \times 1000}{96 \times 100} = 3.4 \times 0.104$$

$$= 0.35°$$

The student is encouraged to derive expressions of this type; certainly equations (8–40) and (8–41) should not be memorized, for they are not remembered long. The L_{iso} values may also be used for calculating sodium chloride equivalents and Sprowls' V values, as discussed in subsequent sections of this chapter.

METHODS OF ADJUSTING TONICITY AND pH

One of several methods may be used to calculate the quantity of sodium chloride, dextrose, and other substances that may be added to solutions of drugs to render them isotonic.

For discussion purposes, the methods are divided into two classes. In the Class I methods, sodium chloride or some other substance is added to the solution of the drug to lower the freezing point of the solution to −0.52° and thus make it isotonic with body fluids. Under this class are included the *Cryoscopic* method and the *Sodium Chloride Equivalent* method. In the Class II methods, water is added to the drug in a sufficient amount to form an isotonic solution. The preparation is then brought to its final volume with an isotonic or a buffered isotonic dilution solution. Included in this class are the *White–Vincent* method and the *Sprowls* method.

Class I Methods

Cryoscopic Method. The freezing point depressions of a number of drug solutions, determined experimentally or theoretically, are found in Table 8–4. According to the previous section, the freezing point depressions of drug solutions that have not been determined experimentally can be estimated from theoretic considerations, knowing only the molecular weight of the drug and the L_{iso} value of the ionic class.

The calculations involved in the cryoscopic method are explained best by an example.

Example 8–12. How much sodium chloride is required to render 100 mL of a 1% solution of apomorphine hydrochloride isotonic with blood serum?

From Table 8–4 it is found that a 1% solution of the drug has a freezing point lowering of 0.08°. To make this solution isotonic with blood, sufficient sodium chloride must be added to reduce the freezing point by an additional 0.44° (0.52 − 0.08). In the freezing point table, it is also observed that a 1% solution of sodium chloride has a freezing point lowering of 0.58°. By the method of proportion,

$$\frac{1\%}{X} = \frac{0.58°}{0.44°}; \; X = 0.76\%$$

Thus, 0.76% sodium chloride will lower the freezing point the required 0.44° and will render the solution isotonic. The solution is prepared by dissolving 1.0 g of apomorphine hydrochloride and 0.76 g of sodium chloride in sufficient water to make 100 mL of solution.

Sodium Chloride Equivalent Method. A second method for adjusting the tonicity of pharmaceutical solutions was developed by Mellen and Seltzer.[38] The *sodium chloride equivalent* or, as referred to by these workers, the "tonicic equivalent" of a drug is the amount of sodium chloride that is equivalent to (i.e., has the same osmotic effect as) 1 gram, or other weight unit, of the drug. The sodium chloride equivalents E for a number of drugs are listed in Table 8–4.

When the E value for a new drug is desired for inclusion in Table 8–4, it can be calculated from the L_{iso} value or freezing point depression of the drug according to the formulas derived by Goyan et al.[39] For a solution containing 1 g of drug in 1000 mL of solution, the concentration c expressed in moles per liter may be written as

$$c = \frac{1 \text{ g}}{\text{molecular weight}} \qquad (8-42)$$

and from equation (8–36)

$$\Delta T_f = L_{iso} \frac{1 \text{ g}}{MW}$$

Now E is the weight of NaCl with the same freezing point depression as 1 g of the drug, and for a NaCl solution containing E grams of drug per 1000 mL,

$$\Delta T_f = 3.4 \frac{E}{58.45} \qquad (8-43)$$

in which 3.4 is the L_{iso} value for sodium chloride and 58.45 is its molecular weight. Equating these two values of ΔT_f yields

$$\frac{L_{iso}}{MW} = 3.4 \frac{E}{58.45} \qquad (8-44)$$

$$E \cong 17 \frac{L_{iso}}{MW} \qquad (8-45)$$

Example 8–13. Calculate the approximate E value for a new amphetamine hydrochloride derivative (molecular weight 187).

Since this drug is a uni-univalent salt, it has an L_{iso} value of 3.4. Its E value is calculated from equation (8–45):

$$E = 17 \frac{3.4}{187} = 0.31$$

Calculations for determining the amount of sodium chloride or other inert substance to render a solution isotonic (across an ideal membrane) simply involve multiplying the quantity of each drug in the prescription by its sodium chloride equivalent and subtracting

TABLE 8–4. ***Isotonic Values****

Substance	*MW*	E	V	$\Delta T_f^{1\%}$	L_{iso}
Alcohol, dehydrated	46.07	0.70	23.3	0.41	1.9
Aminophylline	456.46	0.17	5.7	0.10	4.6
Ammonium chloride	53.50	1.08	36	0.64	3.4
Amphetamine sulfate (benzedrine sulfate)	368.49	0.22	7.3	0.13	4.8
Antipyrine	188.22	0.17	5.7	0.10	1.9
Antistine hydrochloride (antazoline hydrochloride)	301.81	0.18	6.0	0.11	3.2
Apomorphine hydrochloride	312.79	0.14	4.7	0.08	2.6
Ascorbic acid	176.12	0.18	6.0	0.11	1.9
Atropine sulfate	694.82	0.13	4.3	0.07	5.3
Aureomycin hydrochloride	544	0.11	3.7	0.06	3.5
Barbital sodium	206.18	0.29	10.0	0.29	3.5
Benadryl hydrochloride (diphenhydramine hydrochloride)	291.81	0.20	6.6	0.34	3.4
Boric acid	61.84	0.50	16.7	0.29	1.8
Butacaine sulfate (butyn sulfate)	710.95	0.20	6.7	0.12	8.4
Caffeine	194.19	0.08	2.7	0.05	0.9
Caffeine and sodium benzoate	—	0.25	8.7	0.28	—
Calcium chloride · $2H_2O$	147.03	0.51	17.0	0.30	4.4
Calcium gluconate	448.39	0.16	5.3	0.09	4.2
Calcium lactate	308.30	0.23	7.7	0.14	4.2
Camphor	152.23	0.20	6.7	0.12	1.8
Chloramphenicol (chloromycetin)	323.14	0.10	3.3	0.06	1.9
Chlorobutanol (chloretone)	177.47	0.24	8.0	0.14	2.5
Cocaine hydrochloride	339.81	0.16	5.3	0.09	3.2
Cupric sulfate · $5H_2O$	249.69	0.18	6.0	0.11	2.6
Dextrose · H_2O	198.17	0.16	5.3	0.09	1.9
Dibucaine hydrochloride (nupercaine hydrochloride)	379.92	0.13	4.3	0.08	2.9
Emetine hydrochloride	553.56	0.10	3.3	0.06	3.3
Ephedrine hydrochloride	201.69	0.30	10.0	0.18	3.6
Ephedrine sulfate	428.54	0.23	7.7	0.14	5.8
Epinephrine bitartrate	333.29	0.18	6.0	0.11	3.5
Epinephrine hydrochloride	219.66	0.29	9.7	0.17	3.7
Ethylhydrocupreine hydrochloride (optochin)	376.92	0.17	5.7	0.10	3.8
Ethylmorphine hydrochloride (dionin)	385.88	0.16	5.3	0.09	3.6
Eucatropine hydrochloride (euphthalmine hydrochloride)	327.84	0.18	6.0	0.11	3.5
Fluorescein sodium	376	0.31	10.3	0.18	6.9
Glycerin	92.09	0.34	11.3	0.20	1.8
Homatropine hydrobromide	356.26	0.17	5.7	0.10	3.6
Lactose	360.31	0.07	2.3	0.04	1.7
Magnesium sulfate · $7H_2O$	246.50	0.17	5.7	0.10	2.5
Menthol	156.2€	0.20	6.7	0.12	1.8
Meperidine hydrochloride (demerol hydrochloride)	283.79	0.22	7.3	0.12	3.7
Mercuric chloride (mercury bichloride)	271.52	0.13	4.3	0.08	2.1
Mercuric cyanide	252.65	0.15	5.0	0.09	2.2
Mercuric succinimide	396.77	0.14	4.8	0.08	3.3
Methacholine chloride (mecholyl chloride)	195.69	0.32	10.7	0.19	3.7
Methamphetamine hydrochloride (desoxyephedrine hydrochloride)	185.69	0.37	12.3	0.22	4.0
Metycaine hydrochloride	292.82	0.20	6.7	0.12	3.4
Mild silver protein	—	0.18	6.0	0.11	—
Morphine hydrochloride	375.84	0.15	5.0	0.09	3.3
Morphine sulfate	758.82	0.14	4.8	0.08	6.2
Naphazoline hydrochloride (privine hydrochloride)	246.73	0.27	7.7	0.16	3.3
Neomycin sulfate	—	0.11	3.7	0.06	—
Neostigmine bromide (prostigmine bromide)	303.20	0.22	6.0	0.11	3.2
Nicotinamide	122.13	0.26	8.7	0.15	1.9
Penicillin G potassium	372.47	0.18	6.0	0.11	3.9
Penicillin G Procaine	588.71	0.10	3.3	0.06	3.5
Penicillin G sodium	356.38	0.18	6.0	0.11	3.8
Phenacaine hydrochloride (holocaine hydrochloride)	352.85	0.20	5.3	0.11	3.3

TABLE 8–4. *(continued)*

Substance	*MW*	*E*	*V*	$\Delta T_f^{1\%}$	L_{iso}
Phenobarbital sodium	254.22	0.24	8.0	0.14	3.6
Phenol	94.11	0.35	11.7	0.20	1.9
Phenylephrine hydrochloride (neosynephrine hydrochloride)	203.67	0.32	9.7	0.18	3.5
Physostigmine salicylate	413.46	0.16	5.3	0.09	3.9
Physostigmine sulfate	648.45	0.13	4.3	0.08	5.0
Pilocarpine nitrate	271.27	0.23	7.7	0.14	3.7
Potassium acid phosphate (KH_2PO_4)	136.13	0.43	14.2	0.25	3.4
Potassium chloride	74.55	0.76	25.3	0.45	3.3
Potassium iodide	166.02	0.34	11.3	0.20	3.3
Procaine hydrochloride	272.77	0.21	7.0	0.12	3.4
Quinine hydrochloride	396.91	0.14	4.7	0.08	3.3
Quinine and urea hydrochloride	547.48	0.23	7.7	0.14	7.4
Scopolamine hydrobromide (hyoscine hydrobromide)	438.32	0.12	4.0	0.07	3.1
Silver nitrate	169.89	0.33	11.0	0.19	3.3
Sodium acid phosphate ($NaH_2PO_4 \cdot H_2O$)	138.00	0.40	13.3	0.24	3.2
Sodium benzoate	144.11	0.40	13.3	0.24	3.4
Sodium bicarbonate	84.00	0.65	21.7	0.38	3.2
Sodium bisulfite	104.07	0.61	20.3	0.36	3.7
Sodium borate·$10H_2O$	381.43	0.42	14.0	0.25	9.4
Sodium chloride	58.45	1.00	33.3	0.58	3.4
Sodium iodide	149.92	0.39	13.0	0.23	3.4
Sodium nitrate	85.01	0.68	22.7	0.39	3.4
Sodium phosphate, anhydrous	141.98	0.53	17.7	0.31	4.4
Sodium phosphate·$2H_2O$	178.05	0.42	14.0	0.25	4.4
Sodium phosphate·$7H_2O$	268.08	0.29	9.7	0.17	4.6
Sodium phosphate·$12H_2O$	358.21	0.22	7.3	0.13	4.6
Sodium propionate	96.07	0.61	20.3	0.36	3.4
Sodium sulfite, exsiccated	126.06	0.65	21.7	0.38	4.8
Streptomycin sulfate	1457.44	0.07	2.3	0.04	6.0
Strong silver protein	—	0.08	2.7	0.05	—
Sucrose	342.30	0.08	2.7	0.05	1.6
Sulfacetamide sodium	254.25	0.23	7.7	0.14	3.4
Sulfadiazine sodium	272.27	0.24	8.0	0.14	3.8
Sulfamerazine sodium	286.29	0.23	7.7	0.14	3.9
Sulfanilamide	172.21	0.22	7.3	0.13	2.2
Sulfathiazole sodium	304.33	0.22	7.3	0.13	3.9
Tannic acid	—	0.03	1.0	0.02	—
Tetracaine hydrochloride (pontocaine hydrochloride)	300.82	0.18	6.0	0.11	3.2
Tetracycline hydrochloride	480.92	0.14	4.7	0.08	4.0
Tripelennamine hydrochloride (pyribenzamine hydrochloride)	291.83	0.30	7.3	0.17	3.8
Urea	60.06	0.59	19.7	0.35	2.1
Zinc chloride	139.29	0.62	20.3	0.37	5.1
Zinc phenolsulfonate	555.84	0.18	6.0	0.11	5.9
Zinc sulfate·$7H_2O$	287.56	0.15	5.0	0.09	2.5

*The values in Table 8–4 have been obtained from the data of E. R. Hammarlund and K. Pedersen-Bjergaard, J. Am. Pharm. Assoc., Pract. Ed. **19**, 39, 1958; ibid., Sci. Ed. **47**, 107, 1958, and other sources. The values vary somewhat with concentration, and those in the table are for 1 to 3% solutions of the drugs in most instances. A complete table of E and ΔT_f values is found in the *Merck Index*, 11th Edition, Merck, Rahway, NJ, 1989, pp. MISC-79 to MISC-103. For the most recent results of Hammarlund, see J. Pharm. Sci. **70**, 1161, 1981; ibid. **78**, 519, 1989.

Key: MW is the molecular weight of the drug; E is the sodium chloride equivalent of the drug; V is the volume in mL of isotonic solution that can be prepared by adding water to 0.3 g of the drug (the weight of drug in 1 fluid ounce of a 1% solution); $\Delta T_f^{1\%}$ is the freezing point depression of a 1% solution of the drug; and L_{iso} is the molar freezing point depression of the drug at a concentration approximately isotonic with blood and lacrimal fluid.

this value from the concentration of sodium chloride that is isotonic with body fluids, namely, 0.9 g/100 mL.

Example 8–14. A solution contains 1.0 g ephedrine sulfate in a volume of 100 mL. What quantity of sodium chloride must be added to make the solution isotonic? How much dextrose would be required for this purpose?

The quantity of the drug is multiplied by its sodium chloride equivalent E, giving the weight of sodium chloride to which the quantity of drug is equivalent in osmotic pressure

$$\text{Ephedrine sulfate: } 1.0 \text{ g} \times 0.23 = 0.23 \text{ g}$$

The ephedrine sulfate has contributed a weight of material osmotically equivalent to 0.23 g of sodium chloride. Since a total of 0.9 g of sodium chloride is required for isotonicity, 0.67 g (0.90 − 0.23) of NaCl must be added.

If one desired to use dextrose instead of sodium chloride to adjust the tonicity, the quantity would be estimated by setting up the following proportion. Since the sodium chloride equivalent of dextrose is 0.16,

$$\frac{1 \text{ g dextrose}}{0.16 \text{ g NaCl}} = \frac{X}{0.67 \text{ g NaCl}}$$

$$X = 4.2 \text{ g of dextrose}$$

Other agents than dextrose may of course be used to replace NaCl. It is recognized that thimerosal becomes less stable in eye drops when a halogen salt is used as an "isotonic agent" (i.e., an agent like NaCl ordinarily used to adjust the tonicity of a drug solution). Reader[40] found that mannitol, propylene glycol, or glycerin—isotonic agents that did not have a detrimental effect on the stability of thimerosal—could serve as alternatives to sodium chloride. The concentration of these agents for isotonicity is readily calculated by use of the equation (see *Example 8–14*):

$$X = \frac{Y \text{ (additional amount of NaCl for isotonicity)}}{E \text{ (grams of NaCl equivalent to 1 g of the isotonic agent)}} \qquad (8\text{–}46)$$

where X is the grams of isotonic agent required to adjust the tonicity; Y is the additional amount of NaCl for isotonicity, over and above the osmotic equivalence of NaCl provided by the drugs in the solution; and E is the sodium chloride equivalence of the isotonic agent.

Example 8–15. Let us prepare 200 mL of an isotonic aqueous solution of thimerosal, molecular weight 404.84 g/mole. The concentration of this antiinfective drug is 1:5000, or 0.2 g/1000 mL. The L_{iso} for such a compound, a salt of a weak acid and a strong base (a 1:1 electrolyte), is 3.4 and the sodium chloride equivalent E is

$$E = 17\frac{L_{iso}}{MW} = 17\frac{3.4}{404.84} = 0.143$$

The quantity of thimerosal, 0.04 gram for the 200-mL solution, multiplied by its E value, gives the weight of NaCl to which the drug is osmotically equivalent:

$$0.04 \text{ g thimerosal} \times 0.143 = 0.0057 \text{ g NaCl}$$

Since the total amount of NaCl needed for isotonicity is 0.9 g/100 mL, or 1.8 g for the 200-mL solution, and since an equivalent of 0.0057 g of NaCl has been provided by the thimerosal, the additional amount of NaCl needed for isotonicity, Y, is

$$Y = 1.80 \text{ g NaCl needed} - 0.0057 \text{ g NaCl supplied by the drug}$$
$$= 1.794 \text{ g}$$

This is the additional amount of NaCl needed for isotonicity. The result, ~1.8 g NaCl, shows that the concentration of thimerosal is so small that it contributes almost nothing to the isotonicity of the solution. Thus, a concentration of 0.9% NaCl or 1.8 g/200 mL is required.

However, from the work of Reader[40] we know that sodium chloride interacts with mercury compounds such as thimerosal to reduce the stability and effectiveness of this preparation. Therefore, we have decided to replace NaCl with propylene glycol as the isotonic agent.

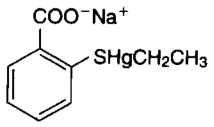
From equation (8–45) we calculate the E value of propylene glycol, a nonelectrolyte with an L_{iso} value of 1.9 and a molecular weight of 76.09 g/mole.

$$E = 17\frac{1.9}{76.09} = 0.42$$

Using equation (8–46), $X = Y/E$,

$$X = 1.794/0.42 = 4.3 \text{ g}$$

in which X = 4.3 g is the amount of propylene glycol required to adjust the 200-mL solution of thimerosal to isotonicity.



Thimerosal (merthiolate, sodium)

Class II Methods

White–Vincent Method. The Class II methods of computing tonicity involve the addition of water to the drugs to make an isotonic solution, followed by the addition of an isotonic or isotonic-buffered diluting vehicle to bring the solution to the final volume. Stimulated by the need to adjust the pH in addition to the tonicity of ophthalmic solutions, White and Vincent[41] developed a simplified method for such calculations. The derivation of the equation is best shown as follows.

Suppose that one wishes to make 30 mL of a 1% solution of procaine hydrochloride isotonic with body fluid. First, the weight of the drug w is multiplied by the sodium chloride equivalent E.

$$0.3 \text{ g} \times 0.21 = 0.063 \text{ g} \qquad (8\text{–}47)$$

This is the quantity of sodium chloride osmotically equivalent to 0.3 g of procaine hydrochloride.

Second, it is known that 0.9 g of sodium chloride, when dissolved in enough water to make 100 mL, yields a solution that is isotonic. The volume V of isotonic solution that can be prepared from 0.063 g of sodium chloride (equivalent to 0.3 g of procaine hydrochloride) is obtained by solving the proportion

$$\frac{0.9 \text{ g}}{100 \text{ mL}} = \frac{0.063 \text{ g}}{V} \qquad (8\text{–}48)$$

$$V = 0.063 \times \frac{100}{0.9} \qquad (8\text{–}49)$$

$$V = 7.0 \text{ mL} \qquad (8\text{–}50)$$

In equation (8–49), the quantity 0.063 is equal to the weight of drug w multiplied by the sodium chloride equivalent E as seen in equation (8–47). The value of the ratio 100/0.9 is 111.1. Accordingly, equation (8–49) may be written

$$V = w \times E \times 111.1 \qquad (8\text{–}51)$$

in which V is the volume in milliliters of isotonic solution that may be prepared by mixing the drug with water, w the weight in grams of the drug given in the problem, and E the sodium chloride equivalent obtained from Table 8–4. The constant, 111.1, represents the volume in milliliters of isotonic solution obtained by dissolving 1 g of sodium chloride in water.

The problem may be solved in one step using equation (8–51):

$$V = 0.3 \times 0.21 \times 111.1$$
$$V = 7.0 \text{ mL}$$

TABLE 8–5. ***Isotonic and Isotonic-Buffered Diluting Solutions****

Isotonic Diluting Solutions	
Isotonic sodium chloride solution	USP
Dextrose solution	5.6%
Sodium nitrate solution	1.3%
Ringer's solution	USP
Isotonic-Buffered Diluting Solutions	
Diluting Solution I, pH 4.7	
Used for salts such as those of epinephrine, cocaine, dionin, metycaine, nupercaine, optochin, phenacaine, pontocaine, procaine, physostigmine, syntropan, and zinc. For dispensing salts of physostigmine and epinephrine, 2g of sodium bisulfite may be added to the solution to minimize discoloration.	
Boric acid, c.p. (H_3BO_3)	20.0 g
Suitable preservative, q.s.	
Sterile distilled water, q.s. ad	1000 mL
Diluting Solution II, pH 6.8	
Primarily used for salts of pilocarpine, which are stable for about a month in this buffer.	
Sodium acid phosphate ($NaH_2PO_4 \cdot H_2O$) monohydrate	4.60 g
Disodium phosphate (Na_2HPO_4) anhydrous	4.73 g
Sodium chloride, c.p.	4.80 g
Suitable preservative, q.s.	
Sterile distilled water, q.s. ad	1000 mL
Diluting Solution III, pH 7.4	
May be used as a neutral collyrium or as a solvent for drugs that are stable in a neutral solution.	
Potassium acid phosphate (KH_2PO_4) anhydrous	1.90 g
Disodium phosphate (Na_2HPO_4) anhydrous	8.10 g
Sodium chloride, c.p.	4.11 g
Suitable preservative, q.s.	
Sterile distilled water q.s. ad	1000 mL
Diluting Solution IV, pH 9	
Used where an alkaline buffer is desired for ophthalmic drugs.	
Boric acid	0.43 g
Sodium borate	4.20 g
Suitable preservative, q.s.	
Sterile distilled water, q.s. ad	1000 mL

*From H. W. Hind and F. M. Goyan, J. Am. Pharm. Assoc., Sci. Ed. **36**, 33, 413, 1947; H. W. Hind and I. J. Szekely, J. Am. Pharm. Assoc., Pract. Ed. **14**, 644, 1953; H. B. Kostenbauder, F. B. Gable and A. Martin, J. Am. Pharm. Assoc., Sci. Ed. **42**, 210, 1953.

In order to complete the isotonic solution, enough isotonic sodium chloride solution, another isotonic solution, or an isotonic-buffered diluting solution is added to make 30 mL of the finished product. Several isotonic and isotonic-buffered diluting solutions are found in Table 8–5. These solutions all have isotonicity values of 0.9% NaCl.

When more than one ingredient is contained in an isotonic preparation, the volumes of isotonic solution, obtained by mixing each drug with water, are additive.

Example 8–16. Make the following solution isotonic with respect to an ideal membrane.

Phenacaine hydrochloride . . . . . .0.06 g
Boric acid . . . . . .0.30 g
Sterilized distilled water, enough to make . . . . . .100.0 mL

$$V = [(0.06 \times 0.20) + (0.3 \times 0.50)] \times 111.1$$

$$V = 18 \text{ mL}$$

The drugs are mixed with water to make 18 mL of an isotonic solution, and the preparation is brought to a volume of 100 mL by adding an isotonic diluting solution.

Sprowls Method. A further simplification of the method of White and Vincent was introduced by Sprowls.[42] He recognized that equation (8–51) could be used to construct a table of values of V when the weight of the drug w was arbitrarily fixed. Sprowls chose as the weight of drug 0.3 g, the quantity for 1 fluid ounce of a 1% solution. The volume V of isotonic solution that can be prepared by mixing 0.3 g of a drug with sufficient water may be computed for drugs commonly used in ophthalmic and parenteral solutions. The method as described by Sprowls[42] is further discussed in several reports by Martin and Sprowls[43] It is now found in the U.S. Pharmacopeia, XXI, p. 1339. A modification of the original table has been made by Hammarlund and Pedersen-Bjergaard[44] and is given in column 4 of Table 8–4, where the volume in milliliters of isotonic solution for 0.3 g of the drug, the quantity for 1 fluid ounce of a 1% solution, is listed. (The volume of isotonic solution in milliliters for 1 g of the drug can also be listed in tabular form if desired by multiplying the values in column 4 by 3.3). The primary quantity of isotonic solution is finally brought to the specified volume with the desired isotonic or isotonic-buffered diluting solutions.

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Problems

8–1. One desires to adjust a solution to pH 8.8 by the use of a boric acid–sodium borate buffer. What approximate ratio of acid and salt is required?

Answer: The acid:salt ratio is 1:0.36

8–2. What is the pH of a solution containing 0.1 mole of ephedrine and 0.01 mole of ephedrine hydrochloride per liter of solution?

Answer: pH = 10.36

8–3. **(a)** What is the pH of a buffer consisting of 0.12 M NaH_2PO_4 and 0.08 M Na_2HPO_4, the former acting as the acid and the latter as the salt or conjugate base (see Cohen et al.[45])? **(b)** What is the value when the ionic strength corrections are made using the Debye–Hückel law? *Hint:* Use equation (8–15). The value for n in the terms pK_n and $(2n - 1)$ is 2 in this problem since the second stage of ionization of phosphoric acid is involved. Thus the equation becomes

$$\text{pH} = 7.21 + \log \frac{[Na_2HPO_4]}{[NaH_2PO_4]} - \frac{0.51 \times 3\sqrt{\mu}}{1 + \sqrt{\mu}}$$

Answers: **(a)** pH = 7.03; **(b)** pH = 6.46

8–4. What is the pH of an elixir containing 0.002 mole/liter of the free acid sulfisoxazole, and 0.20 mole/liter of the 1:1 salt sulfisoxazole diethanolamine? The pK_a of the acid is 5.30. The activity coefficient γ_{salt} can be obtained from the appropriate Debye–Hückel equation for this ionic strength. The effect of any alcohol in the elixir on the value of the dissociation constant may be neglected.

Answer: pH = 7.14

8–5. Ascorbic acid (molecular weight 176.12) is too acidic to administer by the parenteral route. The acidity of ascorbic acid is partially neutralized by adding a basic compound, usually sodium carbonate or sodium bicarbonate. Thus, the injectable product contains sodium ascorbate, ascorbic acid, and the neutralizing agent. The molecular weight of ascorbic acid, together with its pK_a, is found in Table 7–2.

(a) What is the pH of an injectable solution containing only ascorbic acid in the concentration of 55 g per liter of solution? $K_1 = 5 \times 10^{-5}$ and $K_2 = 1.6 \times 10^{-12}$.

(b) What is the molar ratio of sodium ascorbate to ascorbic acid, and the percentage of each compound required to prepare an injectable solution with a pH of 5.7?

Answers: **(a)** pH = 2.40; **(b)** a 25.1:1 ratio of sodium ascorbate to ascorbic acid, or 96.2 mole percent sodium ascorbate and 3.8 percent of ascorbic acid

8–6. Physostigmine salicylate is used in ophthalmic solutions as a mydriatic and to decrease the intraocular pressure in glaucoma.

(a) What is the pH of a 0.5 percent aqueous solution of physostigmine salicylate, molecular weight 413.5? This compound is the salt of a weak acid, and the pH of the solution may be obtained using equation (7–127) as long as the concentration of the salt, C_s, is much greater than $[H_3O^+]$. The *acidity* constant for the physostigmine cation, K_1, is $10^{-14}/(7.6 \times 10^{-7})$, and the acidity constant for salicylic acid, K_2, is 1.06×10^{-3}. The calculation of the pH of a salt of a weak base and a weak acid is demonstrated in *Example 7–22*. We can disregard the second step in the ionization of physostigmine.

(b) How much is the pH increased by addition to the solution of 0.1% physostigmine base, molecular weight 275.34? See the Henderson–Hasselbalch equation (8–10) for the pH of a solution of a weak base and its corresponding salt.

Answers: **(a)** pH = 5.43; **(b)** an increase of 1.93 pH units

8–7. The thermodynamic dissociation exponent pK_1 for carbonic acid at 30° C is 6.33. According to Van Slyke et al.[46] the ionic strength of the blood is roughly 0.16. Compute the apparent dissociation exponent pK'_1 to be used for the carbonic acid of blood at 30° C. Notice that the pH or $-\log a_{H^+}$ is given by the expression

$$pH = pK_1' + \log \frac{[HCO_3^-]}{[H_2CO_3]}$$

$$= pK_1 + \log \frac{[HCO_3^-]}{[H_2CO_3]} + \log \gamma_{HCO_3^-}$$

Therefore,

$$pK_1' = pK_1 + \log \gamma_{(HCO_3^-)} \cong pK_1 - 0.5\sqrt{\gamma}$$

Answer: $pK_1' = 6.13$

8–8. Plot the buffer capacity–pH curve for a barbituric acid–sodium barbiturate buffer of total concentration 0.2 M over the range of pH 1 to 7. What is the maximum buffer capacity and at what pH does β_{max} occur?

Answer: $\beta_{max} = 0.115$ and it occurs at pH 3.98

8–9. What is the buffer capacity of a solution containing 0.20 M acetic acid and 0.10 M sodium acetate?

Answer: $\beta = 0.15$

8–10. Your product research director asks you to prepare a buffer solution of pH 6.5 having a buffer capacity of 0.10. Choose a suitable combination of buffer species and compute the concentrations needed.

One possible answer: Na_2HPO_4 (salt) = 0.052 M
NaH_2PO_4 (acid) = 0.265 M

8–11. To a buffer containing 0.1 mole/liter each of sodium formate and formic acid, 0.01 gram equivalent/liter of sodium hydroxide was added. What is the average buffer capacity of the solution over this pH range?

Answer: $\beta = 0.111$ (if pH is not rounded to 3.84 one may get $\beta = 0.115$ instead of 0.111)

8–12. What is the buffer capacity of a solution containing 0.36 M boric acid at a pH of 7.0? What is the buffer capacity at pH 9.24, i.e., where $pH = pK_a$? At what pH is β a maximum and what is the value of β_{max}? What is the buffer capacity at pH 10.8? Using the calculated values of β, plot the buffer capacity versus pH. If the student wishes to smooth the buffer curve a little better, he or she may also calculate β at pH 8.20 and at 10.0. When these six points are plotted on the graph and a smooth line is drawn through them, a bell-shaped buffer curve is obtained. See Figure 8–4 for the shapes of several buffer curves.

Partial Answer: β at pH 7.0 = 0.0048; β at pH 8.2 = 0.064; β at pH 9.24 = 0.21; β at pH 10.8 = 0.021, β_{max} is found at pH 9.24 where $pH = pK_a$; $\beta_{max} = 0.576C = 0.21$.

8–13. What is the buffer capacity for a Sörensen phosphate buffer **(a)** at pH 5.0 and **(b)** at pH 7.2? The total buffer concentration is 0.067 M, and the dissociation constant is $K_2 = 6.2 \times 10^{-8}$

Answers: **(a)** $\beta = 0.001$; **(b)** $\beta = 0.04$

8–14. A borate buffer contains 2.5 g of sodium chloride (molecular weight 58.5 g/mole); 2.8 g of sodium borate, decahydrate (molecular weight 381.43); 10.5 g of boric acid (molecular weight 61.84); and sufficient water to make 1000 mL of solution. Compute the pH of the solution **(a)** disregarding the ionic strength, and **(b)** taking into account the ionic strength.

Answers: **(a)** pH disregarding ionic strength is 7.87; **(b)** including ionic strength, pH = 7.79

8–15. Calculate the buffer capacity of an aqueous solution of the strong base sodium hydroxide having a hydroxyl ion concentration of 3.0×10^{-3} molar.

Answer: $\beta = 0.0069$

8–16. **(a)** What is the final pH of a solution after mixing 10 mL of a 0.10-M HCl solution with 20 mL of a 0.10-M procaine solution? The pK_b for procaine is found in Table 7–2. **(b)** Does the solution exhibit buffer capacity?

Answers: **(a)** pH = 8.8; **(b)** $\beta_{max} = 0.039$; it shows a weak buffer capacity.

8–17. Assuming that the total bicarbonate buffer concentration in normal blood is about 0.026 mole/liter, what would be the maximum buffer capacity of this buffer and at what pH would β_{max} occur?

Answer: $\beta_{max} = 0.015$ at pH 6.1 (see pp. 177, 178)

8–18. Describe in detail how you would formulate a buffer having approximately the same pH, ionic strength, and buffer capacity as that of blood. The ionic strength of the blood plasma is about 0.16 and the buffer capacity in the physiologic pH range is approximately 0.03 (p. 177). Use the Na_2HPO_4/NaH_2PO_4 buffer and pK_2 of phosphoric acid. Activity coefficients must be considered, and the thermodynamic pK_2 of phosphoric acid must be used to obtain the answer.

Answer: A mixture of 0.044 Na_2HPO_4 and 0.0105 NaH_2PO_4 has a buffer capacity of 0.03 and provides a pH of 7.4. The ionic strength of this mixture is 0.12. The ionic strength may be raised to 0.16 by the addition of 0.04 M NaCl or KCl.

8–19. A titration is conducted beginning with 50 mL of 0.2 N acetic acid and adding **(a)** 10 mL; **(b)** 25 mL; **(c)** 50 mL; and **(d)** 50.1 mL of 0.2 N NaOH. What is the pH after each increment of base has been added?

Answers: **(a)** 4.16; **(b)** 4.76; **(c)** 8.88; **(d)** 10.3

8–20. Plot the pH titration curve for the neutralization of 0.1 N barbituric acid by 0.1 N NaOH. What is the pH of the solution at the equivalence point?

Answer: pH = 8.34

8–21. A 1 fluid ounce (29.573 mL) solution contains 4.5 grains (291.60 mg) of silver nitrate. How much sodium nitrate must be added to this solution to make it isotonic with nasal fluid? Assume that nasal fluid has an isotonicity value of 0.9% NaCl.

Answer: 3.83 grains = 248 mg

8–22. Compute the Sprowls V value, the E value, and the freezing point depression of a 1% solution of diphenhydramine hydrochloride.

Answer: $V = 6.7$ mL, $E = 0.20$, $\Delta T_f = 0.12$

8–23. A 25% solution of phenylpropanolamine hydrochloride is prepared. The physician desires that 0.25 fluid ounce (7.393 mL) of this solution be made isotonic and adjusted to a pH of 6.8. The Sprowls V value is 12.7. Discuss the difficulties that are encountered in filling the physician's request. How might these difficulties be overcome?

8–24. **(a)** Compute the isotonic concentration (molarity) from the L_{iso} values given in Table 8–4 for the following substances: sodium borate·$10H_2O$ (sodium tetraborate), phenylephrine hydrochloride, physostigmine sulfate, and calcium gluconate.

(b) What is the volume of water that should be added to 0.3 gram of these substances to produce an isotonic solution?

Partial Answer: **(a)** 0.0553, 0.149, 0.104, 0.124 mole/liter; **(b)** check your results against Table 8–4—they may differ from the table values.

8–25. Compute the freezing point depression of 1% solutions of the following drugs: **(a)** ascorbic acid, **(b)** calcium chloride, **(c)** ephedrine sulfate, and **(d)** methacholine chloride. The percentages of sodium chloride required to make 100 mL of 1% solutions of these drugs isotonic are 0.81%, 0.48%, 0.76%, and 0.67%, respectively. *Hint:* Refer to *Example 8–11.*

Answers: Check your results against Table 8–4.

8–26. **(a)** Compute the approximate sodium chloride equivalent of MgO (molecular weight = 40.3 g/mole), $ZnCl_2$ (molecular weight = 136.3 g/mole), $Al(OH)_3$ (molecular weight = 77.98 g/mole), and isoniazid (a tuberculostatic drug, weak electrolyte, molecular weight = 137.2 g/mole), using the average L_{iso} values given in Table 8–3. **(b)** From the E value you calculated in (a), compute the freezing point depression of a 1% solution of these drugs. **(c)** Can one actually obtain a 1% aqueous solution of MgO or $Al(OH)_3$?

Answers: **(a)** $E = 0.84$, 0.60, 1.31, and 0.25; **(b)** $\Delta T_f^{1\%} = 0.49°$ C, 0.35° C, 0.76° C, and 0.15° C

8–27. Using the sodium chloride equivalent method, make the following solutions isotonic with respect to the mucous lining of the eye (ocular membrane).

(a) Tetracaine hydrochloride	10 grams
NaCl	x grams
Sterilize distilled water, enough to make 1000 mL	
(b) Tetracaine hydrochloride	0.10 gram
Boric acid	x grams
Sterile distilled water, enough to make 10 mL	

Answers: (a) add 7.2 grams of NaCl; (b) add 0.14 gram of boric acid.

8–28. Make the following solution isotonic with respect to blood:

Chlorpromazine hydrochloride	2.5 grams
Ascorbic acid	0.2 gram
Sodium bisulfite	0.1 gram
Sodium sulfate, anhydrous	0.1 gram
Sterile distilled water, enough to make	100 mL

Hint: First, compute the E values of chlorpromazine HCl and sodium sulfate, not given in Table 8–4, from the approximate L_{iso} values given in Table 8–3. The molecular weight of chlorpromazine hydrochloride is 318.9 daltons* and the molecular weight of sodium sulfate is 142.06 daltons.

Answer: Dissolve the drugs in 66.44 mL of water. This solution is isotonic. Add 0.3 gram of NaCl and bring to a volume of 100 mL.

8–29. A new drug having a molecular weight of 300 g/mole produced a freezing point depression of 0.52° C in a 0.145-M solution. What are the calculated L_{iso} value, the E value, and the V value for this drug?

Answer: $L_{iso} = 3.6$, $E = 0.20$, $V = 6.7$ mL

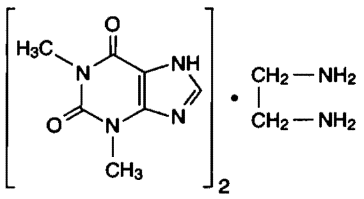
8–30. Using the sodium chloride method, calculate the grams of sodium chloride needed to make 30 mL of a 2% isotonic physostigmine salicylate solution.

Answer: 0.174 gram

8–31. Compute the percent nonionized aminophylline ($pK_b = 5.0$ and molecular weight 421.2 daltons) and its molar concentration after intravenous injection of 10 mL of an aqueous 2.5 w/v solution of aminophylline at 25° C. The normal pH of blood is about 7.4 and the total blood volume is approximately 5 liters. Use the Henderson–Hasselbalch equation in the form

$$pH = pK_w - pK_b - \log \frac{[BH^+]}{[B]}$$

where $\frac{[BH^+]}{[B]}$ is the ratio of ionized to nonionized drug.



Aminophylline

Answer: Percent of nonionized aminophylline = 2.5%, corresponding to 3.0×10^{-6} mole/liter.

*The word *dalton* is used in connection with molecular weight: 1 dalton = 1 g/mole.

10
Solubility and Distribution Phenomena

The topic of solutions was introduced in Chapter 5. We must now look at solutions in a more quantitative manner so as to understand the theory and applications of the phenomenon of solubility. Such knowledge is important to the pharmacist, for it permits him to choose the best solvent medium for a drug or combination of drugs, helps in overcoming certain difficulties that arise in the preparation of pharmaceutical solutions, and, furthermore, can serve as a standard or test of purity. A detailed study of solubility and related properties also yields information about the structure and intermolecular forces of drugs.

The solubility of a compound depends upon the physical and chemical properties of the solute and the solvent, as well as upon such factors as temperature, pressure, the pH of the solution, and, to a lesser extent, the state of subdivision of the solute.

Of the nine possible types of mixtures, based on the three states of matter (p. 102), only gases in liquids, liquids in liquids, and solids in liquids are of particular pharmaceutical importance and will be considered in this chapter.

GENERAL PRINCIPLES

Definitions. A *saturated solution* is one in which the solute is in equilibrium with the solid phase (solute). *Solubility* is defined in quantitative terms as the concentration of solute in a saturated solution at a certain temperature, and in a qualitative way, it may be defined as the spontaneous interaction of two or more substances to form a homogeneous molecular dispersion.

An *unsaturated* or *subsaturated* solution is one containing the dissolved solute in a concentration below that necessary for complete saturation at a definite temperature.

A *supersaturated solution* is one that contains more of the dissolved solute than it would normally contain at a definite temperature, were the undissolved solute present. Some salts such as sodium thiosulfate and sodium acetate can be dissolved in large amounts at an elevated temperature and, upon cooling, fail to crystallize from the solution. Such supersaturated solutions can be converted to stable saturated solutions by seeding the solution with a crystal of solute, by vigorous agitation, or by scratching the walls of the container. Supersaturation presumably occurs when the small nuclei of the solute required for the initiation of crystal formation are more soluble than larger crystals, making it difficult for the nuclei to form and grow with resultant failure of crystallization.

The Phase Rule. Solubility may be described in a concise manner by use of Gibbs' phase rule, which was described on page 37.

$$F = C - P + 2 \qquad (10\text{–}1)$$

in which F is the *number of degrees of freedom*, that is, the number of independent variables (usually temperature, pressure, and concentration) that must be fixed to completely determine the system, C is the smallest number of components that are adequate to describe the chemical composition of each phase, and P is the number of phases. The application of the phase rule to the miscibility of liquids is described on pages 40, 41 and the application to solutions of solids in liquids is given on p. 41.

Solubility Expressions. The solubility of a drug may be expressed in a number of ways. The U.S. Pharmacopeia and National Formulary list the solubility of drugs as the number of milliliters of solvent in which 1 gram of

TABLE 10–1. ***Terms of Approximate Solubility***

Term	Parts of Solvent Required for 1 Part of Solute
Very soluble	Less than 1 part
Freely soluble	1 to 10 parts
Soluble	10 to 30 parts
Sparingly soluble	30 to 100 parts
Slightly soluble	100 to 1000 parts
Very slightly soluble	1000 to 10,000 parts
Practically insoluble, or insoluble	More than 10,000 parts

solute will dissolve. For example, the solubility of boric acid is given in the U.S. Pharmacopeia as follows: 1 g of boric acid dissolves in 18 mL of water, in 18 mL of alcohol, and in 4 mL of glycerin. Solubility is also quantitatively expressed in terms of molality, molarity, and percentage (p. 103).

For substances whose solubilities are not definitely known, the values are described in pharmaceutical compendia by the use of certain general terms, as given in Table 10–1. Solubilities of drugs are found expressed in various units in the *Merck Index*. For exact solubilities of many substances, the reader is referred to the works of Seidell, Landolt–Bornstein, *International Critical Tables*, Lange's *Handbook of Chemistry*, and the *CRC Handbook of Chemistry and Physics*. Techniques suitable for accurately determining the solubilities of solid compounds in liquids and the mutual solubilities of two liquids have been described by Mader and Grady.[1]

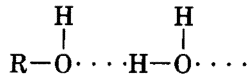
SOLVENT–SOLUTE INTERACTIONS

The reader should review pages 22 to 24 in Chapter 2 on intermolecular forces before continuing with this section. The pharmacist knows that water is a good solvent for salts, sugars, and similar compounds, whereas mineral oil and benzene are often solvents for substances that are normally only slightly soluble in water. These empiric findings are summarized in the statement: "like dissolves like." Such a maxim is satisfying to most of us, but the occasional inquisitive student may be troubled by this vague idea of "likeness." If he sets out to learn in what manner the solute and solvent are alike, he will find himself in a fascinating area of scientific investigation that is still in an unsettled state. The advanced student who is interested in this subject may wish to consult the books by Hildebrand and Scott,[2] Leussing,[3] and Dack.[4]

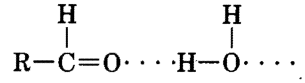
Polar Solvents. The solubility of a drug is due in large measure to the polarity of the solvent, that is, to its dipole moment. Polar solvents dissolve ionic solutes and other polar substances. Accordingly, water mixes in all proportions with alcohol and dissolves sugars and other polyhydroxy compounds.

Hildebrand has shown, however, that a consideration of dipole moments alone is not adequate to explain the solubility of polar substances in water. The ability of the solute to form hydrogen bonds is a far more influential factor than is the polarity as reflected in a high dipole moment. Although nitrobenzene has a dipole moment of 4.2×10^{-18} esu cm and phenol a value of only 1.7×10^{-18} esu cm, nitrobenzene is soluble only to the extent of 0.0155 mole/kg in water, while phenol is soluble to the extent of 0.95 mole/kg at 20° C.

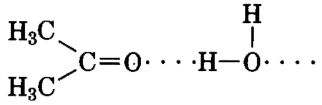
Water dissolves phenols, alcohols, aldehydes, ketones, amines, and other oxygen- and nitrogen-containing compounds that can form hydrogen bonds with water.



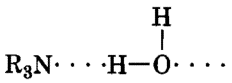
Alcohol



Aldehyde



Ketone



Amine

A difference in acidic and basic character of the constituents in the Lewis electron donor–acceptor sense also contributes to specific interactions in solutions.

The molecules of water in ice are joined together by hydrogen bonds to yield a tetrahedral structure. Although some of the hydrogen bonds are broken when ice melts, water still retains its ice-like structure in large measure at ordinary temperatures. This quasi-crystalline structure is broken down when water is mixed with another substance that is capable of hydrogen bonding. When ethyl alcohol and water are mixed, the hydrogen bonds between the water molecules are replaced partly by hydrogen bonds between water and alcohol molecules.

In addition to the factors already enumerated, the solubility of a substance also depends on structural features such as the ratio of the polar to nonpolar groups of the molecule. As the length of a nonpolar chain of an aliphatic alcohol increases, the solubility of the compound in water decreases. Straight-chain monohydroxy alcohols, aldehydes, ketones, and acids with more than four or five carbons cannot enter into the

hydrogen-bonded structure of water and hence are only slightly soluble. When additional polar groups are present in the molecule, as found in propylene glycol, glycerin, and tartaric acid, water solubility increases greatly. Branching of the carbon chain reduces the nonpolar effect and leads to increased water solubility. Tertiary butyl alcohol is miscible in all proportions with water, whereas *n*-butyl alcohol dissolves to the extent of about 8 g/100 mL of water at 20° C.

In brief, polar solvents such as water act as solvents according to the following mechanisms.[5]

(*a*) Owing to their high dielectric constant, namely about 80 for water, polar solvents reduce the force of attraction between oppositely charged ions in crystals such as sodium chloride (p. 30). Chloroform has a dielectric constant of 5 and benzene one of about 2; hence, ionic compounds are practically insoluble in these solvents.

(*b*) Polar solvents break covalent bonds of potentially strong electrolytes by acid–base reactions since these solvents are amphiprotic (p. 143). For example, water brings about the ionization of HCl as follows:

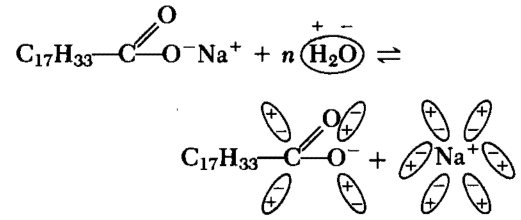
$$HCl + H_2O \rightarrow H_3O^+ + Cl^-$$

Weak organic acids are not ionized appreciably by water; their partial solubility is attributed instead to the hydrogen bond formation with water. Phenols and carboxylic acids, however, are readily dissolved in solutions of strong bases.

$$R{-}\overset{\overset{O}{\parallel}}{C}{-}OH + H_2O \rightarrow \text{negligible}$$

$$R{-}\overset{\overset{O}{\parallel}}{C}{-}OH + NaOH \rightarrow R{-}\overset{\overset{O}{\parallel}}{C}{-}O^-Na^+$$

(*c*) Finally, polar solvents are capable of solvating molecules and ions through dipole interaction forces, particularly hydrogen-bond formation, which leads to the solubility of the compound. The solute must be polar in nature since it often must compete for the bonds of the already associated solvent molecules if it is to win a place in the associated structure. The ion–dipole interaction between the sodium salt of oleic acid and water may be depicted as



Nonpolar Solvents. The solvent action of nonpolar liquids, such as the hydrocarbons, differs from that of polar substances. Nonpolar solvents are unable to reduce the attraction between the ions of strong and weak electrolytes because of the solvents' low dielectric constants. Nor can the solvents break covalent bonds and ionize weak electrolytes since they belong to the group known as aprotic solvents (p. 143), and they cannot form hydrogen bridges with nonelectrolytes. Hence, ionic and polar solutes are not soluble or are only slightly soluble in nonpolar solvents.

Nonpolar compounds, however, can dissolve nonpolar solutes with similar internal pressures (p. 224) through induced dipole interactions. The solute molecules are kept in solution by the weak van der Waals–London type of forces (p. 22). Thus, oils and fats dissolve in carbon tetrachloride, benzene, and mineral oil. Alkaloidal bases and fatty acids also dissolve in nonpolar solvents.

Semipolar Solvents. Semipolar solvents, such as ketones and alcohols, can *induce* a certain degree of polarity in nonpolar solvent molecules, so that, for

TABLE 10–2. ***Polarity of Some Solvents and the Solutes That Readily Dissolve in Each Class of Solvent***

	Dielectric Constant of Solvent ϵ (approx.)	Solvent	Solute	
Decreasing Polarity ↓	80	Water	Inorganic salts, organic salts	Decreasing Water Solubility ↓
	50	Glycols	Sugars, tannins	
	30	Methyl and ethyl alcohols	Caster oil, waxes	
	20	Aldehydes, ketones and higher alcohols, ethers, esters, and oxides	Resins, volatile oils, weak electrolytes including barbiturates, alkaloids, and phenols	
	5	Hexane, benzene, carbon tetrachloride, ethyl ether, petroleum ether	Fixed oils, fats, petrolatum, paraffin, other hydrocarbons	
	0	Mineral oil and fixed vegetable oils		

example, benzene, which is readily polarizable, becomes soluble in alcohol. In fact, semipolar compounds may act as *intermediate solvents* to bring about miscibility of polar and nonpolar liquids. Accordingly, acetone increases the solubility of ether in water. Loran and Guth[6] studied the intermediate solvent action of alcohol on water–castor oil mixtures. Propylene glycol has been shown to increase the mutual solubility of water and peppermint oil and water and benzyl benzoate.[7]

Summary. The simple maxim that *like dissolves like* can now be rephrased by stating that the solubility of a substance may be predicted only in a qualitative way in most cases and only after considerations of polarity, dielectric constant, association, solvation, internal pressures, acid–base reactions, and other factors. In short, solubility depends on chemical, electrical, and structural effects that lead to mutual interactions between the solute and solvent.

A number of common solvent types are listed in the order of decreasing "polarity" in Table 10–2, together with corresponding solute classes. The term *polarity* is loosely used here to represent not only dielectric constants of the solvents and solutes but also the other factors enumerated previously.

SOLUBILITY OF GASES IN LIQUIDS

Pharmaceutical solutions of gases include hydrochloric acid, ammonia water, and effervescent preparations containing carbon dioxide that are dissolved and maintained in solution under positive pressure. Aerosol products in which the propellant is either carbon dioxide or nitrogen, some of which is dissolved under pressure, can also be considered to fall under this classification.

The solubility of a gas in a liquid is the concentration of the dissolved gas when it is in equilibrium with some of the pure gas above the solution. The solubility depends primarily on the *pressure, temperature, presence of salts,* and *chemical reactions* that the gas sometimes undergoes with the solvent.

Effect of Pressure. The pressure of a gas above the solution is an important consideration in gaseous solutions since it changes the solubility of the dissolved gas in equilibrium with it. The effect of the pressure on the solubility of a gas is expressed by *Henry's law,* which states that in a very dilute solution at constant temperature, the concentration of dissolved gas is proportional to the partial pressure of the gas above the solution at equilibrium. The partial pressure of the gas is obtained by subtracting the vapor pressure of the solvent from the total pressure above the solution. If C_2 is the concentration of the dissolved gas in grams per liter of solvent and p is the partial pressure in millimeters of the undissolved gas above the solution, Henry's relationship may be written as

$$C_2 = \sigma p \qquad (10\text{–}2)$$

in which σ is the inverse of the Henry's law constant, k (p. 109). It is sometimes referred to as the *solubility coefficient.* Mole fraction is more properly used here, but in dilute solutions, molarity may be used.

The significance of Henry's law for the pharmacist rests upon the fact that the solubility of a gas increases directly as the pressure on the gas, and conversely, that the solubility of the gas decreases, so that sometimes the gas escapes with violence when the pressure above the solution is released. This phenomenon is commonly recognized in effervescent solutions when the stopper of the container is removed.

Effect of Temperature. Temperature also has a marked influence on the solubility of a gas in a liquid. As the temperature increases, the solubility of most gases decreases, owing to the greater tendency of the gas to expand. The property of expansion, coupled with the pressure phenomenon, requires that the pharmacist exercise caution in opening containers of gaseous solutions in warm climates and under other conditions of elevated temperatures. A vessel containing a gaseous solution or a liquid with a high vapor pressure, such as ethyl nitrite, should be immersed in ice or cold water for some time to reduce the temperature and pressure of the gas before opening the container.

Salting Out. Gases are often liberated from solutions in which they are dissolved by the introduction of an electrolyte such as sodium chloride and sometimes by a nonelectrolyte such as sucrose. This phenomenon is known as *salting out.* The salting-out effect may be demonstrated by adding a small amount of salt to a "carbonated" solution. The resultant escape of gas is due to the attraction of the salt ions or the highly polar nonelectrolyte for the water molecules, which reduces the density of the aqueous environment adjacent to the gas molecules. Salting out may also occur in solutions of liquids in liquids and solids in liquids.

Effect of Chemical Reaction. Henry's law applies strictly to *gases* that are only slightly soluble in solution and that do not react in any way in the solvent. Gases such as hydrogen chloride, ammonia, and carbon dioxide show deviations as a result of chemical reaction between the gas and solvent, usually with a resultant increase in solubility. Accordingly, hydrogen chloride is about 10,000 times more soluble in water than is oxygen.

Solubility Calculations. The solubility of a gas in a liquid may be expressed either by the inverse *Henry's law constant* σ or by the *Bunsen absorption coefficient* α. The Bunsen coefficient is defined as the volume of gas in liters (reduced to standard conditions of 0° C and 760 mm pressure) that dissolves in 1 liter of solvent under a partial pressure of 1 atmosphere of the gas at a definite temperature.

$$\frac{V_{\text{gas,STP}}}{V_{\text{soln}}} = \alpha p \qquad (10\text{–}3)$$

TABLE 10–3. *Bunsen Coefficients (α) for Gases in Water at 0° and 25° C*

Gas	α	
	0° C	25° C
H_2	0.0215	0.0175
N_2	0.0235	0.0143
O_2	0.0478	0.0284
CO_2	1.713	0.759

in which V_{gas} is the volume of gas at standard temperature and pressure, STP, dissolved in a volume V_{soln} of solution at a partial gas pressure p. The Bunsen coefficients α for some gases in water at 0° and 25° C are found in Table 10–3. The application of Henry's law and the calculation of σ and α are illustrated in the following example.

Example 10–1. If 0.0160 g of oxygen dissolves in 1 liter of water at a temperature of 25° C and at an oxygen pressure of 300 mm Hg, calculate (*a*) σ and (*b*) the Bunsen coefficient, α

(*a*)

$$\sigma = \frac{C_2 \text{ (g/liter)}}{p\text{(mm Hg)}} = \frac{0.0160}{300} = 5.33 \times 10^{-5}$$

(*b*) To compute the Bunsen coefficient, one must first reduce the volume of gas to STP. According to the ideal gas equation, $V = nRT/p$

$$V_{gas,STP} = \frac{\frac{0.0160}{32} \times 0.08205 \times 273.15}{1 \text{ atm}} = 0.0112 \text{ at STP}$$

and from equation (10–3)

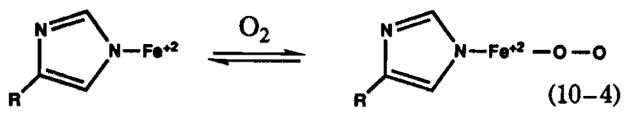
$$\alpha = \frac{V_{gas}}{V_{soln}\, p} = \frac{0.0112}{1 \times \frac{300}{760}} = 0.0284$$

(*c*) How many grams of oxygen can be dissolved in 250 mL of aqueous solution when the total pressure above the mixture is 760 mm Hg? The partial pressure of oxygen in the solution is 0.263 atm, and the temperature is 25° C.

$$\sigma = 5.33 \times 10^{-5} = \frac{C_2 \text{ (g/liter)}}{(0.263 \times 760) \text{ mm}}$$

$$C_2 = 0.0107 \text{ g/liter or } 0.0027 \text{ g/250 mL}$$

Oxygen is carried in the human body *(a)* as dissolved gas in the contents of the red blood cells and *(b)* as O_2 molecules bound to the iron atom of the heme part of hemoglobin. Shown here is part of the heme molecule of



(10–4)

hemoglobin demonstrating the binding of two atoms of oxygen to the iron atom.[8] Hemoglobin is made up of four heme molecules and so has four iron atoms with which to bind four molecules of oxygen. The concentration of O_2 dissolved in the blood ([*a*] above) regulates the uptake and release of oxygen by the iron atoms in hemoglobin ([*b*] above).

Example 10–2. The partial vapor pressure[9], p, of oxygen in the blood is 75 mm Hg and the percent saturation of O_2 in the red blood cells has been determined to be 92.8%. What is the concentration of O_2 dissolved in the red blood cells (rbc's), exclusive of the binding of O_2 by the iron of hemoglobin?

The solubility coefficient, σ (inverse Henry's law constant), may be expressed in volume (cm^3) at a definite temperature and pressure rather than mass (grams or moles) of gas dissolved in the solvent. The value of σ at 37° C for O_2 is 4.1×10^{-5} cm^3 O_2/cm^3 rbc content/mm Hg. Here, the solubility coefficient is actually more closely related to the Bunsen coefficient α than to the inverse Henry's law constant σ. From equation (10–2):

$$\text{oxygen conc. } C_2 = (4.1 \times 10^{-5} \text{ cm}^3 \text{ solute/cm}^3 \text{ rbc/mm Hg}) \times (75 \text{ mm Hg, } O_2 \text{ pressure in blood})$$

$$C_2 = 3.075 \times 10^{-3} \text{ cm}^3 \text{ O}_2/\text{cm}^3 \text{ rbc content}$$

However, we learned above that O_2 in the rbc's is at only 92.8% of saturation. Therefore, $C_2 = 0.928 \times (3.075 \times 10^{-3}) = 2.85 \times 10^{-3}$ cm^3 O_2/cm^3 rbc content at a pressure of 75 mm Hg in the blood.

We now consider the second, and more significant, avenue for the transport of O_2 in the blood. The combining capacity has been determined to be 0.40 cm^3 of O_2 per cm^3 of rbc's; and at the partial pressure of oxygen of 75 mm Hg, the saturation of O_2 on the heme iron sites is not 100% but rather 18.7%. Thus,

$$(0.40 \text{ cm}^3 \text{ O}_2/\text{cm}^3 \text{ rbc content})(0.187) = 0.075 \text{ cm}^3$$

Although this may appear to be a small and inefficient binding of O_2 to hemoglobin, when compared with *(a)* above (the transport of O_2 by solution in the bulk content of the red blood cells), the hemoglobin binding as an O_2 transport system is 26 times more effective in carrying O_2 to the various tissues of the body:

$$\frac{0.075 \text{ cm}^3 \text{ O}_2/\text{cm}^3 \text{ rbc content}}{0.00285 \text{ cm}^3 \text{ O}_2/\text{cm}^3 \text{ rbc content}} = 26.3$$

Tables 10–4 and 10–5 give the k values for a number of gases in the solvents water and benzene. Several examples follow, showing the calculation of the Henry's law constant, k, and the solubilities of gases expressed in mole fraction, molality, or molarity and in grams of solute per liter of solution. The gaseous solutions that follow Henry's law are so dilute that essentially no difference exists between molarity and molality.

The Henry's law constant k as found in columns 3 and 4 of Table 10–4 may be represented as

$$k = \frac{p_2}{X_2} = \frac{\text{pressure of gas (solute) in torrs or atmospheres}}{\text{mole fraction of the gas in solution}} \qquad (10\text{–}5)$$

and the constant k in columns 5 and 6 as

$$k = \frac{p_2}{c \text{ or } m} = \frac{\text{pressure of gas (solute) in torrs}}{\text{molarity, molality, or g/liter of gas in solution}} \qquad (10\text{–}6)$$

TABLE 10–4. *Henry's Law Constants for Gases in Water at 25° C

Gas	Molecular Weight	mm Hg (torrs) per Mole Fraction of Gas	Atm Pressure per Mole Fraction of Gas	mm Hg (torrs) per Molality or Molarity of Gas	mm Hg (torrs) per Gram of Gas per Kilogram H_2O or per Liter of Solution
H_2	2.02	5.34×10^7	7.03×10^4	9.62×10^5	4.76×10^5
He	4.00	1.10×10^8	1.45×10^5	1.99×10^6	4.98×10^5
N_2	28.01	6.51×10^7	8.57×10^4	1.17×10^6	4.18×10^4
O_2	32.00	3.30×10^7	4.34×10^4	5.94×10^5	1.86×10^4
CO	28.01	4.34×10^7	5.71×10^4	7.82×10^5	2.79×10^4
CO_2	44.01	1.25×10^6	1.64×10^3	2.24×10^4	5.09×10^2
CH_4	16.04	31.4×10^6	4.13×10^4	5.65×10^5	3.52×10^4
C_2H_6	30.07	23.0×10^6	3.03×10^4	4.15×10^5	1.38×10^4

*After F. Daniels and R. A. Alberty, *Physical Chemistry*, Wiley, New York, 1955, p. 200.

TABLE 10–5. *Henry's Law Constants for Gases in Benzene at 25° C

Gas	mm Hg (torrs) per Mole Fraction of Gas
H_2	2.75×10^6
N_2	1.79×10^6
CO	1.22×10^6
CO_2	8.57×10^4
CH_4	4.27×10^5

*After F. Daniels and R. A. Alberty, *Physical Chemistry*, Wiley, New York, 1955, p. 200.

Although the k values for CO_2 are found in Table 10–4, this gas is too soluble to adhere well to Henry's law.

The inverse Henry's law constant σ is not listed for the gases in Table 10–4; it is obtained in each case simply by taking the reciprocal of k found in the table. The k values for gases dissolved in solvents other than water may be found in the literature. The k values for several gases in the solvent benzene, at 25° C, are listed in Table 10–5.

Example 10–3. *(a)* What is the solubility of oxygen in water at 1 atm pressure at a temperature of 25° C? Express the results in both molality and molarity.

Useful equations for converting from mole function X_2 to molality m and to molarity c are

$$m = \frac{1000\,X_2}{M_1\,(1 - X_2)} \quad \text{and} \quad c = \frac{1000\,\rho\,X_2}{M_1(1 - X_2) + M_2X_2}$$

where M_1 is the molecular weight of the solvent, M_2 that of the solute, and ρ is the density of the solution. In a solution sufficiently dilute for Henry's law to apply, ρ is essentially 1.0 and M_2X_2 may be ignored in the equation for c. Thus, molality and molarity are roughly equal in dilute solution.

Using k from Table 10–4, we find the solubility of O_2 in water at 1 atm and 25° C using the proportion

$$4.34 \times 10^4 \text{ atm/mole fraction} = \frac{1 \text{ atm}}{X_2};\ X_2 = 2.30 \times 10^{-5}$$

$$\text{molality, } m = \frac{1000(2.30 \times 10^{-5})}{18.015(1 - (2.30 \times 10^{-5}))} = 0.00128 \text{ mole/kg } H_2O$$

molality ≅ molarity, or $c \cong 0.00128$ mole/liter of solution.

(b) Calculate the Henry's law constant k for methane at 1 atm and 25° C, expressed in torr/(mole/kg H_2O).

From Table 10–4,

$$k_{(CH_4)} = 4.13 \times 10^4 \text{ atm/(mole fraction)} = \frac{1 \text{ atm}}{X_2}$$

$$X_2 = 1 \text{ atm}/(4.13 \times 10^4 \text{ atm/(mole fraction)})$$
$$= 2.42 \times 10^{-5} \text{ (mole fraction)}$$

Convert mole fraction of CH_4 to molality.

$$m = \frac{1000(2.42 \times 10^{-5})}{18.015(1 - (2.42 \times 10^{-5}))} = 1.344 \times 10^{-3} \text{ mole/kg } H_2O$$

k in torr/(mole/kg H_2O) is therefore

$$k = \frac{1 \text{ atm} \times 760 \text{ torr/atm}}{1.344 \times 10^{-3} \text{ mole/kg } H_2O} = \frac{760}{1.344 \times 10^{-3}}$$
$$= 5.65 \times 10^5 \text{ torr/(mole/kg } H_2O)$$

(c) Obtain the Henry's law constant for hydrogen, molecular weight $H_2 = 2.02$ g/mole, at a pressure in torrs at 25° C. Express k in torr/(g/liter), where g/liter is essentially equal to g/kg of water in a solution sufficiently dilute for Henry's law to apply. One obtains

$$k_{(H_2)} = \frac{\text{torr}}{X_2 \text{ (mole fraction)}} = 5.34 \times 10^7 \text{ torr/(mole fraction)}$$

$$X_2 = \text{torr}/(5.34 \times 10^7 \text{ torr/(mole fraction)})$$
$$= 1.87 \times 10^{-8} \text{ (mole fraction)}$$

$$m = \frac{1000(1.87 \times 10^{-8})}{18.015(1 - (1.87 \times 10^{-8}))} = 1.04 \times 10^{-6} \text{ mole/kg } H_2O$$
$$\cong 1.04 \times 10^{-6} \text{ mole/liter}$$

To convert moles to grams, we write g = mole × mol. wt.

$$1.04 \times 10^{-6} \text{ mole/liter} \times 2.02 \text{ g/mole} = 2.10 \times 10^{-6} \text{ g/liter}$$

$$k = \frac{1 \text{ torr}}{2.10 \times 10^{-6} \text{ g/liter}} = 4.76 \times 10^5 \text{ torr/(g/liter)}$$

(d) Using the value of k you got in *(c)*, calculate the grams of hydrogen gas dissolved in a liter of aqueous solution at an external pressure on the gas of 1 atm (760 torr) at 25° C.

$$k = 4.76 \times 10^5 \text{ torr/(g/liter)} = \frac{760 \text{ torr}}{c \text{ (g/liter)}}$$

$$c = 760 \text{ torr}/(4.76 \times 10^5 \text{ torr/(g/liter)})$$
$$= 0.00160 \text{ g/liter}$$

(e) To obtain the Henry's law constant, k, for a gas at a temperature other than 25° C, we proceed as follows.

The solubility of O_2 in water at 1 atm pressure and 0° C is 0.070 g/liter. To express k in torr/(g/liter) we simply write

$$k = 760 \text{ torr}/(0.070 \text{ g/liter}) = 1.09 \times 10^4 \text{ torr/(g/l)}$$

In these examples involving the Henry's law constants, the term *mole fraction* is placed after the values of X_2 to indicate that the numbers are expressed as mole fractions—that is, as ratios of

moles—and therefore are dimensionless, having no physical units associated with them.

SOLUBILITY OF LIQUIDS IN LIQUIDS

Frequently two or more liquids are mixed together in the preparation of pharmaceutical solutions. For example, alcohol is added to water to form hydroalcoholic solutions of various concentrations: volatile oils are mixed with water to form dilute solutions known as aromatic waters; volatile oils are added to alcohol to yield spirits and elixirs; ether and alcohol are combined in collodions; and various fixed oils are blended into lotions, sprays, and medicated oils.

Ideal and Real Solutions. According to Raoult's law, $p_i = p_i^\circ X_i$, the partial pressure p_i of a component in a liquid mixture at a definite temperature is equal to the vapor pressure in the pure state multiplied by the mole fraction of the component in the solution. The mixture is said to be ideal when both components of a binary solution obey Raoult's law over the whole range of composition. If one of the components shows a negative deviation, it can be demonstrated by the use of thermodynamics that the other component must also show negative deviation (cf. Fig. 5–2, p. 108). The corresponding statement can also be made for positive deviations from Raoult's law.

Negative deviations lead to increased solubility and are frequently associated with hydrogen bonding between polar compounds (p. 23). The interaction of the solvent with the solute is known as *solvation*. Positive deviations, leading to decreased solubility, are interpreted as resulting from association of the molecules of one of the constituents to form double molecules (dimers) or polymers of higher order. Hildebrand, however, suggests that positive deviation is better accounted for in most cases by the difference in the cohesive forces of the molecules of each constituent. These attractive forces, which may occur in gases, liquids, or solids, are called *internal pressures*.

When the vapor is assumed to be nearly ideal, the internal pressure in cal/cm^3 is obtained by using the equation

$$P_i = \frac{\Delta H_v - RT}{V} \qquad (10\text{–}7)$$

in which ΔH_v is the heat of vaporization and V is the molar volume of the liquid at temperature T.

Example 10–4. The molar heat of vaporization of water at 25° C is 10,500 cal and V is approximately 18.01 cm^3. The gas constant R is 1.987 cal/mole deg. Compute the internal pressure of water.

$$P_i = \frac{10{,}500 - (1.987 \times 298.2)}{18.01}$$

$$= 550 \text{ cal/cm}^3 \text{ or } 22{,}700 \text{ atm}$$

A familiarity with calculations such as those appearing on pages 3 and 4 should allow the student to make this conversion from cal/cm^3 to atmospheres.

When the internal pressures or cohesive forces of the constituents of a mixture such as hexane and water are quite different, the molecules of one constituent cannot mingle with those of the other, and partial solubility results. Polar liquids have high cohesive forces, that is, large internal pressures, and they are solvents only for compounds of similar nature. Nonpolar substances with low internal pressures are "squeezed out" by the powerful attractive forces existing between the molecules of the polar liquid. This results in positive deviation from Raoult's law as shown in Figure 5–3 on page 108. It must be remarked that limited solubility of nonpolar solutes in highly polar solvents, and particularly in those solvents that associate through hydrogen bonds, cannot be attributed entirely to a difference of internal pressures. These factors will be considered in more detail on page 229.

Liquid–liquid systems may be divided into two categories according to the solubility of the substances in one another: (1) complete miscibility and (2) partial miscibility. The term *miscibility* refers to the mutual solubilities of the components in liquid–liquid systems.

Complete Miscibility. Polar and semipolar solvents, such as water and alcohol, glycerin and alcohol, and alcohol and acetone, are said to be completely miscible since they mix in all proportions. Nonpolar solvents such as benzene and carbon tetrachloride are also completely miscible. Completely miscible liquid mixtures in general create no solubility problems for the pharmacist and need not be considered further.

Partial Miscibility. When certain amounts of water and ether or water and phenol are mixed, two liquid layers are formed, each containing some of the other liquid in the dissolved state. The phenol–water system has been discussed in detail in Chapter 2, and the student at this point should review the section dealing with the phase rule. It is sufficient here to reiterate the following points. (1) The mutual solubilities of partially miscible liquids are influenced by temperature. In a system such as phenol and water, the mutual solubilities of the two conjugate phases increase with temperature until, at the critical solution temperature (or upper consolute temperature), the compositions become identical. At this temperature, a homogeneous or single-phase system is formed. (2) From a knowledge of the phase diagram, more especially the tie lines that cut the binodal curve, it is possible to calculate both the composition of each component in the two conjugate phases and the amount of one phase relative to the other. *Example 10–5* gives an illustration of such a calculation.

Example 10–5. A mixture of phenol and water at 20° C has a total composition of 50% phenol. The tie line at this temperature cuts the binodal at points equivalent to 8.4 and 72.2% *w/w* phenol (taken from Fig. 2–14, p. 40). What is the weight of the aqueous layer and of the phenol layer in 500 g of the mixture and how many grams of phenol are present in each of the two layers?

Let Z be the weight in grams of the aqueous layer. Therefore, $(500 - Z)$ is the weight in grams of the phenol layer, and the sum of

the percentages of phenol in the two layers must equal the overall composition of 50% or 500 × 0.50 = 250 g.

$$Z(8.4/100) + (500 - Z)(72.2/100) = 250$$

weight of aqueous layer, Z = 174 g

weight of phenol layer (500 − Z) = 326 g

The weight of phenol in the aqueous layer is

$$174 \times 0.084 = 15 \text{ g}$$

and the weight of phenol in the phenolic layer is

$$326 \times 0.722 = 235 \text{ g}$$

In the case of some liquid pairs, the solubility may increase as the temperature is lowered, and the system will exhibit a *lower consolute temperature*, below which the two members are soluble in all proportions and above which two separate layers form (Fig. 2–15, p. 41). Another type, involving a few mixtures such as nicotine and water (see Fig. 2–16, p. 41), shows both an upper and a lower consolute temperature with an intermediate temperature region in which the two liquids are only partially miscible. A final type exhibits no critical solution temperature; the pair, ethyl ether and water, for example, has neither an upper nor a lower consolute temperature and shows partial miscibility over the entire temperature range at which the mixture exists.

Influence of Foreign Substances.[10] The addition of a substance to a binary liquid system produces a ternary system, that is, one having three components. If the added material is soluble in only one of the two components or if the solubilities in the two liquids are markedly different, the mutual solubility of the liquid pair is decreased. If the original binary mixture has an upper critical solution temperature, the temperature is raised; if it has a lower consolute temperature, it is lowered by the addition of the third component. For example, if 0.1 *M* naphthalene is added to a mixture of phenol and water, it dissolves only in the phenol and raises the consolute temperature about 20°; if 0.1 *M* potassium chloride is added to a phenol–water mixture, it dissolves only in water and raises the consolute temperature approximately 8°. This latter case illustrates the salting-out effect previously referred to under solutions of gases.

When the third substance is soluble in both of the liquids to roughly the same extent, the mutual solubility of the liquid pair is increased; an upper critical solution temperature is lowered and a lower critical solution temperature is raised. The addition of succinic acid or sodium oleate to a phenol–water system brings about such a result. The increase in mutual solubility of two partially miscible solvents by another agent is ordinarily referred to as *blending*. When the solubility in water of a nonpolar liquid is increased by a micelle-forming surface-active agent, the phenomenon is called *micellar solubilization* (p. 410).

Three-Component Systems. The principles underlying systems that may contain one, two, or three partially miscible pairs have been discussed in detail in Chapter 2. Further examples of three-component systems containing one pair of partially miscible liquids are water, CCl_4, and acetic acid; and water, phenol, and acetone. Loran and Guth[6] made a study of the three-component system, water, castor oil, and alcohol, to determine the proper proportions for use in certain lotions and hair preparations, and a triangular diagram is shown in their report. A similar titration with water of a mixture containing peppermint oil and polyethylene glycol is shown in Figure 10–1.[7] Ternary diagrams have also found use in cosmetic formulations involving three liquid phases.[11] Gorman and Hall[12] determined the ternary-phase diagram of the system, methyl salicylate, isopropanol, and water (Fig. 10–2.).

Dielectric Constant and Solubility. Paruta and associates[13] have studied the solubility of barbiturates, parabens, xanthines, and other classes of drugs in a range of solvents of various dielectric constants. The solubility of caffeine in a mixture of dioxane and water as determined in two laboratories is shown in Figure 10–3. The solubility is plotted against dielectric constant, and against solvent solubility parameter, δ, to be discussed later. Gorman and Hall[12] obtained a linear relationship when they plotted log mole fraction of the solute, methyl salicylate, versus the dielectric constant of isopropanol–water mixtures, as seen in Figure 10–4.

Molecular Connectivity. Kier and Hall[14] investigated the solubility of liquid hydrocarbons, alcohols, ethers, and esters in water. They used a topologic (structural) index χ, or chi, which takes on values that depend on the structural features and functional groups of a particular molecule. The technique used by Kier and Hall is referred to as *molecular connectivity*. A zero-order chi term, ${}^0\chi$, first-order chi term, ${}^1\chi$, and higher-order chi terms are used to describe a molecule. The ${}^1\chi$ term is obtained by summing the bonds weighted by the reciprocal square root number of each bond. In the case of propane,

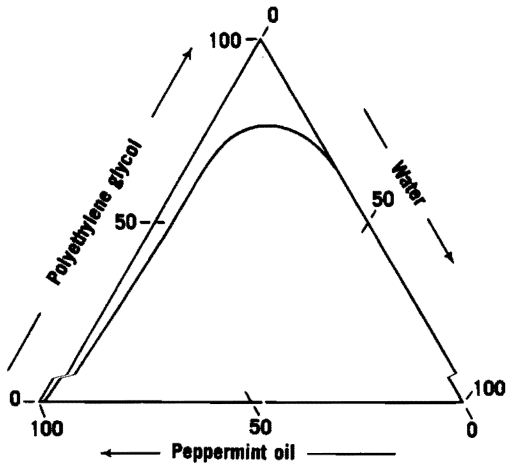


Fig. 10–1. A triangular diagram showing the solubility of peppermint oil in various proportions of water and polyethylene glycol.

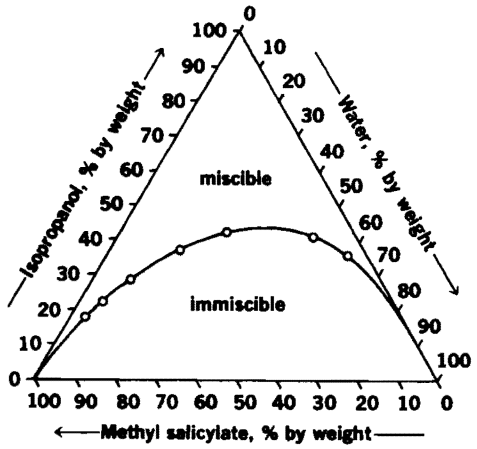
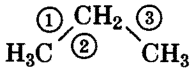


Fig. 10–2. Triangular phase diagram for the three component system, methyl salicylate–isopropanol–water. (From W. G. Gorman and G. D. Hall, J. Pharm. Sci. 53, 1017, 1964, reproduced with permission of the copyright owner.)



disregarding attached hydrogens, carbon 1 is connected through one bond to the central carbon, which is joined to the other carbons by two bonds. The reciprocal square root "valence" is therefore $(1 \cdot 2)^{-1/2} = 0.707$ for the left bond. The right-hand bond has the same reciprocal square root valence, or 0.707. These are summed to yield

$$^1\chi = 0.707 + 0.707 = 1.414$$

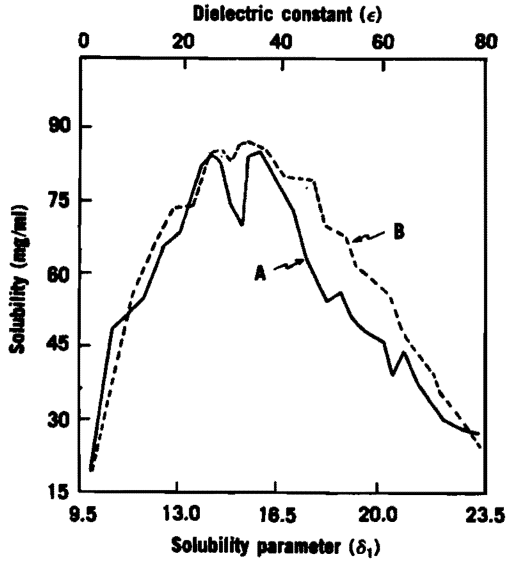


Fig. 10–3. Caffeine in dioxane–water mixtures at 25° C. Solubility profiles were obtained from two studies, *A*[13] and *B*.[34] Solubility in mg/mL is plotted against both dielectric constant (upper scale) and solvent solubility parameter (lower scale). (From A. Martin, A. N. Paruta, and A. Adjei, J. Pharm. Sci. 70, 1115, 1981, reproduced with permission of the copyright owner.)

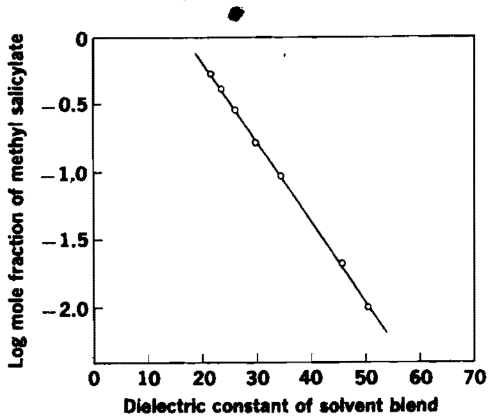
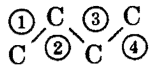


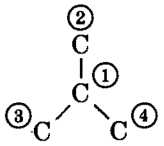
Fig. 10–4. Solubility of methyl salicylate in isopropanol–water blends of differing dielectric constants. (From W. G. Gorman and G. D. Hall, J. Pharm Sci. 53, 1017, 1964, reproduced with permission of the copyright owner.)

for *n*-butane, considering only the carbon atoms and their bonds,



$$^1\chi = (1 \cdot 2)^{-1/2} + (2 \cdot 2)^{-1/2} + (1 \cdot 2)^{-1/2} = 1.914$$

Isobutane,



has a different $^1\chi$ than *n*-butane because of its branching:

$$^1\chi = (1 \cdot 3)^{-1/2} + (1 \cdot 3)^{-1/2} + (1 \cdot 3)^{-1/2} = 1.732$$

For calculating second- and higher-order χ indexes and applications of molecular connectivity in pharmacy, refer to the book by Kier and Hall.[14]

$^1\chi$ may be used to correlate the molal solubilities of aliphatic hydrocarbons, alcohols, and esters in water, using regression analysis (see Chapter 1, p. 15, for regression analysis). The equation found[14] to fit the data for alkanes at 25° C is

$$\ln S = -1.505 - 2.533\ ^1\chi \qquad (10\text{–}8)$$

We learned that the $^1\chi$ value of isobutane was 1.732. Using this value in equation (10–8) yields

$$\ln S = -5.8922;\ S = 2.76 \times 10^{-3} \text{ molal}$$

The experimentally observed solubility of isobutane in water at 25° C is 2.83×10^{-3} molal.

Molecular Surface Area and Solubility. Amidon and associates[15] have published a number of papers dealing with the solubility of liquid nonelectrolytes in polar solvents. They investigated the aqueous solubility of hydrocarbons, alcohols, esters, ketones, ethers, and

carboxylic acids. The method consisted of regression analysis, in which ln (solubility) of the solute is correlated with the total surface area (TSA) of the solute. Excluding olefins, the equation that gave the best correlation with 158 compounds was

$$\log (\text{solubility}) = 0.0168\ (\text{TSA}) + 4.44 \quad (10-9)$$

The TSA of a compound was calculated using a computer program prepared earlier by Hermann.[16,17] Elaborations on the Hermann approach involved dividing the TSA of the solute into *hydrocarbon* and *functional group* surface-area contributions (HYSA and FGSA, respectively).

The following equation was developed by Amidon et al.[15] for calculating molal solubility of hydrocarbons and alcohols in water at 25° C:

$$\ln (\text{solubility}) = -0.0430\ (\text{HYSA}) - 0.0586\ (\text{FGSA}) + 8.003\ (I) + 4.420 \quad (10-10)$$

in which (FGSA) is the surface area for the hydroxyl group. It was found that an indicator variable, I, was needed in equation (10–10) to handle the alcohols. I was given a value of 1 if the compound was an alcohol and 0 if it was a hydrocarbon (no OH groups present).

Example 10–6. Calculate the molar solubility in water at 25° C for *n*-butanol and for cyclohexane using equation (10–10). Determine the percent difference from the observed values. The observed solubilities and the surface areas calculated with the modified computer program of Hermann are found in Table 10–6.

For *n*-butanol:

$$\ln (\text{solubility}) = -0.0430\ (212.9) - 0.0586\ (59.2) + (8.003)\ (1) + 4.420$$

$$\ln (\text{solubility}) = -0.20082$$

Molal solubility = 0.818 (error = 18.7% from the observed value, 1.006)

For cyclohexane:

$$\ln (\text{solubility}) = -0.0430\ (279.1) - 0.586(0) + (8.003)\ (0) + 4.420 = -7.5813$$

Molal solubility = 5.1×10^{-4} (error = 22.8% from the observed value, 6.61×10^{-4})

The method of Amidon et al. may prove applicable for predicting solubilities of complex organic drug molecules that have limited solubility in water.

TABLE 10–6. *Molecular Surface Areas of Alcohols and Hydrocarbons*

	HYSA (angstroms)^2	FGSA (angstroms)^2	Observed Solubility (molal)
n-butanol	212.9	59.2	1.006
Cyclohexanol	240.9	49.6	3.8×10^{-1}
Cyclohexane	279.1	—	6.61×10^{-4}
n-Octane	383	—	5.80×10^{-6}

Key: HYSA = hydrocarbon surface area; FGSA = functional group surface area (OH group in the case of an alcohol).

SOLUBILITY OF SOLIDS IN LIQUIDS

Systems of solids in liquids include the most frequently encountered and probably the most important type of pharmaceutical solutions. The solubility of a solid in a liquid cannot be predicted in a wholly satisfactory manner as yet, except possibly for ideal solutions, because of the complicating factors that must be taken into account.

Pharmaceutical solutions consist of a wide variety of solutes and solvents, as listed in Table 10–2. We shall begin with the ideal solution, proceeding then to regular solutions of nonpolar or moderately polar character and finally to solutions of high polarity, in which solvation and association result in marked deviation from ideal behavior.

In this limited treatment, only the highlights of the derivations are sketched out, and the resulting equations are given without a detailed development of each step in the formulation. It is hoped, however, that the worked examples will show the usefulness of the various equations and that the selected references will lead the interested reader to the original literature where details can be found.

Ideal Solutions. The solubility of a solid in an ideal solution depends on temperature, melting point of the solid, and molar heat of fusion ΔH_f, that is, the heat absorbed when the solid melts. In an ideal solution, the heat of solution is equal to the heat of fusion, which is assumed to be a constant independent of the temperature. Ideal solubility is not affected by the nature of the solvent. The equation derived from thermodynamic considerations for an ideal solution of a solid in a liquid is

$$-\log X_2^i = \frac{\Delta H_f}{2.303R}\left(\frac{T_0 - T}{TT_0}\right) \quad (10-11)$$

in which X_2^i is the ideal solubility of the solute expressed in mole fraction, T_0 is the melting point of the solid solute in absolute degrees, and T is the absolute temperature of the solution.* The superscript ^{i} in the symbol X_2^i refers to an ideal solution, and the subscript $_2$ designates the mole fraction as that of the solute. At temperatures above the melting point, the solute is in the liquid state, and, in an ideal solution, the liquid solute is miscible in all proportions with the solvent. Therefore, equation (10–11) no longer applies when $T > T_0$. The equation is also inadequate at temperatures considerably below the melting point where ΔH_f can no longer be used.

Example 10–7. What is the solubility of naphthalene at 20° C in an ideal solution? The melting point of naphthalene is 80° C, and the molar heat of fusion is 4500 cal/mole.

*Hildebrand and Scott[2] show that calculated results compare better with experimental values if terms involving ΔC_p, the difference in heat capacities of the solid and liquid, are also included in the equation.

$$\log X_2^i = -\frac{4500}{2.303 \times 1.987}\frac{(353 - 293)}{293 \times 353}$$

$$X_2^i = 0.27$$

The mole fraction solubility can be converted to molality (provided the molecular weight M_1 of the solvent is known) by means of the relationship

$$m = \frac{1000X_2}{M_1(1 - X_2)}$$

The value of X_2 in *Example 10–7* may be compared with the results of Scatchard.[18] He found that the mole fraction solubility of naphthalene was 0.24 in benzene, 0.23 in toluene, and 0.21 in carbon tetrachloride at 20° C.

Equation (10–11) can also be written as

$$\log X_2^i = -\frac{\Delta H_f}{2.303R}\frac{1}{T} + \text{constant} \qquad (10\text{–}12)$$

Therefore, a plot of the logarithm of the solubility, expressed in mole fraction, against the reciprocal of the absolute temperature results in a straight line with a slope of $-\Delta H_f/2.303R$ for an ideal solution. By this means, the molar heat of fusion of various drugs may be obtained from their solubility in ideal solutions.

The molar heat of fusion is determined most conveniently in a differential scanning calorimeter (see p. 47). The Drug Standards Laboratory of the United States Pharmacopeial Convention in Washington, D. C., has determined the ΔH_f values for a number of drugs, and these, together with values from other sources, are found in Table 10–7.

Phase Diagrams and the Ideal Solubility Equation.[19] The phase diagram for the system thymol–salol, shown in Figure 2–17 (p. 42), may be constructed with the help of the ideal solubility equation (equations (10–11) and (10–12)). Conversely, if the points along the two lines of Figure 2–17 are obtained experimentally, they may be used together with the ideal solubility equation (equation (10–11) or (10–12)) to calculate the heats of fusion ΔH_f of substances such as salol and thymol, which are completely miscible in the liquid state, immiscible as solids, and form eutectic mixtures. Phase diagrams, such as Figure 2–17, have been used to study matrix-type dosage forms, changes in the solubility of drug mixtures as a function of temperature and composition, and to locate the eutectic point for mixtures of various pharmaceutical excipients.[20–23]

Example 10–8.[24,25] To demonstrate the use of the ideal solubility equation (equation (10–11)), we begin by calculating several points on the phase diagram, Figure 2–17, first taking thymol as the solute and salol as the solvent. This puts us on the right-hand side of the graph. The heat of fusion ΔH_f of thymol is 4126 cal/mole, the melting point is 51.5° C (324.7° K), and the molecular weight is 150.2 g/mole. The melting point of salol is 42.0° C (315.2° K), and its molecular weight is 214.2 g/mole.

(a) Let us calculate the ideal solubilities of thymol, expressed as mole fraction, at 20°, 30°, and 40° C, using the ideal solubility equation (equation (10–11)). Once the mole fraction solubilities are obtained they may be converted to molalities, $m = 1000\ X_2/M_1(1 - X_2)$, and from molalities to weight percent (%[w/w]). The three points may be plotted on the right-hand side of a graph, patterned after Figure 2–17, and a straight line drawn through the points.

The approach taken with thymol as solute and salol as solvent at 40° C (313.2° K) is as follows:

$$\ln X_2 = \frac{-4126}{1.9872}\left(\frac{324.7 - 313.2}{324.7 \cdot 313.2}\right) = 0.235$$

The anti-ln (that is, the exponential, e^x), of $\ln X_2$, −0.235, at 40° C is

$$X_2^{40°} = 0.791 \text{ or } 72.63\% \text{ (w/w)}$$

At 30° and 20° C, the X_2 values are

$$X_2^{30°} = 0.635$$

$$X_2^{20°} = 0.503$$

We now assume that phenyl salicylate (salol), molecular weight 214.2 g/mole, is the solute and thymol is the solvent. It is difficult to find the heat of fusion ΔH_f for salol in the literature; let us work backwards to calculate it. Knowing the melting point of salol, 42° C, and calculating its mole fraction near the temperature (melting point)

TABLE 10–7. *Heats of Fusion for Drugs and Other Molecules**

	ΔH_f (cal/mole)
Anthracene	6,897
Benzoic acid	4,302
Butyl *p*-hydroxybenzoate	6,410
Brompheniramine maleate	11,200
Caffeine	5,044
Cannabidiol	4,660
Cetyl alcohol	8,194
Chlorpromazine hydrochloride	6,730
Estradiol cypionate	7,030
Iodine	3,740
Meprobamate	9,340
Methoxyphenamine hydrochloride	6,960
Methyl *p*-aminobenzoate	5,850
Methyl *p*-hydroxybenzoate	5,400
Methyltestosterone	6,140
Myristic acid	10,846
Naphthalene	4,440
Phenanthrene	4,456
Phenylephrine hydrochloride	6,800
Phenytoin	11,300
p-Aminobenzoic acid	5,000
p-Hydroxybenzoic acid	7,510
Protriptyline hydrochloride	6,140
Stearic acid	13,524
Sulfadiazine	9,740
Sulfamethoxazole	7,396
Sulfapyridine	8,930
Sulfisomidine	10,780
Sulfur	4,020
Testolactone	6,760
Testosterone	6,190
Testosterone enanthate	5,260
Testosterone propionate	5,290
Theobromine	9,818
Theophylline	7,097
Thiopental	7,010
Tolbutamide	6,122

*Data from the Drug Standards Laboratory of the U.S. Pharmacopeial Convention (courtesy U.S. Pharmacopeial Drug Research and Testing Laboratories); *Handbook of Chemistry and Physics*, R. C. Weast, Ed., CRC, Cleveland, Ohio, 1975, pp. 717–719; S. H. Yalkowsky, G. L. Flynn and T. G. Slunick, J. Pharm. Sci. **61**, 852, 1972; K. C. James and M. Roberts, J. Pharm. Pharmacol. **20**, 1045, 1968; S. S. Yang and J. K. Guillory, J. Pharm. Sci. **61**, 26, 1972. (See S. S. Yang and J. K. Guillory, J. Pharm. Sci. **61**, 26, 1972, and H. O. Lin and J. K. Guillory, J. Pharm. Sci. **59**, 973, 1970, for the effect of polymorphism on the ΔH_f of sulfonamides.)

for the pure liquid at, say, 35° C, we obtain, with the help of equation (10–11), a good estimate for the heat of fusion of salol. One gets a more accurate value for ΔH_f where the solute, salol, is in high concentration; that is, near the left-hand side of Figure 2–17.

(b) With salol as the solute (left side of the phase diagram) at 35° C (308.2° K), the solution contains 9% (w/w) thymol and 91% (w/w) salol. One converts to mole fraction of salol, using the equation

$$X_2 = \frac{n_2}{n_2 + n_1}$$

The mole n_2 of salol at 35° C is 91 g/214.2 g/mole = 0.4248 mole and the mole n_1 of thymol is 9 g/150.2 g/mole = 0.0599 mole. The mole fraction is therefore

$$X_2 = \frac{0.4248}{0.4248 + 0.0599} = 0.8764$$

$$\ln X_2 = -0.1319 = -\frac{\Delta H_f}{1.9872}\left(\frac{315.2 - 308.2}{315.2 \cdot 308.2}\right)$$

$$\Delta H_f \text{ (salol)} = 3639 \text{ cal/mole}$$

At 35° C the solution should behave nearly ideal, for salol is in the concentration of 91% (w/w), and the ΔH_f obtained should be a reasonable estimate of the heat of fusion of salol.

Nonideal Solutions. The activity of a solute in a solution is expressed as the concentration multiplied by the activity coefficient. When the concentration is given in mole fraction, the activity is expressed as

$$a_2 = X_2\gamma_2 \qquad (10\text{–}13)$$

in which γ_2 on the mole fraction scale is known as the rational activity coefficient (p. 132). Converting to logarithms, we have

$$\log a_2 = \log X_2 + \log \gamma_2 \qquad (10\text{–}14)$$

In an ideal solution, $a_2 = X_2{}^i$ since $\gamma_2 = 1$, and accordingly the ideal solubility, equation (10–14), may be expressed in terms of activity as

$$-\log a_2 = -\log X_2{}^i = \frac{\Delta H_f}{2.303RT}\left(\frac{T_0 - T}{T_0}\right) \qquad (10\text{–}15)$$

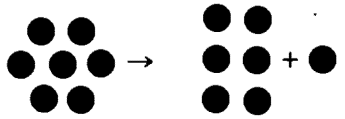
By combining equations (10–14) and (10–15), the mole fraction solubility of a solute in a nonideal solution, expressed in log form, becomes

$$-\log X_2 = \frac{\Delta H_f}{2.303R}\left(\frac{T_0 - T}{T_0\,T}\right) + \log \gamma_2 \qquad (10\text{–}16)$$

Therefore, the mole fraction solubility in various solvents can be expressed as the sum of two terms: the solubility in an ideal solution and the logarithm of the activity coefficient of the solute. As a real solution becomes more ideal, γ_2 approaches unity, and equation (10–16) reduces to equation (10–15). Only rarely, however, does the experimentally determined solubility in real solutions compare favorably with the value calculated by use of the ideal solubility equation. The activity coefficient γ_2, depending on the nature of both the solute and the solvent as well as on the temperature of the solution, must be accounted for before the calculated solubility will correspond well with experimental values.

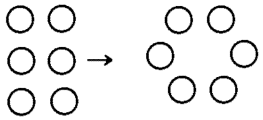
The log γ_2 term of equation (10–16) is obtained by considering the intermolecular forces of attraction that must be overcome, or the work that must be done, in removing a molecule from the solute phase and depositing it in the solvent. This process may be considered as occurring in three steps.[26]

1. The first step involves the removal of a molecule from the solute phase at a definite temperature. The work done in removing a molecule from a solute so that it passes into the vapor state requires breaking the bonds between adjacent molecules. The work involved in breaking the bond between two adjacent molecules is $2w_{22}$, in which the subscript $_{22}$ refers to the interaction between solute molecules. When the molecule escapes from the solute phase, however, the hole it has created closes, and one half of the energy is regained. The gain in potential energy or net work for the process is thus w_{22}, schematically represented as



Solute — Liberation of a molecule from the solute

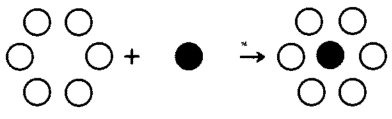
2. The second step involves the creation of a hole in the solvent just large enough to accept the solute molecule. The work required for this step,



Solvent — Creation of a hole in the solvent

is w_{11}, in which the subscript refers to the energy of interaction between solvent molecules.

3. The solute molecule is finally placed in the hole in the solvent,



Solvent — Solute molecule — Solution

and the gain in work or decrease of potential energy in this step is $-w_{12}$. The subscript $_{12}$ stands for the interaction energy of the solute with the solvent. The hole or cavity in the solvent, created in step 2, is now closed, and an additional decrease in energy, $-w_{12}$, occurs, involving net work in this final step of $-2w_{12}$.

The total work as given by this extremely simplified scheme is thus $(w_{22} + w_{11} - 2w_{12})$. The activity coefficient term of the solubility equation, however, has

been shown by Scatchard and by Hildebrand and Wood[18] to be proportional also to the volume of the solute, considered as a supercooled liquid, and to the fraction of the total volume occupied by the solvent. The logarithm of the activity coefficient is given by the more elaborate expression

$$\ln \gamma_2 = (w_{22} + w_{11} - 2w_{12}) \frac{V_2 \Phi_1^2}{RT} \qquad (10-17)$$

in which V_2 is the molar volume or volume per mole of (supercooled) liquid solute and Φ_1 is the volume fraction, or $X_1V_1/(X_1V_1 + X_2V_2)$ of the solvent. R is the gas constant, 1.987 cal/mole deg, and T is the absolute temperature of the solution.

The w terms in equation (10–17) are potential energies or terms representing attractive forces. Since van der Waals forces between molecules follow a geometric mean rule, the term w_{12} can be taken as approximately equal to the *geometric mean* of the solvent and solute terms. That is, the interaction between different molecules is equal to the square root of the product of the attractions among similar molecules, or

$$w_{12} = \sqrt{w_{11}w_{22}} \qquad (10-18)$$

When this substitution is made in equation (10–17), it becomes

$$\ln \gamma_2 = [w_{11} - 2(w_{11}w_{22})^{1/2} + w_{22}] \frac{V_2 \Phi_1^2}{RT} \qquad (10-19)$$

The terms within the brackets are seen to represent a perfect square, and equation (10–19) therefore becomes

$$\ln \gamma_2 = [(w_{11})^{1/2} - (w_{22})^{1/2}]^2 \frac{V_2 \Phi_1^2}{RT} \qquad (10-20)$$

Equation (10–20) can be modified in the following manner. The w terms of equation (10–20) are approximately equal to the a/V^2 term in the van der Waals equation for nonideal gases and liquids (p. 27), and they serve as a measure of the *internal pressures* of the solvent and the solute in nonpolar or moderately polar nonideal solutions. The $(w)^{1/2}$ terms are known as *solubility parameters* and are designated by the symbols δ_1 and δ_2 for solvent and solute respectively. Equation (10–20) is thus written in terms of the common logarithm as

$$\log \gamma_2 = (\delta_1 - \delta_2)^2 \frac{V_2 \Phi_1^2}{2.303RT} \qquad (10-21)$$

In dilute solutions, the volume fraction is nearly unity, and Φ_1^2 may be disregarded as a first approximation. When a rough calculation shows it to be significantly less than 1, a recalculation must be made taking into account the value of Φ_1. this correction will be described in the example to follow.

When the term for $\log \gamma_2$ is substituted in equation (10–16), the mole fraction solubility of a nonpolar or moderately polar solute is obtained as

$$-\log X_2 = \frac{\Delta H_f}{2.303RT}\left(\frac{T_0 - T}{T_0}\right) + \frac{V_2 \Phi_1^2}{2.303RT}(\delta_1 - \delta_2)^2 \qquad (10-22)$$

If R is replaced by 1.987 cal/mole deg and T by 298° K at 25° C, the temperature most frequently employed, we obtain

$$-\log X_2 = \frac{\Delta H_f}{1364}\left(\frac{T_0 - 298}{T_0}\right) + \frac{V_2 \Phi_1^2}{1364}(\delta_1 - \delta_2)^2 \qquad (10-23)$$

The solubility parameters, which express the cohesion between like molecules, may be calculated from heats of vaporization, internal pressures, surface tensions, and other properties, as described by Hildebrand and Scott.[27] The heat of vaporization in conjunction with the molar volume of the species, when available at the desired temperature, probably affords the best means for calculating the solubility parameter. It is roughly the square root of the internal pressure (p. 218) or

$$\delta = \left(\frac{\Delta H_v - RT}{V_l}\right)^{1/2} \qquad (10-24)$$

in which ΔH_v is the heat of vaporization and V_l is the molar volume of the liquid compound at the desired temperature, R is the gas constant, and T is the absolute temperature. If the solute is a solid at this temperature, its molar volume must be obtained at elevated temperature where it is a liquid (i.e., at temperatures above the melting point) and extrapolated to the temperature under consideration. Where this method is not satisfactory for solids, other methods have been devised.[28,29]

Example 10–9. (*a*) Compute the solubility parameter of iodine and then (*b*) determine the mole fraction and molal solubility of iodine in carbon disulfide at 25° C.[30] (*c*) What is the activity coefficient of the solute in this solution? The heat of vaporization of liquid iodine extrapolated to 25° C is 11,493 cal/mole, the average heat of fusion ΔH_f is about 3600 cal at 25° C, the melting point of iodine is 113° C, and its molar volume V_2 is 59 cm^3 at 25° C. The solubility parameter of carbon disulfide is 10.

(*a*)

$$\delta = \left(\frac{11{,}493 - 1.987 \times 298.2}{59}\right)^{1/2} = 13.6$$

(Notice that the value in Table 10–8, obtained from solubility data, is somewhat different from the value obtained here.)

(*b*) X_2 is first calculated assuming that Φ_1^2 is unity.

$$-\log X_2 = \frac{3{,}600}{1364}\left(\frac{386 - 298}{386}\right) + \frac{59}{1364}(10.0 - 13.6)^2$$

$$X_2 = 0.0689$$

Now the volume fraction Φ_1 is equal to $V_1(1 - X_2)/[V_1(1 - X_2) + V_2X_2]$ or, for iodine ($V_2 = 59$ cm^3) in carbon disulfide ($V_1 = 60$ cm^3),

$$\Phi_1 = 0.9322$$

Recalculating X_2 under (*b*) with ${\Phi_1}^2$ as $(0.9322)^2$ included in the second right-hand term of the solubility equation gives

$$X_2 = 0.0815$$

After six such replications (iterations) using a hand calculator, the result becomes $X_2 = 0.0845$. This procedure of repeated calculations is called *iteration.*[30] The experimental value for the solubility in carbon disulfide is recorded by Hildebrand and Scott[31] as 0.0546 at 25° C. The ideal mole fraction solubility ${X_2}^i$ of iodine is 0.250 at 25° C.

The calculated mole fraction solubility of iodine in carbon disulfide may be converted to molal concentration by use of the equation

$$m = \frac{1000\,X_2}{(1 - X_2)M_1} = \frac{1000 \times 0.085}{(1 - 0.085)(76.13)} = 1.22 \text{ mole/kg}$$

(*c*) By comparing equations (10–13) and (10–15), it becomes clear that the ideal solubility is related to the actual solubility at a definite temperature by the expression

$$a_2 = {X_2}^i = X_2\gamma_2$$

Therefore, the activity coefficient of the solute is

$$\gamma_2 = {X_2}^i/X_2 = 0.25/0.055 = 4.55$$

Hildebrand and Scott[31] include the solubility parameters for a number of compounds in their book. A table of solubility parameters has also been compiled by Hansen and Beerbower.[32] The approximate values for some representative compounds of pharmaceutical interest are listed in Tables 10–8 and 10–9. $\delta_{(total)}$ is essentially the δ value for solvent and drug referred to in this section. δ_D, δ_P, and δ_H are partial solubility parameters introduced by Hansen and used for an extended theory of solubility, which is not treated here. The parameter δ_D accounts for nonpolar effects, δ_P for polar effects, and δ_H to express the hydrogen bonding nature of the solute or solvent molecules. The sum of the squares of the partial parameters gives the total cohesive energy density ${\delta_{(total)}}^2$,

$${\delta_{(total)}}^2 = {\delta_D}^2 + {\delta_P}^2 + {\delta_H}^2 \qquad (10\text{–}25)$$

Kesselring et al.[33] have determined both total and partial solubility parameters using gas–liquid chromatography.

The more alike are the δ values of two components, the greater is the mutual solubility of the pair. For example, the δ value of phenanthrene is 9.8; for the solvent carbon disulfide, 10; and for normal hexane, 7.3. Therefore, phenanthrene would be expected to be more soluble in CS_2 than in n-C_6H_{14}. When the solubility parameter of the solute is identical to that of the solvent, the cohesive forces of the solute and the solvent are alike as long as hydrogen bonding and other

TABLE 10–8. *Molar Volume and Solubility Parameters for Some Liquid Compounds*,†*

Liquid	V (cm^3/mole)	Solubility Parameter (cal/cm^3)$^{1/2}$			
		δ_D	δ_P	δ_H	$\delta_{(total)}$
n-Butane	101.4	6.9	0	0	6.9
n-Hexane	131.6	7.3	0	0	7.3
n-Octane	163.5	7.6	0	0	7.6
Diethyl ether	104.8	7.1	1.4	2.5	7.7
Cyclohexane	108.7	8.2	0	0.1	8.2
n-Butyl acetate	132.5	7.7	1.8	3.1	8.5
Carbon tetrachloride	97.1	8.7	0	0.3	8.7
Toluene	106.8	8.8	0.7	1.0	8.9
Ethyl acetate	98.5	7.7	2.6	3.5	8.9
Benzene	89.4	9.0	0	1.0	9.1
Chloroform	80.7	8.7	1.5	2.8	9.3
Acetone	74.0	7.6	5.1	3.4	9.8
Acetaldehyde	57.1	7.2	3.9	5.5	9.9
Carbon disulfide	60.0	10.0	0	0.3	10.0
Dioxane	85.7	9.3	0.9	3.6	10.0
1-Octanol	157.7	8.3	1.6	5.8	10.3
Nitrobenzene	102.7	9.8	4.2	2.0	10.9
1-Butanol	91.5	7.8	2.8	7.7	11.3
1-Propanol	75.2	7.8	3.3	8.5	12.0
Dimethylformamide	77.0	8.5	6.7	5.5	12.1
Ethanol	58.5	7.7	4.3	9.5	13.0
Dimethyl sulfoxide	71.3	9.0	8.0	5.0	13.0
Methanol	40.7	7.4	6.0	10.9	14.5
Propylene glycol	73.6	8.2	4.6	11.4	14.8
Ethylene glycol	55.8	8.3	5.4	12.7	16.1
Glycerin	73.3	8.5	5.9	14.3	17.7
Formamide	39.8	8.4	12.8	9.3	17.9
Water	18.0	7.6	7.8	20.7	23.4

*From C. Hansen and A. Beerbower, in *Encyclopedia of Chemical Technology*, Suppl. Vol., 2nd Edition, A. Standen, Ed., Wiley, New York, 1971, pp. 889–910.
δ_D, δ_P, and δ_H are partial solubility parameters defined briefly above. $\delta_{(total)}$ is essentially the solvent solubility parameter, δ_1, defined by Hildebrand and used throughout this section.

†It must be cautioned that a number of solvents in this table and throughout the book are not suitable as solvents in medicinal or nutritive products. Dioxane, for example, is both toxic and irritating to the skin.

TABLE 10–9. *Molar Volume and Solubility Parameters of Crystalline Compounds (Tentative Values)**

Solid Compound	V (cm^3/mole)	Solubility Parameter $(cal/cm^3)^{1/2}$			
		δ_D	δ_P	δ_H	$\delta_{(total)}$
Benzoic acid	104	8.9	3.4	4.8	10.7
Caffeine	144	10.1	3.5	9.1	14.1
Methyl paraben	145	9.3	4.4	6.0	11.8
Naphthalene	123	9.4	1.0	1.9	9.6
Phenobarbital	137	10.3	4.8	5.3	12.6
Sulfadiazine	182	9.5	4.8	6.6	12.5
Testosterone propionate	294	9.2	2.9	2.8	10.0
Tolbutamide	229	9.7	2.9	4.1	10.9

*Refer to the footnote in Table 10–8 for a definition of δ_D, δ_P, *and* δ_H. $\delta_{(total)}$ is essentially the solute δ_2 value referred to in this section.

complicating interactions are not involved. Then $\delta_1 - \delta_2 = 0$, and the last term of equation (10–23) becomes zero. The solubility of the solute then depends alone on the ideal solubility term of the equation, involving the heat of fusion, the melting point of the solute, and the temperature of the solution.

James et al.[29] investigated the solubility of testosterone esters in a number of aliphatic straight- and branched-chain alkanes, cyclic and aromatic hydrocarbons, and halogen derivatives. They determined the δ value of testosterone propionate and other esters and arrived at values of 9.5 to 10.0 $(cal/cm^3)^{1/2}$ for testosterone propionate. The Hildebrand solubility theory was used with some success by James and his associates to predict the solubilities of steroidal esters in hydrocarbon solvents.

In the use of solubility parameters, a distinction should also be made between those compounds that form hydrogen bonds and those that do not. The δ values may be used to predict the miscibility of hydrogen-bonding solvents or of non–hydrogen-bonding solvents, but they are not always applicable when members of the two different classes are mixed.

The nonideal solutions to which the Scatchard–Hildebrand equation applies are called *regular solutions*. Regular solutions may be better understood by reference to several properties of ideal solutions. First, the molecules of an ideal solution exhibit complete freedom of motion and randomness of distribution in the solution. Secondly, an ideal solution forms with no change in heat content, that is to say, heat is not absorbed or evolved during the mixing process. Furthermore, there is no change in volume when the components of an ideal solution are mixed. The partial free energy change involved in the transfer of a mole of solute from the solute phase to a saturated solution is written, for an ideal solution, as

$$\overline{\Delta G_2} = RT \ln X_2 \qquad (10\text{–}26)$$

Since the change in heat content ΔH is zero

$$\overline{\Delta G_2} = \overline{\Delta H_2} - T\,\overline{\Delta S_2} = -T\,\overline{\Delta S_2} \qquad (10\text{–}27)$$

and the entropy for the solute in the ideal solution is

$$\overline{\Delta S_2} = -\overline{\Delta G_2}/T = -R \ln X_2 \qquad (10\text{–}28)$$

The molecules of regular solutions, like those of ideal solutions, possess sufficient kinetic energy to prevent ordering and a loss in entropy; and a regular solution, like an ideal solution, exhibits complete randomness. The entropy change in forming a regular solution is given by the same formula as that for an ideal solution,

$$\overline{\Delta S_2} = -R \ln X_2 \qquad (10\text{–}29)$$

On the other hand, owing to cohesion among the solute molecules and among the solvent molecules, regular solutions exhibit positive deviation from Raoult's law. Unlike ideal solutions, they absorb heat when the components are mixed. It can be shown from thermodynamic considerations that the heat change when 1 mole of solute is added to a large quantity of regular solution is equal to $RT \ln \gamma_2$, which may be set equal to the solubility parameter term in the solubility equation (cf. equation (10–21)).

$$\overline{\Delta H_2} = RT \ln \gamma_2 = V_2 \Phi_1^2 (\delta_1 - \delta_2)^2 \qquad (10\text{–}30)$$

These relationships can be used to derive the solubility expression, equation (10–22) as demonstrated in the following paragraph. For a nonideal solution, X_2 in equation (10–26) must be replaced by the activity a_2 or

$$\overline{\Delta G_2} = RT \ln a_2 \qquad (10\text{–}31)$$

From equations (10–15) and (10–31)

$$-\overline{\Delta G_2} = \frac{\Delta H_f (T_0 - T)}{T_0} \qquad (10\text{–}32)$$

Writing the familiar free energy equation

$$\overline{\Delta G_2} = \overline{\Delta H_2} - T\,\overline{\Delta S_2} \qquad (10\text{–}33)$$

or

$$T\,\overline{\Delta S_2} = -\overline{\Delta G_2} + \overline{\Delta H_2} \qquad (10\text{–}34)$$

gives

$$-RT \ln X_2 = \frac{\Delta H_f (T_0 - T)}{T_0} + V_2 \Phi_1^2 (\delta_1 - \delta_2)^2 \qquad (10\text{–}35)$$

by the application of equations (10–29), (10–30),

(10–32) and (10–34). Then equation (10–35) may be written as

$$-\log X_2 = \frac{\Delta H_f}{2.303RT}\left(\frac{T_0 - T}{T_0}\right) + \frac{V_2\Phi_1^2}{2.303RT}(\delta_1 - \delta_2)^2$$

which is identical with equation (10–22).

Extended Hildebrand Solubility Approach. A modification of the Scatchard–Hildebrand equation has been developed[34] and is referred to as the *extended Hildebrand solubility approach* (EHS). The extended method allows one to calculate the solubility of polar and nonpolar solutes in solvents ranging from nonpolar hydrocarbons to highly polar solvents such as alcohols, glycols, and water. Although formulated specifically for crystalline solids in liquid solution, the EHS approach should also apply to liquid–liquid and gas–liquid systems.

It is well recognized that the established regular solution theory, represented by equation (10–22), usually provides poor predictions of solubility for drugs and other crystalline solids in polar solvents. Polar systems are quite irregular, involving self-association of solute or solvent, solvation of the solute by the solvent molecules, or complexation of two or more solute species in the solution. The intermolecular attachments consist of hydrogen bonds, charge transfer complexes (Chapter 11), and other types of Lewis acid–base interactions.

The solubility equation used in the EHS approach is

$$-\log X_2 = -\log X_2^i + A(w_{11} + w_{22} - 2W) \qquad (10\text{–}36)$$

in which the last term corresponds to the expression for $\log \gamma_2$, equation (10–17) of Hildebrand and Scatchard. In equation (10–36), A stands for $V_2\Phi_1^2/(2.303RT)$ and W is used for w_{12} from equation (10–17). The negative logarithm of the ideal solubility, $-\log X_2^i$, may be calculated from a knowledge of ΔH_f, T_0, and T as shown in equation (10–15).

Alternatively, it may be obtained from ΔS_f:

$$-\log X_2^i = \frac{\Delta S_f}{R}\log\frac{T_o}{T} \qquad (10\text{–}37)$$

as suggested by Hildebrand et al.[35] ΔS_f, the entropy of fusion at the melting point, is determined using the expression

$$\Delta H_f = T_o \Delta S_f \qquad (10\text{–}38)$$

According to the EHS approach, the term involving the logarithm of the activity coefficient γ_2 is partitioned into two terms, one representing mainly physical or van der Waals forces γ_v and an additional term γ_R representing residual, presumably stronger, forces:

$$\log \gamma_2 = \log \gamma_v + \log \gamma_R \qquad (10\text{–}39)$$

in which

$$\log \gamma_v = A(\delta_1 - \delta_2)^2 = A(\delta_1^2 + \delta_2^2 - 2\delta_1\delta_2) \qquad (10\text{–}40)$$

and

$$\log \gamma_R = A(2\delta_1\delta_2 - 2W) \qquad (10\text{–}41)$$

Equation (10–39) is written, in terms of equations (10–40) and (10–41) as:

$$\log \frac{X_2^i}{X_2} = \log \gamma_2 = A(\delta_1 - \delta_2)^2 + 2A(\delta_1\delta_2 - W)$$

or

$$-\log X_2 = -\log X_2^i + A(\delta_1^2 + \delta_2^2 - 2W) \qquad (10\text{–}42)$$

Investigators[34] have applied the EHS approach to polar and nonpolar solutes in individual solvents as well as mixed solvent systems.

Equation (10–42) differs from equation (10–22) in that the geometric mean is replaced by W. Equation (10–42) ordinarily provides an accurate prediction of the mole fraction solubility of a polar drug in binary solvent systems (i.e., two solvents mixed in various proportions) as demonstrated in *Examples 10–10* and *10–11*. W is obtained for a solute in a particular solvent system by rearranging equation (10–42):

$$\frac{\log (X_2^i/X_2)}{A} = \frac{\log \gamma_2}{A} = \delta_1^2 + \delta_2^2 - 2W$$

$$W = \frac{1}{2}(\delta_1^2 + \delta_2^2 - (\log \gamma_2)/A) \qquad (10\text{–}43)$$

The solubility parameters, δ_1 and δ_2, are known quantities. Log γ_2 is obtained from a knowledge of the drug's ideal solubility, X_2^i, and its mole fraction solubility, X_2, in a particular solvent system. The observed solubilities of caffeine in mixtures of dioxane and water are shown in Figure 10–5 together with the back-calculated solubility curve obtained by use of the

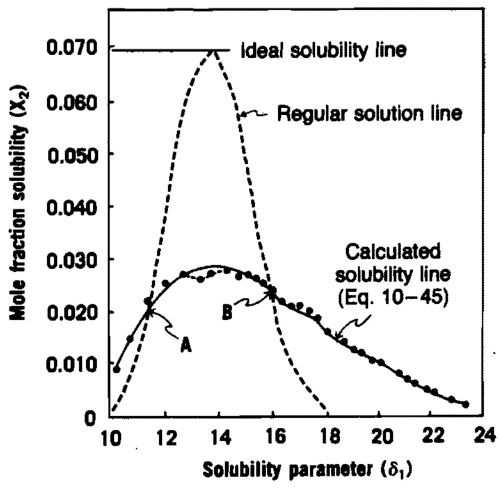


Fig. 10–5. Mole fraction solubility of caffeine at 25° C in dioxane–water mixtures. *A* and *B* are points at which real solubility equals regular solution solubility and W = $\delta_1\delta_2$. Filled circles are experimental solubility points. (From A. Adjei, J. Newburger and A. Martin, J. Pharm. Sci. 69, 659, 1980, reproduced with permission of the copyright owner.)

TABLE 10–10. *Several Observed and Calculated Solubilities of Caffeine in Dioxane–Water Systems at 25° C**

Volume % water	δ_1	log X_2	A	W†	$W_{(calc)}$‡	$X_{2(obs)}$	$X_{2(calc)}$§
0	10.01	0.90646	0.10257	140.901	141.120	0.0085	0.0094
20	12.70	0.40443	0.09467	173.729	173.729	0.0270	0.0270
40	15.39	0.41584	0.09269	211.403	211.380	0.0263	0.0261
50	16.73	0.50555	0.09369	232.469	233.465	0.0214	0.0214
60	18.07	0.62665	0.09520	255.191	255.220	0.0162	0.0164
80	20.76	0.94347	0.09837	305.913	305.951	0.0078	0.0080
100	23.45	1.47643	0.10179	362.919	362.343	0.0023	0.0022

*$\delta_2 = 13.8$; $-\log X_2^i = 1.1646$.
†W is calculated from equation (10–43). Its units are cal/cm^3.
‡$W_{(calc)}$ is obtained using the quartic expression (10–45).
§$X_{2(calc)}$ is calculated using equation (10–42) with W replaced by $W_{(calc)}$.

extended Hildebrand approach. The calculations are illustrated in *Example 10–10*, part of the data for which are found in Tables 10–9 and 10–10.

Example 10–10. Compute the value of W for a solution of caffeine in the pure solvent, dioxane ($\delta = 10.01$), in pure water ($\delta = 23.45$), and in a 50:50 volume percent of dioxane and water ($\delta = 16.73$) at 25° C. ΔH_f is 5044 cal/mole, and $T_0 = 512°$ C. According to equation (10–38), $\Delta S_f = 9.85$ cal/mole deg. Using equation (10–37), the logarithm of the ideal mole fraction solubility, $-\log X_2^i$ is found to be 1.16460, or $X_2^i = 0.068454$. The molar volume, V_2, of caffeine is 144 cm^3/mole at 25° C. The volume fractions, ϕ_1, of dioxane, water, and a 50:50 mixture of dioxane and water are 0.985809, 0.982066, and 0.942190, respectively. Using the definition of A, following equation (10–36), one obtains A^* for caffeine in dioxane as 0.102570; in water, 0.101793; and in the 50:50 mixture, 0.093694.

The mole fraction solubilities of caffeine in the three solvents at 25° C are found experimentally to be 0.008491 in dioxane, 0.002285 in water, and 0.021372 in the 50:50 mixture of dioxane and water.

Using equation (10–43), one obtains for log γ_2/A for the three solutions

$$\frac{\log (0.068454/0.008491)}{0.102570} = 8.83728 \text{ in dioxane}$$

$$\frac{\log (0.068454/0.002285)}{0.101793} = 14.50505 \text{ in water}$$

and

$$\frac{\log (0.068454/0.021372)}{0.093694} = 5.39580 \text{ in the 50:50 mixture}$$

W values are then obtained again with the help of equation (10–43):

In dioxane:

$$8.83728 = (10.01)^2 + (13.8)^2 - 2W$$
$$W = 140.90141$$

In water:

$$14.50425 = (23.45)^2 + (13.8)^2 - 2W$$
$$W = 362.91913$$

In the 50:50 mixture:

$$5.39574 = (16.73)^2 + (13.8)^2 - 2W$$
$$W = 232.46858$$

The desirability of a theoretic approach is the ability to calculate solubilities of a drug in mixed and pure solvents, using only fundamental physical chemical properties of solute and solvent. Unfortunately, W at present cannot be obtained by a consideration of the molecular characteristics of the species in solution. It has been found, however, that when the experimentally derived W values (as calculated in *Example 10–10*) are regressed against a power series in δ_1, for the various solvents of the mixture, a polynomial equation is obtained that may be used for the accurate back-calculation of solubilities. A power series in the second degree (quadratic) may be used for this purpose. Using the complete set of 30 solubility values (see Table 10–10 for some of these), the quadratic equation is obtained:

$$W_{(calc)} = 79.411400 + 1.868572\delta_1 + 0.435648\delta_1^2 \quad (10–44)$$

The quartic equation is:

$$W_{(calc)} = 15.075279 + 17.627903\delta_1 - 0.966827\delta_1^2 + 0.053912\delta_1^3 - 0.000758\delta_1^4 \quad (10–45)$$

Using equation (10–44) or (10–45) and a hand calculator, one can readily calculate the solubility of caffeine in any combination of dioxane and water at 25° C.

Example 10–11†. Calculate the solubility of caffeine ($\delta_2 = 13.8$) at 25° C in a 40:60 volume percent mixture of dioxane and water. Use the quadratic expression, equation (10–44), to obtain $W_{(calc)}$.

One first obtains the δ_1 value of the 40:60 mixture of dioxane and water using the equation

$$\delta_1 = \phi_d\delta_d + \phi_w\delta_w$$

in which ϕ_d and ϕ_w are the volume fractions, 0.40 and 0.60, of the solvents dioxane and water and δ_d and δ_w are their solubility parameters.

$$\delta_1 = 0.40(10.01) + 0.60(23.45) = 18.07$$

Then $W_{(calc)}$ is obtained by back-calculation:

$$W_{(calc)} = 79.41140 + 1.86857(18.07) + 0.43565(18.07)^2$$
$$W_{(calc)} = 255.427 \qquad W_{(exp)} = 255.191$$

*A is obtained from a knowledge of $X_{2(obs)}$, and these values are used for convenience in this example. When the solubility is not known, it is necessary to obtain A by use of an iteration (replication) procedure as described on page 225.

†As mentioned in the footnote of Table 10–8, dioxane is externally irritating and internally toxic and cannot be used in drug or food products. It is chosen as a solvent in *Example 10–11* simply because it is miscible with water and has an appropriate solubility parameter. Such agents must be carefully tested for untoward effects before any use is made of them in man or animal.

This value for $W_{(calc)}$ is substituted in equation (10–42) in which $-\log X_2^i$ for caffeine is 1.1646 and A is 0.09520.

$$-\log X_2 = 1.1646 + 0.09520[(18.07)^2 + (13.8)^2 - 2(255.427)]$$

$$-\log X_2 = 1.74635$$

$$X_{2(calc)} = 0.0179 \qquad X_{2(exp)} = 0.0162$$

Some values, calculated as shown in *Examples 10–10* and *10–11*, are found in Table 10–10. The $X_{2(calc)}$ values in Table 10–10 were back-calculated using a quartic expression, equation (10–45), rather than the quadratic equation used in *Example 10–11*, which accounts for the small difference in results.

Solvation and Association in Solutions of Polar Compounds. We saw in equation (10–30) that heat must be absorbed when the solute is mixed with the solvent to form a regular solution. This happens because the squared term $(\delta_1 - \delta_2)^2$ can lead only to positive values (or zero). We can refer back to equation (10–17), however, where we find the term w_{12}, which expresses the interaction of the solute and solvent molecules. If we remove the restriction that this term must follow the rule of the geometric mean given in formula (10–18), we allow $2w_{12}$ to be $> w_{11} + w_{22}$ and ΔH may then become negative. This leads to a negative deviation from Raoult's law and applies when specific interactions, such as hydrogen bonding (p. 213), occur between the solute and the solvent. Such specific combinations of the solvent with the solute are known as *solvation*.

When the interaction occurs between like molecules of one of the components in a solution, the phenomenon is referred to as *association*. This type of interaction is exemplified by the dimerization of benzoic acid in some nonpolar solvents or the interlinking of water molecules by hydrogen bonding. It leads to positive heats of solution and to positive deviations from Raoult's law. The association of water molecules is reflected in a large w_{11} in equation (10–17). When water is mixed with a nonpolar solute, w_{11} is much larger than w_{22}, and w_{12} is small. Such a situation obviously leads to low solubility. The specific interaction effects, known as *solvation* and *association*, cannot be accounted for in a satisfactory way by the Scatchard–Hildebrand formula (equation (10–22)) but rather require a more refined treatment, which is outside the scope of this book.

Solubility and the Heat of Solution. Solubility as a function of temperature for nonelectrolytes, weak electrolytes, or strong electrolytes in highly nonideal solutions can be calculated using the *heat of solution*, ΔH_{soln}, instead of the heat of fusion in an expression analogous to the ideal solubility expression (equation (10–11), p. 221). For nonelectrolytes and weak electrolytes, the following equation is used[36,37]:

$$\ln (c''/c') = \frac{\Delta H_{soln}}{R} \frac{(T'' - T')}{(T'T'')} \qquad (10\text{–}46)$$

For strong electrolytes, R is replaced by νR, in which ν is the number of ions produced in the dissociation of the electrolyte. The terms c' and c'' are concentrations such as molar, molal, mole fraction, grams/liter, or percent. These concentration terms appear in equation (10–46) as ratios, c''/c', so as to cancel the concentration units, as long as the same units are used for both c' and c''. The concentration term c' corresponds to the Kelvin temperature T', and c'' corresponds to T''. ΔH_{soln} is the heat of solution in cal/mole and R is the universal gas constant expressed as 1.9872 cal mole^{-1} deg^{-1}.

Using equation (10–46), the solubility of a solute in a particular solvent can be determined at one temperature if the heat of solution ΔH_{soln} and the solubility at another temperature are known.

Example 10–12. The solubility of urea (molecular weight 60.06 g/mole) in water at 298° K is 1.20 g/g H_2O; the ΔH_{soln} for urea in water at 25° C is 2820 cal/mole. What is the molal solubility of urea at 5° C?

$$\ln (1.20) - \ln c' = \frac{2820}{1.9872}\left(\frac{298 - 278}{298 \cdot 278}\right)$$

$\ln c' = -0.16$ and $c' = 0.85$ g/g H_2O or 850 g/kg H_2O

850 g/kg $H_2O \div 60.06$ g/mole = 14.2 mole/kg H_2O

The experimental solubility of urea on the molal scale is 14.2 mole/kg H_2O.

Solubility of Strong Electrolytes. The effect of temperature on the solubility of some salts in water is shown in Figure 10–6. A rise in temperature increases the solubility of a solid that absorbs heat (*endothermic* process) when it dissolves. This effect conforms with the Le Chatelier principle, which states that a system tends to adjust itself in a manner so as to counteract a stress such as an increase of temperature. Conversely, if the solution process is *exothermic*, that is, if heat is evolved, the temperature of the solution rises and the container feels warm to the touch. The solubility in this case decreases with an elevation of the temperature, again following Le Chatelier's principle. Most solids belong to the class of compounds that absorb heat when they dissolve.

Sodium sulfate exists in the hydrated form, $Na_2SO_4 \cdot 10H_2O$, up to a temperature of about 32° C, the solution process (dissolution) is endothermic, and solu-

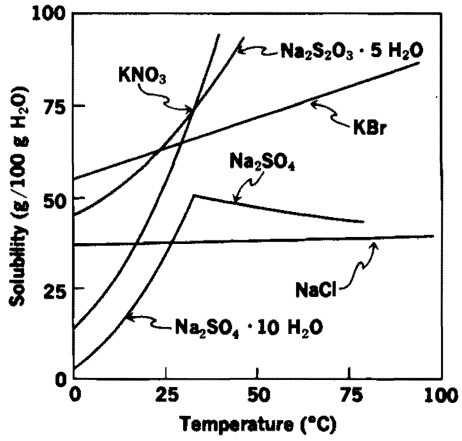


Fig. 10–6. The influence of temperature on the solubility of various salts.

bility increases with temperature. Above this point, the compound exists as the anydrous salt, Na_2SO_4, the dissolution is exothermic, and solubility decreases with an increase of temperature (Fig. 10–6). Sodium chloride does not absorb or evolve an appreciable amount of heat when it dissolves in water; thus, its solubility is not altered much by a change of temperature, and the heat of solution is approximately zero, as observed in Figure 10–6.

These phenomena can be explained in terms of the heat of solution, ΔH. The quantity ΔH is properly known as the *partial* or *differential heat of solution*. It is the heat absorbed per mole when a small quantity of solute is added to a large quantity of solution. It may also be defined as the rate of change of the heat of solution per mole of solute in a solution of any specified concentration. The *total* or *integral heat of solution* is the heat absorbed when 1 mole of solute is dissolved in enough solvent to produce a solution of specified concentration.

The heat of solution of a crystalline substance is the sum of the *heat of sublimation* of the solid, as given by the *crystal lattice energy*, and the *heat of hydration* (solvation) of the ions in solution (Table 10–11).

$$\Delta H \text{ (solution)} = \Delta H_{\text{subl}} + \Delta H_{\text{hyd}} \qquad (10\text{–}47)$$

The lattice energy is the energy required to separate 1 mole of a crystal into its ions in the gaseous state or to vaporize the solid:

$$NaCl_{\text{solid}} \rightarrow Na^+_{\text{gas}} + Cl^-_{\text{gas}}$$

The heat of hydration is the heat liberated when the gaseous ions are hydrated; it is influenced by the radius of an ion, since for ions of the same valence, the smaller the ionic radius, the greater is the electrostatic field surrounding the ion and the larger is the heat of hydration. The hydration process can be represented as

$$Na^+_{\text{gas}} + Cl^-_{\text{gas}} \xrightarrow{H_2O} Na^+_{\text{aq}} + Cl^-_{\text{aq}}$$

If the heat of hydration, that is, the heat liberated when the ions are hydrated, is sufficient to provide the energy needed to overcome the lattice forces and thus "pull" the ions away from the crystal, the salt will be soluble. In an ideal solution, no hydration (solvation) occurs, and the heat absorbed is that alone that is required to transform the crystals to the liquid state. For this reason, only the heat of fusion ΔH_f is included in the ideal solubility expression, equation (10–11) on page 221.

The heats of solution and solubilities of some salts are shown in Table 10–11. A positive value of ΔH indicates an absorption of heat; a negative value signifies that heat is evolved. The heat of hydration and the lattice energy of sodium chloride are so similar that the process is only slightly endothermic and the temperature has little effect on the solubility. The large heat of solution of silver chloride (large endothermic value) accounts for the insolubility of the salt in water. This is due to the large lattice energy brought about by the great polarizability of the silver ion (p. 87).

Gibbs' phase rule, page 37, is applied to the solubility of a solid in a liquid in the following manner. Since the pressure is ordinarily fixed at 1 atm and hence need not be specified, the rule becomes

$$\mathbf{F} = C - P + 1$$

A subsaturated solution of sodium chloride in water, for example, consists of a single homogeneous phase and two components, salt and water. The number of degrees of freedom is thus $\mathbf{F} = 2 - 1 + 1 = 2$. This means that two variables, both temperature and composition, must be stated to define the system completely. When the solution is saturated with the solute, sodium chloride, and excess solute is present, two phases exist, and the number of degrees of freedom is $\mathbf{F} = 2 - 2 + 1 = 1$. Hence, the conclusion reached by applying the phase rule is that the solubility of sodium chloride in water has a fixed value at any specified temperature. This statement of course is true not only for this specific system but for solubility in general.

Solubility of Slightly Soluble Electrolytes. When slightly soluble electrolytes are dissolved to form saturated solutions, the solubility is described by a special constant, known as the *solubility product*, K_{sp}, of the compound. The solubility products of a number of substances used in pharmacy are listed in Table 10–12.

TABLE 10–11. ***Heats of Solution and Solubility of Some Chlorides***

Compound	Crystal Energy (kcal/mole)	Heat of Hydration (kcal/mole)	ΔH_{soln}* (kcal/mole) (25° C)	Solubility (g/100 g H_2O) (20° C)
AgCl	207	−192	+15.0	1.5×10^{-4}
LiCl	199	−209	−10.0	78.5
NaCl	184	−183	+1.0	36.0
CsCl	152	−147	+5.0	186.5
KCl	167	−164	+3.0	23.8
KBr	161	−156	+5.0	65.0

*A negative value for ΔH, the heat of solution, indicates an evolution of heat (exothermic), and a positive value indicates an absorption of heat (endothermic) during solution.

TABLE 10–12. *Solubility Products of Some Slightly Soluble Electrolytes in Water*

Substance	Solubility Product K_{sp}	Temperature (°C)
Aluminum hydroxide	7.7×10^{-13}	25
Barium carbonate	8.1×10^{-9}	25
Barium sulfate	1×10^{-10}	25
Calcium carbonate	9×10^{-9}	25
Calcium sulfate	6.1×10^{-5}	20
Ferric hydroxide	1×10^{-36}	18
Ferrous hydroxide	1.6×10^{-14}	18
Lead carbonate	3.3×10^{-14}	18
Lead sulfate	1.1×10^{-8}	18
Magnesium carbonate	2.6×10^{-5}	12
Magnesium hydroxide	1.4×10^{-11}	18
Mercurous chloride	2×10^{-18}	25
Mercurous iodide	1.2×10^{-28}	25
Potassium acid tartrate	3.8×10^{-4}	18
Silver bromide	7.7×10^{-13}	25
Silver chloride	1.25×10^{-10}	25
Silver iodide	1.5×10^{-16}	25
Zinc hydroxide	1.8×10^{-14}	18
Zinc sulfide	1.2×10^{-23}	18

Silver chloride is an example of such a slightly soluble salt. The excess solid in equilibrium with the ions in saturated solution at a specific temperature is represented by the equation

$$AgCl_{solid} \rightleftharpoons Ag^+ + Cl^- \qquad (10\text{–}48)$$

and since the salt dissolves only with difficulty and the ionic strength is low, the equilibrium expression may be written in terms of concentrations instead of activities:

$$\frac{[Ag^+][Cl^-]}{[AgCl_{solid}]} = K \qquad (10\text{–}49)$$

Moreover, since the concentration of the solid phase is essentially constant,

$$[Ag^+][Cl^-] = K_{sp} \qquad (10\text{–}50)$$

The equation is only approximate for sparingly soluble salts, or in the presence of other salts, when activities rather than concentrations should be used. It does not hold for salts that are freely soluble in water such as sodium chloride.

As in the case of other equilibrium expressions, the concentration of each ion is raised to a power equal to the number of ions appearing in the formula. Thus, for aluminum hydroxide, $Al(OH)_3$,

$$Al(OH)_{3\ solid} \rightleftharpoons Al^{3+} + 3OH^-$$

$$[Al^{3+}][OH^-]^3 = K_{sp} \qquad (10\text{–}51)$$

Example 10–13. The measured solubility of silver chloride in water at 20° C is 1.12×10^{-5} mole/liter. This is also the concentration of the silver ion and the chloride ion, since silver chloride, being a strong electrolyte, is nearly completely dissociated. Calculate the solubility product of this salt.

$$K_{sp} = (1.12 \times 10^{-5}) \times (1.12 \times 10^{-5})$$
$$= 1.25 \times 10^{-10}$$

If an ion in common with AgCl, that is, Ag^+ or Cl^-, is added to a solution of silver chloride, the equilibrium is altered. The addition of sodium chloride, for example, increases the concentration of chloride ions so that momentarily

$$[Ag^+][Cl^-] > K_{sp}$$

and some of the AgCl precipitates from the solution until the equilibrium $[Ag^+][Cl^-] = K_{sp}$ is reestablished. Hence, the result of adding a *common ion* is to *reduce* the solubility of a slightly soluble electrolyte, unless, of course, the common ion forms a complex with the salt whereby the net solubility may be increased.

Example 10–14. What is the solubility x of silver chromate in moles/liter in an aqueous solution containing 0.04 *M* silver nitrate? The solubility of silver chromate in water is 8×10^{-5} and its solubility product is 2.0×10^{-12}. The dissociation of silver chromate may be represented as

$$Ag_2CrO_4 \rightleftharpoons 2Ag^+ + CrO_4^{=}$$

$$K_{sp} = 2.0 \times 10^{-12} = (2x + 0.04)^2 x = 4x^3 + 0.16x^2 + 0.0016x$$

Since the terms in x^3 and x^2 are so small that they may be neglected, the result is

$$x = [Ag_2CrO_4] = \frac{2.0 \times 10^{-12}}{1.6 \times 10^{-3}} = 1.25 \times 10^{-9} \text{ mole/liter}$$

Salts having no ion in common with the slightly soluble electrolyte produce an effect opposite to that of a common ion: at moderate concentration, they *increase* rather than decrease the solubility because they lower the activity coefficient. As mentioned previously, the exact equilibrium expression involves activities. For silver chloride,

$$K_{sp} = a_{Ag^+} a_{Cl^-} \qquad (10\text{–}52)$$

Since activities may be replaced by the product of concentrations and activity coefficients,

$$K_{sp} = [Ag^+][Cl^-]\gamma_{Ag^+}\gamma_{Cl^-} = [Ag^+][Cl^-]\gamma_{\pm}^2$$

$$\frac{K_{sp}}{\gamma_{\pm}^2} = [Ag^+][Cl^-]$$

and

$$\text{Solubility} = [Ag^+] = [Cl^-] = \frac{\sqrt{K_{sp}}}{\gamma_{\pm}} \qquad (10\text{–}53)$$

Example 10–15. Calculate the solubility of silver chloride in a 0.1-*M* solution of ammonium sulfate. The ionic strength of 0.1 *M* $(NH_4)_2SO_4$ is 0.3, and the activity coefficient of a 1:1 electrolyte such as silver chloride at this ionic strength is about 0.70.

$$\text{Solubility} = \frac{\sqrt{1.2 \times 10^{-10}}}{0.70}$$
$$= 1.6 \times 10^{-5} \text{ mole/liter}$$

Therefore, the addition of an electrolyte that does not have an ion in common with AgCl causes an increase in the solubility of silver chloride.

Other useful conclusions may be reached by use of the solubility product principle. If the pharmacist wishes to prevent precipitation of a slightly soluble salt in water,

he may add some substance that will tie up and reduce the concentration of one of the ions. More of the salt will then pass from the undissolved to the dissolved state until the solubility product constant is reached and the equilibrium is reestablished. For example, if the ferric ion in a solution of the slightly soluble base, $Fe(OH)_3$, can be combined by complex formation with sodium citrate, more Fe^{3+} will pass into solution so as to keep K_{sp} constant. In this manner, the solubility of iron compounds is increased by citrates and similar compounds.

Solubility of Weak Electrolytes. Many important drugs belong to the class of weak acids and bases. They react with strong acids and bases and, within definite ranges of pH, exist as ions that are ordinarily soluble in water.

Although carboxylic acids containing more than five carbons are relatively insoluble in water, they react with dilute sodium hydroxide, carbonates, and bicarbonates to form soluble salts. The fatty acids containing more than 10 carbon atoms form soluble soaps with the alkali metals and insoluble soaps with other metal ions. They are soluble in solvents having low dielectric constants; for example, oleic acid ($C_{17}H_{33}COOH$) is insoluble in water but is soluble in alcohol and in ether.

Hydroxy acids, such as tartaric and citric acids, are quite soluble in water since they are solvated through their hydroxyl groups. The potassium and ammonium bitartrates are not very soluble in water, although most alkali metal salts of tartaric acid are soluble. Sodium citrate is used sometimes to dissolve water-insoluble acetylsalicylic acid since the soluble acetylsalicylate ion is formed in the reaction. The citric acid that is produced is also soluble in water, but the practice of dissolving aspirin by this means is questionable since the acetylsalicylate is also hydrolyzed rapidly.

Aromatic acids react with dilute alkalies to form water-soluble salts, but they may be precipitated as the free acids if stronger acidic substances are added to the solution. They may also be precipitated as heavy metal salts should heavy metal ions be added to the solution. Benzoic acid is soluble in sodium hydroxide solution, alcohol, and fixed oils. Salicylic acid is soluble in alkalies and in alcohol. The OH group of salicyclic acid cannot contribute to the solubility since it is involved in an intramolecular hydrogen bond (p. 24).

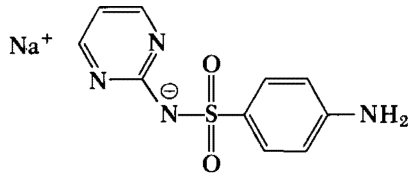
Phenol is weakly acidic and only slightly soluble in water but is quite soluble in dilute sodium hydroxide solution.

$$C_6H_5OH + NaOH \rightarrow C_6H_5O^- + Na^+ + H_2O$$

Phenol is a weaker acid than H_2CO_3 and is thus displaced and precipitated by CO_2 from its dilute alkali solution. For this reason, carbonates and bicarbonates cannot increase the solubility of phenols in water.

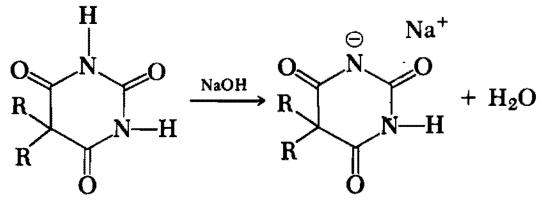
Many organic compounds containing a basic nitrogen atom in the molecule are important in pharmacy. These include the alkaloids, sympathomimetic amines, antihistamines, local anesthetics, and others. Most of these weak electrolytes are not very soluble in water but are soluble in dilute solutions of acids; such compounds as atropine sulfate and tetracaine hydrochloride are formed by reacting the basic compounds with acids. Addition of an alkali to a solution of the salt of these compounds precipitates the free base from solution if the solubility of the base in water is low.

The aliphatic nitrogen of the sulfonamides is sufficiently negative so that these drugs act as slightly soluble weak acids rather than as bases. They form water-soluble salts in alkaline solution by the following mechanism. The oxygens of the sulfonyl ($—SO_2—$) group withdraw electrons, and the resulting electron deficiency of the sulfur atom results in the electrons of the N:H bond being held more closely to the nitrogen atom. The hydrogen therefore is bound less firmly, and, in alkaline solution, the soluble sulfonamide anion is readily formed.



Sulfadiazine anion in a sodium hydroxide solution

The sodium salts of the sulfonamides are precipitated from solution by the addition of a strong acid, or by a salt of a strong acid and a weak base such as ephedrine hydrochloride.



Reaction of barbituric acid derivative with sodium hydroxide to form the anion of the weak acid

The barbiturates, like the sulfonamides, are weak acids because the electronegative oxygen of each acidic carbonyl group tends to withdraw electrons and to create a positive carbon atom. The carbon in turn attracts electrons from the nitrogen group and causes the hydrogen to be held less firmly. Thus, in sodium hydroxide solution, the hydrogen is readily lost, and the molecule exists as a soluble anion of the weak acid. Butler et al.[38] have demonstrated that, in highly alkaline solutions, the second hydrogen ionizes. The pK_1 for phenobarbital is 7.41 and the pK_2 is 11.77. Although the barbiturates are soluble in alkalies, they are precipitated as the free acids when a stronger acid is added and the pH of the solution is lowered.

Calculating the Solubility of Weak Electrolytes as Influenced by pH. From what has been said about the effects of acids and bases on solutions of weak electrolytes, it becomes evident that the solubility of weak electrolytes is strongly influenced by the pH of the solution. For example, a 1% solution of phenobarbital sodium is soluble at pH values high in the alkaline range. The soluble ionic form is converted into molecular phenobarbital as the pH is lowered, and below 8.3, the drug begins to precipitate from solution at room temperature. On the other hand, alkaloidal salts such as atropine sulfate begin to precipitate as the pH is elevated.

To ensure a clear homogeneous solution and maximum therapeutic effectiveness, the preparations should be adjusted to an optimum pH. The pH below which the salt of a weak acid, sodium phenobarbital, for example, begins to precipitate from aqueous solution is readily calculated in the following manner.

Representing the free acid form of phenobarbital as HP and the soluble ionized form as P^-, the equilibria in a saturated solution of this slightly soluble weak electrolyte are

$$HP_{solid} \rightleftharpoons HP_{sol} \qquad (10-54)$$

$$HP_{sol} + H_2O \rightleftharpoons H_3O^+ + P^- \qquad (10-55)$$

Since the concentration of the un-ionized form in solution HP_{sol} is essentially constant, the equilibrium constant for the solution equilibrium, equation (10–54) is

$$S_o = [HP]_{sol} \qquad (10-56)$$

and the constant for the acid–base equilibrium, equation (10–55), is

$$K_a = \frac{[H_3O^+][P^-]}{[HP]} \qquad (10-57)$$

or

$$[P^-] = K_a \frac{[HP]}{[H_3O^+]} \qquad (10-58)$$

in which the subscript "sol" has been deleted from $[HP]_{sol}$, since no confusion should result from this omission.

The total solubility S of phenobarbital consists of the concentration of the undissociated acid [HP] and the conjugate base or ionized form $[P^-]$:

$$S = [HP] + [P^-] \qquad (10-59)$$

Substituting S_o for [HP] from equation (10–56) and the expression from equation (10–58) for $[P^-]$ yields

$$S = S_o + K_a \frac{S_o}{[H_3O^+]} \qquad (10-60)$$

$$S = S_o \left(1 + \frac{K_a}{[H_3O^+]}\right) \qquad (10-61)$$

Equation (10–61) has been expressed in various forms by Krebs and Speakman[39] Albert,[40] Higuchi,[41] Kostenbauder et al.,[42] and others.

When the electrolyte is weak and does not dissociate appreciably, the solubility of the acid in water or acidic solutions is S_o = [HP], which, for phenobarbital is approximately 0.005 mole/liter, in other words, 0.12%.

The solubility equation may be written in logarithmic form, beginning with equation (10–60). By rearrangement, we obtain

$$(S - S_o) = K_a \frac{S_o}{[H_3O^+]}$$

$$\log (S - S_o) = \log K_a + \log S_o - \log [H_3O^+]$$

and finally

$$pH_p = pK_a + \log \frac{S - S_o}{S_o} \qquad (10-62)$$

in which pH_p is the pH below which the drug separates from solution as the undissociated acid.

In pharmaceutical practice, a drug such as phenobarbital is usually added to an aqueous solution in the soluble salt form. Of the initial quantity of salt, sodium phenobarbital, that can be added to a solution of a certain pH, some of it is converted into the free acid HP and some remains in the ionized form P^- (equation (10–59). The amount of salt that can be added initially before the solubility [HP] is exceeded is therefore equal to S. As seen from equation (10–62), pH_p depends on the initial molar concentration S of salt added, the molar solubility of the undissociated acid S_o, and the pK_a. Equation (10–62) has been used to determine the pK_a of sulfonamides and other drugs (see references 49 to 52). Solubility and pH data may also be used to obtain the pK_1 and pK_2 values of dibasic acids as suggested by Zimmerman[43] and by Blanchard et al.[44]

Example 10–16. Below what pH will free phenobarbital begin to separate from a solution having an initial concentration of 1 g of sodium phenobarbital per 100 mL at 25° C? The molar solubility S_o of phenobarbital is 0.0050 and the pK_a = 7.41 at 25° C. The secondary dissociation of phenobarbital, referred to previously, may ordinarily be disregarded. The molecular weight of sodium phenobarbital is 254.

The molar concentration of salt initially added is

$$\frac{\text{g/liter}}{\text{mol. wt.}} = \frac{10}{254} = 0.039 \text{ mole/liter}$$

$$pH_p = 7.41 + \log \frac{(0.039 - 0.005)}{0.005} = 8.24$$

An analogous derivation may be carried out to obtain the equation for the solubility of a weak base as a function of the pH of a solution. The expression is

$$pH_p = pK_w - pK_b + \log \frac{S_o}{S - S_o} \qquad (10-63)$$

in which S is the concentration of the drug initially added as the salt and S_o is the molar solubility of the free base in water. Here pH_p is the pH *above* which the

drug begins to precipitate from solution as the free base.

The Influence of Solvents on the Solubility of Drugs. Weak electrolytes may behave like strong electrolytes and like nonelectrolytes in solution. When the solution is of such a pH that the drug is entirely in the ionic form, it behaves as a solution of a strong electrolyte and solubility does not constitute a serious problem. However, when the pH is adjusted to a value at which un-ionized molecules are produced in sufficient concentration to exceed the solubility of this form, precipitation occurs. In this discussion, we are now interested in the solubility of nonelectrolytes and the undissociated molecules of weak electrolytes. The solubility of undissociated phenobarbital in various solvents is discussed here because it has been studied to some extent by pharmaceutical investigators.

Frequently a solute is more soluble in a mixture of solvents than in one solvent alone. This phenomenon is known as *cosolvency*, and the solvents that, in combination, increase the solubility of the solute are called *cosolvents*. Approximately 1 g of phenobarbital is soluble in 1000 mL of water, in 10 mL of alcohol, in 40 mL of chloroform, and in 15 mL of ether at 25° C. The solubility of phenobarbital in water–alcohol–glycerin mixtures is plotted on a semilogarithm grid in Figure 10–7 from the data of Krause and Cross.[45]

By drawing lines parallel to the abscissa in Figure 10–7 at a height equivalent to the required phenobarbital concentration, it is a simple matter to obtain the relative amounts of the various combinations of alcohol, glycerin and water needed to achieve solution. For example, at 22% alcohol, 40% glycerin, and the remainder water (38%), 1.5% *w/v* of phenobarbital is dissolved, as seen by following the vertical and horizontal lines drawn on Figure 10–7.

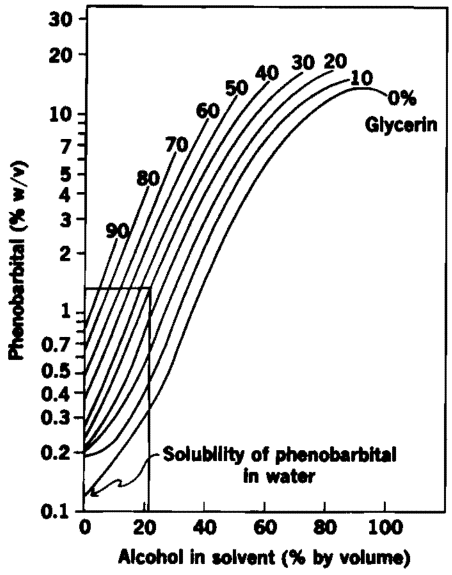


Fig. 10–7. The solubility of phenobarbital in a mixture of water, alcohol, and glycerin at 25° C. The vertical axis is a logarithmic scale representing the solubility of phenobarbital in g/100 mL. (After G. M. Krause and J. M. Cross, J. Am. Pharm. Assoc., Sci. Ed. 40, 137, 1951, reproduced with permission of the copyright owner.)

Combined Effect of pH and Solvents. The solvent affects the solubility of a weak electrolyte in a buffered solution in two ways:

1. The addition of alcohol to a buffered aqueous solution of a weak electrolyte increases the solubility of the un-ionized species by adjusting the polarity of the solvent to a more favorable value.
2. Being less polar than water, alcohol decreases the dissociation of a weak electrolyte, and the solubility of the drug goes down as the dissociation constant is decreased (pK_a is increased).

Stockton and Johnson[46] and Higuchi et al.[47] studied the effect of an increase of alcohol concentration on the dissociation constant of sulfathiazole, and Edmonson and Goyan[48] investigated the effect of alcohol on the solubility of phenobarbital.

Agarwal and Blake[49] and Schwartz et al.[50] determined the solubility of phenytoin as a function of pH and alcohol concentration in various buffer systems and calculated the apparent dissociation constant. Kramer and Flynn[51] examined the solubility of hydrochloride salts of organic bases as a function of pH, temperature, and solvent composition. They described the determination of the pK_a of the salt from the solubility profile at various temperatures and in several solvent systems. Chowhan[52] measured and calculated the solubility of the organic carboxylic acid, naproxen, and its sodium, potassium, calcium, and magnesium salts. The observed solubilities were in excellent agreement with the pH-solubility profiles based on equation (10–62).

The results of Edmonson and Goyan[48] are shown in Figure 10–8, where one observes that the pK_a of phenobarbital, 7.41, is raised to 7.92 in a hydroalcoholic solution containing 30% by volume of alcohol. Furthermore, as can be seen in Figure 10–7 the solubility S_0 of un-ionized phenobarbital is increased from 0.12 g/100 mL or 0.005 *M* in water to 0.64% or 0.0276 *M* in a 30%

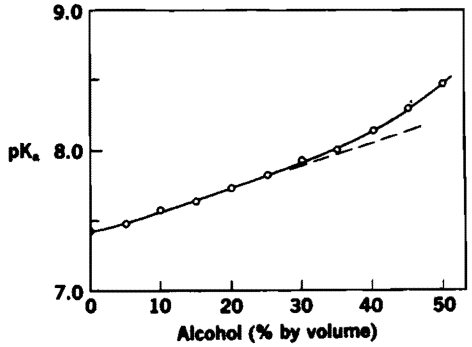


Fig. 10–8. The influence of alcohol concentration on the dissociation constant of phenobarbital. (After T. D. Edmonson and J. E. Goyan, J. Am. Pharm. Assoc., Sci. Ed. 47, 810, 1958, reproduced with permission of the copyright owner.)

alcoholic solution. The calculation of solubility as a function of pH involving these results is illustrated in the following example.

Example 10–17. What is the minimum pH required for the complete solubility of the drug in a stock solution containing 6 g of phenobarbital sodium in 100 mL of a 30% by volume alcoholic solution? From equation (10–62):

$$pH_p = 7.92 + \log \frac{(0.236 - 0.028)}{0.028}$$

$$pH_p = 7.92 + 0.87 = 8.79$$

For comparison, the minimum pH for complete solubility of phenobarbital in an aqueous solution containing no alcohol is computed using equation (10–62).

$$pH_p = 7.41 + \log \frac{(0.236 - 0.005)}{0.005} = 9.07$$

From the calculations of *Example 10–17*, it is seen that although the addition of alcohol increases the pK_a, it also increases the solubility of the un-ionized form of the drug over that found in water sufficiently so that the pH may be reduced somewhat before precipitation occurs.

Equations (10–62) and (10–63) can be made more exact if activities are used instead of concentrations to account for interionic attraction effects. This refinement, however, is seldom required for practical work, in which the values calculated from the approximate equations just given serve as satisfactory estimates.

Influence of Surfactants. Weakly acidic and basic drugs may be brought into solution by the solubilizing action of surface-active agents. Solubilization of drugs in micelles is discussed as a colloidal phenomenon on pages 410 to 414, but it is appropriate here to describe the influence of surface-active agents on the solubility of drugs in quantitative terms along with the solubilizing effects of solvents, such as glycerin and ethanol.

Rippie et al.[53] investigated the micellar solubilization of weak electrolytic drugs by aqueous solutions of the nonionic surfactant polysorbate 80. The terminology of Rippie and associates is used in the following description of the theory.

The total solubility D_T of an acidic drug is expressed as the sum of the concentrations of species in solution:

$$D_T = (D) + (D^-) + [D] + [D^-] \qquad (10–64)$$

in which (D) and (D^-) are nonionized acid and ionized acid, respectively, not in the micelles; $[D]$ and $[D^-]$ are nonionized and ionized acid, respectively, present in the micelles. The drug is considered to partition between the aqueous solution and the surfactant micelles according to the expression

$$K' = \frac{[D]_0}{(D)_0} \qquad (10–65)$$

for the nonionized acid, and

$$K'' = \frac{[D^-]_0}{(D^-)_0} \qquad (10–66)$$

for the ionized acid.

The subscript $_0$ represents concentrations expressed relative to individual phase volumes rather than the total volume of the system. In terms of total volume, equations (10–65) and (10–66) become

$$K' = \frac{[D][1 - (M)]}{(D)(M)} \qquad (10–67)$$

$$K'' = \frac{[D^-][1 - (M)]}{(D^-)(M)} \qquad (10–68)$$

The concentration term, (M), is the volume fraction of surfactant as micelles in solution; the amount in true solution would be small and can be neglected. Now, $1 - (M)$ can be set equal to unity in equations (10–67) and (10–68), yielding

$$[D] = K' (D)(M) \qquad (10–69)$$

$$[D^-] = K'' (D^-)(M) \qquad (10–70)$$

The total drug solubility, D_T^*, in a solution at a definite pH and in the absence of the surfactant ($D_T^* \equiv S$ in equation (10–59)) is defined as

$$D_T^* = (D) + (D^-) \qquad (10–71)$$

The fraction, $(D)/D_T^*$, of un-ionized drug in the aqueous phase is

$$\frac{(D)}{D_T^*} = \frac{(H^+)}{K_a + (H^+)} \qquad (10–72)$$

or

$$D_T^* = (D) \frac{K_a + (H^+)}{(H^+)} \qquad (10–73)$$

Using the relationships just given, Rippie et al.[53] obtained the expression

$$\frac{D_T}{D_T^*} = 1 + (M) \left[\frac{(H^+)K' + K_a K''}{K_a + (H^+)}\right] \qquad (10–74)$$

in which D_T is total drug solubility in the presence of surfactant, according to equation (10–64). With equation (10–74), one may calculate total drug solubility in a solution of a definite pH and having a volume fraction (M) of surfactant present in the form of micelles.

Example 10–18. Calculate the solubility of sulfisoxazole at 25° C in (*a*) a pH 6.0 buffer and (*b*) a pH 6.0 buffer containing 4% by volume (i.e., 0.04 volume fraction) polysorbate 80 (Tween 80). The aqueous solubility of nonionized sulfisoxazole at 25° C is 0.15 g/liter, its $K_a = 7.60 \times 10^{-6}$, and the apparent partition coefficient of the molecular drug, K', and its anion, K'', between polysorbate 80 micelles and water are 79 and 15, respectively. (K' and K'' are dimensionless constants.)

(*a*) From equation (10–73), the total drug solubility at pH 6 in the absence of the surfactant is

$$D_T^* = 0.15 \text{ g/liter} \left[\frac{(7.6 \times 10^{-6}) \text{ moles/liter} + (1.0 \times 10^{-6}) \text{ moles/liter}}{(1.0 \times 10^{-6}) \text{ moles/liter}}\right] = 1.29 \text{ g/liter}$$

(*b*) From equation (10–74), the total solubility of sulfisoxazole in a pH 6 buffer in the presence of 4% Tween 80 is

$$D_T = (1.29)\left\{1 + (0.04) \times \left[\frac{(1 \times 10^{-6})(79) + (7.6 \times 10^{-6})(15)}{(7.6 \times 10^{-6}) + (1 \times 10^{-6})}\right]\right\}$$

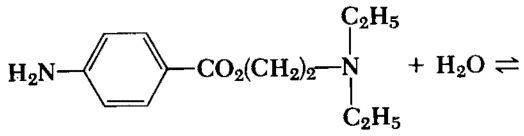
$$D_T = 2.45 \text{ g/liter}$$

The presence of the surfactant has almost doubled the concentration of the drug in solution.

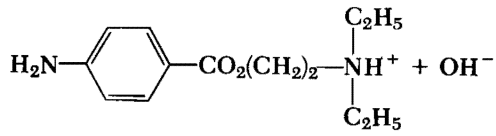
The total solubility of a basic drug corresponding to that for an acidic drug, equation (10–64), in a solution containing a micellar surfactant, is

$$D_T = (D^+) + (D) + [D^+] + [D] \qquad (10\text{–}75)$$

in which D^+ is the cationic acid species and D is the nonionized base. The ionization of a molecular (nonionic) base, procaine, is represented as



(R_3N)
Procaine
(nonionic base)



(R_3NH^+)
Procaine cation
(ionic acid conjugate to
Procaine base) (10–76)

The dissociation equilibrium for this reaction is written

$$K_b = \frac{[R_3NH^+][OH^-]}{[R_3N]} \qquad (10\text{–}77)$$

The dissociation also may be written in terms of the procaine cation to obtain the acid dissociation constant, K_a,

$$R_3NH^+ + H_2O \rightleftharpoons R_3N + H_3O^+ \qquad (10\text{–}78)$$

$$K_a = \frac{[R_3N][H_3O^+]}{[R_3NH^+]} \qquad (10\text{–}79)$$

As noted earlier in the text, the following relationship holds between a molecular base and its cationic acid (also between a molecular acid and its anionic base):

$$K_aK_b = K_w \qquad (10\text{–}80)$$

and

$$pK_a + pK_b = pK_w \qquad (10\text{–}81)$$

For a molecular base such as procaine,

$$(D) = D_T^* \left[\frac{K_a}{K_a + (H^+)}\right] \qquad (10\text{–}82)$$

$$(D^+) = D_T^* \left[\frac{H^+}{K_a + (H^+)}\right] \qquad (10\text{–}83)$$

and

$$\frac{D_T}{D_T^*} = 1 + (M)\left[\frac{K_aK' + (H^+)K''}{K_a + (H^+)}\right] \qquad (10\text{–}84)$$

in which (D) is the free acid not in the micelle, (D^+) is the cationic acid, conjugate to the molecular base, not in the micelle, and the other terms have the same meanings as defined earlier. The expressions permit the calculation of solubilization of a weakly basic drug, such as procaine, in aqueous solutions of a micellar solubilizing agent such as polysorbate 80.

Example 10–19. The aqueous solubility of procaine base at 25° C is 5 g/liter, its K_a is 1.4×10^{-9}, and the apparent partition coefficient for the molecular base is $K' = 30$; for its cationic acid, $K'' = 7.0$. Calculate the solubility of procaine in a pH 7.40 buffer containing 3% (*w/v*) polysorbate 80.

(*a*)

$$D_T^* = (D)\left[\frac{K_a + (H^+)}{K_a}\right] = (5.0)\left[\frac{(1.4 \times 10^{-9}) + (3.98 \times 10^{-8})}{(1.40 \times 10^{-9})}\right]$$

$$= 147.2 \text{ g/liter}$$

(*b*)

$$D_T = 147.2\left\{1 + (0.03) \times \left[\frac{(1.4 \times 10^{-9})(30) + (3.98 \times 10^{-8})(7)}{(1.40 \times 10^{-9}) + (3.98 \times 10^{-8})}\right]\right\}$$

$$= 181.6 \text{ g/liter}$$

What is the fraction of the drug in the aqueous phase and the fraction in the micelles?

$$\frac{\text{Total drug in aqueous phase, } D_T^*}{\text{Total drug in aqueous phase and micelles, } D_T} = \frac{147.2 \text{ g/liter}}{181.6 \text{ g/liter}} = 0.81$$

Thus, the fraction 0.81 of procaine exists in the aqueous phase, and the remainder, 0.19, resides in the micelles. The solubility of procaine is increased by one quarter over that in aqueous buffer owing to the surfactant micelles.

Influence of Complexation in Multicomponent Systems. Many liquid pharmaceutical preparations consist of more than a single drug in solution. Fritz et al.[54] have shown that when several drugs together with pharmaceutical adjuncts interact in solution to form insoluble complexes, simple solubility profiles of individual drugs cannot be used to predict solubilities in mixtures of ingredients. Instead, the specific multicomponent systems must be studied to estimate the complicating effects of species interactions.

Influence of Other Factors on the Solubility of Solids. The size and shape of small particles (those in the micrometer range) also affect solubility. Solubility increases with decreasing particle size according to the approximate equation

$$\log \frac{s}{s_0} = \frac{2\gamma V}{2.303RTr} \qquad (10\text{–}85)$$

in which s is the solubility of the fine particles; s_0 is the solubility of the solid consisting of relatively large particles; γ is the surface tension of the particles, which, for solids, unfortunately, is extremely difficult to obtain; V is the molar volume (volume in cm^3 per mole of particles); r is the final radius of the particles in cm;

R is the gas constant (8.314×10^7 erg/deg mole); and T is the absolute temperature. The equation may be used for solid or liquid particles such as those in suspensions or emulsions. The following example is taken from the book by Hildebrand and Scott.[55]

Example 10–20. A solid is to be comminuted so as to increase its solubility by 10%, i.e., s/s_o is to become 1.10. What must be the final particle size, assuming that the surface tension of the solid is 100 dynes/cm and the volume per mole is 50 cm^3? The temperature is 27° C.

$$r = \frac{2 \times 100 \times 50}{2.303 \times 8.314 \times 10^7 \times 300 \times 0.0414}$$
$$= 4.2 \times 10^{-6} \text{ cm} = 0.042 \ \mu\text{m}$$

The effects of particle size on the solubility of a solid have been reviewed in some detail by May and Kolthoff,[56] and the interested reader should refer to their report.

The configuration of a molecule and the kind of arrangement in the crystal also has some influence on solubility, and a symmetric particle may be less soluble than an unsymmetric one. This is because solubility depends in part on the work required to separate the particles of the crystalline solute. The molecules of the amino acid α-alanine form a compact crystal with high lattice energy and consequently low solubility. The molecules of α-amino-*n*-butyric acid pack less efficiently in the crystal, partly because of the projecting side chains, and the crystal energy is reduced. Consequently, α-amino-*n*-butyric acid has a solubility of 1.80 moles/liter and α-alanine only 1.66 moles/liter in water at 25° C, although the hydrocarbon chain of α-amino-*n*-butyric acid is the longer of the two compounds.

DISTRIBUTION OF SOLUTES BETWEEN IMMISCIBLE SOLVENTS

If an excess of liquid or solid is added to a mixture of two immiscible liquids, it will distribute itself between the two phases so that each becomes saturated. If the substance is added to the immiscible solvents in an amount insufficient to saturate the solutions, it will still become distributed between the two layers in a definite concentration ratio.

If C_1 and C_2 are the equilibrium concentrations of the substance in solvent$_1$ and solvent$_2$, the equilibrium expression becomes

$$\frac{C_1}{C_2} = K \qquad (10\text{–}86)$$

The equilibrium constant K is known as the *distribution ratio, distribution coefficient,* or *partition coefficient.* Equation (10–86), which is known as the *distribution law,* is strictly applicable only in dilute solutions in which activity coefficients may be neglected.

Example 10–21. When boric acid is distributed between water and amyl alcohol at 25° C, the concentration in water was found to be 0.0510 mole/liter and in amyl alcohol it was found to be 0.0155 mole/liter. What is the distribution coefficient?

$$K = \frac{C_{H_2O}}{C_{alc}} = \frac{0.0510}{0.0155} = 3.29$$

No convention has been established with regard to whether the concentration in the water phase or in the organic phase should be placed in the numerator. Therefore, the result may also be expressed as

$$K = \frac{C_{alc}}{C_{H_2O}} = \frac{0.0155}{0.0510} = 0.304$$

One should always specify in which of these two ways the distribution constant is being expressed.

A knowledge of partition is important to the pharmacist, for the principle is involved in several areas of current pharmaceutical interest. These include preservation of oil–water systems, drug action at nonspecific sites, and the absorption and distribution of drugs throughout the body. Certain aspects of these topics are discussed in the following sections.

Effect on Partition of Ionic Dissociation and Molecular Association. The solute may exist partly or wholly as associated molecules in one of the phases or it may dissociate into ions in either of the liquid phases. The distribution law applies only to the concentration of the species common to both phases, namely, the *monomer* or simple molecules of the solute.

Consider the distribution of benzoic acid between an oil phase and a water phase. When it is neither associated in the oil nor dissociated into ions in the water, equation (10–86) can be used to compute the distribution constant. When association and dissociation occur, however, the situation becomes more complicated. The general case in which benzoic acid associates in the oil phase and dissociates in the aqueous phase is shown schematically in Figure 10–9.

Two cases will be treated. *First,* according to Garrett and Woods,[57] benzoic acid is considered to be distributed between the two phases, peanut oil and water. Although benzoic acid undergoes dimerization (association to form two molecules) in many nonpolar solvents, it does not associate in peanut oil. It ionizes in water to

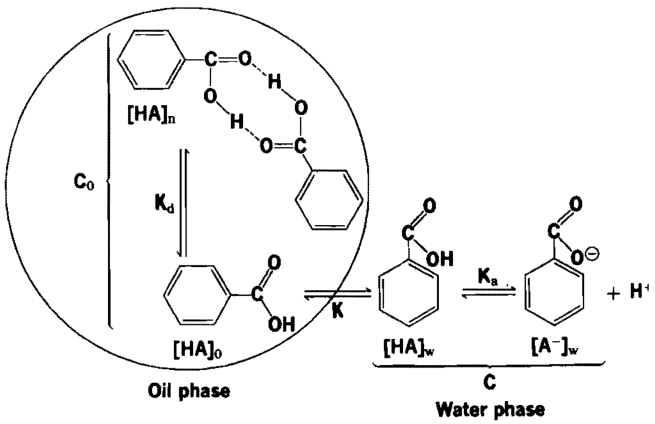


Fig. 10–9. Schematic representation of the distribution of benzoic acid between a water and an oil phase. (The oil phase is depicted as a magnified oil droplet in an oil-in-water emulsion.)

a degree, however, depending on the pH of the solution. Therefore, in Figure 10–9 for the case under consideration, C_o, the total concentration of benzoic acid in the oil phase, is equal to $[HA]_o$, the monomer concentration in the oil phase, since association does not occur in peanut oil.

The species common to both the oil and water phases are the unassociated and undissociated benzoic acid molecules. The distribution is expressed as

$$K = \frac{[HA]_o}{[HA]_w} = \frac{C_o}{[HA]_w} \qquad (10-87)$$

in which K is the *true distribution coefficient* $[HA]_o = C_o$ is the molar concentration of the simple benzoic acid molecules in the oil phase, and $[HA]_w$ is the molar concentration of the undissociated acid in the water phase.

The total acid concentration obtained by analysis of the aqueous phase is

$$C_w = [HA]_w + [A^-]_w \qquad (10-88)$$

and the experimentally observed or *apparent distribution coefficient* is

$$K' = \frac{[HA]_o}{[HA]_w + [A^-]_w} = \frac{C_o}{C_w} \qquad (10-89)$$

As seen in Figure 10–9, the observed distribution coefficient depends on two equilibria: the distribution of the undissociated acid between the immiscible phases as expressed in equation (10–87), and the species distribution of the acid in the aqueous phase, which depends on the hydrogen ion concentration $[H_3O^+]$ and the dissociation constant K_a of the acid.

$$K_a = \frac{[H_3O^+][A^-]_w}{[HA]_w} \qquad (10-90)$$

Association of benzoic acid in peanut oil does not occur, and K_d (the equilibrium constant for dissociation of associated benzoic acid into monomer in the oil phase) may be neglected in this case.

Given these equations and the fact that the concentration C of the acid in the aqueous phase before distribution, assuming equal volumes of the two phases, is*

$$C \doteq C_o + C_w \qquad (10-91)$$

one arrives at the combined result,†

$$\frac{K_a + [H_3O^+]}{C_w} = \frac{K_a}{C} + \frac{K+1}{C}[H_3O^+] \qquad (10-92)$$

Expression (10–92) is a linear equation of the form, $y = a + bx$, and therefore a plot of $(K_a + [H_3O^+])/C_w$ against $[H_3O^+]$ yields a straight line with a slope $b = (K + 1)/C$ and an intercept $a = K_a/C$. The true distribution coefficient K can thus be obtained over the range of hydrogen ion concentration considered. Alternatively, the true distribution constant could be obtained according to equation (10–87) by analysis of the oil phase and of the water phase at a sufficiently low pH (≅2.0) at which the acid would exist completely in the un-ionized form. One of the advantages of equation (10–92), however, is that the oil phase need not be analyzed; only the hydrogen ion concentration and C_w, the total concentration remaining in the aqueous phase at equilibrium, need be determined.

Example 10–22. According to Garrett and Woods,[57] the plot of $(K_a + [H_3O^+])/C_w$ against $[H_3O^+]$ for benzoic acid distributed between equal volumes of peanut oil and a buffered aqueous solution yielded a slope $b = 4.16$ and an intercept $a = 4.22 \times 10^{-5}$. The K_a of benzoic acid is 6.4×10^{-5}. Compute the true partition coefficient, K, and compare it with the value $K = 5.33$ obtained by the authors.

$$b = (K + 1)/C$$

or

$$K = bC - 1$$

---

*The meaning of C in equation (10–91) is understood readily by considering a simple illustration. Suppose one begins with 1 liter of oil and 1 liter of water, and after benzoic acid has been distributed between the two phases, the concentration C_o of benzoic acid in the oil is 0.01 mole/liter and the concentration C_w of benzoic acid in the aqueous phase is 0.01 mole/liter. Accordingly, there is 0.02 mole/2 liter or 0.01 mole of benzoic acid per liter of total mixture after distribution equilibrium has been attained. Equation (10–91) gives

$$C = C_o + C_w = 0.01 \text{ mole/liter} + 0.01 \text{ mole/liter}$$
$$= 0.02 \text{ mole/liter}$$

The concentration C obviously is not the total concentration of the acid in the mixture at equilibrium but, rather, twice this value. C is therefore seen to be the concentration of benzoic acid in the water phase (or the oil phase) *before* the distribution is carried out.

†Equation (10–92) is obtained as follows. Substituting for $[A^-]_w$ from equation (10–90) into equation (10–89) gives

$$K' = \frac{[HA]_o}{[HA]_w + \dfrac{K_a[HA]_w}{[H_3O^+]}} = \frac{[HA]_o[H_3O^+]}{[HA]_w(K_a + [H_3O^+])} \qquad (a)$$

Then $[HA]_w$ from equation (10–87) is substituted into (*a*) to eliminate $[HA]_o$ from the equation:

$$K' = \frac{[HA]_o[H_3O^+]}{[HA]_o/K(K_a + [H_3O^+])} = \frac{K[H_3O^+]}{K_a + [H_3O^+]} \qquad (b)$$

The apparent distribution constant is eliminated by substituting equation (*b*) into equation (10–89) to give

$$\frac{K[H_3O^+]}{K_a + [H_3O^+]} = \frac{C_o}{C_w}$$

or

$$C_o = \frac{K[H_3O^+]C_w}{K_a + [H_3O^+]} \qquad (c)$$

C_o is eliminated by substituting equation (*c*) into equation (10–91):

$$C = \frac{K[H_3O^+]C_w}{K_a + [H_3O^+]} + C_w$$
$$= \frac{K[H_3O^+]C_w + (K_a + [H_3O^+])C_w}{K_a + [H_3O^+]} \qquad (d)$$

Rearranging equation (*d*) gives the final result:

$$\frac{K_a + [H_3O^+]}{C_w} = \frac{[H_3O^+](K+1) + K_a}{C}$$

Since

$$a = K_a/C \text{ or } C = \frac{K_a}{a}$$

the expression becomes

$$K = \frac{bK_a}{a} - 1 = \frac{bK_a - a}{a}$$

and

$$K = \frac{(4.16 \times 6.4 \times 10^{-5}) - 4.22 \times 10^{-5}}{4.22 \times 10^{-5}} = 5.31$$

Second, let us now consider the case in which the solute is associated in the organic phase and exists as simple molecules in the aqueous phase. If benzoic acid is distributed between benzene and acidified water, it exists mainly as associated molecules in the benzene layer and as undissociated molecules in the aqueous layer.

The equilibrium between simple molecules HA and associated molecules $(HA)_n$ in benzene is

$$\underset{\text{Associated molecules}}{(HA)_n} \rightleftharpoons \underset{\text{Simple molecules}}{n(HA)}$$

and the equilibrium constant expressing the dissociation of associated molecules into simple molecules in this solvent is

$$K_d = \frac{[HA]_o^n}{[(HA)_n]} \qquad (10-93)$$

or

$$[HA]_o = \sqrt[n]{K_d}\sqrt[n]{[(HA)_n]} \qquad (10-94)$$

Since benzoic acid exists predominantly in the form of double molecules in benzene, C_o may replace $[(HA)_2]$ where C_o is the total molar concentration of the solute in the organic layer. Then equation (10–94) may be written approximately as

$$[HA]_o \cong \text{constant} \times \sqrt{C_o} \qquad (10-95)$$

In conformity with the distribution law as given in equation (10–87), the true distribution coefficient is always expressed in terms of simple species common to both phases, that is, in terms of $[HA]_w$ and $[HA]_o$. In the benzene–water system, $[HA]_o$ is given by equation (10–95), and the modified distribution constant becomes

$$K'' = \frac{[HA]_o}{[HA]_w} = \frac{\sqrt{C_o}}{[HA]_w} \qquad (10-96)$$

The results for the distribution of benzoic acid between benzene and water, as given by Glasstone,[58] are found in Table 10–13.

A third case, involving both association in the organic phase and dissociation in the aqueous phase, might be treated at this point but will be deferred until a later section. It follows directly from the two cases already presented, as will be illustrated in *Example 10–25* dealing with preservative action. Various cases of distribution are treated most adequately by Davies and Hallam.[59]

TABLE 10–13. *Distribution of Benzoic Acid between Benzene and Acidified Water at 6° C**

	The concentrations are expressed in moles per liter	
$[HA]_w$	C_o	$K'' = \sqrt{C_o}/[HA]_w$
0.00329	0.0156	38.0
0.00579	0.0495	38.2
0.00749	0.0835	38.6
0.0114	0.195	38.8

*From S. Glasstone, *Textbook of Physical Chemistry,* Van Nostrand, New York, 1946, p. 738.

Extraction. To determine the efficiency with which one solvent can extract a compound from a second solvent—an operation commonly employed in analytic chemistry and in organic chemistry—we follow Glasstone.[60] Suppose that w grams of a solute are extracted repeatedly from V_1 mL of one solvent with successive portions of V_2 mL of a second solvent, which is immiscible with the first. Let w_1 be the weight of the solute remaining in the original solvent after extracting with the first portion of the other solvent. Then the concentration of solute remaining in the first solvent is (w_1/V_1) g/mL and the concentration of the solute in the extracting solvent is $(w - w_1)/V_2$ g/mL. The distribution coefficient is thus

$$K = \frac{\text{concentration of solute in original solvent}}{\text{concentration of solute in extracting solvent}}$$

$$K = \frac{w_1/V_1}{(w - w_1)V_2} \qquad (10-97)$$

or

$$w_1 = w\frac{KV_1}{KV_1 + V_2} \qquad (10-98)$$

The process can be repeated, and after n extractions[60]

$$w_n = w\left(\frac{KV_1}{KV_1 + V_2}\right)^n \qquad (10-99)$$

By use of this equation, it can be shown that most efficient extraction results when n is large and V_2 is small, in other words, when a large number of extractions are carried out with small portions of extracting liquid. The development just described assumes complete immiscibility of the two liquids. When ether is used to extract organic compounds from water, this is not true; however, the equations provide approximate values that are satisfactory for practical purposes. The presence of other solutes, such as salts, may also affect the results by complexing with the solute or by salting out one of the phases.

Example 10–23. The distribution coefficient for iodine between water and carbon tetrachloride at 25° C is $K = C_{H_2O}/C_{CCl_4} = 0.012$. How many grams of iodine are extracted from a solution in water containing 0.1 g in 50 mL by one extraction with 10 mL of CCl_4? How many grams are extracted by two 5-mL portions of CCl_4?

$$w_1 = 0.10 \times \frac{0.012 \times 50}{(0.012 \times 50) + 10}$$

$$= 0.0057 \text{ g remain or } 0.0943 \text{ g are extracted}$$

$$w_2 = 0.10 \times \left(\frac{0.012 \times 50}{(0.012 \times 50) + 5}\right)^2$$

$$= 0.0011 \text{ g of iodine}$$

Thus, 0.0011 g of iodine remains in the water phase, and the two portions of CCl_4 have extracted 0.0989 g.

Solubility and Partition Coefficients. Hansch et al.[61] observed a relationship between aqueous solubilities of nonelectrolytes and partitioning. Yalkowsky and Valvani[62] obtained an equation to determine the aqueous solubility of liquid or crystalline organic compounds:

$$\log S = -\log K - 1.11\frac{\Delta S_f(\text{mp} - 25)}{1364} + 0.54 \qquad (10\text{–}100)$$

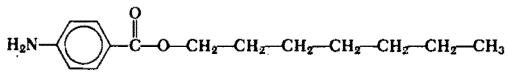
in which S is aqueous solubility in moles/liter, K is the octanol–water partition coefficient, ΔS_f is the molar entropy of fusion, and mp is the melting point of a solid compound on the centigrade scale. For a liquid compound, mp is assigned a value of 25 so that the second right-hand term of equation (10–100) becomes zero.

The entropy of fusion and the partition coefficient may be estimated from the chemical structure of the compound. For rigid molecules, $\Delta S_f = 13.5$ entropy units (eu). For molecules with n greater than five nonhydrogen atoms in a flexible chain,

$$\Delta S_f = 13.5 + 2.5(n - 5) \text{ eu} \qquad (10\text{–}101)$$

Leo et al.[61] have provided partition coefficients for a large number of compounds. When experimental values are not available, group contribution methods (Leo et al.,[61] Rekker[63]) are available for estimating partition coefficients.

Example 10–24. Estimate the molar aqueous solubility of heptyl *p*-aminobenzoate, mp 75° C at 25° C.



It is first necessary to calculate ΔS_f and log K.

There are nine nonhydrogens in the flexible chain (C, O, and seven carbons). Using equation (10–101), we obtain:

$$\Delta S_f = 13.5 + 2.5\,(9 - 5) = 23.5 \text{ eu}$$

For the partition coefficient, Leo et al.[61] give log K of benzoic acid a value of 1.87, the contribution of NH_2 is −1.16, and $CH_2 = 0.50$ or $7 \times 0.50 = 3.50$ for the seven carbon atoms in the chain.

$$\log K \text{ (heptyl } p\text{-aminobenzoate)} = 1.87 - 1.16 + 3.50 = 4.21$$

These values are substituted into equation (10–100):

$$\log S = -4.21 - 1.11\left(\frac{23.5\,(75 - 25)}{1364}\right) + 0.54$$

$$\log S = -4.63$$

$$S_{(\text{calc})} = 2.36 \times 10^{-5}\,M$$

$$S_{(\text{obs})} = 2.51 \times 10^{-5}\,M$$

Preservative Action of Weak Acids in Oil–Water Systems. Solutions of foods, drugs, and cosmetics are subject to deterioration by the enzymes of microorganisms that act as catalysts in decomposition reactions. These enzymes are produced by yeasts, molds, and bacteria, and such microorganisms must be destroyed or inhibited to prevent deterioration. Sterilization and the addition of chemical preservatives are common methods used in pharmacy to preserve drug solutions against attack by various microorganisms. Benzoic acid in the form of its soluble salt, sodium benzoate, is often used for this purpose since it produces no injurious effects in humans when taken internally in small quantities.

Rahn and Conn[64] showed that the preservative or bacteriostatic action of benzoic acid and similar acids is due almost entirely to the undissociated acid and not to the ionic form. These investigators found that the yeast, *Saccharomyces ellipsoideus*, which grows normally at a pH of 2.5 to 7.0 in the presence of strong inorganic acids or salts, ceased to grow in the presence of undissociated benzoic acid when the concentration of the acid reached 25 mg/100 mL. The preservative action of undissociated benzoic acid as compared with the ineffectiveness of the benzoate ion is presumably due to the relative ease with which the un-ionized molecule penetrates living membranes, and conversely, the difficulty with which the ion does so. The undissociated molecule, consisting of a large nonpolar portion, is soluble in the lipoidal membrane of the microorganism and penetrates rapidly.

Bacteria in oil–water systems are generally located in the aqueous phase and at the oil–water interface. Therefore, the efficacy of a weak acid, such as benzoic acid, as a preservative for these systems is largely a result of the concentration of the undissociated acid in the aqueous phase.

To calculate the total concentration of benzoic acid that must be added to preserve an oil–water mixture, we proceed as follows. Let us take the peanut oil–water mixture considered by Garrett and Woods[57] and begin by writing the expression

$$C = qC_o + C_w = q[\text{HA}]_o + [\text{HA}]_w + [\text{A}^-]_w \qquad (10\text{–}102)$$

in which $q = V_o/V_w$, the volume ratio of the two phases, is needed when the volumes are not equal. C is the original concentration of the acid in the water phase before the aqueous solution is equilibrated with peanut oil. C_o is the molar concentration of the simple undissociated molecules in the oil, because the acid does not dimerize or dissociate in the organic phase. C_w, the molar concentration of benzoic acid in water, is equal to the sum of the two terms, $[\text{HA}]_w$ and $[\text{A}^-]_w$, in this ionizing solvent. It is furthermore assumed that concentrations are approximately equal to activities.

The distribution of total benzoic acid among the various species in this system depends upon the distribution coefficient K, the dissociation constant K_a of the acid in the aqueous phase, the phase volume ratio, and the hydrogen ion concentration of the aqueous phase. To account for the first effect, we introduce the term $K = [HA]_o/[HA]_w$ or $[HA]_o = K[HA]_w$ into equation (10–102). We write the dissociation constant, $K_a = [H_3O^+][A^-]_w/[HA]_w$, or the ionic species $[A^-]_w = K_a[HA]_w/[H_3O^+]$, to account for the influence of K_a and $[H_3O^+]$ and substitute it also into equation (10–102). The expression then becomes

$$C = Kq[HA]_w + [HA]_w + K_a[HA]_w/[H_3O^+] \quad (10–103)$$

Factoring out $[HA]_w$, we have

$$C = (Kq + 1 + K_a/[H_3O^+])[HA]_w \quad (10–104)$$

or

$$[HA]_w = \frac{C}{Kq + 1 + K_a/[H_3O^+]} \quad (10–105)$$

Equations (10–104) and (10–105) may be used to calculate the concentration C of total acid that must be added to the entire two-phase system to obtain a final specified concentration $[HA]_w$ of undissociated acid in the aqueous phase buffered at a definite pH or hydrogen ion concentration.[65]

Kazmi and Mitchell[66] and Bean et al.[67] have also proposed calculations for preserving solubilized and emulsified systems that are slightly different from that of Garrett and Woods.

Example 10–25. If benzoic acid is distributed between equal volumes of peanut oil and water, what must be the original concentration in the water phase in order that 0.25 mg/mL of undissociated acid remains in the aqueous phase buffered at a pH of 4.0? The partition coefficient $K = [HA]_o/[HA]_w$ is 5.33 and the dissociation constant of the acid in water is 6.4×10^{-5}. Since the two phases are present in equal amounts, $q = V_o/V_w = 1$. Equation (10–104) is employed.

$$C = \left(5.33 + 1 + \frac{6.4 \times 10^{-5}}{10^{-4}}\right) 0.25$$

$$= 1.74 \text{ mg/mL}$$

In the case in which benzoic acid exists as a dimer in the oil phase, the modified distribution coefficient is $K'' = (1/[HA]_w)\sqrt{C_o}$, therefore equation (10–102) becomes

$$C = K''^2q[HA]_w^2 + [HA]_w + K_a[HA]_w/[H_3O^+] \quad (10–106)$$

and finally

$$C = K''^2q[HA]_w + 1 + (K_a/[H_3O^+])[HA]_w \quad (10–107)$$

Example 10–26. How much undissociated benzoic acid (molecular weight 122 g/mole) remains in the aqueous phase of an emulsion consisting of 100 mL of benzene and 200 mL of water buffered at a pH of 4.2? Is this quantity sufficient to preserve the emulsion? The amount of benzoic acid initially added to the 200 mL of aqueous phase was 0.50 g. The dissociation constant of the acid is 6.4×10^{-5} (pK_a = 4.2), the hydrogen ion concentration of the solution is also 6.4×10^{-5}, and q is $V_o/V_w = 100/200 = 0.5$. The distribution coefficient $K'' = \sqrt{C_o}/[HA]_w \cong 38.5$ as seen in Table 10–13.

$$C = \left\{[(38.5)^2 \times 0.5 \times [HA]_w] + 1 + \frac{6.4 \times 10^{-5}}{6.4 \times 10^{-5}}\right\}[HA]_w$$

$$\frac{0.50 \text{ mole/liter}}{(122)(0.200)} = (741[HA]_w + 2)[HA]_w$$

$$741[HA]_w^2 + 2[HA]_w - 0.0205 = 0$$

$$[HA]_w = \frac{-2 + \sqrt{4 + 60.75}}{1482}$$

$$= 4.079 \times 10^{-3} \text{ mole/liter or } 0.0996 \text{ g/200 mL aqueous phase}$$

Drug Action and Partition Coefficients. At the turn of the century, Meyer and Overton proposed the hypothesis that narcotic action of a nonspecific drug is a function of the distribution coefficient of the compound between a lipoidal medium and water. Later it was concluded that narcosis was a function only of the concentration of the drug in the lipids of the cell. Thus, a wide variety of drugs of different chemical types should produce equal narcotic action at equal concentration in the lipoidal cell substance. Actually, as will be seen shortly, this is a restatement of the theory, first proposed by Ferguson and generally accepted today, that equal degrees of narcotic action should occur at equal thermodynamic activities of the drugs in solution.

The activity of a vapor is obtained approximately by use of the equation (p. 134)

$$\frac{p_{nar}}{p^\circ} = a_{nar} \quad (10–108)$$

If p_{nar} is the partial pressure of a narcotic in solution just necessary to bring about narcosis, and p° is the vapor pressure of the pure liquid, narcosis will occur at a thermodynamic activity of a_{nar}.

Example 10–27. The vapor pressure p° of pure propane is 13 atm and that of butane is 3 atm at 37° C. The partial vapor pressure of propane for narcosis in mice is 0.9 and that for butane is 0.2.[68] Compute the thermodynamic activities of these two compounds required for equinarcotic action.

(*a*) For propane:

$$a_{nar} = \frac{p_{nar}}{p^\circ} = \frac{0.9}{13} = 0.069$$

(*b*) For butane:

$$a_{nar} = \frac{p_{nar}}{p^\circ} = \frac{0.2}{3} = 0.067$$

A still more striking confirmation of the rule that equal degrees of narcosis occur at equal thermodynamic activities (rather than at equal partition coefficients as originally proposed by Meyer and Overton) is shown in Table 10–14. Here it is seen that ethanol, *n*-propanol, and *n*-butanol have distribution coefficients of the same order and all would be expected to show similar narcotic action. Thymol, on the other hand, has a partition coefficient roughly 10,000 times that of the straight-chain alcohols, although its narcotic action is equal to that of the normal alcohols.

TABLE 10–14. *Narcotic Action of Various Compounds*

Substance	Concentration of Compound in Water in Moles/Liter Required for Narcotic Action in Tadpoles	Partition Coefficient of Narcotic Compound $K = \frac{C_{\text{oleyl alcohol}}}{C_{\text{water}}}$	Approximate Activity of Narcotic in Water or Lipoidal Phase ($a_w \cong a_o$)
Ethanol	0.33	0.10	0.033
n-Propanol	0.11	0.35	0.039
n-Butanol	0.03	0.65	0.020
Thymol	0.000047	950	0.045

We can now show that although the distribution coefficients differ, the thermodynamic activities of the compounds are all approximately the same for equal narcotic action. The partition coefficient may be written

$$K = \frac{\text{concentration in organic phase}}{\text{concentration in water phase}} = \frac{a_o/\gamma_o}{a_w/\gamma_w} \quad (10-109)$$

The student will notice that partition coefficients may be written in terms of concentration rather than activities. Since the activities, a_o and a_w, are equal at equilibrium, K would always equal 1.0. It is the differences in *concentration* we are interested in, and K is therefore defined as expressed in equation (10–109).

When a system is in equilibrium with respect to a compound distributed between two phases, the activities of the solute in the two phases may be taken to be identical, or $a_o = a_w$. Therefore, from (10–109),

$$K = \frac{a/\gamma_o}{a/\gamma_w} = \frac{\gamma_w}{\gamma_o} \quad (10-110)$$

It can be assumed that the organic solution is approximately ideal so that γ_O is unity. Then, equation (10–110) reduces to

$$K \cong \gamma_w \quad (10-111)$$

or *the partition coefficient is equal to the activity coefficient* of the compound in the aqueous phase. Finally, when the narcotic concentration in water is multiplied by the activity coefficient, obtained from equation (10–111) in terms of the partition coefficient, the thermodynamic activity for narcosis is obtained:

$$\begin{pmatrix}\text{narcotic concentration} \\ \text{in the aqueous phase}\end{pmatrix} \times (\text{partition coefficient}) = a_{nar} \quad (10-112)$$

This value for the narcotic in the external phase will also give the thermodynamic activity in the lipoidal or biophase since, as already noted, at equilibrium the activities in the two phases must be the same. The molar concentrations of the narcotics in the external aqueous phase are listed in Table 10–14 together with the oil–water partition coefficients. The thermodynamic activity, calculated according to equation (10–112), is shown in column 4 of Table 10–14. Since the activity coefficients of the drugs in the lipoidal phase are considered to be approximately unity, the *concentrations* in the biophase should be roughly equal to the calculated activities. Therefore, the modified rule of Meyer that isonarcotic action occurs at equal concentrations of the drugs in the lipoidal phase is understandable.

The oil–water partition coefficient is an indication of the lipophilic or hydrophobic character of a drug molecule. Passage of drugs through lipid membranes and interaction with macromolecules at receptor sites sometimes correlate well with the octanol–water partition coefficient of the drug. In the last few sections, the student has been introduced to the distribution of drug molecules between immiscible solvents together with some important applications of partitioning and may wish to pursue the subject further; towards this end, references 69 through 72 provide information on the subject. Three excellent books[73,74,75] on solubility in the pharmaceutical sciences will be of interest to the serious student of the subject.

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*Problems**

10–1. The solubility of sulfamethoxypyridazine (SMP) in a 10% by volume mixture of dioxane and 90% by volume of water is 1.8 mg/mL at 25° C. Calculate (a) molarity, (b) molality, and (c) mole fraction of SMP. The density of the liquid, dioxane, is 1.0313 g/mL, of the solution 1.0086 g/mL, of water 0.9970 g/mL, and of the solvent mixture 1.0082 g/mL. The molecular weight of SMP is 280.32 g/mole, that of dioxane is 88.10, and that of water is 18.015.

Answers: (a) 6.421×10^{-3} M; (b) 6.378×10^{-3} m; (c) $X_2 = 1.251 \times 10^{-4}$

10–2. How many liters of carbon dioxide, reduced to standard conditions of temperature and pressure (25° C and 1 atm, respectively), will dissolve in 1 liter of water at 25° C when the partial pressure of the gas is 0.7 atm?

Answer: 0.53 liter

10–3. Henry's law $p_2 = kX_2$ was discussed in Chapter 5, page 109, and was used in *Problems 5–11, 5–12* and *5–13*. Rather than the Henry's law constant, k, its reciprocal, $\sigma = 1/k$ (pp. 215–216), is sometimes used in problems dealing with the solubility of gases in liquids. What is the solubility of oxygen in water at 25° C and a partial pressure of 610 mm Hg if the reciprocal Henry's law constant, $\sigma = 1/k$, is expressed as σ = concentration (g/liter H_2O)/pressure (mm Hg) = 5.38×10^{-5}?

Answer: 0.0328 g/liter

10–4. Divers ordinarily breathe from tanks of air containing 20% O_2 and 80% N_2. However, He (helium) is less soluble in the blood than N_2 and is now often used to replace N_2.

If the partial pressure of helium in the blood of a diver, using a tank of 20% O_2 and 80% He, is 187.5 mm Hg and the percent of saturation in the red blood cell content is found to be 85.5%, what is the amount of helium that dissolves in the blood? No helium is bound by the hemoglobin of the blood. Express the solubility in moles per kilogram of blood, assuming that the blood behaves as a solvent essentially the same as water. See Table 10–4 for the k value (the Henry's law constant) of helium. Assume that k at 25° C applies with little error at 37° C, the body temperature which is applicable here.

Answer: The concentration of He in the blood at 37° C and a pressure of 187.5 mm Hg is 8.06×10^{-5} moles/kg blood.

10–5. What is the mole fraction solubility of N_2 in water at 25° C and 1 atm pressure? What is the molal solubility? The molecular weight of water is 18.015 g/mole.

Answer: 9.37×10^{-6}, expressed as mole fraction; in molality, the result is 5.20×10^{-4} mole/kg H_2O

10–6. A diver, breathing a mixture of oxygen and helium, descends in a fresh-water lake at sea level to a depth of 30 meters. It is desired that the partial pressure of oxygen at this depth be 0.20 atm.

(a) What is the percent by volume of oxygen in the mixture at this depth? *Hint:* The pressure in atmospheres at a given depth may be computed from the expression: $g\rho h$, where ρ is the density of water, g is the gravity acceleration, and h is the depth (see *Problem 1–10*). Assume that $\rho = 1$ g/cm^3.

(b) At what depth will the diver be subjected to a pressure of 2.5 atmospheres, i.e., 1 atm in air above the lake plus 1.5 atm below the surface of the lake?

(c) At a depth of 50 meters below the surface of the lake what is the pressure in atmospheres? Remember to add on the 1 atm pressure in air above the lake. Incidentally, a diver can withstand a pressure for a short period of time of about 6 atm, corresponding to a depth of about 60 meters.

(d) As stated in Problem 10–4, divers often use a mixture of oxygen, 20% by volume, and helium, 80% by volume. Calculate the mole fraction solubility of helium, He, in water (or in blood where the solubility is essentially the same as in water at 1 atm [in air]) and 25° C. The Henry's law constant for He in water at 25° C is 1.45×10^5 (atm/mole fraction).

(e) At a depth of 30 meters in the lake, the pressure is 3.9 atm and the partial pressure of He is 0.8×3.9 atm or 3.12 atm. The value, 0.8, corresponds to the percentage of He in the gas mixture, 80%. Compute the mole fraction solubility of He in the blood at a partial pressure of 3.12 atm, i.e., at a depth of 30 meters.

(f) Convert the solubility to molality, i.e., moles per kilogram of blood. The blood of an adult consists of approximately 6 kg. Calculate the total moles of He in the blood of the diver at a measured depth in the lake of 30 meters.

(g) Using the ideal gas law, $V_2 = nRT/P$, with R expressed as liter atmosphere per mole degree, and n as the number of moles of He in the blood at a partial pressure P of 3.12 atm, calculate the volume of He in the blood at a depth of 30 meters in the lake. The temperature T is that of the blood, 310° K.

(h) A diver must not surface too quickly, for the sudden decrease in pressure reduces the solubility and releases the gas from the blood as bubbles that may block the blood vessels and cause a painful and possibly life-threatening condition called "bends." What is the volume of He that is suddenly released as bubbles into the bloodstream if the diver surfaces rapidly so as to reduce the He pressure from (2.3 + 1) atm to the surface (1 atm)? For this calculation, one may use the relation, $V_2/V_1 = P_2/P_1$ to obtain the volume of He in the blood at the surface of the lake.

Answers: (a) 5.1%; (b) 25.85 meter; (c) 5.8 atm; (d) 5.52×10^{-6}; (e) $X_2 = 2.15 \times 10^{-5}$; (f) 1.193×10^{-3} mole/kg blood—the total amount is 0.00716 mole He in the blood of an adult; (g) 58.4 mL of He in 6 kg of blood; (h) 106.5 mL of He released abruptly into the blood as bubbles.

10–7.† According to Chiou and Niazi,[21] succinic acid and griseofulvin form eutectic mixtures (see p. 42). The table here shows the melting temperatures of the mixtures, the compositions of which are given in percent, w/w. The molecular weights of succinic acid and griseofulvin are 118.09 g/mole and 352.8 g/mole, respectively.

Data for *Problem 10–7*

Succinic acid		Griseofulvin	
Temp. (°C)	% (w/w)	Temp. (°C)	% (w/w)
187.2	98	218	99
186.6	96	210	90
183.8	80	200	80
181	65	192	70
177.6	55	—	—
173.3	44	—	—

Plot the phase diagram using temperature in °C against mole fraction (see Fig 2–17, p. 42, for a similar diagram), and from it determine the melting points, T_o, in °C for the two pure components, their heats of fusion, ^oH_f, and the eutectic point of the mixture of succinic acid and griseofulvin.

The ideal solubility expression, equation (10–12), page 222, may be used as a linear regression equation to calculate ΔH_f for both compounds, using the two branches of the plot. The two melting points are obtained from the intercepts on the vertical axes of the

*Problems 10–4 and 10–6 are modified from J. W. Moncrief and W. H. Jones, *Elements of Physical Pharmacy*, Addison-Wesley, Reading, Mass., 1977, p. 122 and R. Chang, *Physical Chemistry with Applications to Biological Systems*, 2nd ed., Macmillan, New York 1977, pp. 23, 24, 175.

†Dr. J. Kieth Guillory suggested this problem and kindly assisted in the preparation of problems from which this one was made.

graph or may be obtained from the two linear regression equations by setting $X_2^i = 1$. The eutectic point is found by extrapolating both lines to their common intersection. To begin the calculations, one should convert °C to °K and % (w/w) to mole fraction.

Answers:

Compound	ΔH_f (cal/mole)	T_0 °K (°C)	T_0 Literature value
Succinic acid	10,411	460.4 (187.3)	185–187° C
Griseofulvin	13,744	492.3 (219.3)	220° C

The eutectic point, obtained from the intersection of the two lines, corresponds to a mixture of 0.30 griseofulvin and 0.70 succinic acid on the mole fraction scale. The melting point of the eutectic mixture is 173° C.

10–8. At the critical solution temperature of 65.85° C for the phenol–water system, p. 40, the critical composition is 34% by weight of phenol. How many grams of water are dissolved in 1000 g of the solution at this temperature?

Answer: 660 g

10–9. A 200-g mixture of phenol and water at 55° C has a total composition of 20% by weight of phenol. The two liquids have the respective compositions of 13% and 60% phenol. What is the weight in grams of the aqueous layer and of the phenol layer and how many grams of phenol are present in each layer?

Answer: The aqueous layer weighs 170.2 g and contains 22.1 g of phenol; the phenol layer weighs 29.8 g and contains 17.9 g of phenol

10–10. Calculate the Kier–Hall[14] value $^1\chi$ for n-hexane. Using equation (10–8) for the solubility of aliphatic hydrocarbons in water, obtain the molar solubility of n-hexane.

Answer: $^1\chi = 2.914$; $\ln S = 8.886$; $S_{(calc)} = 1.38 \times 10^{-4}$ mole/liter; $S_{(obs)} = 1.11 \times 10^{-4}$ mole/liter

10–11. Using equation (10–10) from Amidon et al.,[15] calculate the molal solubility in water at 25° C of (a) cyclohexanol and (b) n-octane. Compute the percentage difference of the calculated from the observed solubilities. See Table 10–6 for the HYSA, the FGSA value for the hydroxyl group, and the observed solubilities for the two compounds, cyclohexanol and n-octane.

Answers: (a) 0.431 m (−13.4% error); (b) 5.85×10^{-6} m (−0.86% error)

10–12. The melting points and molar heat of fusion of three indomethacin polymorphs, I, II, and VII, are found in the table:[76]

Data for *Problem 10–12*

Indomethacin Polymorph	Melting point °C (°K)	ΔH_f cal/mole
I	158 (431)	9550
II	153 (426)	9700
VII	95 (368)	2340

Calculate the ideal mole fraction solubilities at 25° C of the three indomethacin polymorphs, and rank the solubilities in descending order. Is melting point or ΔH_f more useful in ordering the solubilities of the three polymorphs?

Answer: The ideal solubilities, ranked in decreasing order, are

Polymorph	VII	II	I
X_2^i	0.4716	0.0073	0.0069

10–13. Calculate the ideal mole fraction solubility, X_2^i of benzoic acid at 25° C. The melting point of benzoic acid is 122° C (395.15 °K) and the molar heat of fusion is 4139 cal/mole.

Answer: $X_2^i = 0.18$

10–14. The melting points (mp) and heat of fusion for the following three sulfonamides are

Data for *Problem 10–14*

Compound	mp °C (°K)	ΔH_f cal/mole
Sulfamethoxypyridazine	180.4 (453.55)	8110
Sulfameter	211.6 (484.75)	9792
Sulfisomidine	242.2 (515.35)	10781

Calculate the ideal solubilities of these three sulfonamide analogs at 25° C.

Answer:

Compound	Sulfamethoxy-pyridazine	Sulfameter	Sulfisomidine
X_2^i	0.0092	0.0017	0.00047

10–15. In 1893 Schröder[36] measured the solubility of naphthalene in chlorobenzene and obtained the following data for the mole fraction solubility X_2 of naphthalene at a number of temperatures, T, in degrees Kelvin (°K). The δ values (solubility parameter) of naphthalene and chlorobenzene are both 9.6 $(cal/cm^3)^{1/2}$.

Data for *Problem 10–15*

X_2^i	0.840	0.742	0.482	0.392	0.309	0.232
T (°K)	343.5	337.5	317.5	307.5	297.0	285.5

The melting point T_f of naphthalene is 80.2° C (353.4° K). It is assumed that the solubilities X_2 in the table are ideal solubilities, since the δ value of the solvent is equal to that of the solute. This assumption permits the use of equation (10–11) or (10–12) to obtain the heat of fusion and the entropy of fusion from the slope and intercept, respectively, of a plot of $1/T$ (x-axis) ($°K^{-1}$) versus $\ln X_2^i$ (y-axis). The intercept along the vertical $\ln X_2^i$ axis occurs where $1/T$ on the horizontal axis becomes zero, i.e., where T becomes infinite!

(a) Using linear regression, obtain the heat of fusion, ΔH_f, from the slope $\Delta H_f/R$, in which R is the gas constant, 1.9872 cal $mole^{-1}$ deg^{-1}; $\Delta S_f/R$ allows calculation of the entropy of fusion from the integration constant of equation (10–12).

(b) Compare the ΔH_f value obtained from the slope of the regression line with the average ΔH_f obtained from use of equation (10–11), which yields six ΔH_f values.

Answers: (a) ΔH_f (from regression) = 4310 cal/mole; $\Delta S_f = 12.18$ cal/(mole deg); (b) the average value of ΔH_f from the six values obtained by the use of equation (10–11) is 4382 cal/mole, about 2% larger than the value obtained using equation (10–12). The student's values may differ slightly depending on the rounding off of the decimals.

10–16. Benzoic acid forms an ideal solution in a mixture of 0.7 part of ethanol and 0.3 part of ethyl acetate. The mole fraction solubility at 25° C in this mixture is 0.179. The melting point of benzoic acid is 122.4° C. Calculate the heat of fusion of benzoic acid at 25° C.

Answer: ΔH_f = 4144 cal/mole. The CRC *Handbook of Chemistry and Physics*, 63rd ed., gives ΔH_f of benzoic acid as 4139 cal/mole.

10–17. Compute the mole fraction and the molal solubility of benzoic acid in ethyl acetate at 25° C assuming regular solution behavior. Refer to *Example 10–9* and Wenner[30] for the calculations involved. What is the activity and the activity coefficient of the solute in this solution? The solubility parameter of benzoic acid is 11.3 $(cal/cm^3)^{1/2}$ and the molar volume of the supercooled liquid at 25° C is 104.4 cm^3/mole. The solubility parameter of ethyl acetate may be obtained from its heat of vaporization ΔH_v at 25° C = 97.5 cal/g. The molar volume of ethyl acetate at 25° C is obtained from the molecular weight 88.1 divided by its density at 25° C, 0.90 g/cm^3. The heat of fusion of benzoic acid is 33.9 cal/g and the molecular weight is 122 g/mole. The melting point of benzoic acid is 122° C. For purposes of successive approximations, one may assume that $V_1 = V_2$ so that $\phi_1 \approx 1 - X_2$, although the full equation for ϕ, *Example 10–9*, is ordinarily used.

Answer: $X_2 = 0.082$; $a_2 = X_2^i = 0.18$; $\gamma = 2.21$

10–18. If the mole fraction solubility X_2 of naphthalene in chlorobenzene can be considered as the ideal solubility X_2^i for naphthalene, and if X_2^i is 0.444 for naphthalene in chlorobenzene at 40° C (313° K), a determination of the mole fraction solubility in other solvents at 40° C should allow calculation of the activity coefficient, γ_2, in each solvent. What is γ_2 for naphthalene at 40° C in each of the following solvents?

Data for *Problem 10–18*

Solvent	X_2 (40° C)
Acetone	0.378
Hexane	0.222
Methanol	0.0412
Acetic acid	0.117
Water	1.76×10^{-5}
Chlorobenzene	0.444

Relative to the γ_2 values, what might one conclude about the solubility of naphthalene in these various solvents?

Answers:

Solvent	γ_2 (40° C)
Acetone	1.2
Hexane	2.0
Methanol	10.8
Acetic acid	3.8
Water	2.5×10^4
Chlorobenzene	1.0

10–19. The units of solubility parameter (δ) in the cgs system are $(cal/cm^3)^{1/2}$. **(a)** Obtain a conversion factor to express δ in SI units, $(MPa)^{1/2}$. **(b)** Express the solubility parameter of chloroform, caffeine, tolbutamide, and hydrocortisone in SI units. The solubility parameters in cgs units are 9.3, 14.1, 10.9, and 12.4 $(cal/cm^3)^{1/2}$, respectively.

Answers: **(a)** the conversion factor is 1 $(cal/cm^3)^{1/2}$ = 2.0455 $(MPa)^{1/2}$; **(b)** the δ value for each drug above in SI units is, respectively, 19.0, 28.8, 22.3, and 25.4 $(MPa)^{1/2}$

10–20. The cgs system of units is ordinarily used in this chapter for the calculation of solubilities. However, it is sometimes useful to convert to SI units. For a solution of benzoic acid in water, necessary values are expressed in the cgs units as follows. The molar volume, V_2, for benzoic acid is 104.3 cm^3/mole and for water V_1 = 18.015 cm^3/mole. The heat of fusion of benzoic acid is 4302 cal/mole and the melting point is 395.6° K. The solubility parameters δ_1 and δ_2 for the solvent, water, and the solute, benzoic acid, are, respectively, 23.4 $(cal/cm^3)^{1/2}$ and 11.5 $(cal/cm^3)^{1/2}$. The gas constant R is given in the cgs system as 1.9872 cal deg^{-1} $mole^{-1}$. **(a)** Convert each of these quantities into the SI system of units. **(b)** Compute the mole fraction solubility of benzoic acid in water at 25° C from the Hildebrand equation using the SI units obtained. Assume that $\phi_1 = 1$. Convert the mole fraction to molality. *Hint:* Use the conversion factor obtained in *Problem 10–19* to express the solubility parameters in SI units.

Answers: **(a)** $V_2 = 104.3 \times 10^{-6}$ m^3/mole, $V_1 = 18.015 \times 10^{-6}$ m^3/mole, $\Delta H_f = 17999.6$ J/mole, $\delta_1 = 47.9$ $(MPa)^{1/2}$, $\delta_2 = 23.5$ $(MPa)^{1/2}$; **(b)** $X_2 = 3.04 \times 10^{-3}$, $m = 0.169$ mole/(kg H_2O).

10–21. The heat of vaporization of the solvent carbon disulfide is 6682 cal/mole and the molar volume is 60.4 cm^3/mole at 25° C. Compute the internal pressure and the solubility parameter of carbon disulfide.

Answer: $P_i \cong 101$ cal/cm^3; $\delta = 10$ $(cal/cm^3)^{1/2}$

10–22. It has been stated in the literature that the a/V^2 term in the van der Waals equation (equations (2–13) and (2–14), pp. 26, 27) is approximately equal to the cohesive energy density, i.e., to the square of the solubility parameter, δ, or $a = \delta^2 V^2$. The CRC *Handbook of Chemistry and Physics*, 63rd ed., page D-195, gives the value of a for n-hexane as 24.39 and a for benzene as 18.00 $liter^2$ atm $mole^{-2}$. Using these handbook values for the van der Waals a—the value for attractive forces between molecules—calculate the solubility parameter δ of n-hexane and of benzene.

The accepted δ values for these two liquids (see Table 10–8) are 7.3 and 9.1 $(cal\ cm^{-3})^{1/2}$, respectively. Do you agree that a/V^2 is a good estimate of δ^2? *Hint:* You will need the conversion factor, 1 liter atm = 24.2179 cal. Express the pressure in atmospheres, the volume in liters, and R as 0.08206 liter atm $mole^{-1}$ deg^{-1}. The molar volume of benzene is 89.4 cm^3 $mole^{-1}$ and the molar volume of n-hexane is 131.6 cm^3 $mole^{-1}$.

Answer: $(a/V^2)^{1/2} \pm \delta$(n-hexane) = 5.8 $(cal/cm^3)^{1/2}$; $(a/V^2)^{1/2} \pm \delta$(benzene) = 7.4 $(cal/cm^3)^{1/2}$

10–23. Calculate the solute–solvent interaction energy, W_{calc}, for a solution of caffeine in 20% water–80% dioxane (Table 10–10) at 25° C using equation (10–44). With this value for $W_{(calc)}$ and the solubility parameter of the mixed solvent (Table 10–10), calculate the solubility of caffeine in this mixture. The value for A is 0.09467 cm^3/cal, δ_2 (caffeine) = 13.8 $(cal/cm^3)^{1/2}$, and $-\log X_2^i = 1.1646$.

Answer: $W_{(calc)} = 173.4079$ cal/cm^3; $X_{2(calc)} = 0.024$. The results in Table 10–10, $W_{(calc)} = 173.729$ cal/cm^3 and $X_{2(calc)} = 0.027$, were obtained using the more accurate quartic expression, equation (10–45).

10–24. (a) What is the $W_{(calc)}$ value for caffeine in a mixture of dioxane and water having a δ_1 value of 17.07 $(cal/cm^3)^{1/2}$? This mixture contains 47.5% by volume of dioxane and 52.5% water. Calculate $W_{(calc)}$ using both the quadratic (equation 10–44) and the quartic (equation 10–45) expressions.

(b) The A value at 25° C is 0.093711 cm^3/cal. The δ_2 value of caffeine is 13.8 $(cal/cm^3)^{1/2}$. The negative log ideal solubility of caffeine at 25° C is $-\log X_2^i = 1.1646$. Calculate the solubility of caffeine in mole fraction and in moles/liter using both $W_{(calc)}$ results (quadratic and quartic) of part (a). The density ρ of the solution is 1.0493 g/cm^3. The molecular weight M_2 of caffeine is 194.19 g/mole, and that of dioxane 88.016 g/mole.

$$\text{Solubility in (moles/liter)} = \frac{1000\ \rho\ (X_2)}{M_1(1 - X_2) + X_2 M_2} \qquad \text{(p. 104)}$$

M_1, the average molecular weight of the solvent at a volume percent of 47.5 dioxane, is given approximately by the use of molecular weights and volume fractions:

M_1 = (88.10 g/mole)(0.475) + (18.015 g/mole)(0.525) ≈ 51.3 g/mole

Partial Answer: Using equation (10–45), $W_{(calc)}$ = 238.06175 cal/cm^3; mole fraction solubility $X_{2(calc)}$ = 0.0200; molar solubility (calculated) = 0.39; molar solubility (experimental) = 0.40 mole/liter.

10–25. Calculate the values of W (equation 10–43), $\delta_1\delta_2$, and the ratio $W/\delta_1\delta_2$ for ketoprofen, an analgesic, in a 70:30 volume percent mixture (δ_1 = 10.32) and a 50:50 volume percent mixture (δ_1 = 11.00) of chloroform–ethanol at 25° C. The ideal solubility of ketoprofen is X_2^i = 0.1516 and its molar volume V_2 = 196 cm^3/mole. The solvent volume fraction ϕ_1 of the two mixtures is 0.6694 and 0.6820, respectively, and the mole fraction solubilities of ketoprofen in the mixtures are X_2 = 0.1848 and X_2 = 0.1622. The solubility parameter of ketoprofen, calculated from the peak solubility value in the chloroform–ethanol mixtures, is δ_2 = 9.8 (cal/cm^3)$^{1/2}$.

Answer:

Mixture	A	W	$\delta_1\delta_2$	$W/\delta_1\delta_2$
70:30	0.0644	101.9389	101.136	1.0079
50:50	0.0668	108.7395	107.800	1.0087

Notice that the use of W instead of $\delta_1\delta_2$ in the Hildebrand equation gives the exact solubility of X_2 = 0.1848. The use of $-2\delta_1\delta_2$ instead of $-2W$ gives a result, X_2 = 0.0813, that is some 56% in error. $W/\delta_1\delta_2$ is nearly unity, viz. 1.0079, which means that W is only slightly different from $\delta_1\delta_2$. Yet, the very small difference causes the use of $-2W$ in the Hildebrand equation to give the exact solubility of ketoprofen in a 70:30 mixture of chloroform and ethanol, and the use of $-2\delta_1\delta_2$ to give a less exact solubility value.

10–26. Calculate the values of A, W, $\delta_1\delta_2$, and $W/\delta_1\delta_2$ for solutions of sulfamethoxypyridazine (SMP) in benzene, δ_1 = 9.07, and in benzyl alcohol, δ_1 = 11.64 (cal/cm^3)$^{1/2}$, at 25° C. The ideal solubility X_2^i of SMP is 9.1411 × 10^{-3}, and its molar volume, V_2, is 172.5 cm^3/mole. The volume fractions ϕ_1 of the solvents benzene and benzyl alcohol are 0.9999 and 0.9757, respectively. The solubility parameter δ_2 of the solute, SMP, is 12.89. The mole fraction solubilities X_2 of SMP in benzene and in benzyl alcohol are 0.0636 × 10^{-3} and 14.744 × 10^{-3} respectively.

Answers:

Solvent	A cm^3/cal	W cal/cm^3	$\delta_1\delta_2$ cal/cm^3	$W/\delta_1\delta_2$
Benzene	0.1264	115.6739	116.9123	0.9894
Benzyl alcohol	0.1204	151.6831	150.0396	1.0110

10–27. The presence of usual components such as sweetening agents in syrup formulas may affect the solubility of preservatives so that changes in temperature yield precipitation and leave the product unprotected. The molar solubility of sorbic acid used as a preservative was studied at 20° C and 37° C as a function of the concentration of glucose.[77]

Data for *Problem 10–27:* Molar Solubility of Sorbic Acid

% Glucose in water	20° C	37° C
0	0.013	0.022
15	0.011	0.019
30	0.009	0.016
45	0.007	0.014
60	0.005	0.011

(a) Plot on the same graph the molar solubility of sorbic acid at 20° C and 37° C (vertical axis) against the percent of glucose in water (horizontal axis) and find a quantitative relationship between these variables. Comment on your results.

(b) The change in the aqueous molar solubility, S, of sorbic acid with addition of glucose is determined by the standard free energy of transfer of sorbic acid from water (w) to the glucose solution (s). Show that these thermodynamic functions, $\Delta G°_{tr}$ and $\Delta H°_{tr}$, can be computed from the following expressions:

$$\Delta G°_{tr} = -RT \ln \frac{S_s}{S_w}$$

and

$$\ln \frac{(S_{s2}/S_{s1})}{(S_{w2}/S_{w1})} = \frac{\Delta H°_{tr}}{R}\left(\frac{T_2 - T_1}{T_1T_2}\right)$$

(c) As an example, compute $\Delta G°_{tr}$ and $\Delta H°_{tr}$ for the transfer of sorbic acid from water to a 45% solution of glucose at both 20° C and 37° C. Compare your results to the *change in solubility* of sorbic acid from water to 45% glucose at both temperatures. *Hint:* Observe the sign and magnitude of these thermodynamic functions.

Partial Answer: (c) $\Delta G°_{tr}$ (20° C) = 360.6 cal/mole; $\Delta G°_{tr}$ (37° C) = 278.6 cal/mole; $\Delta H°_{tr}$ = 1775 cal/mole

10–28. Suppose you traveled to the hypothetical planet Ariston, where the temperature ranged from −100° to 0° C. You were asked to join the scientists at the Ariston National Laboratories to prepare a solution of solid carbon dioxide dissolved in ethanol at −80° C (193° K) to be used in a new rocket engine being developed. The melting point of CO_2 is −56° C and that of ethanol is −114.1° C. At −80° C, the normal room temperature on Ariston, CO_2 exists as a solid and ethanol as a liquid. The boiling point of ethanol is 78.5° C and it re-mains as a liquid from about −114° C to +78.5° C, where it becomes a gas.

(a) Calculate the ideal solubility of solid CO_2 at −80° C. The heat of fusion of CO_2 is 1900 cal/mole.

(b) The density of ethanol at several temperatures is given in the table:

Data for *Problem 10–28*

T (°K)	273.2	283.2	293.2	298.2	303.2
t (°C)	0	10	20	25	30
Density (g/cm^3)	0.80625	0.79788	0.78945	0.78521	0.78097

Regress the density (y values) against t °C (x values) and compute the density and molar volume (cm^3/mole) of ethanol at −80° C. The molecular weight of ethanol is 46.07 gram/mole.

(c) The solubility parameter at temperatures other than 25° C may be determined approximately for a liquid from the densities of the liquid at 25° C and at the new temperature.[78]

$$\delta_{T_1} = \delta_{25°}\left(\frac{\rho_{25°}}{\rho_{T_1}}\right)^{1.25}$$

Use the density of ethanol from the table above (at 25° C) and your result at −80° C, and compute δ for ethanol at −80° C; the δ value for ethanol at 25° C is 12.8 (cal/cm^3)$^{1/2}$.

(d) Estimate the solubility of solid CO_2 in ethanol at −80° C under which conditions it is expected to form a regular solution. The heat of vaporization of CO_2 is 3460 cal/mole. Obtain the solubility parameter at −80° C from this value, knowing that the molar volume at −80° C is V_2 = 38 cm^3/mole. The δ value for CO_2 may be calculated using the expression

$$\delta_{CO_2} = \left(\frac{\Delta H_2^v - RT}{V_2}\right)$$

where ΔH_2^v is the heat of vaporization, R is the gas constant 1.9872 cal/(mole deg), and T is the absolute temperature, 193° K. You will

need the molar volume, V_1, of ethanol and its solubility parameter at −80° C (193° K) (see answers (b) and (c)). You can assume that the volume fraction ϕ_1 of ethanol is 1.00 for the first round of calculations. Then by six or more iteration steps, obtain the more correct solubility (see p. 224, 225).

(e) Once you have calculated the mole fraction solubility of CO_2 in ethanol at −80° C, convert the solubility into units of molality. The molecular weight of CO_2 is 44.01 g/mole.

Answers: (a) X_2^i (CO_2, −80° C) = 0.5782; (b) ρ (ethanol, −80° C) = 0.87370, V_1 = 52.73 cm^3/mole; (c) δ (ethanol, −80° C) = 11.2 $(cal/cm^3)^{1/2}$; δ (CO_2, −80° C) = 9.0 $(cal/cm^3)^{1/2}$; (d) X_2 (CO_2, −80° C) = 0.4887 after eight iterations. If ϕ_1 is unity, we obtain the first result of iteration, viz. X_2 = 0.3579; (e) molality = 20.7 moles/kg

10–29. The solubility of sodium carbonate, decahydrate, $Na_2CO_3 \cdot 10H_2O$ (washing soda), is 21.52 g/100 g of water at 0° C, and the heat of solution ΔH_{soln} is 13,500 cal/mole. When a substance such as washing soda is added to ice at 0° C, the freezing point of water is lowered and a liquid solution of sodium carbonate is formed at 0° C. Calculate the solubility of sodium carbonate decahydrate at 25° C.

Answer: The solubility of $Na_2CO_3 \cdot 10H_2O$ is 43.13 g/(100 g H_2O) using equation (10–46). Note that Na_2CO_3 contributes three ions in solution, i.e., ν = 3. The experimental value is 50 g/(100 g H_2O) at 25° C, a 14% difference from the calculated value.

10–30. The solubility of $Ba(OH)_2 \cdot 8H_2O$ in water at three temperatures is reported by Daniels and Alberty[79] as follows:

Data for *Problem 10–30*

Temperature (°C)	0.0	10.0	20.0
Molal solubility	0.0974	0.1447	0.227

Use the modification of equation (10–46), that is,

$$\ln m_2 = -\frac{\Delta H_{soln}}{R}\frac{1}{T} + I$$

which provides the heat of solution, ΔH_{soln}, when a graph of the data is plotted with ln m_2 (m_2 is the molality of the solute) on the vertical axis and $1/T$ (T is the absolute temperature) on the horizontal axis. The slope of the line, obtained by linear regression analysis and multiplied by R = 1.9872 cal $mole^{-1}$ deg^{-1}, gives ΔH_{soln} in cal/mole. I in the equation is an integration constant and is the point of intersection on the vertical axis.

Use the equation above to obtain ΔH_{soln}, the heat of solution in the range of 0° C to 20° C and to predict the solubility of barium hydroxide octahydrate at 30° C in water.

Answer: ΔH_{soln} = 6719 cal/mole; calculated molal solubility at 30° C = 0.327 m; experimental solubility[79] = 0.326 m

10–31. If the solubility product of silver chromate is 2×10^{-12} at 25° C, what is the solubility in mole/liter of silver chromate?

Answer: 7.9×10^{-5} mole/liter

10–32. What is the solubility of the electrolyte, magnesium hydroxide, (a) in moles/liter and (b) in g/100 mL if the solubility product is 1.4×10^{-11}? The molecular weight of $Mg(OH)_2$ is 58.34.

Answers: (a) 1.5×10^{-4} mole/liter; (b) 8.8×10^{-4} g/dL. The symbol dL stands for deciliter = 100 mL.

10–33. Brequinar sodium dissociates as brequinar$^-$ and Na^+. Its apparent solubility product K'_{sp} = 0.0751. (a) Compute the solubility of this compound.[80] (b) Compute the solubility product K_{sp}, using the mean activity coefficient, $\gamma_\pm$. (c) Compute the solubility after addition of a 0.05-M solution of KCl.

Answers: (a) 0.274 mole/liter; (b) K_{sp} = 0.0335; (c) 0.280 mole/liter

10–34. the crystal lattice energy of AgCl is 207 kcal/mole and its heat of hydration is −192 kcal/mole. (a) What is the heat of solution of AgCl in kcal/mole and in kJ/mole (b) The solubility of AgCl in water at 10° C is 8.9×10^{-5} g/dL of solution. What is the solubility of AgCl at 25° C? AgCl dissociates into two ionic species in solution.

Answers: (a) ΔH_{soln} = 15 kcal/mole (Table 10–11); in kJ/mole; ΔH_{soln} = 62.8; (b) 1.74×10^{-4} g/dL of solution. The experimental value is 1.93×10^{-4} % (w/v).

Note: For the strong electrolytes such as NaCl and KBr, which are very soluble in water, the use of equation (10–46) does not give very reasonable results for solubility. As seen in this example, the solubility for a slightly soluble strong electrolyte such as silver chloride at various temperatures is reasonable in comparison with observed values (i.e., within 10%).

10–35. The crystal lattice energies of potassium bromide and potassium chloride are 673 and 699 kJ/mole; their heats of hydration are −651 kJ/mole and −686 kJ/mole, respectively. What is the heat of solution ΔH_{soln} of KBr and of KCl?. Express the results in kJ/mole, then convert to kcal/mole.

Answer: for KBr, ΔH_{soln} = 22 kJ/mole = 5.3 kcal/mole; for KCl, ΔH_{soln} = 13 kJ/mole = 3.1 kcal/mole

10–36. What is the solubility of barium sulfate in a solution having an ionic strength μ of 0.25 and $K_{sp} = 1 \times 10^{-10}$ at 25° C? The activity coefficient for a bi-bivalent salt at this ionic strength is 0.23.

Answer: 4.3×10^{-5} mole/liter

10–37. The solubility of boric acid in an aqueous solvent containing 25% by volume of sorbitol was found by Sciarra et al.[81] to be 2.08 molal at 35° C. The heat of solution of boric acid in this mixed solvent is 3470 cal/mole. Calculate the molal solubility of boric acid at 50° C in this solvent.

Answer: 2.71 molal

10–38. The molar solubility of sulfathiazole in water is 0.002, the pK_a is 7.12, and the molecular weight of sodium sulfathiazole is 304. What is the lowest pH allowable for complete solubility in a 5% solution of the salt?

Answer: pH_p = 9.03

10–39. What is the pH_p of a 2% solution of sodium phenobarbital in a hydroalcoholic solution containing 15% by volume of alcohol? The solubility of phenobarbital in 15% alcohol is 0.22%. The pK_a of phenobarbital in this solution is 7.6. The molecular weight of sodium phenobarbital is 254.22 g/mole and that of phenobarbital is 232.23 g/mole.

Answer: pH_p = 8.5

10–40. Calculate pH_p for a 0.5% solution of cocaine hydrochloride. The molecular weight of the salt is 339.8, and the molar solubility of the base is 5.60×10^{-3}. The pK_b of cocaine is 5.59.

Answer: pH_p = 8.20

10–41. Using data in Figures 10–7 and 10–8, calculate the minimum pH required for complete solubility of sodium phenobarbital in a solution containing 3 g of the drug in 100 mL of a mixed alcohol–water solvent. (a) Calculate pH_p, the minimum pH for the drug, in each aqueous solvent consisting of 10%, 20%, 30%, 40%, and 50% by volume of ethanol. (b) Plot pH_p versus percent by volume of alcohol in the solvent. The procedure may be checked by comparing the results with the calculations illustrated in *Example 10–17*, page 235. The molecular weight of phenobarbital is 232.23 g/mole and that of sodium phenobarbital is 254.22.

Answer:

% Alcohol	10	20	30	40	50
pH_p	8.73	8.63	8.55	8.02	*

*At about 50% alcohol and above, phenobarbital in a 3g/100 mL solution of the drug will not precipitate no matter how low the pH.

10–42. The molar solubility of codeine, S_o, in water at 25° C is approximately 0.0279 mole/liter; the pK_a of codeine (actually, the conjugate acid of the base, codeine) is 8.21 at 25° C; and the molecular weight of codeine phosphate · $\frac{1}{2}H_2O$ (U.S.P.) is 406.37 dalton.* What

*Recall that the word *dalton* is another term for the units g/mole, i.e., for molecular weight units.

is the highest pH allowable for complete solubility in an aqueous solution of 60 mg of the salt per 5 mL of solution?

Answer: The pH above which the free base precipitates from solution is 9.45.

10–43. A prescription calls for 7 grains (1 gram = 15.432 grains) of phenobarbital in 60 mL of solution. The vehicle consists of 20% by volume of glycerin, 5% by volume of alcohol, and the balance water. From Figure 10–7 it is observed that about 25% by volume of alcohol is required in the solution to dissolve this quantity of phenobarbital. How much U.S.P. alcohol (95% by volume) must be added?

Answer: 13.3 mL

10–44. If a container of pure water is shaken in the air, the water will dissolve atmospheric carbon dioxide until the dissolved gas is in equilibrium with that in the air. At atmospheric pressure the solubility of CO_2 is found to be 1×10^{-5} mole/liter. The dissociation constant K_1 of carbonic acid is approximately equal to 4×10^{-7}. Compute the pH of water saturated with CO_2. *Hint:* $[H_3O^+] = \sqrt{K_1 c}$, in which c is the equilibrium concentration of the gas in water.

Answer: pH = 5.7

10–45. (a) Calculate the solubility at 25° C of sulfisoxazole in an aqueous buffer having a pH of 5.12. (b) Repeat the calculation for the pH 5.12 buffer solution when 3.0% Tween 80 is included in the solution. See *Example 10–18* for K_a, K', and K'', and for the aqueous solubility of nonionized sulfisoxazole at 25° C. (c) Calculate the fraction of sulfisoxazole solubilized in the Tween 80 micelles in this solution.

Answers: (a) 0.30 g/liter; (b) 0.723 g/liter; (c) 0.585

10–46. Calculate the molar solubility of butyl p-hydroxybenzoate (mp 68° C) in water at 25° C using equation (10–100), page 240. The log K for benzoic acid is 1.87; the contribution by an OH group is −1.16 and by a CH_2 group is 0.50, according to Leo et al.[81]

Answer: ΔS_f = 16.0 e.u. log $K_{(calc)}$ = 2.71, log S = −2.73, $S_{(calc)}$ = 1.86×10^{-3} M, $S_{(obs)} = 1.29 \times 10^{-3}$ M

10–47. Pinal and Yalkowsky[82] extended their earlier equations[83] to estimate the aqueous solubility of weak electrolytes. The new equation is

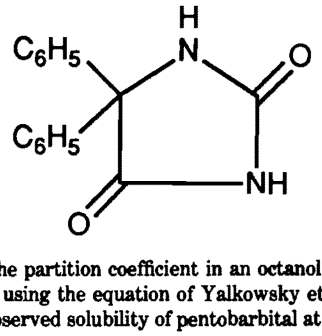
$$\log S = -\frac{\Delta S_f (T_m - T)}{2.303RT} - \log K + \log \alpha + 0.8 \quad (10\text{–}113)$$

where T_m and T are respectively the absolute temperature at the melting point and the temperature at which the experiment is done. The other symbols have the same meaning as in equation (10–100), page 240; α is an ionization term defined as

$$\alpha = \left(1 + \frac{10^{-pK_a}}{10^{-pH}}\right)$$

for monoprotic acids.

(a) Compute the aqueous solubility of phenytoin (a derivative of hydantoin used as an antiepileptic drug) at pH 7.1 and 25° C. The pK_a of phenytoin is 8.30, the melting point is 296.9° C, and the partition coefficient K is 208.9. The entropy of fusion can be calculated according to equation (10–101), page 240, where n is the number of carbons in the longest hydrocarbon chain or flexible ring. Phenytoin has the formula



(b) Compute the partition coefficient in an octanol–water system for pentobarbital using the equation of Yalkowsky et al.[82] (equation (10–113)). The observed solubility of pentobarbital at 33° C and pH 8 is 0.01107 mole/liter. the pK_a is 8.07 and ΔS_f = 12.67 entropy units (e.u.) (i.e., 12.67 cal/mole deg). The melting point is 128.5° C.

Answers: (a) n, the number of carbons in the calculation of ΔS_f is n = 6; ΔS_f = 16 e.u.; α = 1.063; log S = −4.6835; S, the aqueous solubility of phenytoin, = 2.07×10^{-5} mole/liter; (b) log K = 2.16; K = 144.5

10–48. If 0.15 g of succinic acid in 100 mL of ether is shaken with a 10-mL portion of water, how much succinic acid is left in the ether layer? The distribution coefficient K = (conc. in ether)/(conc. in water) = 0.125 at 25° C. How much succinic acid is left in the ether when the phase is extracted with an additional 10 mL of water?

Answer: 0.083 g after first extraction; 0.046 g after second extraction

10–49. How much benzoic acid, $K_a = 6.3 \times 10^{-5}$, will remain undissociated in the aqueous phase of a 50% oil–water emulsion if the initial concentration of benzoic acid in the aqueous phase is 0.5%? The aqueous phase is buffered at pH 5 and the o/w partition coefficient = 5.33. Assume that benzoic acid remains as a monomer in the oil phase.

Answer: 0.396 mg/mL

10–50. Propionic acid is added to the aqueous phase of a 20% oil–water emulsion, and 0.65 mg/mL of free acid remains in the aqueous phase after equilibrium has been attained between the two phases. In a 20% emulsion, $q = V_o/V_w$ = 20/80 = 0.25. The aqueous phase is buffered at pH 3.5. Propionic acid is found to dimerize in the oil phase and the distribution constant, $K'' = \sqrt{C}/[HA_w]$, is equal to 15.0. The K_a of propionic acid is 1.4×10^{-5}. Compute the initial concentration C of propionic acid to be introduced into the aqueous phase. The molecular weight of propionic acid is 74.08 g/mole.

Answer: C = 1.0 mg/mL

10–51. To determine the *intrinsic partition coefficient* K_{in} of pilocarpine base in a study of transcorneal permeation, the octanol–water aqueous buffer partition coefficient, K_{obs}, was obtained experimentally at various temperatures and pH values (Mitra and Mikkelson[84]). The results are presented in Table 10–15.

TABLE 10–15. *Observed Partition Coefficients K_{obs} at Various pH's and Temperatures. (Data for Problem 10–51)*

pH	6.25	6.50	6.70	6.85	7.00	7.25
$[H_3O^+]$ ($\times 10^7$)	5.62	3.16	2.00	1.41	1.00	0.56
T (°C)	Observed Partition Coefficients, K_{obs}					
27	0.24	0.38	0.52	0.63	0.72	0.89
30	0.31	0.46	0.62	0.78	0.84	1.06
40	—	0.65	0.88	1.06	1.23	1.49

(a) According to Mitra and Mikkelson,[84] the observed partition coefficient K_{obs} is related to the hydrogen ion concentration of the aqueous phase $[H_3O^+]$ by the expression

$$\frac{1}{K_{obs}} = \frac{1}{K_{in}K_a}[H_3O^+] + \frac{1}{K_{in}}$$

where the intrinsic partition coefficient K_{in} of the free base, pilocarpine is independent of pH. The term K_a is the ionization constant in water of the conjugate acid of pilocarpine, i.e., the pilocarpinium cation. Plot the reciprocal of the observed partition coefficient, $1/K_{obs}$, versus the hydrogen ion concentration, $[H_3O^+]$. Using linear regression analysis obtain the intrinsic partition coefficient, K_{in}, for pilocarpine base between octanol and an aqueous phosphate buffer, and the acidic ionization constant K_a for the pilocarpinium cation at temperatures 27°, 30°, and 40° C. The cation does not partition into octanol.

(b) The intrinsic partition coefficient of pilocarpine base in the logarithmic form $\ln K_{in}$ may be expressed in terms of the thermodynamic quantities $\Delta H°$, $\Delta S°$, and $\Delta G°$ using the van't Hoff equation:

$$\ln K_{in} = -\frac{\Delta H°}{R}\frac{1}{T} + \frac{\Delta S°}{R}$$

Regress $\ln K_{in}$ against $1/T$, at the three absolute temperatures 27° C = 300.15° K, 30° C = 303.15° K, and 40° C = 313.15° K. Solve for $\Delta H°$ and $\Delta S°$ and obtain $\Delta G°$ at the three temperatures. Interpret the magnitude and the sign of these three thermodynamic quantities as they relate to the partitioning process.

Answers: **(a)**

Temperature (°C)	K_{in}	K_a	pK_a
27	1.324	1.25×10^{-7}	6.90
30	1.433	1.54×10^{-7}	6.81
40	2.106	1.42×10^{-7}	6.85

(b) $\Delta H°$ = 6777 cal/mole ≈ 6.8 kcal/mole; $\Delta S°$ = 23 cal/(mole deg); $\Delta G°$ = −159 cal/mole at 27° C, −228 cal/mole at 30° C, and −460 cal/mole at 40° C

$\Delta H°$ is positive, which mitigates against the partitioning process, yet $\Delta S°$ is sufficiently positive to provide a spontaneous reaction. The negative $\Delta G°$ values corroborate the conclusion that the process is spontaneous (for the solute in its standard state). The large positive $\Delta S°$ value suggests that pilocarpine base is solvated in the aqueous phase in an orderly structure of water, which is broken down to a more random arrangement of drug and solvent in the octanol phase.