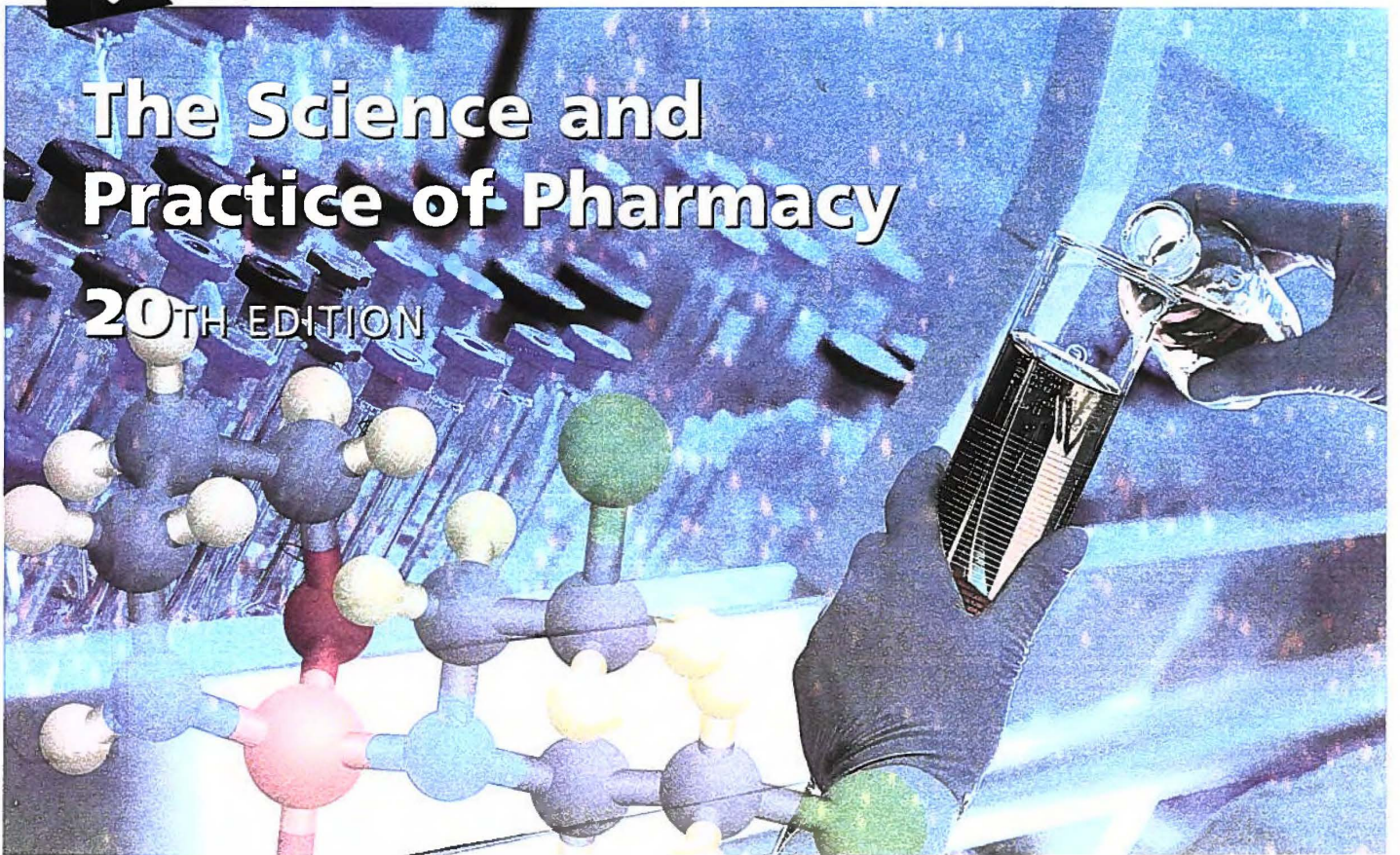


REMINGTON

The Science and Practice of Pharmacy

20TH EDITION



Remington: The Science and Practice of Pharmacy

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New York, NY 10017



Dr. Remington (seated right) reading galley proof. Galley proofs of USP monographs hang on the far wall, and USP Circulars are being collated on the billiard table.

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Remington: The Science and Practice of Pharmacy . . . *A treatise on the theory and practice of the pharmaceutical sciences, with essential information about pharmaceutical and medicinal agents; also, a guide to the professional responsibilities of the pharmacist as the drug information specialist of the health team . . . A textbook and reference work for pharmacists, physicians, and other practitioners of the pharmaceutical and medical sciences.*

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Ionic Solutions and Electrolytic Equilibria

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ELECTROLYTES

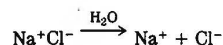
In a preceding chapter, attention was directed to the colligative properties of nonelectrolytes, or substances whose aqueous solutions do not conduct electricity. Substances whose aqueous solutions conduct electricity are known as *electrolytes* and are typified by inorganic acids, bases, and salts. In addition to the property of electrical conductivity, solutions of electrolytes exhibit anomalous colligative properties.

COLLIGATIVE PROPERTIES

In general, for nonelectrolytes, a given colligative property of two equimolar solutions will be identical. This generalization, however, cannot be made for solutions of electrolytes.

Van't Hoff pointed out that the osmotic pressure of a solution of an electrolyte is considerably greater than the osmotic pressure of a solution of a nonelectrolyte of the same molal concentration. This anomaly remained unexplained until 1887 when Arrhenius proposed a hypothesis that forms the basis for our modern theories of electrolyte solutions.

This theory postulated that when electrolytes are dissolved in water they split up into charged particles known as *ions*. Each of these ions carries one or more electrical charges, with the total charge on the positive ions (*cations*) being equal to the total charge on the negative ions (*anions*). Thus, although a solution may contain charged particles, it remains neutral. The increased osmotic pressure of such solutions is due to the increased number of particles formed in the process of ionization. For example, sodium chloride is assumed to dissociate as



It is evident that each molecule of sodium chloride that is dissociated produces two ions, and if dissociation is complete, there will be twice as many particles as would be the case if it were not dissociated at all. Furthermore, if each ion has the same effect on osmotic pressure as a molecule, it might be expected that the osmotic pressure of the solution would be twice that of a solution containing the same molal concentration of a nonionizing solute.

Osmotic-pressure data indicate that, in very dilute solutions of salts that yield two ions, the pressure is very nearly double that of solutions of equimolar concentrations of nonelectrolytes. Similar magnification of vapor-pressure lowering, boiling-point elevation, and freezing-point depression occurs in dilute solutions of electrolytes.

Van't Hoff defined a factor, *i*, as the ratio of the colligative effect produced by a concentration, *m*, of electrolyte, divided by the effect observed for the same concentration of nonelectrolyte, or

$$i = \frac{\pi}{(\pi)_0} = \frac{\Delta P}{(\Delta P)_0} = \frac{\Delta T_b}{(\Delta T_b)_0} = \frac{\Delta T_f}{(\Delta T_f)_0} \quad (1)$$

in which π , ΔP , ΔT_b , ΔT_f refer to the osmotic pressure, vapor-pressure lowering, boiling-point elevation, and freezing-point depression, respectively, of the electrolyte. The terms $(\pi)_0$ and so on refer to the nonelectrolyte of the same concentration. In general, with strong electrolytes (those assumed to be 100% ionized), the van't Hoff factor is equal to the number of ions produced when the electrolyte goes into solution (2 for NaCl and MgSO₄, 3 for CaCl₂ and Na₂SO₄, 4 for FeCl₃ and Na₃PO₄, etc).

In very dilute solutions the osmotic pressure, vapor-pressure lowering, boiling-point elevation, and freezing-point depression of solutions of electrolytes approach values two, three, four, or more times greater (depending on the type of strong electrolyte) than in solutions of the same molality of nonelectrolyte, thus confirming the hypothesis that an ion has the same primary effect as a molecule on colligative properties. It bears repeating, however, that two other effects are observed as the concentration of electrolyte is increased.

The first effect results in less than 2-, 3-, or 4-fold intensification of a colligative property. This reduction is ascribed to interionic attraction between the positive and negatively charged ions, in consequence of which the ions are not dissociated completely from each other and do not exert their full effect on vapor pressure and other colligative properties. This deviation generally increases with increasing concentration of electrolyte.

The second effect intensifies the colligative properties and is attributed to the attraction of ions for solvent molecules (called *solvation*, or, if water is the solvent, *hydration*), which holds the solvent in solution and reduces its escaping tendency, with a consequent enhancement of the vapor-pressure lowering. Solvation also reduces interionic attraction and, thereby, further lowers the vapor pressure.

CONDUCTIVITY

The ability of metals to conduct an electric current results from the mobility of electrons in the metals. This type of conductivity is called *metallic conductance*. On the other hand, various chemical compounds—notably acids, bases, and salts—conduct electricity by virtue of ions present or formed, rather than by

electrons. This is called *electrolytic conductance*, and the conducting compounds are electrolytes. Although the fact that certain electrolytes conduct electricity in the molten state is important, their behavior when dissolved in a solvent, particularly in water, is of greater concern in pharmaceutical science.

The electrical conductivity (or conductance) of a solution of an electrolyte is merely the reciprocal of the resistance of the solution. Therefore, to measure conductivity is actually to measure electrical resistance, commonly with a *Wheatstone bridge apparatus*, and then to calculate the conductivity. Figure 17-1 is a representation of the component parts of the apparatus.

The solution to be measured is placed in a glass or quartz cell having two inert electrodes, commonly made of platinum or gold and coated with spongy platinum to absorb gases, across which passes an alternating current generated by an oscillator at a frequency of about 1000 Hz. The reason for using alternating current is to reverse the electrolysis that occurs during flow of current that would cause polarization of the electrodes and lead to abnormal results. The size of the electrodes and their distance apart may be varied to reduce very high resistance or increase very low resistance to increase the accuracy and precision of measurement. Thus, solutions of high conductance (low resistance) are measured in cells having small electrodes relatively far apart, whereas solutions of low conductance (high resistance) are measured in cells with large electrodes placed close to each other.

Electrolytic resistance, like metallic resistance, varies directly with the length of the conducting medium and inversely with its cross-sectional area. The known resistance required for the circuit is provided by a resistance box containing calibrated coils. Balancing of the bridge may be achieved by sliding a contact over a wire of uniform resistance until no (or minimum) current flows through the circuit, as detected either visually with a cathode-ray oscilloscope or audibly with earphones.

The resistance, in ohms, is calculated by the simple procedure used in the Wheatstone bridge method. The reciprocal of the resistance is the conductivity, the units of which are *reciprocal ohms* (also called *mho*). As the numerical value of the conductivity will vary with the dimensions of the conductance cell, the value must be calculated as *specific conductance*, L , which is the conductance in a cell having electrodes of 1-cm² cross-sectional area and 1 cm apart. If the dimensions of the cell used in the experiment were known, calculating the specific conductance would be possible. Nevertheless, this information actually is not required, because calibrating a cell by measuring in it the conductivity of a standard solution of known specific conductance is possible—and much more convenient—and then calculating a *cell constant*. Because this constant is a function only of the dimensions of the cell, it can be used to

convert all measurements in that cell to specific conductivity. Solutions of known concentration of pure potassium chloride are used as standard solutions for this purpose.

EQUIVALENT CONDUCTANCE—In studying the variation of conductance of electrolytes with dilution it is essential to make allowance for dilution so that the comparison of conductances may be made for identical amounts of solute. This may be achieved by expressing conductance measurements in terms of *equivalent conductance*, Λ , which is obtained by multiplying the specific conductance, L , by the volume in milliliters, V_e , of a solution containing 1 g-eq of solute. Thus,

$$\Lambda = LV_e = \frac{1000L}{C} \quad (2)$$

where C is the concentration of electrolyte in the solution in g-eq/L, that is, the normality of the solution. For example, the equivalent conductance of 0.01 *N* potassium chloride solution, which has a specific conductance of 0.001413 mho/cm, may be calculated in either of the following ways:

$$\Lambda = 0.001413 \times 100,000 = 141.3 \text{ mho cm}^2/\text{eq}$$

or

$$\Lambda = \frac{1000 \times 0.001413}{0.01} = 141.3$$

STRONG AND WEAK ELECTROLYTES—Electrolytes are classified broadly as *strong electrolytes* and *weak electrolytes*. The former category includes solutions of strong acids, strong bases, and most salts; the latter includes weak acids and bases, primarily organic acids, amines, and a few salts. The usual criterion for distinguishing between strong and weak electrolytes is the extent of *ionization*. An electrolyte existing entirely or very largely as ions is considered a strong electrolyte, while one that is a mixture of some molecular species along with ions derived from it is a weak electrolyte. For the purposes of this discussion, classification of electrolytes as strong or weak will be based on certain conductance characteristics exhibited in aqueous solution.

The equivalent conductances of some electrolytes, at different concentrations, are given in Table 17-1 and for certain of these electrolytes again in Figure 17-2, where the equivalent conductance is plotted against the square root of concentration. By plotting the data in this manner a linear relationship is observed for strong electrolytes, while a steeply rising curve is noted for weak electrolytes; this difference is a characteristic that distinguishes strong and weak electrolytes. The interpretation of the steep rise in the equivalent conductance of weak electrolytes is that the degree of ionization increases with dilution, becoming complete at infinite dilution.

Interionic interference effects generally have a minor role in the conductivity of weak electrolytes. With strong electrolytes, which are usually completely ionized, the increase in equivalent conductance results not from increased ionization but from diminished ionic interference as the solution is diluted, in

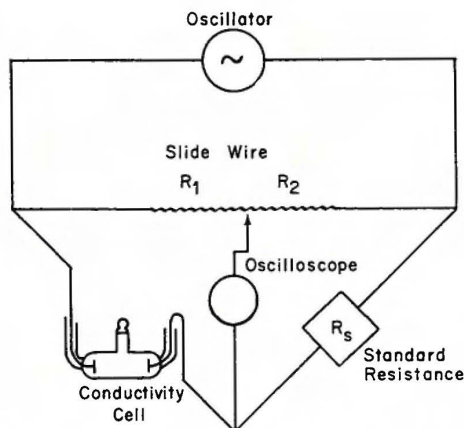


Figure 17-1. Alternating current Wheatstone bridge for measuring conductivity.

Table 17-1. Equivalent Conductances^a at 25°

g-Eq/L	HCl	HOAc	NaCl	KCl	NaI	KI	NaOAc
Inf dil	426.1	390.6 ^a	126.5	149.9	126.9	150.3	91.0
0.0005	422.7	67.7	124.5	147.8	125.4	—	89.2
0.0010	421.4	49.2	123.7	146.9	124.3	—	88.5
0.0050	415.8	22.9	120.6	143.5	121.3	144.4	85.7
0.0100	412.0	16.3	118.5	141.3	119.2	142.2	83.8
0.0200	407.2	11.6	115.8	138.3	116.7	139.5	81.2
0.0500	399.1	7.4	111.1	133.4	112.8	135.0	76.9
0.1000	391.3	5.2	106.7	129.0	108.8	131.1	72.8

^a The equivalent conductance at infinite dilution for acetic acid, a weak electrolyte, is obtained by adding the equivalent conductances of hydrochloric acid and sodium acetate and subtracting that of sodium chloride.

consequence of which ions have greater freedom of mobility (ie, increased conductance).

The value of the equivalent conductance extrapolated to infinite dilution (zero concentration), designated by the symbol Λ_0 , has special significance. It represents the equivalent conductance of the completely ionized electrolyte when the ions are so far apart that there is no interference with their migration due to interionic interactions. It has been shown, by Kohlrausch, that the equivalent conductance of an electrolyte at infinite dilution is the sum of the equivalent conductances of its component ions at infinite dilution, expressed symbolically as

$$\Lambda_0 = l_0(\text{cation}) + l_0(\text{anion}) \quad (3)$$

The significance of Kohlrausch's law is that each ion, at infinite dilution, has a characteristic value of conductance that is independent of the conductance of the oppositely charged ion with which it is associated. Thus, if the equivalent conductances of various ions are known, the conductance of any electrolyte may be calculated simply by adding the appropriate ionic conductances.

As the fraction of current carried by cations (*transference number* of the cations) and by anions (*transference number* of anions) in an electrolyte may be determined readily by experiment, ionic conductances are known. Table 17-2 gives the

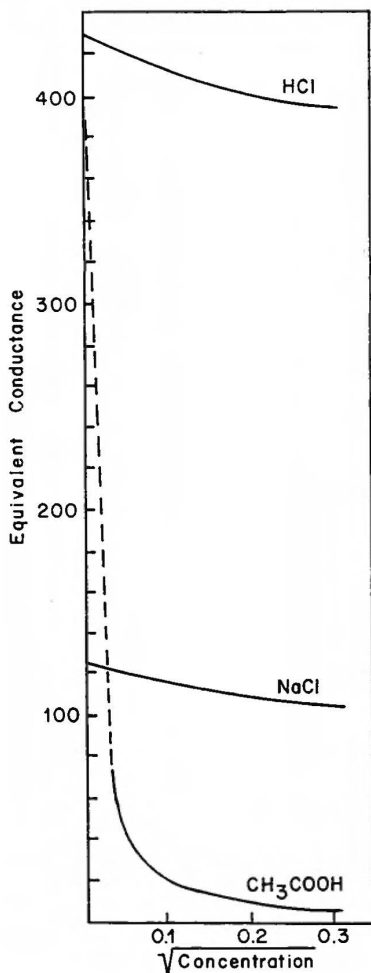


Figure 17-2. Variation of equivalent conductance with square root of concentration.

Table 17-2. Equivalent Ionic Conductivities at Infinite Dilution, at 25°

CATIONS	l_0	ANIONS	l_0
H ⁺	349.8	OH ⁻	198.0
Li ⁺	38.7	Cl ⁻	76.3
Na ⁺	50.1	Br ⁻	78.4
K ⁺	73.5	I ⁻	76.8
NH ₄ ⁺	61.9	AcO ⁻	40.9
½Ca ²⁺	59.5	½SO ₄ ²⁻	79.8
½Mg ²⁺	53.0		

equivalent ionic conductances at infinite dilution of some cations and anions. It is not necessary to have this information to calculate the equivalent conductance of an electrolyte, for Kohlrausch's law permits the latter to be calculated by adding and subtracting values of Λ_0 for appropriate electrolytes. For example, the value of Λ_0 for acetic acid may be calculated as

$$\Lambda_0(\text{CH}_3\text{COOH}) = \Lambda_0(\text{HCl}) + \Lambda_0(\text{CH}_3\text{COONa}) - \Lambda_0(\text{NaCl})$$

which is equivalent to

$$l_0(\text{H}^+) + l_0(\text{CH}_3\text{COO}^-) = l_0(\text{H}^+) + l_0(\text{Cl}^-) + (l_0(\text{Na}^+) + l_0(\text{CH}_3\text{COO}^-) - l_0(\text{Na}^+) - l_0(\text{Cl}^-))$$

This method is especially useful for calculating for weak electrolytes such as acetic acid. As evident from Figure 17-2, the Λ_0 value for acetic acid cannot be determined accurately by extrapolation because of the steep rise of conductance in dilute solutions. For strong electrolytes, on the other hand, the extrapolation can be made very accurately. Thus, in the example above, the values of for HCl, CH₃COONa, and NaCl are determined easily by extrapolation as the substances are strong electrolytes. Substitution of these extrapolated values, as given in Table 17-2, yields a value of 390.6 for the value of Λ_0 for CH₃COOH.

IONIZATION OF WEAK ELECTROLYTES—When Arrhenius introduced his theory of ionization he proposed that the degree of ionization, α , of an electrolyte is measured by the ratio

$$\alpha = \Lambda/\Lambda_0 \quad (4)$$

where Λ is the equivalent conductance of the electrolyte at any specified concentration of solution and Λ_0 is the equivalent conductance at infinite dilution. As strong electrolytes were then not recognized as being 100% ionized, and interionic interference effects had not been evaluated, he believed the equation to be applicable to both strong and weak electrolytes. It now is known that the apparent variation of ionization of strong electrolytes arises from a change in the mobility of ions at different concentrations, rather than from varying ionization, so the equation is not applicable to strong electrolytes. It does provide, however, a generally acceptable approximation of the degree of ionization of weak electrolytes, for which deviations resulting from neglect of activity coefficients and of some change of ionic mobilities with concentration are, for most purposes, negligible. The following example illustrates the use of the equation to calculate the degree of ionization of a typical weak electrolyte.

Example—Calculate the degree of ionization of $1 \times 10^{-3} N$ acetic acid, the equivalent conductance of which is 48.15 mho cm²/eq. The equivalent conductance at infinite dilution is 390.6 mho cm²/eq.

$$\alpha = \frac{48.15}{390.6} = 0.12$$

$$\% \text{ ionization} = 100\alpha = 12\%$$

The degree of dissociation also can be calculated using the van't Hoff factor, i , and

$$\alpha = \frac{i-1}{v-1} \quad (5)$$

where v is the number of ions into which the electrolyte dissociates.

Example—A $1.0 \times 10^{-3} N$ solution of acetic acid has a van't Hoff factor equal to 1.12. Calculate the degree of dissociation of the acid at this concentration.

$$\alpha = \frac{i-1}{v-1} = \frac{1.12-1}{2-1} = 0.12$$

This result agrees with that obtained using equivalent conductance and Equation 4.

MODERN THEORIES

The Arrhenius theory explains why solutions of electrolytes conduct electricity, and why they exhibit enhanced colligative properties. The theory is satisfactory for solutions of weak electrolytes. Several deficiencies, however, do exist when it is applied to solutions of strong electrolytes. It does not explain the failure of strong electrolytes to follow the law of mass action as applied to ionization; discrepancies exist between the degree of ionization calculated from the van't Hoff factor and the conductivity ratio for strong electrolyte solutions having concentrations greater than about 0.5 M .

These deficiencies can be explained by the following observations

1. In the molten state, strong electrolytes are excellent conductors of electricity. This suggests that these materials are already ionized in the crystalline state. Further support for this is given by x-ray studies of crystals, which indicate that the units comprising the basic lattice structure of strong electrolytes are ions.
2. Arrhenius neglected the fact that ions in solution, being oppositely charged, tend to associate through electrostatic attraction. In solutions of weak electrolytes, the number of ions is not large and it is not surprising that electrostatic attractions do not cause appreciable deviations from theory. In dilute solutions, in which strong electrolytes are assumed to be 100% ionized, the number of ions is large, and interionic attractions become major factors in determining the chemical properties of these solutions. These effects should, and do, become more pronounced as the concentration of electrolyte or the valence of the ions is increased.

It is not surprising, therefore, that the Arrhenius theory of partial ionization involving the law of mass action and neglecting ionic charge does not hold for solutions of strong electrolytes. Neutral molecules of strong electrolytes, if they do exist in solution, must arise from interionic attraction rather than from incomplete ionization.

ACTIVITY AND ACTIVITY COEFFICIENTS—Due to increased electrostatic attractions as a solution becomes more concentrated, the concentration of an ion becomes less efficient as a measure of its net effectiveness. A more efficient measure of the physical or chemical effectiveness of an ion is known as its *activity*, which is a measure of the concentration of an ion related to its concentration at a universally adopted reference-standard state. The relationship between the activity and the concentration of an ion can be expressed as

$$a = m\gamma \quad (6)$$

where m is the molal concentration, γ is the activity coefficient, and a is the activity. The activity also can be expressed in terms of molar concentration, c , as

$$a = f c \quad (7)$$

where f is the activity coefficient on a molar scale. In dilute solutions (below 0.01 M) the two activity coefficients are identical, for all practical purposes.

The activity coefficient may be determined in various ways, such as measuring colligative properties, electromotive force,

solubility, or distribution coefficients. For a strong electrolyte, the mean ionic activity coefficient, γ_{\pm} or f_{\pm} , provides a measure of the deviation of the electrolyte from ideal behavior. The mean ionic activity coefficients on a molal basis for several strong electrolytes are given in Table 17-2. It is characteristic of the electrolytes that the coefficients at first decrease with increasing concentration, pass through a minimum and finally increase with increasing concentration of electrolyte.

IONIC STRENGTH—Ionic strength is a measure of the intensity of the electrical field in a solution and may be expressed as

$$\mu = \frac{1}{2} \sum c_i z_i^2 \quad (8)$$

where z_i is the valence of ion i . The mean ionic activity coefficient is a function of ionic strength as are such diverse phenomena as solubilities of sparingly soluble substances, rates of ionic reactions, effects of salts on pH of buffers, electrophoresis of proteins, and so on.

The greater effectiveness of ions of higher charge on a specific property, compared with the effectiveness of the same number of singly charged ions, generally coincides with the ionic strength calculated by Equation 8. The variation of ionic strength with the valence (charge) of the ions comprising a strong electrolyte should be noted.

For univalent cations and univalent anions (called *uniunivalent* or 1-1) electrolytes, the ionic strength is identical with molarity. For bivalent cation and univalent anion (*biunivalent* or 2-1) electrolytes, or univalent cation and bivalent anion (*unibivalent* or 1-2) electrolytes, the ionic strength is three times the molarity. For bivalent cation and bivalent anion (*bibivalent* or 2-2) electrolytes, the ionic strength is four times the molarity. These relationships are evident from the following example.

Example—Calculate the ionic strength of 0.1 M solutions of NaCl, Na_2SO_4 , MgCl_2 , and MgSO_4 , respectively, for

$$\text{NaCl } \mu = \frac{1}{2} (0.1 \times 1^2 + 0.1 \times 1^2) = 0.1$$

$$\text{Na}_2\text{SO}_4 \mu = \frac{1}{2} (0.2 \times 1^2 + 0.1 \times 2^2) = 0.3$$

$$\text{MgCl}_2 \mu = \frac{1}{2} (0.1 \times 2^2 + 0.2 \times 1^2) = 0.3$$

$$\text{MgSO}_4 \mu = \frac{1}{2} (0.1 \times 2^2 + 0.1 \times 2^2) = 0.4$$

The ionic strength of a solution containing more than one electrolyte is the sum of the ionic strengths of the individual salts comprising the solution. For example, the ionic strength of a solution containing NaCl, Na_2SO_4 , MgCl_2 , and MgSO_4 , each at a concentration of 0.1 M , is 1.1.

DEBYE-HUCKEL THEORY—The *Debye-Huckel equations*, which are applicable only to very dilute solutions (about 0.02 μ), may be extended to somewhat more concentrated solutions (about 0.1 μ) in the simplified form

$$\log f_i = \frac{-0.51 z_i^2 \sqrt{\mu}}{1 + \sqrt{\mu}} \quad (9)$$

The mean ionic activity coefficient for aqueous solutions of electrolytes at 25° can be expressed as

$$\log f_{\pm} = \frac{-0.51 z_+ z_- \sqrt{\mu}}{1 + \sqrt{\mu}} \quad (10)$$

in which z_+ is the valence of the cation and z_- is the valence of the anion. When the ionic strength of the solution becomes high (approximately 0.3 to 0.5), these equations become inadequate and a linear term in μ is added. This is illustrated for the mean ionic activity coefficient,

$$\log f_{\pm} = \frac{-0.51 z_+ z_- \sqrt{\mu}}{1 + \sqrt{\mu}} + K_{\pm} \mu \quad (11)$$

Table 17-3. Values of Some Salting-Out Constants for Various Barbiturates at 25°

BARBITURATE	KCl	KBr	NaCl	NaBr
Amobarbital	0.168	0.095	0.212	0.143
Aprobarbital	0.136	0.062	0.184	0.120
Barbital	0.092	0.042	0.136	0.088
Phenobarbital	0.092	0.034	0.132	0.078
Vinbarbital	0.125	0.036	0.143	0.096

in which K_s is a *salting-out* constant chosen empirically for each salt. This equation is valid for solutions with ionic strength up to approximately 1.

SALTING-OUT EFFECT—The aqueous solubility of a slightly soluble organic substance generally is affected markedly by the addition of an electrolyte. This effect is particularly noticeable when the electrolyte concentration reaches 0.5 *M* or higher. If the aqueous solution of the organic substance has a dielectric constant lower than that of pure water, its solubility is decreased and the substance is *salted-out*. The use of high concentrations of electrolytes, such as ammonium sulfate or sodium sulfate, for the separation of proteins by differential precipitation is perhaps the most striking example of this effect. The aqueous solutions of a few substances such as hydrocyanic acid, glycine, and cystine have a higher dielectric constant than that of pure water, and these substances are *salted-in*. These phenomena can be expressed empirically as

$$\log S = \log S_0 \pm K_s m \quad (12)$$

in which S_0 represents the solubility of the organic substance in pure water and S is the solubility in the electrolyte solution. The slope of the straight line obtained by plotting $\log S$ versus m is positive for salting-in and negative for salting-out. In terms of ionic strength this equation becomes

$$\log S = \log S_0 \pm K'_s \mu \quad (13)$$

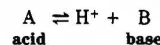
where $K'_s = K_s$ for univalent salts, $K'_s = K_s/3$ for univalent salts, and $K'_s = K_s/4$ for bivalent salts. The salting-out constant depends on the temperature as well as the nature of both the organic substance and the electrolyte. The effect of the electrolyte and the organic substance can be seen in Table 17-3. In all instances, if the anion is constant, the sodium cation has a greater salting-out effect than the potassium cation, probably due to the higher charge density of the former. Although the reasoning is less clear, it appears that, for a constant cation, chloride anion has a greater effect than bromide anion upon the salting-out phenomenon.

ACIDS AND BASES

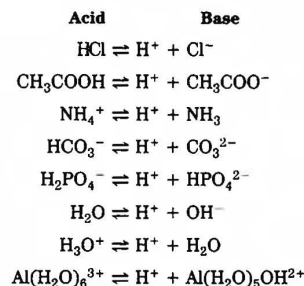
Arrhenius defined an acid as a substance that yields hydrogen ions in aqueous solution and a base as a substance that yields hydroxyl ions in aqueous solution. Except for the fact that hydrogen ions neutralize hydroxyl ions to form water, no complementary relationship between acids and bases (eg, that between oxidants and reductants) is evident in Arrhenius' definitions for these substances; rather, their oppositeness of character is emphasized. Moreover, no account is taken of the behavior of acids and bases in nonaqueous solvents. Also, although acidity is associated with so elementary a particle as the proton (hydrogen ion), basicity is attributed to so relatively complex an association of atoms as the hydroxyl ion. It would seem that a simpler concept of a base could be devised.

PROTON CONCEPT—In pondering the objections to Arrhenius' definitions, Brønsted and Bjerrum in Denmark and Lowry in England developed, and in 1923 announced, a more satisfactory, and more general, theory of acids and bases. According to this theory, an acid is a substance capable of yielding

a proton (hydrogen ion), whereas a base is a substance capable of accepting a proton. This complementary relationship may be expressed by

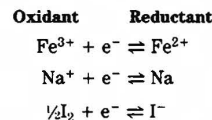


The pair of substances thus related through mutual ability to gain or lose a proton is called a conjugate acid–base pair. Specific examples of such pairs are

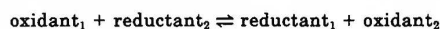


It is apparent that not only molecules, but also cations and anions, may function as acids or bases.

The complementary nature of the acid–base pairs listed is reminiscent of the complementary relationship of pairs of oxidants and reductants where, however, the ability to gain or lose one or more electrons—rather than protons—is the distinguishing characteristic.

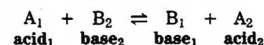


However, these examples of acid–base pairs and oxidant–reductant pairs represent reactions that are possible in principle only. Ordinarily acids will not release free protons any more than reductants will release free electrons. That is, protons and electrons, respectively, can be transferred only from one substance (an ion, atom, or molecule) to another. Thus, it is a fundamental fact of chemistry that oxidation of one substance will occur only if reduction of another substance occurs simultaneously. Stated in another way, electrons will be released from the reductant (oxidation) only if an oxidant capable of accepting electrons (reduction) is present. For this reason oxidation–reduction reactions must involve two conjugate oxidant–reductant pairs of substances:



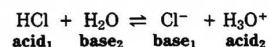
where Subscript 1 represents one conjugate oxidant–reductant pair and Subscript 2 represents the other.

Similarly, an acid will not release a proton unless a base capable of accepting it is present simultaneously. This means that any actual manifestation of acid–base behavior must involve interaction between two sets of conjugate acid–base pairs, represented as



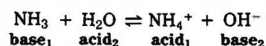
In such a reaction, which is called *protolysis* or a *protolytic reaction*, A_1 and B_1 constitute one conjugate acid–base pair, and A_2 and B_2 the other; the proton given up by A_1 (which thereby becomes B_1) is transferred to B_2 (which becomes A_2).

When an acid, such as hydrochloric, is dissolved in water, a *protolytic reaction* occurs.

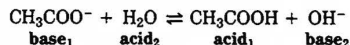


The ionic species H_3O^+ , called *hydronium* or *oxonium* ion, always is formed when an acid is dissolved in water. Often, for purposes of convenience, this is written simply as H^+ and is called hydrogen ion, although the "bare" ion practically is non-existent in solution.

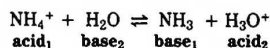
When a base (eg, ammonia) is dissolved in water, the reaction of protolysis is



The proton theory of acid–base function makes the concept of hydrolysis superfluous. When, for example, sodium acetate is dissolved in water, this acid–base interaction occurs



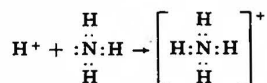
In an aqueous solution of ammonium chloride the reaction is



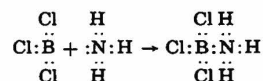
Transfer of protons (protolysis) is not limited to dissimilar conjugate acid–base pairs. In the preceding examples H_2O sometimes behaves as an acid and at other times as a base. Such an amphoteric substance is called, in Brønsted's terminology, an *amphiprotic substance*.

ELECTRON-PAIR CONCEPT—The proton concept of acids and bases provides a more general definition for these substances, but it does not indicate the basic reason for proton transfer, nor does it explain how such substances as sulfur trioxide, boron trichloride, stannic chloride, or carbon dioxide—none of which is capable of donating a proton—can behave as acids. Both deficiencies of the proton theory are avoided in the more inclusive definition of acids and bases proposed by Lewis in 1923. In 1916 he proposed that sharing of a pair of electrons by two atoms established a bond (covalent) between the atoms; therefore, an acid is a substance capable of sharing a pair of electrons made available by another substance called a base, thereby forming a *coordinate covalent bond*. The base is the substance that donates a share in its electron pair to the acid.

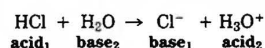
The following equation illustrates how Lewis' definitions explain the transfer of a proton (hydrogen ion) to ammonia to form ammonium ion.



The reaction of boron trichloride, which according to the Lewis theory is an acid, with ammonia is similar, for the boron lacks an electron pair if it is to attain a stable octet configuration, while ammonia has a pair of electrons that may be shared, thus,



LEVELING EFFECT OF A SOLVENT—When the strong acids such as HClO_4 , H_2SO_4 , HCl , or HNO_3 are dissolved in water, the solutions—if they are of identical normality and are not too concentrated—all have about the same hydrogen-ion concentration, indicating the acids to be of about the same strength. The reason for this is that each one of the acids undergoes practically complete protolysis in water.



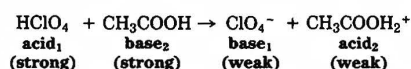
This phenomenon, called the *leveling effect of water*, occurs whenever the added acid is stronger than the hydronium ion. Such a reaction manifests the tendency of proton-transfer re-

actions to proceed spontaneously in the direction of forming a weaker acid or weaker base.

Since the strongest acid that can exist in an amphiprotic solvent is the conjugate acid form of the solvent, any stronger acid will undergo protolysis to the weaker solvent acid. HClO_4 , H_2SO_4 , HCl , or HNO_3 are all stronger acids than the hydronium ion, so they are converted in water to the hydronium ion.

When the strong bases sodium hydride, sodium amide, or sodium ethoxide are dissolved in water, each reacts with water to form sodium hydroxide. These reactions illustrate the leveling effect of water on bases. Because the hydroxide ion is the strongest base that can exist in water, any base stronger than the hydroxide ion undergoes protolysis to hydroxide.

Intrinsic differences in the acidity of acids become evident if they are dissolved in a relatively poor proton acceptor such as anhydrous acetic acid. Perchloric acid (HClO_4), a strong acid, undergoes practically complete reaction with acetic acid to produce the *acetonium* ion (acid_2):



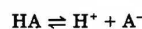
but sulfuric acid and hydrochloric acid behave as weak acids. It is because perchloric acid is a very strong acid when dissolved in glacial acetic acid that it has found many important applications in analytical chemistry as a titrant for a variety of substances that behave as bases in acetic acid. Because of its ability to differentiate the acidity of various acids, it is called a *differentiating solvent for acids*; this property results from its relatively weak proton-acceptor tendency. A solvent that differentiates basicity of different bases must have a weak proton-donor tendency; it is called a *differentiating solvent for bases*. Liquid ammonia is typical of solvents in this category.

Solvents that have both weak proton-donor and proton-acceptor tendencies are called *aprotic solvents* and may serve as differentiating solvents for both acids and bases; they have little if any action on solutes and serve mainly as inert dispersion media for the solutes. Useful aprotic solvents are benzene, toluene, or hexane.

IONIZATION OF ACIDS AND BASES—Acids and bases commonly are classified as strong or weak acids and strong or weak bases depending on whether they are ionized extensively or slightly in aqueous solutions. If, for example, 1 N aqueous solutions of hydrochloric acid and acetic acid are compared, it is found that the former is a better conductor of electricity, reacts much more readily with metals, catalyzes certain reactions more efficiently, and possesses a more acid taste than the latter. Both solutions, however, will neutralize identical amounts of alkali. A similar comparison of 1 N solutions of sodium hydroxide and ammonia reveals the former to be more *active* than the latter, although both solutions will neutralize identical quantities of acid.

The differences in the properties of the two acids is attributed to differences in the concentration of hydrogen (more accurately hydronium) ion, the hydrochloric acid being ionized to a greater extent and thus containing a higher concentration of hydrogen ion than acetic acid. Similarly, most of the differences between the sodium hydroxide and ammonia solutions are attributed to the higher hydroxyl-ion concentration in the former.

The ionization of incompletely ionized acids may be considered a reversible reaction of the type

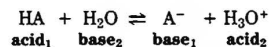


where HA is the molecular acid and A^- is its anion. An equilibrium expression based on the law of mass action may be applied to the reaction

$$K_a = \frac{[\text{H}^+][\text{A}^-]}{[\text{HA}]} \quad (14)$$

where K_a is the ionization or dissociation constant, and the brackets signify concentration. For any given acid in any specified solvent and at any constant temperature, K_a remains relatively constant as the concentration of acid is varied, provided the acid is weakly ionized. With increasingly stronger acids, however, progressively larger deviations occur.

Although the strength of an acid commonly is measured in terms of the ionization or dissociation constant defined in Equation 14, the process of ionization probably is never as simple as shown above. A proton simply will not detach itself from one molecule unless it is accepted simultaneously by another molecule. When an acid is dissolved in water, the latter acts as a base, accepting a proton (Brønsted's definition of a base) by donating a share in a pair of electrons (Lewis' definition of a base). This reaction may be written as



Application of the law of mass action to this reaction gives

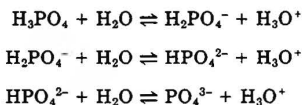
$$K = \frac{[\text{H}_3\text{O}^+][\text{A}^-]}{[\text{HA}][\text{H}_2\text{O}]} \quad (15)$$

Because $[\text{H}_2\text{O}]$ is a constant, this equation may be written

$$K_a = \frac{[\text{H}_3\text{O}^+][\text{A}^-]}{[\text{HA}]} \quad (16)$$

This equation is identical with Equation 14 because $[\text{H}_3\text{O}^+]$ is numerically equal to $[\text{H}^+]$.

Acids that are capable of donating more than one proton are termed *polyprotic*. The ionization of a polyprotic acid occurs in stages and can be illustrated by considering the equilibria involved in the ionization of phosphoric acid:



Application of the law of mass action to this series of reactions gives

$$K_1 = \frac{[\text{H}_2\text{PO}_4^-][\text{H}_3\text{O}^+]}{[\text{H}_3\text{PO}_4]} \quad (17)$$

$$K_2 = \frac{[\text{HPO}_4^{2-}][\text{H}_3\text{O}^+]}{[\text{H}_2\text{PO}_4^-]} \quad (18)$$

$$K_3 = \frac{[\text{PO}_4^{3-}][\text{H}_3\text{O}^+]}{[\text{HPO}_4^{2-}]} \quad (19)$$

If the three expressions for the ionization constants are multiplied together, an overall ionization, K , can be obtained

$$K = K_1K_2K_3 = \frac{[\text{PO}_4^{3-}][\text{H}_3\text{O}^+]^3}{[\text{H}_3\text{PO}_4]} \quad (20)$$

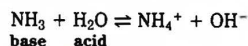
Each of the successive ionizations is suppressed by the hydronium ion formed from preceding stages according to Le Chatelier's principle. The successive dissociation constants always decrease in value, as successive protons must be removed from species that always are charged more negatively. This can be seen from the data in Table 17-4, in which K_1 for phosphoric acid is approximately 100,000 times greater than K_2 , which is in turn approximately 100,000 times greater than K_3 . Although successive dissociation constants are always smaller, the difference is not always as great as it is for phosphoric acid. Tartaric acid, for example, has $K_1 = 9.12 \times 10^{-4}$ and $K_2 = 4.27 \times 10^{-5}$.

Ionization of a base can be illustrated by using the specific substance NH_3 for an example. According to Brønsted and

Table 17-4. Dissociation Constants in Water at 25°

SUBSTANCE		K
Weak acids		
Acetic		1.75×10^{-3}
Acetylsalicylic		3.27×10^{-4}
Barbital		1.23×10^{-8}
Barbituric		1.05×10^{-4}
Benzoic		6.30×10^{-5}
Benzyl penicillin		1.74×10^{-3}
Boric	K_1	5.8×10^{-10}
Caffeine		1×10^{-14}
Carbonic	K_1	4.31×10^{-7}
	K_2	4.7×10^{-11}
Citric (1H ₂ O)	K_1	7.0×10^{-4}
	K_2	1.8×10^{-5}
	K_3	4.0×10^{-7}
Dichloroacetic		5×10^{-2}
Ethylenediaminetetraacetic acid (EDTA)	K_1	1×10^{-2}
	K_2	2.14×10^{-3}
	K_3	6.92×10^{-7}
	K_4	5.5×10^{-11}
Formic		1.77×10^{-4}
Glycerophosphoric	K_1	3.4×10^{-2}
	K_2	6.4×10^{-7}
Glycine	K_1	4.5×10^{-3}
	K_2	1.7×10^{-10}
Lactic		1.39×10^{-4}
Mandelic		4.29×10^{-4}
Monochloroacetic		1.4×10^{-3}
Oxalic (2H ₂ O)	K_1	5.5×10^{-2}
	K_2	5.3×10^{-5}
Phenobarbital		3.9×10^{-8}
Phenol		1×10^{-10}
Phosphoric	K_1	7.5×10^{-3}
	K_2	6.2×10^{-8}
	K_3	2.1×10^{-13}
Picric		4.2×10^{-1}
Propionic		1.34×10^{-5}
Saccharin		2.5×10^{-2}
Salicylic		1.06×10^{-3}
Succinic	K_1	6.4×10^{-5}
	K_2	2.3×10^{-6}
Sulfadiazine		3.3×10^{-7}
Sulfamerazine		8.7×10^{-8}
Sulfapyridine		3.6×10^{-9}
Sulfathiazole		7.6×10^{-8}
Tartaric	K_1	9.6×10^{-4}
	K_2	4.4×10^{-5}
Trichloroacetic		1.3×10^{-1}
Weak bases		
Acetanilide		4.1×10^{-14} (40°)
Ammonia		1.74×10^{-5}
Apomorphine		1.0×10^{-7}
Atropine		4.5×10^{-5}
Benzocaine		6.0×10^{-12}
Caffeine		4.1×10^{-14} (40°)
Cocaine		2.6×10^{-6}
Codeine		9×10^{-7}
Ephedrine		2.3×10^{-5}
Morphine		7.4×10^{-7}
Papaverine		8×10^{-9}
Physostigmine	K_1	7.6×10^{-7}
	K_2	5.7×10^{-13}
Pilocarpine	K_1	7×10^{-8}
	K_2	2×10^{-13}
Procaine		7×10^{-6}
Pyridine		1.4×10^{-9}
Quinine	K_1	1.0×10^{-6}
	K_2	1.3×10^{-10}
Reserpine		4×10^{-8}
Strychnine	K_1	1×10^{-6}
	K_2	2×10^{-12}
Theobromine		4.8×10^{-14} (40°)
Thiourea		1.1×10^{-15}
Urea		1.5×10^{-14}

Lewis, when the base NH_3 is dissolved in water, the latter acts as an acid, donating a proton to NH_3 , which accepts it by offering a share in a pair of electrons on the nitrogen atom. This reaction is written



The equilibrium expression for this reaction is

$$K = \frac{[\text{NH}_4^+][\text{OH}^-]}{[\text{NH}_3][\text{H}_2\text{O}]} \quad (21)$$

With $[\text{H}_2\text{O}]$ constant, this expression may be written

$$K_b = \frac{[\text{NH}_4^+][\text{OH}^-]}{[\text{NH}_3]} \quad (22)$$

IONIZATION OF WATER—Although it is a poor conductor of electricity, pure water does ionize through a process known as *autoprotolysis*, in the following manner:



Application of the law of mass action to this reaction gives

$$K = \frac{[\text{H}_3\text{O}^+][\text{OH}^-]}{[\text{H}_2\text{O}]^2} \quad (23)$$

where K is the equilibrium constant for the reaction. Because the concentration of H_2O (molecular water) is very much greater than either the hydronium-ion or hydroxyl-ion concentrations, it can be considered to be constant and can be combined with K to give a new constant, K_w , known as the *ion product* of water, and Equation 23 becomes

$$K_w = [\text{H}_3\text{O}^+][\text{OH}^-] \quad (24)$$

The numerical value of K_w varies with temperature; at 25° it is approximately equal to 1×10^{-14} .

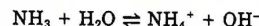
Since the autoprotolysis of pure water yields one hydronium ion for each hydroxyl ion produced, $[\text{H}_3\text{O}^+]$ equal to $[\text{OH}^-]$. At 25° each has a value of 1×10^{-7} mol/L ($1 \times 10^{-7} \times 1 \times 10^{-7} = K_w = 1 \times 10^{-14}$). A solution in which $[\text{H}_3\text{O}^+]$ is equal to $[\text{OH}^-]$ is termed a *neutral* solution.

If an acid is added to water, the hydronium-ion concentration will be increased and the equilibrium between hydronium and hydroxyl ions will be disturbed *momentarily*. To restore equilibrium, some of the hydroxyl ions, originally present in the water, will combine with a *part* of the added hydronium ions to form nonionized water molecules, until the product of the concentrations of the two ions has been reduced to 10^{-14} . When equilibrium again is restored, the concentrations of the two ions no longer will be equal. If, for example, the hydronium-ion concentration is 1×10^{-3} N when equilibrium is established, the concentration of hydroxyl ion will be 1×10^{-11} (the product of the two concentrations being equal to 10^{-14}). As $[\text{H}_3\text{O}^+]$ is much greater than $[\text{OH}^-]$, the solution is said to be *acid* or *acidic*.

In a similar manner, the addition of an alkali to pure water momentarily disturbs the equilibrium between hydronium and hydroxyl ions. To restore equilibrium, some of the hydronium ions originally present in the water will combine with part of the added hydroxyl ions to form nonionized water molecules. The process continues until the product of the hydronium and hydroxyl ion concentrations again is equal to 10^{-14} . Assuming that the final hydroxyl-ion concentration is 1×10^{-4} N, the concentration of hydronium ion in the solution will be 1×10^{-10} . Because $[\text{OH}^-]$ is much greater than $[\text{H}_3\text{O}^+]$, the solution is said to be *basic* or *alkaline*.

RELATIONSHIP OF K_a AND K_b —A particularly interesting and useful relationship between the strength of an acid and its conjugate base, or a base and its conjugate acid, exists. For illustration, consider the strength of the base NH_3 and its

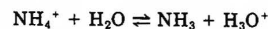
conjugate acid NH_4^+ in water. The behavior of NH_3 as a base is expressed by



for which the equilibrium, as formulated earlier, is

$$K_b = \frac{[\text{NH}_4^+][\text{OH}^-]}{[\text{NH}_3]} \quad (25)$$

The behavior of NH_4^+ as an acid is represented by



The equilibrium constant for this is

$$K_a = \frac{[\text{NH}_3][\text{H}_3\text{O}^+]}{[\text{NH}_4^+]} \quad (26)$$

Multiplying Equations 25 and 26

$$K_a K_b = \frac{[\text{NH}_3][\text{H}_3\text{O}^+][\text{NH}_4^+][\text{OH}^-]}{[\text{NH}_4^+][\text{NH}_3]} \quad (27)$$

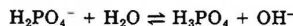
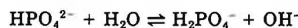
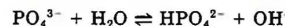
It is obvious that

$$K_w = K_a K_b \quad (28)$$

where K_w is the ion product of water as defined in Equation 24.

The utility of this relationship, which is a general one for any conjugate acid–base pair, is evident from the following deductions: (1) The strength of an acid may be expressed in terms either of the K_a or the K_b of its conjugate base, or *vice versa*; (2) the K_a of an acid may be calculated if the K_b of its conjugate base is known, or *vice versa*; and (3) the stronger an acid is, the weaker its conjugate base, or *vice versa*.

Bases that are capable of interacting with more than one proton are termed *polyacidic*, and can be illustrated by



Applying the law of mass action to this series of reactions, and using the concepts outlined in Equations 25 to 28, the relationship between the various K_a and K_b values for phosphoric acid are

$$K_w = K_{a1} \times K_{b3} = K_{a2} \times K_{b2} = K_{a3} \times K_{b1} \quad (29)$$

where K_{a1} , K_{a2} , and K_{a3} refer to the equilibria given by Equations 17, 18, and 19, respectively; K_{b1} , K_{b2} , and K_{b3} refer to the reaction of PO_4^{3-} , HPO_4^{2-} , and H_2PO_4^- , respectively, with water.

ELECTRONEGATIVITY AND DISSOCIATION CONSTANTS—Table 17-4 gives the dissociation constants of several weak acids and weak bases, in water, at 25° . Strong acids and strong bases do not obey the law of mass action, so dissociation constants cannot be formulated for these strong electrolytes.

Table 17-4 shows that great variations occur in the strength of weak acids and weak bases. The effect of various substituents on the strength of acids and bases depends on the electronegativity of the substituent atom or radical. For example, the substitution of one chlorine atom into the molecule of acetic acid increases the degree of ionization of the acid. Substitution of two chlorine atoms further increases the degree of ionization, and introduction of three chlorine atoms produces a still stronger acid. Acetic acid ionizes primarily because the oxygen atom adjacent to the hydrogen atom of the carboxyl group has a stronger affinity for electrons than the hydrogen atom. Thus, when acetic acid is dissolved in water, the polar molecules of the water have a stronger affinity for the hydrogen of acetic

acid than the hydrogen atoms of water. The acetic acid ionizes as a consequence of this difference in affinities.

When an atom of chlorine is introduced into the acetic acid molecule, forming ClCH_2COOH , the electrons in the molecule are attracted very strongly to the chlorine because of its relatively high electronegativity; the bond between the hydrogen and the oxygen in the carboxyl group is thereby weakened, and the degree of ionization increased. Introduction of two or three chlorine atoms weakens the bond further and increases the strength of the acid. On the other hand, substitution of chlorine into the molecule of ammonia reduces the strength of the base because of its decreased affinity for the hydrogen ion.

IONIC STRENGTH AND DISSOCIATION CONSTANTS—

Most solutions of pharmaceutical interest are in a concentration range such that the ionic strength of the solution may have a marked effect on ionic equilibria and observed dissociation constants. One method of correcting dissociation constants for solutions with an ionic strength up to about 0.3 is to calculate an apparent dissociation constant, pK'_a , as

$$pK'_a = pK_a + \frac{0.51(2Z - 1)\sqrt{\mu}}{1 + \sqrt{\mu}} \quad (30)$$

in which pK_a is the tabulated thermodynamic dissociation constant, Z is the charge on the acid, and μ is the ionic strength.

Example—Calculate pK'_2 for succinic acid at an ionic strength of 0.1. Assume that pK_2 is 5.63. The charge on the acid species is -1.

$$pK'_2 = 5.63 + \frac{0.51(-2 - 1)\sqrt{0.1}}{1 + \sqrt{0.1}} = 5.63 - 0.37 = 5.26$$

DETERMINATION OF DISSOCIATION CONSTANTS

—Although the dissociation constant of a weak acid or base can be obtained in a wide variety of ways including conductivity measurements, absorption spectrometry and partition coefficients, the most widely used method is potentiometric pH measurement (see *Potentiometry*, page 242). The simplest method involving potentiometric pH measurement is based on the measurement of the hydronium-ion concentration of a solution containing equimolar concentrations of the acid and a strong-base salt of the acid. The principle of this method is evident from an inspection of Equation 16; when equimolar concentrations of HA (the acid) and A^- (the salt) are present, the dissociation constant, K_a , numerically is equal to the hydronium-ion concentration (also, the pK_a of the acid is equal to the pH of the solution). Although this method is simple and rapid, the dissociation constant obtained is not sufficiently accurate for many purposes.

To obtain the dissociation constant of a weak acid with a high degree of accuracy and precision, a dilute solution of the acid (about 10^{-3} to $10^{-4} M$) is titrated with a strong base, and the pH of the solution taken after each addition of base. The resulting data can be handled in a wide variety of ways, perhaps the best of which is the method proposed by Benet and Goyan.¹ The proton balance equation for a weak acid, HA, being titrated with a strong base such as KOH, would be

$$[\text{K}^+] + [\text{H}_3\text{O}^+] = [\text{OH}^-] + [\text{A}^-] \quad (31)$$

in which $[\text{K}^+]$ is the concentration of the base added. Equation 31 can be rearranged to give

$$Z = [\text{A}^-] = [\text{K}^+] + [\text{H}_3\text{O}^+] - [\text{OH}^-] \quad (32)$$

When a weak monoprotic acid is added to water, it can exist in the unionized form, HA, and in the ionized form, A^- . After equilibrium is established, the sum of the concentrations of both species must be equal to C_a , the stoichiometric (added) concentration of acid, or

$$C_a = [\text{HA}] + [\text{A}^-] = [\text{HA}] + Z \quad (33)$$

The term $[\text{HA}]$ can be replaced using Equation 16 to give

$$C_a = \frac{[\text{H}_3\text{O}^+]Z}{K_a} + Z \quad (34)$$

which can be rearranged to

$$Z = C_a - \frac{Z[\text{H}_3\text{O}^+]}{K_a} \quad (35)$$

According to Equation 35, if Z , which is obtained from the experimental data using Equation 32, is plotted versus the terms $Z[\text{H}_3\text{O}^+]$, a straight line results with a slope equal to $1/K_a$, and an intercept equal to C_a . In addition to obtaining an accurate estimate for the dissociation constant, the stoichiometric concentration of the substance being titrated is also obtained. This is of importance when the substance being titrated cannot be purified, or has an unknown degree of solvation. Similar equations can be developed for obtaining the dissociation constant for a weak base.¹

The dissociation constants for diprotic acids can be obtained by defining P as the average number of protons dissociated per mole of acid, or

$$P = Z/C_a \quad (36)$$

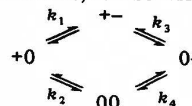
and

$$\frac{[\text{H}_3\text{O}^+]^2 P}{(2 - P)} = K_1 K_2 + \frac{K_1 [\text{H}_3\text{O}^+] (1 - P)}{(2 - P)} \quad (37)$$

A plot of Equation 37 should yield a straight line with a slope equal to K_1 and an intercept of $K_1 K_2$. Dividing the intercept by the slope yields K_2 .

MICRO DISSOCIATION CONSTANTS—The dissociation constants for polyprotic acids, as determined by potentiometric titration, are known generally as *macro*, or *titration*, constants. As it is known that carboxyl groups are stronger acids than protonated amino groups, there is no difficulty in assigning K_1 and K_2 , as determined by Equation 37, to the carboxyl and amino groups, respectively, of a substance such as glycine hydrochloride.

In other chemicals or drugs such as phenylpropanolamine, in which the two acidic groups are the phenolic and the protonated amino group, the assignment of dissociation constants is more difficult. This is because, in general, both groups have dissociation constants of equal magnitude. Thus, there will be two ways of losing the first proton and two ways of losing the second, resulting in four possible species in solution. This can be illustrated using the convention of assigning a plus (+) to a positively charged group, a 0 to an uncharged group, and a minus (-) to a negatively charged group. Thus, +0 would represent the fully protonated phenylpropanolamine, +- the dipolar ion, 00 the uncharged molecule, and 0- the anion. The total ionization scheme, therefore, can be written



The micro constants are related to the macro constants as

$$K_1 = k_1 + k_2 \quad (38)$$

$$K_1 K_2 = k_1 k_3 = k_2 k_4 \quad (39)$$

It can be seen from Equation 38 that unless k_1 or k_2 is very much smaller than the other, the observed macro constant is a composite of the two and cannot be assigned to one or the other acidic group in a nonambiguous way.

Methods for determining k_1 are given by Riegelman *et al.*² and Niebergall *et al.*³ Once k_1 , K_1 , and K_2 have been determined, all of the other micro constants can be obtained from Equations 38 and 39.

The numerical values of hydronium-ion concentration may vary enormously; for a normal solution of a strong acid the value is nearly 1, while for a normal solution of a strong base it is approximately 1×10^{-14} ; there is a variation of 100,000,000,000,000 between these two limits. Because of the inconvenience of dealing with such large numbers, in 1909 Sørensen proposed that hydronium-ion concentration be expressed in terms of the logarithm (log) of its reciprocal. To this value he assigned the symbol pH. Mathematically it is written

$$\text{pH} = \log \frac{1}{[\text{H}_3\text{O}^+]} \quad (40)$$

Since the logarithm of 1 is zero, the equation also may be written

$$\text{pH} = -\log [\text{H}_3\text{O}^+] \quad (41)$$

from which it is evident that pH also may be defined as the negative logarithm of the hydronium-ion concentration. In general, this type of notation is used to indicate the negative logarithm of the term that is preceded by the p , which gives rise to the following

$$\text{pOH} = -\log [\text{OH}^-] \quad (42)$$

$$\text{p}K = -\log K \quad (43)$$

Thus, taking logarithms of Equations 28 and 24 gives

$$\text{p}K_a + \text{p}K_b = \text{p}K_w \quad (44)$$

$$\text{pH} + \text{pOH} = \text{p}K_w \quad (45)$$

The relationship of pH to hydronium-ion and hydroxyl-ion concentrations may be seen in Table 17-5.

The following examples illustrate the conversion from exponential to p notation.

1. Calculate the pH corresponding to a hydronium-ion concentration of 1×10^{-4} g-ion/L.

Solution:

$$\begin{aligned} \text{pH} &= \log \frac{1}{1 \times 10^{-4}} \\ &= \log 10,000 \text{ or } \log (1 \times 10^4) \end{aligned}$$

$$\log (1 \times 10^4) = +4$$

$$\text{pH} = 4$$

Table 17-5. Hydronium-ion and Hydroxyl-ion Concentrations

	pH	NORMALITY IN TERMS OF HYDRONIUM ION	NORMALITY IN TERMS OF HYDROXYL ION
	0	1	10^{-14}
	1	10^{-1}	10^{-13}
	2	10^{-2}	10^{-12}
Increasing acidity	3	10^{-3}	10^{-11}
	4	10^{-4}	10^{-10}
	5	10^{-5}	10^{-9}
	6	10^{-6}	10^{-8}
Neutral point	7	10^{-7}	10^{-7}
	8	10^{-8}	10^{-6}
	9	10^{-9}	10^{-5}
	10	10^{-10}	10^{-4}
	11	10^{-11}	10^{-3}
Increasing alkalinity	12	10^{-12}	10^{-2}
	13	10^{-13}	10^{-1}
	14	10^{-14}	1

2. Calculate the pH corresponding to a hydronium ion-concentration of 0.000036 N (or g-ion/L). (*Note:* This more frequently is written as a number multiplied by a power of 10, thus, 3.6×10^{-5} for 0.000036.)

Solution:

$$\begin{aligned} \text{pH} &= \log \frac{1}{3.6 \times 10^{-5}} \\ &= \log 28,000 \text{ or } \log (2.8 \times 10^4) \end{aligned}$$

$$\log (2.8 \times 10^4) = \log 2.8 + \log 10^4$$

$$\log 2.8 = +0.44$$

$$\log 10^4 = +4.00$$

$$\text{pH} = 4.44$$

This problem also may be solved as follows:

$$\text{pH} = -\log (3.6 \times 10^{-5})$$

$$\log 3.6 = +0.56$$

$$\log 10^{-5} = -5.00$$

$$= -4.44 = \log (3.6 \times 10^{-5})$$

$$\text{pH} = -(-4.44) = +4.44 = 4.44$$

The following examples illustrate the conversion of p notation to exponential notation.

1. Calculate the hydronium-ion concentration corresponding to a pH of 4.44.

Solution:

$$\text{pH} = \log \frac{1}{[\text{H}_3\text{O}^+]}$$

$$4.44 = \log \frac{1}{[\text{H}_3\text{O}^+]}$$

$$\frac{1}{[\text{H}_3\text{O}^+]} = \text{antilog of } 4.44 = 28,000 \text{ (rounded off)}$$

$$[\text{H}_3\text{O}^+] = \frac{1}{28,000} = 0.000036 \text{ or } 3.6 \times 10^{-5}$$

This calculation also may be made as

$$+4.44 = -\log [\text{H}_3\text{O}^+]$$

$$\text{or } -4.44 = +\log [\text{H}_3\text{O}^+]$$

In finding the antilog of -4.44 it should be kept in mind that the *mantissa* (the number to the right of the decimal point) of a log to the base 10 (the common or Briggsian logarithm base) is *always positive* but that the characteristic (the number to the left of the decimal point) may be *positive or negative*. As the entire log -4.44 is negative, it is obvious that one cannot look up the antilog of -0.44 . However, the number -4.44 also may be written $(-5.00 + 0.56)$, or as more often written, $\bar{5}.56$; the bar across the characteristic indicates that it alone is negative, while the rest of the number is positive. Looking up the antilog of 0.56 it is found to be 3.6; as the antilog of -5.00 is 10^{-5} , it follows that the hydronium-ion concentration must be 3.6×10^{-5} mols/L.

2. Calculate the hydronium-ion concentration corresponding to a pH of 10.17.

Solution:

$$10.17 = -\log[\text{H}_3\text{O}^+]$$

$$-10.17 = \log[\text{H}_3\text{O}^+]$$

$$-10.17 = (-11.00 + 0.83) = \bar{11}.83$$

The antilog of 0.83 = 6.8.
 The antilog of -11.00 = 10^{-11}
 The hydronium-ion concentration is therefore 6.8×10^{-11} mol/L.

In the section *Ionization of Water*, it was shown that the hydronium-ion concentration of pure water, at 25°, is 1×10^{-7} N, corresponding to a pH of 7.

This figure, therefore, is designated as the neutral point, and all values below a pH of 7 represent acidity—the smaller the number, the greater the acidity. Values above 7 represent alkalinity—the larger the number, the greater the alkalinity. The pH scale usually runs from 0 to 14, but mathematically there is no reason why negative numbers or numbers above 14 should not be used. In practice, however, such values are never encountered because solutions that might be expected to have such values are too concentrated to be ionized extensively or the interionic attraction is so great as to materially reduce ionic activity.

The pH of the purest water obtainable, so-called 'conductivity water', is 7 when the measurement is made carefully under conditions to exclude carbon dioxide and prevent errors inherent in the measuring technique (such as acidity or alkalinity of the indicator). Upon agitating this water in the presence of carbon dioxide in the atmosphere (equilibrium water), the value drops rapidly to 5.7. This is the pH of nearly all distilled water that has been exposed to the atmosphere for even a short time and often is called 'equilibrium' water.

It should be emphasized strongly that the generalizations stated concerning neutrality, acidity, and alkalinity hold exactly only when (1) the solvent is water, (2) the temperature is 25°, and (3) there are no other factors to cause deviation from the simply formulated equilibria underlying the definition of pH given in the preceding discussion.

SPECIES CONCENTRATION

When a weak acid, H_nA is added to water, $n + 1$ species, including the un-ionized acid, can exist. After equilibrium is established, the sum of the concentrations of all species must be equal to C_a , the stoichiometric (added) concentration of acid. Thus, for a triprotic acid H_3A ,

$$C_a = [H_3A] + [H_2A^-] + [HA^{2-}] + [A^{3-}] \quad (46)$$

In addition, the concentrations of all acidic and basic species in solution vary with pH, and can be represented solely in terms of equilibrium constants and the hydronium-ion concentration. These relationships may be expressed as

$$[H_nA] = [H_3O^+]^n C_a / D \quad (47)$$

$$[H_{n-j}A^{j-}] = [H_3O^+]^{n-j} K_1 \dots K_j C_a / D \quad (48)$$

in which n represents the total number of dissociable hydrogens in the parent acid, j is the number of protons dissociated, C_a is the stoichiometric concentration of acid, and K represents the acid dissociation constants. The term D is a power series in $[H_3O^+]$ and K , starting with $[H_3O^+]$ raised to the n th power. The last term is the product of all the dissociation constants. The intermediate terms can be generated from the last term by substituting $[H_3O^+]$ for K_n to obtain the next-to-last term, then substituting $[H_3O^+]$ for K_{n-1} to obtain the next term, and onward until the first term is reached. The following examples show the denominator, D , to be used for various types of acids:

$$H_3A: D = [H_3O^+]^3 + K_1[H_3O^+]^2 + K_1K_2[H_3O^+] + K_1K_2K_3 \quad (49)$$

$$H_2A: D = [H_3O^+]^2 + K_1[H_3O^+] + K_1K_2 \quad (50)$$

$$HA: D = [H_3O^+] + K_1 \quad (51)$$

The numerator in all instances is C_a , multiplied by the term from the denominator that has $[H_3O^+]$ raised to the $n - j$ power. Thus, for diprotic acids such as carbonic, succinic, tartaric, and so on.

$$[H_2A] = \frac{[H_3O^+]^2 C_a}{[H_3O^+]^2 + K_1[H_3O^+] + K_1K_2} \quad (52)$$

$$[HA^-] = \frac{K_1[H_3O^+] C_a}{[H_3O^+]^2 + K_1[H_3O^+] + K_1K_2} \quad (53)$$

$$[A^{2-}] = \frac{K_1K_2 C_a}{[H_3O^+]^2 + K_1[H_3O^+] + K_1K_2} \quad (54)$$

Example—Calculate the concentrations of all succinic acid species in a 1.0×10^{-3} M solution of succinic acid at pH 6. Assume that $K_1 = 6.4 \times 10^{-6}$ and $K_2 = 2.3 \times 10^{-6}$.

Equations 52-54 have the same denominator, D , which can be calculated as

$$\begin{aligned} D &= [H_3O^+]^2 + K_1[H_3O^+] + K_1K_2 \\ &= 1.0 \times 10^{-12} + 6.4 \times 10^{-6} \times 1.0 \times 10^{-6} + 6.4 \\ &\quad \times 10^{-6} \times 2.3 \times 10^{-6} \\ &= 1.0 \times 10^{-12} + 6.4 \times 10^{-11} + 14.7 \times 10^{-11} \\ &= 21.2 \times 10^{-11} \end{aligned}$$

Therefore,

$$\begin{aligned} [H_2A] &= \frac{[H_3O^+]^2 C_a}{D} \\ &= \frac{1.0 \times 10^{-12} \times 1.0 \times 10^{-3}}{21.2 \times 10^{-11}} = 4.7 \times 10^{-6} M \end{aligned}$$

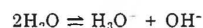
$$\begin{aligned} [HA^-] &= \frac{K_1[H_3O^+] C_a}{D} \\ &= \frac{6.4 \times 10^{-11} \times 1.0 \times 10^{-3}}{21.2 \times 10^{-11}} = 3.0 \times 10^{-4} M \end{aligned}$$

$$\begin{aligned} [A^{2-}] &= \frac{K_1K_2 C_a}{D} \\ &= \frac{14.7 \times 10^{-11} \times 1.0 \times 10^{-3}}{21.2 \times 10^{-11}} = 6.9 \times 10^{-4} M \end{aligned}$$

PROTON-BALANCE EQUATION

In the Brønsted-Lowry system, the total number of protons released by acidic species must equal the total number of protons consumed by basic species. This results in a very useful relationship known as the *proton-balance equation* (PBE), in which the sum of the concentration terms for species that form by proton consumption is equated to the sum of the concentration terms for species that are formed by the release of protons. The PBE forms the basis of a unified approach to pH calculations, as it is an exact accounting of all proton transfers occurring in solution.

When HCl is added to water, for example, it dissociates yielding one Cl^- for each proton released. Thus, Cl^- is a species formed by the release of a proton. In the same solution, and actually in all aqueous solutions



where H_3O^+ is formed by proton consumption and OH^- is formed by proton release. Thus, the PBE is

$$[H_3O^+] = [OH^-] + [Cl^-] \quad (55)$$

In general, the PBE can be formed in the following manner:

1. Start with the species added to water.
2. Place all species that can form when protons are released on the right side of the equation.

- Place all species that can form when protons are consumed on the left side of the equation.
- Multiply the concentration of each species by the number of protons gained or lost to form that species.
- Add $[\text{H}_3\text{O}^+]$ the left side of the equation and $[\text{OH}^-]$ to the right side of the equation. These result from the interaction of two molecules of water as shown above.

Example—When H_3PO_4 is added to water, the species H_2PO_4^- forms with the release of one proton; HPO_4^{2-} forms with the release of two protons; and PO_4^{3-} forms with the release of three protons, which gives the following PBE:

$$[\text{H}_3\text{O}^+] = [\text{OH}^-] + [\text{H}_2\text{PO}_4^-] + 2[\text{HPO}_4^{2-}] + 3[\text{PO}_4^{3-}] \quad (56)$$

Example—When Na_2HPO_4 is added to water, it dissociates into two Na^+ and one HPO_4^{2-} . The sodium ion is neglected in the PBE because it is not formed from the release or consumption of protons. The species HPO_4^{2-} , however, may react with water to give H_2PO_4^- with the consumption of one proton, H_3PO_4 with the consumption of two protons, and PO_4^{3-} with the release of one proton to give the following PBE:

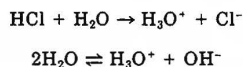
$$[\text{H}_3\text{O}^+] + [\text{H}_2\text{PO}_4^-] + 2[\text{H}_3\text{PO}_4] = [\text{OH}^-] + [\text{PO}_4^{3-}] \quad (57)$$

CALCULATIONS

The pH of solutions of acids, bases, and salts may be calculated using the concepts presented in the preceding sections.

Strong Acids or Bases

When a strong acid such as HCl is added to water, the following reactions occur:



The PBE for this system would be

$$[\text{H}_3\text{O}^+] = [\text{OH}^-] + [\text{Cl}^-] \quad (58)$$

In most instances ($C_a > 4.5 \times 10^{-7} M$) the $[\text{OH}^-]$ would be negligible compared to the Cl^- and the equation simplifies to

$$[\text{H}_3\text{O}^+] = [\text{Cl}^-] = C_a \quad (59)$$

Thus, the hydronium-ion concentration of a solution of a strong acid would be equal to the stoichiometric concentration of the acid. This would be anticipated, because strong acids generally are assumed to be 100% ionized.

The pH of a 0.005 M solution of HCl therefore is calculated as

$$\text{pH} = -\log 0.005 = 2.30$$

In a similar manner the hydroxyl-ion concentration for a solution of a strong base such as NaOH would be

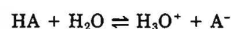
$$[\text{OH}^-] = [\text{Na}^+] = C_b \quad (60)$$

and the pH of a 0.005 M solution of NaOH would be

$$\begin{aligned} \text{pOH} &= -\log 0.005 = 2.30 \\ \text{pH} &= \text{p}K_w - \text{pOH} = 14.00 - 2.30 = 11.70 \end{aligned}$$

Weak Acids or Bases

If a weak acid, HA, is added to water, it will equilibrate with its conjugate base, A^- , as



Accounting for the ionization of water gives the following PBE for this system:

$$[\text{H}_3\text{O}^+] = [\text{OH}^-] + [\text{A}^-] \quad (61)$$

The concentration of A^- as a function of hydronium-ion concentration can be obtained as shown previously to give

$$[\text{H}_3\text{O}^+] = [\text{OH}^-] + \frac{K_a C_a}{[\text{H}_3\text{O}^+] + K_a} \quad (62)$$

Algebraic simplification yields

$$[\text{H}_3\text{O}^+] = K_a \frac{(C_a - [\text{H}_3\text{O}^+] + [\text{OH}^-])}{([\text{H}_3\text{O}^+] - [\text{OH}^-])} \quad (63)$$

In most instances for solutions of weak acids, $[\text{H}_3\text{O}^+] \gg [\text{OH}^-]$, and the equation simplifies to give

$$[\text{H}_3\text{O}^+]^2 + K_a[\text{H}_3\text{O}^+] - K_a C_a = 0 \quad (64)$$

This is a quadratic equation* that yields

$$[\text{H}_3\text{O}^+] = \frac{-K_a + \sqrt{K_a^2 + 4K_a C_a}}{2} \quad (65)$$

since $[\text{H}_3\text{O}^+]$ can never be negative. Furthermore, if $[\text{H}_3\text{O}^+]$ is less than 5% of C_a , Equation 64 is simplified further to give

$$[\text{H}_3\text{O}^+] = \sqrt{K_a C_a} \quad (66)$$

It generally is preferable to use the simplest equation to calculate $[\text{H}_3\text{O}^+]$. However, when $[\text{H}_3\text{O}^+]$ is calculated, it must be compared to C_a in order to determine whether the assumption $C_a \gg [\text{H}_3\text{O}^+]$ is valid. If the assumption is not valid, the quadratic equation should be used.

Example—Calculate the pH of a $5.00 \times 10^{-5} M$ solution of a weak acid having a $K_a = 1.90 \times 10^{-5}$.

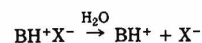
$$\begin{aligned} [\text{H}_3\text{O}^+] &= \sqrt{K_a C_a} \\ &= \sqrt{1.90 \times 10^{-5} \times 5.00 \times 10^{-5}} \\ &= 3.08 \times 10^{-5} M \end{aligned}$$

As C_a ($5.00 \times 10^{-5} M$) is not much greater than $[\text{H}_3\text{O}^+]$, the quadratic equation (Equation 65) should be used.

$$\begin{aligned} [\text{H}_3\text{O}^+] &= \frac{-1.90 \times 10^{-5} + \sqrt{(1.90 \times 10^{-5})^2 + 4(5.00 \times 10^{-5})}}{2} \\ &= 7.06 \times 10^{-3} \\ \text{pH} &= -\log (7.06 \times 10^{-3}) = 2.15 \end{aligned}$$

Note that the assumption $[\text{H}_3\text{O}^+] \gg [\text{OH}^-]$ is valid. The hydronium-ion concentration calculated from Equation 66 has a relative error of about 100% when compared to the correct value obtained from Equation 65.

When a salt obtained from a strong acid and a weak base—such as ammonium chloride, morphine sulfate, or pilocarpine hydrochloride—is dissolved in water, it dissociates as

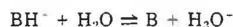


in which BH^+ is the protonated form of the base B, and X^- is the anion of a strong acid. Because X^- is the anion of a strong acid, it is too weak a base to undergo any further reaction with

* The general solution to a quadratic equation of the form

$$aX^2 + bX + c = 0 \quad \text{is} \quad X = \frac{-b \pm \sqrt{b^2 - 4ac}}{2a}$$

water. The protonated base, however, can act as a weak acid to give



Thus, Equations 65 and 66 are valid, with C_b being equal to the concentration of the salt in solution. If K_a for the protonated base is not available, it can be obtained by dividing K_b for the base B, into K_w .

Example—Calculate the pH of a 0.026 M solution of ammonium chloride. Assume that K_b for ammonia is 1.74×10^{-5} and K_w is 1.00×10^{-14} .

$$\begin{aligned} K_w &= \frac{K_a}{K_b} = \frac{1.00 \times 10^{-14}}{1.74 \times 10^{-5}} = 5.75 \times 10^{-10} \\ [\text{H}_3\text{O}^+] &= \sqrt{K_a C_b} \\ &= \sqrt{5.75 \times 10^{-10} \times 2.6 \times 10^{-2}} \\ &= 3.87 \times 10^{-6} \text{ M} \\ \text{pH} &= -\log(3.87 \times 10^{-6}) = 5.41 \end{aligned}$$

As C_b is much greater than $[\text{H}_3\text{O}^+]$ and $[\text{H}_3\text{O}^+]$ is much greater than $[\text{OH}^-]$, the assumptions are valid and the value calculated for pH is sufficiently accurate.

Weak Bases

When a weak base, B, is dissolved in water it ionizes to give the conjugate acid as



The PBE for this system is

$$[\text{BH}^+] + [\text{H}_3\text{O}^+] = [\text{OH}^-] \quad (67)$$

Substituting $[\text{BH}^+]$ as a function of hydronium-ion concentration and simplifying, in the same manner as shown for a weak acid, gives

$$[\text{OH}^-] = K_b \frac{(C_b - [\text{OH}^-] + [\text{H}_3\text{O}^+])}{([\text{OH}^-] - [\text{H}_3\text{O}^+])} \quad (68)$$

If $[\text{OH}^-] \gg [\text{H}_3\text{O}^+]$, as is true generally, then

$$[\text{OH}^-]^2 = K_b[\text{OH}^-] - K_b C_b = 0 \quad (69)$$

which is a quadratic with the following solution:

$$[\text{OH}^-] = \frac{-K_b + \sqrt{K_b^2 + 4K_b C_b}}{2} \quad (70)$$

If $C_b \gg [\text{OH}^-]$, the quadratic equation simplifies to

$$[\text{OH}^-] = \sqrt{K_b C_b} \quad (71)$$

Once $[\text{OH}^-]$ is calculated, it can be converted to pOH, which can be subtracted from p K_w to give pH.

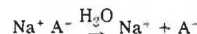
Example—Calculate the pH of a 4.50×10^{-2} M solution of a weak base having $K_b = 2.00 \times 10^{-4}$. Assume that $K_w = 1.00 \times 10^{-14}$.

$$\begin{aligned} [\text{OH}^-] &= \sqrt{K_b C_b} \\ &= \sqrt{2.00 \times 10^{-4} \times 4.50 \times 10^{-2}} \\ &= \sqrt{9.00 \times 10^{-6}} = 3.00 \times 10^{-3} \text{ M} \end{aligned}$$

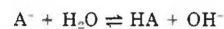
Both assumptions are valid.

$$\begin{aligned} \text{pOH} &= -\log 3.00 \times 10^{-3} = 2.52 \\ \text{pH} &= 14.00 - 2.52 = 11.48 \end{aligned}$$

When salts obtained from strong bases and weak acids (eg, sodium acetate, sodium sulfathiazole, or sodium benzoate) are dissolved in water, they dissociate as



in which A^- is the conjugate base of the weak acid, HA. The Na^+ undergoes no further reaction with water. The A^- , however, acts as a weak base to give



Thus, Equations 70 and 71 are valid, with C_b being equal to the concentration of the salt in solution. The value for K_b can be obtained by dividing K_a for the conjugate acid, HA, into K_w .

Example—Calculate the pH of a 0.05 M solution of sodium acetate. Assume that K_a for acetic acid = 1.75×10^{-5} and $K_w = 1.00 \times 10^{-14}$.

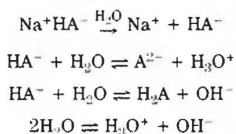
$$\begin{aligned} K_b &= \frac{K_w}{K_a} = \frac{1.00 \times 10^{-14}}{1.75 \times 10^{-5}} \\ &= 5.71 \times 10^{-10} \\ \text{OH}^- &= \sqrt{K_b C_b} = \sqrt{5.71 \times 10^{-10} \times 5.0 \times 10^{-2}} \\ &= 5.34 \times 10^{-6} \text{ M} \end{aligned}$$

Both assumptions are valid:

$$\begin{aligned} \text{pOH} &= -\log(5.34 \times 10^{-6}) = 5.27 \\ \text{pH} &= 14.00 - 5.27 = 8.73 \end{aligned}$$

Ampholytes

Substances such as NaHCO_3 and NaH_2PO_4 are termed *ampholytes*, and are capable of functioning both as acids and bases. When an ampholyte of the type NaHA is dissolved in water, the following series of reactions can occur:



The total PBE for the system is

$$[\text{H}_3\text{O}^+] + [\text{H}_2\text{A}] = [\text{OH}^-] + [\text{A}^{2-}] \quad (72)$$

Substituting both $[\text{H}_2\text{A}]$ and $[\text{A}^{2-}]$ as a function of $[\text{H}_3\text{O}^+]$ (see Equations 52 and 54), yields

$$\begin{aligned} [\text{H}_3\text{O}^+] + \frac{[\text{H}_3\text{O}^+]^2 C_s}{[\text{H}_3\text{O}^+]^2 + K_1[\text{H}_3\text{O}^+] + K_1 K_2} \\ = \frac{K_w}{[\text{H}_3\text{O}^+]} + \frac{K_1 K_2 C_s}{[\text{H}_3\text{O}^+]^2 + K_1[\text{H}_3\text{O}^+] + K_1 K_2} \quad (73) \end{aligned}$$

This gives a fourth-order equation in $[\text{H}_3\text{O}^+]$, which can be simplified using certain judicious assumptions to

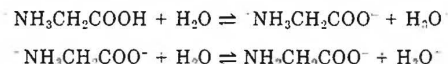
$$[\text{H}_3\text{O}^+] = \sqrt{\frac{K_1 K_2 C_s}{K_1 + C_s}} \quad (74)$$

In most instances, $C_s \gg K_1$, and the equation further simplifies to

$$[\text{H}_3\text{O}^+] = \sqrt{K_1 K_2} \quad (75)$$

and $[\text{H}_3\text{O}^+]$ becomes independent of the concentration of the salt. A special property of ampholytes is that the concentration of the species HA^- is maximum at the pH corresponding to Equation 75.

When the simplest amino acid salt, glycine hydrochloride, is dissolved in water, it acts as a diprotic acid and ionizes as



The form, $\text{NH}_3\text{CH}_2\text{COO}^-$, is an ampholyte because it also can act as a weak base:

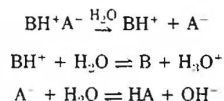


This type of substance, which carries both a charged acidic and a charged basic moiety on the same molecule is termed a *zwitterion*. Because the two charges balance each other, the molecule acts essentially as a neutral molecule. The pH at which the zwitterion concentration is maximum is known as the *isoelectric point*, which can be calculated from Equation 75.

On the acid side of the isoelectric point, amino acids and proteins are cationic and incompatible with anionic materials such as the naturally occurring gums used as suspending and/or emulsifying agents. On the alkaline side of the isoelectric point, amino acids and proteins are anionic and incompatible with cationic materials such as benzalkonium chloride.

Salts of Weak Acids and Weak Bases

When a salt such as ammonium acetate (which is derived from a weak acid and a weak base) is dissolved in water, it undergoes the following reactions:



The total PBE for this system is

$$[\text{H}_3\text{O}^+] + [\text{HA}] = [\text{OH}^-] + [\text{B}] \quad (76)$$

Replacing [HA] and [B] as a function of $[\text{H}_3\text{O}^+]$, gives

$$[\text{H}_3\text{O}^+] + \frac{[\text{H}_3\text{O}^+]\text{C}_s}{[\text{H}_3\text{O}^+] + K_a} = [\text{OH}^-] + \frac{K_a'\text{C}_s}{[\text{H}_3\text{O}^+] + K_a'} \quad (77)$$

in which C_s is the concentration of salt, K_a is the ionization constant of the conjugate acid formed from the reaction between A^- and water, and K_a' is the ionization constant for the protonated base, BH^+ . In general, $[\text{H}_3\text{O}^+]$, $[\text{OH}^-]$, K_a , and K_a' usually are smaller than C_s and the equation simplifies to

$$[\text{H}_3\text{O}^+] = \sqrt{K_a K_a'} \quad (78)$$

Example—Calculate the pH of a 0.01 M solution of ammonium acetate. The ammonium ion has a K_a equal to 5.75×10^{-10} , which represents K_a' in Equation 78. Acetic acid has a K_a of 1.75×10^{-6} , which represents K_a in Equation 78:

$$\begin{aligned} [\text{H}_3\text{O}^+] &= \sqrt{1.75 \times 10^{-6} \times 5.75 \times 10^{-10}} \\ &= 1.00 \times 10^{-7} \\ \text{pH} &= -\log(1.00 \times 10^{-7}) = 7.00 \end{aligned}$$

All of the assumptions are valid.

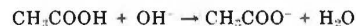
BUFFERS

The terms *buffer*, *buffer solution*, and *buffered solution*, when used with reference to hydrogen-ion concentration or pH, refer to the ability of a system, particularly an aqueous solution, to resist a change of pH on adding acid or alkali, or on dilution with a solvent.

If an acid or base is added to water, the pH of the latter is changed markedly, for water has no ability to resist change of pH; it is completely devoid of buffer action. Even a very weak acid such as carbon dioxide changes the pH of water, decreasing it from 7 to 5.7 when the small concentration of carbon dioxide present in air is equilibrated with pure water. This extreme susceptibility of distilled water to a change of pH upon adding very small amounts of acid or base is often of great concern in pharmaceutical operations. Solutions of neutral salts, such as sodium chloride, similarly lack ability to resist change of pH on adding acid or base: such solutions are called *unbuffered*.

Characteristic of *buffered solutions*, which undergo small changes of pH on addition of acid or base, is the presence either of a weak acid and a salt of the weak acid, or a weak base and a salt of the weak base. An example of the former system is acetic acid and sodium acetate; and of the latter, ammonium hydroxide and ammonium chloride. From the proton concept of acids and bases discussed earlier, it is apparent that such buffer action involves a conjugate acid–base pair in the solution. It will be recalled that acetate ion is the conjugate base of acetic acid, and that ammonium ion is the conjugate acid of ammonia (the principal constituent of what commonly is called ammonium hydroxide).

The mechanism of action of the acetic acid–sodium acetate buffer pair is that the acid, which exists largely in molecular (nonionized) form, combines with hydroxyl ion that may be added to form acetate ion and water; thus,



The acetate ion, which is a base, combines with the hydrogen (more exactly hydronium) ion that may be added to form essentially nonionized acetic acid and water, represented as

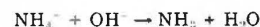


As will be illustrated later by an example, the change of pH is slight as long as the amount of hydronium or hydroxyl ion added does not exceed the capacity of the buffer system to neutralize it.

The ammonia–ammonium chloride pair functions as a buffer because the ammonia combines with hydronium ion that may be added to form ammonium ion and water; thus,



Ammonium ion, which is an acid, combines with added hydroxyl ion to form ammonia and water, as

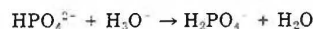


Again, the change of pH is slight if the amount of added hydronium or hydroxyl ion is not in excess of the capacity of the system to neutralize it.

Besides these two general types of buffers, a third appears to exist. This is the buffer system composed of two salts, as monobasic potassium phosphate, KH_2PO_4 , and dibasic potassium phosphate, K_2HPO_4 . This is not, however, a new type of buffer: it is actually a weak-acid/conjugate-base buffer in which an ion, H_2PO_4^- , serves as the weak acid, and HPO_4^{2-} is its conjugate base. When hydroxyl ion is added to this buffer the following reaction takes place:

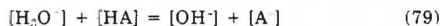


and when hydronium ion is added,



It is apparent that the mechanism of action of this type of buffer is essentially the same as that of the weak-acid/conjugate-base buffer composed of acetic acid and sodium acetate.

CALCULATIONS—A buffer system composed of a conjugate acid–base pair, NaA-HA (such as sodium acetate and acetic acid), would have a PBE of



Replacing [HA] and [A⁻] as a function of hydronium-ion concentration gives

$$[\text{H}_3\text{O}^+] + \frac{[\text{H}_3\text{O}^+]C_b}{[\text{H}_3\text{O}^+] + K_a} = [\text{OH}^-] + \frac{K_a C_a}{[\text{H}_3\text{O}^+] + K_a} \quad (80)$$

where C_b is the concentration of the salt, NaA, and C_a is the concentration of the weak acid, HA. This equation can be rearranged to give

$$[\text{H}_3\text{O}^+] = K_a \frac{(C_a - [\text{H}_3\text{O}^+] + [\text{OH}^-])}{(C_b + [\text{H}_3\text{O}^+] - [\text{OH}^-])} \quad (81)$$

In general, both C_a and C_b are much greater than $[\text{H}_3\text{O}^+]$, which is in turn much greater than $[\text{OH}^-]$ and the equation simplifies to

$$[\text{H}_3\text{O}^+] = \frac{K_a C_a}{C_b} \quad (82)$$

or, expressed in terms of pH, as

$$\text{pH} = \text{p}K_a + \log \frac{C_b}{C_a} \quad (83)$$

This equation generally is called the *Henderson-Hasselbalch equation*. It applies to all buffer systems formed from a single conjugate acid-base pair, regardless of the nature of the salts. For example, it applies equally well to the following buffer systems: ammonia-ammonium chloride, monosodium phosphate-disodium phosphate, and phenobarbital-sodium phenobarbital. In the ammonia-ammonium chloride system, ammonia is obviously the base and the ammonium ion is the acid (C_a equal to the concentration of the salt). In the phosphate system, monosodium phosphate is the acid and disodium phosphate is the base. For the phenobarbital buffer system, phenobarbital is the acid and the phenobarbital anion is the base (C_b equal to the concentration of sodium phenobarbital).

As an example of the application of this equation, the pH of a buffer solution containing acetic acid and sodium acetate, each in 0.1 M concentration, may be calculated. The K_a of acetic acid, as defined above, is 1.8×10^{-5} , at 25°

Solution:

First, the $\text{p}K_a$ of acetic acid is calculated:

$$\begin{aligned} \text{p}K_a &= -\log K_a = -\log 1.8 \times 10^{-5} \\ &= -\log 1.8 - \log 10^{-5} \\ &= -0.26 - (-5) = +4.74 \end{aligned}$$

Substituting this value into Equation 83:

$$\text{pH} = \log \frac{0.1}{0.1} + 4.74 = +4.74$$

The Henderson-Hasselbalch equation predicts that any solutions containing the same molar concentration of acetic acid as of sodium acetate will have the same pH. Thus, a solution of 0.01 M concentration of each will have the same pH, 4.74, as one of 0.1 M concentration of each component. Actually, there will be some difference in the pH of the solutions, for the *activity coefficient* of the components varies with concentration. For most practical purposes, however, the approximate values of pH calculated by the equation are satisfactory. It should be pointed out that the buffer of higher concentration of each component will have a much greater capacity for neutralizing added acid or base and this point will be discussed further in the discussion of buffer capacity.

The Henderson-Hasselbalch equation is useful also for calculating the ratio of molar concentrations of a buffer system required to produce a solution of specific pH. As an example,

suppose that an acetic acid-sodium acetate buffer of pH 4.5 must be prepared. What ratio of the buffer components should be used?

Solution:

Rearranging Equation 83, which is used to calculate the pH of weak acid-salt type buffers, gives

$$\begin{aligned} \log \frac{[\text{base}]}{[\text{acid}]} &= \text{pH} - \text{p}K_a \\ &= 4.5 - 4.76 = -0.26 = (9.76 - 10) \\ \frac{[\text{base}]}{[\text{acid}]} &= \text{antilog of } (9.76 - 10) = 0.575 \end{aligned}$$

The interpretation of this result is that the *proportion* of sodium acetate to acetic acid should be 0.575 mol of the former to 1 mol of the latter to produce a pH of 4.5. A solution containing 0.0575 mol of sodium acetate and 0.1 mol of acetic acid per liter would meet this requirement, as would also one containing 0.00575 mol of sodium acetate and 0.01 mol of acetic acid per liter. The actual concentration selected would depend chiefly on the desired buffer capacity.

BUFFER CAPACITY—The ability of a buffer solution to resist changes in pH upon addition of acid or alkali may be measured in terms of *buffer capacity*. In the preceding discussion of buffers, it has been seen that, in a general way, the concentration of acid in a weak-acid/conjugate-base buffer determines the capacity to “neutralize” added base, while the concentration of salt of the weak acid determines the capacity to neutralize added acid. Similarly, in a weak-base/conjugate-acid buffer the concentration of the weak base establishes the buffer capacity toward added acid, while the concentration of the conjugate acid of the weak base determines the capacity toward added base. When the buffer is equimolar in the concentrations of weak acid and conjugate base, or of weak base and conjugate acid, it has equal buffer capacity toward added strong acid or strong base.

Van Slyke, the biochemist, introduced a quantitative expression for evaluating buffer capacity. This may be defined as the amount, in gram-equivalents (g-eq) per liter, of strong acid or strong base required to be added to a solution to change its pH by 1 unit; a solution has a buffer capacity of 1 when 1 L requires 1 g-eq of strong base or acid to change the pH 1 unit. (In practice, considerably smaller increments are measured, expressed as the ratio of acid or base added to the change of pH produced.) From this definition it is apparent that the smaller the pH change in a solution caused by the addition of a specified quantity of acid or alkali, the greater the buffer capacity of the solution.

The following examples illustrate certain basic principles and calculations concerning buffer action and buffer capacity.

Example 1—What is the change of pH on adding 0.01 mol of NaOH to 1 L of 0.10 M acetic acid?

(a) Calculate the pH of a 0.10 molar solution of acetic acid:

$$\begin{aligned} [\text{H}_3\text{O}^+] &= \sqrt{K_a C_a} = \sqrt{1.75 \times 10^{-5} \times 1.0 \times 10^{-1}} = 4.18 \times 10^{-3} \\ \text{pH} &= -\log 4.18 \times 10^{-3} = 2.38 \end{aligned}$$

(b) On adding 0.01 mol of NaOH to a liter of this solution, 0.01 mol of acetic acid is converted to 0.01 mol of sodium acetate, thereby decreasing C_a to 0.09 M, and $C_b = 1.0 \times 10^{-2}$ M. Using the Henderson-Hasselbalch equation gives

$$\text{pH} = 1.76 + \log \frac{0.01}{0.09} = 1.76 - 0.95 = 3.81$$

The pH change is, therefore, 1.43 unit. The buffer capacity as defined above is calculated to be

$$\frac{\text{mols of NaOH added}}{\text{change in pH}} = 0.011$$