

Remington: The Science and Practice of Pharmacy

Nineteenth Edition

Volume I

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Remington: The Science and Practice of Pharmacy

Volume I

19TH
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Remington: Practice of

ALFONSO R GENNARO

*Chairman of the Editorial Board
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The Science and Pharmacy

1995

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CHAPTER 17

Ionic Solutions and Electrolytic Equilibria

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Electrolytes

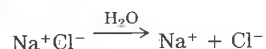
In a preceding chapter, attention was directed to the colligative properties of nonelectrolytes, or substances whose aqueous solutions do not conduct electricity. Substances whose aqueous solutions conduct electricity are known as electrolytes and are typified by inorganic acids, bases and salts. In 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 equimolal 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 which 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 which 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 which yield two ions, the pressure is very nearly double that of solutions of equimolal 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 and ΔT_f refer to the osmotic pressure, vapor-pressure lowering, boiling-point elevation and freezing-point depression, respectively, of the electrolyte. The terms $(\pi)_0$, etc 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 2, 3, 4 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 positively 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. While 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. Hence, to measure conductivity is actually to measure electrical resistance, commonly with a Wheatstone-bridge apparatus, and then to calculate the conductivity. Fig 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

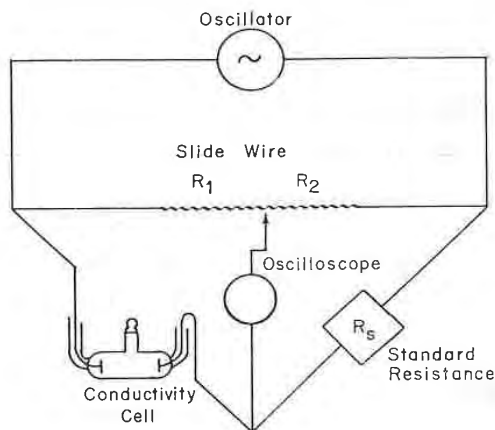


Fig 1. Alternating current Wheatstone bridge for measuring conductivity.

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 and which 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 in order 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, while 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 *mhos*). As the numerical value of the conductivity will vary with the dimensions of the conductance cell, the value must be calculated in terms of *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, it would be possible to calculate the specific conductance, but this information actually is not required, because it is possible—and much more convenient—to calibrate a cell by measuring in it the conductivity of a standard solution of known specific conductance and then calculating a "cell constant." Since 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 the degree of dilution in order 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 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, ie, 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—It is customary to classify electrolytes 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 a substantial proportion of molecular species along with ions derived therefrom is a weak electrolyte. For the purposes of this discussion, classification of electrolytes as strong or weak will be on the basis of certain conductance characteristics exhibited in aqueous solution.

The equivalent conductances of a number of electrolytes, at different concentrations, are given in Table 1 and for certain of these electrolytes again in Fig 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 which 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 usually are completely ionized, the increase in equivalent conductance results not from increased ionization but rather from diminished ionic interference as the solution is diluted, in 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 a 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

Table 1—Equivalent Conductances 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
0.001	421.4	49.2	123.7	146.9	124.3	...	88.5
0.005	415.8	22.9	120.6	143.5	121.3	144.4	85.7
0.01	412.0	16.3	118.5	141.3	119.2	142.2	83.8
0.02	407.2	11.6	115.8	138.3	116.7	139.5	81.2
0.05	399.1	7.4	111.1	133.4	112.8	135.0	76.9
0.1	391.3	5.2	106.7	129.0	108.8	131.1	72.8

^aThe 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 (see text for explanation).

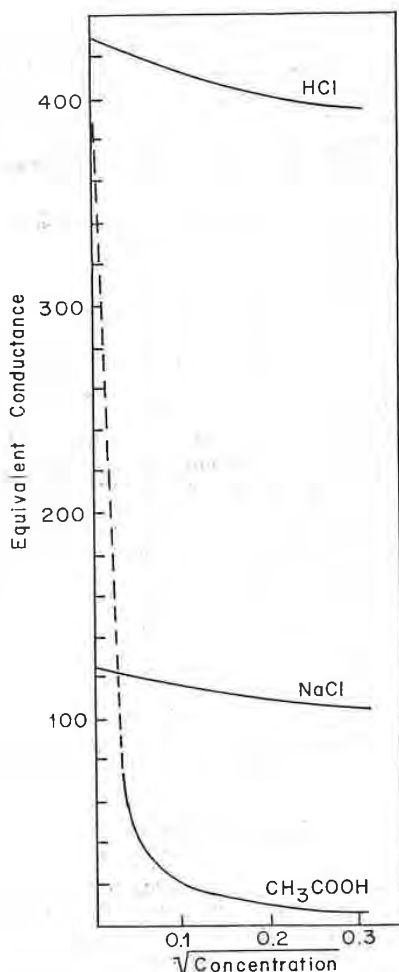


Fig 2. Variation of equivalent conductance with square root of concentration.

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. Since 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 2 gives the equivalent ionic conductances at infinite dilution of some cations and anions. It is not necessary to have this information in order 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

Table 2—Equivalent Ionic Conductivities at Infinite Dilution, at 25°

Cations	Λ_0	Anions	Λ_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
$\frac{1}{2}\text{Ca}^{2+}$	59.5	$\frac{1}{2}\text{SO}_4^{2-}$	79.8
$\frac{1}{2}\text{Mg}^{2+}$	53.0		

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 Λ_0 for weak electrolytes such as acetic acid. As is evident from Fig 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 Λ_0 for HCl, CH₃COONa and NaCl are determined easily by extrapolation since the substances are strong electrolytes. Substitution of these extrapolated values, as given in Table 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. Since 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, 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.

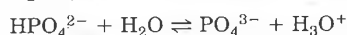
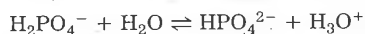
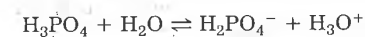
$$\alpha = \frac{i - 1}{v - 1} = \frac{1.12 - 1}{2 - 1} = 0.12$$

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

Modern Theories

The Arrhenius theory explains why solutions of electrolytes conduct electricity, 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

equilibria involved in the ionization of phosphoric acid:



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

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

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

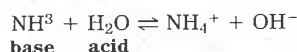
$$K_3 = \frac{[\text{PO}_4^{3-}][\text{H}_3\text{O}^+]}{[\text{HPO}_4^{2-}]} \quad (19)$$

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

$$K = K_1 K_2 K_3 = \frac{[\text{PO}_4^{3-}][\text{H}_3\text{O}^+]^3}{[\text{H}_3\text{PO}_4]} \quad (20)$$

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, since successive protons must be removed from species that always are charged more negatively. This can be seen from the data in Table 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 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



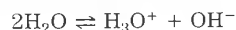
The equilibrium expression for this reaction is

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

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. Since 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 Eq. 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} .

Table 4—Dissociation Constants in Water at 25°

Substance		K
Weak acids		
Acetic		1.75×10^{-5}
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 (H_2O)	K_1	7.0×10^{-4}
	K_2	1.8×10^{-5}
	K_3	4.0×10^{-7}
Dichloroacetic		5×10^{-2}
Ethylenediaminetetra-	K_1	1×10^{-2}
acetic acid (EDTA)	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 ($2\text{H}_2\text{O}$)	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^{-11} (40°)
Thiourea		1.1×10^{-15}
Urea		1.5×10^{-14}

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

$$a = fc \quad (7)$$

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, distribution coefficients, etc. For a strong electrolyte, the mean ionic activity coefficient, $\gamma_{\pm}$, 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 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, etc.

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 Eq 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 uniuniva-

lent 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 (univalent 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-Hückel Theory—The Debye-Hückel 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

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

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 particularly is 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

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

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

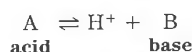
Barbiturate	KCl	KBr	NaCl	NaBr
Amobarbital	0.168	0.095	0.212	0.143
Aprobarbital	0.136	0.062	0.184	0.120
Barbital	0.092	0.042	0.136	0.088
Phenobarbital	0.092	0.034	0.132	0.078
Vinbarbital	0.125	0.036	0.143	0.096

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 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.

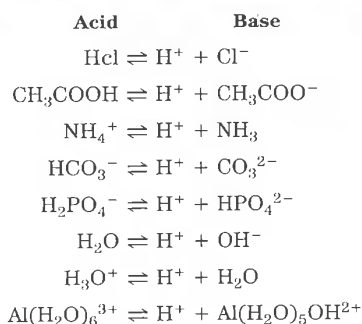
Acids and Bases

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, for example) 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, while 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), while a base is a substance capable of accepting a proton. This complementary relationship may be expressed by



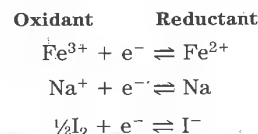
The pair of substances thus related through mutual ability to gain or lose a proton is called a *conjugate acid-base pair*. Specific examples of such pairs are



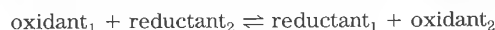
It is apparent that not only molecules, but also cations and anions, may function as acids or bases.

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.

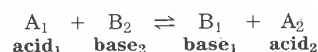


However, these examples of acid-base pairs and oxidant-reductant pairs represent reactions that are possible in principle only. Ordinarily acids will not release free protons any more than reductants will release free electrons. That is, protons and electrons, respectively, can be transferred only from 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:



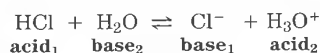
where Subscript 1 represents one conjugate oxidant-reductant pair and Subscript 2 represents the other.

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



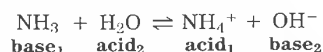
In such a reaction, which is called *protolysis* or a *protolytic reaction*, A_1 and B_1 constitute one conjugate acid-base pair and A_2 and B_2 the other; the proton given up by A_1 (which thereby becomes B_1) is transferred to B_2 (which becomes A_2).

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

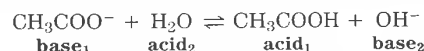


The ionic species H_3O^+ , called *hydronium* or *oxonium* ion, always is formed when an acid is dissolved in water. Often, for purposes of convenience, this is written simply as H^+ and is called hydrogen ion, although the "bare" ion practically is nonexistent in solution.

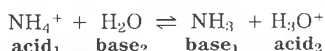
When a base, eg, ammonia, is dissolved in water the reaction of protolysis is



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



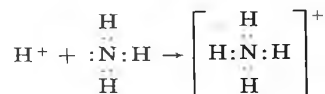
In an aqueous solution of ammonium chloride the reaction is



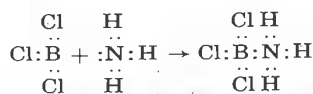
Transfer of protons (protolysis) is not limited to dissimilar conjugate acid-base pairs. In the preceding examples H_2O sometimes behaves as an acid and at other times as a base. Such an amphoteric substance is called, in Brønsted's terminology, an *amphiprotic substance*.

Electron-Pair Concept—While the proton concept of acids and bases provides a more general definition for these substances, 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

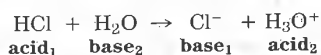
behave as acids. Both deficiencies of the proton theory are avoided in the more inclusive definition of acids and bases proposed by Lewis in 1923. In 1916 he proposed that sharing of a pair of electrons by two atoms established a bond (covalent) between the atoms; therefore, an acid is a substance capable 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 which 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.

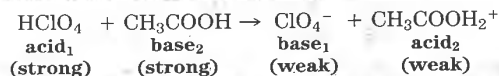


This phenomenon, called the leveling effect of water, occurs whenever the added acid is stronger than the hydronium ion. Such a reaction manifests the tendency of proton-transfer reactions to proceed spontaneously in the direction of forming a weaker acid or weaker base.

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. Since HClO_4 , H_2SO_4 , HCl or HNO_3 are all stronger acids than the hydronium ion, 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. Since the hydroxide ion is the strongest base which 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):



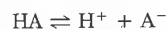
but sulfuric acid and hydrochloric acid behave as weak acids. It is because perchloric acid is a very strong acid when dissolved in glacial acetic acid that it has found many important applications in analytical chemistry as a titrant for a variety of substances which behave as bases in acetic acid. 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. Typical of solvents in this category is liquid ammonia. 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, therefore, 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

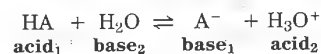


where HA is the molecular acid and A^- is its anion. An equilibrium expression based on the law of mass action may be applied to the reaction

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

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 Eq. 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



Application of the law of mass action to this reaction gives

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

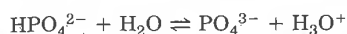
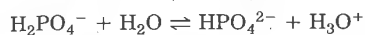
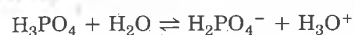
since $[\text{H}_2\text{O}]$ is a constant this equation may be written

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

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

Acids which 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

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

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

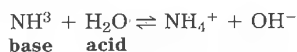
$$K_3 = \frac{[\text{PO}_4^{3-}][\text{H}_3\text{O}^+]}{[\text{HPO}_4^{2-}]} \quad (19)$$

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

$$K = K_1 K_2 K_3 = \frac{[\text{PO}_4^{3-}][\text{H}_3\text{O}^+]^3}{[\text{H}_3\text{PO}_4]} \quad (20)$$

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, since successive protons must be removed from species that always are charged more negatively. This can be seen from the data in Table 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 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



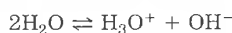
The equilibrium expression for this reaction is

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

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. Since 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 Eq. 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} .

Table 4—Dissociation Constants in Water at 25°

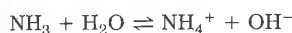
Substance		K
Weak acids		
Acetic		1.75×10^{-3}
Acetylsalicylic		3.27×10^{-4}
Barbital		1.23×10^{-8}
Barbituric		1.05×10^{-4}
Benzoic		6.30×10^{-5}
Benzyl penicillin		1.74×10^{-3}
Boric	K_1	5.8×10^{-10}
Caffeine		1×10^{-14}
Carbonic	K_1	4.31×10^{-7}
	K_2	4.7×10^{-11}
Citric ($1\text{H}_2\text{O}$)	K_1	7.0×10^{-4}
	K_2	1.8×10^{-5}
	K_3	4.0×10^{-7}
Dichloroacetic		5×10^{-2}
Ethylenediaminetetra- acetic 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 ($2\text{H}_2\text{O}$)	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}

Since the autoprotolysis of pure water yields one hydronium ion for each hydroxyl ion produced, $[\text{H}_3\text{O}^+]$ must be equal to $[\text{OH}^-]$. At 25° each has a value of 1×10^{-7} mols/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}). Since $[\text{H}_3\text{O}^+]$ 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} . Since $[\text{OH}^-]$ is much greater than $[\text{H}_3\text{O}^+]$, the solution is said to be *basic* or *alkaline*.

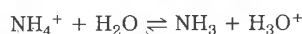
Relationship of K_a and K_b .—A particularly interesting and useful relationship between the strength of an acid and its conjugate base, or a base and its conjugate acid, exists. For illustration, consider the strength of the base NH_3 and its conjugate acid NH_4^+ , in water. The behavior of NH_3 as 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 which is

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

Multiplying Eqs 25 and 26

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

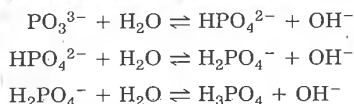
It is obvious that

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

where K_w is the ion product of water as defined in Eq 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 which 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 Eqs 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 Eqs 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 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 that dissociation constants cannot be formulated for these strong electrolytes.

Table 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 has the hydrogen atom. Thus, when acetic acid is dissolved in water the polar molecules of the latter have a stronger affinity for the hydrogen of acetic acid than the latter. 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 and 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.

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

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 228). 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 Eq 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.

In order 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

$$[K^+] + [H_3O^+] = [OH^-] + [A^-] \quad (31)$$

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

$$Z = [A^-] = [K^+] + [H_3O^+] - [OH^-] \quad (32)$$

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

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

The term, $[HA]$, can be replaced using Eq 16 to give

$$C_a = \frac{[H_3O^+][Z]}{K_a} + Z \quad (34)$$

which can be rearranged to

$$Z = C_a - \frac{Z[H_3O^+]}{K_a} \quad (35)$$

According to Eq 35, if Z , which is obtained from the experimental data using Eq 32, is plotted versus the terms $Z[H_3O^+]$, 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 obtained also. 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

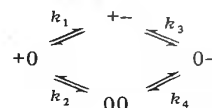
$$P = Z/C_a \quad (36)$$

and

$$\frac{[H_3O^+]^2 P}{(2 - P)} = K_1 K_2 + \frac{K_1 [H_3O^+](1 - P)}{(2 - P)} \quad (37)$$

A plot of Eq 37 should yield a straight line with a slope equal to K_1 and an intercept of 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. Since 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 Eq 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 + to a positively charged group, a 0 to an uncharged group and a - 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 Eq 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 Eqs 38 and 39.

pH

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} ; ie, a variation of 100,000,000,000,000 between these two limits. Because of the inconvenience of dealing with such large numbers, Sørensen, in 1909, 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

$$pH = \log \frac{1}{[H_3O^+]} \quad (40)$$

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

$$pH = -\log [H_3O^+] \quad (41)$$

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

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

$$pK = -\log K \quad (43)$$

Thus, taking logarithms of Eqs 28 and 24 gives

$$pK_a + pK_b = pK_w \quad (44)$$

$$pH + pOH = pK_w \quad (45)$$

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

Table 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}
Increasing acidity	2	10^{-2}	10^{-12}
	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}
Increasing alkalinity	10	10^{-10}	10^{-4}
	11	10^{-11}	10^{-3}
	12	10^{-12}	10^{-2}
	13	10^{-13}	10^{-1}
	14	10^{-14}	1

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:

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

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

$$\begin{aligned}\text{pH} &= \log \frac{1}{3.6 \times 10^{-5}} \\ &= \log 28,000 \text{ or } \log (2.8 \times 10^4) \\ \log (2.8 \times 10^4) &= \log 2.8 + \log 10^4 \\ \log 2.8 &\approx +0.44 \\ \log 10^4 &= +4.00 \\ \text{pH} &= 4.44\end{aligned}$$

This problem also may be solved as follows

$$\begin{aligned}\text{pH} &= -\log (3.6 \times 10^{-5}) \\ \log 3.6 &= +0.56 \\ \log 10^{-5} &= -5.00 \\ &= -4.44 = \log (3.6 \times 10^{-5}) \\ \text{pH} &= -(-4.44) = +4.44 = 4.44\end{aligned}$$

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

$$\begin{aligned}\text{pH} &= \log \frac{1}{[\text{H}_3\text{O}^+]} \\ 4.44 &= \log \frac{1}{[\text{H}_3\text{O}^+]} \\ \frac{1}{[\text{H}_3\text{O}^+]} &= \text{antilog of } 4.44 = 28,000 \text{ (rounded off)} \\ [\text{H}_3\text{O}^+] &= \frac{1}{28,000} = 0.000036 \text{ or } 3.6 \times 10^{-5}\end{aligned}$$

This calculation also may be made as

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

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, $\bar{5}.56$, where 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 and, 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

$$\begin{aligned}10.17 &= -\log[\text{H}_3\text{O}^+] \\ -10.17 &= \log[\text{H}_3\text{O}^+] \\ -10.17 &= (-11.00 + 0.83) = \bar{11}.83\end{aligned}$$

The antilog of 0.83 = 6.8

The antilog of $-11.00 = 10^{-11}$

The hydronium-ion concentration is therefore 6.8×10^{-11} mols/L.

In the section on *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 which might be expected to have such values are too concentrated to be ionized extensively or the inter-ionic attraction is so great as to materially reduce ionic activity.

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 unionized 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

$$C_a = [\text{H}_3\text{A}] + [\text{H}_2\text{A}^-] + [\text{HA}^{2-}] + [\text{A}^{3-}] \quad (46)$$

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

$$[\text{H}_n\text{A}] = [\text{H}_3\text{O}^+]^n C_a / D \quad (47)$$

$$[\text{H}_{n-j}\text{A}^{-j}] = [\text{H}_3\text{O}^+]^{n-j} K_1 \cdots K_j C_a / D \quad (48)$$

* The pH of the purest water obtainable, so-called “conductivity” water, is 7.0 when the measurement is carefully made 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.

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, etc, until the first term is reached. The following examples show the denominator, D , to be used for various types of acids:

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

$$H_2: D = [H_3O^+]^2 + K_1[H_3O^+] + K_1K_2 \quad (50)$$

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

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, etc

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

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

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

Example—Calculate the concentrations of all succinic acid species in a $1.0 \times 10^{-3} M$ solution of succinic acid at pH 6.0. Assume that $K_1 = 6.4 \times 10^{-5}$ and $K_2 = 2.3 \times 10^{-6}$.

Eqs 52–54 have the same denominator, D , which can be calculated as

$$\begin{aligned} D &= [H_3O^+]^2 + K_1[H_3O^+] + K_1K_2 \\ &= 1.0 \times 10^{-12} + 6.4 \times 10^{-5} \times 1.0 \times 10^{-6} + 6.4 \\ &\quad \times 10^{-5} \times 2.3 \times 10^{-6} \\ &= 1.0 \times 10^{-12} + 6.4 \times 10^{-11} + 14.7 \times 10^{-11} \\ &= 21.2 \times 10^{-11} \end{aligned}$$

Therefore

$$\begin{aligned} [H_2A] &= \frac{[H_3O^+]^2 C_a}{D} \\ &= \frac{1.0 \times 10^{-12} \times 1.0 \times 10^{-3}}{21.2 \times 10^{-11}} = 4.7 \times 10^{-6} M \\ [HA^-] &= \frac{K_1[H_3O^+] C_a}{D} \\ &= \frac{6.4 \times 10^{-11} \times 1.0 \times 10^{-3}}{21.2 \times 10^{-11}} = 3.0 \times 10^{-4} M \\ [A^{2-}] &= \frac{K_1K_2 C_a}{D} \\ &= \frac{14.7 \times 10^{-11} \times 1.0 \times 10^{-3}}{21.2 \times 10^{-11}} = 6.9 \times 10^{-4} M \end{aligned}$$

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 spe-

cies 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, since 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.
3. Place all species that can form when protons are consumed on the left side of the equation.
4. Multiply the concentration of each species by the number of protons gained or lost to form that species.
5. Add $[H_3O^+]$ to the left side of the equation and $[OH^-]$ to the right side of the equation. These result from the interaction of two molecules of water as shown 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 to give the following PBE:

$$[H_3O^+] = [OH^-] + [H_2PO_4^-] + 2[HPO_4^{2-}] + 3[PO_4^{3-}] \quad (56)$$

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 since 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:

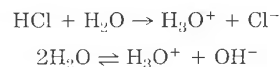
$$[H_3O^+] + [H_2PO_4^-] + 2[H_3PO_4] = [OH^-] + [PO_4^{3-}] \quad (57)$$

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

$$[H_3O^+] = [OH^-] + [Cl^-] \quad (58)$$

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

$$[H_3O^+] = [Cl^-] = C_a \quad (59)$$

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, since strong acids generally are assumed to be 100% ionized.

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

$$pH = -\log 0.005 = 2.30$$

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

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

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* which 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 , Eq 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 5.00×10^{-5} *M* solution of a weak acid having a $K_a = 1.90 \times 10^{-5}$.

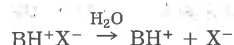
$$\begin{aligned}[\text{H}_3\text{O}^+] &= \sqrt{K_a C_a} \\ &= \sqrt{1.90 \times 10^{-5} \times 5.00 \times 10^{-5}} \\ &= 3.08 \times 10^{-5} \text{ M}\end{aligned}$$

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

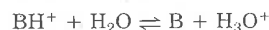
$$\begin{aligned}[\text{H}_3\text{O}^+] &= \frac{-1.90 \times 10^{-5} + \sqrt{(1.90 \times 10^{-5})^2 + 4(5.00 \times 10^{-5})}}{2} \\ &= 7.06 \times 10^{-3} \\ \text{pH} &= -\log (7.06 \times 10^{-3}) = 2.15\end{aligned}$$

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

When a salt obtained from a strong acid and a weak base—eg, ammonium chloride, morphine sulfate, pilocarpine hydrochloride, etc.—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. Since X[−] is the anion of a strong acid, it is too weak a base to undergo any further reaction with water. The protonated base, however, can act as a weak acid to give



Thus, Eqs 65 and 66 are valid, with C_a 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} .

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

Since C_a 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 $\text{p}K_w$ 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.

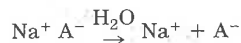
$$\begin{aligned}\text{pOH} &= -\log 3.00 \times 10^{-3} = 2.52 \\ \text{pH} &= 14.00 - 2.52 = 11.48\end{aligned}$$

When salts obtained from strong bases and weak acids (eg, sodium acetate, sodium sulfathiazole, sodium benzoate, etc)

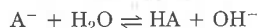
* The general solution to a quadratic equation of the form

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

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, Eqs 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 $K_w = 1.00 \times 10^{-14}$.

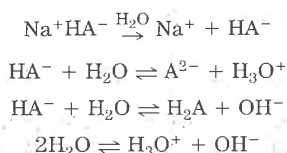
$$\begin{aligned} K_b &= \frac{K_w}{K_a} = \frac{1.00 \times 10^{-14}}{1.75 \times 10^{-5}} \\ &= 5.71 \times 10^{-10} \\ \text{OH}^- &= \sqrt{K_b C_b} = \sqrt{5.71 \times 10^{-10} \times 5.0 \times 10^{-2}} \\ &= 5.34 \times 10^{-6} \text{ M} \end{aligned}$$

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 Eqs 52 and 54), yields

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

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

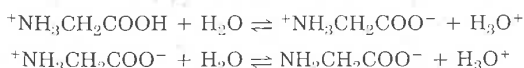
$$[\text{H}_3\text{O}^+] = \sqrt{\frac{K_1 K_2 C_s}{K_1 + C_s}} \quad (73)$$

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

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

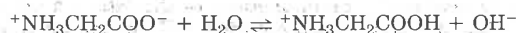
and $[\text{H}_3\text{O}^+]$ becomes independent of the concentration of the salt. A special property of ampholytes is that the concentration of the species HA^- is maximum at the pH corresponding to Eq 74.

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 since it also can

act as a weak base:

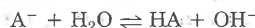
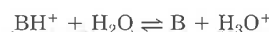
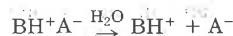


This type of substance, which carries both a charged acidic and a charged basic moiety on the same molecule is termed a *zwitterion* and, since the two charges balance each other, the molecule acts essentially as a neutral molecule. The pH at which the *zwitterion* concentration is maximum is known as the isoelectric point, which can be calculated from Eq 74.

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

$$[\text{H}_3\text{O}^+] + [\text{HA}] = [\text{OH}^-] + [\text{B}] \quad (75)$$

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

$$[\text{H}_3\text{O}^+] + \frac{[\text{H}_3\text{O}^+] C_s}{[\text{H}_3\text{O}^+] + K_a} = [\text{OH}^-] + \frac{K_a' C_s}{[\text{H}_3\text{O}^+] + K_a'} \quad (76)$$

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

$$[\text{H}_3\text{O}^+] = \sqrt{K_a K_a'} \quad (77)$$

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 Eq 77. Acetic acid has a K_a of 1.75×10^{-5} , which represents K_a in Eq 77:

$$\begin{aligned} [\text{H}_3\text{O}^+] &= \sqrt{1.75 \times 10^{-5} \times 5.75 \times 10^{-10}} \\ &= 1.00 \times 10^{-7} \\ \text{pH} &= -\log(1.00 \times 10^{-7}) = 7.00 \end{aligned}$$

All of the assumptions are valid.

Buffers

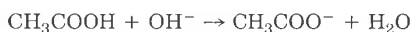
The terms *buffer*, *buffer solution* and *buffered solution*, when used with reference to hydrogen-ion concentration or pH, refer to the ability of a system, particularly an aqueous solution, to resist a change of pH on adding acid or alkali, or on dilution with a solvent.

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 on 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.

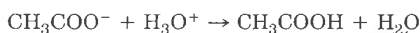
Characteristic of buffered solutions, which undergo small changes of pH on addition of acid or base, is the presence either of a weak acid and a salt of the weak acid, or a weak base

and a salt of the weak base. An example of the former system is acetic acid and sodium acetate; 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

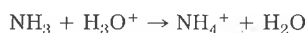


while the acetate ion, which is a base, combines with hydrogen (more exactly hydronium) ion that may be added to form essentially nonionized acetic acid and water, represented as

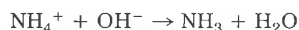


As will be illustrated later by an example, the change of pH is slight as long as the amount of hydronium or hydroxyl ion added does not exceed the capacity of the buffer system to neutralize it.

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

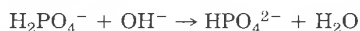


Ammonium ion, which is an acid, combines with added hydroxyl ion to form ammonia and water, as

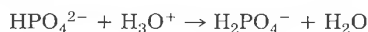


Again, the change of pH is slight if the amount of added hydronium or hydroxyl ion is not in excess of the capacity of the system to neutralize it.

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, $\text{NaA} - \text{HA}$ (such as sodium acetate and acetic acid), would have a PBE of

$$[\text{H}_3\text{O}^+] + [\text{HA}] = [\text{OH}^-] + [\text{A}^-] \quad (78)$$

Replacing $[\text{HA}]$ and $[\text{A}^-]$ as a function of hydronium-ion concentration gives

$$[\text{H}_3\text{O}^+] + \frac{[\text{H}_3\text{O}^+]\text{C}_b}{[\text{H}_3\text{O}^+] + K_a} = [\text{OH}^-] + \frac{K_a\text{C}_a}{[\text{H}_3\text{O}^+] + K_a} \quad (79)$$

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

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

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

$$[\text{H}_3\text{O}^+] = \frac{K_a\text{C}_a}{\text{C}_b} \quad (81)$$

or, expressed in terms of pH, as

$$\text{pH} = \text{p}K_a + \log \frac{\text{C}_b}{\text{C}_a} \quad (82)$$

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, phenobarbital–sodium phenobarbital, etc. 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 Eq 82

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

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, however, 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 under *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 is to be prepared. What ratio of the buffer components should be used?

Solution

Rearranging Eq 82, 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 numerical 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

$$[\text{H}_3\text{O}^+] = \sqrt{K_a C_a} = \sqrt{1.75 \times 10^{-4} \times 1.0 \times 10^{-1}} = 4.18 \times 10^{-3}$$

$$\text{pH} = -\log 4.18 \times 10^{-3} = 2.38$$

(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 $C_b = 1.0 \times 10^{-3}$ *M*. Using the Henderson-Hasselbach equation gives

$$\text{pH} = 4.76 + \log \frac{0.01}{0.09} = 4.76 - 0.95 = 3.81$$

The pH change is, therefore, 0.93 unit. The buffer capacity as defined above is calculated to be

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

Example 2—What is the change of pH on adding 0.1 mol of NaOH to 1 L of buffer solution 0.1 *M* in acetic acid and 0.1 *M* in sodium acetate?

(a) The pH of the buffer solution before adding NaOH is

$$\text{pH} = \log \frac{[\text{base}]}{[\text{acid}]} + \text{p}K_a$$

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

(b) On adding 0.01 mol of NaOH per liter to this buffer solution, 0.01 mol of acetic acid is converted to 0.01 mol of sodium acetate, thereby decreasing the concentration of acid to 0.09 *M* and increasing the concentration of base to 0.11 *M*. The pH is calculated as

$$\text{pH} = \log \frac{0.11}{0.09} + 4.76$$

$$= 0.087 + 4.76 = 4.85$$

The change of pH in this case is only 0.09 unit, about $\frac{1}{10}$ the change in the preceding example. The buffer capacity is calculated as

$$\frac{\text{mols of NaOH added}}{\text{change of pH}} = \frac{0.01}{0.09} = 0.11$$

Thus, the buffer capacity of the acetic acid-sodium acetate buffer solution is approximately 10 times that of the acetic acid solution.

As is in part evident from these examples, and may be further evidenced by calculations of pH changes in other systems, the degree of buffer action and, therefore, the buffer capacity, depend on the kind and concentration of the buffer components, the pH region involved and the kind of acid or alkali added.

Strong Acids and Bases as "Buffers"—In the foregoing discussion, buffer action was attributed to systems of (1) weak acids and their conjugate bases, (2) weak bases and their conjugate acids and (3) certain acid-base pairs which can function in the manner either of System 1 or 2.

The ability to resist change in pH on adding acid or alkali is possessed also by relatively concentrated solutions of strong acids and strong bases. If to 1 L of pure water having a pH of 7.0 is added 1 mL of 0.01 *M* hydrochloric acid, the pH is reduced to about 5.0. If the same volume of the acid is added to 1 L of 0.001 *M* hydrochloric acid, which has a pH of about 3, the hydronium-ion concentration is increased only about 1% and the pH is reduced hardly at all. The nature of this buffer action is quite different from that of the true buffer solutions. The very simple explanation is that when 1 mL of 0.01 *M* HCl, which represents 0.00001 g-eq of hydronium ions, is added to the 0.0000001 g-eq of hydronium ions in 1 L of pure water, the hydronium-ion concentration is increased 100-fold (equivalent to two pH units), but when the same amount is added to the 0.001 g-eq of hydronium ions in 1 L of 0.001 *M* HCl, the increase is only 1/100 the concentration already present. Similarly, if 1 mL of 0.01 *M* NaOH is added to 1 L of pure water, the pH is increased to 9, while if the same volume is added to 1 L of 0.001 molar NaOH, the pH is increased almost immeasurably.

In general, solutions of strong acids of pH 3 or less, and solutions of strong bases of pH 11 or more, exhibit this kind of buffer action by virtue of the relatively high concentration of hydronium or hydroxyl ions present. The USP includes among its *Standard Buffer Solutions* a series of hydrochloric acid buffers, covering the pH range 1.2 to 2.2, which also contain potassium chloride. The salt does not participate in the buffering mechanism, as is the case with salts of weak acids; instead, it serves as a nonreactive constituent required to maintain the proper electrolyte environment of the solutions.

Determination of pH

Colorimetry

A relatively simple and inexpensive method for determining the approximate pH of a solution depends on the fact that some conjugate acid base pairs (indicators) possess one color in the acid form and another color in the base form. Assume that the acid form of a particular indicator is red, while the base form is yellow. The color of a solution of this indicator will range from red, when it is sufficiently acid, to yellow, when it is sufficiently alkaline.

In the intermediate pH range (the transition interval) the color will be a blend of red and yellow depending upon the ratio of the base to the acid form. In general, although there are slight differences between indicators, color changes apparent to the eye cannot be discerned when the ratio of base to acid form, or acid to base form exceeds 10:1. The use of Eq 82 indicates that the transition range of most indicators is equal to the $\text{p}K_a$ of the indicator ± 1 pH unit, or a useful range of approximately two pH units. Standard indicator solutions can be made at known pH values within the transition range of the indicator, and the pH of an unknown solution determined by adding the indicator to it and comparing the resulting color with the standard solutions. Details of this procedure can be found in RPS-14. Another method for using these indicators is to apply them to thin strips of filter paper. A drop of the unknown solution is placed on a piece of the indicator paper

and the resulting color compared to a color chart supplied with the indicator paper. These papers are available in a wide variety of pH ranges.

Potentiometry

Electrometric methods for the determination of pH are based on the fact that the difference of electrical potential between two suitable electrodes dipping into a solution containing hydronium ions depends on the concentration (or activity) of the latter. The development of a potential difference is not a specific property of hydronium ions. A solution of any ion will develop a potential proportional to the concentration of that ion if a suitable pair of electrodes is placed in the solution.

The relationship between the potential difference and concentration of an ion in equilibrium with the electrodes may be derived as follows. When a metal is immersed into a solution of one of its salts, there is a tendency for the metal to go into solution in the form of ions. This tendency is known as the *solution pressure* of the metal and is comparable to the tendency of sugar molecules, eg, to dissolve in water. The metallic ions in solution tend, on the other hand, to become discharged by forming atoms, this effect being proportional to the *osmotic pressure* of the ions.

In order for an atom of a metal to go into solution as a positive ion, electrons, equal in number to the charge on the ion, must be left behind on the metal electrode with the result that the latter becomes negatively charged. The positively charged ions in solution, however, may become discharged as atoms by taking up electrons from the metal electrode. Depending on which effect predominates, the electrical charge on the electrode will be either positive or negative and may be expressed quantitatively by the following equation proposed by Nernst in 1889:

$$E = \frac{RT}{nF} \ln \frac{p}{P} \quad (83)$$

where E is the potential difference or electromotive force, R is the gas constant (8.316 joules), T is the absolute temperature, n is the valence of the ion, F is the Faraday of electricity (96,500 coulombs), p is the osmotic pressure of the ions and P is the solution pressure of the metal.

Inasmuch as it is impossible to measure the potential difference between one electrode and a solution with any degree of certainty, it is customary to use two electrodes and to measure the potential difference between them. If two electrodes, both of the same metal, are immersed in separate solutions containing ions of that metal, at osmotic pressure p_1 and p_2 , respectively, and connected by means of a tube containing a nonreacting salt solution (a so-called *salt bridge*), the potential developed across the two electrodes will be equal to the difference between the potential differences of the individual electrodes; thus

$$E = E_1 - E_2 = \frac{RT}{nF} \ln \frac{p_1}{P_1} - \frac{RT}{nF} \ln \frac{p_2}{P_2} \quad (84)$$

Since both electrodes are of the same metal, $P_1 = P_2$ and the equation may be simplified to

$$E = \frac{RT}{nF} \ln p_1 - \frac{RT}{nF} \ln p_2 = \frac{RT}{nF} \ln \frac{p_1}{p_2} \quad (85)$$

In place of osmotic pressures it is permissible, for dilute solutions, to substitute the concentrations c_1 and c_2 which were found (see Chapter 16), to be proportional to p_1 and p_2 . The equation then becomes

$$E = \frac{RT}{nF} \ln \frac{c_1}{c_2} \quad (86)$$

If either c_1 or c_2 is known, it is obvious that the value of the other may be found if the potential difference, E , of this cell can be measured.

For the determination of hydronium-ion concentration or pH, an electrode at which an equilibrium between hydrogen gas and hydronium ion can be established must be used, in place of metallic electrodes. Such an electrode may be made by electrolytically coating a strip of platinum, or other noble metal, with platinum black and saturating the latter with pure hydrogen gas. This device functions as a *hydrogen electrode*. Two such electrodes may be assembled as shown in Fig 3.

In this diagram one electrode dips into Solution A, containing a known hydronium-ion concentration, and the other electrode dips into Solution B, containing an unknown hydronium-ion concentration. The two electrodes and solutions, sometimes called half-cells, then are connected by a bridge of neutral salt solution, which has no significant effect on the solutions it connects. The potential difference across the two electrodes is measured by means of a potentiometer, P . If the concentration, c_1 , of hydronium ion in Solution A is 1 N , Eq 86 simplifies to

$$E = \frac{RT}{nF} \ln \frac{1}{c_2} \quad (87)$$

or in terms of Briggsian logarithms

$$E = 2.303 \frac{RT}{nF} \log_{10} \frac{1}{c_2} \quad (88)$$

If for $\log_{10} 1/c_2$ there is substituted its equivalent pH, the equation becomes

$$E = 2.303 \frac{RT}{nF} \text{pH} \quad (89)$$

and finally by substituting numerical values for R , n , T and F , and assuming the temperature to be 20°, the following simple relationship is derived:

$$E = 0.0581 \text{ pH or } \text{pH} = \frac{E}{0.0581} \quad (90)$$

The hydrogen electrode dipping into a solution of known hydronium-ion concentration, called the *reference electrode*, may be replaced by a calomel electrode, one type of which is shown in Fig 4. The elements of a calomel electrode are mercury and calomel in an aqueous solution of potassium chloride. The potential of this electrode is constant, regardless of the hydronium-ion concentration of the solution into which it dips. The potential depends on the equilibrium which is set up between mercury and mercurous ions from the calomel, but the concentration of the latter is governed, according to the solubility-product principle, by the concentration of chloride ions, which are derived mainly from the potassium chloride in the solution. Therefore, the potential of this electrode varies with the concentration of potassium chloride in the electrolyte.

Because the calomel electrode always indicates voltages which are higher, by a constant value, than those obtained

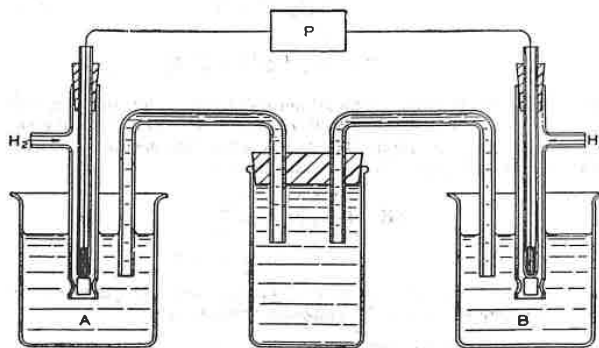


Fig 3. Hydrogen-ion concentration chain.

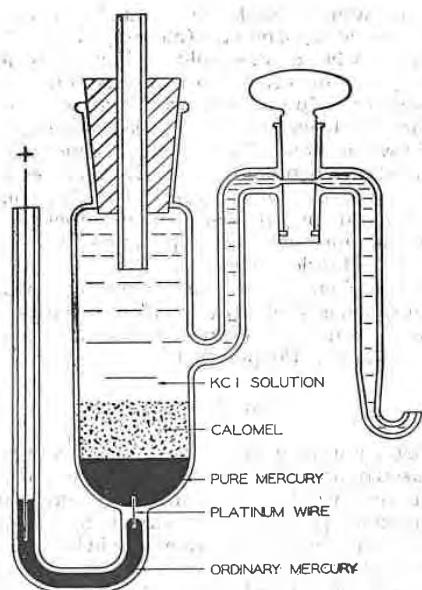


Fig 4. Calomel electrode.

when the normal hydrogen electrode chain shown in Fig 3 is used, it is necessary to subtract the potential due to the calomel electrode itself from the observed voltage. As the magnitude of this voltage depends on the concentration of potassium chloride in the calomel-electrode electrolyte, it is necessary to know the concentration of the former. For most purposes a saturated potassium chloride solution is used which produces potential difference of 0.2488 V. Accordingly, before using Eq 85 for the calculation of pH from the voltage of a cell made up of a calomel and a hydrogen electrode dipping into the solution to be tested, 0.2488 V must be subtracted from the observed potential difference. Expressed mathematically, Eq 91 is used for calculating pH from the potential difference of such a cell.

$$\text{pH} = \frac{E - 0.2488}{0.0581} \quad (91)$$

In measuring the potential difference between the electrodes, it is imperative that very little current be drawn from the cell, for with current flowing the voltage changes, owing to polarization effects at the electrode. Because of this it is not possible to make accurate measurements with a voltmeter which requires appreciable current to operate it. In its place a potentiometer is used which does not draw a current from the cell being measured.

There are many limitations to the use of the hydrogen electrode:

It cannot be used in solutions containing strong oxidants such as ferric iron, dichromates, nitric acid, peroxide or chlorine or reductants, such as sulfurous acid and hydrogen sulfide.

It is affected by the presence of organic compounds which are reduced fairly easily.

It cannot be used successfully in solutions containing cations that fall below hydrogen in the electrochemical series.

Erratic results are obtained in the measurement of unbuffered solutions unless special precautions are taken.

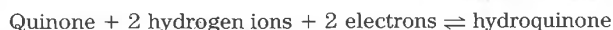
It is troublesome to prepare and maintain.

Since other electrodes more convenient to use now are available, the hydrogen electrode today is used rarely. Nevertheless, it is the ultimate standard for pH measurements.

To avoid some of the difficulties with the hydrogen electrode, the *quinhydrone* electrode was introduced and was popular for a long time, particularly for measurements of acid solutions. The unusual feature of this electrode is that it

consists of a piece of gold or platinum wire or foil dipping into the solution to be tested, in which has been dissolved a small quantity of quinhydrone. A calomel electrode may be used for reference, just as in determinations with the hydrogen electrode.

Quinhydrone consists of an equimolecular mixture of quinone and hydroquinone; the relationship between these substances and hydrogen-ion concentration is



In a solution containing hydrogen ions the potential of the quinhydrone electrode is related logarithmically to hydronium-ion concentration if the ratio of the hydroquinone concentration to that of quinone is constant and practically equal to one. This ratio is maintained in an acid solution containing an excess of quinhydrone, and measurements may be made quickly and accurately; however, quinhydrone cannot be used in solutions more alkaline than pH 8.

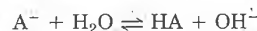
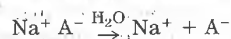
An electrode which, because of its simplicity of operation and freedom from contamination or change of the solution being tested, has replaced both the hydrogen and quinhydrone electrodes is the *glass electrode*. It functions by virtue of the fact that when a thin membrane of a special composition of glass separates two solutions of different pH, there is developed across the membrane a potential difference which depends on the pH of both solutions. If the pH of one of the solutions is known, the other may be calculated from the potential difference. In practice, the glass electrode usually consists of a bulb of the special glass fused to the end of a tube of ordinary glass. Inside the bulb is placed a solution of known pH, in contact with an internal silver-silver chloride or other electrode. This glass electrode and another reference electrode are immersed in the solution to be tested and the potential difference is measured. A potentiometer providing electronic amplification of the small current produced is employed. The modern instruments available permit reading the pH directly and provide also for compensation of variations due to temperature in the range of 0–50° and to the small but variable asymmetry potential inherent in the glass electrode.

Pharmaceutical Significance

In the broad realm of knowledge concerning the preparation and action of drugs few, if any, variables are so important as pH. For the purpose of this presentation, four principal types of pH-dependence of drug systems will be discussed: solubility, stability, activity and absorption.

Drug Solubility

If a salt, NaA, is added to water to give a concentration C_s , the following reactions occur:



If the pH of the solution is lowered, more of the A^- would be converted to the unionized acid, HA, in accordance with Le Chatelier's principle. Eventually, a pH will be obtained, below which the amount of HA formed exceeds its aqueous solubility, S_0 , and the acid will precipitate from solution; this pH can be designated as pH_p . At this point, at which the amount of HA formed just equals S_0 , a mass balance on the total amount of drug in solution yields

$$C_s = [\text{HA}] + [\text{A}^-] = S_0 + [\text{A}^-] \quad (92)$$

Replacing $[\text{A}^-]$ as a function of hydronium-ion concentration gives

$$C_s = S_0 + \frac{K_a C_s}{[\text{H}_3\text{O}^+]_p + K_a} \quad (93)$$

where K_a is the ionization constant for the conjugate acid, HA, and $[H_3O^+]_p$ refers to the hydronium-ion concentration above which precipitation will occur. This equation can be rearranged to give

$$[H_3O^+]_p = K_a \frac{S_0}{C_s - S_0} \quad (94)$$

Taking logarithms gives

$$pH_p = pK_a + \log \frac{C_s - S_0}{S_0} \quad (95)$$

Thus, the pH below which precipitation occurs is a function of the amount of salt added initially, the pK_a and the solubility of the free acid formed from the salt.

The analogous equation for salts of weak bases and strong acids (such as pilocarpine hydrochloride, cocaine hydrochloride or codeine phosphate) would be

$$pH_p = pK_a + \log \frac{S_0}{C_s - S_0} \quad (96)$$

in which pK_a refers to the protonated form of the weak base.

Example—Below what pH will free phenobarbital begin to precipitate from a solution initially containing 1.3 g of sodium phenobarbital/100 mL at 25°? The molar solubility of phenobarbital is 0.0050 and its pK_a is 7.41. The molecular weight of sodium phenobarbital is 254.

The molar concentration of salt initially added is

$$C_s = \frac{\text{g/L}}{\text{mol wt}} = \frac{13}{254} = 0.051 M$$

$$pH_p = 7.41 + \log \frac{0.051 - 0.005}{0.005}$$

$$= 7.41 + 0.96 = 8.37$$

Example—Above what pH will free cocaine begin to precipitate from a solution initially containing 0.0294 mole of cocaine hydrochloride/L? The pK_b of cocaine is 5.59, and its molar solubility is 5.60×10^{-3} .

$$pK_a = pK_w - pK_b = 14.00 - 5.59 = 8.41$$

$$pH_p = 8.41 + \log \frac{0.0056}{0.0294 - 0.0056}$$

$$= 8.41 + (-0.63) = 7.78$$

Drug Stability

One of the most diversified and fruitful areas of study is the investigation of the effect of hydrogen-ion concentration on the stability or, in more general terms, the reactivity of pharmaceutical systems. The evidence for enhanced stability of systems when these are maintained within a narrow range of pH, as well as of progressively decreasing stability as the pH departs from the optimum range, is abundant. Stability (or instability) of a system may result from gain or loss of a proton (hydrogen ion) by a substrate molecule—often accompanied by an electronic rearrangement—which reduces (or increases) the reactivity of the molecule. Instability results when the substance desired to remain unchanged is converted to one or more other, unwanted, substances. In aqueous solution, instability may arise through the catalytic effect of acids or bases, the former by transferring a proton to the substrate molecule, the latter by accepting a proton.

Specific illustrations of the effect of hydrogen-ion concentration on the stability of medicinals are myriad; only a few will be given here, these being chosen to show the importance of pH adjustment of solutions that require sterilization.

Morphine solutions are not decomposed during a 60-minute exposure at a temperature of 100° if the pH is less than 5.5; neutral and alkaline solutions, however, are highly unstable. Minimum hydrolytic decomposition of solutions of cocaine occurs in the range of pH of 2 to 5; in one study a

solution of cocaine hydrochloride, initially at a pH of 5.7, remained stable during 2 months (although the pH dropped to 4.2 in this time), while another solution buffered to about pH 6 underwent approximately 30% hydrolysis in the same time. Similarly, solutions of procaine hydrochloride containing some hydrochloric acid showed no appreciable decomposition; when dissolved in water alone, 5% of the procaine hydrochloride hydrolyzed, while when buffered to pH 6.5, from 19 to 35% underwent decomposition by hydrolysis. Solutions of thiamine hydrochloride may be sterilized by autoclaving without appreciable decomposition if the pH is below 5; above this, thiamine hydrochloride is unstable.

The stability of many disperse systems, and especially of certain emulsions, is often pH-dependent. Information concerning specific emulsion systems, and the effect of pH upon them, may be found in Chapter 20.

Drug Activity

Drugs that are weak acids or weak bases, and hence may exist in ionized or nonionized form (or a mixture of both), may be active in one form but not in the other; often such drugs have an optimum pH range for maximum activity. Thus, mandelic acid, benzoic acid or salicylic acid have pronounced antibacterial activity in nonionized form but have practically no such activity in ionized form. Accordingly, these substances require an acid environment to function effectively as antibacterial agents. For example, sodium benzoate is effective as a preservative in 4% concentration at pH 7.0, in 0.06 to 0.1% concentration at pH 3.5 to 4.0 and in 0.02 to 0.03% concentration at pH 2.3 to 2.4. Other antibacterial agents, on the other hand, are active principally, if not entirely, in cationic form. Included in this category are the acridines and quaternary ammonium compounds.

Drug Absorption

The degree of ionization and lipid solubility of a drug are two important factors that determine the rate of absorption of drugs from the gastrointestinal tract and, indeed, their passage through cellular membranes generally. Drugs which are weak organic acids or bases, and which in nonionized form are soluble in lipids, apparently are absorbed through cellular membranes by virtue of the lipoidal nature of the membranes. Completely ionized drugs, on the other hand, are absorbed poorly, if at all. Rates of absorption of a variety of drugs are related to their ionization constants and in many cases may be predicted quantitatively on the basis of this relationship. Thus, not only the degree of the acidic or basic character of a drug but consequently also the pH of the physiological medium (gastric or intestinal fluid, plasma, cerebrospinal fluid, etc) in which a drug is dissolved or dispersed—since this pH determines the extent to which the drug will be converted to ionic or nonionic form—become important parameters of drug absorption. Further information on drug absorption is given in Chapter 41.

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CHAPTER 18

Reaction Kinetics

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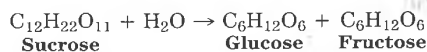
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Reaction kinetics is the study of rate of chemical change and the way in which this rate is influenced by the conditions of the concentration of reactants, products and other chemical species which may be present, and by factors such as solvent, pressure and temperature. Reaction kinetics permits the formulation of models for the intermediate steps through which reactants are converted to other chemical compounds, and it is a powerful tool for the elucidation of mechanisms by which chemical reactions proceed. In application to pharmaceuticals, such information permits a rational approach to the stabilization of drug products and prediction of shelf life and optimum storage conditions.

The treatment presented here is intended as a general introduction to the subject. A comprehensive review of experimental approaches and interpretation of data, and a compilation of information relative to studies on pharmaceuticals, has been published by Garrett.¹

Reaction Rate and Reaction Order

The rate of a reaction is the velocity with which a reactant, or reactants, undergoes a chemical change. The first quantitative study of a rate of reaction was performed in 1850 by Wilhelm, who observed the velocity of hydrolysis (inversion) of sucrose to glucose and fructose in aqueous solution, under the catalytic influence of acid. The equation for the overall reaction is



The rate at which the concentration of sucrose, designated c , decreases with time, t , was found to be proportional to the concentration of unhydrolyzed sucrose. The change may be expressed in the notation of calculus by the differential equation

$$-dc/dt = kc \quad (1)$$

where $-dc/dt$ is the velocity (rate) with which the concentration of sucrose decreases (the minus sign indicates a decrease) as it undergoes hydrolysis, and k is a constant called the *velocity constant* or *rate constant*.

The term *reaction order* refers to the way in which concentration of a reactant, or reactants, influences the rate of a chemical reaction.

First-Order Reactions—When the rate of a reaction is proportional to the first power of the concentration of a reactant and may be expressed mathematically in the form of Eq 1, the reaction is said to be first-order with respect to the reactant.

The hydrolysis of sucrose is not strictly first-order since the rate varies also with the concentration of water. The amount of water required for the hydrolysis of sucrose is so small, however, relative to the large quantity present, that there is no significant change in the concentration of water; for practical purposes, therefore, the concentration of water is constant.

It may be noted here that the rate constant, k , for the hydrolysis of sucrose increases with the hydrogen-ion concentration of the medium because of the catalytic effect of hydrogen ion on the reaction.

Equation 1 may be written

$$\frac{dc}{c} = -kdt \quad (2)$$

which, on integration, yields in natural logarithm form

$$\ln c = -kt + \text{constant} \quad (3)$$

or in common logarithm form

$$\log c = -\frac{kt}{2.303} + \text{constant} \quad (4)$$

Both Eqs 3 and 4 will be recognized as producing straight lines if $\ln c$ or $\log c$ is plotted against t ; this is an identifying characteristic of reactions in which the rate of reaction is proportional to the concentration of a single reactant, that is, of a *first-order reaction* (see Fig 1). The rate constant k may be calculated readily from the slope of the line, which is $-k/2.303$.

Concentration usually is expressed in mols/liter and time in seconds, although other convenient units may be employed. The rate constant, k , for a first-order reaction has units of reciprocal time (time^{-1}).

If Eq 4 is integrated between the limits of concentration c_0 at the beginning of the reaction when time is zero and when the concentration is c , at a later time t , Eq 5 is obtained:

$$\log \frac{c_0}{c} = \frac{k}{2.303} t \quad (5)$$

which on rearrangement becomes

$$k = \frac{2.303}{t} \log \frac{c_0}{c} \quad (6)$$

A modification of this equation, in which a is the initial amount of reactant and x is the amount that has reacted in time t , is

$$k = \frac{2.303}{t} \log \frac{a}{a-x} \quad (7)$$

Equation 6 may be used to calculate k for first-order reactions when both the concentration at the beginning of the reaction (c_0) and at elapsed time t are known. Sometimes, c_0 either is not known or is not a suitable reference concentration, in which cases the concentrations c_1 at time t_1 , and c_2 at a later time t_2 , are used to calculate k by the following modification of the preceding equation:

$$k = \frac{2.303}{t_2 - t_1} \log \frac{c_1}{c_2} \quad (8)$$

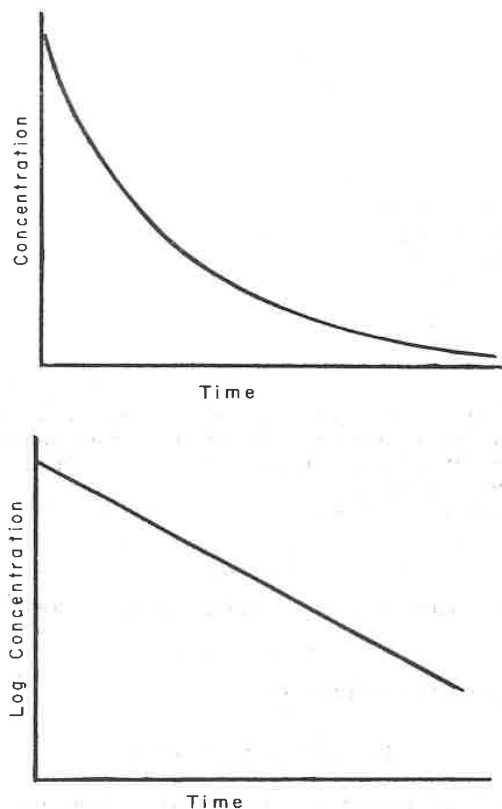


Fig 1. A first-order reaction. Top: Concentration versus time plot; bottom: log concentration versus time plot.

A useful exponential form of Eq 6, when the latter is written in natural logarithm notation, is

$$c = c_0 e^{-kt} \quad (9)$$

Although reaction rates may be expressed quantitatively in terms of numerical values of k , for many purposes a more useful expression is in terms of the *half-life* of a reaction, which is the time, $t_{1/2}$, required for half of the substance (reactant) to undergo reaction. Writing Eq 6 in the form

$$k = \frac{2.303}{t_{1/2}} \log \frac{c_0}{c_0/2} = \frac{0.693}{t_{1/2}} \quad (10)$$

it is apparent that

$$t_{1/2} = \frac{0.693}{k} \quad (11)$$

From Eq 11 it is obvious that, for first-order reactions, a constant time interval is required for disappearance of one-half of the substance present at the beginning of the interval, irrespective of the concentration of the substance. Thus, in a first-order reaction, 50% of an initial amount of reactant remains after the first half-life period, 25% after the second, 12.5% after the third and so on.

It also can be shown by an expression similar to Eq 10 that the time interval required for loss of *any* specified fraction of the reactant will be constant irrespective of the concentration of reactant. Thus, a term sometimes used in studies of drug stability is the time required for the loss of 10% of the original concentration, or time required for concentration to decrease to 90% of the original concentration. This interval is referred to as $t_{0.90}$.

It is apparent, also, that an infinite period of time would be required for all of the substance to undergo reaction. It is thus impossible to measure first-order reaction rates to completion of the reaction, and plots such as those of Fig 1 can not be extrapolated to zero concentration. It might be noted, however, that if a first-order reaction is followed through 10 half-lives, less than 0.1% of the original concentration of reactant remains. In practical studies of rate of reaction it is common to determine the change of concentration with time through two or three half-life periods.

First-order rate processes are not restricted to chemical reactions. The passive diffusion of drugs across biological membranes, and processes of drug absorption, distribution, metabolism and excretion often can be shown to occur at rates proportional to the concentration of a drug and thus be described as first-order rate processes. The rate of growth of microorganisms and rate of killing or inactivation of microorganisms by heat or chemical agents usually are first-order processes.

Second-Order Reactions—A second-order reaction is one in which the experimentally determined rate of reaction is found to be proportional to the concentration of each of two reactants or to the second power of the concentration of one reactant. If substances A and B undergo reaction at a rate proportional to the concentration of each (c_A and c_B , respectively), then

$$-\frac{dc_A}{dt} = -\frac{dc_B}{dt} = k \cdot c_A c_B \quad (12)$$

If a and b represent the molar concentrations of A and B at the start of the reaction, and x is the number of mols of each which has reacted at time t the reaction rate, dx/dt , may be expressed as

$$\frac{dx}{dt} = k(a-x)(b-x) \quad (13)$$

If the initial concentrations of A and B are equal, Eq 13 simplifies to

$$\frac{dx}{dt} = k(a-x)^2 \quad (14)$$

On integration

$$\frac{1}{(a-x)} = k \cdot t + \text{constant} \quad (15)$$

The constant may be evaluated by substituting 0 for x when $t = 0$ so that

$$k = \frac{1}{t} \cdot \frac{x}{a(a-x)} \quad (16)$$

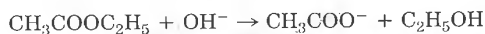
If the initial concentrations of A and B are not equal, integration of Eq 13, by partial fractions, and evaluation of the integration constant, gives

$$k = \frac{2.303}{t(a-b)} \log \frac{b(a-x)}{a(b-x)} \quad (17)$$

A reaction is second-order if, on substitution of the required analytical data into Eq 16 or 17 (whichever applies), constant values of k at different times of reaction are obtained. Alternatively, a plot of $x/a(a-x)$ vs t (see Eq 16) will result in a straight line when a equals b in a second-order reaction; when a is not equal to b a plot of $\log b(a-x)/a(b-x)$ versus t (see Eq 17) will give the straight line, if the reaction is second-order.

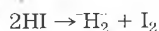
An example of a second-order reaction in which two reactants are involved is the saponification of an ester, such as

ethyl acetate, in alkaline solution.



The course of this reaction may be followed by determining by titration at specified times, the decrease in concentration of hydroxide ions as these are consumed in the reaction.

When only one reactant is involved in a second-order reaction, Eqs 14, 15 and 16 apply. A reaction of this type is the decomposition of hydrogen iodide, which in the gaseous state undergoes the reaction



The reaction rate in this case is expressed by

$$-\frac{dc_{\text{HI}}}{dt} = k \cdot c_{\text{HI}}^2 \quad (18)$$

The half-life of a second-order reaction has significance only when a single reactant or when two reactants, each at the same initial concentration, are involved. In both these cases the time, $t_{1/2}$, required for one-half of the reactant or reactants (at equal concentration) to undergo reaction may be calculated from Eq 15 to be

$$t_{1/2} = \frac{1}{ka} \quad (19)$$

It is obvious that while the half-life for a first-order reaction (see Eq 11) is independent of the concentration of the reactant, it varies inversely as the initial concentration of reactant in a second-order reaction.

First- and second-order reactions are by far the most common types of rate processes encountered regarding drug stability. If a reaction is of higher order than first-order, it often is convenient to adjust experimental conditions so that the concentrations of all but one of the reactants remain constant throughout the experiment. If, for example, the concentration of hydroxide ion in the saponification of an ester is in great excess of the concentration of ester, or if a buffer system is employed to control hydroxide-ion concentration, then the concentration of hydroxide ion essentially is invariant throughout the course of the experiment.

The observed rate of the reaction, therefore, depends only on the changing concentration of the ester, and the reaction is said to be *apparent first-order* or *pseudo first-order*. The apparent first-order rate constant thus obtained is $k(\text{OH}^-)$ and, of course, is different for each hydroxide-ion concentration. The actual rate constant, k , can be obtained easily by dividing the experimentally determined apparent first-order rate constant, $k(\text{OH}^-)$, by the concentration of hydroxide ion maintained throughout the study.

In the study of complex reactions, it is often desirable to use this approach of maintaining the concentration of all but one of the reactants constant to facilitate determination of the dependency of the reaction rate on each of the reactants in turn.

Third-Order Reactions—A third-order reaction is one in which the experimentally determined rate of reaction is found to be proportional to the concentration of each of three reactants, or proportional to the concentration of one of two reactants and to the second power of the concentration of the other, or proportional to the third power of the concentration of a single reactant. Third-order reactions are very rare.

For the case of a reaction between one molecule each of A, B and C, at molar concentrations a , b and c , respectively, the rate equation is

$$-\frac{dc_A}{dt} = -\frac{dc_B}{dt} = -\frac{dc_C}{dt} = k \cdot c_A c_B c_C \quad (20)$$

Using the notation of Eq 13, this becomes

$$\frac{dx}{dt} = k(a-x)(c-x) \quad (21)$$

When $a = b = c$

$$\frac{dx}{dt} = k(-x)^3 \quad (22)$$

On integration

$$\frac{1}{2(a-x)^2} = k \cdot t + \text{constant} \quad (23)$$

Evaluating the constant by substituting 0 for x when $t = 0$, gives

$$k = \frac{1}{2t} \left[\frac{1}{(a-x)^2} - \frac{1}{a^2} \right] \quad (24)$$

Zero-Order Reactions—In some reactions the rate is independent of the concentration of reactant or reactants, and these are termed *zero-order* reactions. Photochemical reactions—in which the rate-determining factor is the light intensity, rather than the concentration of reactant—are examples which may be found to be zero-order. In such cases the rate is expressed as

$$-dc/dt = k \quad (25)$$

If a compound for which decomposition in solution is first-order is present in excess of its maximum solubility (a suspension), the concentration of reactant in solution will be invariant so long as there is excess solid reactant present, and the observed reaction rate will be of the form of

$$-dc/dt = k \cdot c_s \quad (26)$$

where c_s is a constant. Such reactions are *apparent zero-order* reactions.

Complex Reactions—Many chemical reactions are not simple reactions of zero-, first-, second- or third-order. Often, they consist of a combination of two or more reactions; sometimes, the overall reaction can be characterized as one of these orders, but the rate equation may be a complicated function involving first-, second- or third-order intermediate steps. Experiment may indicate a reaction order which is nonintegral, or fractional, when reactions are complex. Nevertheless, concentrations of the various reactants usually can be controlled to permit a determination of the order of a reaction with respect to each reactant, and by this means the integral reaction order with respect to each component can be established.

Among the complicating factors that may be involved in the kinetic study of a complex reaction are *simultaneous reactions*, *consecutive reactions* and *opposing reactions*.

Simultaneous Reactions—Consider a Substance, A, that is converted simultaneously into B and C, each at characteristic rates:



The equation for rate of disappearance of A is the first-order equation

$$-\frac{dc_A}{dt} = k_1 c_A + k_2 c_A = (k_1 + k_2) c_A \quad (27)$$

Integration and arrangement in exponential form yields

$$c_A = c_{A_0} e^{-(k_1+k_2)t} \quad (28)$$

where c_{A_0} is the initial concentration of A at $t = 0$ and c_A is the concentration at time t .

The equation for the rate of formation of B is given by

$$\frac{dc_B}{dt} = k_1 c_A = k_1 c_{A_0} e^{-(k_1+k_2)t} \quad (29)$$

Integrating and arranging in exponential form

$$c_B = -\frac{k_1 c_{A_0}}{(k_1 + k_2)} e^{-(k_1+k_2)t} + \text{constant} \quad (30)$$

setting $c_B = 0$ when $t = 0$

$$\text{constant} = \frac{k_1 c_{A_0}}{(k_1 + k_2)} \quad (31)$$

then

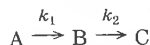
$$c_B = \frac{k_1 c_{A_0}}{(k_1 + k_2)} [1 - e^{-(k_1+k_2)t}] \quad (32)$$

since $c_A + c_B + c_C = c_{A_0}$ (initial concentration of A) it follows that

$$c_C = \frac{k_2 c_{A_0}}{(k_1 + k_2)} [1 - e^{-(k_1+k_2)t}] \quad (33)$$

An inspection of Eqs 32 and 33 shows that the fraction of A ultimately converted to B (at infinite time) is $k_1/(k_1 + k_2)$; the fraction converted to C is $k_2/(k_1 + k_2)$.

Consecutive Reactions—If two first-order reactions occur consecutively, thus



the rate equations for each substance are

$$-\frac{dc_A}{dt} = k_1 c_A \quad (34)$$

$$-\frac{dc_B}{dt} = -k_1 c_A + k_2 c_B \quad (35)$$

$$\frac{dc_C}{dt} = k_2 c_B \quad (36)$$

If $t = 0$ and setting $c_A = c_{A_0}$, $c_B = 0$ and $c_C = 0$, Eq 33 on integration and arrangement in exponential form becomes

$$c_A = c_{A_0} e^{-k_1 t} \quad (37)$$

and substituting for c_A in Eq 35 and integrating gives

$$c_B = \frac{k_1 c_{A_0}}{(k_2 - k_1)} [e^{-k_1 t} - e^{-k_2 t}] \quad (38)$$

Since $c_A + c_B + c_C = c_{A_0}$ (initial concentration of A), then

$$c_C = c_{A_0} \left[1 + \frac{1}{(k_1 - k_2)} (k_2 e^{-k_1 t} - k_1 e^{-k_2 t}) \right] \quad (39)$$

Opposing Reactions—The rate equation for an opposing (reversible) first-order reaction, represented by



may be expressed as

$$\frac{dc_A}{dt} = -k_1 c_A + k_2 c_B \quad (40)$$

At equilibrium the velocity of the forward reaction, $k_1 c_A$, is equal to the velocity of the reverse reaction, $k_2 c_B$, and $dc_A/dt = 0$. If the initial concentration of A is designated c_{A_0} , and the concentrations of A and B at equilibrium are c_{A_e} and c_{B_e} , respectively, then

$$\frac{c_{B_e}}{c_{A_e}} = \frac{c_{A_0} - c_{A_e}}{c_{A_e}} = \frac{k_1}{k_2} = K \quad (41)$$

where K is the equilibrium constant of the reaction.

Effects on Reaction Rate

Temperature

The application of heat to increase the rate of a chemical reaction is a common laboratory procedure. The rate of most solvolytic reactions of pharmaceuticals is increased roughly 2- to 3-fold by a 10° increase in temperature in the vicinity of room temperature.

Arrhenius noted, in 1889, that the variation with temperature of the rate constant of chemical reactions could be expressed by

$$k = s e^{-E_a/RT} \quad (42)$$

where E_a is the Arrhenius *activation energy* (the difference between the average energy of reactive molecules and the average energy of all molecules), $e^{-E_a/RT}$ is the Boltzmann factor which represents the fraction of molecules having the energy E_a , s is a constant called the frequency factor, R is the gas constant (1.987 cal/°K-mole) and T is the absolute temperature.

In logarithmic form the Arrhenius equation becomes

$$\log k = \log s - \frac{E_a}{2.303 RT} \quad (43)$$

If this equation is valid—and it is for a large number of reactions—a straight line is obtained on plotting $\log k$ against the reciprocal of the absolute temperature. The value of E_a may be calculated from the slope of the line, which is $-E_a/2.303 R$; the intercept on the $\log k$ axis is $\log s$ (see Fig 2).

Differentiating the natural logarithm form of Eq 43 with respect to temperature gives

$$\frac{d \ln k}{dT} = \frac{E_a}{RT^2} \quad (44)$$

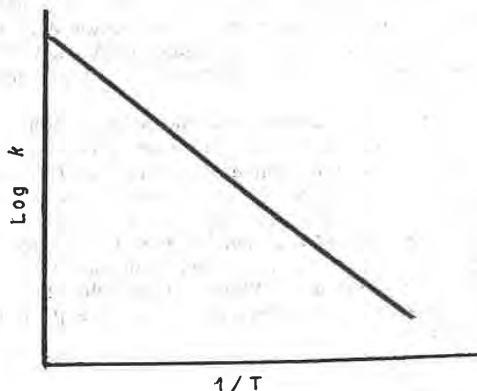


Fig 2. Variation of rate constant with temperature, illustrating the applicability of the Arrhenius equation.

and, on integration between the limits k_2 and k_1 at temperatures T_2 and T_1 , yields

$$\log \frac{k_2}{k_1} = \frac{E_a}{2.303R} \left(\frac{T_2 - T_1}{T_1 T_2} \right) \quad (45)$$

This equation makes it possible to calculate E_a for a reaction when the rate constants are known at two temperatures, or to calculate the rate constant at one temperature, if E_a and the rate constant at another temperature are known.

Most solvolytic reactions of pharmaceuticals exhibit activation energies in the range of 8 to 20 kcal/mol. Using Eq 45 and the appropriate activation energy, one readily can calculate that a reaction having an activation energy of 8 kcal/mol would show an increase of approximately 1.5-fold in k for a temperature increase from 25 to 35°; a reaction having an activation energy of 20 kcal/mol would show an increase of 3.0-fold in k for a similar temperature increase.

When two molecules undergo chemical interaction, it is reasonable to suppose that they first must come close enough to each other to effect a "collision" and then, if conditions are right, undergo a rearrangement of certain electrons to form the bonds characteristic of new molecules. This means that while "collision" is a prerequisite for interaction, not all collisions lead to chemical change. If all collisions did lead to reaction, all chemical reactions would occur with great rapidity since collision frequencies are very high. The explanation is that the colliding molecules must possess at least the amount of energy E_a before reaction can occur. This energy, called the *activation energy*, must be sufficient to overcome the mutual repulsion of the interacting molecules and enable them to approach each other close enough to effect certain bond ruptures and simultaneously establish new bonds characteristic of the products. The greater this energy requirement, the smaller the proportion of colliding molecules that will have the necessary energy, and the slower the reaction.

In the Arrhenius equation, s is a factor related to frequency of collisions, and $e^{-E_a/RT}$ is the probability that at temperature T a collision will occur with sufficient energy to provide a "successful" collision.

It would appear that in the reaction



there is an activated complex or transition state, represented by $[AB]^*$, which is not a complex in the usual sense but involves a critical intermediate geometric configuration in which the bonds of the reactants are weakened and the bonds of the products begin to form. If the complex has sufficient energy to effect the changes, the reaction proceeds; if it has not, it reverts to the state of the separate reactants.

The question arises as to the significance of the energy of activation in first-order reactions where only one kind of molecule undergoes chemical change. In this case collision with, or close proximity to, a molecule of different species is not involved. Here again, only those molecules that possess energy equal to the activation energy can react. Molecules can acquire the added energy by collisions of the proper kind; hence, collisions also play an important role in reactions involving a single molecular species.

The concept of energy of activation, in relationship to the energy of the reactants and of the products, is illustrated in Fig 3.

Other Effects

Specific Acid and Specific Base Catalysis—The term *specific acid catalysis* refers to catalysis by the hydrated proton or hydrogen ion, and *specific base catalysis* refers to catalysis by the hydroxide ion.

If the rate of hydrolysis of an ester, such as ethyl acetate, is studied at a constant pH in a strongly buffered solution, the rate of disappearance of intact ester will be an apparent first-order reaction. If the reaction is studied in solutions buff-

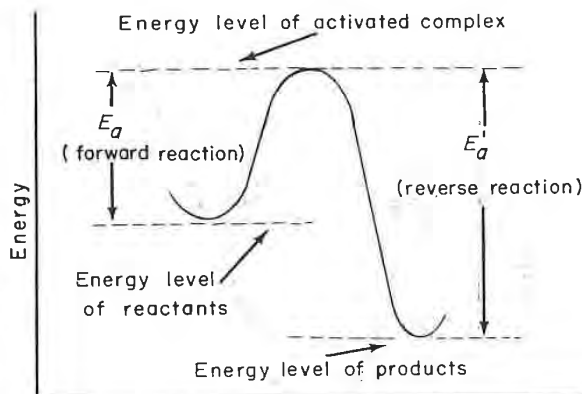


Fig 3. Relation between activation energy and energy levels of reactants, products and activated complex.

ered at several different pH values in a sufficiently acid pH region, a different apparent first-order rate constant will be observed for each pH value.

The observed rate depends on the concentration of both the ester and hydrogen ion and actually is a second-order reaction, although at a constant hydrogen-ion concentration it is an apparent first-order reaction.

$$k_{\text{observed}} = k_1(\text{H}^+) \quad (46)$$

The observed apparent first-order rate constant determined in buffered solution, therefore, is proportional to the hydrogen-ion concentration. The variation in observed rate constant with pH can be illustrated by taking logarithms of Eq 46.

$$\log k_{\text{observed}} = \log k_1 + \log (\text{H}^+) \quad (47)$$

$$\log k_{\text{observed}} = \log k_1 - \text{pH} \quad (48)$$

Thus, a plot of logarithm k_{observed} versus pH should be linear with a slope of -1 .

Similarly, if the same hydrolysis reaction is studied in buffered solution at several pH values in a sufficiently alkaline region of the pH scale, the observed apparent first-order rate constants will be found to vary with hydroxide-ion concentration.

$$k_{\text{observed}} = k_2(\text{OH}^-) \quad (49)$$

$$\log k_{\text{observed}} = \log k_2 + \log (\text{OH}^-) = \log k_2 + \log \frac{K_w}{(\text{H}^+)} \quad (50)$$

$$\log k_{\text{observed}} = \log k_2 + \log K_w + \text{pH} \quad (51)$$

A plot of logarithm k_{observed} versus pH would be a straight line with a slope of $+1$.

The complete rate expression for hydrolysis of the compound described above at all pH values, therefore, would be

$$-dc/dt = [k_1(\text{H}^+) + k_2(\text{OH}^-)]c \quad (52)$$

At any specified pH value

$$k_{\text{observed}} = k_1(\text{H}^+) + k_2(\text{OH}^-) \quad (53)$$

The complete logarithm k_{observed} versus pH profile would be similar to that illustrated in Fig 4² for the hydrogen-ion- and hydroxide-ion- (specific acid and specific base) catalyzed hydrolysis of the ester atropine. The pH at which the minimum rate of hydrolysis is observed is a function of the relative magnitude of the specific rate constants k_1 and k_2 .

In the atropine example the minimum rate of hydrolysis is at pH 3.7. If for a specific chemical species $k_1 = k_2$, the expected minimum rate of reaction for that species would be expected to occur at pH 7 (for a temperature of 25°, at which $\text{p}K_w = 14$, and $(\text{H}^+) = (\text{OH}^-)$ at pH 7.0).

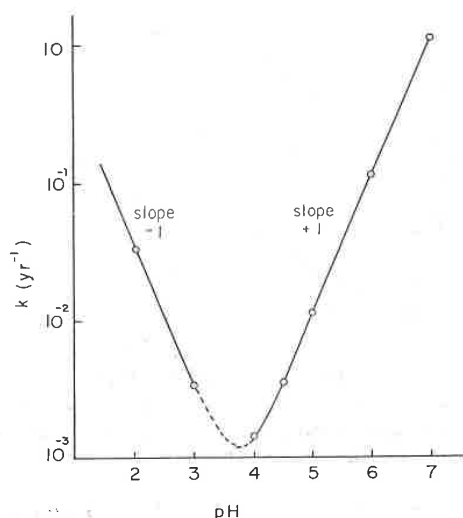


Fig 4. Apparent first-order rate of hydrolysis of atropine as a function of pH at 30°. The reaction is an illustration of specific hydrogen- and hydroxide-ion catalysis (courtesy, Kondritzer and Zvirblis²).

At pH values below the minimum, in the plot of logarithm k_{observed} versus pH, the hydrogen-ion-catalyzed reaction is much more significant than the hydroxide-ion-catalyzed reaction, and the plot has a slope of -1 . At pH values above the minimum in the plot, the hydroxide-ion-catalyzed reaction is the much more important reaction and the plot has a slope of $+1$.

If a reaction is catalyzed not only by hydrogen ion and hydroxide ion, but also by the solvent (also called the uncatalyzed reaction), a plot of the logarithm k_{observed} versus pH might appear as in Fig 5, indicating a flat region where the rate of reaction apparently is not pH dependent. In this region the solvent reaction is much more important than that of either the hydrogen ion or hydroxide ion. The apparent first-order rate constant for such a reaction is

$$k_{\text{observed}} = k_0 + k_1(\text{H}^+) + k_2(\text{OH}^-) \quad (54)$$

For compounds which are weak acids or weak bases, and,

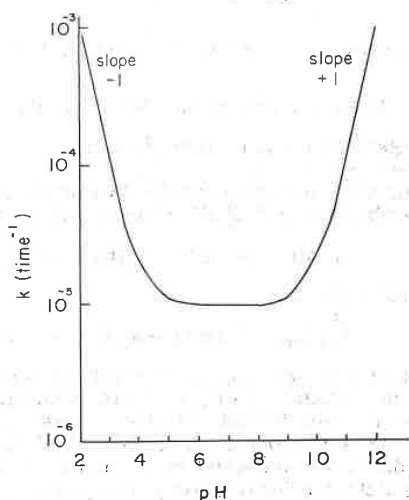
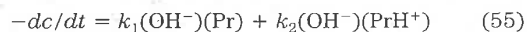


Fig 5. Apparent first-order rate of decomposition as a function of pH for a hypothetical case where $k_{\text{H}^+} = k_{\text{OH}^-} = 1 \times 10^{-1}$, $k_0 = 1 \times 10^{-5}$. The uncatalyzed reaction predominates in the pH region 5 to 9.

therefore, can exist in both ionized and nonionized species, the pH rate profiles become more complex. Often, both the ionized and nonionized species are subject to decomposition and catalysis by hydrogen and hydroxide ion, but each of the drug species may react at a different rate. For example, hydrolysis of the weakly basic drug procaine can be represented by²



where Pr is the nonionized procaine molecule and PrH^+ is the protonated form. The concentration of each species can be related to the total procaine concentration by the relationships

$$(\text{Pr}) = \frac{(\text{OH}^-)}{K_b + (\text{OH}^-)} \cdot (\text{Total Procaine}) \text{ and}$$

$$(\text{PrH}^+) = \frac{K_b}{K_b + (\text{OH}^-)} \cdot (\text{Total Procaine}) \quad (56)$$

where K_b is the classical dissociation constant for the weak base procaine.

The complete rate expression for procaine hydrolysis is, therefore, from Eqs 55 and 56

$$-dc/dt = \left[\frac{k_1(\text{OH}^-)^2}{K_b + (\text{OH}^-)} + \frac{k_2(\text{OH}^-)K_b}{K_b + (\text{OH}^-)} \right] c \quad (57)$$

The pH dependency of procaine hydrolysis is illustrated graphically in Fig 6³ by a plot of logarithm k_{observed} versus pOH for the pH region 7–13.

General Acid or Base Catalysis—Acid or base catalysis is not restricted to the effect of hydrogen or hydroxide ion. Undissociated acids and bases often can be demonstrated to produce a catalytic effect and, in some instances metal ions and various anions can serve as catalysts.

Mutarotation of glucose in acetate buffer is catalyzed by hydrogen ion, hydroxide ion, acetate ion and undissociated acetic acid. Also, the rate of barbiturate hydrolysis in ammonia buffers is increased by increasing buffer concentration at constant pH as a result of catalysis by NH_3 . Hydrolysis of the

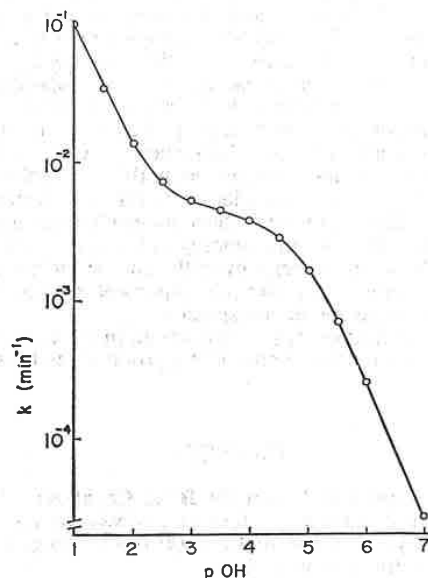
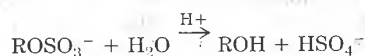


Fig 6. Apparent first-order rate of hydrolysis of procaine as a function of hydroxide-ion concentration at 40° (courtesy, Higuchi et al³).

amide function of chloramphenicol exhibits, in addition to solvent and specific acid-base catalysis, general acid-base catalysis in phosphate and citrate buffers. General acid-base catalysis is to be anticipated if there is evidence of a significant solvent catalysis as illustrated in the pH-rate profile of Fig 5.

Ionic Strength—In general the effects of increasing concentrations of electrolytes on reaction rate can be predicted by consideration of the influence of ionic strength on inter-ionic attraction. The Debye-Hückel equation may be used to demonstrate that increased ionic strength would be expected to decrease the rate of reaction between oppositely charged ions, and increase the rate of reaction between similarly charged ions. Thus, the hydrogen-ion-catalyzed hydrolysis of sulfate esters is inhibited by increasing electrolyte concentration.

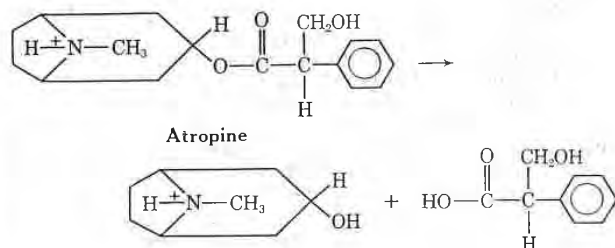


Reactions between ions and dipolar molecules, and reactions between neutral molecules, generally are less sensitive to ionic strength effects than are reactions between ionic compounds. However, reactions which result in formation of oppositely charged ions as products may exhibit considerable increase in rate with increasing ionic strength.

Dielectric Constant of Solvent—Reactions involving ions of opposite charge are accelerated by solvents of low dielectric constant. The rate of hydrogen-ion-catalyzed hydrolysis of sulfate esters, eg, is much greater in low dielectric constant solvents, such as methylene chloride, than in water.

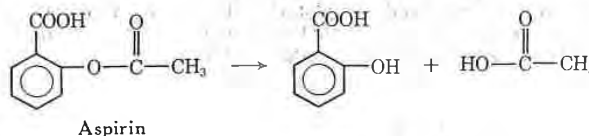
Reaction between similarly charged species is favored by high-dielectric-constant solvents. Reaction between neutral molecules, which produce a highly polar transition state, such as the reaction of triethylamine with ethyl iodide to produce a quaternary ammonium salt, also will be enhanced by high-dielectric-constant solvents.

Hydrolysis (Solvolysis)—Hydrolysis of esters such as procaine, aspirin or atropine represents one of the more common types of drug instability. Ester hydrolysis is either hydrogen- or hydroxide-ion catalyzed, although the catalysis which is important from the viewpoint of drug-product stability depends upon the specific compound and the pH of the solution. Amides generally are more stable than esters but are subject to catalysis by hydrogen and hydroxide ions; and often by general acids and bases. Some examples of the kinds of functional groups subject to hydrolytic cleavage and species shown to be catalysts for the reactions are presented below.



Hydrolysis of the ester function of atropine is typical of ester hydrolysis in that the only important reactions are catalysis by hydrogen ion or hydroxide ion. Figure 4 illustrates a pH-rate profile which might be considered typical for such a reaction. Below pH 3 the principal reaction is hydrogen-ion-catalyzed hydrolysis of the protonated form of atropine. Above pH 5 the principal reaction is hydroxide-ion-catalyzed

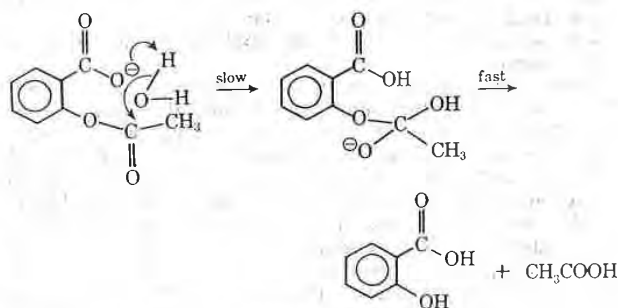
hydrolysis of the same species. Maximum stability at 30° is at pH 3.7.



Hydrolytic cleavage of aspirin to salicylic acid and acetic acid was studied by Edwards,⁴ who obtained the interesting pH-rate profile reproduced in Fig 7. The unusual pH-rate profile obtained for aspirin was attributed to a reaction of the form

$$-dc/dt = k_1(\text{H}^+)(\text{HA}) + k_2(\text{H}^+)(\text{A}^-) + k_3(\text{OH}^-)(\text{A}^-) + k_0(\text{A}^-) \quad (58)$$

where HA represents undissociated aspirin and A⁻ represents aspirin anion. The pH-independent anion hydrolysis indicated for the pH region 5 to 9 has been attributed to intramolecular catalysis by orthocarboxylate anion, rather than to general acid-base catalysis by water. It is principally this intramolecular catalysis which is responsible for the high instability of aqueous solutions of aspirin in the pharmaceutically useful pH range. Fersht and Kirby⁵ represented the intramolecular carboxylate ion reaction as a general base catalysis of attack by a water molecule. For nucleophiles such as ethanol, the terminal hydroxyl of polyethylene glycol (PEG) and the lysine ε-amino function in serum albumin also



can participate in this reaction in the same manner as water. Thus, from aspirin in ethanol solution, ethyl acetate appears as a product, in polyethylene glycol a polyethylene glycol acetate is formed and in a solution containing serum albumin

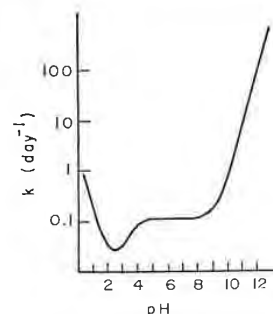
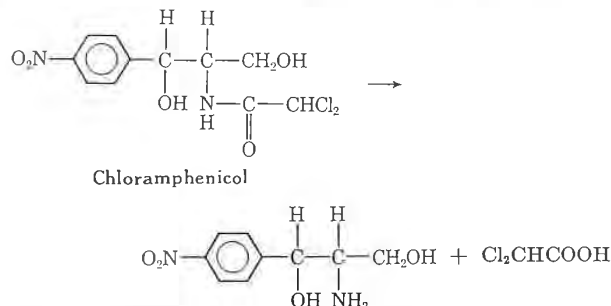


Fig 7. Apparent first-order rate of hydrolysis of aspirin as a function of pH at 17° (courtesy, Edwards⁴).

(both *in vitro* and *in vivo*) aspirin produces an acetylated serum albumin. Whitworth *et al*⁶ reasoned that an aspirin solution prepared in a PEG solvent containing no free hydroxyl groups would provide an aspirin solution of improved stability. They used acetylated PEG 400 as a solvent for aspirin and demonstrated that in such a solvent less than 1% aspirin loss occurred after 30 days at 45°.



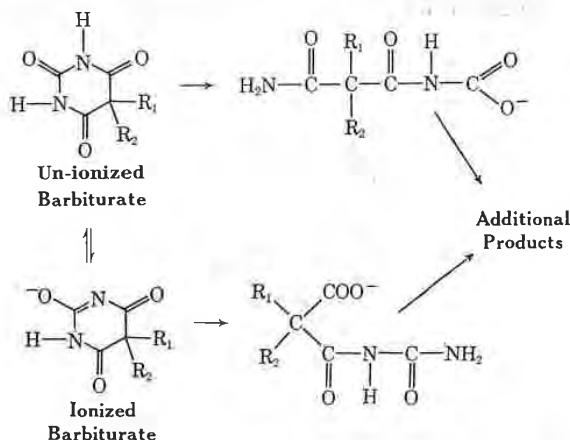
Chloramphenicol decomposition below pH 7 proceeds primarily through hydrolytic cleavage of the amide function. The reaction may be represented as

$$-dc/dt = [k_0 + k_1(\text{H}^+) + k_2(\text{OH}^-) + k_{\text{HB}}(\text{HB}) + k_{\text{B}}(\text{B})]c \quad (59)$$

In addition to hydrogen- and hydroxide-ion catalysis there is an uncatalyzed (or water) reaction, and there may be general acid-base catalysis, represented above by the buffer species HB and B. In general, the rate of hydroxide-ion-catalyzed hydrolysis of amides is greater than rate of hydronium-ion-catalyzed hydrolysis. Amides generally are much more stable than esters.

Penicillins and cephalosporins are important exceptions to this rule because the amide bond is part of a strained four-membered ring (beta-lactam). The decomposition of these compounds in aqueous solution is catalyzed by hydrogen ion, solvent, hydroxide ion, sugars and many buffer species. Maximum stability occurs at about pH 7, but beta-lactam antibiotics are too unstable to be formulated as solutions. For example, a buffered aqueous solution of penicillin G under refrigeration has a useful life of only about 1 week. Formation of the penicillenic acid by water-catalyzed rearrangement in acidic and neutral solutions is thought to be the first step in the degradation process.⁷

Barbiturate hydrolysis involves hydroxide-ion attack on both the undissociated acid and the ionized species. Hy-

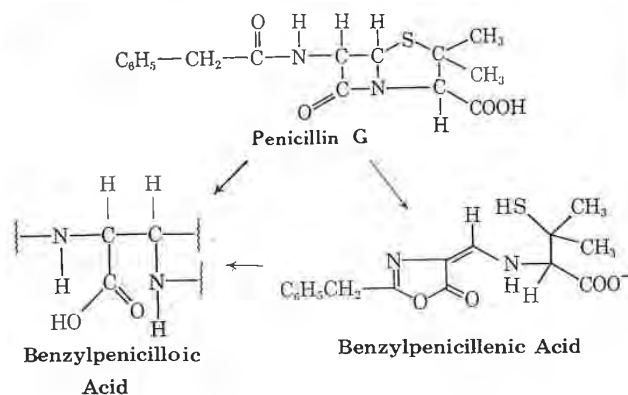


drogen-ion-catalyzed hydrolysis is not observed in the pH range of interest in pharmaceutical products.

$$-dc/dt = k_1(\text{OH}^-)(\text{HP}) + k_2(\text{OH}^-)(\text{P}^-) \quad (60)$$

Hydrolysis of the amide (peptide) bond also occurs in protein and peptide drugs. This can occur by cleavage of the primary peptide linkage (R-NH-CO-R) between adjacent amino acids in the peptide chain. Hydrolysis of the free side-chain amide groups of asparagine and glutamine (deamidation) is another degradation pathway for proteins. Insulin and recombinant human growth hormone undergo deamidation in solution. Further discussion of drugs resulting from biotechnology can be found in Chapter 49.

Racemization—Many drugs are optically active and racemization is a common mechanism of degradation resulting in loss of biological activity. In proteins, a mixture of the D and L enantiomers is formed by base-catalyzed reaction of the natural L configuration. Acid-catalyzed racemization of epinephrine or base-catalyzed racemization of pilocarpine result in a loss of pharmacological activity.



Oxidation—Compounds such as phenols, aromatic amines, aldehydes, ethers and unsaturated aliphatic compounds are subject to oxidation upon exposure to air or oxidizing chemicals. Epinephrine, ascorbic acid, phenothiazines and vitamin A are examples of important pharmaceutical products which are oxidized readily. Proteins can undergo oxidative degradation by oxidation of methionine (a thioether) to its corresponding sulfoxide. Oxidation of the carbon-carbon double bonds in unsaturated fatty acids, eg, oleic acid, results in rancidity of fats and oils.

Of particular concern are oxidations which occur when solutions are exposed to atmospheric oxygen. Such reactions are termed autoxidation (or self-oxidation) and are complex reactions which proceed via what is termed a free-radical mechanism. A free radical is a highly unstable (highly reactive) species containing an unpaired electron. Autoxidation reactions are autocatalytic in that free-radical reactions generate additional free radicals, causing a chain reaction. A technique used to protect pharmaceuticals susceptible to autoxidation is to include in the formulation agents which will react readily with free radicals, but which will terminate the chain propagation either by forming relatively stable radicals (resonance stabilized) or by forming products which do not include additional free radicals.

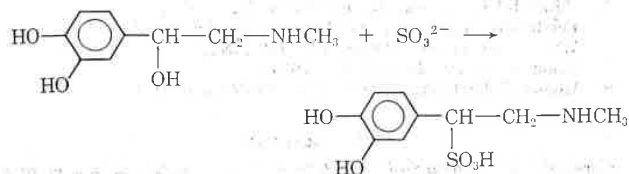
Photochemical Decomposition—Numerous dyes and drugs are subject to photochemical decomposition. Light-catalyzed oxidations and reductions of photoexcited species are common and are often mechanistically complex reactions involving free-radical intermediates. Pharmaceuticals such as riboflavin, nifedipine and phenothiazines are examples of common drugs which are extremely light sensitive.

Interaction between Components—Because drugs are often combined in solution with buffers, antioxidants, flavoring agents, antimicrobial preservatives and other drugs, potential interaction between the components of a formulation must be considered in pharmaceutical formulation development. Some obvious interactions, such as the possibility of the reaction of a drug having a primary amino function with an aldehyde such as vanillin to produce a Schiff base can be predicted, but a number of interesting, less-well-recognized reactions have been encountered.

In addition to buffer species acting as general acid-base catalysts, as previously indicated, some buffer species undergo specific interactions with drug molecules to form new chemical compounds. The formation of amides in aqueous solution, between amines such as benzocaine and buffers such as citric acid has been observed.

The aromatic function of procaine reacts with glucose to form procaine *N*-glycoside; also, phenylethylamine reacts with dehydroacetic acid to form a Schiff base-type compound. Catechols have been shown to catalyze penicillin hydrolysis.

It has been demonstrated that bisulfite, an agent commonly employed to protect epinephrine against oxidative decomposition, is capable of inducing epinephrine degradation through attack on the optically active side chain.



Although a solution of folic acid alone is stable to light, a combination of riboflavin and folic acid showed rapid loss of folic acid through formation of a coupled oxidation-reduction system in which riboflavin was photoreduced, with folic acid being used as a reducing substrate and being itself irreversibly oxidized. In the dark and in the presence of oxygen, the riboflavin was regenerated, and when the solution was again irradiated the cycle was repeated with further destruction of folic acid. The riboflavin is termed a *photosensitizer* in this reaction and would cause the decomposition, not only of folic acid, but also of ascorbic acid or any other easily oxidized substrate.

The presence of micellar surfactants and certain high-molecular-weight polymers commonly employed in pharmaceuticals also has been shown to lead to decreased drug stability in some cases. Both nonionic and anionic surfactants, as well as polymers such as polyvinylpyrrolidone, accelerate the photodecomposition of riboflavin in aqueous solution. Nonionic surfactants also are capable of increasing the rate of hydrolysis of sulfate esters which may be incorporated in or on the micellar surface.

Physical Instability—The introduction of an increasing number of drugs derived from developments in biotechnology necessitates greater awareness of instability occurring as a result of loss of drug activity through structural changes unrelated to disruption of covalent bonds. Protein-based drugs may lose activity as a result of a change in superstructure (secondary, tertiary, quaternary) which is independent of chemical modification. Superstructure changes which may alter protein drug activity include denaturation (unfolding), aggregation, surface adsorption and precipitation. Treatments with potential for inducing such changes include temperature change (increase or decrease), pH extremes and agitation or foaming resulting from shaking. High shear encountered in manufacturing or in drug delivery systems also may denature protein drugs.

Detection of instability of a physical nature generally re-

quires one or more biological assays, or physical assay methods which are sensitive to the critical superstructure change.

Drug Stabilization

Some drug decomposition reactions, such as photolytic and oxidative reactions, are relatively easy to avoid by protecting the components from light (photodecomposition) or exclusion of oxygen and use of chain-terminating reagents or free-radical scavengers to minimize free-radical-mediated reactions. Solvolysis reactions, however, can not be stopped by such procedures, but several techniques may be employed to retard reactions sufficiently to permit the formulation of a suitable drug product. The following approaches may be useful in attempts to retard solvolytic reactions.

Selection of Optimum pH, Buffer and Solvent—Consideration of the mechanism of the reaction and the way in which the reaction rate is influenced by pH, buffer species and solvent permits selection of the optimum conditions for drug stability. Often, however, ideal conditions for maximum stability may be unacceptable from the viewpoint of pharmaceutically acceptable formulation or therapeutic efficacy, and it may be necessary to prepare a formulation with conditions less than optimum for drug stability. If a suitable compromise between conditions for maximum stability and conditions for a pharmaceutically acceptable formulation can not be achieved, techniques such as those described below may be useful in retarding solvolysis reactions.

Specific Complexing Agents—The technique of stabilization by forming complexes in solution was introduced by Higuchi and Lachman,⁸ who demonstrated that the rate of hydrolysis of the ester function of benzocaine was retarded significantly in the presence of caffeine, a reagent with which the benzocaine formed a soluble complex. It was demonstrated further that, in these systems, the complexed drug did not hydrolyze at all, and that the observed rate of hydrolysis could be ascribed to the concentration of the free or uncomplexed drug which was in equilibrium with the drug complex.

Boric acid chelation of the catechol function of epinephrine stabilizes epinephrine against attack by bisulfite and sulfite. The complex of povidone (polyvinylpyrrolidone) and iodine has been used for many years as a topical antiseptic because of its higher iodine concentration, slow release of iodine from the complex and lower toxicity.

Surfactants—It has been demonstrated that the incorporation of benzocaine into surfactant micelles could retard significantly the rate of ester hydrolysis. Nonionic and anionic surfactants retarded the hydroxide-ion-catalyzed hydrolysis, but cationic surfactants somewhat increased the rate of hydroxide-ion-catalyzed hydrolysis. Similar observations have been reported for a number of drugs which are sufficiently lipophilic to be solubilized by surfactant micelles.

Suspensions—If the solubility of a labile drug is reduced, and the drug prepared in a suspension form, the rate at which the drug degrades will be related only to the concentration of dissolved rather than to the total concentration of drug in the product. Thus, it has been demonstrated that penicillin G procaine suspensions degraded at a rate proportional to the low concentration of penicillin in solution. Since the penicillin in solution was in equilibrium with excess solid penicillin G procaine, the penicillin concentration in solution was constant and the observed order of reaction was apparently zero-order.

Refrigeration—Storage at temperatures below room temperature usually will retard solvolytic reactions. Storage in the frozen state generally is an effective means of retarding degradative reactions. Several antibiotics are sold as frozen solutions in flexible plastic bags. An exception is sodium ampicillin dissolved in 5% dextrose solution, which showed approximately 10% decomposition after 4 hours of storage at 5° and more than 13% loss after storage for the same period in the frozen state at -20°.

Stability Testing of Pharmaceutical Products

If a product is sufficiently stable to be marketed, it would require relatively long storage at room temperature, or at the actual temperature at which it will be stored prior to its ultimate use, to permit observation of the rate at which the product degrades under normal storage conditions.

To avoid this undesirable delay in evaluating possible formulations, the manufacturer attempts to predict stability under conditions of room temperature, or actual storage conditions, by using data for the rate of decomposition obtained at several elevated temperatures. This prediction is accomplished by an Arrhenius plot to predict, from high-temperature data, the rate of product breakdown to be expected at actual storage conditions. See Chapter 38.

Prediction based on data obtained at elevated temperature generally is satisfactory for solution dosage forms. Success is more uncertain when nonhomogeneous products are involved. Suspensions of drugs may not provide linear Arrhenius plots because often there is the possibility that the solid phase, which exists at elevated temperature, may not be the same solid phase which exists at room temperature, and differences in the solubility of the several solid phases which may exist can invalidate the usual Arrhenius plots.

Such difficulties should be anticipated when polymorphic crystal forms or several different solvates are known to exist for a specific solute. Also, when solid dosage forms, such as tablets, are subjected to high temperatures, changes in the quantity of moisture in the product greatly may influence the stability of the product.

Arrhenius plots also suffer limitations in application to reactions which have relatively low activation energies, and therefore are not accelerated greatly by an increase in temperature. While it usually is desirable to determine drug stability by analyzing samples for the amount of intact drug remaining—in instances where there is very little drug decomposition, and particularly when it is not convenient to accelerate the reaction by increasing temperature—it sometimes is advantageous to determine initial reaction rates from the determination of the amount of reaction product formed.

Using modern methods of analysis such as high-perfor-

mance liquid chromatography (HPLC), it is often possible to measure the rate of formation of a degradation product. Using this technique, very small amounts of degradation (less than 1% loss of parent compound) can be detected, resulting in a more sensitive indication of product stability than that obtained by analyzing potency.

Since manufacturers are interested most in the time required to produce just a few-percent breakdown in their product, it is not uncommon to employ terminology such as $t_{0.90}$ or $t_{0.95}$, which is the time required for the drug to decompose to 90% or 95%, respectively, of original potency. This terminology is completely analogous to the terminology $t_{1/2}$, or $t_{0.50}$, used to represent the half-life period.

An Arrhenius-type plot, analogous to that illustrated in Fig 2, can be obtained by plotting the logarithm of the time required for the specified fractional decomposition versus the reciprocal of absolute temperature. The time required for the product to decrease in potency to 90% of original potency at room temperature then can be obtained directly from the plot.

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CHAPTER 23

Inorganic Pharmaceutical Chemistry

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Inorganic chemicals have been used in pharmacy and medicine for many reasons, ranging from therapeutic agents to nutritional supplements to pharmaceutical necessities. In this chapter a review of some chemical principles and properties of elements is followed by a discussion of the wide variety of useful inorganic chemicals.

Basis of Chemical Reactions

Although many subatomic particles have been identified during recent decades, only the protons and neutrons of the nucleus of an atom and the extranuclear electrons will be considered here.

Each atom of an element is described uniquely by two pure numbers, its atomic number and its atomic weight. The atomic number gives the number of protons present in the nucleus and, therefore, its positive charge. Since the ground state atom must be neutral, this in turn defines the number of extranuclear electrons. The difference between the atomic number and the atomic weight of a given *isotope* of an element defines the number of neutrons in the nucleus. (Atomic weights in the tables are not whole numbers because they represent the weighted average of the atomic weights of all isotopes present.)

The electrons are arranged in major quantum groups (energy levels or orbitals) occupying the space about the nucleus. Each electron is assigned four quantum numbers:

The principle quantum number, n , describes the relative position of an energy level with respect to the other energy levels present.

The subquantum number, l , describes the different electron distributions possible for a given value of n .

The magnetic quantum number, m_l , is best described as the magnetic contribution to the angular momentum due to the movement of the electrons in space.

The magnetic spin quantum number, m_s , is the magnetic component contributed by the spin of the electron.

The permitted values for n are 1, 2, 3, ..., for l are 0, 1, 2, ..., ($n - 1$), for m_l are $-l, \dots, 0, \dots, +l$, and for m_s $\pm \frac{1}{2}$. Returning to the subquantum number l ; when l is 0 the electrons occupying the suborbital are known as s electrons, when l is 1, p electrons, when 2, d electrons and when 3, f electrons. Thus if 2 electrons occupy suborbital 0 of major quantum group 3, they are represented as $3s^2$.

In assigning electrons to the atom the Aufbau Principle is used. It is an application of Quantum Theory, Hund's Rules and the Pauli Exclusion Principle. Simply stated, a given entering electron must occupy the lowest unoccupied energy level of the atom. In other words, each electron must have a unique set of quantum numbers.

As a result of the above process, all atoms, except hydrogen and the inert gases, have one or more completely occupied lower major quantum groups and have the suborbitals of their highest major quantum group only partially filled. The elec-

trons of this outer, partially filled, energy level give each element its distinct chemical properties. These are the valence electrons.

Chemical reactions entail the removal of valence electrons, adding electrons to a partly filled valence shell, or sharing a pair of valence electrons between two atoms. Most atoms attempt to achieve a rare gas outer shell, (ns^2 or ns^2np^6), by these processes. The energy required for the removal of the electron of least energy is known as the first ionization potential. It is unique for each element. The metals have low ionization potentials and, therefore, readily form cations. Nonmetals have high ionization potentials.

The attraction of a nucleus for electrons is termed its electronegativity. Metals have low electronegativities (they are electropositive), while nonmetals (especially the halogens) have high electronegativities. This allows the latter to attract additional electrons to form anions.

When atoms with widely differing electronegativities react, eg, sodium, 0.93, and chlorine, 3.98, an electron transfer takes place. The one valence electron of sodium ($3s^1$) enters the incompletely filled ($3s^23p^5$) valence shell of the chlorine. Sodium now has an inert gas (Ne) electron structure with a +1 charge. The chlorine achieves the argon structure with a -1 charge. There is no formal electron-pair bond between the two entities. A crystal of sodium chloride consists of equal numbers of sodium and chloride ions held in place by the interaction of the spherically symmetrical positive cation field and the spherically symmetrical negative anion field. These ionic (electrostatic) compounds are characterized by high boiling and melting points and most are water-soluble.

If two reacting atoms have similar electronegativities, eg, two hydrogen atoms, a sharing of electrons takes place. One electron is donated to the bond from an incompletely filled suborbital of each atom. A covalent bond is formed by the overlap of the two atomic orbitals involved. With the formation of the bond a molecule results. The bonding electrons are no longer restricted to their atomic orbitals. They now are free to move in a molecular orbital between the two atoms in what is known as a σ molecular orbital.

When the electronegativities of the two atoms involved in the formation of a covalent bond are not identical the atom with the higher electronegativity tends to attract the electrons of the molecule more strongly than its partner. This leads to polarization of the molecule and a dipole results. The extent of polarization is directly proportional to the difference in electronegativities. Such bonds are said to have partial ionic character.

In practice, only the most electropositive atoms reacting with the most electronegative atoms result in purely electrostatic compounds, and only atoms with equal electronegativities form purely covalent bonds. Those bonds formed from elements between these extremes have partial covalent or partial electrostatic character.

Atoms with orbitals occupied by an unshared pair of electrons can share this electron pair with an atom lacking two or more electrons in its valence shell. The bond formed is said

*Deceased.

to be a coordinate covalent bond. Once this bond has been formed it can not be distinguished from an ordinary covalent bond; the difference lies only in the manner of formation. The formation of the ammonium ion from an ammonia molecule, which has an unshared electron pair, and a hydrogen ion, which has an empty *s*-orbital, illustrates this type of reaction.

Covalent compounds have low melting and boiling points, and usually are insoluble in water. Solubility in water can be induced by introducing an acid or base group into the molecule. Reaction with base or acid will now give a soluble salt.

Other types of bonding exist. Those of interest are weakly bonded; the compounds formed decompose more readily than the electrostatic and covalent types. Hydrogen-bonding (bridging) is quite common. Dipole-dipole bonding also is possible; very weak associations result.

Complexes are compounds or ions formed when an atom or cation, *central unit*, acts as a center about which anions or molecules, *ligands*, arrange themselves. The central unit is said to have a *coordination number* equal to the number of complexing ligands. The maximum number of ligands which can arrange themselves about the central unit is known as its *maximum coordination number* and is a function of the size of the central unit. Usual maximum coordination numbers are 2, 4, 6 or 8. The number of ligands which can coordinate with the central unit also is a function of ligand size. Thus, even though the maximum coordination number of aluminum is 6, only four of the relatively large chloride ions can be accommodated as ligands, eg, $[\text{AlF}_6]^{3-}$ vs $[\text{AlCl}_4]^{-}$ (see Chapter 14).

The bonding involved in the formation of complexes can be coordinate covalent or electrostatic. Bonds depending on permanent dipoles are also common, eg, hydrates.

Nomenclature

The great advances in chemistry during the past several decades have made necessary constant revision of systems of

nomenclature, designed to give precise information with respect to the composition of chemical compounds. Whereas oil of vitriol and lunar caustic at one time were useful names, today they must be looked upon as trivial.

Classical Nomenclature—Prior to elucidation of the structure of coordination complexes, the naming of compounds was handled reasonably well by using nonnumerical prefixes and suffixes and Latin or Greek numerical prefixes. In general the main function of these prefixes and suffixes was to indicate the oxidation state of elements of variable valence, although some were intended to connote structural characteristics.

Systematic nomenclature must consider two problems; order of citation and stoichiometry. Order of citation is usually well defined; for salts and salt-like compounds the most electropositive element is named first, eg, sodium chloride. For nonmetals the International Union of Pure and Applied Chemistry (IUPAC) recommends the following order of citation:

B, Si, C, Sb, As, P, N, H, Se, S, I, Br, Cl, O, F.

Cations with a single oxidation state simply are named as the element. If a cation has two oxidation states the suffix *-ous* is used to indicate the lower oxidation state, eg, mercurous, and the suffix *-ic* for the higher oxidation state, eg, mercuric. (Obviously this system breaks down when an element exists in more than two oxidation states.) The simple anions are named using the suffix *-ide*. While the newer Stock system of nomenclature uses only the English names of the elements, classical nomenclature uses the stems of the Latin names in identifying the cations of copper, gold, tin, lead and iron.

For the oxygenated anions a system of prefixes and suffixes was developed to indicate the oxidation state of the central atom. These are illustrated in Table 1 using the chlorine anions.

Sometimes one or more oxygen atoms of the anion are replaced by another element. The stem of the name of the substituting element is used as a prefix to the name for the fully oxygenated anion, eg, $\text{Na}_2\text{S}_2\text{O}_3$, sodium thiosulfate or Na_3AsS_4 , sodium thioarsenate (sodium tetrathioarsenate).

In addition to variable oxidation numbers, oxygenated acids (and their salts) present two other nomenclature problems: (1) a variation in the degree of hydration of the parent acid anhydride and (2) the naming of the different salts arising from partial neutralization of polyprotic acids. Table 2 shows the prefixes used for naming the different phosphoric acids (P^{5+}).

For salts of diprotic acids the salt resulting from neutralization of only one proton per acid molecule is named by using the prefix *bi-* or the words hydrogen or acid with the anion, eg, NaHCO_3 , sodium bicarbonate, acid carbonate or hydrogen carbonate. The latter is preferred. Several methods have been devised for the triprotic acids. These are shown in Table 3. Due to very strongly basic reaction of the solutions of Na_3PO_4 and other tertiary phosphates, the pharmacist must be alert especially when using containers labelled sodium phosphate.

It is evident from Table 3 that the numerical Greek prefixes hemi-, mono-, sesqui-, di-, tri-, tetra-, penta-, hexa-, hepta-, octa-, ennea- (nona-) and deca-, also are used in naming compounds. In fact there are compounds, eg, N_2O_4 , dinitrogen tetraoxide, which must be named using numerical prefixes since modern systems of nomenclature are unable to identify them precisely.

Stock Nomenclature—Classical nomenclature is satisfactory for simpler compounds involving atoms with one or two

Table 1—Nomenclature for Oxygenated Acids and Salts

Cl Oxid state	Acid formula	Acid name	Anion name
-1	HCl	<i>Hydrochloric acid</i>	<i>chloride</i>
+1	HClO	<i>Hypochlorous acid</i>	<i>hypochlorite</i>
+3	HClO ₂	<i>Chlorous acid</i>	<i>chlorite</i>
+5	HClO ₃	<i>Chloric acid</i>	<i>chlorate</i>
+7	HClO ₄	<i>Perchloric acid</i>	<i>perchlorate</i>

Table 2—Nomenclature for the Phosphoric Acids

Water molecules	Resultant acid	Name
$\text{H}_2\text{O} + 1/2\text{P}_2\text{O}_5$	HPO_3	<i>Metaphosphoric acid</i>
$2\text{H}_2\text{O} + \text{P}_2\text{O}_5$	$\text{H}_4\text{P}_2\text{O}_7$	<i>pyrophosphoric acid</i>
$3\text{H}_2\text{O} + \text{P}_2\text{O}_5$	H_3PO_4	<i>diphosphoric acid</i>
		<i>orthophosphoric acid</i>
$5\text{H}_2\text{O} + 3\text{P}_2\text{O}_5$	$\text{H}_5\text{P}_3\text{O}_{10}$	<i>phosphoric acid</i> ^a
		<i>triposphoric acid</i>

^aThe phosphoric acid of commerce and science is orthophosphoric acid.

Table 3—Nomenclature of the Phosphate Salts

Formula	NaH_2PO_4	Na_2HPO_4	Na_3PO_4
Preferred name	sodium dihydrogen phosphate	sodium monohydrogen phosphate	sodium phosphate
Other names	monobasic sodium phosphate primary sodium phosphate	dibasic sodium phosphate secondary sodium phosphate	tribasic sodium phosphate tertiary sodium phosphate
USP XXI	monobasic sodium phosphate	dibasic sodium phosphate	

Table 4—Nomenclature for Common Ligands

Ligand	Preferred prefix	Ligand	Preferred prefix
H ₂ O	aqua	HS ⁻	mercapto
NH ₃	ammine	S ²⁻	thio (sulfo) ^a (sulfido)
CO	carbonyl	S ₂ ²⁻	disulfido
F ⁻	fluoro	SO ₃ ²⁻	sulfato
Cl ⁻	chloro	SO ₄ ²⁻	sulfato
Br ⁻	bromo	S ₂ O ₃ ²⁻	thiosulfato
I ⁻	iodo	NO ⁻	nitrosyl
O ²⁻	oxo (oxy)	ONO ⁻	nitrito
O ₂ ²⁻	peroxo (peroxy)	NO ₂ ⁻	nitro
OH ⁻	hydroxo (hydroxy)	CN ⁻	cyano
C ₂ O ₄ ²⁻	oxalato	SCN ⁻	thiocyanato
NH ₂ CH ₂ CH ₂ NH ₂	ethylenediamine, or <i>en</i>	NCS ⁻	isothiocyanato

^aForms in parentheses are also used.

oxidation states. It cannot indicate proper stoichiometry when atoms having three or more oxidation states are involved. The Stock system of nomenclature attempts to overcome the problem.

In the Stock system simple cations are named as the element followed by its oxidation state, expressed in Roman numerals enclosed in parentheses, eg, Fe²⁺, iron(II), Fe³⁺, iron(III) or Fe⁶⁺, iron(VI). Simple anions use the suffix *-ide* as before. However, complex anions are named using the stem of the name of the central unit and the suffix *-ate* followed by its oxidation state, in Roman numerals, enclosed in parentheses. The ligand(s) involved are cited before the central unit of the complex. If two or more different ligands are present they are cited in alphabetical order, ignoring Greek prefixes. The number of each of the individual ligands involved is indicated by the use of Greek numerical prefixes. These latter rules also govern the citing of ligands associated with complex cations. The preferred nomenclature for common ligands is given in Table 4.

Stock names are not used for complex anions with well established classical names. These include sulfate, sulfite, nitrate, nitrite, carbonate, phosphate, thiosulfate, cyanate and thiocyanate.

Ewens-Bassett—Sometimes it is advantageous to cite the charge on a complex ion rather than the oxidation state of the central unit. The Ewens-Bassett system gives the charge of the complex ion in Arabic numerals enclosed in parentheses, after the name. Other than this, the rules for naming a compound are similar to the Stock system. Thus, the common ferrocyanide ion, [Fe(CN)₆]⁴⁻, becomes hexacyanoferrate(II) using Stock nomenclature, and hexacyanoferrate(-4) using the Ewens-Bassett system. Table 5 gives some examples of modern nomenclature.

A more thorough review of inorganic nomenclature may be found in Discher *et al.*¹ or Huheey, Keiter and Keiter.² A comprehensive report on the subject will be found in Report of

the Commission on Nomenclature of Inorganic Chemistry, issued by IUPAC.³

The Periodic Table and Families of Elements

The periodic table constitutes a valuable tool which systematizes the physical and chemical properties of the elements. A table is shown on the inside back cover of this textbook.

The utility of the periodic table lies in its ability to provide clues to the physical and chemical behavior of the elements and their compounds. Mendeleev, the chemist who first arranged atoms systematically, could predict the existence of unknown elements of his time, and their behavior, eg, eka-silicon, now known as germanium. A knowledge of periodic relationships enabled atomic scientists to postulate the properties of unknown post-uranic elements successfully so that procedures could be designed for their recovery from atomic reaction products.

Based on periodic law, the periodic table arranges the elements into horizontal rows, with the same outermost, partly filled, major quantum groups and into vertical columns which have elements with the same valence electron structures. As a result, in any given vertical group (family) the members exhibit similar behavior patterns. Differences are a matter of degree, depending upon atomic radius and the type of closed shell underlying the valence electron(s).

The preferred way of designating columns in the periodic table is controversial. In this chapter the vertical groups of the periodic table are identified by the Roman numerals, I to VIII, except for the inert gases which are assigned as Group 0. Each group divides into two subfamilies, A and B. In this chapter the "typical elements" will be designated the A subgroup, eg, I-A, the alkali metals, and the transition element members of the family will be designated the B subgroup. Group VIII is not divided into A and B subgroups. It consists of three triads of elements. The members of a given triad are remarkably similar in both physical and chemical properties, eg, the first triad, cobalt, nickel and iron.

Hydrogen (1s¹) and helium (1s²) constitute the first row of the periodic table. While helium clearly is the first member of Group 0, hydrogen customarily is placed at the head of both Group I-A, the alkalis, and Group VII-A, the halogens. Like the alkali metals, it exists as the monovalent cation, H⁺, but like the halogens, it also can exist as the monovalent anion, H⁻, the hydride ion.

Many of the vertical groups of the periodic table have common names. Group 0, the inert gases, Group I-A, the alkali metals, Group II-A, the alkaline earths and Group VII-A, the halogens, already have been identified. Additional named groups are Group VI-A, the chalcogens, Group I-B, the coinage elements and Group II-B, the volatile elements.

Those elements in which a *d*-orbital is filled partially, starting at Group III-B and ending at Group II-B, are known as the transition elements. Horizontal similarities exist to a varying degree in the transition elements, especially in the lower ox-

Table 5—Examples of Modern Nomenclature

Formula	Classic name	Stock name	Ewens-Bassett ^a
K ₂ [HgI ₄]	Potassium mercuric iodide	Potassium tetraiodomercurate(II)	(-2)
[Ag(NH ₃) ₂] ⁺	Silver ammonia ion	Diamminesilver(I) ion	(+1)
Na ₃ [Au(S ₂ O ₃) ₂]	Sodium gold thiosulfate	Sodium dithiosulfatoaurate(I)	(-3)
[Fe(H ₂ O) ₆]Cl ₃	Hydrated ferric chloride	Hexaaquairon(III) chloride	(+3)
BiOCl	Bismuthyl chloride	Bismuth(III) chloride oxide	^c
[Ni(CO) ₄]	Nickel carbonyl	Tetracarbonyl nickel(0)	^c
[(NH ₃) ₅ CoO ₂ Co(NH ₃) ₅] ⁴⁺	...	Decammine-μ-peroxodicobalt(III) ion ^b	(+4)
Na ₂ [Fe(CN) ₅ (NO)]·2H ₂ O	Sodium nitroprusside	Sodium pentacyanonitrosylferrate(III) dihydrate	(-2)

^aThis number, as shown, substitutes for the Roman numeral of the Stock name.^bThis ion illustrates the use of μ to indicate a bridging structure, in this case the peroxo group.^cNot applicable.

Table 6—The Elements of Group 0^a

Element	Helium	Neon	Argon	Krypton	Xenon	Radon
Symbol	He	Ne	Ar	Kr	Xe	Rn
Atomic number	2	10	18	36	54	86
Atomic weight ^b	4.003	20.18	39.95	83.80	131.3	(222) ^d
Orbital electrons	1s ²	[He]2s ² 2p ⁶	[Ne]3s ² 3p ⁶	[Ar]3d ¹⁰ 4s ² 4p ⁶	[Kr]4d ¹⁰ 5s ² 5p ⁶	[Xe]4f ¹⁴ 5d ¹⁰ 6s ² 6p ⁶
Atomic radius (Å)	1.80	1.60	1.92	2.00	2.20	2.29
Ionization potential ^c ev	24.6	21.6	15.8	14.0	12.1	10.7
% by volume in air	5 × 10 ⁻⁴	15 × 10 ⁻⁴	0.94	11 × 10 ⁻⁵	9 × 10 ⁻⁶	...

^aPhysical data are from Ref 4. Atomic and ionic radii are from Pauling⁵ and modified by the work of Shannon and Prewitt.⁶ See also Ref 7.

^bGiven to four significant figures.

^cFirst ionization potential, unless otherwise noted.

^dAtomic weights in parenthesis are now known exactly.

Note: The above apply to Table 6 to 17.

dation states. As an example, the element palladium, to the left of silver, forms an insoluble chloride, PdCl₂, which is soluble in ammonia.

The lanthanides and actinides (inner transition elements) are fourteen member families in which *f* orbitals have one to fourteen electrons. Each family has very strong horizontal similarities since the electrons in the partly filled external *s*, *p* and *d* orbitals are identical for most.

Because the energy levels of the electrons in the *d* and *f* orbitals of the transition elements and the inner transition elements, respectively, differ only slightly, these elements give rise to colored compounds. The energy emitted when an excited electron falls to a vacant lower level within the *d* or *f* orbitals is that of radiation in the visible range of light.

Starting at the upper right corner of the periodic table, as one proceeds down and to the left, the elements assume increasing metallic character; they become more basic, and less electronegative (more electropositive). The simple anions become less stable and the simple cations more stable. Thus, it may be said the nonmetals occupy the upper right area of the periodic table and the metallic elements are found to the left and toward the bottom. The so-called "heavy metals" are found in the two bottom rows. Metallic elements, for the most part, are protein precipitants, the major exception being the alkali metals. Being protein precipitants, metals, especially heavy metals, are toxic. For example Ba, Tl, Pb and Hg are violent poisons.

From the above it is obvious there must be an area in the periodic table where the elements are equally acidic and basic, that is, *amphoteric*. If a line is drawn diagonally through hydrogen and beryllium and through aluminum, germanium, antimony and polonium, the elements on the line and some adjacent to it, are amphoteric. Thus, as a base, aluminum forms compounds such as aluminum chloride, and equally well, as an acid it forms sodium aluminate.

In every "typical" element family the first member of the family can be quite unlike the other members. It more closely resembles the second member of the adjacent group to the right. These diagonally related elements are known as "diagonals" or "bridge" elements. They are

IA	IIA	IIIA	IVA	VA	VIA	VIIA
Li	Be	B	C	N	O	F
Na	Mg	Al	Si	P	S	Cl

Beryllium and aluminum constitute a bridge pair. Beryllium fluoride is water soluble (but poorly ionized) while the fluorides of magnesium and the other alkaline earths are sparingly soluble. Unlike magnesium and the alkaline earths, beryllium readily acts as the central ion of complexes, both in the solid state and in solution. Like aluminum, beryllium is amphoteric, gives rise to alums, catalyses the Friedel-Craft reaction, etc.

Tables 6 to 17 summarize some useful properties and facts concerning the groups of the periodic table. The second and third row "triads" of Group VIII and the lanthanides and actinides are not included in these tables because they present no important applications in pharmacy and medicine.

The orbital electrons are important since they predict the possible oxidation states, the shielding of the nuclear charge and the polarizability for each element. Those oxidation states which have been identified for each element also are listed.

The atomic radius and the ionic radii give an indication of the relative size of the members of a family. The negative ions of an element are always larger than the neutral atom; the positive ions are always smaller. Because of the increasing effective nuclear charge for a given element, cations of higher charge always are smaller than those with a lower charge. This is important since it gives an indication of the effective coordination number of cations and atoms as central units of complexes.

The ionization potential* is a measure of the energy required to remove an electron by overcoming the attractive force of the nucleus. Note—This use of the word *potential* is improper; ionization potential is a measure of energy. It is related to atomic size; removal of the first electron from beryllium and barium requires 9.3 ev and 5.2 ev, respectively. Because the removal of one electron effectively increases the nuclear charge by one unit, the second ionization potential is about double that of the first, 18.2 ev and 9.95 ev for beryllium and barium, respectively.

Electronegativity, discussed previously, gives an indication of the type of bonding resulting when two atoms react. It gives an indication of the extent of polarization in covalent compounds. It also is used to determine the order of citation in the naming of binary compounds (page 316).

Elements of Group 0

Because the inert gases were unknown at the time, Mendeleev made no provision for them in his proposed atomic table. With their subsequent discovery Group 0 seemed the most appropriate designation. The group fits very nicely into Mendeleev's arrangement. Its presence explains the extreme transition of properties in going from the very electronegative halogen family to the very electropositive alkali metal family. This shift in properties in going from halogen to inert

gas to alkali metal is shown clearly by the change in the valence electron structures:

$$(n-1)s^2(n-1)p^5$$

$$\rightarrow (n-1)s^2(n-1)p^6 \rightarrow (n-1)s^2(n-1)p^6ns^1$$

All Group 0 elements except radon occur in the atmosphere. Helium also occurs in commercial quantities in certain natural

Table 7—Elements of Group I-A

Element	Hydrogen	Lithium	Sodium	Potassium	Rubidium	Cesium	Francium
Symbol	H	Li	Na	K	Rb	Cs	Fr
Atomic number	1	3	11	19	37	55	87
Atomic weight	1.008	6.941	22.99	39.10	85.47	132.91	(223)
Orbital electrons	1s ¹	[He]2s ¹	[Ne]3s ¹	[Ar]4s ¹	[Kr]5s ¹	[Xe]6s ¹	[Rn]7s ¹
Oxidation states	-1, +1	+1	+1	+1	+1	+1	+1
Atomic radius (Å)	0.37	1.50	1.86	2.31	2.44	2.62	...
Ionic radius (Å)	1.36 (-1) ^a	0.60 (+1)	0.95 (+1)	1.33 (+1)	1.48 (+1)	1.69 (+1)	1.76 (+1)
Ionic (hydrated) radius (Å)	...	3.40	2.76	3.32	2.28	2.28	...
Ionization potential	13.527	5.39	5.14	4.34	4.18	3.89	...
Electronegativity, ^b ev	2.1	0.98	0.93	0.82	0.82	0.79	0.7
% of earth's crust	0.127	6.5 × 10 ⁻³	2.8	2.6	3.1 × 10 ⁻²	7 × 10 ⁻⁴	...

^aHydride ion; figure in parenthesis is the oxidation state.^bPauling scale.⁵

gases in southwestern US. Argon, neon, krypton and xenon are produced from liquid air by fractional distillation. Helium is produced similarly from the natural gases named above. Radon is recovered from the natural decay products of radium.

The inert gases are monoatomic and are colorless, odorless gases under ordinary conditions of temperature and pressure. They vary widely in atomic mass and atomic volume. These differences are reflected in the values of their physical constants (Table 6).

Each inert gas, except helium, is characterized by an outermost electron shell of the "inert gas" structure, ns^2np^6 (Table 6). Helium has the $1s^2$ structure; the ns^2 structure is achieved in many stable cations, eg, Pb^{2+} . Since all electrons are paired, the chemical inertness of the group is predictable and is reflected in terms of peak ionization potentials and various other characteristics. However, under unusual reaction conditions, there is evidence of hydrate formation. Some relatively stable fluorides, eg, XeF_2 , XeF_4 and XeF_6 , a crystalline sodium perxenate, and possibly a perkryptate, are known.

However, in comparison with other elements, those of Group 0 still are classed logically as chemically inert.

Helium, because of its low density and low solubility in blood is used to prepare synthetic airs (page 337).

Argon is relatively plentiful since it is a by-product of the fractionation of liquid air for the production of oxygen and nitrogen. It is used as an inert atmosphere for industrial processes in which nitrogen, the usual inert atmosphere, reacts with the materials present.

Krypton and xenon have been investigated for possible use as anesthetics. However, the sparsity of these elements in nature imposes severe limitations on such use. ^{133}Xe is used for diagnostic studies both by inhalation and intravenous injection.

Radon is used instead of radium in the treatment of certain types of cancer. Sealed tubes containing the gas are embedded in the tissues to be treated. Both radium and radon emit alpha particles in the first stage of their radioactive decay. Radon is a public health concern since it has been found in the basements of some private homes.

Elements of Group I

The elements of this group, (Tables 7 and 8), are characterized by having only one valence electron, ns^1 . The subgroups differ in that Group I-A has an underlying, stable, inert gas shell, $(n-1)s^2(n-1)p^6ns^1$, while in Group I-B this has been replaced by a completed d -shell, $(n-1)d^{10}ns^1$.

These elements are strongly metallic, giving rise to cations, M^+ . Since electrons can be removed from the underlying d -shell, Group I-B elements can exhibit higher positive oxidation states, M^{2+} , and M^{3+} .

Elements of Group I-A

This group comprises the most reactive of all the metallic elements and the activity increases with atomic number. The cations of these elements are stable chemically; the free elements are not found in nature. The single positive charge of

the nucleus is screened effectively by the inert gas shell, thus these cations have little or no polarizing effect on anions and molecules and therefore do not form complexes.

The hydroxides give alkaline solutions, alkalinity increasing

Table 8—The Elements of Groups I-B and II-B

Element	Copper	Silver	Gold	Zinc	Cadmium	Mercury
Symbol	Cu	Ag	Au	Zn	Cd	Hg
Atomic number	29	47	79	30	48	80
Atomic weight	63.54	107.87	196.97	65.38	112.4	200.59
Orbital electrons	[Ar]3d ¹⁰ 4s ¹	[Kr]4d ¹⁰ 5s ¹	[Xe]4f ¹⁴ 5d ¹⁰ 6s ¹	[Ar]3d ¹⁰ 4s ²	[Kr]4d ¹⁰ 5s ²	[Xe]4f ¹⁴ 5d ¹⁰ 6s ²
Oxidation states	+1, +2	+1, +2	+1, (+2), +3	+2	+2	+1, +2
Atomic radius (Å)	1.40	1.70	1.70	1.40	1.60	1.50
Ionic (crystal) radii (Å)	0.96 (+1) 0.72 (+2)	1.26 (+1) 0.89 (+2)	1.37 (+1) 0.99 (+3)	...	...	1.27 (+1) 1.16 (+2)
Ionization potential, ev	7.724	7.574	9.223	6.92	8.99	10.42
Electronegativity	1.90	1.93	2.54	1.65	1.69	2.00
% of earth's crust	10 ⁻¹	10 ⁻⁸	10 ⁻⁹	1.3 × 10 ⁻²	1.5 × 10 ⁻⁵	ca 10 ⁻⁶

with atomic number. Alkali metal salts of common inorganic and organic acids are ionic, usually colorless and, with few exceptions, readily soluble in water. Aqueous solutions of the salts are neutral to strongly basic depending on the strength of the anion as a Brønsted base (page 180). Most distinguishing properties of the salts and their solutions are due to the anion present rather than the cation, eg, if colored, the anion is responsible.

The cations hydrate in aqueous media, the degree of solvation decreases with increasing atomic number. In the crystalline state only lithium and sodium regularly form hydrates. Potassium and ammonium salts, (below), rarely are hydrated; if hydrated, the water usually is associated with the anion.

Sodium and Potassium

Except for those properties due to mass and degree of hydration, sodium and potassium compounds are remarkably similar. Sodium salts are selected more frequently for use on a strictly economic basis. In addition, because of the lower atomic weight of sodium, there usually are more reactive units per gram when using sodium salts. (Greater hydration of the sodium versus the potassium salts may partially or entirely erase this latter advantage.) Despite the foregoing factors, subtle differences often favor use of the potassium salt. Generally, a given potassium salt is more soluble in nonpolar solvents. Potassium salts generally are less deliquescent than the corresponding sodium salt, eg, potassium permanganate is used rather than the deliquescent sodium permanganate. Finally, the living cell differentiates between the two cations; sodium is the cation of the extracellular fluids, while potassium is the cation of the intracellular fluids.

Sodium compounds are used widely in pharmacy and medicine. With a few exceptions, eg, sodium chloride in electrolyte replenishers, the therapeutic activity is referable to the anionic component of the salt. Sodium is commonly the cation of choice to optimize the pharmaceutical utility of organic medicaments, eg, methiodal sodium, phenobarbital sodium or sodium citrate.

Because of the propensity of sodium ion to promote retention of water in the tissues, sodium salts are used with caution in the treatment of cardiac and renal conditions in which edema is a problem. Some drugs, eg, hydrochlorothiazide, promote excretion of potassium ion to an extent requiring auxiliary dietary intake of potassium, usually as the chloride or gluconate. Potassium ion has a diuretic effect. The thiazides also cause the excretion of magnesium ion.

Rubidium and Cesium

Rubidium and its cation are very similar in behavior to potassium. Neither rubidium nor cesium find application in pharmacy and medicine at this time.

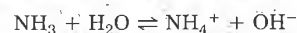
Lithium

Being a bridge element, the behavior of this element and its compounds often is decidedly different from that of the other members of the alkali family. At room temperature the free metal is much less reactive with water; on burning it forms the normal oxide rather than the peroxide. Lithium carbonates and phosphates are only slightly water soluble. Its chloride is soluble in organic solvents. Lithium salts are highly hydrated. In all of these properties lithium resembles magnesium, and to some extent calcium, more closely than sodium.

Lithium has no normal physiological role. In its former therapeutic applications, eg, lithium bromide, the activity was inherent in the anion. However, because of the toxic character of the lithium ion, as revealed by use of lithium chloride in salt substitutes, continued use of these lithium compounds is not justified. Lithium Carbonate, USP and Lithium Citrate USP has been found valuable in the treatment of hypomanic and manic states. However, these patients must be monitored carefully for blood lithium levels because of the toxicity of the cation.

Ammonia and Ammonium Compounds

Ammonia [NH_3] coordinates readily with a proton to form the ammonium ion [NH_4^+]. This ion displays many of the properties of the alkali metal ions. Its salts show striking resemblances to potassium and rubidium salts, with which they are commonly isomorphous. The relationship extends to solubilities, as evidenced by the general water-solubility of ammonium salts of inorganic and organic acids, but the low water-solubility of such salts as the bitartrate, chloroplatinate and perchlorate. However, there are important differences. "Ammonium hydroxide" (mainly a solution of ammonia molecules in water) is feebly basic. The equilibrium



lies strongly to the left unless the hydroxyl ion is removed by neutralization. Solutions of ammonium salts are acidic rather than basic.

Ammonium salts commonly used therapeutically include the carbonate (page 338), chloride and bromide. The bromide is used as a central depressant. Both the chloride and carbonate are common ingredients in expectorant preparations.

In aqueous solution form, ammonia is used in pharmacy as a mild alkali. It often is preferred to the alkali bases because of its volatility, any excess being detected by its odor and it is removed readily by heat. The ammonia in household use contains 10% NH_3 and is known as 16° ammonia (degrees Baumé, a concentration term).

Elements of Group I-B

These elements have been known in antiquity. Because they occur in the free metallic state, are relatively easy to recover from their ores and are very malleable, they have been used throughout historical times to make decorative vessels and jewelry. They have been employed for centuries as a measure of monetary wealth and for the fabrication of coins, hence the family name, **coinage metals**.

These elements and their compounds are strikingly different from those of Group I-A. Colored compounds are numerous. The hydroxides and many of the simple salts are insoluble in water. All readily act as the central unit of complexes. The soluble compounds of these elements are toxic. A summary of important characteristics is given in Table 8.

Copper

Of the monovalent compounds, copper(I) oxide, Cu_2O , and copper(I) chloride, Cu_2Cl_2 , are used most frequently. Important copper(II) (cupric) salts are the oxide, CuO , and sulfate, $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$. Copper compounds are toxic.

Copper is an essential trace element. Small quantities enhance the physiological utilization of iron. It occurs in the respiratory pigment, hemocyanin, in many enzymes and is distributed widely in foods.

Copper compounds have been used in a variety of medicinal applications. Copper gluconate, cupric chloride dihydrate and cupric sulfate pentahydrate are the officially cited copper compounds at this time. The radioactive ^{64}Cu isotope has

been employed in mineral metabolism studies. Copper(II) sulfate is the basis for Fehling's and Benedict's Solutions; the classical test solutions for reducing sugars. Various copper compounds find commercial application as fungicides and insecticides and are particularly effective algacides.

Silver

With the exception of the nitrate and fluoride, the common salts of silver in the +1 oxidation state are insoluble or only slightly soluble in water. Many, including the oxide, react with and dissolve in ammonia water; the iodide and sulfide are important exceptions. Silver also forms a +2 series of salts. Silver has an oligodynamic action. Water distilled in contact with silver metal remains sterile over long periods of time.

Because of the ability of silver ion to precipitate protein and chloride in the affected tissue, silver compounds, eg, silver nitrate, are employed to provide local germicidal action. Silver Sulfadiazine is used topically as a germicide. Silver is released slowly from these *in situ* precipitates to give lasting germicidal action. Cosmetic problems can result because of discoloration due to the photosensitivity of silver ion.

Preparations containing silver or silver compounds in colloidal solution once were used widely as topical antiseptics, eg, Mild Silver Protein. By increasing their concentration, silver ions may be used to bring about protein precipitation. To reduce brittleness some silver chloride (5%) is formed in silver nitrate by adding hydrochloric acid or potassium chloride. The product, Toughened Silver Nitrate, is cast into sticks and used as a styptic.

The ready reducibility of silver ion to elemental silver gives rise to various instability problems and incompatibilities. Since silver compounds are light sensitive, they must be pro-

tected by the use of light-resistant containers. The soluble silver salts are toxic. However, the toxicity usually is limited, owing to local precipitation of adherent layers of silver protein and silver chloride.

Gold

Two series of gold compounds exist, eg, AuCl, gold(I) chloride (aurous chloride) and AuCl₃, gold(III) chloride (auric chloride). Gold readily acts as the center for the formation of complexes, eg, Na₃[Au(S₂O₃)₂], sodium dithiosulfatoaurate(I), sodium dithiosulfatoaurate(-3), gold sodium thiosulfate.

Chemically gold salts are characterized by instability to heat, light and even very mild reducing agents. Simple gold(I) salts can undergo "autoxidation," giving rise to finely divided metal and the corresponding gold(III) compound. The stability of the gold ions is improved by complexation. This particularly is true if a sulfur linkage is available. Because of the ease of reduction, gold compounds must be handled with exceptional care and, if possible, dispensed separately.

At the present time, gold compounds are employed in the treatment of lupus erythematosus and rheumatoid arthritis. Aurothioglucose and Gold Sodium Thiomalate are listed in the USP. Since these gold compounds are absorbed poorly when given orally, parenteral administration is required. Dimercaprol is used as an antidote if the patient shows signs of gold toxicity. Auranofin, [(2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranosato)(triethylphosphine)gold], is available in a tablet dosage form and is showing some success in the oral treatment of rheumatoid arthritis.

The radioactive isotope, ¹⁹⁸Au, is employed therapeutically in the treatment of certain malignancies (Chapter 51).

Elements of Group II

Each element in this group is characterized by the presence of two s electrons in the outermost orbital. Subgroup II-A elements have a (n-1)s²(n-1)p⁶ns² outer electron struc-

ture except for the small beryllium atom whose structure is 1s²2s². Subgroup II-B differs in that its underlying electron structure is the filled d-orbital, (n-1)d¹⁰ns².

Elements of Group II-A

While this group is called the alkaline earth group, there is some question whether magnesium, and especially beryllium, should be included under that title.

Except for amphoteric beryllium, these elements are strictly metallic. Like the alkali metals, because of chemical reactivity, they do not occur free in nature. They function uniformly in the +2 oxidation state (Table 9). The similarity existing between calcium, strontium and barium is especially striking.

Calcium, strontium and barium react readily with water to

form hydroxides with the simultaneous evolution of hydrogen. Magnesium reacts similarly but only at elevated temperatures. The hydroxides of beryllium and magnesium are insoluble in water; that of beryllium is amphoteric. Although less soluble than the alkali hydroxides, the hydroxides of calcium, strontium and barium give strongly basic solutions. The carbonates, phosphates, sulfates and fluorides are insoluble; they are important in analytical work.

Except for hydrate formation, the three heavier members of

Table 9—The Elements of Group II-A

Element	Beryllium	Magnesium	Calcium	Strontium	Barium	Radium
Symbol	Be	Mg	Ca	Sr	Ba	Ra
Atomic number	4	12	20	38	56	88
Atomic weight	9.012	24.31	40.08	87.62	137.3	226.03
Orbital electrons	[He]2s ²	[Ne]3s ²	[Ar]4s ²	[Kr]5s ²	[Xe]6s ²	[Rn]7s ²
Oxidation states	+2	+2	+2	+2	+2	+2
Atomic radius (Å)	0.90	1.70	1.74	1.92	1.98	
Ionic (crystal) radius (Å)	0.31 (+2) ^a	0.65 (+2)	0.99 (+2)	1.13 (+2)	1.35 (+2)	1.43 (+2)
(coordination number 6)						
Ionization potential, ev (II) ^b	9.3	7.6	6.1	5.7	5.2	5.252
	18.2	15.0	11.9	11.0	9.95	10.099
Electronegativity	1.57	1.31	1.00	0.95	0.89	0.9
% of earth's crust	6 × 10 ⁻⁴	2.1	3.6	0.03	0.025	1.3 × 10 ⁻¹⁰

^aCoordination number 4.

^bSecond ionization potential.

the family do not form complex ions. Magnesium forms a few crystalline complexes of the type K_2MgF_4 .

Beryllium

Being amphoteric, this element appears both as simple salts and beryllates. The cation complexes readily, eg, $[Be(H_2O)_4]^{2+}$ or $[Be(NH_3)_4]^{2+}$.

Being a bridge element, beryllium resembles aluminum in its behavior. This similarity is so striking that many early workers considered beryllium a lighter member of the aluminum family before Mendeleev correctly placed it in Group II.

While its ionic diameter is considerably greater than that of beryllium, the higher +3 charge on the aluminum ion results in a polarizing ability similar to that of beryllium. Both elements dissolve in caustic alkalis and both form a protective coating on their surface when placed in nitric acid. The halides of both elements have similar solubilities in organic solvents. Both elements act as Lewis acids and give rise to alums.

Beryllium metal and its compounds are extremely toxic when ingested, inhaled or absorbed through the skin. None of its compounds are employed as therapeutic agents.

Magnesium

This is a relatively abundant element that is chemically active. The cation, Mg^{2+} , is stable under all conditions ordinarily met in pharmaceutical practice.

Magnesium compounds are employed for a variety of purposes in therapeutics. Many of its insoluble compounds are used as gastric antacids, (page 335). The hydroxide and sulfate are used as cathartics, (page 338) and the sulfate, as an anticonvulsant. A concentrated solution of the sulfate often is applied topically for its anti-inflammatory action. Toxic manifestations following magnesium administration are relatively rare; calcium gluconate given intravenously is an effective antidote. The stearate is employed as a lubricant in the preparation of compressed tablets. The artificial radioactive isotope ^{27}Mg , has been employed in research involving photosynthesis.

There is an increasing awareness of the critical importance of magnesium ions in human biochemistry. Since ion-specific electrode potentiometry now allows measurement of free, unbound magnesium ions, plasma concentrations may be measured and the concentration in the cytosol may be inferred. As the second most plentiful cation inside the cell and a natural calcium channel blocker, magnesium ions are important in many cardiovascular diseases. Successful absorption

from the gastrointestinal tract appears to depend on the nature of the magnesium salt that is used.

Calcium

Calcium is a relatively reactive metal whose cation is stable. However, soluble calcium salts undergo metathesis with soluble borates, carbonates, citrates, oxalates, phosphates, sulfates and tartrates to yield insoluble calcium compounds. These reactions often lead to pharmaceutical incompatibilities.

Calcium is indispensable to life. Calcium, and to a much lesser degree, magnesium, is the cation of hydroxyapatite, the major constituent (98%) of the bones and teeth. Calcium is essential to many physiological processes. Therapeutic categories represented by official calcium compounds include: antacid (page 335) and calcium replenishers.

Calcium is frequently the cation of choice to carry therapeutically active anions, eg, calcium aminosalicylate, calcium cyclobarbitol. In some instances this is referable to better physical characteristics of the calcium compound; in others it is a deliberate attempt to avoid an unnecessary intake of sodium. The artificial radioactive ^{45}Ca isotope has been employed in studies involving mineral metabolism.

Strontium

The behavior of this element is very similar to calcium. Ingested, its distribution is similar to that of calcium. At this time it has no application in pharmacy or medicine. In the past it has been used as the carrier cation for therapeutically active anions, eg, strontium bromide.

Barium

Chemically, this element is the most active of Group II-A. Its cation is stable under all ordinary conditions. Barium hydroxide is soluble and is a strong base. Because of this, it often finds application in analytical and synthetic operations.

In sharp contrast to the lighter members of Group II-A all barium compounds, which are soluble either in water or in dilute acid are poisonous. The most readily available antidote for barium ingestion is magnesium sulfate (Epsom Salt).

With the exception of barium sulfate, which finds use as a radiopaque (page 338), barium compounds are not employed as medicinal agents. Barium hydroxide lime is employed as a carbon dioxide absorber (page 337). Artificial radioactive isotopes of barium have been employed in pharmacokinetic investigations.

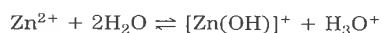
Elements of Group II-B

Because zinc, cadmium and mercury (Table 8) have comparatively low boiling points, 907°, 768° and 357°, respectively; they are referred to frequently as the volatile metals. The common oxidation state is +2, but mercury also exists in the +1 state. This latter state is achieved by the formation of a covalent, two electron bond between two mercury atoms. Thus the mercury(I) ion (mercurous) is always written Hg_2^{2+} . The filled $(n-1)d^{10}$ orbital is stable in this family. Unlike Group I-B there are no oxidation states involving loss of a d -electron. There is increasing covalent character in the salts of these elements, eg, fused zinc chloride conducts while the mercury chlorides do not.

These elements readily complex with most common ligands and concentrated solutions exhibit autocomplexation. Only zinc is sufficiently amphoteric to form a stable oxygen complex, ZnO_2^{2-} , the zincate ion.

Zinc

All soluble zinc salts show some degree of hydrolysis,



Thus, all zinc salts of weak Brønsted bases show an acid reaction.

Zinc has many therapeutic applications in the treatment of various external surfaces of the body (page 337) and in conditions such as wound healing and taste acuity. Strong zinc sulfate solution is used as an emetic; its emetic action is so rapid that little or no zinc salt is absorbed.

Zinc is present in all living organisms; it is distributed widely in foods. It is an essential trace element and an essential component of carbonic anhydrase and many other enzymes.

Zinc compounds soluble in water or in the gastric fluid, eg, ZnO , may be poisonous. There is a relatively wide margin of safety between the required intake and toxic intake. The most readily available antidote is sodium bicarbonate (baking soda).

Artificial radioactive isotopes of zinc have been employed in studies of mineral metabolism.

Cadmium

This element is truly intermediate in properties to zinc and mercury. Soluble cadmium compounds are astringent;

CdSO_4 has been used both as a topical astringent and for eye infections. Cadmium sulfide has been introduced for the treatment of seborrheic dermatitis (page 336). A disease found in Japan, known as itai-itai, is believed to be caused by drinking water contaminated with cadmium.

Mercury

This member of the family is a true metal. As indicated previously, it alone of the family has two series of salts.

Mercury and its compounds are extremely toxic. Mercury metal, because of its low boiling point, has an appreciable vapor pressure even at room temperature. If mercury is spilled it should be recovered immediately. Mercury that falls into cracks and other difficult to clean places is removed best by covering with powdered sulfur, allowing several days for conversion to sulfide and then vacuuming. All common mercury salts are poisonous. The best antidote for mercury

poisoning, particularly the bichloride, is Sodium Formaldehyde Sulfoxylate NF. (Chapter 80). Egg albumen may be used in an emergency if the poisoning is discovered shortly after ingestion. The white of one egg should be administered for each 250 mg. of mercuric chloride ingested. Emesis should be induced promptly thereafter.

In former years, metallic mercury was important therapeutically as a cathartic and parasiticide, but it has been replaced largely by more efficacious and less toxic medicaments. Surviving mercury compounds are used largely for their germicidal effect, eg, ammoniated mercury and yellow mercuric oxide. Yellow mercuric oxide, with a K_{sp} of 3×10^{-26} , is an extremely insoluble compound. Mercury also survives in some organomercury compounds, eg, meralluride or nitromersol.

The radioactive nuclides ^{197}Hg and ^{203}Hg are used in a diagnostic capacity (Chapter 51).

Elements of Group III

This group of the periodic table includes some thirty-six elements which, on the basis of external electron structure, divide into the usual Group III-A (Table 10) with five elements, and Group III-B with 31 elements. Subgroup III-B further divides into the usual transition elements (Table 11), the lanthanides (fourteen elements) and actinides (fourteen elements). (See the periodic table on the back cover.) The

lanthanide cerium, as cerium(IV), is a widely used analytical reagent. Since the lanthanides and actinides have no applications in pharmacy further discussion is unnecessary.

The members of this family are very reactive and do not appear in nature in the free state. They have no known biological role.

Elements of Group III-A

In this family of elements an electron appears in the p orbital of the valence shell for the first time; each element has the structure ns^2np^1 . Theoretically two oxidation states are possible. The first, +1, arises by the loss of the single p electron. The resulting helide structure, ns^2 , has sufficient stability to give rise to stable ions, eg, Ga^+ , In^+ , Tl^+ . Aluminum has this oxidation state only at elevated temperatures and it is not evident with B, Sc, Y, La.

With the loss of all three valence electrons the +3 oxidation state appears in all the elements of the family. With increasing atomic number the +3 state becomes more electrovalent in character. Boron trichloride is a covalent compound, aluminum chloride is for practical purposes covalent and gallium(III) chloride has some covalent character. Since a normal octet is not achieved in these compounds, an electron deficient structure results. As there are only three electron pairs in the valence shell the electron-pair repulsive forces are weaker, and the molecules become electron-pair acceptors. Because of the weaker repulsive forces, these MX_3 molecules give rise to triangular structures with hybrid sp^2 orbitals. The metal occupies the center of the triangle.

By accepting a fourth electron-pair the octet is completed and sp^3 hybrids form. The addends rearrange to give tetrahedral structures with the metal ion in the center of the tetrahedron.

Since the initial compounds, eg, AlCl_3 , are electron-pair deficient, they are Lewis acids. As such, they act as catalysts for the Friedel-Crafts synthesis.

Members of this family give rise to an interesting series of double salts, the alums. The common formula is $\text{M}^+\text{M}^{3+}_2(\text{SO}_4)_4 \cdot 24\text{H}_2\text{O}$, where M^+ is a monovalent ion, eg, Na^+ , K^+ , Rb^+ , NH_4^+ , Tl^+ and M^{3+} is a trivalent ion, eg, Al^{3+} , Tl^{3+} , Cr^{3+} or Fe^{3+} . The prototype of these double salts is alum, $\text{K}_2\text{Al}_2(\text{SO}_4)_4 \cdot 24\text{H}_2\text{O}$.

Boron

This element appears only in the +3 oxidation state and is a nonmetal. Several oxyacids are known. Metaboric acid,

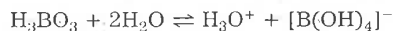
Table 10—The Elements of Group III-A

Element	Boron	Aluminum	Gallium	Indium	Thallium
Symbol	B	Al	Ga	In	Tl
Atomic number	5	13	31	49	81
Atomic weight	10.81	26.98	69.72	114.8	204.37
Orbital electrons	$[\text{He}]2s^22p^1$	$[\text{Ne}]3s^23p^1$	$[\text{Ar}]3d^{10}4s^24p^1$	$[\text{Kr}]4d^{10}5s^25p^1$	$[\text{Xe}]4f^{14}5d^{10}6s^26p^1$
Oxidation states	+3	(+1), +3	+1, +2, +3	+1, +3	+1, +3
Atomic radius (Å)	0.82	1.25	1.26	1.44	2.0
Ionic (crystal) radius (Å)			1.90 (+1)	1.90 (+1)	1.64 (+1)
(coordination number 6)	0.20 (+3) ^a	0.675 (+3)	0.76 (+3)	0.94 (+3)	1.03 (+3)
Ionization potential, ev	8.30	5.95	6.0	5.8	6.1
(II) ^b	25.15	18.82	20.4	18.8	20.3
(III) ^b	37.92	28.44	30.6	27.9	29.7
Electronegativity	2.04	1.61	1.81	1.78	1.62
% of earth's crust	3×10^{-4}	8.13	1.5×10^{-3}	10^{-5}	$\text{ca } 10^{-4}$

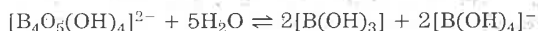
^aCoordination number 4.

^bSecond and third ionization potential.

(HBO₂)_n, and the metaborate ion do not exist as monomers. Orthoboric acid, (H₃BO₃)_n, exists as a hydrogen bonded layered structure, which explains the flaky form in which it is available. Discrete H₃BO₃ molecules exist in the gaseous state and in solution. It is a weak acid, ionizing in solution.



The pH of a 0.1M solution is 5.3. In addition there is a tetraborate, available as borax, usually formulated as Na₂B₄O₇·10H₂O. In water the tetraborate ion reacts as



The strong alkalinity of solutions of all borates is due to the reaction



Boric acid is soluble in polyhydroxy compounds, eg, glycerol. In anhydrous media esterification takes place to form "glyceroborate." In aqueous media glyceroboric acid forms an acid which is valuable in the analytical determination of boric acid.

Since it is a bridge element, certain properties of boron resemble those of silicon, its diagonal neighbor in Group IV-A. The boron hydrides and boranes resemble the silanes (page 327). The borohydride ion, [BH₄]⁻, is available commercially as the sodium salt, which is a valuable reducing agent.

Boron and its compounds are toxic, both by ingestion and by absorption through broken or inflamed skin. Numerous fatalities have occurred; especially depressing are those of infants due to the use of dusting powders containing boric acid.

Boric acid and the borates have no germicidal activity and, at best, are feebly bacteriostatic. On the basis of their toxicity and negligible antiseptic value the use of these compounds is unwarranted.

Boric acid in various dosage forms is employed as a topical anti-infective; in solution it is used as an eye wash. Sodium borate is bacteriostatic and is a frequent ingredient of cold creams, eye washes and mouthwashes. Sodium perborate is an oxidizing type of local anti-infective. Various borate buffers are used in collyria. A common incompatibility in the use of these buffers is the precipitation of insoluble borates from neutral or alkaline buffers. All common metals, except the alkalies, precipitate as insoluble borates.

Boric Acid and Sodium Borate (borax) are cited in the NF.

Aluminum

Aluminum is the most abundant of the metals and the third most abundant element, being exceeded in natural occurrence only by oxygen and silicon. The metal and its hydroxide are amphoteric but only those compounds in which it acts as a base are pharmaceutically important. As a result of its high charge, small diameter and electron-pair deficiency, the aluminum(III) ion is incapable of independent existence in polar solvents. Due to the very high field strength surrounding this ion, complexation always takes place.

Many insoluble aluminum compounds find use as gastric antacids (page 335). Because of their astringency, soluble aluminum salts are used for various skin conditions and in antiperspirants and deodorants (page 337). Kaolin is used as an adsorbent and demulcent, and bentonite is useful as a suspending agent (page 337). In paste form, elemental aluminum is employed topically as a protective (page 337).

There is some concern about chronic aluminum toxicity and its effect on the brain, possibly manifesting itself in the elderly. The use of aluminum sulfate at very low levels in water purification is being questioned.

Gallium, Indium and Thallium

These remaining elements of Group III-A are not of interest in pharmacy except for the use of their radioactive isotopes as diagnostic aids, ⁶⁷Ga, ¹¹¹In, ¹¹³In and ²⁰¹Tl (see Chapter 51).

Thallium compounds are among the most toxic and are absorbed from the intestine and through the skin from ointments and creams. Its action is somewhat similar to that of arsenic. Deaths have been recorded from a thallium cosmetic use. Thallium compounds have been used in insecticides, especially ant poisons. Thallium(I) is similar to potassium ion in that TlOH is a strong base and their salts are isomorphous. Thallium(III) is similar in behavior to aluminum(III) and gold(III).

Gallium is interesting because, except for mercury, it has the lowest melting point of the metals (29.75°). It also is unusual for its +2 oxidation state. Since this requires an odd electron it is difficult to explain since gallium(II) compounds are not paramagnetic. It has been postulated that equal numbers of gallium(I) and gallium(III) ions may exist in these compounds to give a formula M⁺[MX₄]⁻. Gallium(III) has properties very similar to iron(III). In fact, gallium(III) binds to transferrin, an iron transport protein, and appears to be useful in treating cancer-related hypercalcemia.

Indium is quite similar to both aluminum and gallium. It too, under very special conditions, exists as a divalent chloride.

Elements of Group III-B

Some properties are given in Table 11. These three elements exhibit only the +3 oxidation state and are quite similar. The differences are mostly of degree, dependent on the increasing atomic radius. Since scandium is the smallest, it has the greatest polarizing power and most readily forms complexes

of the type K₃ScF₆. Yttrium has properties approximately midway between scandium and lanthanum. This gradation of properties is shown nicely with the three hydroxides: Sc(OH)₃ is a weak base, Y(OH)₃ is stronger and La(OH)₃ is a very strong base.

Table 11—Transition Elements

Element	Group III-B			Group IV-B		
	Scandium	Yttrium	Lanthanum	Titanium	Zirconium	Hafnium
Symbol	Sc	Y	La	Ti	Zr	Hf
Atomic number	21	39	57	22	40	72
Atomic weight	44.96	88.91	138.9	47.90	91.22	178.5
Orbital electrons	[Ar]3d ¹ 4s ²	[Kr]4d ¹ 5s ²	[Xe]5d ¹ 6s ²	[Ar]3d ² 4s ²	[Kr]4d ² 5s ²	[Xe]4f ¹⁴ 5d ² 6s ²
Oxidation states	3+	3+	3+	2+, 3+, 4+	2+, 4+	(2+), 4+
Atomic radius (Å)	1.51	1.8	1.87	1.36	1.45	1.44
Ionic radii (Å)	0.81 (3+)	0.93 (3+)	1.15 (3+)	1.00 (2+)	...	...
(coordination no 6)				0.75 (4+)	0.86 (4+)	0.85 (4+)
Ionization potential, ev	6.7	6.5	5.6	6.82	6.84	ca 5.5
Electronegativity	1.54	1.53	1.3	...	...	...
% of earth's crust	0.44	0.022	4.5 × 10 ⁻⁴	0.629	0.028	...

Elements of Group IV

The elements of this group are similar in that each has four valence electrons, two of which are s electrons. However, the remaining two valence electrons enter different orbitals to give the structure ns^2np^2 for Group IV-A and $(n-1)d^2ns^2$ for Group IV-B. Because of this there is a strong tendency for all

members of the family except carbon and silicon to form "inert pair" ions. Except for the larger atoms many of the compounds are covalent or predominantly covalent. All elements of the family show the +4 oxidation state. Important characteristics of these elements are found in Tables 11 and 12.

Elements of Group IV-A

Carbon and silicon usually are considered apart from germanium, tin and lead because of their nonmetallic character and property of catenation. Boron, with which silicon forms a bridge element pair, is quite similar to silicon. The +2 oxidation state rarely is encountered in carbon and silicon. The bonding in carbon is covalent, corresponding silicon bonds have a somewhat greater electrovalent character. Simple carbon compounds are either linear, CO_2 , planar triangular, CO_3^{2-} or tetrahedral, CCl_4 . Since the radius of the carbon atom is small, and it lacks d -orbitals to expand its valence shell, carbon never increases its coordination number beyond four. Unlike carbon, because of its available d -orbitals, silicon can achieve sp^3d^2 hybridization and appears in the octahedral configuration, SiF_6^{2-} , with a maximum coordination number of six. Similarly, germanium, tin and lead have a maximum coordination number of six.

Carbon is exclusively nonmetallic. Metallic properties appear with silicon and germanium and become predominant in tin and lead. The oxides of carbon and silicon are acidic while those of the other elements of the group are amphoteric. The electron configuration, atomic size, electronegativity, etc., of the carbon atom combine to give the chemistry of carbon a uniqueness which is the basis for the classical division of the field of chemistry into inorganic and organic disciplines. Silicon also is unique for the extensive range of complex, insoluble aluminosilicates it forms (page 324).

Carbon

Carbon appears widely distributed in nature, both in the free and combined states. The free element is produced in various forms, eg, coke, lampblack or charcoal. Activated charcoals are prepared from ligneous materials (sometimes pretreated with a dehydrating agent) by carbonization in the absence of air. This is followed by heat and/or chemical treatment to increase surface area and porosity. Activated charcoal is available in two forms, finely powdered (300 to 350 mesh) for use in liquid media, and coarse, hard, porous particles for gas absorption. The fine form is official in the USP. It is used as an adsorbent in the treatment of diarrhea.

Carbon dioxide usually is obtained as a by-product from either the production of alcohol by fermentation or by recovery from the stack gases of power plants. Unlike carbon monoxide, its toxicity is not due to interaction with hemoglobin, but through suffocation. Carbon dioxide is an effective respiratory stimulant (page 338), cited in the USP.

Under appropriate conditions, carbon forms many binary compounds, eg, cyanogen, carbon disulfide, carbon tetrachloride and numerous carbides. Its important inorganic acids are carbonic, percarbonic (peroxocarbonic) and the pseudobinary hydrocyanic acid, (HCN). All are weak acids and are available primarily in the form of salts.

Sodium bicarbonate and the slightly soluble carbonates or basic carbonates of calcium, magnesium and aluminum find extensive use as gastric antacids. Potassium bicarbonate is used as a source of potassium ion in electrolyte replenishers. Bismuth subcarbonate is an astringent and protective (page 337). Ammonium carbonate is an effective reflex stimulant (page 338) and expectorant (page 338).

Silicon

Next to oxygen, silicon is the most abundant element on earth. It does not appear free in nature. Silicon forms an inert oxide, silicon dioxide (silica), which occurs abundantly in nature in both amorphous and crystalline states, eg, sand, quartz, opal or siliceous earths.

Siliceous earth (diatomaceous earth, Fuller's earth, Kieselguhr, Celite) and infusorial earth are the siliceous skeletal remains of diatoms and infusoria. The deposits are in the form of spicules, rods and stars of silica. Because of their shapes these materials act as excellent, inert, nonadsorbent filter aids. Because of their moderate hardness they are used as mild abrasives. Purified Siliceous Earth is official in the NF.

Synthetic amorphous silicas are manufactured by two methods. *Silica fume* is prepared by condensation of silica from its vapor phase. *Silica gel* is prepared by hydrolysis of inorganic or organic orthosilicates. Structurally, both forms may be considered condensation polymers of the silicic acids. They are available in various commercial grades, differing in such variables as particle size, degree of hydration, surface type (silanol and/or siloxane), porosity and hardness. By selection of the product having the desired properties, amorphous silicas find employment as gas adsorbents, desiccants, carriers, fillers, thickeners and abrasives. Colloidal Silicon Dioxide (fumed form) is official in the NF; Silicon Dioxide, a more general monograph title, replaces the title Silica Gel and now provides for both forms of SiO_2 , silica gel and precipitated silica.

Silicosis is a lung condition resembling chronic tuberculosis, developing after long exposure (7 years or more) to "respirable dust" (silica particles 5 μ m or less in mean diameter).

Table 12—The Elements of Group IV-A

Element	Carbon	Silicon	Germanium	Tin	Lead
Symbol	C	Si	Ge	Sn	Pb
Atomic number	6	14	32	50	82
Atomic weight	12.01	28.08	72.59	118.69	207.2
Orbital electrons	[He]2s ² 2p ²	[Ne]3s ² 3p ²	[Ar]3d ¹⁰ 4s ² 4p ²	[Kr]4d ¹⁰ 5s ² 5p ²	[Xe]4f ¹⁴ 5d ¹⁰ 6s ² 6p ²
Oxidation states	4- to 4+	4- to 4+	2+, 4+	2+, 4+	2+, 4+
Atomic radius (Å)	0.77	1.17	1.22	1.41	1.54
Ionic (crystal) radii	2.60 (4-)	2.71 (4-)	0.87 (2+)	0.93 (2+)	1.20 (2+)
(coordination no 6)	0.30 (4+) ^a	0.54 (4+)	0.67 (4+)	0.83 (4+)	0.91 (4+)
Ionization potential, ev	11.264	8.149	8.09	7.38	7.38
Electronegativity	2.55	1.90	2.01	1.58	1.87
% of earth's crust	2.7 × 10 ⁻²	27.7	7 × 10 ⁻⁴	6 × 10 ⁻⁴	1 × 10 ⁻³

^aCoordination number 4.

Silicon forms numerous silicic acids, eg, metasilicic acid, $[\text{H}_2\text{SiO}_3]$, orthosilicic acid, $[\text{H}_4\text{SiO}_4]$ or disilicic acid, $[\text{H}_6\text{Si}_2\text{O}_7]$. These and others occur in nature as silicates. Except for the alkali salts, silicates are insoluble in water or acids, but they are attacked readily by hydrofluoric acid, forming gaseous silicon tetrafluoride. The alkali silicates do not occur in nature but are prepared by fusion of finely divided silica with the desired alkali base or carbonate.

The "insoluble" silicates have structural arrangements dominated by the large diffuse oxide ion. Since cations of high charge, eg, Si^{4+} or Al^{3+} , are small and compact, they have only a secondary role in determining the structures. Physical properties, eg, density, hardness, refractive index, are determined almost completely by the oxygen-"packing" arrangement.

There are two "close-packed" oxide ion arrangements, cubic and hexagonal. In each, the oxygen arranges in identical layers; the difference arises from the placement of the layers with respect to one another. Two types of openings are possible between neighboring spheres. The smaller openings are occupied by small cations, eg, Si^{4+} , resulting in a tetrahedral arrangement of four oxide ions around each cation. The larger openings between adjacent oxide ions are occupied by somewhat larger cations, eg, Li^+ , Mg^{2+} , Fe^{3+} . Six oxide ions surround each cation in an octahedral arrangement. The aluminum ion, which is intermediate in size, can occupy either tetrahedral or octahedral spaces. When cations too large to occupy either of the inter-oxide ion spaces, eg, NH_4^+ , Na^+ , K^+ , Ca^{2+} , are present, the oxide structure opens in one of two ways. Groups of the oxide ion layers separate to give an overall layered structure with the large cations forming a new layer between. The *clays* have this structure. Or, the oxide ions may spread in a three-dimensional manner to give room-like cavities within the structure. The cavities are occupied by the large cations. Feldspars and zeolites have this latter structure.

A persistent problem preventing early workers from successfully elucidating silicate structures was their failure to recognize that ions of the ideal structure may be substituted to some extent by other ions of the same radius, irrespective of charge. This phenomenon, "isomorphous replacement," is widespread among the silicates. Because of this, empirical formulas, based on analytical data, are meaningless. The illustrative formulas used in the following discussions are "ideal" formulas. Because of isomorphous replacement, the actual formula of a given silicate may differ somewhat from the ideal.

Before discussing specific insoluble silicates it must be said that all are chemically inert. The properties which distinguish them and determine their use are structural or related to surface phenomena.

Chain silicates are unidimensional arrangements of silicate tetrahedra sharing two oxygens per tetrahedron; in effect each chain is a macroanion. Since these chains consist of Si-O bonds having 50% covalent character, they are difficult to break. Electrical neutrality is maintained by placing a sufficient number of cations, usually K^+ and/or Ca^{2+} , between the chains. Electrostatic forces being weaker than covalent forces, these crystals cleave readily to give rise to the typical fibrous structure of asbestos, eg, serpentine asbestos, $(\text{HO})_6\text{Mg}_6(\text{Si}_4\text{O}_{11})_2\cdot\text{H}_2\text{O}$. These asbestos chains are useful as filter aids and as insulation. Asbestosis is a pulmonary condition similar to silicosis.

Attapulgite, $\text{Mg}_5(\text{Si}_8\text{O}_{20})(\text{OH})_2\cdot 8\text{H}_2\text{O}$, is a double-chain structure with rather large open spaces between the chains. These spaces are occupied by water molecules which provide hydrogen bonding to hold the chains together. It has adsorptive properties similar to kaolin.

The layer silicates include talc (talcum, soapstone), the micas, the chlorites (no relationship to ClO_2^-) and the three clay minerals, the montmorillonites (bentonites), kaolins, (kaolinite) and the illites.

Talc, $\text{Mg}_3(\text{OH})_2\text{Si}_4\text{O}_{10}$, is the softest mineral known. There are no cementing cations or molecules between silicate layers; they are held together by van der Waals forces. Consequently, the talc layers cleave easily to give the characteristic

smooth, unctuous feel. Talc adheres readily to the skin, is chemically inert and has very low adsorptive powers. It is used in dusting powders as a protective and lubricant, to prevent irritation due to friction. It also is used in medicated dusts and used widely in cosmetic applications. While there are no problems in its use on intact skin, talc must not be used on broken skin, wounds or surgical incisions. This precludes its former use as a dusting powder and lubricant for surgical gloves.

Because of its inertness and nonadsorptive character, talc is a useful filter aid. Only particles which are passed by a No 80 sieve, but retained by a No 100 sieve, should be used. Finer particles suspend and are not removed easily by subsequent filtration. Talc is official in the USP.

In mica, $\text{Al}_2[(\text{OH})_2(\text{Si}_3\text{O}_{10})]\text{K}$, and chlorite, $\text{Mg}_3[(\text{OH})_2(\text{Si}_4\text{O}_{10})]$, negatively charged silicate layers are bound together by cations. Thus, these silicates cleave readily along the cation layer since the electrostatic forces are weaker than the covalent bonds within the silicate layer. Neither has pharmaceutical applications.

The clays, montmorillonite (Smectite), $\text{Al}_4[(\text{OH})_4(\text{Si}_8\text{O}_{20})]\cdot 3\text{H}_2\text{O}$ and kaolinite, $[(\text{OH})_6\text{Al}_4][(\text{OH})_2(\text{Si}_4\text{O}_{10})]$, are layer structures built of alternating layers of aluminum oxide (hydrargillite) and silicate. The montmorillonites have higher $\text{SiO}_2\text{:Al}_2\text{O}_3$ ratios with much isomorphous replacement of aluminum. Magnesium never is present in the kaolins.

The distinguishing feature of the bentonite (montmorillonite) clays is the insertion of up to three distinct layers of hydrogen bridged water molecules between the aluminosilicate layers. Not all water hydrogens are needed to bond the water molecules within their layer; the unused hydrogens bind the layers to each other and to the aluminosilicate layers. These water layers may be removed, one at a time, by heat. The thickness of the individual crystals decreases in steps as each water layer is removed. By treating with water, the water layers are restored, one at a time, with a return to the original thickness. This may be repeated indefinitely. Because of this phenomenon, bentonite clays are known as "swelling clays."

The bentonites have gelling properties which make them useful suspending agents, ion-exchange properties and detergent properties. Bentonite and Bentonite Magma are official in the NF, as is Purified Bentonite, a colloidal montmorillonite.

Kaolins are found always in the form of microcrystals of colloidal dimensions. The properties are somewhat similar to bentonite. They are used as clarifying agents and are good excipients for inorganic salts. They find employment as intestinal adsorbents and protectives. Externally they are used as dusting powders. Kaolin is official in the USP.

The three-dimensional, or lattice silicates have been described previously. In the feldspars, KAlSi_3O_8 , the most common rock, the large cations, eg, K^+ , are trapped in enlarged cavities within the aluminosilicate network. On the other hand, in the zeolites, $\text{CaAl}_2\text{Si}_4\text{O}_{12}\cdot 6\text{H}_2\text{O}$, and in the synthetic *molecular sieves*, these cavities have connecting openings, or hallways, between one another and to the exterior of the crystal. Thus the cations (and water molecules) in these cavities are free to move about within the crystal and may be exchanged with external cations. These latter silicates are valuable as ion exchangers, desiccants, carriers for catalysts and for the separation of organic gases, eg, ethylene from ethane. Certain forms of molecular sieves have been tried as antacids. See *Clathrates*, Chapter 14.

Pumice is a porous rock of volcanic origin, usually found in the vitreous state. Being a three dimensionally linked sodium aluminosilicate it is a hard, chemically inert, nonadsorptive material. In the powdered form it is used as a filter medium and dispersing agent. It is found in dental preparations as an abrasive.

Magnesium trisilicate is prepared by precipitation, using a soluble silicate and a soluble magnesium salt. Although it has an analytical composition approaching disilicate, it is actually a mixture of magnesium hydroxide, hydrated magnesium oxide and silica gel. The insoluble magnesium compounds are responsible for the antacid action; the silica gel

acts as a protective. Magnesium trisilicate also is employed as a suspending agent.

Glass—Glass is a generic term used to identify vitreous silicate materials prepared by fusing a base, eg, Na_2CO_3 and CaCO_3 , with pure silica. On cooling, a clear vitreous mass results. There is no clearly defined melting point; a gradual softening takes place on heating as a result of the somewhat haphazard arrangement of the silicon-oxygen bonds. Certain other cations may be included: manganese dioxide, to hide the blue-green color of the iron usually present in silica; borates, to reduce the coefficient of expansion; potassium ion to give a brown and light-resistant glass; etc.

Since the surface of the glass is an exposed oxide network, it can be reactive. On standing in contact with aqueous solutions, alkali will leach from it. This leaching is accelerated by heat, eg, sterilization. The surface of glass also has adsorbing powers, but this can be a problem only in extremely dilute solutions. The compendia usually specify the type of glass container to be used for certain materials and include tests for four types of glass.

Silanes and Siloxanes—The close relationship between carbon and silicon has prompted much interest in the "organic chemistry of silicon." The compounds involved are analogs of carbon compounds or compounds in which silicon functions in place of one or more of the carbon atoms. Simple silanes and their derivatives, such as silane [SiH_4], silanol [SiH_3OH], disiloxane [$\text{H}_3\text{SiOSiH}_3$], etc., have been known for a long time. The present interest is in complex compounds that contain both carbon and silicon. The silicones (alkylsiloxanes) are condensation polymers of various types of alkylsilanols and represent a field finding extensive commercial application. Simethicone USP, a polymeric dimethylsiloxane, is employed as an antifoaming agent. It has found use as an antiflatulent in gastric bloating and in postoperative gaseous distention in the GI tract. For further discussion, see *Silicones*, in Chapter 52.

Germanium

The properties of this element are intermediate to those of silicon and tin. It has no applications in the health sciences. Germanium has remarkable electrical properties which make it valuable in the manufacture of semiconductors and other microelectronic parts.

Tin

Tin forms compounds in both +2 and +4 oxidation states. The lower oxidation state is somewhat electrostatic but the higher state is largely covalent in character. Both oxides are amphoteric, giving rise to stannate(II) (stannite), $[\text{SnO}_2]^{2-}$, and stannate(IV) (stannate), $[\text{SnO}_3]^{2-}$, ions.

The only official compound is stannous fluoride [tin(II) fluoride], applied topically as a dental prophylactic. Experimental evidence demonstrates the superiority of this fluoride over other soluble fluorides for this application. The ready susceptibility of tin(II) fluoride to oxidative and hydrolytic decomposition causes problems in the preparation and storage of suitable dosage forms. Various tin dioxide [tin(IV) oxide] preparations have been used externally for their germicidal effect, particularly against staphylococcal organisms often resistant to other germicides.

Lead

This element is the most metallic of the group. However, some residual amphoteric character is present, particularly in the +4 oxidation state. At one time lead compounds found employment in pharmacy and medicine, usually as astringents. Because of its highly toxic nature as a "cumulative poison" it is no longer used. It is absorbed readily in the intestinal tract and broken skin, and deposited in the bone.

Elements of Group IV-B

Because of their minor importance, a detailed treatment is unnecessary. Some important characteristics are given in Table 11. All members of the group occur in nature only in the combined state. The +2 and +4 oxidation states are common to all. All members of the group possess amphoteric properties and their cations readily form complexes.

Titanium

Titanium forms three oxides (TiO , Ti_2O_3 and TiO_2) and corresponding binary salts. The soluble salts of divalent and trivalent titanium are violet or red and are powerful reducing agents.

The most important compound is the dioxide, TiO_2 , which is official in the USP. It is used as a solar-ray protective. As such, it is a popular ingredient in various lotions and creams

for the prevention of sunburn. This action is the result of its high covering power as a white pigment, a consequence of its high refractive index.

Zirconium and Hafnium

Hafnium occurs in small quantities in zirconium ores. As a consequence, unless highly purified, zirconium compounds include varying percentages of hafnium. Zirconium as the hydrous oxide or carbonate has been used as a lotion or cream for contact dermatitis. The hydrous oxide also was used in deodorant and antiperspirant preparations. However, it has been discovered that zirconium is toxic, and these uses have been discontinued. At present there are no applications of these two elements in the health sciences.

Elements of Group V

The elements of this group have five valence electrons. Two of the electrons occupy s orbitals. The three remaining

electrons are in different orbitals in the A and B subgroups, giving the structures ns^2np^3 and $(n-1)d^3ns^2$, respectively.

Elements of Group V-A

This group displays strikingly regular gradations in properties ranging from exclusively nonmetallic nitrogen to almost exclusively metallic bismuth (Table 13). Oxidation states of +3 and +5 are common to all. Bismuth functions primarily in the +3 state. All members except bismuth also exist in a -3 oxidation state. Hydrides are of the covalent MH_3 type,

characterized by an unshared electron pair. This allows these hydrides to form coordinate covalent bonds. The oxides of nitrogen and phosphorus are acidic. Those of arsenic and antimony are amphoteric, but are sufficiently acidic for the elements to be classified as nonmetals. The common oxide of bismuth, Bi_2O_3 , is basic; the less-important pentoxide is acidic.

Table 13—The Elements of Group V-A

Element	Nitrogen	Phosphorous	Arsenic	Antimony	Bismuth
Symbol	N	P	As	Sb	Bi
Atomic number	7	15	33	51	83
Atomic weight	14.01	30.97	74.92	121.75	208.98
Orbital electrons	[He]2s ² 2p ³	[Ne]3s ² 3p ³	[Ar]3d ¹⁰ 4s ² 4p ³	[Kr]4d ¹⁰ 5s ² 5p ³	[Xe]4f ¹⁴ 5d ¹⁰ 6s ² 6p ³
Oxidation states	3-, 1+, 3+, 5+	3-, 3+, 5+	3-, 3+, 5+	3-, 3+, 5+	3-, 3+, 5+
Atomic radius (Å)	0.70	1.06	1.21	1.41	1.5
Ionic (crystal) radii (Å)	1.32 (3+)	0.58 (3+)	0.72 (3+)	0.90 (3+)	1.17 (3+)
(coordination no 6)	0.27 (5+)	0.52 (5+)	0.60 (5+)	0.74 (5+)	0.90 (5+)
Ionization potential, ev	14.48	11.10	10.5	8.5	8.0
Electronegativity	3.04	2.19	2.18	2.05	2.02
% of earth's crust	4.6 × 10 ⁻⁸	0.12	5 × 10 ⁻⁴	10 ⁻⁴	2 × 10 ⁻⁵

Nitrogen

Nitrogen occurs free in the atmosphere (78%) and combined in nitrates and organic compounds. It is a colorless, tasteless and odorless, inert gas. It is nonflammable and does not support combustion. Due to its stable triple-bond structure, the N₂ molecule shows little reactivity with other elements. The free nitrogen atom is very reactive.

The inertness of nitrogen is the result of the bonding existing in the molecule. There is a σ bond between the atoms, and two π bonds which fuse to form an electron cloud (doughnut) encasing the entire molecule. This electron cloud effectively prevents breaking of the σ bond for reaction with other elements. The cyanide ion and carbon monoxide have electron structures similar to that of the nitrogen molecule and also show an extraordinary stability.

Nitrogen is prepared primarily by the fractional distillation of liquid air. At the temperature of the electric arc it combines with oxygen forming nitrogen(V) oxide, which is converted into nitric acid. In the presence of catalysts and at great pressure and elevated temperature, it combines with hydrogen to form ammonia.

Unlike phosphorus and the other members of the family, nitrogen does not expand its coordination sphere beyond three. The nitric acid of chemistry is the meta acid. There is no ortho acid, hypothetically H₃NO₄. Nitrogen in the +5 state is too small to accommodate four oxygen atoms.

Therapeutically inactive, elemental Nitrogen NF₃ is employed pharmaceutically as an inert atmosphere in ampules and other containers of substances that would be affected adversely by air. Nitrogen(I) Oxide (nitrous oxide) USP, is an inhalatory general anesthetic (page 337). Sodium Nitrite USP, is used as an antidote to cyanide poisoning; it also is a vasodilator but is slower acting than the organic nitrite and nitrate esters commonly used for this purpose. The nitrate ion frequently is used as an anion for medicinally active cations; eg, silver nitrate, thiamine mononitrate.

Very significant work has shown that the simple, paramagnetic molecule, nitric oxide, NO, is an important neurotransmitter produced by neurons and other cells and causing responses such as vasodilation by acting as a ligand for iron in a heme group with a resulting lowering of blood pressure. This knowledge rationalizes the action of drugs such as the organic nitrites and sodium nitroprusside.

Nitrite ion is toxic; it reacts with hemoglobin to form methemoglobin. Nitrites are also potentially dangerous since they can form *N*-nitroso derivatives of amines and amides, which may be carcinogenic. Nitrate ion is reducible to nitrite in the intestine and may cause methemoglobinemia. For the above reasons the use of nitrates and nitrites as food preservatives has been questioned.

Phosphorus

Phosphorus exists in two common allotropic forms, yellow and red. Yellow phosphorus (white phosphorus) has a distinctive, disagreeable, ozone-like odor. On exposure to air, or when heated at about 50°, it ignites spontaneously. It is almost insoluble in water, but is soluble in chloroform, ben-

zene or carbon disulfide. It is poisonous and on the skin it causes severe, slow to heal burns. Copper(II) sulfate is used as an antidote.

Red phosphorus is a brown to red amorphous powder. It is nonpoisonous and nonflammable in air, except at high temperatures. It is insoluble in any common solvent.

The use of inorganic phosphorus compounds in modern medicine is restricted primarily to the orthophosphates. Tribasic calcium, magnesium and aluminum phosphates are used as gastric antacids, and the monobasic alkali phosphates are effective urinary acidifiers. Dibasic sodium phosphate is the active ingredient in various saline cathartics and enemas.

Phosphoric Acid NF₃ is used to form soluble salts of insoluble medicinal bases. The dihydrogen phosphate-mono-hydrogen phosphate system is a valuable buffer in physiological ranges. Hypophosphorus Acid NF₃ is an antioxidant, used primarily with iodide and iron(II) salts. The radioactive isotope, ³²P, is employed therapeutically (Chapter 51).

Phosphorus is essential to plant and animal life. A complex basic calcium phosphate constitutes the main inorganic component of bones and teeth. Dihydrogen phosphate and monohydrogen phosphate ions constitute the ion pair of one of the buffer systems of the blood and body fluids. The phosphate moiety has important roles in the metabolism of various organic materials; eg, carbohydrates.

Arsenic

Inorganic arsenic compounds rarely are employed in modern medicine. There no longer are official compounds; arsenic trioxide and potassium arsenite were the last. They were used as alternatives, tonics and antileukemics. Sodium arsenate, ⁷⁴As, has been used as a diagnostic aid.

Arsenic compounds are poisonous. If still in the GI tract, a freshly prepared mixture of iron(III) and magnesium hydroxides is administered orally as an antidote. If already absorbed, dimercaprol by intramuscular injection is effective.

Antimony

Antimony compounds have physiological reactions resembling those of arsenic. The compounds are potentially toxic. Except for Antimony Potassium Tartrate (antimonyl potassium tartrate, tartar emetic) USP, and for Antimony Sodium Tartrate USP, antimony compounds are no longer in common medical usage. Both antimony potassium and antimony sodium tartrates are used in the treatment of schistosomiasis, a parasitic disease involving flukes.

Bismuth

With the exception of sodium bismuthate, [NaBiO₃], in which the bismuth functions anionically in the +5 oxidation state; the important bismuth compounds of commerce are the Bi³⁺ variety. The basic salts, bismuth subcarbonate, bismuth subgallate and bismuth subnitrate are employed for their astringent, mildly germicidal and antacid properties. Bismuth Subnitrate, Bismuth Subgallate and Milk of Bismuth are official in the USP. Milk of Bismuth owes its antacid

Table 14—Transition Elements

Element	Group V-B			Group VI-B		
	Vanadium	Niobium	Tantalum	Chromium	Molybdenum	Tungsten
Symbol	V	Nb	Ta	Cr	Mo	W
Atomic number	23	41	73	24	42	74
Atomic weight	50.94	92.91	180.95	52.00	95.94	183.85
Orbital electrons	[Ar]3d ³ 4s ²	[Kr]4d ⁴ 5s ¹	[Xe]4f ¹⁴ 5d ³ 6s ²	[Ar]3d ⁵ 4s ¹	[Kr]4d ⁵ 5s ¹	[Xe]4f ¹⁴ 5d ⁴ 6s ²
Oxidation states	2+, 3+, 4+, 5+	2+, 3+, 4+, 5+	2+, 3+, 4+, 5+	2+, 3+, 4+, 6+	2+, 3+, 4+, 6+	2+, 3+, 4+, 6+
Atomic radius (Å)	1.22	1.34	1.34	1.18	1.30	1.30
Ionic (crystal) radii (Å)	0.40 (5+)	0.70 (5+)	0.73 (5+)	0.76 (3+)	0.79 (4+)	0.80 (4+)
(coordination no 6)				0.58 (6+)	0.73 (6+)	0.74 (6+)
Ionization potential, ev	6.71	6.79	ca 6	6.77	7.38	7.98
Electronegativity			1.33	1.66	2.2	2.36
% of earth's crust	0.021			2 × 10 ⁻²	ca 5 × 10 ⁻⁴	ca 1.5 × 10 ⁻⁴

properties to the hydroxyl and carbonate ions present. Because of the adherent properties it provides protective action. The small amount of dissolved bismuthyl ion present exerts a mild antiseptic effect. Colloidal bismuth subcitrate is used clinically in the treatment of peptic ulcer disease.

Hydrogen sulfide, from the breakdown of proteins in the gut, reacts with bismuthyl ion to form the insoluble, dark brown, bismuth(III) sulfide. As a result stools appear black. Soluble bismuth compounds are poisonous; intramuscular dimercaprol is an effective antidote.

Elements of Group V-B

Unlike previous transition elements, the valence electron structure of these elements is not identical. Vanadium and tantalum have a $(n-1)d^3ns^2$ structure while niobium has the structure, $(n-1)d^4ns^1$ (Table 14). The difference has no apparent effect on their chemistry. In addition to the Group V oxidation states, +3 and +5, these elements also appear in a +2 and +4 oxidation state. The -3 oxidation state does not occur. There is a close similarity between niobium and

tantalum. Tantalum, because of its size, has a maximum coordination number of eight and the compounds of these elements are colored.

The Group V-B elements are of little pharmaceutical importance as only tantalum metal is employed therapeutically. Since tantalum is unaffected by the body fluids, it is used in sheet form, for the surgical repair of bones. Muscle tissue will attach itself to tantalum as though it were bone.

Elements of Group VI

The members of this group have six valence electrons. Although theoretically a -2 oxidation state is possible for all, -2 and -1 appear only in the subgroup A elements. The

common positive oxidation states are +4 and +6; +1 and +2 also exist.

Elements of Group VI-A

There is a very clear gradation of properties in this family (the Chalcogens). Oxygen is nonmetallic in character while polonium is metallic; the other members show both characteristics. Polonium is further distinguished by its natural radioactivity.

The sulfur-selenium-tellurium triad displays especially strong family relationships. Allotropic varieties of each element in the triad are numerous. Although there are quantitative differences, each functions generally in the -2, +4 and +6 oxidation states, forming many analogous compounds.

Some of the more important characteristic properties of Group VI-A elements are presented in Table 15.

Oxygen

In free form, oxygen constitutes about one-fifth of air, by weight. The primeval atmosphere of the earth probably had no oxygen. In combined form, it constitutes about seven-eighths, by weight, of water and important fractional parts of

Table 15—The Elements of Group VI-A

Element	Oxygen	Sulfur	Selenium	Tellurium	Polonium
Symbol	O	S	Se	Te	Po
Atomic number	8	16	34	52	84
Atomic weight	16.00	32.06	78.96	127.6	(209)
Orbital electrons	[He]2s ² 2p ⁴	[Ne]3s ² 3p ⁴	[Ar]3d ¹⁰ 4s ² 4p ⁴	[Kr]4d ¹⁰ 5s ² 5p ⁴	[Xe]4f ¹⁴ 5d ¹⁰ 6s ² 6p ⁴
Oxidation states	2-, 1-	2-, 2+, 6+	2-, 4+, 6+	2-, 4+, 6+	4+, 6+
Atomic radius (Å)	0.66	1.04	1.16	1.37	1.53
Ionic (crystal) radii (Å)					
simple anion	1.26 (2-)	1.70 (2-)	1.84 (2-)	2.07 (2-)	1.08 (4+)
coordination no 6		0.43 (6+)	0.56 (6+)	0.57 (6+)	0.81 (6+)
Ionization potential, ev	13.61	10.36	9.75	9.0	
Electronegativity	3.44	2.58	2.55	2.1	2.0
% of earth's crust	46.6	0.052	10 ⁻⁷	10 ⁻⁷	10 ⁻¹⁴

minerals such as CaCO_3 or Fe_2O_3 . The industrial process for preparing oxygen is the fractional distillation of liquid air. When liquid air is allowed to evaporate under controlled conditions, the nitrogen and inert gases escape initially, followed by nearly pure oxygen.

The weighted atomic mass of the mixture of naturally occurring oxygen isotopes formerly was the standard for all chemical atomic weights. This standard has been replaced by the most abundant carbon isotope, ^{12}C . The isotopes of oxygen have been separated and introduced into specific molecules as tracer elements.

Oxygen USP, is employed as a therapeutic gas in the treatment of conditions involving hypoxia. Ozone, O_3 , an allotropic form of oxygen, is a powerful oxidizing agent. Ozonized air (air treated to convert some of its oxygen into ozone) is used in various disinfecting and bleaching operations.

Chemically, oxygen is very reactive, combining directly, under appropriate conditions, with all elements except mercury, silver, gold and members of the platinum family. It is electronegative with respect to all elements except fluorine. The oxides of nonmetallic elements are acidic, while those of metals are basic. The oxides of many elements, eg, antimony and tellurium, are amphoteric. In all, oxygen has the -2 oxidation number.

Hydrogen peroxide and the peroxides are a series of oxygen compounds in which oxygen has an oxidation number of -1 . They are valuable oxidizing and reducing agents.

Hydrogen peroxide is prepared by the electrolysis of a concentrated solution of either sulfuric acid or ammonium sulfate. Persulfate, $[\text{S}_2\text{O}_8^{2-}]$, forms in the anode compartment. After electrolysis the anolyte is reacted with water and the hydrogen peroxide formed is separated by distillation under reduced pressure.

Pure concentrated hydrogen peroxide is stable. However, commercial preparations must be stabilized; usually, a preservative is added, eg, acetanilid. Traces of mineral acid, eg, phosphoric acid, often are added, as the stability increases in acid medium.

Hydrogen peroxide is available as the 3%, 6%, 30%, 70% and 90% solutions. Concentration also is expressed as volume strength, the volume of oxygen gas released from one volume of solution; ten volume is 3%. Hydrogen Peroxide Concentrate USP, is the 30% solution. It is a powerful oxidant and must not be used on the skin, etc. Hydrogen Peroxide Topical Solution USP, is the 3% solution. It is a mild, fast acting, oxidizing germicide which will destroy most pathogenic bacteria. Hydrogen peroxide, 6%, is the only common bleach mild enough for use on hair.

Hydrogen peroxide is available as a solution in anhydrous glycerine (1.5%) and as urea peroxide, a stable crystalline 1:1 compound, usually in 4 to 10% solution in anhydrous glycerine. A monograph for Carbamide Peroxide is found in the USP and the monograph for Carbamide Peroxide Topical Solution USP, has a generic purity rubric statement. These preparations are preferable to hydrogen peroxide in treatment of oral and ear infections. Zinc peroxide and sodium perborate have been listed in past compendia.

Sulfur

This element exists in several allotropic forms. At room temperature α -sulfur (rhombic sulfur) is the stable form. At the equilibrium point, 96° , β -sulfur (monoclinic sulfur) becomes the stable form. Other allotropes exist. Commercial, Sublimed Sulfur USP, and Precipitated Sulfur, USP, are α -sulfur. Precipitated sulfur has a smaller particle size than sublimed; therefore, it is more reactive.

As an ointment, precipitated sulfur is used as the scabicide. Sulfur ointments and lotions are used in dermatological applications as keratolytics. Elemental sulfur also has fungicidal action. Sublimed sulfur is used as a cathartic.

Sulfur appears in three series of compounds. The first, based on the -2 oxidation state, gives rise to hydrogen sulfide and the sulfides. The second and third series, based on $+4$

and $+6$ oxidation states, give rise to the two sulfur oxides and their acids and salts.

Hydrogen sulfide, and soluble sulfides in solution, react readily with suspended, finely divided sulfur to give rise to mixtures of polysulfides, S_2^{2-} , S_3^{2-} , S_4^{2-} , S_5^{2-} , usually written S_n^{2-} .

Sulfurated Potash USP, consists largely of potassium polysulfides, sulfate and thiosulfate. It is prepared by careful heating of a mixture of potassium carbonate and sublimed sulfur. The compound is very soluble in water, giving an alkaline reaction. The polysulfide component is soluble in ethanol. Sulfurated potash is used in the form of lotions, ointments and aqueous solutions for the treatment of psoriasis and other chronic skin conditions and has parasitocidal activity.

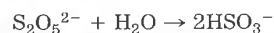
Sulfurated potash must be stored in tightly sealed containers to prevent reaction with carbon dioxide and oxygen. It is incompatible with acid.

White Lotion USP is prepared by adding freshly prepared, filtered, sulfurated potash solution to zinc sulfate solution. The order of mixing is important. It is an astringent and protective.

Selenium Sulfide (and Lotion) USP, is employed as a 2.5% suspension in the topical treatment of seborrheic dermatitis (dandruff). Care is essential to prevent introduction into the eyes or mouth. In addition the hands must be cleansed thoroughly after using since selenium is toxic. Cadmium sulfide also is used in the treatment of seborrheic dermatitis. While less irritating, it requires the same precautions as selenium sulfide.

Sulfur Dioxide NF, usually is prepared industrially by burning sulfur. It is the acid anhydride of sulfurous acid and its salts, the sulfites. All are used in pharmaceutical practice as antioxidants and preservatives.

Attempts to crystallize sodium bisulfite yield, instead, normal sodium sulfite crystals. If the crystallization is carried out under a sulfur dioxide atmosphere crystals of the metabisulfite, $\text{Na}_2\text{S}_2\text{O}_5$, form. On dissolving metabisulfite in water, a solution of bisulfite results



Sodium Metabisulfite NF should be used when sodium bisulfite is specified. It is used as an antioxidant. A monograph for Potassium Metabisulfite is included in the NF.

Sodium Thiosulfate USP is prepared from the sulfite by reaction with sulfur. Since the sulfite ion has an unshared electron pair, and elemental sulfur lacks one electron pair for completion of a stable octet, a coordinate covalent bond forms easily, giving the thiosulfate ion. It is used as an antidote for cyanide poisoning. It is a valuable analytical reagent for the determination of iodine.

In the $+6$ oxidation state sulfur gives rise to sulfuric acid and the sulfates. Sulfuric acid is an important acid and is listed in the NF. Several sulfates are cited officially but with the exception of sodium sulfate (saline cathartic), all applications are ascribed more appropriately to the cation present, eg, barium sulfate or bleomycin sulfate.

Selenium and Tellurium

In general, selenium and tellurium compounds are analogous to those of sulfur. Observed differences are largely those to be expected in terms of relative atomic size and electronegativity.

While selenium is toxic in large doses, it is an important trace element. It is absorbed very slowly through the skin. Toxicity usually is not a problem if it is applied to small areas of unbroken, unirritated skin. Prolonged contact with the skin results in contact dermatitis. The use of selenium sulfide, the only official compound, has been described under *Sulfides*. Selenomethionine Se 75 Injection USP is used in the diagnosis of pancreatic tumors and growths.

Tellurium has no medicinal applications at this time.

Table 16—The Elements of Group VII-A

Element	Fluorine	Chlorine	Bromine	Iodine	Astatine
Symbol	F	Cl	Br	I	At
Atomic number	9	17	35	53	85
Atomic weight	19	35.45	79.90	126.90	(210)
Orbital electrons	[He]2s ² 2p ⁵	[Ne]3s ² 3p ⁵	[Ar]3d ¹⁰ 4s ² 4p ⁵	[Kr]4d ¹⁰ 5s ² 5p ⁵	[Xe]4f ¹⁴ 5d ¹⁰ 6s ² 6p ⁵
Oxidation states	1-	1-, 1+, 3+, 5+, 7+	1-, 1+, (3+), 5+	1-, 1+, (3+), 5+, 7+	...
Atomic radius (Å)	0.64	0.99	1.14	1.33	...
Ionic (crystal) radii (Å)					
halide anion	1.19	1.67	1.82	2.06	...
coordination no 6	0.022 (7+)	0.41 (7+)	0.53 (7+)	0.67 (7+)	0.76 (7+)
Ionization potential, ev	17.42	13.01	11.84	10.44	...
Electronegativity	3.98	3.16	2.96	2.66	2.2
% of earth's crust	8 × 10 ⁻²	3 × 10 ⁻²	1.6 × 10 ⁻⁴	3 × 10 ⁻⁵	...

Elements of Group VI-B

The elements of this group are metallic in behavior. The lower oxidation state oxides are basic while those of the higher oxidation states are acidic, giving rise to the chromates, molybdates and tungstates. The cations of high oxidation numbers have a tendency to unite with oxygen to give stable -yl cations, eg, CrO²⁺, chromyl. These elements show great similarity in behavior to their horizontal neighbors in Groups V-B and VII-B. Some properties are given in Table 14.

Chromium and molybdenum are essential trace elements. Monographs for Chromic Chloride (and Injection) and Ammonium Molybdate (and Injection) are found in the USP. Chromium has a wide margin of safety between amounts usually ingested and those showing adverse effects. The radioactive isotope, ⁵¹Cr, is employed as a biological tracer in certain hematological procedures (Chapter 51). Their compounds are important in analytical pharmaceutical operations.

Elements of Group VII

The elements of Group VII subdivide into Group VII-A, (Table 16), members of which have an outer electron configuration ns²np⁵, and Group VII-B, (Table 17), with the (n-1)d⁵ns² valence electron configuration.

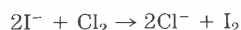
The halogens are nonmetallic in character while the transi-

tion elements of the family are metallic. Except for the higher oxidation states of +5 and especially +7 the elements of the subgroups and their compounds are quite dissimilar. While the free halogens are colored, almost all of their compounds are not.

Elements of Group VII-A

Examination of the valence electron structure of these elements suggests -1, +1, +3, +5 and +7 as possible oxidation states. Fluorine, the most electronegative element, appears only as the simple fluoride ion (which readily acts as a ligand). Only chlorine forms compounds in all five oxidation states.

The halogen binary compounds may be ionic and/or covalent, depending on electronegativity differences. All halogens unite with hydrogen to form covalent gaseous hydrogen halides. These gases are extremely soluble in water, giving rise to very strong acids, eg, hydrochloric acid. The ionic binary compounds show a displacement series: a halogen of lower atomic weight will displace a halide ion of higher atomic weight



Thus, of the halogens, fluorine is the strongest oxidizing agent

and iodine the weakest. Conversely, iodide is the strongest reducing agent and fluoride the weakest. In fact, the fluoride ion is the most stable of all simple anions.

Chlorine, bromine and iodine form well-defined oxides, oxyacids and their salts, in most of the positive oxidation states. The stability of the higher oxidation states increases with increasing atomic weight. (For the nomenclature of these acids and salts, see Table 1.)

Fluorine

Fluorine is the most reactive of the electronegative elements. With the exception of gold and platinum it attacks all metals at ordinary temperatures. It combines directly with all nonmetals, including the other halogens. Beryllium fluoride is one

Table 17—Transition Elements

Element	Group VII-B			Group VIII-First Triad		
	Manganese	Technetium	Rhenium	Iron	Cobalt	Nickel
Symbol	Mn	Tc	Re	Fe	Co	Ni
Atomic number	25	43	75	26	27	28
Atomic weight	54.94	(98)	186.2	55.85	58.93	58.71
Orbital electrons	[Ar]3d ⁵ 4s ²	[Kr]4d ⁵ 5s ²	[Xe]4f ¹⁴ 5d ⁵ 6s ²	[Ar]3d ⁶ 4s ²	[Ar]3d ⁷ 4s ²	[Ar]3d ⁸ 4s ²
Oxidation states	2+, 3+, 4+, 6+, 7+	2+, 3+, 4+, 6+, 7+	3+, 4+, 5+, 6+, 7+	2+, 3+	2+, 3+	2+, 3+
Atomic radius (Å)	1.17	1.27	1.25	1.17	1.16	1.15
Ionic (crystal) radii (Å)	0.81 (2+)		0.81 (3+)	0.75 (2+)	0.79 (2+)	0.83 (2+)
(coordination no 6)	0.40 (6+)	0.56 (7+)	0.69 (5+)	0.69 (3+)	0.69 (3+)	0.70 (3+)
Ionization potential, ev	7.43	7.23	7.87	7.83	ca 8.5	7.6
Electronegativity	1.55	1.9	1.9	1.85	1.88	1.91
% of earth's crust	0.085	zero (?)	10 ⁻⁷	5	2.3 × 10 ⁻³	8 × 10 ⁻³

of the very few fluorides not ionized completely. Fluorine is an essential element and is present in the teeth and bone.

Sodium Fluoride, Sodium Fluoride Tablets, Sodium Fluoride Oral Solution, Stannous Fluoride (Tin(II) Fluoride), Stannous Fluoride Gel, Sodium Fluoride and Phosphoric Acid Gel, Sodium Fluoride and Phosphoric Acid Topical Solution and Sodium Monofluorophosphate are listed in the USP. Stannous fluoride is oxidized easily by oxygen of the air to give the tin(IV) ion which is ineffective as a dental prophylactic. For this reason solutions of this salt must be prepared freshly at the time of use. A developing cloudiness of the solution indicates that the oxidation is proceeding since the tin(IV) ion formed is precipitated as the insoluble hydroxide.

In addition to its use over several decades as a dental prophylactic, fluoride also has found use, in larger doses, in the treatment of osteoporosis. However, in spite of its officially sanctioned addition to some drinking water, controversy over the advisability and safety of ingesting fluoride at the 1 ppm level for long periods persists.

The use of fluoride to prevent, halt or reverse osteoporosis is questionable since studies have been reported in which a positive correlation exists between the use of fluoridated water and an *elevated* risk of hip fracture.

Chlorine

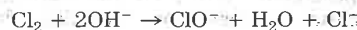
Elemental chlorine is a very reactive nonmetallic element. Most common chlorides are water soluble, the main exceptions being AgCl , Hg_2Cl_2 and Cu_2Cl_2 . A few, eg, PbCl_2 , are slightly soluble. The oxygenated chlorine compounds are mostly water soluble.

Hydrochloric acid, NH_4Cl , is a pharmaceutical necessity for purposes such as neutralizing, stabilizing or solubilizing other substances. In diluted form, it is a gastric acidifier but other compounds, more readily amenable to administration, usually are preferred. Sodium, potassium and calcium chlorides are employed in electrolyte replenishers; the first named is the sole ingredient of physiological salt solution. Ammonium chloride is an expectorant and a systemic acidifying agent. The chloride ion is frequently the carrier of choice for other metal cations such as those of zinc, aluminum and mercury, but with these the medicinal value is referable to the metal rather than the chloride.

Sodium Hypochlorite Solution USP is an effective germicide, viricide and deodorant because of the oxidizing power of hypochlorous acid. The hypochlorite ion is reduced rapidly by organic matter.

Dilution of Sodium Hypochlorite Solution (Dakin's Solution) to the 0.5 or 0.1% or even more dilute concentrations, together with an adjustment of pH to less alkaline values, are required to produce a solution that is suitable for use on human tissues, eg, in burn wound therapy.

Sodium hypochlorite is prepared by electrolysis of sodium chloride solutions under conditions such that the chlorine formed at the anode reacts with the hydroxyl ion resulting from removal of hydrogen ion as hydrogen gas at the cathode



Sodium chloride is always an impurity in the resulting solution. To improve its stability the pH is adjusted to 10 or greater.

Bleaching powder, *calcium hypochlorite*, is one of the most effective and least expensive disinfectants. The product is formed by passing chlorine gas over moist, slaked lime. Its composition is variable but hydroxide, hypochlorite and chloride ions are present in the mixture.

Potassium chlorate occasionally is present in mouth washes, vaginal douches and other local cleansing preparations; however, its antiseptic value is too weak to be of any value.

Bromine

Bromine is a dark reddish brown, fuming liquid with a suffocating odor. The fumes are highly irritating to the mu-

cous membranes and they burn and blister the skin. It attacks most metals and organic tissue. Chemically, bromine resembles chlorine with slight differences referable to the comparative size of the two atoms and their electronegativities.

Bromine is a powerful caustic and germicide but is not employed as such. It is a common chemical reagent. Utmost care should be exercised in handling bromine. All work with bromine should be done under ideal conditions of ventilation. If the skin is exposed to bromine, the area should be washed immediately with a solution of sodium bicarbonate and treated with glycerine. *Caution: Bromine containers should be opened only after they have been cooled thoroughly.*

Bromine has no known biological role. In proper dosage the bromide ion provides central depressant action. Sodium, potassium and ammonium bromides are employed commonly. Excessive continued dosage may elicit a toxic condition, brominism.

Iodine

Except for astatine, iodine is the most metallic of the halogens. Its oxo-salts are very stable while the simple anion is oxidized slowly by the oxygen of the air. When reacting with the other halogens it assumes the cationic role, eg, ICl_3 . Many workers consider IOH the hydroxide of iodine. Iodine is an effective antimicrobial.

Iodine solutions include potassium or sodium iodide to enhance the solubility of the iodine by the formation of polyiodide ions. Loss of the element to air is reduced greatly since polyiodide solutions have a lower iodine vapor pressure. Iodine, Potassium Iodide, Sodium Iodide and various iodine solutions are cited in the USP, as is Povidone-Iodine. Povidone is a synthetic polymer which has a special affinity for iodine molecules. The advantages of povidone-iodine are reduced volatility of the iodine and a decreased irritation on application. Iodine also is available in the form of cationic and nonionic surface active salts, used as sanitizing agents.

Iodine is essential for proper thyroid functioning and is utilized physiologically either in the elemental form or as potassium or sodium iodide. In proper dosage, iodide ion exerts expectorant action; examples are hydrogen iodide (as hydriodic acid syrup) and potassium iodide. The radioactive isotopes, ^{125}I and ^{131}I , have diagnostic and therapeutic applications (Chapter 51).

Elemental iodine is toxic, and corn starch and sodium thiosulfate are effective chemical antidotes.

Astatine

Astatine is a synthetic radioactive element. It resembles iodine but is more metallic. It has no pharmaceutical applications.

Pseudohalogens (Halogenoids)

Inorganic anions such as CN^- , CNO^- , CNS^- , N_3^- and $[\text{Fe}(\text{CN})_6]^{3-}$ resemble the halide anions and are known as pseudohalogens. The similarity of the cyanide ion especially is marked; it has properties intermediate to those of the chloride and bromide ions. Similarities include insoluble silver salts soluble in ammonia, preparation of HX by adding concentrated sulfuric acid to the sodium salt, preparation of X_2 by adding MnO_2 and concentrated sulfuric acid to the sodium salt, formation of polyions, etc.

The most striking difference is the very weak acidic character of the pseudohalogen hydrides, eg, the pK_a of HCN is 8.9 while that of HCl is $\text{ca} - 10$.

The pseudohalogens have no pharmaceutical applications.

Elements of Group VII-B

The elements of this group are metallic in character. The higher oxides give rise to very stable oxo-salts with the +6 and +7 oxidation states, eg, manganate (MnO_4^{2-}), pertechnetate (TeO_4^{2-}). A summary of important properties appears in Table 17. Compounds of these elements are colored.

Manganese

Pharmaceutically, manganese is the most important element in this group. Potassium Permanganate USP is categorized as a local anti-infective of the oxidizing type and is also an astringent and a powerful deodorant and cleanser. It is used in the form of dilute (0.01 to 1%) solutions. As the compound reacts, manganese(IV) oxide precipitates on the skin causing a temporary darkening of the surface. Gastric lavage using dilute permanganate solutions is antidotal for various alkaloids and other toxic substances that have been ingested in small amounts and are readily susceptible to oxidation.

Caution must be exercised to keep permanganate from contact with organic and other easily oxidized compounds

either in the dry state or in solution. Dangerous explosions may occur.

Manganese is an essential trace element, being necessary for the activation of a variety of enzymes, eg, pyruvate carboxylase. Manganese Chloride, Manganese Gluconate and Manganese Sulfate are listed in the USP. It is included in mineral supplements, but there are no well-defined deficiency states in man.

Technetium

Technetium (from Greek *technetos*, meaning artificial) was so named because it was the first element produced artificially. Radioactive technetium, ^{99}Tc , is used diagnostically in various forms (Chapter 51).

Rhenium

Rhenium is a very rare element and finds few technical applications. Alone and in combination with other metals, it has been employed as a catalyst for dehydrogenation.

Elements of Group VIII

This group of elements represents those in which the single electron already present in each of the five *d*-orbitals is being paired with a second electron of opposite spin. The group consists of three elements (triads) in each of the long rows and fills the space between the elements of Groups VII-B and I-B.

The first triad follows manganese and includes iron, cobalt and nickel (Table 17), known as the ferrous metals. They are characterized by their strong ferromagnetism. The second triad follows technetium and includes ruthenium, rhodium and palladium. The third triad follows rhenium and includes osmium, iridium and platinum. The elements of these latter two triads are known as the platinum metals. The term *noble metals* also is used. The platinum metals are characterized by their extreme inertness to chemical reaction.

These elements are definitely metallic and all participate readily in the formation of coordination complexes. The compounds of the first row triad are stable under most conditions while those of the second triad are moderately stable. However, osmium, iridium and platinum compounds are unstable and easily revert to the free element. All form colored compounds.

None of the elements of the second triad have compounds of medicinal value, but platinum, a member of the third triad, is used in cancer chemotherapy as *cis*-diamminedichloroplatinum(II), cisplatin; monographs for Cisplatin and Cisplatin for Injection are found in the USP. Carboplatin, *cis*-diammine (1,1-cyclobutanedicarboxylato)platinum, is another compound used in cancer therapy.

Elements of the First Triad

The important oxidation states are +2, achieved by the loss of the two *s* electrons, and +3 in which an additional *d* electron is lost (Table 17). The stability of the +2 oxidation state increases from iron to nickel. The free metals and the +2 cations are important reducing agents. The cations have a tendency to form both cationic and anionic complex ions of high stability.

Iron

Iron is distributed widely in nature. It functions in divalent and trivalent states to form iron(II), ferrous and iron(III), ferric compounds, respectively. Iron(II) compounds are usually green in the hydrated state and white in the anhydrous state. Iron(III) salts are usually yellow to brown in the hydrated state but vary in color when anhydrous. Aqueous solutions of iron(III) salts hydrolyze strongly to give acid solutions. Iron(II) salts undergo slight hydrolysis and are oxidized easily in solution. The behavior of the iron(III) ion is similar to that of aluminum(III).

Iron, in either oxidation state, readily forms soluble coordination complexes with ligands such as phosphate, citrate, tartrate and amines. Iron does not precipitate from many of these complexes with the usual iron precipitants.

Iron is an essential trace element. It is the important element in the transportation of oxygen by hemoglobin. It func-

tions in various cytochromes which are essential oxidative enzymes of the body cells.

A study carried out in Finland has cast doubt on the advisability of the routine use of hematinics since men with higher levels of ferritin (an iron storage protein) were found to be more prone to experience heart attacks. Interpretation of the results included speculation about iron's ability to give rise to free radicals after reaction with oxygen. The caveat that persists is that ferritin levels must be measured and found to be low before an iron deficiency is pronounced requiring use of a hematinic. The use of hematinics without substantiated need is not advised.

Numerous iron(II) and iron(III) compounds, complexes and solutions have been used as hematinics in the past. However, because of their greater gastrointestinal irritation and poor absorption, iron(III) compounds and their preparations are used rarely today. Ferrous Fumarate (and Tablets), Ferrous Gluconate (and Tablets, Capsules and Elixir), Ferrous Sulfate (and Oral Solution, Syrup, and Tablets) and Dried Ferrous Sulfate are official in the USP. Iron Dextran Injection [colloidal iron(III) hydroxide with partially hydrolyzed dextran] and Iron Sorbitex Injection [a complex of iron with sorbitol and citric acid] are cited in the USP as injectable forms for patients with poor gastrointestinal tolerance or poor absorption of iron. Reduced iron formerly was used as a hematinic. It survives today in the fortification of foods, eg, flour.

Iron(III) compounds are astringent (page 337). Sodium nitroprusside USP, $\text{Na}_2[\text{Fe}(\text{CN})_5(\text{NO})] \cdot 2\text{H}_2\text{O}$, is a vasodilator. A monograph for Sterile Sodium Nitroprusside is provided in the USP.

Cobalt

The important cobalt salts of commerce are those of cobalt(II). Most contain water of hydration and are red in color, but when rendered anhydrous they are blue. Because of this color change anhydrous cobalt(II) chloride is included in dehydrating agents for gases to indicate when they are spent.

There is evidence that the presence of traces of cobalt may

catalyze the physiological utilization of iron. This has led to the introduction of medicinal specialty products containing iron in association with cobalt designed for use in the treatment of iron deficiency anemias. Cyanocobalamin (vitamin B_{12}), is the only cobalt compound officially cited. The radioactive isotopes, ^{57}Co and ^{60}Co , are used diagnostically and therapeutically (Chapter 51).

Nickel

The important nickel compounds are in the +2 oxidation state. There are no nickel compounds of medical importance.

Water

Water is omnipresent. About 75% of the earth's surface is covered with liquid water. Land masses in polar regions are covered with thick sheets of ice. In vapor form, water is an important constituent of the earth's atmosphere. In combined form, water occurs abundantly in many minerals, eg, gypsum ($\text{CaSO}_4 \cdot 2\text{H}_2\text{O}$). In addition, water occurs in all animal and vegetable tissues; it constitutes some 70% of the human body and over 90% of vegetables such as cucumbers and watermelons.

Together with ammonia and hydrogen fluoride, water is distinguished from other covalent hydrides by the strong hydrogen bonds existing between adjacent molecules. Despite the ability of fluoride ion to form stronger hydrogen bonds than oxide, hydrogen-bonding reaches its peak in water because two protons are available per molecule. Hydrogen fluoride has only one available proton per molecule and ammonia has only one open site per molecule for hydrogen-bonding.

Because of the extensive hydrogen-bonding, the physical properties of water are unique among the other hydrides. Most obvious is the existence of water as a liquid under normal conditions. All other covalent hydrides are gases. The heat of fusion and melting point, heat of vaporization and boiling point, specific heat, surface tension, viscosity and dielectric constant of water are all much higher in absolute value than those of other covalent hydrides. The world as we know it would be impossible without these unusual properties of water.

Water is a chemically stable compound. Even at 2000°K less than 1% is dissociated into its elements. The K_w for water is only 10^{-14} . Despite this relative nonreactivity it acts as a solvent, especially for ionic compounds, a ligand, as acid or base and an oxidizing or reducing agent. In traces, water is frequently a catalyst. The acid-base properties are discussed later.

Because of its strong permanent dipole, water often acts as a ligand in complex substances. Almost all cations form one or more hydrates, divalent cations being more highly hydrated than the monovalent because of their stronger electrostatic fields. Having reduced field strengths because of their greater size, large cations (eg, cesium) do not hydrate. Many anions hydrate, eg, $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ is actually $[\text{Cu}(\text{H}_2\text{O})_4][\text{SO}_4 \cdot \text{H}_2\text{O}]$.

Water acts as a solvent for an unusual range of substances. This solvent action results from one or more of its properties, small size, strong permanent dipole, high dielectric constant and availability of protons for hydrogen-bonding.

Natural Waters

Naturally occurring waters contain dissolved minerals indigenous to the region. Such waters are described variously as mineral waters, lithia waters, sulfur waters, etc. Owners of springs or other sources of such waters often claim fanciful therapeutic effects but, in general, these claims have not been substantiated.

Natural waters contain varying amounts of suspended matter, eg, clay, sand, microorganisms, fragments of plants and

animals. Commonly, they are a very dilute solution (ppm) of calcium, magnesium, iron(III), sodium and potassium ions having as counterions, bicarbonate, sulfate and chloride. The dissolved bicarbonate constitutes *temporary* hardness while sulfate and chloride constitute *permanent* hardness. In addition, natural water contains traces of dissolved atmospheric gases, ammonia and metabolic decomposition products. Waters in inhabited areas often include dissolved minerals, eg, nitrate, phosphate and organic compounds from homes, industry and farms. Detergents and dissolved traces of insecticides and herbicides are proving especially troublesome. The Environmental Protection Agency (EPA) has water-quality criteria for a number of priority pollutants.

Potable Water

This is water that is "fit to drink." Providing potable water is one of the most important functions of modern communities. The overall process involves the removal of insoluble matter through appropriate coagulating, settling and filtering processes; destruction of pathogenic microorganisms by aeration, chlorination or other methods; and improvement of palatability through aeration and filtration through charcoal. Activated charcoal also removes some harmful trace impurities, eg, trihalomethanes, not removed or destroyed by previous operations. In regions where water is excessively hard, "softening" is effected by partial removal of dissolved salts by precipitation as carbonates (Ca^{2+} and Mg^{2+}) and hydroxide [iron(III)], by adding lime or ammonia. In order to assure an adequate provision of the essential element fluorine, fluoridation is accomplished by adding sodium fluosilicate. Standards for potable water are issued by the EPA.

In emergencies water may be purified (rendered free of viable microorganisms) by boiling for 15 to 20 minutes, or by treatment with halazone or iodine.

Purified Water and Other Waters Used in Pharmacy

Purified water is prepared by distillation, ion-exchange (deionized, demineralized), reverse osmosis or other methods. Potable water, meeting EPA standards, is used in its preparation. The object is the removal of dissolved solids. Ion-exchange and reverse osmosis are particularly effective in removing electrolytes. Distillation is not effective in the removal of weak electrolytes and nonelectrolytes if they are volatile.

Purified water may be rendered sterile and pyrogen-free by repeated distillation.

Primarily because of its solvent powers and physiological inertness, water is an extremely important pharmaceutical agent. It is official in six different monographs: Purified Water, Water for Injection, Bacteriostatic Water for Injection, Sterile Water for Inhalation, Sterile Water for Injection and Sterile Water for Irrigation.

Heavy Water

The isotopes of hydrogen have been named deuterium (two neutrons) and tritium (three neutrons). The presence of three neutrons in tritium results in an unstable nucleus. However, like hydrogen, deuterium is stable and gives rise to deuterium oxide, D_2O . This compound occurs in ordinary water in a few ppm. Because of its greater molecular weight, the physi-

cal properties of deuterium oxide differ from those of water, eg, bp 101.4° , sp gr 1.10.

Deuterium oxide has no known therapeutic role. It has been used as a research tool in biological and pharmacological investigations. Use of deuterium oxide, for drinking purposes, has caused retardation, or stunted growth in experimental mammals. It is available commercially and finds use as a moderator in nuclear reactors and as a solvent in nuclear magnetic resonance studies.

Acids, Bases and Buffers

Acids and Bases

Acid-base theories range from the limited classic Arrhenius Theory to the comprehensive theory due to G N Lewis. In between are the Franklin Solvent System of acids and bases and the Brønsted Proton Donor Theory.

Since the body functions with aqueous media and pharmaceuticals frequently are dispensed in aqueous solution, the Brønsted Theory is convenient for use in pharmacy. A molecule or ion which can provide a proton (proton donor) is an acid; one which can accept a proton (proton acceptor) is a base. On accepting a proton, a base becomes an acid; on losing its proton, the acid becomes a base. An acid and its base are related by the presence or absence of a proton, and are known as a "conjugate pair." Neutralization is the transfer of a proton from the acid of one conjugate pair to the base of another conjugate pair. Some conjugate pairs of pharmaceutical interest are given in Table 18. It is evident that acids and bases may be cations, neutral molecules or anions. Some structures may be members of two different conjugate pairs, as an acid in one and as a base in the other.

A strong acid is an acid which loses its proton easily, a weak acid holds its proton tenaciously. The conjugate base of a strong acid is a weak base while that of a weak acid is a strong base. In neutralization the proton goes to the strongest of the bases present. The percent ionization and the ionization constant are measures of the strength of a given acid.

Acids and bases are used in pharmacy for analytical procedures, as buffer systems, and to dissolve insoluble medicinals. To accomplish the latter the insoluble compound must have a functional group capable of acting as a strong base or as an acid. Lidocaine Hydrochloride Injection USP and Niacin Injection USP are examples. The former is prepared by reacting lidocaine with hydrochloric acid; the diethylamino group is a stronger base than either the water molecule or the chloride ion. Lidocaine goes into solution as a cation. Niacin Injection is prepared by reacting niacin with either sodium carbonate or sodium hydroxide; the carboxyl group loses its proton to the carbonate or hydroxyl ion and the niacin goes into solution as an anion.

In neutralization, as above, the pharmacist must be cognizant of two requirements which are not important in ordinary chemical neutralizations. The counterion being introduced, chloride ion and sodium ion, respectively, in the above examples, must be compatible physiologically with the body fluids. Also, since strong acids or bases are being used, there

can be no excess acid or base because of the corrosive nature of these reagents.

Acids and bases are also necessary for the preparation of effervescent mixtures, a medicinal dosage form sometimes used to render a medicinal more palatable for oral administration. Sodium bicarbonate is used as the carbon dioxide source. Solid acids, eg, citric acid, tartaric acid or sodium dihydrogen phosphate are used, frequently in combination. Reaction rate is very important in these formulations. Sodium bicarbonate must have the correct particle size; if too fine the reaction is too violent, if too coarse the reaction is too slow. To lower the activity of the acid, a normal salt of the acid is included in the mixture as a diluent.

Some acids and bases listed in the compendia at present are: Calcium Hydroxide, Potassium Bicarbonate, Potassium Hydroxide, Sodium Bicarbonate, Sodium Carbonate, Sodium Hydroxide, Ammonia Solution, Acetic Acid, Hydrochloric Acid and Diluted Hydrochloric Acid, Nitric Acid, Sulfuric Acid, Phosphoric Acid and Diluted Phosphoric Acid.

Stability and storage problems of these compounds must be considered. All strong bases are subject to reaction with carbon dioxide if proper closures are not maintained. Volatile compounds, eg, ammonia and hydrogen chloride, must be sealed tightly at all times, as must hygroscopic compounds such as sodium hydroxide.

Buffers

Buffers are used to maintain the pH of a medicinal at an optimal value. A buffer is a solution of a weak acid and its conjugate base, the base being provided by one of its soluble salts. Refer to Chapter 17 for an extensive discussion of pH and buffers.

Table 18—Conjugate Acid-Base Pairs

Acid	Base	Acid	Base
H_2O	OH^-	H_2SO_4	HSO_4^-
H_3O^+	H_2O	HSO_4^-	SO_4^{2-}
NH_4^+	NH_3	H_3PO_4	$H_2PO_4^-$
RNH_3^+	RNH_2	$H_2PO_4^-$	HPO_4^{2-}
HCl	Cl^-	$[Al(H_2O)_6]^{3+}$	$[Al(H_2O)_5(OH)]^{2+}$
H_2CO_3	HCO_3^-	$[Al(H_2O)_5(OH)]^{2+}$	$[Al(H_2O)_4(OH)_2]^+$
HCO_3^-	CO_3^{2-}	$H_3BO_3 \cdot H_2O$	$[B(OH)_4]^-$

Physiologic Control of pH

Brønsted acids and bases have been used to maintain and adjust the pH of body fluids for many years. By far the greatest interest has been in development of gastric antacids. However, an adequate number of suitable reagents are available for systemic pH adjustments.

Gastric Antacids

The present official magnesium antacids include Magnesium Hydroxide, Milk of Magnesia, Magnesia Tablets, Magne-

sia and Alumina Oral Suspension (and Tablets), Magnesium Carbonate, Magnesium Carbonate and Sodium Bicarbonate for Oral Suspension, Magnesium Oxide, Magnesium Phosphate and Magnesium Trisilicate. The official aluminum antacids include Aluminum Hydroxide Gel, Dried Aluminum Hydroxide Gel (and Capsules and Tablets), Aluminum Phosphate Gel, Dihydroxyaluminum Aminoacetate (and Magma, and Capsules and Tablets), Dihydroxyaluminum Sodium Carbonate (and Tablets), Alumina, Magnesia and Calcium Carbonate Oral Suspension (and Tablets), Alumina and Magnesium Tri-

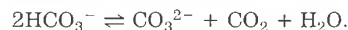
silicate Oral Suspension (and Tablets) and the Alumina and Magnesia preparations already listed. The calcium antacids include: Precipitated Calcium Carbonate (and Tablets), Calcium Carbonate and Magnesia Tablets and Calcium and Magnesium Carbonates Tablets. Magaldrate, an aluminum magnesium hydroxide sulfate, is official, as is its Oral Suspension and Tablets. Miscellaneous official antacids include Milk of Bismuth, Sodium Bicarbonate and Potassium Bicarbonate.

There are other gastric antacid dosage form monographs, some including simethicone, an antilflatulent, and they are Magnesium Oxide Capsules (and Tablets); Basic Aluminum Carbonate Gel; Dried Basic Aluminum Carbonate Gel Capsules (and Tablets); Alumina and Magnesium Carbonate Oral Suspension (and Tablets); Alumina, Magnesium Carbonate and Magnesium Oxide Tablets; Alumina, Magnesia and Simethicone Oral Suspension (and Tablets); Calcium Carbonate Oral Suspension and Magaldrate and Simethicone Oral Suspension (and Tablets). A monograph for Magnesium Hydroxide Paste which contains about 31 g of magnesium hydroxide per 100 g describes a suspension that is an intermediate in the

manufacture of Milk of Magnesia and other suspensions of magnesium hydroxide.

Systemic Alkalizers and Acidifiers

Sodium Bicarbonate USP and Potassium Bicarbonate USP, are used as systemic alkalizers. Because the bicarbonates are unstable to heat, chemical problems arise in the sterilization of bicarbonate solutions,



To depress the forward reaction the solution can be saturated with carbon dioxide. To prevent the loss of the gas, which would result in the permanent formation of the strong carbonate base, the ampules used must be sealed tightly before sterilization, and made of glass sufficiently strong to withstand the gas pressure developed during sterilization. On cooling the reverse reaction becomes dominant.

Ammonium Chloride USP, Monobasic Sodium Phosphate USP and Calcium Chloride USP are employed as systemic acidifiers. Refer to Chapter 53 for a discussion of alkalizers and acidifiers.

Electrolytes and Essential Trace Elements

While the roles and behavior of inorganic elements in these categories are discussed elsewhere in this book (Chapter 54) it is instructive to review the physical and chemical properties which make possible their respective roles. Examination of orbital electron structures, ionic radii, oxidation states, etc., as given in Tables 7 through 17, can yield valuable clues to their behavior.

The transition elements have incompletely filled 18-electron outer shells and each can exist in several different oxidation states. In most cases the shift between two electron states is relatively easy, eg



As a result the transition elements can act as electron *sinks* and are active in those systems involved in oxidation or reduction reactions.

On the other hand an element such as zinc achieves a completely filled outer 18-electron shell on becoming zinc ion. In the 2+ oxidation state this shell becomes stable. Unlike the tightly held spherical 8-electron shell the 18-electron shell is "mushy" and deformed or polarized easily by external fields. In turn, it can cause polarization of other moieties. This ion is not found in redox systems, but rather in systems such as carbonic anhydrase, which aid in the splitting or forming of molecules.

Unlike the incompletely filled shells of the transition elements or the 18-electron shell of the zinc ion, 8-electron shell ions ordinarily are stable and are not deformed easily by external fields. Those 8-electron outer shell ions with a high charge eg, calcium, have intense charge densities in the volume surrounding the ion. This results in strong interactions with the fields of other moieties to form strong permanent associations. However, an 8-electron shell effectively screens the single charge of ions such as sodium. They are, therefore, chemically inert with very weak interactions with other ions. This explains their simple roles in the body fluids as osmotic regulators, etc.

There are a number of monographs for parenteral infusions

intended to supply electrolytes, water and carbohydrates as nutrients. In addition to new monographs in the USP for Ringer's and Dextrose Injection and Lactated Ringer's and Dextrose Injection (with Half-Strength and Modified variations), a series of monographs has been introduced with the designation *Multiple Electrolytes* in each title; these monographs offer choices of cations from Na^+ , K^+ , Ca^{2+} , Mg^{2+} and NH_4^+ , of anions from chloride, acetate, citrate, lactate, gluconate, phosphate and sulfate, plus a choice of carbohydrate nutrient from invert sugar and dextrose. These monographs indicate an awareness of the importance of inorganic cations (including magnesium) and provide a variety of choices to allow treatment of patients on an individualized basis.

In addition to providing official standards for various infusions used as parenteral rehydration solutions or electrolyte replenishers, USP has a generic monograph for Oral Rehydration Salts, an article that is a dry mixture of sodium chloride, sodium bicarbonate (or sodium citrate), potassium chloride and dextrose to be dissolved and used to treat chronic diarrhea.

There has been an increased awareness, in recent years, of the importance of minerals in the diet and of the value of mineral supplements. Generally, gluconates, like other organic salts, are less irritating to the GI tract and, thus, the following metal gluconates are found in the USP: Zinc, Sodium, Copper, Magnesium and Manganese. A monograph in the USP for Selenious Acid Injection, provides a source of selenium as a mineral supplement.

In a new section entitled *Nutritional Supplements*, monographs for Mineral Capsules and Mineral Tablets are found in the USP; the minerals present in these dosage forms are potassium, calcium, magnesium, phosphorous, zinc, iron, manganese, copper, molybdenum, fluorine, chromium, iodine and selenium.

When it is necessary to administer trace elements parenterally, the monograph entitled *Trace Elements*, USP describes a sterile solution that may be used to administer zinc, copper, chromium, manganese, selenium, iodine and molybdenum.

Topical Agents

Oxidizing Germicides

Hydrogen Peroxide, Sodium Hypochlorite and Iodine and/or their various solutions are cited in the USP. The uses of

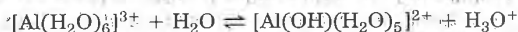
these preparations are discussed in Chapter 76. Hypochlorous acid, the active moiety in sodium hypochlorite solution, owes its germicidal activity to both oxidizing and chlorinating activity.

Precipitating Germicides

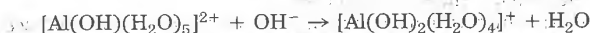
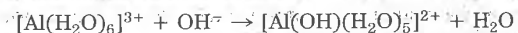
Silver Nitrate, Silver Nitrate Ophthalmic Solution and Toughened Silver Nitrate are listed in USP, as is Ammoniated Mercury (and its ointments). Zinc Acetate, Zinc Chloride, Zinc Sulfate and Zinc Undecylenate also are official. Only two boron compounds are cited: Boric Acid and Sodium Borate. The antimony compounds listed are Antimony Potassium Tartrate USP and Antimony Sodium Tartrate USP. The applications of these compounds are discussed in Chapter 76.

Astringents

Aluminum ion in solution is an excellent local astringent over wide concentration ranges. It also is mildly antiseptic. Aluminum Chloride USP, once was used in this application, however, the high acidity of its solutions caused problems. The acidity results from ionization of the hexaaquo ion



and is about that of acetic acid. Today, the mixture of two compounds (aluminum hydroxychloride, aluminum chlorhydrate, aluminum chlorhydrol), obtained by partial neutralization of aluminum chloride is used,



The reaction is stopped before complete conversion to the dihydroxy hydrate. The resulting solution (or dried product) retains the excellent astringent (and deodorant) properties of the aluminum ion but the pH of the solutions approximates neutrality (5 to 6). Aluminum Subacetate Topical Solution USP, is essentially a solution of the above ions prepared from aluminum sulfate using carbonate ion (CaCO_3) as the base. Aluminum Sulfate and Ammonium Alum and Potassium Alum are found in the USP and also are used as astringents. Alum may be either the potassium or ammonium form. It is shaped into "pencils" to be used as a styptic.

Iron(III) and aluminum ions are very similar. Iron(III) is astringent, and preparations of ferric salts for such use formerly were recognized. While it is efficient in this capacity its staining property is a major disadvantage. Lime water, a saturated solution of fresh calcium hydroxide, is used as a local astringent. Bismuth subnitrate and the other bismuth sub-salts are used as astringents and protectives.

Protectives

In order to possess good adhering properties protectives must be in very finely powdered form. They also must be relatively inert, insoluble compounds. A wide range of compounds are suitable as protectives. They usually are used externally, but some applications involve the gastrointestinal tract. Some are slightly soluble, eg, ZnO, and give some astringent action; others, eg, kaolin, have adsorbent action.

Zinc Oxide, Calamine (and Calamine Lotion and Phenolated Calamine Lotion) and Zinc Stearate (all USP) are used for their protective and slightly astringent properties. Calamine is the calcined native zinc oxide ore. The iron oxide impurity gives calamine a flesh color which is cosmetically more appealing. Zinc stearate, a mixture of fatty acid zinc soaps, has an unctuous feel. White Lotion USP is used for its astringent and protective powers.

Magnesium trisilicate, basic aluminum carbonate and chalk are used as protectives, as are the various insoluble bismuth sub-salts. Talc is used because of its smooth, unctuous feel. Kaolin and bentonite are used as they also have some absorptive properties; titanium dioxide is used as a solar screen.

Inorganic Pigments

The most important innocuous pigments are the iron oxides. They give colors throughout the visible spectrum. Three variables are involved: particle size, oxidation state and degree of hydration.

Miscellaneous Inorganic Applications

Artificial Atmospheres

Five gases are official: nitrogen, oxygen, helium, carbon dioxide and nitrogen(I) oxide (nitrous oxide or laughing gas). Nitrogen is used as a diluent for oxygen and may be used as a protective atmosphere for easily oxidized medicinals.

Helium, because of its low density compared to nitrogen, is used to prepare a gaseous mixture composed of 20% oxygen and helium. This mixture is used to alleviate respiration difficulties. Because of the low solubility of helium in blood the same mixture is used as an atmosphere for those performing under high atmospheric pressures (deep-sea divers, caisson workers). When ordinary air is used, rapid decompression causes bubbles of gaseous nitrogen to form in the blood. The painful, and sometimes fatal, condition known as *bends* results.

Oxygen is used when respiratory problems exist. Ordinarily, it is diluted with nitrogen or helium; 100% oxygen should not be used continuously. In hyperbaric oxygen therapy, oxygen is breathed inside a tank at up to three atmospheres of pressure. While the amount of oxygen carried by the hemoglobin is little affected, the higher oxygen pressure increases the amount of dissolved oxygen in the plasma (Henry's Law).

It is possible to produce oxygen that is medically useful on site, eg in a hospital or nursing home, by the use of oxygen concentrators. There are two types of membranes that are used in the concentrators, viz, permeable plastic membranes

and molecular sieves. The monograph for Oxygen 93 Percent USP sets standards for the oxygen produced by the molecular-sieve process.

Nitrogen(I) oxide usually requires 20 to 25% oxygen during administration. It is used for surgical operations of short duration. Xenon has a general anesthetic action but is too rare for use. Magnesium ion has anesthetic action, however, the anesthetic dose and the toxic dose of magnesium are too close for use as a general anesthetic. Magnesium Sulfate Injection USP is used as an anticonvulsant and central depressant.

Carbon Dioxide Absorbers

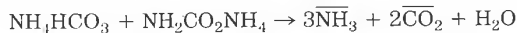
When, as in general anesthesia, a patient rebreathes air, dangerous levels of carbon dioxide build up. To prevent this carbon dioxide absorbers are used. Soda Lime NF, is prepared by fusing calcium hydroxide with sodium hydroxide and/or potassium hydroxide with sufficient diatomaceous earth to yield a hard, nonfriable product. For Barium Hydroxide Lime USP, barium hydroxide is substituted for the alkali hydroxide. The particles formed must be large enough to allow free passage of air, but small enough to give a large surface area for absorption. The particles must be hard to prevent dust formation with handling. Entrainment of absorber dust in the breathed air could cause serious alkali burns in the respiratory tract. A colored indicator is included in the

preparation to indicate when the carbon dioxide capacity is depleted.

Respiratory Stimulants

Carbon dioxide is used as a respiratory stimulant, usually with 5 to 7% oxygen. Since it is the normal respiratory stimulant it is of no value where the respiratory center is already depressed. Carbon dioxide also is used as an inert gas in the headspace over medicinals in sealed containers.

Ammonium Carbonate NF is used as a respiratory stimulant. The name is a misnomer; it is a mixture of ammonium bicarbonate and ammonium carbamate. At room temperature it decomposes to ammonia and carbon dioxide, two respiratory stimulants.



The substance must be stored in tightly sealed containers. Aromatic Ammonia Spirit USP is prepared from ammonium carbonate, strong ammonia solution, various aromatic oils, alcohol and water. Light-resistant containers must be used.

Expectorants

Water vapor is an excellent expectorant, currently considered the best. Ammonium chloride and carbonate, and ammonium and potassium iodides, are used commonly as expectorants. Hydriodic acid syrup was official at one time. If the iodides are used in solution they must be protected by an antioxidant, eg, sodium thiosulfate.

Laxatives, Enemas and Irrigation Solutions

Cathartics are divided into classes according to mode of action. With the exception of sulfur, the inorganic cathartics are saline (osmotic, bulk) laxatives. For laxative action one or both of the ions of the salt must not be absorbed, or be absorbed with difficulty. This sets up an osmotic imbalance in the intestinal tract which the body attempts to correct by secreting water into the intestine. The large volume of fluid in the intestine acts as a mechanical stimulus for peristalsis.

The commonly used salts of the monohydrogen phosphate, monohydrogen tartrate, tartrate and citrate ions are absorbed slowly, but in laxative doses their osmotic action is rapid and effective. They are swept out of the intestinal tract before appreciable absorption can take place. Sulfate ion is relatively nonabsorbable and is used either as the magnesium or sodium salt (Epsom salt and Glauber's salt, respectively). Insoluble laxatives, eg, Milk of Magnesia, must be dissolved in the stomach before they can exert a laxative effect. The soluble magnesium sulfate and citrate of magnesia are used widely as laxatives. However, soluble magnesium salts frequently are not recommended as laxatives because of the danger of absorbing free magnesium ion. Dibasic Sodium Phosphate, Sodium Phosphates Oral Solution, Sodium Citrate and Citric Acid Oral Solution, Potassium Sodium Tartrate, Milk of Magnesia and Sodium Sulfate are cited officially.

PEG 3350 and Electrolytes for Oral Solution USP (Polyethylene-glycol 3350, NaHCO_3 , NaCl , Na_2SO_4 and KCl) is a dry mixture that is to be dissolved at the time of use and then consumed within a prescribed time in order to function as a cathartic and accomplish oral colonic lavage in preparation for a barium enema or a colonoscopic examination.

Sulfur, when ingested, has an irritant laxative effect. The element is thought to be reduced to hydrogen sulfide by reducing agents present in the intestinal fluid. Hydrogen sulfide is a mild intestinal irritant.

Sodium Phosphates Enema USP is a mixture of dibasic and monobasic sodium phosphates or dibasic sodium phosphate and phosphoric acid in water to give a pH of 5.0 to 5.8.

Some solutions are used for irrigating various parts of the body. For example, Citric Acid, Magnesium Oxide and Sodium Carbonate Irrigation USP is defined as a sterile solution, which, after the chemical reactions between citric acid and the other two compounds are completed and the resulting solution is sterilized, is suitable for use as a urinary bladder irrigant; its acidic pH is conducive to dissolving any bladder calculi in patients such as those using an indwelling catheter.

Radiopaques and Imaging Agents

These are compounds capable of interfering with the passage of X-rays. This interference is directly proportional to atomic number. The soft tissues of the body are composed of atoms of very low atomic number, 1, 6, 7, 8, 15 and 16, which do not interfere sufficiently to be discerned. To make the soft tissues, the lumen of organs and body channels show, high atomic number atoms must be used. Because of the toxicity of these elements the choices are limited. Only two, barium, and iodine, atomic numbers 56 and 53, have proved useful. Barium Sulfate USP and Barium Sulfate for Suspension USP are used for studies of the intestinal tract. Iodine is incorporated into organic molecules designed to concentrate in the organ or cavity to be studied, eg, Iopanoic Acid USP, designed for visualization of the gall bladder. Each molecule of the acid has three iodine atoms.

The introduction and development of *Magnetic Resonance Imaging* (MRI) (Chapter 51) as a means of getting images of parts of the body by noninvasive methods has made medical diagnoses simpler and more scientific. The use of gadolinium (element 64) as a cationic diethylenetriamine pentaacetic acid complex with a meglumine anion has facilitated dramatically visualization of intracranial lesions by paramagnetic enhancement.

Structural Repairs

Occasionally, temporary or permanent replacement of support structures is necessary. The materials used should be chemically inert and insoluble in the body fluids. They must be nontoxic. They must have the strength to withstand any physical stress to which they are subjected. Tantalum has been used as a bone replacement for temporary braces of long bones, and to close openings in the skull. Silver has found similar applications. It reacts slightly with body fluids, but since insoluble silver chloride is the principal product this is not a serious threat. Mercury amalgams of gold and silver are used for dental fillings but this venerable use of mercury is being questioned because of possible chronic toxicity. Zinc-eugenol cement also is used for dental fillings.

Plaster of Paris is used for temporary support structures, especially for broken bones. While the formula, $\text{CaSO}_4 \cdot \frac{1}{2}\text{H}_2\text{O}$, suggests a hemihydrate there is experimental evidence indicating the existence of local gypsum ($\text{CaSO}_4 \cdot 2\text{H}_2\text{O}$) nuclei in anhydrous calcium sulfate.

Plaster of Paris also is used for taking dental impressions; since it expands slightly on setting, it fills all spaces completely to give a true surface replica.

Epilogue

Because of space considerations many less important and older inorganic medicinals have been omitted. The chemistry given necessarily is abbreviated. For further details of basic chemistry and omitted uses and products see Discher *et al.*¹ For more thorough discussions of the etiology and treatment involving inorganic substances see the appropriate chapters of this text or of Block *et al.*⁸ For the chemistry and use of many products no longer in general use or entirely abandoned refer to one of the older editions of Rogers, Soine and Wilson.⁹

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CHAPTER 36

Tonicity, Osmoticity, Osmolality and Osmolarity

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Basic Definitions

If a solution is placed in contact with a membrane that is permeable to molecules of the solvent, but not to molecules of the solute, the movement of solvent through the membrane is called osmosis. Such a membrane often is called *semipermeable*. As the several types of membranes of the body vary in their permeability, it is well to note that they are *selectively* permeable. Most normal living cell membranes maintain various solute concentration gradients. A selectively permeable membrane may be defined either as one that does not permit free, unhampered diffusion of all the solutes present, or as one that maintains at least one solute concentration gradient across itself. Osmosis, then, is the diffusion of water through a membrane that maintains at least one solute concentration gradient across itself.

Assume Solution A is on one side of the membrane, and Solution B of the same solute but of a higher concentration is on the other side; the solvent will tend to pass into the more concentrated solution until equilibrium has been established. The pressure required to prevent this movement is the *osmotic pressure*. It is defined as the excess pressure, or pressure greater than that above the pure solvent, which must be applied to Solution B to prevent passage of solvent through a perfect semipermeable membrane from A to B. The concentration of a solution with respect to effect on osmotic pressure is related to the number of particles (unionized molecules, ions, macromolecules, aggregates) of solute(s) in solution and thus is affected by the degree of ionization or aggregation of the solute. See Chapter 16 for review of colligative properties of solutions.

Body fluids, including blood and lacrimal fluid, normally have an osmotic pressure which often is described as corresponding to that of a 0.9% solution of sodium chloride. The body also attempts to keep the osmotic pressure of the contents of the gastrointestinal tract at about this level, but there the normal range is much wider than that of most body fluids. The 0.9% sodium chloride solution is said to be *iso-osmotic* with physiological fluids. The term *isotonic*, meaning equal tone, is in medical usage commonly used interchangeably with isoosmotic. However, terms such as isotonic and tonicity should be used *only* with reference to a physiologic fluid. Isoosmotic actually is a physical term which compares the osmotic pressure (or another colligative property, such as freezing-point depression) of two liquids, neither of which may be a physiological fluid, or which may be a physiological fluid only under certain circumstances. For example, a solution of boric acid that is isoosmotic with both blood and lacrimal fluid is isotonic only with the lacrimal fluid. This solution causes hemolysis of red blood cells because molecules of boric acid pass freely through the erythrocyte membrane regardless of concentration. Thus, isotonicity infers a sense of physiological compatibility where isoosmoticity need

not. As another example, a "chemically defined elemental diet" or enteral nutritional fluid can be iso-osmotic with the contents of the gastrointestinal tract, but would not be considered a physiological fluid, or suitable for parenteral use.

A solution is isotonic with a living cell if there is no net gain or loss of water by the cell, or other change in the cell when it is in contact with that solution. Physiological solutions with an osmotic pressure lower than that of body fluids, or of 0.9% sodium chloride solution, are referred to commonly as being *hypotonic*. Physiological solutions having a greater osmotic pressure are termed *hypertonic*.

Such qualitative terms are of limited value, and it has become necessary to state osmotic properties in quantitative terms. To do so, a term must be used that will represent all the particles which may be present in a given system. The term used is *osmol*. An osmol is defined as the weight, in grams, of a solute, existing in a solution as molecules (and/or ions, macromolecules, aggregates, etc), which is osmotically equivalent to a mole of an ideally behaving nonelectrolyte. Thus, the osmol-weight of a nonelectrolyte, in a dilute solution, generally is equal to its gram-molecular-weight. A milliosmol, abbreviated mOsm, is the weight stated in milligrams.

If one extrapolates this concept of relating an osmol and a mole of a nonelectrolyte as being equivalent, then one also may define an osmol in the following ways. It is the amount of solute which will provide one Avogadro's number (6.02×10^{23}) of particles in solution and it is the amount of solute which, on dissolution in 1 kg of water, will result in an osmotic pressure increase of 17,000 torr at 0° or 19,300 torr at 37°. One mOsmol is one-thousandth of an osmol. For example, 1 mole of anhydrous dextrose is equal to 180 g. One osmol of this nonelectrolyte is also 180 g. One mOsmol would be 180 mg. Thus 180 mg of this solute dissolved in 1 kg of water will produce an increase in osmotic pressure of 19.3 torr at body temperature.

For a solution of an electrolyte such as sodium chloride, one molecule of sodium chloride represents one sodium and one chloride ion. Hence, one mol will represent 2 osmols of sodium chloride theoretically. Accordingly, 1 osmol NaCl = 58.5 g/2 or 29.25 g. This quantity represents the sum total of 6.02×10^{23} ions as the total number of particles. Ideal solutions infer very dilute solutions or infinite dilution. However, as the concentration is increased, other factors enter. With strong electrolytes, interionic attraction causes a decrease in their effect on colligative properties. In addition, and in opposition, for all solutes, including nonelectrolytes, solvation and possibly other factors operate to intensify their colligative effect. Therefore, it is very difficult and often impossible to predict accurately the osmoticity of a solution. It may be possible to do so for a dilute solution of a single, pure and well-characterized solute, but not for most parenteral and enteral medicinal and/or nutritional fluids; experimental determination likely is required.

Therapeutic Considerations

It generally is accepted that osmotic effects have a major place in the maintenance of homeostasis (the state of equilibrium in the living body with respect to various functions and to the chemical composition of the fluids and tissues, eg, temperature, heart rate, blood pressure, water content or blood sugar). To a great extent these effects occur within or between cells and tissues where they cannot be measured. One of the most troublesome problems in clinical medicine is the maintenance of adequate body fluids and proper balance between extracellular and intracellular fluid volumes in seriously ill patients. It should be kept in mind, however, that fluid and electrolyte abnormalities are not diseases, but are the manifestations of disease.

The physiological mechanisms which control water intake and output appear to respond primarily to serum osmoticity. Renal regulation of output is influenced by variation in rate of release of pituitary antidiuretic hormone (ADH) and other factors in response to changes in serum osmoticity. Osmotic changes also serve as a stimulus to moderate thirst. This mechanism is sufficiently sensitive to limit variations in osmoticity in the normal individual to less than about 1%. Body fluid continually oscillates within this narrow range. An increase of plasma osmoticity of 1% will stimulate ADH release, result in reduction of urine flow and, at the same time, stimulate thirst that results in increased water intake. Both the increased renal reabsorption of water (without solute) stimulated by circulating ADH and the increased water intake tend to lower serum osmoticity.

The transfer of water through the cell membrane occurs so rapidly that any lack of osmotic equilibrium between the two fluid compartments in any given tissue usually is corrected within a few seconds and, at most, within a minute or so. However, this rapid transfer of water does not mean that complete equilibration occurs between the extracellular and intracellular compartments throughout the entire body within this same short period of time. The reason is that fluid usually enters the body through the gut and then must be transported by the circulatory system to all tissues before complete equilibration can occur. In the normal person it may require 30 to 60 min to achieve reasonably good equilibration throughout the body after drinking water. Osmoticity is the property that largely determines the physiologic acceptability of a variety of solutions used for therapeutic and nutritional purposes.

Pharmaceutical and therapeutic consideration of osmotic effects has been, to a great extent, directed toward the side effects of ophthalmic and parenteral medicinals due to abnormal osmoticity, and to either formulating to avoid the side effects or finding methods of administration to minimize them. More recently this consideration has been extended to total (central) parenteral nutrition, to enteral hyperalimentation ("tube" feeding) and to concentrated-fluid infant formulas.¹ Also, in recent years, the importance of osmometry of serum and urine in the diagnosis of many pathological conditions has been recognized.

There are a number of examples of the direct therapeutic effect of osmotic action, such as the intravenous use of mannitol as a diuretic which is filtered at the glomeruli and thus increases the osmotic pressure of tubular urine. Water must then be reabsorbed against a higher osmotic gradient than otherwise, so reabsorption is slower and diuresis is observed. The same fundamental principle applies to the intravenous administration of 30% urea used to affect intracranial pressure in the control of cerebral edema. Peritoneal dialysis fluids tend to be somewhat hyperosmotic to withdraw water and nitrogenous metabolites. Two to five percent sodium chloride solutions or dispersions in an oleaginous base (Muro, *Bausch & Lomb*) and a 40% glucose ointment are used topically for corneal edema. Ophthalmic glycerin employed for its osmotic effect to clear edematous cornea to facilitate an ophthalmoscopic or gonioscopic examination. Glycerin solutions in 50% concentration [Osmoglyn (*Alcon*)] and isosorbide solution [Ismotec (*Alcon*)]

are oral osmotic agents for reducing intraocular pressure. The osmotic principle also applies to plasma extenders such as polyvinylpyrrolidone and to saline laxatives such as magnesium sulfate, magnesium citrate solution, magnesium hydroxide (via gastric neutralization), sodium sulfate, sodium phosphate and sodium biphosphate oral solution and enema (*Fleet*).

An interesting osmotic laxative which is a nonelectrolyte is a lactulose solution. Lactulose is a nonabsorbable disaccharide which is colon-specific, wherein colonic bacteria degrade some of the disaccharide to lactic and other simple organic acids. These, *in toto*, lead to an osmotic effect and laxation. An extension of this therapy is illustrated by Cephulac (*Marion Merrell Dow*) solution, which uses the acidification of the colon via lactulose degradation to serve as a trap for ammonia migrating from the blood to the colon. The conversion of ammonia of blood to the ammonium ion in the colon ultimately is coupled with the osmotic effect and laxation, thus expelling undesirable levels of blood ammonia. This product is employed to prevent and treat frontal systemic encephalopathy.

Osmotic laxation is observed with the oral or rectal use of glycerin and sorbitol. Epsom salt has been used in baths and compresses to reduce edema associated with sprains. Another approach is the indirect application of the osmotic effect in therapy via osmotic pump drug delivery systems.²

Osmolality and Osmolarity

It is necessary to use several additional terms to define expressions of concentration in reflecting the osmoticity of solutions. The terms include osmolality, the expression of osmolal concentration and osmolarity, the expression of osmolar concentration.

Osmolality—A solution has an osmolal concentration of one when it contains 1 osmol of solute/kg of water. A solution has an osmolality of n when it contains n osmoles/kg of water. Osmolal solutions, like their counterpart molal solutions, reflect a weight-to-weight relationship between the solute and the solvent. Since an osmol of any nonelectrolyte is equivalent to 1 mol of that compound, then a 1 osmolal solution is synonymous to a 1 molal solution for a typical nonelectrolyte.

With a typical electrolyte like sodium chloride, 1 osmol is approximately 0.5 mol of sodium chloride. Thus, it follows that a 1 osmolal solution of sodium chloride essentially is equivalent to a 0.5 molal solution. Recall that a 1 osmolal solution of dextrose or sodium chloride each will contain the same particle concentration. In the dextrose solution there will be 6.02×10^{23} molecules/kg of water and in the sodium chloride solution one will have 6.02×10^{23} total ions/kg of water, one-half of which are Na^+ ions and the other half Cl^- ions.

As in molal solutions, osmolal solutions usually are employed where quantitative precision is required, as in the measurement of physical and chemical properties of solutions (ie, colligative properties). The advantage of the w/w relationship is that the concentration of the system is not influenced by temperature.

Osmolarity—The relationship observed between molality and osmolality is shared similarly between molarity and osmolarity. A solution has an osmolar concentration of 1 when it contains 1 osmol of solute/L of solution. Likewise, a solution has an osmolarity of n when it contains n osmoles/L of solution. Osmolar solutions, unlike osmolal solution, reflect a weight in volume relationship between the solute and final solution. A 1 molar and 1 osmolar solution would be identical for nonelectrolytes. For sodium chloride a 1 osmolar solution would contain 1 osmol of sodium chloride per liter which approximates a 0.5 molar solution. The advantage of employing osmolar concentrations over osmolal concentrations is the ability to relate a specific number of osmoles or milliosmoles to a volume, such as a liter or mL. Thus, the osmolar concept is simpler and more practical. Volumes of

solution, rather than weights of solution, are more practical in the delivery of liquid dosage forms.

Many health professionals do not have a clear understanding of the difference between osmolality and osmolality. In fact, the terms have been used interchangeably. A 1 osmolar solution of a solute always will be more concentrated than a 1 osmolal solution. With dilute solutions the difference may be acceptably small. For example, a 0.9% *w/v* solution of sodium chloride in water contains 9 g of sodium chloride/L of solution, equivalent to 0.308 osmolar; or 9 g of sodium chloride/996.5 g of water, equivalent to 0.309 osmolal, less than a 1% error. For concentrated solutions, the % difference between osmolality and osmolality is much greater and may be highly significant; 3.5% for 5% *w/v* dextrose solution and 25% for 25% *w/v* dextrose solution. One should be alerted to the sizable errors which may occur with concentrated solutions or fluids, such as those employed in total parenteral nutrition, enteral hyperalimentation and oral nutritional fluids for infants.

Reference has been made to the terms hypertonic and hypotonic. Analogous terms are hyperosmotic and hypoosmotic. Assuming normal serum osmolality to be 285 mOsmol/kg, as serum osmolality increases due to water deficit, the following signs and symptoms usually are found to accumulate progressively at approximately these values: 294 to 298—thirst (if the patient is alert and communicative); 299 to 313—dry mucous membranes; 314 to 329—weakness, doughy skin; above 330—disorientation, postural hypotension, severe weakness, fainting, CNS changes, stupor and coma. As serum osmolality decreases due to water excess the following may occur: 275 to 261—headache; 262 to 251—drowsiness, weakness; 250 to 233—disorientation, cramps; below 233—seizures, stupor and coma.

As indicated previously, the mechanisms of the body actively combat such major changes by limiting the variation in osmolality for normal individuals to less than about 1% (approximately in the range 282 to 288 mOsmol/kg, based on the above assumption).

The value given for normal serum osmolality above was described as an assumption because of the variety of values found in the literature. Serum osmolality often is stated loosely to be about 300 mOsmol/L. Various references report 280 to 295 mOsmol/L, 275 to 300 mOsmol/L, 290 mOsmol/L, 306 mOsmol/L and 275 to 295 mOsmol/kg.

Reference has been made to confusion in the use of the terms osmolality and osmolality, a distinction of special importance for nutritional fluids. Awareness of high concentrations of infant formula should give warning as to possible risks. Unfortunately, the osmoticity of infant formulas, tube feedings and total parenteral nutrition solutions has not been described adequately either in textbooks or in the literature,³ and the labels of many commercial nutritional fluids do not, in any way, state their osmoticity. Only recently have enteral fluids been characterized in terms of osmoticity. Some product lines now are accenting isoosmotic enteral nutritional supplements. Often, when the term osmolality is used, one cannot discern whether this simply is incorrect terminology, or if osmolality actually has been calculated from osmolality.

Another current practice which can cause confusion, is the use of the terms *normal* and/or *physiological* for isotonic sodium chloride solution (0.9%). The solution surely is isoosmotic. However, as to being physiological, the concentration of ions are each of 154 mEq/L while serum contains about 140 mEq of sodium and about 103 mEq of chloride.

The range of mOsmol values found for serum raises the question as to what really is meant by the terms hypotonic and hypertonic for medicinal and nutritional fluids. One can find the statement that fluids with an osmolality of 50 mOsmol or more above normal are hypertonic and, if 50 mOsmol or more below normal, are hypotonic. One also can find the statement that peripheral infusions should not have an osmolality exceeding 700 to 800 mOsmol/L.⁴ Examples of osmol concentrations of solutions used in peripheral infusions are: (D5W) 5% dextrose solution—252 mOsmol/L; (D10W) 10%

dextrose solution—505 mOsmol/L; Lactated Ringer's 5% Dextrose—525 mOsmol/L. When a fluid is hypertonic, undesirable effects often can be decreased by using relatively slow rates of infusion, and/or relatively short periods of infusion. 25% dextrose solution (D25W)—4.25% Amino Acids is a representative example of a highly osmotic hyperalimentation solution. It has been stated that when osmolal loading is needed, a maximum safe tolerance for a normally hydrated subject would be an approximate increase of 25 mOsmol/kg of water over 4 hours.³

Computation of Osmolality

Several methods are used to obtain numerical values of osmolality. The osmolar concentration, sometimes referred to as the "theoretical osmolality," is calculated from the *w/v* concentration using the following equation:

$$\frac{\text{g}}{\text{L}} \times \frac{\text{mols}}{\text{g}} \times \frac{\text{osmol}}{\text{mol}} \times \frac{1000 \text{ mOsmol}}{\text{osmol}} = \frac{\text{mOsmol}}{\text{L}} \quad (1)$$

The number of osmols/mol is equal to 1 for nonelectrolytes and is equal to the number of ions per molecule for strong electrolytes.

This calculation, omits consideration of factors such as solvation and interionic forces. By this method of calculation 0.9% sodium chloride has an osmolar concentration of 308 mOsmol/L and a concentration of 154 mOsmol/L in either sodium or chloride ion.

Two other methods compute osmolality from values of osmolality. The determination of osmolality will be discussed later. One method has a strong theoretical basis of physical-chemical principles⁵ using values of the partial molal volume(s) of the solute(s). A 0.9% sodium chloride solution, found experimentally to have an osmolality of 286 mOsmol/kg, was calculated to have an osmolality of 280 mOsmol/L, rather different from the value of 308 mOsmol/L calculated as above. The method, using partial molal volumes, is relatively rigorous, but many systems appear to be too complex and/or too poorly defined to be dealt with by this method.

The other method is based on calculating the weight of water from the solution density and concentration

$$\frac{\text{g water}}{\text{mL solution}} = \frac{\text{g solution}}{\text{mL solution}} - \frac{\text{g solute}}{\text{mL solution}}$$

then

$$\text{osmolality} \left(\frac{\text{mOsmol}}{\text{L solution}} \right) = \text{osmolality} \left(\frac{\text{mOsmol}}{1000 \text{ g water}} \right) \times \frac{\text{g water}}{\text{mL solution}}$$

The experimental value for the osmolality of 0.9% sodium chloride solution was 292.7 mOsmol/kg; the value computed for osmolality was 291.4 mOsmol/L. This method uses easily obtained values of density of the solution and of its solute content and can be used with all systems. For example, the osmolality of a nutritional product was determined by the freezing-point depression method to be 625 mOsmol/kg;⁷ its osmolality was calculated as $625 \times 0.839 = 524 \text{ mOsmol/L}$.

Monographs in the USP for solutions which provide intravenous replenishment of fluid, nutrient(s) or electrolyte(s), and for osmotic diuretics such as Mannitol Injection, require the osmolal concentration be stated on the label in osmols/L, except that where the contents are less than 100 mL, or where the label states the article is not for direct injection but is to be diluted before use, the label alternatively may state the total osmolal concentration in mOsmol/mL.

An example of the use of the first method described above is the computation of the approximate osmolal concentration ("theoretical osmolality") of a Lactated Ringer's 5% Dextrose Solution (Abbott), which is labeled to contain, per L, dextrose (hydrous) 50 g, sodium chloride 6 g, potassium chloride 300 mg, calcium chloride 200 mg and sodium lactate

3.1 g. Also stated is that the total osmolar concentration of the solution is approximately 524 mOsmol per L, in part contributed by 130 mEq of Na^+ , 109 mEq of Cl^- , 4 mEq of K^+ , 3 mEq of Ca^{2+} and 28 mEq of lactate ion.

The derivation of the osmolar concentrations from the stated composition of the solution may be verified by calculations using Eq 1.

Dextrose

$$\frac{50 \text{ g}}{\text{L}} \times \frac{1 \text{ mol}}{198 \text{ g}} \times \frac{1 \text{ osmol}}{\text{mol}} \times \frac{1000 \text{ mOsmol}}{\text{Osmol}} = 252 \text{ mOsmol/L}$$

Sodium Chloride

$$\begin{aligned} \frac{6 \text{ g}}{\text{L}} \times \frac{1 \text{ mol}}{58.4 \text{ g}} \times \frac{2 \text{ osmol}}{\text{mol}} \times \frac{1000 \text{ mOsmol}}{\text{osmol}} \\ = 205 \frac{\text{mOsmol}}{\text{L}} \left\{ \begin{array}{l} (102.7 \text{ mOsmol Na}^+) \\ (102.7 \text{ mOsmol Cl}^-) \end{array} \right\} \end{aligned}$$

Potassium Chloride

$$\begin{aligned} \frac{0.3 \text{ g}}{\text{L}} \times \frac{1 \text{ mol}}{74.6 \text{ g}} \times \frac{2 \text{ osmol}}{\text{mol}} \times \frac{1000 \text{ mOsmol}}{\text{osmol}} \\ = \frac{8.04 \text{ mOsmol}}{\text{L}} \left\{ \begin{array}{l} (4.02 \text{ mOsmol K}^+) \\ (4.02 \text{ mOsmol Cl}^-) \end{array} \right\} \end{aligned}$$

Calcium Chloride

$$\begin{aligned} \frac{0.2 \text{ g}}{\text{L}} \times \frac{1 \text{ mol}}{111 \text{ g}} \times \frac{3 \text{ osmol}}{\text{mol}} \times \frac{1000 \text{ mOsmol}}{\text{osmol}} \\ = \frac{5.41 \text{ mOsmol}}{\text{L}} \left\{ \begin{array}{l} (1.80 \text{ mOsmol Ca}^{2+}) \\ (3.61 \text{ mOsmol Cl}^-) \end{array} \right\} \end{aligned}$$

Sodium Lactate

$$\begin{aligned} \frac{3.1 \text{ g}}{\text{L}} \times \frac{1 \text{ mol}}{112 \text{ g}} \times \frac{2 \text{ osmol}}{\text{mol}} \times \frac{1000 \text{ mOsmol}}{\text{osmol}} \\ = \frac{55.4 \text{ mOsmol}}{\text{L}} \left\{ \begin{array}{l} (27.7 \text{ mOsmol Na}^+) \\ (27.7 \text{ mOsmol lactate}) \end{array} \right\} \end{aligned}$$

The total osmolar concentration of the five solutes in the solution is 526, in good agreement with the labeled total osmolar concentration of approximately 524 mOsmol/L.

The mOsmol of sodium in 1 L of the solution is the sum of the mOsmol of the ion from sodium chloride and sodium lactate, ie, $102 + 27.6 = 129.6$ mOsmol. Chloride ions come from the sodium chloride, potassium chloride and calcium chloride, the total osmolar concentration being $102 + 4.02 + 3.61 = 109.6$ mOsmol. The mOsmol values of potassium, calcium and lactate are calculated to be 4.02, 1.80 and 27.6, respectively.

The osmolality of a mixture of complex composition, such as an enteral hyperalimentation fluid, cannot be calculated with any acceptable degree of certainty and, therefore, the *osmolality* of such preparations should be determined experimentally.

Undesirable Effects of Abnormal Osmoticity

Ophthalmic Medication—It is generally accepted that ophthalmic preparations intended for instillation into the cul-de-sac of the eye should, if possible, be approximately isotonic to avoid irritation (see Chapter 89). It also has been stated that the abnormal tonicity of contact lens solutions can cause the lens to adhere to the eye and/or cause burning or dryness and photophobia.

Parenteral Medication—Osmoticity is of great importance in parenteral injections, its effects depending on the degree of deviation from tonicity, the concentration, the location of the injection, the volume injected, the speed of the injection, the rapidity of dilution and diffusion, etc. When formulating parenterals, solutions otherwise hypotonic usually have their tonicity adjusted by the addition of dextrose or sodium chloride. Hypertonic parenteral drug solutions cannot be adjusted. Hypotonic and hypertonic solutions usually are administered slowly in small volumes, or into a large vein such as the subclavian, where dilution and distribution occur rapidly. Solutions that differ from the serum in tonicity gen-

erally are stated to cause tissue irritation, pain on injection and electrolyte shifts, the effect depending on the degree of deviation from tonicity.

Excessive infusion of *hypotonic* fluids may cause swelling of red blood cells, hemolysis and water invasion of the body's cells in general. When this is beyond the body's tolerance for water, water intoxication results, with convulsions and edema, such as pulmonary edema.

Excessive infusion of *isotonic* fluids can cause an increase in extracellular fluid volume, which can result in circulatory overload.

Excessive infusion of *hypertonic* fluids leads to a wide variety of complications. For example, the sequence of events when the body is presented with a large intravenous load of hypertonic fluid, rich in dextrose, is as follows: hyperglycemia, glycosuria and intracellular dehydration, osmotic diuresis, loss of water and electrolytes, dehydration and coma.

One cause of osmotic diuresis is the infusion of dextrose at a rate faster than the ability of the patient to metabolize it (as greater than perhaps 400 to 500 mg/kg/hr for an adult on total parenteral nutrition). A heavy load of unmetabolizable dextrose increases the osmoticity of blood and acts as a diuretic; the increased solute load requires more fluid for excretion, 10 to 20 mL of water being required to excrete each gram of dextrose. Solutions, such as those for total parenteral nutrition, should be administered by means of a metered constant-infusion apparatus over a lengthy period (usually more than 24 hours) to avoid sudden hyperosmotic dextrose loads. Such solutions may cause osmotic diuresis; if this occurs, water balance is likely to become negative because of the increased urinary volume, and electrolyte depletion may occur because of excretion of sodium and potassium secondary to the osmotic diuresis. If such diuresis is marked, body weight falls abruptly and signs of dehydration appear. Urine should be monitored for signs of osmotic diuresis, such as glycosuria and increased urine volume.

If the intravenous injection rate of hypertonic solution is too rapid, there may be catastrophic effects on the circulatory and respiratory systems. Blood pressure may fall to dangerous levels, cardiac irregularities or arrest may ensue, respiration may become shallow and irregular and there may be heart failure and pulmonary edema. Probably the precipitating factor is a bolus of concentrated solute suddenly reaching the myocardium and the chemoreceptors in the aortic arch and carotid sinus.³

Abrupt changes in serum osmoticity can lead to cerebral hemorrhage. It has been shown experimentally that rapid infusions of therapeutic doses of hypertonic saline with osmotic loads produce a sudden rise in cerebrospinal fluid (CSF) pressure and venous pressure (VP) followed by a precipitous fall in CSF pressure. This particularly may be conducive to intracranial hemorrhage, as the rapid infusion produces an increase in plasma volume and venous pressure at the same time the CSF pressure is falling. During the CSF pressure rise, there is a drop in hemoglobin and hematocrit, reflecting a marked increase in blood volume.

Hyperosmotic medications, such as sodium bicarbonate (osmolality of 1560 at 1 mEq/mL), which are administered intravenously, should be diluted prior to use and should be injected slowly to allow dilution by the circulating blood. Rapid "push" injections may cause a significant increase in blood osmoticity.⁵

As to other possibilities, there may be crenation of red blood cells and general cellular dehydration. Hypertonic dextrose or saline, etc, infused through a peripheral vein with small blood volume may traumatize the vein and cause thrombophlebitis. Infiltration can cause trauma and necrosis of tissues. Safety, therefore, demands that all intravenous injections, especially highly osmotic solutions, be performed slowly, usually being given preferably over a period not less than that required for a complete circulation of the blood, eg, 1 minute. The exact danger point varies with the

state of the patient, the concentration of the solution, the nature of the solute and the rate of administration.

Hyperosmotic solutions also should not be discontinued suddenly. In dogs, marked increase in levels of intracranial pressure occur when hyperglycemia produced by dextrose infusions is reversed suddenly by stopping the infusion and administering saline. It also has been shown that the CSF pressure in humans rises during treatment of diabetic ketoacidosis in association with a fall in the plasma concentration of dextrose and a fall in plasma osmolality. These observations may be explained by the different rates of decline in dextrose content of the brain and of plasma. The concentration of dextrose in the brain may fall more slowly than in the plasma, causing a shift of fluid from the extracellular fluid space to the intracellular compartment of the CNS, resulting in increased intracranial pressure.

Osmometry and the Clinical Laboratory

Serum and urine osmometry may assist in the diagnosis of certain fluid and electrolyte problems. However, osmometry values have little meaning unless the clinical situation is known. Osmometry is used in renal dialysis as a check on the electrolyte composition of the fluid. In the clinical laboratory, as stated above, the term "osmolality" is used generally, but usually is reported as mOsmol/L. It may seem unnecessary to mention that osmolality depends not only on the number of solute particles, but also on the quantity of water in which they are dissolved. However, it may help one to understand the statement that the normal range of urine osmolality is 50 to 1400 mOsmol/L, and for a random specimen is 500 to 800 mOsmol/L.

Serum Osmoticity

Sodium is by far the principal solute involved in serum osmoticity. Therefore, abnormal serum osmoticity is most likely to be associated with conditions that cause abnormal sodium concentration and/or abnormal water volume.

Thus, hyperosmotic serum is likely to be caused by an increase in serum sodium and/or loss of water. It may be associated with diabetes insipidus, hypercalcemia, diuresis during severe hyperglycemia or with early recovery from renal shutdown. Alcohol ingestion is said to be the most common cause of the hyperosmotic state and of coexisting coma and the hyperosmotic state. An example of hyperosmoticity is a comatose diabetic with a serum osmoticity of 365 mOsmol/L.

In a somewhat analogous fashion, hypoosmotic serum is likely to be due to decrease in serum sodium and/or excess of water. It may be associated with the postoperative state (especially with excessive water replacement therapy), treatment with diuretic drugs and low-salt diet (as with patients with heart failure, cirrhosis, etc), adrenal disease (eg, Addison's disease, adrenogenital syndrome) or SIADH (syndrome of inappropriate ADH secretion). There are many diseases which cause ADH to be released inappropriately (ie, in spite of the fact that serum osmoticity and volume may have been normal initially). These include oat-cell carcinoma of the lung, bronchogenic carcinoma, congestive heart failure, inflammatory pulmonary lesions, porphyria, severe hypothyroidism or cerebral disease (such as tumor, trauma, infection, vascular abnormalities, etc). It also may be found with some patients with excessive diuretic use. Serum and urine osmoticity are measured when SIADH is suspected. In SIADH there is hypoosmoticity of the blood in association with a relative hyperosmoticity of urine. The usual cause is a malfunction of the normal osmotic response of osmoreceptors, an excess of exogenous vasopressin, or a production of a vasopressin-like hormone that is not under the regular control of serum osmoticity. The diagnosis is made by simultaneous measurement of urine and serum osmolality. The serum osmolality will be lower than normal and much lower than the urine osmolality, indicating inappropriate secretion of a concentrated urine in the presence of a dilute serum.

Cardiac, renal and hepatic disease characteristically reduce the sodium/osmolality ratio; this being partially attributed to the effects of increased blood sugar, urea or unknown metabolic products. Patients in shock may develop disproportionately elevated measured osmolality compared to calculated osmolality, which points toward the presence of circulating metabolic products.

There are several approximate methods for estimating serum osmolality from clinical laboratory values for sodium ion, etc. They may be of considerable value in an emergency situation.

1. Serum osmolality may be estimated from

$$\text{mOsmol} = (1.86 \times \text{sodium}) + \frac{\text{blood sugar}}{18} + \frac{\text{BUN}}{2.8} + 5$$

(Na in mEq/L, blood sugar and BUN in mg/100 mL)

2. A quick approximation is

$$\text{mOsmol} = 2 \text{ Na} + \frac{\text{BS}}{20} + \frac{\text{BUN}}{3}$$

3. The osmolality is usually, *but not always*, very close to two times the sodium reading plus 10.

Urine Osmoticity

The two main functions of the kidney are glomerular filtration and tubular reabsorption. Clinically, tubular function is measured best by tests that determine the ability of the tubules to concentrate and dilute the urine. Tests of urinary dilution are not as sensitive in the detection of disease, as are tests of urinary concentration. As concentration of urine occurs in the renal medulla (interstitial fluids, loops of Henle, capillaries of the medulla and collecting tubules), the disease processes that disturb the function or structure of the medulla produce early impairment of the concentrating power of the kidney. Such diseases include acute tubular necrosis, obstructive uropathy, pyelonephritis, papillary necrosis, medullary cysts, hypokalemic and hypercalcemic nephropathy and sickle-cell disease.

Measurement of urine osmolality is an accurate test for the diluting and concentrating ability of the kidneys. In the absence of ADH, the daily urinary output is likely to be 6 to 8 L, or more. The normal urine osmolality depends on the clinical setting; normally, with maximum ADH stimulation, it can be as much as 1200 mOsmol/kg, and with maximum ADH suppression as little as 50 mOsmol/kg. Simultaneous determination of serum and urine osmolality often is valuable in assessing the distal tubular response to circulating ADH. For example, if the patient's serum is hyperosmolal, or in the upper limits of normal ranges, and the patient's urine osmolality measured at the same time is much lower, a decreased responsiveness of the distal tubules to circulating ADH is suggested.

Measurement of urine osmolality during water restriction is an accurate, sensitive test of decreased renal function. For example, under the conditions of one test, normal osmolality would be greater than 800 mOsmol/kg. With severe impairment the value would be less than 400 mOsmol/kg. Knowledge of urine osmolality may point to a problem even though other tests are normal (eg, the Fishberg concentration test, BUN, PSP excretion, creatinine clearance or IV pyelogram). Knowledge of its value may be useful especially in diabetes mellitus, essential hypertension and silent pyelonephritis. The urine/serum osmolality ratio should be calculated and should be equal to or greater than 3.

Osmoticity and Enteral Hyperalimentation

Some aspects of nutrition are discussed briefly here because of the potential major side effects due to abnormal osmoticity of nutritional fluids, and because there exists in-

creasing dialogue on nutrition among pharmacists, dietitians, nurses and physicians. An example is the professional organization, ASPEN (The American Society for Parenteral and Enteral Nutrition), with membership open to all of the above health practitioners. It is desirable, therefore, that pharmacists be able to discuss these matters with these other health professionals in terms of nutrition as well as medicine.

Osmoticity has been of special importance in the intravenous infusion of large volumes of highly concentrated nutritional solutions. Their hyperosmoticity has been a major factor in the requirement that they be injected centrally into a large volume of rapidly moving blood, instead of using peripheral infusion. Use of such solutions and knowledge of their value have led, more recently, to the use of similar formulations administered, not parenterally, but by instillation into some part of the gastrointestinal tract, orally, by nasogastric tube, feeding gastrostomy or by needle-catheter jejunostomy. This method has given excellent total nutrition, for a period of time, to many patients and obviously avoids some of the problems associated with injections.

Enteral nutritional formulas can be modular allowing individual supplementation of protein, carbohydrate or fat. Other formulas are called "defined formula diets" and contain protein, carbohydrate, fat, minerals and vitamins. These nutritionally complete formulations can be monomeric (or oligomeric), based on amino acids, short peptides and simple carbohydrates or polymeric, based on complex protein and carbohydrates.

These diets are necessarily relatively high in osmoticity because their smaller molecules result in more particles per gram than in normal foods. An example is a fluid consisting of: L-amino acids, dextrose oligosaccharides, vitamins (including fat-soluble vitamins), fat as a highly purified safflower oil or soybean oil, electrolytes, trace minerals and water. As it contains fat, that component is not in solution and therefore should have no direct effect on osmoticity. However, the potential for interactions can cause some significant changes in total particle concentration and indirectly affect the osmoticity.⁸

Although easily digested, dextrose contributes more particles than most other carbohydrate sources, such as starch, and is more likely to cause osmotic diarrhea, especially with bolus feeding. Osmoticity is improved (decreased) by replacing dextrose with dextrose oligosaccharides (carbohydrates that yield on hydrolysis 2 to 10 monosaccharides). Flavoring also increases the osmoticity of a product, different flavors causing varying increases.

Commercial diets are packaged as fluids or as powders for reconstitution. Reconstitution is usually with water. These products are categorized on caloric density, (calories/mL), protein content or osmolality (mOsm/kg of H₂O). Parenteral nutritional products, on the other hand, are labeled in terms of osmolarity (mOsm/L).

The enteric route for hyperalimentation frequently is overlooked in many diseases or post-trauma states, if the patient is not readily responsive to traditional oral feedings. Poor appetite, chronic nausea, general apathy and a degree of somnolence or sedation are common concomitants of serious disease. This frequently prevents adequate oral alimentation and results in progressive energy and nutrient deficits. Often, supplementary feedings of a highly nutritious formula are taken poorly or refused entirely. However, the digestive and absorptive capabilities of the gastrointestinal tract are frequently intact and, when challenged with appropriate nutrient fluids, can be used effectively. By using an intact GI tract for proper alimentation, the major problems of sepsis and metabolic derangement which relate to intravenous hyperalimentation largely are obviated, and adequate nutritional support is simplified greatly. Because of this increased safety and ease of administration, the enteric route for hyperalimentation should be used whenever possible.⁹

When ingested in large amounts or concentrated fluids, the osmotic characteristics of certain foods can cause an upset in the normal water balance within the body. For a given weight

of solute the osmolality of the solution is inversely proportional to the size of the particles. Nutritional components can be listed in an approximate order of decreasing osmotic effect per gram, as¹⁰

1. Electrolytes such as sodium chloride
2. Relatively small organic molecules such as dextrose (glucose) and amino acids
3. Dextrose oligosaccharides
4. Starches
5. Proteins
6. Fats (as fats are not water-soluble they have no osmotic effect)

Thus, in foods, high proportions of electrolytes, amino acids and simple sugars have the greatest effect on osmolality, and as a result, on tolerance. The approximate osmolality of a few common foods and beverages is

	mOsmol/kg
Whole milk	295
Tomato juice	595
Orange juice	935
Ice cream	1150

When nutrition of high osmoticity is ingested, large amounts of water will transfer to the stomach and intestines from the fluid surrounding those organs in an attempt to lower the osmoticity. The higher the osmoticity, the larger the amount of water required; a large amount of water in the GI tract can cause distention, cramps, nausea, vomiting, hypermotility and shock. The food may move through the tract too rapidly for the water to be reabsorbed, and result in diarrhea; severe diarrhea can cause dehydration. The hyperosmotic enteral effects have been observed by the administration of undiluted hypertonic oral medication;¹¹ Table I from this work lists average osmolality values of some commercially available drug solutions and suspensions. Thus, there is some analogy to the effect of hyperosmotic intravenous infusions.

Hyperosmotic feedings may result in mucosal damage in the GI tract. Rats given hyperosmotic feeding showed transient decrease in disaccharidase activity, and an increase in alkaline phosphatase activity. They also showed morphologic alterations in the microvilli of the small intestines. After a period of severe gastroenteritis, the bowel may be unusually susceptible to highly osmotic formulas, and their use may increase the frequency of diarrhea. Infant formulas that are hyperosmotic may affect preterm infants adversely during the early neonatal period, and they may produce or predispose neonates to necrotizing enterocolitis when delivered to the jejunum through a nasogastric tube.

The body attempts to keep the osmoticity of the contents of the stomach and intestines at approximately the same level as that of the fluid surrounding them. As a fluid of lower osmoticity requires the transfer of less water to dilute it, it should be tolerated better than one of higher osmoticity. As to tolerance, there is a great variation from one individual to another in sensitivity to the osmoticity of foods. The majority of patients receiving nutritional formulas, either orally or by tube, are able to tolerate feedings with a wide range of osmoticities if administered slowly and if adequate additional fluids are given. However, certain patients are more likely to develop symptoms of intolerance when receiving fluids of high osmoticity. These include debilitated patients, patients with GI disorders; pre- and postoperative patients, gastrostomy- and jejunostomy-fed patients and patients whose GI tracts have not been challenged for an extended period of time. Thus, osmoticity always should be considered in the selection of the formula for each individual patient. With all products, additional fluid intake may be indicated for individuals with certain clinical conditions. Frequent feedings of small volume or a continual instillation (pumped) may be of benefit initially in establishing tolerance to a formula. For other than isosmotic formulas, feedings of reduced concentration (osmolality less than 400 mOsmol/kg) also may be helpful initially if tolerance problems arise in sensitive individuals. Concentration and size of feeding then can be increased gradually to normal as tolerance is established.

A common disturbance of intake encountered in elderly individuals relates to excess solid intake rather than to reduced water intake. For example, an elderly victim of a cerebral vascular accident who is being fed by nasogastric tube may be given a formula whose solute load requires a greatly increased water intake. Thus, tube feeding containing 120 g of protein and 10 g of salt will result in the excretion of more than 1000 mOsmol of solute. This requires the obligatory excretion of a volume of urine between 1200 and 1500 mL when the kidneys are capable of normal concentration ability. As elderly individuals often have significant impairment in renal function, water loss as urine may exceed 2000 to 2500 mL per day. Such an individual would require 3 to 4 L of water/day simply to meet the increased demand created by this high solute intake. Failure of the physician to provide such a patient with the increased water intake needed will result in a progressive water deficit which rapidly may become critical. The importance of knowing the complete composition of the tube feeding formulas used for incapacitated patients cannot be overemphasized.

Osmolality Determination

The need for experimental determination of osmolality has been established. In regard to this there are four properties of solutions that depend only on the number of "particles" in the solution. They are osmotic pressure elevation, boiling point elevation, vapor pressure depression and freezing point depression. These are called colligative properties and if one of them is known, the others can be calculated from its value. Osmotic pressure elevation is the most difficult to measure satisfactorily. The boiling-point elevation may be determined but the values are rather sensitive to changes in barometric pressure. Also, for an aqueous solution the molal boiling-point elevation is considerably less than the freezing-point depression. Thus, it is less accurate than the freezing-point method. Determinations of vapor-pressure lowering are quite easy, rapid and convenient. A vapor-pressure osmometer with a precision of <2 mOsmol/kg is reported by Dickerson, *et al.*¹¹ Another commonly used method is that of freezing-point depression, which can be determined quite readily with a fair degree of accuracy (see *Freezing-Point Depression*, Chapter 16). It should be noted that the data in Appendix A can be converted readily to vapor pressure lowering if desired.

The results of investigations by Lund *et al.*¹² indicate that the freezing point of normal, healthy human blood is -0.52° . Inasmuch as water is the medium in which the various constituents of blood are either suspended or dissolved in this method, it is assumed that any aqueous solution freezing at -0.52° is isotonic with blood. Now it is rare that a simple aqueous solution of the therapeutic agent to be injected parenterally has a freezing point of -0.52° , and to obtain this freezing point it is necessary either to add some other therapeutically inactive solute if the solution is hypotonic (freezing point above -0.52°) or to dilute the solution if it is hypertonic (freezing point below -0.52°). The usual practice is to add either sodium chloride or dextrose to adjust hypotonic parenteral solutions to isotonicity. Certain solutes, including ammonium chloride, boric acid, urea, glycerin and propylene glycol, cause hemolysis even when they are present in a concentration that is isoosmotic and such solutions obviously are not isotonic. See Appendix A.

In a similar manner solutions intended for ophthalmic use may be adjusted to have a freezing point identical to that of lacrimal fluid, namely, -0.52° . Ophthalmic solutions with higher freezing points usually are made isotonic by the addition of boric acid or sodium chloride.

In laboratories where the necessary equipment is available, the method usually followed for adjusting hypotonic solutions is to determine the freezing-point depression produced by the ingredients of a given prescription or formula, and then to add a quantity of a suitable inert solute calculated to lower the freezing point to -0.52° , whether the solution is for paren-

teral injection or ophthalmic application. A final determination of the freezing-point depression may be made to verify the accuracy of the calculation. If the solution is hypertonic, it must be diluted if an isotonic solution is to be prepared, but it must be remembered that some solutions cannot be diluted without impairing their therapeutic activity. For example, solutions to be used for treating varicose veins require a high concentration of the active ingredient (solute) to make the solution effective. Dilution to isotonic concentration is not indicated in such cases.

Freezing-Point Calculations

As explained in the preceding section, freezing-point data often may be employed in solving problems of isotonicity adjustment. Obviously, the utility of such data is limited to those solutions where the solute does not penetrate the membrane of the tissue, eg, red blood cells, with which it is in contact. In such cases, Appendix A, giving the freezing-point depression of solutions of different concentrations of various substances, provides information essential for solving the problem.

For most substances listed in the table the concentration of an isotonic solution, ie, one that has a freezing point of -0.52° , is given. If this is not listed in the table, it may be determined with sufficient accuracy by simple proportion using, as the basis for calculation, that figure which most nearly produces an isotonic solution. Actually the depression of the freezing point of a solution of an electrolyte is not absolutely proportional to the concentration but varies according to dilution; for example, a solution containing 1 g of procaine hydrochloride in 100 mL has a freezing-point depression of 0.12° , whereas a solution containing 3 g of the same salt in 100 mL has a freezing-point depression of 0.33° , not 0.36° ($3 \times 0.12^\circ$). Since the adjustment to isotonicity need not be absolutely exact, approximations may be made. Nevertheless, adjustments to isotonicity should be as exact as practicable.

Effect of Solvents.—Besides water, certain other solvents frequently are employed in nose drops, ear drops and other preparations to be used in various parts of the body. Liquids such as glycerin, propylene glycol or alcohol may compose part of the solvent. In solving isotonicity adjustment problems for such solutions it should be kept in mind that while these solvent components contribute to the freezing-point depression they may or may not have an effect on the "tone" of the tissue to which they are applied, ie, an *isoosmotic* solution may not be *isotonic*. It is apparent that, in such cases, the utility of the methods described above or, for that matter, of any other method of evaluating "tonicity" is questionable.

Tonicity Testing by Observing Erythrocyte Changes

Observation of the behavior of human erythrocytes when suspended in a solution is the ultimate and direct procedure for determining whether the solution is isotonic, hypotonic or hypertonic. If hemolysis or marked change in the appearance of the erythrocytes occurs, the solution is not isotonic with the cells. If the cells retain their normal characteristics, the solution is isotonic.

Hemolysis may occur when the osmotic pressure of the fluid in the erythrocytes is greater than that of the solution in which the cells are suspended, but the specific chemical reactivity of the solute in the solution often is far more important in producing hemolysis than is the osmotic effect. There is no certain evidence that any single mechanism of action causes hemolysis. The process appears to involve such factors as pH, lipid solubility, molecular and ionic sizes of solute particles and possibly inhibition of cholinesterase in cell membranes and denaturing action on plasma membrane protein.

Some investigators test the tonicity of injectable solutions by observing variations of red-blood-cell volume produced by

these solutions. This method appears to be more sensitive to small differences in tonicity than those based on observation of a hemolytic effect. Much useful information concerning the effect of various solutes on erythrocytes has been obtained by this procedure and a summary of many of these data is given in RPS-14, page 1562.

Methods of Adjusting Tonicity

There are several methods for adjusting the tonicity of an aqueous solution provided, of course, that the solution is hypotonic when the drug and additives are dissolved. The most prominent of these methods are the freezing point depression method, the sodium chloride equivalent method and the isotonic solution V-value method. The first two of these methods can be used with a three step problem solving process based on sodium chloride.

1. Identify a reference solution and the associated tonicity parameter.
2. Determine the contribution of the drug(s) and additive(s) to the total tonicity.
3. Determine the amount of sodium chloride needed by subtracting the contribution of the actual solution from the reference solution.

The result of Step 3 also indicates whether the actual solution is hypotonic, isotonic or hypertonic. If the actual solution contributes less to the total tonicity than the reference solution, then the actual solution is hypotonic. If, however, the actual solution contributes a greater amount to tonicity than the reference solution, the actual solution is hypertonic and can be adjusted to isotonicity only by dilution. This may not be possible on therapeutic grounds.

The amount of sodium chloride resulting in Step 3 also can be converted into an amount of other materials, such as dextrose, to render the actual solution isotonic.

Freezing Point Depression Method—The freezing point method makes use of a "D value" (found in Appendix A) which has the units of °C/(x% drug). For example, in Appendix A, dexamethasone sodium phosphate has D values of 0.050°C/(0.5% drug), 0.180°C/(2.0% drug), 0.52°C/(6.75% drug), etc. It is apparent that the D value is nearly proportional to concentration. If a D value is needed for a concentration of drug not listed in Appendix A, a D value can be calculated from the Appendix by direct proportion, using a D value closest to the concentration of drug in the actual solution.

The reference solution for the freezing point depression method is 0.9% sodium chloride which has a freezing point depression of $\Delta T_f = 0.52^\circ\text{C}$.

Using the three steps described above, the dexamethasone sodium phosphate solution in Example 1 can be rendered isotonic as follows:

Example 1

Dexamethasone Sodium Phosphate	0.1%
Purified Water qs	30 mL
Mft Isotonic Solution	

Step 1—Reference solution: 0.9% sodium chloride.
 $\Delta T_f = 0.52^\circ\text{C}$
 $D = 0.050^\circ\text{C}/0.5\%$ dexamethasone sod phosphate)

Step 2—Contribution of drug.

$$\frac{0.050^\circ\text{C}}{0.5\% \text{ drug}} \times 0.1\% \text{ drug} = 0.010^\circ$$

Step 3—Reference solution — actual solution.

$$0.52^\circ - 0.01^\circ = 0.51^\circ$$

Sodium chloride needed.

$$\frac{0.9\% \text{ NaCl}}{0.52^\circ} \times 0.51^\circ = 0.883\% \text{ NaCl}$$

$$\frac{0.883 \text{ g NaCl}}{100 \text{ mL}} \times 30 \text{ mL} = 0.265 \text{ g NaCl}$$

The above solution could be made isotonic with any appropriate material other than sodium chloride by using the D value for that material. For example, to make the solution isotonic with dextrose with a D value, D =

$$0.091^\circ/1\%;$$

$$\frac{1\% \text{ Dextrose}}{0.091^\circ} \times 0.51^\circ = 5.60\% \text{ Dextrose}$$

$$\frac{5.60 \text{ g Dextrose}}{100 \text{ mL}} \times 30 \text{ mL} = 1.68 \text{ g Dextrose}$$

Example 2

Naphazoline HCl (N.HCl)	0.02%
Zinc Sulfate	0.25%
Purified Water qs	30 mL
Mft Isotonic solution	

Step 1—Reference solution: 0.9% sodium chloride.
 $\Delta T_f = 0.52^\circ$
 $D = 0.14^\circ/1\%$ (naphazoline HCl)
 $D = 0.086^\circ/1\%$ (zinc sulfate)

Step 2—Contribution of drugs.

$$\frac{0.14^\circ\text{C}}{1\% \text{ N.HCl}} \times 0.02\% \text{ N.HCl} = 0.003^\circ$$

$$\frac{0.086^\circ\text{C}}{1\% \text{ ZnSO}_4} \times 0.25\% \text{ ZnSO}_4 = 0.022^\circ$$

$$0.003^\circ + 0.022^\circ = 0.025^\circ$$

Step 3—Reference solution — actual solution.

$$0.52^\circ - 0.025^\circ = 0.495^\circ$$

Sodium chloride needed.

$$\frac{0.9\% \text{ NaCl}}{0.52^\circ} \times 0.495^\circ = 0.857\% \text{ NaCl}$$

$$\frac{0.857 \text{ g NaCl}}{100 \text{ mL}} \times 30 \text{ mL} = 0.257 \text{ g NaCl}$$

The above solution could be made isotonic with any appropriate material other than sodium chloride by utilizing the D value for that material. For example, to make the solution isotonic with dextrose with a D value, D = 0.091°C/1%;

$$\frac{1\% \text{ Dextrose}}{0.091^\circ} \times 0.495^\circ = 5.44\% \text{ Dextrose}$$

$$\frac{5.44 \text{ g Dextrose}}{100 \text{ mL}} \times 30 \text{ mL} = 1.63 \text{ g Dextrose}$$

Sodium Chloride Equivalent Method—A sodium chloride equivalent, "E value," is defined as the weight of sodium chloride which will produce the same osmotic effect as 1 g of the drug. For example, in Appendix A, dexamethasone sodium phosphate has an E value of 0.18 g NaCl/g drug at 0.5% drug concentration, 0.17 g NaCl/g drug at 1% drug concentration and a value of 0.16 g NaCl/g drug at 2% drug. This slight variation in the sodium chloride equivalent with concentration is due to changes in interionic attraction at different concentration of drug; the E value is not directly proportional to concentration as was the freezing-point depression.

The reference solution for the sodium chloride equivalent method is 0.9% sodium chloride as it was for the freezing-point depression method.

The dexamethasone sodium phosphate solution in Example 1 can be rendered isotonic using the sodium chloride equivalent method as follows:

Example 1

Dexamethasone Sodium Phosphate	0.1%
Purified Water qs	30 mL
Mft Isotonic Solution	

Step 1—Reference solution: 0.9% sodium chloride.

$$\frac{0.9 \text{ g NaCl}}{100 \text{ mL}} \times 30 \text{ mL} = 0.270 \text{ g NaCl}$$

$$E = 0.18 \text{ g NaCl/g drug}$$

Step 2—Contribution of drug.

$$\frac{0.18 \text{ g NaCl}}{1 \text{ g drug}} \times \frac{0.1 \text{ g drug}}{100 \text{ mL}} \times 30 \text{ mL} = 0.0054 \text{ g NaCl}$$

Step 3—Reference solution — actual solution.

$$0.270 \text{ g NaCl} - 0.0054 \text{ g NaCl} = 0.265 \text{ g NaCl}$$

The above solution can be made isotonic with a material other than sodium chloride, such as dextrose, by using the *E* value of that material. For example, to make the solution isotonic with dextrose, *E* = 0.16 g NaCl/g dextrose, the amount of sodium chloride needed in Step 3, can be converted to dextrose as follows:

$$\frac{1 \text{ g Dextrose}}{0.16 \text{ g NaCl}} \times 0.265 \text{ g NaCl} = 1.66 \text{ g Dextrose}$$

Example 2

Naphazoline HCl (N.HCl)	0.02%
Zinc Sulfate	0.25%
Purified Water qs	30 mL
Mft Isotonic Solution	

Step 1—Reference solution: 0.9% sodium chloride.

$$\frac{0.9 \text{ g NaCl}}{100 \text{ mL}} \times 30 \text{ mL} = 0.270 \text{ g NaCl}$$

$$E = 0.27 \text{ g NaCl/g N.HCl}$$

$$E = 0.15 \text{ g NaCl/g ZnSO}_4$$

Step 2—Contribution of drugs.

$$\frac{0.27 \text{ g NaCl}}{1 \text{ g N.HCl}} \times \frac{0.02 \text{ g N.HCl}}{100 \text{ mL}} \times 30 \text{ mL} = 0.002 \text{ g NaCl}$$

$$\frac{0.15 \text{ g NaCl}}{1 \text{ g ZnSO}_4} \times \frac{0.25 \text{ g ZnSO}_4}{100 \text{ mL}} \times 30 \text{ mL} = 0.011 \text{ g NaCl}$$

$$0.002 \text{ g NaCl} + 0.011 \text{ g NaCl} = 0.013 \text{ g NaCl}$$

Step 3—Reference solution — actual solution.

$$0.270 \text{ g NaCl} - 0.013 \text{ g NaCl} = 0.257 \text{ g NaCl}$$

The above solution can be made isotonic with a material other than sodium chloride, such as dextrose, by using the *E* value of that material. For example, to make the solution isotonic with dextrose, *E* = 0.16 g NaCl/g dextrose, the amount of sodium chloride needed in Step 3 can be converted to dextrose as follows:

$$\frac{1 \text{ g Dextrose}}{0.16 \text{ g NaCl}} \times 0.257 \text{ g NaCl} = 1.61 \text{ g Dextrose}$$

Isotonic Solution V-Values—The “V value” of a drug is the volume of water to be added to a specified weight of drug (0.3 g or 1.0 g depending on the table used) to prepare an isotonic solution. Appendix B gives such values for some commonly used drugs. The reason for providing data for 0.3 g of drug is for convenience in preparing 30 mL (approximately 1 fluidounce) of solution, a commonly prescribed volume. The basic principle underlying the use of V values is to prepare an isotonic solution of the prescribed drug and then dilute this solution to final volume with a suitable isotonic vehicle.

The two solutions in the previous examples can be prepared as follows using the V value method:

Example 1

Dexamethasone Sodium Phosphate	0.1%
Purified Water qs	30 mL
Mft Isotonic Solution	

Step 1—The V value for dexamethasone sodium phosphate can be calculated from the sodium chloride equivalent, *E*, as outlined in the footnote in Appendix B.

$$\frac{100 \text{ mL Soln}}{0.9 \text{ g NaCl}} \times \frac{0.17 \text{ g NaCl}}{1 \text{ g drug}} \times 0.3 \text{ g drug} = 5.67 \text{ mL Soln}$$

for a dilute solution: 5.67 mL Soln $\approx$ 5.67 mL H₂O

$$\therefore V = (5.67 \text{ mL H}_2\text{O}) / (0.3 \text{ g drug})$$

Step 2—Amount of drug needed.

$$\frac{0.1 \text{ g drug}}{100 \text{ mL}} \times 30 \text{ mL} = 0.030 \text{ g drug}$$

Volume of water needed to prepare an isotonic solution.

$$\frac{5.67 \text{ mL H}_2\text{O}}{0.3 \text{ g drug}} \times 0.030 \text{ g drug} = 0.57 \text{ mL H}_2\text{O}$$

Step 3—To prepare the solution, dissolve 0.030 g of drug in 0.57 mL water, and qs to volume with a suitable isotonic vehicle such as 0.9% sodium chloride solution, 5.51% dextrose or an isotonic phosphate buffer.

Example 2

Naphazoline HCl (N.HCl)	0.02%
Zinc Sulfate	0.25%
Purified Water qs	30 mL
Mft Isotonic Solution	

Step 1—The V value for naphazoline HCl can be calculated from the sodium chloride equivalent, *E*, as outlined in the footnote in Appendix B; the V value for zinc sulfate is taken directly from Appendix B.

$$\frac{100 \text{ mL Soln}}{0.9 \text{ g NaCl}} \times \frac{0.27 \text{ g NaCl}}{1 \text{ g N.HCl}} \times 0.3 \text{ g N.HCl} = 9.00 \text{ mL Soln}$$

for a dilute solution: 9.00 mL Soln $\approx$ 9.00 mL H₂O

$$\therefore V = (9.00 \text{ mL H}_2\text{O}) / (0.3 \text{ g N.HCl})$$

$$V = 5.00 \text{ mL H}_2\text{O} / 0.3 \text{ g ZnSO}_4$$

Step 2—Amount of drugs needed.

$$\frac{0.02 \text{ g N.HCl}}{100 \text{ mL}} \times 30 \text{ mL} = 0.006 \text{ g N.HCl}$$

$$\frac{0.25 \text{ g ZnSO}_4}{100 \text{ mL}} \times 30 \text{ mL} = 0.075 \text{ g ZnSO}_4$$

Volume of water needed to prepare an isotonic solution.

$$\frac{9.00 \text{ mL H}_2\text{O}}{0.3 \text{ g N.HCl}} \times 0.006 \text{ g drug} = 0.18 \text{ mL H}_2\text{O}$$

$$\frac{5.00 \text{ mL H}_2\text{O}}{0.3 \text{ g ZnSO}_4} \times 0.075 \text{ g ZnSO}_4 = 1.25 \text{ mL H}_2\text{O}$$

$$0.18 \text{ mL H}_2\text{O} + 1.25 \text{ mL H}_2\text{O} = 1.43 \text{ mL H}_2\text{O}$$

Step 3—To prepare the solution, dissolve 0.006 g of naphazoline HCl and 0.075 g zinc sulfate in 1.43 mL water, and qs to volume with a suitable isotonic vehicle such as 0.9% sodium chloride solution, 5.51% dextrose or an isotonic phosphate buffer.

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Appendix A—Sodium Chloride Equivalents, Freezing-Point Depressions and Hemolytic Effects of Certain Medicinals in Aqueous Solution

	0.5%		1%		2%		3%		5%		Isoosmotic concentration ^a				
	E	D	E	D	E	D	E	D	E	D	%	E	D	H	pH
Acetizoate methylglucamine	0.09		0.08		0.08		0.08		0.08		12.12	0.07		0	7.1
Acetizoate sodium	0.10	0.027	0.10	0.055	0.10	0.109	0.10	0.163	0.10	0.273	9.64	0.09	0.52	0	6.9†
Acetylcysteine	0.20	0.055	0.20	0.113	0.20	0.227	0.20	0.341			4.58	0.20	0.52	100*	2.0
Adrenaline HCl											4.24			68	4.5
Alphaprodine HCl	0.19	0.053	0.19	0.105	0.18	0.212	0.18	0.315			4.98	0.18	0.52	100	5.3
Alum (potassium)			0.18				0.15		0.15		6.35	0.14		24*	3.4
Amantadine HCl	0.31	0.090	0.31	0.180	0.31	0.354					2.95	0.31	0.52	91	5.7
Aminoacetic acid	0.42	0.119	0.41	0.235	0.41	0.470					2.20	0.41	0.52	0*	6.2
Aminohippuric acid	0.13	0.035	0.13	0.075											
Aminophylline				0.098 ^c											
Ammonium carbonate	0.70	0.202	0.70	0.405							1.29	0.70	0.52	97	7.7
Ammonium chloride			1.12								0.8	1.12	0.52	93	5.0
Ammonium lactate	0.33	0.093	0.33	0.185	0.33	0.370					2.76	0.33	0.52	98	5.9
Ammonium nitrate	0.69	0.200	0.69	0.400							1.30	0.69	0.52	91	5.3
Ammonium phosphate, dibasic	0.58	0.165	0.55	0.315							1.76	0.51	0.52	0	7.9
Ammonium sulfate	0.55	0.158	0.55	0.315							1.68	0.54	0.52	0	5.3
Amobarbital sodium			0.25	0.143 ^c			0.25				3.6	0.25	0.52	0	9.3
d-Amphetamine HCl											2.64			98	5.7
Amphetamine phosphate			0.34	0.20			0.27	0.47			3.47	0.26	0.52	0	4.5
Amphetamine sulfate			0.22	0.129 ^c			0.21	0.36			4.23	0.21	0.52	0	5.9
Amprotropine phosphate											5.90			0	4.2
Amylcaïne HCl			0.22				0.19				4.98	0.18		100	5.6
Anileridine HCl	0.19	0.052	0.19	0.104	0.19	0.212	0.18	0.316	0.18	0.509	5.13	0.18	0.52	12	2.6
Antazoline phosphate											6.05			90	4.0
Antimony potassium tartrate			0.18				0.13		0.10						
Antipyrine			0.17	0.10			0.14	0.24	0.14	0.40	6.81	0.13	0.52	100	6.1
Apomorphine HCl			0.14	0.080 ^c											
Arginine glutamate	0.17	0.048	0.17	0.097	0.17	0.195	0.17	0.292	0.17	0.487	5.37	0.17	0.52	0	6.9
Ascorbic acid				0.105 ^c							5.05		0.52 ^b	100*	2.2
Atropine methylbromide			0.14				0.13		0.13		7.03	0.13		0	5.2
Atropine methylnitrate											6.52			0	5.0
Atropine sulfate			0.13	0.075			0.11	0.19	0.11	0.32	8.85	0.10	0.52	0	5.0
Bacitracin			0.05	0.03			0.04	0.07	0.04	0.12					
Barbital sodium			0.30	0.171 ^c			0.29	0.50			3.12	0.29	0.52	0	9.8
Benzalkonium chloride			0.16				0.14		0.13						
Benzotropine mesylate	0.26	0.073	0.21	0.115	0.15	0.170	0.12	0.203	0.09	0.242					
Benzyl alcohol			0.17	0.09 ^c			0.15								
Bethanechol chloride	0.50	0.140	0.39	0.225	0.32	0.368	0.30	0.512			3.05	0.30		0	6.0
Bismuth potassium tartrate			0.09				0.06		0.05						
Bismuth sodium tartrate			0.13				0.12		0.11		8.91	0.10		0	6.1
Boric acid			0.50	0.288 ^c							1.9	0.47	0.52	100	4.6
Brompheniramine maleate	0.10	0.026	0.09	0.050	0.08	0.084									
Bupivacaine HCl	0.17	0.048	0.17	0.096	0.17	0.193	0.17	0.290	0.17	0.484	5.38	0.17	0.52	83	6.8
Butabarbital sodium	0.27	0.078	0.27	0.155	0.27	0.313	0.27	0.470			3.33	0.27	0.52	0	6.8
Butacaine sulfate			0.20	0.12			0.13	0.23	0.10	0.29					
Caffeine and sodium benzoate			0.26	0.15			0.23	0.40			3.92	0.23	0.52	0	7.0
Caffeine and sodium salicylate			0.12	0.12			0.17	0.295	0.16	0.46	5.77	0.16	0.52	0	6.8
Calcium aminosalicilate											4.80			0	6.0
Calcium chloride			0.51	0.298 ^c							1.70	0.53	0.52	0	5.6
Calcium chloride (6 H ₂ O)			0.35	0.20							2.5	0.36	0.52	0	5.7
Calcium chloride, anhydrous			0.68	0.39							1.3	0.69	0.52	0	5.6
Calcium disodium edetate	0.21	0.061	0.21	0.120	0.21	0.240	0.20	0.357			4.50	0.20	0.52	0	6.1
Calcium gluconate			0.16	0.091 ^c			0.14	0.24							
Calcium lactate			0.23	0.13			0.12	0.36			4.5	0.20	0.52	0	6.7
Calcium lactobionate	0.08	0.022	0.08	0.043	0.08	0.085	0.07	0.126	0.07	0.197					
Calcium levulinate			0.27	0.16			0.25	0.43			3.58			0	7.2
Calcium pantothenate											5.50			0	7.4
Camphor			0.12 ^d												
Capreomycin sulfate	0.04	0.011	0.04	0.020	0.04	0.042	0.04	0.063	0.04	0.106					
Carbachol			0.205 ^c								2.82			0	5.9
Carbenicillin sodium	0.20	0.059	0.20	0.118	0.20	0.236	0.20	0.355			4.40	0.20	0.52	0	6.6
Carboxymethylcellulose sodium	0.03	0.007	0.03	0.017	0.145										

Appendix A—Continued

	0.5%		1%		2%		3%		5%		Isoosmotic concentration ^a				
	E	D	E	D	E	D	E	D	E	D	%	E	D	H	pH
Cephaloridine	0.09	0.023	0.07	0.041	0.06	0.074	0.06	0.106	0.05						
Chloramine-T											4.10			100*	9.1
Chloramphenicol				0.06 ^d											
Chloramphenicol sodium succinate	0.14	0.038	0.14	0.078	0.14	0.154	0.13	0.230	0.13	0.382	6.83	0.13	0.52	partial	6.1
Chlordiazepoxide HCl	0.24	0.068	0.22	0.125	0.19	0.220	0.18	0.315	0.17	0.487	5.50	0.16	0.52	66	2.7
Chlorobutanol (hydrated)			0.24	0.14											
Chloroprocaine HCl	0.20	0.054	0.20	0.108	0.18	0.210									
Chloroquine phosphate	0.14	0.039	0.14	0.082	0.14	0.162	0.14	0.242	0.13	0.379	7.15	0.13	0.52	0	4.3
Chloroquine sulfate	0.10	0.028	0.09	0.050	0.08	0.090	0.07	0.127	0.07	0.195					
Chlorpheniramine maleate	0.17	0.048	0.15	0.085	0.14	0.165	0.13	0.220	0.09	0.265					
Chlortetracycline HCl	0.10	0.030	0.10	0.061	0.10	0.121									
Chlortetracycline sulfate			0.13	0.08			0.10	0.17							
Citric acid			0.18	0.10			0.17	0.295	0.16	0.46	5.52	0.16	0.52	100*	1.8
Clindamycin phosphate	0.08	0.022	0.08	0.046	0.08	0.095	0.08	0.144	0.08	0.242	10.73	0.08	0.52	58*	6.8
Cocaine HCl			0.16	0.090 ^c			0.15	0.26	0.14	0.40	6.33	0.14	0.52	47	4.4
Codeine phosphate			0.14	0.080 ^c			0.13	0.23	0.13	0.38	7.29	0.12	0.52	0	4.4
Colistimethate sodium	0.15	0.045	0.15	0.085	0.15	0.170	0.15	0.253	0.14	0.411	6.73	0.13	0.52	0	7.6
Cupric sulfate			0.18	0.100 ^c			0.15		0.14		6.85	0.13		trace*	3.9
Cyclizine HCl	0.20	0.060													
Cyclophosphamide	0.10	0.031	0.10	0.061	0.10	0.125									
Cytarabine	0.11	0.034	0.11	0.066	0.11	0.134	0.11	0.198	0.11	0.317	8.92	0.10	0.52	0	8.0
Deferoxamine mesylate	0.09	0.023	0.09	0.047	0.09	0.093	0.09	0.142	0.09	0.241					
Demecarium bromide	0.14	0.038	0.12	0.069	0.10	0.108	0.08	0.139	0.07	0.192					
Dexamethasone sodium phosphate	0.18	0.050	0.17	0.095	0.16	0.180	0.15	0.260	0.14	0.410	6.75	0.13	0.52	0	8.9
Dextroamphetamine HCl	0.34	0.097	0.34	0.196	0.34	0.392					2.64	0.34	0.52	0	4.7
Dextroamphetamine phosphate			0.25	0.14			0.25	0.44			3.62	0.25	0.52	0	4.7
Dextroamphetamine sulfate	0.24	0.069	0.23	0.134	0.22	0.259	0.22	0.380			4.16	0.22	0.52	0	5.9
Dextrose			0.16	0.091 ^c			0.16	0.28	0.16	0.46	5.51	0.16	0.52	0	5.9
Dextrose (anhydrous)			0.18	0.101 ^c			0.18	0.31			5.05	0.18	0.52	0	6.0
Diatrizoate sodium	0.10	0.025	0.09	0.049	0.09	0.098	0.09	0.149	0.09	0.248	10.55	0.09	0.52	0	7.9
Dibucaine HCl				0.074 ^c											
Dicloxacillin sodium (1 H ₂ O)	0.10	0.030	0.10	0.061	0.10	0.122	0.10	0.182							
Diethanolamine	0.31	0.089	0.31	0.177	0.31	0.358					2.90	0.31	0.52	100	11.3
Dihydrostreptomycin sulfate			0.06	0.03			0.05	0.09	0.05	0.14	19.4	0.05	0.52	0	6.1
Dimethylpyridine maleate	0.13	0.039	0.12	0.070	0.11	0.120									
Dimethyl sulfoxide	0.42	0.122	0.42	0.245	0.42	0.480					2.16	0.42	0.52	100	7.6
Diperodon HCl	0.15	0.045	0.14	0.079	0.13	0.141									
Diphenhydramine HCl				0.161 ^c							5.70			88*	5.5
Diphenidol HCl	0.16	0.045	0.16	0.09	0.16	0.180									
Doxapram HCl	0.12	0.035	0.12	0.070	0.12	0.140	0.12	0.210							
Doxycycline hyclate	0.12	0.035	0.12	0.072	0.12	0.134	0.11	0.186	0.09	0.264					
Dyphylline	0.10	0.025	0.10	0.052	0.09	0.104	0.09	0.155	0.08	0.245					
Echothiophate iodide	0.16	0.045	0.16	0.090	0.16	0.179									
Edetate disodium	0.24	0.070	0.23	0.132	0.22	0.248	0.21	0.360			4.44	0.20	0.52	0	4.7
Edetate trisodium monohydrate	0.29	0.079	0.29	0.158	0.28	0.316	0.27	0.472			3.31	0.27	0.52	0	8.0
Emetine HCl				0.058 ^c				0.17		0.29					
Ephedrine HCl			0.30	0.165 ^c			0.28				3.2	0.28		96	5.9
Ephedrine sulfate			0.23	0.13			0.20	0.35			4.54	0.20	0.52	0	5.7
Epinephrine bitartrate			0.18	0.104			0.16	0.28	0.16	0.462	5.7	0.16	0.52	100*	3.4
Epinephrine hydrochloride			0.29	0.16 ^b			0.26				3.47	0.26			
Ergonovine maleate				0.089 ^c											
Erythromycin lactobionate	0.08	0.020	0.07	0.040	0.07	0.078	0.07	0.115	0.06	0.187					
Ethyl alcohol											1.39			100	6.0
Ethylenediamine				0.253 ^c							2.08			100*	11.4
Ethylmorphine HCl			0.16	0.088 ^c			0.15	0.26	0.15	0.43	6.18	0.15	0.52	38	4.7
Eucatropine HCl				0.11 ^d											
Ferric ammonium citrate (green)											6.83			0	5.2
Floxuridine	0.14	0.040	0.13	0.076	0.13	0.147	0.12	0.213	0.12	0.335	8.47	0.12	0.52	3*	4.5
Fluorescein sodium			0.31	0.181 ^c			0.27	0.47			3.34	0.27	0.52	0	8.7
Fluphenazine 2-HCl	0.14	0.041	0.14	0.082	0.12	0.145	0.09	0.155						0*	5.9
d-Fructose											5.05			0	5.4
Furthrethonium iodide	0.24	0.070	0.24	0.133	0.22	0.250	0.21	0.360			4.44	0.20	0.52	0	5.9
Galactose											4.92				
Gentamicin sulfate	0.05	0.015	0.05	0.030	0.05	0.060	0.05	0.093	0.05	0.153					
D-Glucuronic acid											5.02			48*	1.6
Glycerin				0.203 ^c							2.6			100	5.9
Glycopyrrolate	0.15	0.042	0.15	0.084	0.15	0.166	0.14	0.242	0.13	0.381	7.22	0.12	0.52	92*	4.0
Gold sodium thiomalate	0.10	0.032	0.10	0.061	0.10	0.111	0.09	0.159	0.09	0.250				0	6.3
Hetacillin potassium	0.17	0.048	0.17	0.095	0.17	0.190	0.17	0.284	0.17	0.474	5.50	0.17	0.52		
Hexafluorenum bromide	0.12	0.033	0.11	0.065											
Hexamethonium tartrate	0.16	0.045	0.16	0.089	0.16	0.181	0.16	0.271	0.16	0.456	5.68	0.16	0.52		
Hexamethylene sodium acetaminosalicylate	0.18	0.049	0.18	0.099	0.17	0.199	0.17	0.297	0.16	0.485	5.48	0.16	0.52	0*	4.0

Appendix A—Continued

	0.5%		1%		2%		3%		5%		Isoosmotic concentration ^a				pH
	E	D	E	D	E	D	E	D	E	D	%	E	D	H	
Hexobarbital sodium				0.15 ^c											
Hexylcaine HCl											4.30			100	4.8
Histamine 2HCl	0.40	0.115	0.40	0.233	0.40	0.466					2.24	0.40	0.52	79	3.7
Histamine phosphate				0.149 ^c							4.10			0	4.6
Histidine HCl											3.45			40	3.9
Holocaine HCl			0.20	0.12											
Homatropine hydrobromide			0.17	0.097 ^c			0.16	0.28	0.16	0.46	5.67	0.16	0.52	92	5.0
Homatropine methylbromide			0.19	0.11			0.15	0.26	0.13	0.38					
4-Homosulfanilamide HCl											3.69			0	4.9
Hyaluronidase	0.01	0.004	0.01	0.007	0.01	0.013	0.01	0.020	0.01	0.033					
Hydromorphone HCl											6.39			64	5.6
Hydroxyamphetamine HBr				0.15 ^d							3.71			92	5.0
8-Hydroxyquinoline sulfate											9.75			59	2.5
Hydroxystilbamidine isethionate	0.20	0.060	0.16	0.090	0.12	0.137	0.10	0.170	0.07	0.216					
Hyoscyamine hydrobromide											6.53			68	5.9
Imipramine HCl	0.20	0.058	0.20	0.110	0.13	0.143									
Indigotindisulfonate sodium	0.30	0.085	0.30	0.172											
Intracaine HCl											4.97			85	5.0
Iodophthalein sodium				0.07 ^c							9.58			100	9.4
Isometheptene mucate	0.18	0.048	0.18	0.095	0.18	0.196	0.18	0.302			4.95	0.18	0.52	0	6.2
Isoproterenol sulfate	0.14	0.039	0.14	0.078	0.14	0.156	0.14	0.234	0.14	0.389	6.65	0.14	0.52	trace	4.5
Kanamycin sulfate	0.08	0.021	0.07	0.041	0.07	0.083	0.07	0.125	0.07	0.210					
Lactic acid				0.239 ^c							2.30			100*	2.1
Lactose			0.07	0.040 ^c			0.08		0.09		9.75	0.09		0*	5.8
Levallorphan tartrate	0.13	0.036	0.13	0.073	0.13	0.143	0.12	0.210	0.12	0.329	9.40	0.10	0.52	59*	6.9
Levorphanol tartrate	0.12	0.033	0.12	0.067	0.12	0.136	0.12	0.203							
Lidocaine HCl				0.13 ^c							4.42			85	4.3
Lircomycin HCl	0.16	0.045	0.16	0.090	0.15	0.170	0.14	0.247	0.14	0.400	6.60	0.14	0.52	0	4.5
Lobeline HCl				0.09 ^b											
Lyapolate sodium	0.10	0.025	0.09	0.051	0.09	0.103	0.09	0.157	0.09	0.263	9.96	0.09	0.52	0	6.5†
Magnesium chloride				0.45							2.02	0.45		0	6.3
Magnesium sulfate			0.17	0.094 ^c			0.15	0.26	0.15	0.43	6.3	0.14	0.52	0	6.2
Magnesium sulfate, anhydrous	0.34	0.093	0.32	0.184	0.30	0.345	0.29	0.495			3.18	0.28	0.52	0	7.0
Mannitol				0.098 ^c					5.07					0*	6.2
Maphenide HCl	0.27	0.075	0.27	0.153	0.27	0.303	0.26	0.448			3.55	0.25	0.52		
Menadiol sodium diphosphate											4.36			0	8.2
Menadione sodium bisulfite											5.07			0	5.3
Menthol				0.12 ^d											
Meperidine HCl				0.125 ^c							4.80			98	5.0
Mepivacaine HCl	0.21	0.060	0.21	0.116	0.20	0.230	0.20	0.342			4.60	0.20	0.52	45	4.5
Merbromin				0.08 ^b											
Mercuric cyanide			0.15				0.14		0.13						
Mersalyl				0.06 ^b											
Mesoridazine besylate	0.10	0.024	0.07	0.040	0.05	0.058	0.04	0.071	0.03	0.087					
Metaraminol bitartrate	0.20	0.060	0.20	0.112	0.19	0.210	0.18	0.308	0.17	0.505	5.17	0.17	0.52	59	3.8
Methacholine chloride				0.184 ^c							3.21			0	4.5
Methadone HCl				0.101 ^c							8.59			100*	5.0
Methamphetamine HCl				0.213 ^c							2.75			97	5.9
Methdilazine HCl	0.12	0.035	0.10	0.056	0.08	0.080	0.06	0.093	0.04	0.112					
Methenamine			0.23				0.24				3.68	0.25		100	8.4
Methiodal sodium	0.24	0.068	0.24	0.136	0.24	0.274	0.24	0.410			3.81	0.24	0.52	0	5.9
Methital sodium	0.26	0.074	0.25	0.142	0.24	0.275	0.23	0.407			3.85	0.23	0.52	78	9.8
Methocarbamol	0.10	0.030	0.10	0.060											
Methotrimeprazine HCl	0.12	0.034	0.10	0.060	0.07	0.077	0.06	0.094	0.04	0.125					
Methoxyphenamine HCl	0.26	0.075	0.26	0.150	0.26	0.300	0.26	0.450			3.47	0.26	0.52	96	5.4
p-Methylaminoethanolphenol tartrate	0.18	0.048	0.17	0.095	0.16	0.190	0.16	0.282	0.16	0.453	5.83	0.16	0.52	0	6.2
Methyldopate HCl	0.21	0.063	0.21	0.122	0.21	0.244	0.21	0.365			4.28	0.21	0.52	partial	3.0
Methylergonovine maleate	0.10	0.028	0.10	0.056											
N-Methylglucamine	0.20	0.057	0.20	0.111	0.18	0.214	0.18	0.315	0.18	0.517	5.02	0.18	0.52	4	11.3
Methylphenidate HCl	0.22	0.065	0.22	0.127	0.22	0.258	0.22	0.388			4.07	0.22	0.52	66	4.3
Methylprednisolone Na succinate	0.10	0.025	0.09	0.051	0.09	0.102	0.08	0.143	0.07	0.200					
Minocycline HCl	0.10	0.030	0.10	0.058	0.09	0.107	0.08	0.146							
Monoethanolamine	0.53	0.154	0.53	0.306							1.70	0.53	0.52	100	11.4
Morphine HCl			0.15	0.086 ^c			0.14								
Morphine sulfate			0.14	0.079 ^c			0.11	0.19	0.09	0.26					
Nalorphine HCl	0.24	0.070	0.21	0.121	0.18	0.210	0.17	0.288	0.15	0.434	6.36	0.14	0.52	63	4.1
Naloxone HCl	0.14	0.042	0.14	0.083	0.14	0.158	0.13	0.230	0.13	0.367	8.07	0.11	0.52	35	5.2
Naphazoline HCl			0.27	0.14 ^d			0.24				3.99	0.22		100	5.3
Neosarsphenamine											2.32			17	7.8
Neomycin sulfate			0.11	0.063 ^c			0.09	0.16	0.08	0.232					
Neostigmine bromide			0.22	0.127 ^c			0.19				4.98			0	4.6
Neostigmine methylsulfate			0.20	0.115 ^c			0.18		0.17		5.22	0.17			

Appendix A—Continued

	0.5%		1%		2%		3%		5%		Isoosmotic concentration ^a				
	E	D	E	D	E	D	E	D	E	D	%	E	D	H	pH
Nicotinamide			0.26	0.148 ^c			0.21	0.36			4.49	0.20	0.52	100	7.0
Nicotinic acid			0.25	0.144 ^c											
Nikethamide				0.100 ^c							5.94			100	6.9
Novobiocin sodium	0.12	0.033	0.10	0.057	0.07	0.073									
Oleandomycin phosphate	0.08	0.017	0.08	0.038	0.08	0.084	0.08	0.129	0.08	0.255	10.82	0.08	0.52	0	5.0
Orphenadrine citrate	0.13	0.037	0.13	0.074	0.13	0.144	0.12	0.204	0.10	0.285					
Oxophenarsine HCl											3.67			trace*	2.3
Oxymetazoline HCl	0.22	0.063	0.22	0.124	0.20	0.232	0.19	0.335			4.92	0.18	0.52	86	5.7
Oxyquinoline sulfate	0.24	0.068	0.21	0.113	0.16	0.182	0.14	0.236	0.11	0.315					
d-Pantothenyl alcohol	0.20	0.053	0.18	0.100	0.17	0.193	0.17	0.283	0.16	0.468	5.60	0.16	0.52	92	6.8
Papaverine HCl			0.10	0.061 ^c											
Paraldehyde	0.25	0.071	0.25	0.142	0.25	0.288	0.25	0.430			3.65	0.25	0.52	97	5.3
Pargyline HCl	0.30	0.083	0.29	0.165	0.29	0.327	0.28	0.491			3.18	0.28	0.52	91	3.8
Penicillin G, potassium			0.18	0.102 ^c			0.17	0.29	0.16	0.46	5.48	0.16	0.52	0	6.2
Penicillin G, procaine				0.06 ^d											
Penicillin G, sodium			0.18	0.100 ^c			0.16	0.28	0.16	0.46	5.90			18	5.2
Pentazocine lactate	0.15	0.042	0.15	0.085	0.15	0.169	0.15	0.253	0.15	0.420					
Pentobarbital sodium				0.145 ^c							4.07			0	9.9
Pentolinium tartrate											5.95			55*	3.4
Phenacaine HCl				0.09 ^d											
Pheniramine maleate				0.09 ^d											
Phenobarbital sodium			0.24	0.135 ^c			0.23	0.40			3.95	0.23	0.52	0	9.2
Phenol			0.35	0.20							2.8	0.32	0.52	0*	5.6
Phentolamine mesylate	0.18	0.052	0.17	0.096	0.16	0.173	0.14	0.244	0.13	0.364	8.23	0.11	0.52	83	3.5
Phenylephrine HCl			0.32	0.184 ^c			0.30				3.0	0.30		0	4.5
Phenylephrine tartrate											5.90			58*	5.4
Phenylethyl alcohol	0.25	0.070	0.25	0.141	0.25	0.283									
Phenylpropanolamine HCl			0.38	0.219 ^c							2.6	0.35		95	5.3
Physostigmine salicylate			0.16	0.090 ^c											
Physostigmine sulfate				0.074 ^c											
Pilocarpine HCl			0.24	0.138 ^c			0.22	0.38			4.08	0.22	0.52	89	4.0
Pilocarpine nitrate			0.23	0.132 ^c			0.20	0.35			4.84	0.20	0.52	88	3.9
Piperocaine HCl				0.12 ^d							5.22			65	5.7
Polyethylene glycol 300	0.12	0.034	0.12	0.069	0.12	0.141	0.12	0.216	0.13	0.378	6.73	0.13	0.52	53	3.8
Polyethylene glycol 400	0.08	0.022	0.08	0.047	0.09	0.098	0.09	0.153	0.09	0.272	8.50	0.11	0.52	0	4.4
Polyethylene glycol 1500	0.06	0.015	0.06	0.036	0.07	0.078	0.07	0.120	0.07	0.215	10.00	0.09	0.52	4	4.1
Polyethylene glycol 1540	0.02	0.005	0.02	0.012	0.02	0.028	0.03	0.047	0.03	0.094					
Polyethylene glycol 4000	0.02	0.004	0.02	0.008	0.02	0.020	0.02	0.033	0.02	0.067					
Polymyxin B sulfate			0.09	0.052			0.06	0.10	0.04	0.12					
Polysorbate 80	0.02	0.005	0.02	0.010	0.02	0.020	0.02	0.032	0.02	0.055					
Polyvinyl alcohol (99% hydrol)	0.02	0.004	0.02	0.008	0.02	0.020	0.02	0.035	0.03	0.075					
Polyvinylpyrrolidone	0.01	0.003	0.01	0.006	0.01	0.010	0.01	0.017	0.01	0.035					
Potassium acetate	0.59	0.172	0.59	0.342							1.53	0.59	0.52	0	7.6
Potassium chlorate											1.88			0	6.9
Potassium chloride			0.76	0.439 ^c							1.19	0.76	0.52	0	5.9
Potassium iodide			0.34	0.196 ^c							2.59	0.34	0.52	0	7.0
Potassium nitrate			0.56	0.324 ^c							1.62	0.56		0	5.9
Potassium phosphate			0.46	0.27							2.08	0.43	0.52	0	8.4
Potassium phosphate, monobasic			0.44	0.25							2.18	0.41	0.52	0	4.4
Potassium sulfate			0.44								2.11	0.43		0	6.6
Pralidoxime chloride	0.32	0.092	0.32	0.183	0.32	0.364					2.87	0.32	0.52	0	4.6
Prilocaine HCl	0.22	0.062	0.22	0.125	0.22	0.250	0.22	0.375			4.18	0.22	0.52	45	4.6
Procainamide HCl			0.22	0.13			0.19	0.33	0.17	0.49					
Procaine HCl			0.21	0.122 ^c			0.19	0.33	0.18		5.05	0.18	0.52	91	5.6
Prochlorperazine edisylate	0.08	0.020	0.06	0.033	0.05	0.048	0.03	0.056	0.02	0.065					
Promazine HCl	0.18	0.050	0.13	0.077	0.09	0.102	0.07	0.112	0.05	0.137					
Proparacaine HCl	0.16	0.044	0.15	0.086	0.15	0.169	0.14	0.247	0.13	0.380	7.46	0.12	0.52		
Propiomazine HCl	0.18	0.050	0.15	0.084	0.12	0.133	0.10	0.165	0.08	0.215					
Propoxycaïne HCl											6.40			16	5.3
Propylene glycol											2.00			100	5.5
Pyrithiazine HCl	0.22	0.065	0.17	0.095	0.11	0.123	0.08	0.140	0.06	0.170					
Pyridostigmine bromide	0.22	0.062	0.22	0.125	0.22	0.250	0.22	0.377			4.13	0.22	0.52	0	7.2
Pyridoxine HCl											3.05			31*	3.2
Quinacrine methanesulfonate				0.06 ^c											
Quinine bisulfate			0.09	0.05			0.09	0.16							
Quinine dihydrochloride			0.23	0.130 ^c			0.19	0.33	0.18		5.07	0.18	0.52	trace*	2.5
Quinine hydrochloride			0.14	0.077 ^c			0.11	0.19							
Quinine and urea HCl			0.23	0.13			0.21	0.36			4.5	0.20	0.52	64	2.9
Resorcinol				0.161 ^c							3.30			96	5.0
Rolitetracycline	0.11	0.032	0.11	0.064	0.10	0.113	0.09	0.158	0.07	0.204					
Rose Bengal	0.08	0.020	0.07	0.040	0.07	0.083	0.07	0.124	0.07	0.198	14.9	0.06	0.52		
Rose Bengal B	0.08	0.022	0.08	0.044	0.08	0.087	0.08	0.131	0.08	0.218					
Scopolamine HBr			0.12	0.07			0.12	0.21	0.12	0.35	7.85	0.11	0.52	8	4.8
Scopolamine methylnitrate			0.16				0.14		0.13		6.95	0.13		0	6.0

Appendix A—Continued

	0.5%		1%		2%		3%		5%		Isoosmotic concentration ^a				
	E	D	E	D	E	D	E	D	E	D	%	E	D	H	pH
Secobarbital sodium			0.24	0.14			0.23	0.40			3.9	0.23	0.52	trace	9.8
Silver nitrate			0.33	0.190 ^c							2.74	0.33	0.52	0*	5.0
Silver protein, mild			0.17	0.10			0.17	0.29	0.16	0.46	5.51	0.16	0.52	0	9.0
Silver protein, strong				0.06 ^d											
Sodium acetate			0.46	0.267							2.0	0.45	0.52		
Sodium acetazolamide	0.24	0.068	0.23	0.135	0.23	0.271	0.23	0.406			3.85	0.23	0.52		
Sodium aminosalicylate				0.170 ^c							3.27			0	7.3
Sodium ampicillin	0.16	0.045	0.16	0.090	0.16	0.181	0.16	0.072	0.16	0.451	5.78	0.16	0.52	0	8.5
Sodium ascorbate											3.00			0	6.9
Sodium benzoate			0.40	0.230 ^c							2.25	0.40	0.52	0	7.5
Sodium bicarbonate			0.65	0.375							1.39	0.65	0.52	0	8.3
Sodium biphosphate (H ₂ O)			0.40	0.23							2.45	0.37	0.52	0	4.1
Sodium biphosphate (2 H ₂ O)			0.36								2.77	0.32		0	4.0
Sodium bismuth thioglycollate	0.20	0.055	0.19	0.107	0.18	0.208	0.18	0.303	0.17	0.493	5.29			0	8.3
Sodium bisulfite			0.61	0.35							1.5	0.61	0.52	0*	3.0
Sodium borate			0.42	0.241 ^c							2.6	0.35	0.52	0	9.2
Sodium bromide											1.60			0	6.1
Sodium cacodylate			0.32				0.28				3.3	0.27		0	8.0
Sodium carbonate, monohydrated			0.60	0.346							1.56	0.58	0.52	100	11.1
Sodium cephalothin	0.18	0.050	0.17	0.095	0.16	0.179	0.15	0.259	0.14	0.400	6.80	0.13	0.52	partial	8.5
Sodium chloride			1.00	0.576 ^c			1.00	1.73	1.00	2.88	0.9	1.00	0.52	0	6.7
Sodium citrate			0.31	0.178 ^c			0.30	0.52			3.02	0.30		0	7.8
Sodium colistimethate	0.16	0.045	0.15	0.087	0.14	0.161	0.14	0.235	0.13	0.383	6.85	0.13	0.52	0	8.4
Sodium hypophosphite											1.60			0	7.3
Sodium iodide			0.39	0.222 ^c							2.37	0.38	0.52	0	6.9
Sodium iodohippurate											5.92			0	7.3
Sodium lactate											1.72			0	6.5
Sodium lauryl sulfate	0.10	0.029	0.08	0.046	0.07	0.068	0.05	0.086			5.30			0	8.4
Sodium mercaptomerin											1.38	0.65	0.52	5*	4.5
Sodium metabisulfite			0.67	0.386 ^c							6.00	0.15	0.52	0	5.8
Sodium methicillin	0.18	0.050	0.18	0.099	0.17	0.192	0.16	0.281	0.15	0.445					
Sodium nafcillin	0.14	0.039	0.14	0.078	0.14	0.158	0.13	0.219	0.10	0.285					
Sodium nitrate			0.68								1.36	0.66		0	6.0
Sodium nitrite			0.84	0.480 ^c							1.08	0.83		0*	8.5
Sodium oxacillin	0.18	0.050	0.17	0.095	0.16	0.177	0.15	0.257	0.14	0.408	6.64	0.14	0.52	0	6.0
Sodium phenylbutazone	0.19	0.054	0.18	0.104	0.17	0.202	0.17	0.298	0.17	0.488	5.34	0.17	0.52		
Sodium phosphate			0.29	0.168			0.27	0.47			3.33	0.27	0.52	0	9.2
Sodium phosphate, dibasic (2 H ₂ O)			0.42	0.24							2.23	0.40	0.52	0	9.2
Sodium phosphate, dibasic (12 H ₂ O)			0.22				0.21				4.45	0.20		0	9.2
Sodium propionate			0.61	0.35							1.47	0.61	0.52	0	7.8
Sodium salicylate			0.36	0.210 ^c							2.53	0.36	0.52	0	6.7
Sodium succinate	0.32	0.092	0.32	0.184	0.31	0.361					2.90	0.31	0.52	0	8.5
Sodium sulfate, anhydrous			0.58	0.34							1.61	0.56	0.52	0	6.2
Sodium sulfite, exsiccated			0.65	0.38							1.45			0	9.6
Sodium sulfobromophthalein	0.07	0.019	0.06	0.034	0.05	0.060	0.05	0.084	0.04	0.123					
Sodium tartrate	0.33	0.098	0.33	0.193	0.33	0.385					2.72	0.33	0.52	0	7.3
Sodium thiosulfate			0.31	0.181 ^c							2.98	0.30	0.52	0	7.4
Sodium warfarin	0.18	0.049	0.17	0.095	0.16	0.181	0.15	0.264	0.15	0.430	6.10	0.15	0.52	0	8.1
Sorbitol (½ H ₂ O)											5.48			0	5.9
Sparteine sulfate	0.10	0.030	0.10	0.056	0.10	0.111	0.10	0.167	0.10	0.277	9.46	0.10	0.52	19*	3.5
Spectinomycin HCl	0.16	0.045	0.16	0.092	0.16	0.185	0.16	0.280	0.16	0.460	5.66	0.16	0.52	3	4.4
Streptomycin HCl			0.17	0.10 ^c			0.16	0.16							
Streptomycin sulfate			0.07	0.036 ^c			0.06	0.10	0.06	0.17					
Sucrose			0.08	0.047 ^c			0.09	0.16	0.09	0.26	9.25	0.10	0.52	0	6.4
Sulfacetamide sodium			0.23	0.132 ^c			0.23	0.40			3.85	0.23	0.52	0	8.7
Sulfadiazine sodium			0.24	0.14			0.24	0.38			4.24	0.21	0.52	0	9.5
Sulfamerazine sodium			0.23	0.13			0.21	0.36			4.53	0.20	0.52	0	9.8
Sulfapyridine sodium			0.23	0.13			0.21	0.36			4.55	0.20	0.52	5	10.4
Sulfathiazole sodium			0.22	0.13			0.20	0.35			4.82	0.19	0.52	0	9.9
Tartaric acid				0.143 ^c							3.90			75*	1.7
Tetracaine HCl			0.18	0.109 ^c			0.15	0.26	0.12	0.35					
Tetracycline HCl			0.14	0.081 ^c			0.10								
Tetrahydrozoline HCl											4.10			60*	6.7
Theophylline				0.02 ^b											
Theophylline sodium glycinate											2.94			0	8.9
Thiamine HCl				0.139 ^c							4.24			87*	3.0
Thiethylperazine maleate	0.10	0.030	0.09	0.050	0.08	0.089	0.07	0.119	0.05	0.153					
Thiopental sodium				0.155 ^c							3.50			74	10.3
Thiopropazate diHCl	0.20	0.053	0.16	0.090	0.12	0.137	0.10	0.170	0.08	0.222					
Thioridazine HCl	0.06	0.015	0.05	0.025	0.04	0.042	0.03	0.055	0.03	0.075					
Thiotepa	0.16	0.045	0.16	0.090	0.16	0.182	0.16	0.278	0.16	0.460	5.67	0.16	0.52	10*	8.2
Tridihexethyl chloride	0.16	0.047	0.16	0.096	0.16	0.191	0.16	0.280	0.16	0.463	5.62	0.16	0.52	97	5.4
Triethanolamine.	0.20	0.058	0.21	0.121	0.22	0.252	0.22	0.383			4.05	0.22	0.52	100	10.7
Trifluoperazine 2HCl	0.18	0.052	0.18	0.100	0.13	0.144									
Triflupromazine HCl	0.10	0.031	0.09	0.051	0.05	0.061	0.04	0.073	0.03	0.092					

Appendix A—Continued

	0.5%		1%		2%		3%		5%		Isoosmotic concentration ^a				
	E	D	E	D	E	D	E	D	E	D	%	E	D	H	pH
Trimeprazine tartrate	0.10	0.023	0.06	0.035	0.04	0.045	0.03	0.052	0.02	0.061					
Trimethadione	0.23	0.069	0.23	0.133	0.22	0.257	0.22	0.378			4.22	0.21	0.52	100	6.0
Trimethobenzamide HCl	0.12	0.033	0.10	0.062	0.10	0.108	0.09	0.153	0.08	0.232					
Tripelennamine HCl				0.13 ^d							5.50			100	6.3
Tromethamine	0.26	0.074	0.26	0.150	0.26	0.300	0.26	0.450			3.45	0.26	0.52	100	10.2
Tropicamide	0.10	0.030	0.09	0.050											
Trypan blue	0.26	0.075	0.26	0.150											
Trypsinamide				0.11 ^c											
Tubocurarine chloride				0.076 ^c											
Urea			0.59	0.34							1.63	0.55	0.52	100	6.6
Urethan				0.18 ^b							2.93			100	6.3
Uridine	0.12	0.035	0.12	0.069	0.12	0.138	0.12	0.208	0.12	0.333	8.18	0.11	0.52	0*	6.1
Valethamate bromide	0.16	0.044	0.15	0.085	0.15	0.168	0.14	0.238	0.11	0.324					
Vancomycin sulfate	0.06	0.015	0.05	0.028	0.04	0.049	0.04	0.066	0.04	0.098					
Viomycin sulfate				0.08	0.05			0.07	0.12	0.07	4.68	0.19	0.52	88	5.0
Xylometazoline HCl	0.22	0.065	0.21	0.121	0.20	0.232	0.20	0.342			5.40			0*	5.4
Zinc phenolsulfonate											7.65	0.12	0.52		
Zinc sulfate			0.15	0.086 ^c			0.13	0.23	0.12	0.35					

^a The unmarked values were taken from Hammarlund et al.¹³⁻¹⁶ and Sapp et al.¹⁷

^b Adapted from Lund et al.¹²

^c Adapted from BPC.¹⁸

^d Obtained from several sources.

^e E: sodium chloride equivalents; D: freezing-point depression, °C; H: hemolysis, %, at the concentration which is iso-osmotic with 0.9% NaCl, based on freezing-point determination or equivalent test; pH: approximate pH of solution studied for hemolytic action; *: change in appearance of erythrocytes and/or solution.^{17-19†} pH determined after addition of blood.

NB—See also, Budavari S, ed: *Merck Index*, 11th ed, Merck & Co, Rahway NJ, 1988; pp MISC 79-103.

Appendix B—Isotonic Solution V-Values^{20a,b}

Drug (0.3 g)	Water needed for isotonicity, mL	Drug (0.3 g)	Water needed for isotonicity, mL	Drug (0.3 g)	Water needed for isotonicity, mL
Alcohol	21.7	Epinephrine hydrochloride	9.7	Silver nitrate	11.0
Ammonium chloride	37.3	Ethylmorphine hydrochloride	5.3	Silver protein, mild	5.7
Amobarbital sodium	8.3	Fluorescein sodium	10.3	Sodium acetate	15.3
Amphetamine phosphate	11.3	Glycerin	11.7	Sodium bicarbonate	21.7
Amphetamine sulfate	7.3	Holocaine hydrochloride	6.7	Sodium biphosphate, anhydrous	15.3
Antipyrine	5.7	Homatropine hydrobromide	5.7	Sodium biphosphate	13.3
Apomorphine hydrochloride	4.7	Homatropine methylbromide	6.3	Sodium bisulfite	20.3
Ascorbic acid	6.0	Hyoscyamine sulfate	4.7	Sodium borate	14.0
Atropine methylbromide	4.7	Neomycin sulfate	3.7	Sodium iodide	13.0
Atropine sulfate	4.3	Oxytetracycline hydrochloride	4.3	Sodium metabisulfite	22.3
Bacitracin	1.7	Penicillin G, potassium	6.0	Sodium nitrate	22.7
Barbital sodium	10.0	Penicillin G, sodium	6.0	Sodium phosphate	9.7
Bismuth potassium tartrate	3.0	Pentobarbital sodium	8.3	Sodium propionate	20.3
Boric acid	16.7	Phenobarbital sodium	8.0	Sodium sulfite, exsiccated	21.7
Butacaine sulfate	6.7	Physostigmine salicylate	5.3	Sodium thiosulfate	10.3
Caffeine and sodium benzoate	8.7	Pilocarpine hydrochloride	8.0	Streptomycin sulfate	2.3
Calcium chloride	17.0	Pilocarpine nitrate	7.7	Sulfacetamide sodium	7.7
Calcium chloride (6 H ₂ O)	11.7	Piperocaine hydrochloride	7.0	Sulfadiazine sodium	8.0
Chlorobutanol (hydrated)	8.0	Polymyxin B sulfate	3.0	Sulfamerazine sodium	7.7
Chlortetracycline sulfate	4.3	Potassium chloride	25.3	Sulfapyridine sodium	7.7
Cocaine hydrochloride	5.3	Potassium nitrate	18.7	Sulfathiazole sodium	7.3
Cupric sulfate	6.0	Potassium phosphate, monobasic	14.7	Tetracaine hydrochloride	6.0
Dextrose, anhydrous	6.0	Procainamide hydrochloride	7.3	Tetracycline hydrochloride	4.7
Dibucaine hydrochloride	4.3	Procaine hydrochloride	7.0	Viomycin sulfate	2.7
Dihydrostreptomycin sulfate	2.0	Scopolamine hydrobromide	4.0	Zinc chloride	20.3
Ephedrine hydrochloride	10.0	Scopolamine methylnitrate	5.3	Zinc sulfate	5.0
Ephedrine sulfate	7.7	Secobarbital sodium	8.0		

^a Table of "Isotonic Solution Values" showing volumes in mL of water to be added to 300 mg of the specified drug in sterile water to produce an isotonic solution. The addition of an isotonic vehicle (commonly referred to as diluting solution) to make 30 mL yields a 1% solution. Solutions prepared as directed above are isoosmotic with 0.9% sodium chloride solution but may not be isotonic with blood (see Appendix A for hemolysis data).

^b V-values for drugs which do not appear in Appendix B, but are listed in Appendix A can be calculated from the sodium chloride equivalent for 1% drug.

Example—Calculate the V-value for anileridine HCl (Appendix A defines E = 0.19).

$$\frac{100 \text{ mL Soln}}{0.9 \text{ g NaCl}} \times \frac{0.19 \text{ g NaCl}}{1 \text{ g drug}} \times 0.3 \text{ g drug} = 6.33 \text{ mL Soln}$$

for dilute solution 6.33 mL soln $\approx$ 6.33 mL water

$$\therefore V = 6.33 \text{ mL water/0.3 g drug.}$$