10
Solubility and Distribution Phenomena

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

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

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

GENERAL PRINCIPLES

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

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

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

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

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

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

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

TABLE 10–1. *Terms of Approximate Solubility*

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

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

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

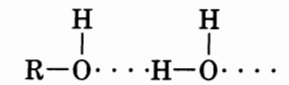
SOLVENT–SOLUTE INTERACTIONS

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

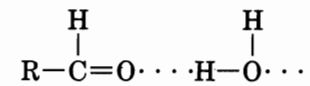
Polar Solvents. The solubility of a drug is due in large measure to the polarity of the solvent, that is, to its dipole moment. Polar solvents dissolve ionic solutes and other polar substances. Accordingly, water mixes in all proportions with alcohol and dissolves sugars and other polyhydroxy compounds.

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

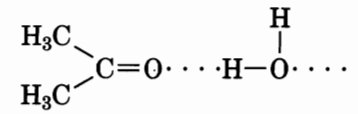
Water dissolves phenols, alcohols, aldehydes, ketones, amines, and other oxygen- and nitrogen-containing compounds that can form hydrogen bonds with water.



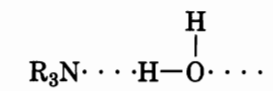
Alcohol



Aldehyde



Ketone



Amine

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

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

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

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

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

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

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

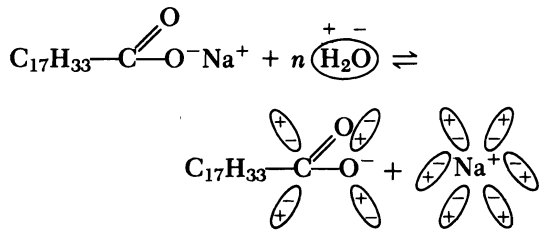
$$HCl + H_2O \rightarrow H_3O^+ + Cl^-$$

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

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

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

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



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

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

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

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

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

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

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

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

SOLUBILITY OF GASES IN LIQUIDS

Pharmaceutical solutions of gases include hydrochloric acid, ammonia water, and effervescent preparations containing carbon dioxide that are dissolved and maintained in solution under positive pressure. Aerosol products in which the propellant is either carbon dioxide or nitrogen, some of which is dissolved under pressure, can also be considered to fall under this classification.

The solubility of a gas in a liquid is the concentration of the dissolved gas when it is in equilibrium with some of the pure gas above the solution. The solubility depends primarily on the *pressure, temperature, presence of salts,* and *chemical reactions* that the gas sometimes undergoes with the solvent.

Effect of Pressure. The pressure of a gas above the solution is an important consideration in gaseous solutions since it changes the solubility of the dissolved gas in equilibrium with it. The effect of the pressure on the solubility of a gas is expressed by *Henry's law,* which states that in a very dilute solution at constant temperature, the concentration of dissolved gas is proportional to the partial pressure of the gas above the solution at equilibrium. The partial pressure of the gas is obtained by subtracting the vapor pressure of the solvent from the total pressure above the solution. If C_2 is the concentration of the dissolved gas in grams per liter of solvent and p is the partial pressure in millimeters of the undissolved gas above the solution, Henry's relationship may be written as

$$C_2 = \sigma p \qquad (10\text{–}2)$$

in which σ is the inverse of the Henry's law constant, k (p. 109). It is sometimes referred to as the *solubility coefficient.* Mole fraction is more properly used here, but in dilute solutions, molarity may be used.

The significance of Henry's law for the pharmacist rests upon the fact that the solubility of a gas increases directly as the pressure on the gas, and conversely, that the solubility of the gas decreases, so that sometimes the gas escapes with violence when the pressure above the solution is released. This phenomenon is commonly recognized in effervescent solutions when the stopper of the container is removed.

Effect of Temperature. Temperature also has a marked influence on the solubility of a gas in a liquid. As the temperature increases, the solubility of most gases decreases, owing to the greater tendency of the gas to expand. The property of expansion, coupled with the pressure phenomenon, requires that the pharmacist exercise caution in opening containers of gaseous solutions in warm climates and under other conditions of elevated temperatures. A vessel containing a gaseous solution or a liquid with a high vapor pressure, such as ethyl nitrite, should be immersed in ice or cold water for some time to reduce the temperature and pressure of the gas before opening the container.

Salting Out. Gases are often liberated from solutions in which they are dissolved by the introduction of an electrolyte such as sodium chloride and sometimes by a nonelectrolyte such as sucrose. This phenomenon is known as *salting out.* The salting-out effect may be demonstrated by adding a small amount of salt to a "carbonated" solution. The resultant escape of gas is due to the attraction of the salt ions or the highly polar nonelectrolyte for the water molecules, which reduces the density of the aqueous environment adjacent to the gas molecules. Salting out may also occur in solutions of liquids in liquids and solids in liquids.

Effect of Chemical Reaction. Henry's law applies strictly to *gases* that are only slightly soluble in solution and that do not react in any way in the solvent. Gases such as hydrogen chloride, ammonia, and carbon dioxide show deviations as a result of chemical reaction between the gas and solvent, usually with a resultant increase in solubility. Accordingly, hydrogen chloride is about 10,000 times more soluble in water than is oxygen.

Solubility Calculations. The solubility of a gas in a liquid may be expressed either by the inverse *Henry's law constant* σ or by the *Bunsen absorption coefficient* α. The Bunsen coefficient is defined as the volume of gas in liters (reduced to standard conditions of 0° C and 760 mm pressure) that dissolves in 1 liter of solvent under a partial pressure of 1 atmosphere of the gas at a definite temperature.

$$\frac{V_{\text{gas,STP}}}{V_{\text{soln}}} = \alpha p \qquad (10\text{–}3)$$

TABLE 10–3. *Bunsen Coefficients (α) for Gases in Water at 0° and 25° C*

Gas	α	
	0° C	25° C
H_2	0.0215	0.0175
N_2	0.0235	0.0143
O_2	0.0478	0.0284
CO_2	1.713	0.759

in which V_{gas} is the volume of gas at standard temperature and pressure, STP, dissolved in a volume V_{soln} of solution at a partial gas pressure p. The Bunsen coefficients α for some gases in water at 0° and 25° C are found in Table 10–3. The application of Henry's law and the calculation of σ and α are illustrated in the following example.

Example 10–1. If 0.0160 g of oxygen dissolves in 1 liter of water at a temperature of 25° C and at an oxygen pressure of 300 mm Hg, calculate (*a*) σ and (*b*) the Bunsen coefficient, α

(*a*)

$$\sigma = \frac{C_2 \text{ (g/liter)}}{p\text{(mm Hg)}} = \frac{0.0160}{300} = 5.33 \times 10^{-5}$$

(*b*) To compute the Bunsen coefficient, one must first reduce the volume of gas to STP. According to the ideal gas equation, $V = nRT/p$

$$V_{gas,STP} = \frac{\frac{0.0160}{32} \times 0.08205 \times 273.15}{1 \text{ atm}} = 0.0112 \text{ at STP}$$

and from equation (10–3)

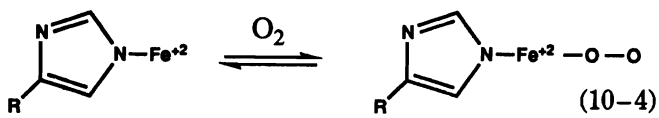
$$\alpha = \frac{V_{gas}}{V_{soln}\, p} = \frac{0.0112}{1 \times \frac{300}{760}} = 0.0284$$

(*c*) How many grams of oxygen can be dissolved in 250 mL of aqueous solution when the total pressure above the mixture is 760 mm Hg? The partial pressure of oxygen in the solution is 0.263 atm, and the temperature is 25° C.

$$\sigma = 5.33 \times 10^{-5} = \frac{C_2 \text{ (g/liter)}}{(0.263 \times 760) \text{ mm}}$$

$$C_2 = 0.0107 \text{ g/liter or } 0.0027 \text{ g/250 mL}$$

Oxygen is carried in the human body *(a)* as dissolved gas in the contents of the red blood cells and *(b)* as O_2 molecules bound to the iron atom of the heme part of hemoglobin. Shown here is part of the heme molecule of



(10–4)

hemoglobin demonstrating the binding of two atoms of oxygen to the iron atom.[8] Hemoglobin is made up of four heme molecules and so has four iron atoms with which to bind four molecules of oxygen. The concentration of O_2 dissolved in the blood ([*a*] above) regulates the uptake and release of oxygen by the iron atoms in hemoglobin ([*b*] above).

Example 10–2. The partial vapor pressure[9], p, of oxygen in the blood is 75 mm Hg and the percent saturation of O_2 in the red blood cells has been determined to be 92.8%. What is the concentration of O_2 dissolved in the red blood cells (rbc's), exclusive of the binding of O_2 by the iron of hemoglobin?

The solubility coefficient, σ (inverse Henry's law constant), may be expressed in volume (cm^3) at a definite temperature and pressure rather than mass (grams or moles) of gas dissolved in the solvent. The value of σ at 37° C for O_2 is 4.1×10^{-5} cm^3 O_2/cm^3 rbc content/mm Hg. Here, the solubility coefficient is actually more closely related to the Bunsen coefficient α than to the inverse Henry's law constant σ. From equation (10–2):

$$\text{oxygen conc. } C_2 = (4.1 \times 10^{-5} \text{ cm}^3 \text{ solute/cm}^3 \text{ rbc/mm Hg}) \times (75 \text{ mm Hg, } O_2 \text{ pressure in blood})$$

$$C_2 = 3.075 \times 10^{-3} \text{ cm}^3 \text{ O}_2/\text{cm}^3 \text{ rbc content}$$

However, we learned above that O_2 in the rbc's is at only 92.8% of saturation. Therefore, $C_2 = 0.928 \times (3.075 \times 10^{-3}) = 2.85 \times 10^{-3}$ cm^3 O_2/cm^3 rbc content at a pressure of 75 mm Hg in the blood.

We now consider the second, and more significant, avenue for the transport of O_2 in the blood. The combining capacity has been determined to be 0.40 cm^3 of O_2 per cm^3 of rbc's; and at the partial pressure of oxygen of 75 mm Hg, the saturation of O_2 on the heme iron sites is not 100% but rather 18.7%. Thus,

$$(0.40 \text{ cm}^3 \text{ O}_2/\text{cm}^3 \text{ rbc content})(0.187) = 0.075 \text{ cm}^3$$

Although this may appear to be a small and inefficient binding of O_2 to hemoglobin, when compared with *(a)* above (the transport of O_2 by solution in the bulk content of the red blood cells), the hemoglobin binding as an O_2 transport system is 26 times more effective in carrying O_2 to the various tissues of the body:

$$\frac{0.075 \text{ cm}^3 \text{ O}_2/\text{cm}^3 \text{ rbc content}}{0.00285 \text{ cm}^3 \text{ O}_2/\text{cm}^3 \text{ rbc content}} = 26.3$$

Tables 10–4 and 10–5 give the k values for a number of gases in the solvents water and benzene. Several examples follow, showing the calculation of the Henry's law constant, k, and the solubilities of gases expressed in mole fraction, molality, or molarity and in grams of solute per liter of solution. The gaseous solutions that follow Henry's law are so dilute that essentially no difference exists between molarity and molality.

The Henry's law constant k as found in columns 3 and 4 of Table 10–4 may be represented as

$$k = \frac{p_2}{X_2} = \frac{\text{pressure of gas (solute) in torrs or atmospheres}}{\text{mole fraction of the gas in solution}} \qquad (10\text{–}5)$$

and the constant k in columns 5 and 6 as

$$k = \frac{p_2}{c \text{ or } m} = \frac{\text{pressure of gas (solute) in torrs}}{\text{molarity, molality, or g/liter of gas in solution}} \qquad (10\text{–}6)$$

TABLE 10–4. ***Henry's Law Constants for Gases in Water at 25° C****

Gas	Molecular Weight	mm Hg (torrs) per Mole Fraction of Gas	Atm Pressure per Mole Fraction of Gas	mm Hg (torrs) per Molality or Molarity of Gas	mm Hg (torrs) per Gram of Gas per Kilogram H_2O or per Liter of Solution
H_2	2.02	5.34×10^7	7.03×10^4	9.62×10^5	4.76×10^5
He	4.00	1.10×10^8	1.45×10^5	1.99×10^6	4.98×10^5
N_2	28.01	6.51×10^7	8.57×10^4	1.17×10^6	4.18×10^4
O_2	32.00	3.30×10^7	4.34×10^4	5.94×10^5	1.86×10^4
CO	28.01	4.34×10^7	5.71×10^4	7.82×10^5	2.79×10^4
CO_2	44.01	1.25×10^6	1.64×10^3	2.24×10^4	5.09×10^2
CH_4	16.04	31.4×10^6	4.13×10^4	5.65×10^5	3.52×10^4
C_2H_6	30.07	23.0×10^6	3.03×10^4	4.15×10^5	1.38×10^4

*After F. Daniels and R. A. Alberty, *Physical Chemistry*, Wiley, New York, 1955, p. 200.

TABLE 10–5. ***Henry's Law Constants for Gases in Benzene at 25° C****

Gas	mm Hg (torrs) per Mole Fraction of Gas
H_2	2.75×10^6
N_2	1.79×10^6
CO	1.22×10^6
CO_2	8.57×10^4
CH_4	4.27×10^5

*After F. Daniels and R. A. Alberty, *Physical Chemistry*, Wiley, New York, 1955, p. 200.

Although the k values for CO_2 are found in Table 10–4, this gas is too soluble to adhere well to Henry's law.

The inverse Henry's law constant σ is not listed for the gases in Table 10–4; it is obtained in each case simply by taking the reciprocal of k found in the table. The k values for gases dissolved in solvents other than water may be found in the literature. The k values for several gases in the solvent benzene, at 25° C, are listed in Table 10–5.

Example 10–3. *(a)* What is the solubility of oxygen in water at 1 atm pressure at a temperature of 25° C? Express the results in both molality and molarity.

Useful equations for converting from mole function X_2 to molality m and to molarity c are

$$m = \frac{1000\,X_2}{M_1(1 - X_2)} \quad \text{and} \quad c = \frac{1000\,\rho\,X_2}{M_1(1 - X_2) + M_2X_2}$$

where M_1 is the molecular weight of the solvent, M_2 that of the solute, and ρ is the density of the solution. In a solution sufficiently dilute for Henry's law to apply, ρ is essentially 1.0 and M_2X_2 may be ignored in the equation for c. Thus, molality and molarity are roughly equal in dilute solution.

Using k from Table 10–4, we find the solubility of O_2 in water at 1 atm and 25° C using the proportion

$$4.34 \times 10^4 \text{ atm/mole fraction} = \frac{1 \text{ atm}}{X_2};\ X_2 = 2.30 \times 10^{-5}$$

$$\text{molality, } m = \frac{1000(2.30 \times 10^{-5})}{18.015(1 - (2.30 \times 10^{-5}))} = 0.00128 \text{ mole/kg } H_2O$$

molality ≅ molarity, or $c \cong 0.00128$ mole/liter of solution.

(b) Calculate the Henry's law constant k for methane at 1 atm and 25° C, expressed in torr/(mole/kg H_2O).

From Table 10–4,

$$k_{(CH_4)} = 4.13 \times 10^4 \text{ atm/(mole fraction)} = \frac{1 \text{ atm}}{X_2}$$

$$X_2 = 1 \text{ atm}/(4.13 \times 10^4 \text{ atm/(mole fraction)})$$

$$= 2.42 \times 10^{-5} \text{ (mole fraction)}$$

Convert mole fraction of CH_4 to molality.

$$m = \frac{1000(2.42 \times 10^{-5})}{18.015(1 - (2.42 \times 10^{-5}))} = 1.344 \times 10^{-3} \text{ mole/kg } H_2O$$

k in torr/(mole/kg H_2O) is therefore

$$k = \frac{1 \text{ atm} \times 760 \text{ torr/atm}}{1.344 \times 10^{-3} \text{ mole/kg } H_2O} = \frac{760}{1.344 \times 10^{-3}}$$

$$= 5.65 \times 10^5 \text{ torr/(mole/kg } H_2O)$$

(c) Obtain the Henry's law constant for hydrogen, molecular weight $H_2 = 2.02$ g/mole, at a pressure in torrs at 25° C. Express k in torr/(g/liter), where g/liter is essentially equal to g/kg of water in a solution sufficiently dilute for Henry's law to apply. One obtains

$$k_{(H_2)} = \frac{\text{torr}}{X_2 \text{ (mole fraction)}} = 5.34 \times 10^7 \text{ torr/(mole fraction)}$$

$$X_2 = \text{torr}/(5.34 \times 10^7 \text{ torr/(mole fraction)})$$

$$= 1.87 \times 10^{-8} \text{ (mole fraction)}$$

$$m = \frac{1000(1.87 \times 10^{-8})}{18.015(1 - (1.87 \times 10^{-8}))} = 1.04 \times 10^{-6} \text{ mole/kg } H_2O$$

$$\cong 1.04 \times 10^{-6} \text{ mole/liter}$$

To convert moles to grams, we write g = mole × mol. wt.

$$1.04 \times 10^{-6} \text{ mole/liter} \times 2.02 \text{ g/mole} = 2.10 \times 10^{-6} \text{ g/liter}$$

$$k = \frac{1 \text{ torr}}{2.10 \times 10^{-6} \text{ g/liter}} = 4.76 \times 10^5 \text{ torr/(g/liter)}$$

(d) Using the value of k you got in *(c)*, calculate the grams of hydrogen gas dissolved in a liter of aqueous solution at an external pressure on the gas of 1 atm (760 torr) at 25° C.

$$k = 4.76 \times 10^5 \text{ torr/(g/liter)} = \frac{760 \text{ torr}}{c \text{ (g/liter)}}$$

$$c = 760 \text{ torr}/(4.76 \times 10^5 \text{ torr/(g/liter)})$$

$$= 0.00160 \text{ g/liter}$$

(e) To obtain the Henry's law constant, k, for a gas at a temperature other than 25° C, we proceed as follows.

The solubility of O_2 in water at 1 atm pressure and 0° C is 0.070 g/liter. To express k in torr/(g/liter) we simply write

$$k = 760 \text{ torr}/(0.070 \text{ g/liter}) = 1.09 \times 10^4 \text{ torr/(g/l)}$$

In these examples involving the Henry's law constants, the term *mole fraction* is placed after the values of X_2 to indicate that the numbers are expressed as mole fractions—that is, as ratios of

moles—and therefore are dimensionless, having no physical units associated with them.

SOLUBILITY OF LIQUIDS IN LIQUIDS

Frequently two or more liquids are mixed together in the preparation of pharmaceutical solutions. For example, alcohol is added to water to form hydroalcoholic solutions of various concentrations: volatile oils are mixed with water to form dilute solutions known as aromatic waters; volatile oils are added to alcohol to yield spirits and elixirs; ether and alcohol are combined in collodions; and various fixed oils are blended into lotions, sprays, and medicated oils.

Ideal and Real Solutions. According to Raoult's law, $p_i = p_i^\circ X_i$, the partial pressure p_i of a component in a liquid mixture at a definite temperature is equal to the vapor pressure in the pure state multiplied by the mole fraction of the component in the solution. The mixture is said to be ideal when both components of a binary solution obey Raoult's law over the whole range of composition. If one of the components shows a negative deviation, it can be demonstrated by the use of thermodynamics that the other component must also show negative deviation (cf. Fig. 5–2, p. 108). The corresponding statement can also be made for positive deviations from Raoult's law.

Negative deviations lead to increased solubility and are frequently associated with hydrogen bonding between polar compounds (p. 23). The interaction of the solvent with the solute is known as *solvation*. Positive deviations, leading to decreased solubility, are interpreted as resulting from association of the molecules of one of the constituents to form double molecules (dimers) or polymers of higher order. Hildebrand, however, suggests that positive deviation is better accounted for in most cases by the difference in the cohesive forces of the molecules of each constituent. These attractive forces, which may occur in gases, liquids, or solids, are called *internal pressures*.

When the vapor is assumed to be nearly ideal, the internal pressure in cal/cm^3 is obtained by using the equation

$$P_i = \frac{\Delta H_v - RT}{V} \qquad (10\text{–}7)$$

in which ΔH_v is the heat of vaporization and V is the molar volume of the liquid at temperature T.

Example 10–4. The molar heat of vaporization of water at 25° C is 10,500 cal and V is approximately 18.01 cm^3. The gas constant R is 1.987 cal/mole deg. Compute the internal pressure of water.

$$P_i = \frac{10{,}500 - (1.987 \times 298.2)}{18.01}$$

$$= 550 \text{ cal/cm}^3 \text{ or } 22{,}700 \text{ atm}$$

A familiarity with calculations such as those appearing on pages 3 and 4 should allow the student to make this conversion from cal/cm^3 to atmospheres.

When the internal pressures or cohesive forces of the constituents of a mixture such as hexane and water are quite different, the molecules of one constituent cannot mingle with those of the other, and partial solubility results. Polar liquids have high cohesive forces, that is, large internal pressures, and they are solvents only for compounds of similar nature. Nonpolar substances with low internal pressures are "squeezed out" by the powerful attractive forces existing between the molecules of the polar liquid. This results in positive deviation from Raoult's law as shown in Figure 5–3 on page 108. It must be remarked that limited solubility of nonpolar solutes in highly polar solvents, and particularly in those solvents that associate through hydrogen bonds, cannot be attributed entirely to a difference of internal pressures. These factors will be considered in more detail on page 229.

Liquid–liquid systems may be divided into two categories according to the solubility of the substances in one another: (1) complete miscibility and (2) partial miscibility. The term *miscibility* refers to the mutual solubilities of the components in liquid–liquid systems.

Complete Miscibility. Polar and semipolar solvents, such as water and alcohol, glycerin and alcohol, and alcohol and acetone, are said to be completely miscible since they mix in all proportions. Nonpolar solvents such as benzene and carbon tetrachloride are also completely miscible. Completely miscible liquid mixtures in general create no solubility problems for the pharmacist and need not be considered further.

Partial Miscibility. When certain amounts of water and ether or water and phenol are mixed, two liquid layers are formed, each containing some of the other liquid in the dissolved state. The phenol–water system has been discussed in detail in Chapter 2, and the student at this point should review the section dealing with the phase rule. It is sufficient here to reiterate the following points. (1) The mutual solubilities of partially miscible liquids are influenced by temperature. In a system such as phenol and water, the mutual solubilities of the two conjugate phases increase with temperature until, at the critical solution temperature (or upper consolute temperature), the compositions become identical. At this temperature, a homogeneous or single-phase system is formed. (2) From a knowledge of the phase diagram, more especially the tie lines that cut the binodal curve, it is possible to calculate both the composition of each component in the two conjugate phases and the amount of one phase relative to the other. *Example 10–5* gives an illustration of such a calculation.

Example 10–5. A mixture of phenol and water at 20° C has a total composition of 50% phenol. The tie line at this temperature cuts the binodal at points equivalent to 8.4 and 72.2% *w/w* phenol (taken from Fig. 2–14, p. 40). What is the weight of the aqueous layer and of the phenol layer in 500 g of the mixture and how many grams of phenol are present in each of the two layers?

Let Z be the weight in grams of the aqueous layer. Therefore, $(500 - Z)$ is the weight in grams of the phenol layer, and the sum of

the percentages of phenol in the two layers must equal the overall composition of 50% or 500 × 0.50 = 250 g.

$$Z(8.4/100) + (500 - Z)(72.2/100) = 250$$

$$\text{weight of aqueous layer, } Z = 174 \text{ g}$$

$$\text{weight of phenol layer } (500 - Z) = 326 \text{ g}$$

The weight of phenol in the aqueous layer is

$$174 \times 0.084 = 15 \text{ g}$$

and the weight of phenol in the phenolic layer is

$$326 \times 0.722 = 235 \text{ g}$$

In the case of some liquid pairs, the solubility may increase as the temperature is lowered, and the system will exhibit a *lower consolute temperature*, below which the two members are soluble in all proportions and above which two separate layers form (Fig. 2–15, p. 41). Another type, involving a few mixtures such as nicotine and water (see Fig. 2–16, p. 41), shows both an upper and a lower consolute temperature with an intermediate temperature region in which the two liquids are only partially miscible. A final type exhibits no critical solution temperature; the pair, ethyl ether and water, for example, has neither an upper nor a lower consolute temperature and shows partial miscibility over the entire temperature range at which the mixture exists.

Influence of Foreign Substances.[10] The addition of a substance to a binary liquid system produces a ternary system, that is, one having three components. If the added material is soluble in only one of the two components or if the solubilities in the two liquids are markedly different, the mutual solubility of the liquid pair is decreased. If the original binary mixture has an upper critical solution temperature, the temperature is raised; if it has a lower consolute temperature, it is lowered by the addition of the third component. For example, if 0.1 *M* naphthalene is added to a mixture of phenol and water, it dissolves only in the phenol and raises the consolute temperature about 20°; if 0.1 *M* potassium chloride is added to a phenol–water mixture, it dissolves only in water and raises the consolute temperature approximately 8°. This latter case illustrates the salting-out effect previously referred to under solutions of gases.

When the third substance is soluble in both of the liquids to roughly the same extent, the mutual solubility of the liquid pair is increased; an upper critical solution temperature is lowered and a lower critical solution temperature is raised. The addition of succinic acid or sodium oleate to a phenol–water system brings about such a result. The increase in mutual solubility of two partially miscible solvents by another agent is ordinarily referred to as *blending*. When the solubility in water of a nonpolar liquid is increased by a micelle-forming surface-active agent, the phenomenon is called *micellar solubilization* (p. 410).

Three-Component Systems. The principles underlying systems that may contain one, two, or three partially miscible pairs have been discussed in detail in Chapter 2. Further examples of three-component systems containing one pair of partially miscible liquids are water, CCl_4, and acetic acid; and water, phenol, and acetone. Loran and Guth[6] made a study of the three-component system, water, castor oil, and alcohol, to determine the proper proportions for use in certain lotions and hair preparations, and a triangular diagram is shown in their report. A similar titration with water of a mixture containing peppermint oil and polyethylene glycol is shown in Figure 10–1.[7] Ternary diagrams have also found use in cosmetic formulations involving three liquid phases.[11] Gorman and Hall[12] determined the ternary-phase diagram of the system, methyl salicylate, isopropanol, and water (Fig. 10–2.).

Dielectric Constant and Solubility. Paruta and associates[13] have studied the solubility of barbiturates, parabens, xanthines, and other classes of drugs in a range of solvents of various dielectric constants. The solubility of caffeine in a mixture of dioxane and water as determined in two laboratories is shown in Figure 10–3. The solubility is plotted against dielectric constant, and against solvent solubility parameter, δ, to be discussed later. Gorman and Hall[12] obtained a linear relationship when they plotted log mole fraction of the solute, methyl salicylate, versus the dielectric constant of isopropanol–water mixtures, as seen in Figure 10–4.

Molecular Connectivity. Kier and Hall[14] investigated the solubility of liquid hydrocarbons, alcohols, ethers, and esters in water. They used a topologic (structural) index χ, or chi, which takes on values that depend on the structural features and functional groups of a particular molecule. The technique used by Kier and Hall is referred to as *molecular connectivity*. A zero-order chi term, $^0\chi$, first-order chi term, $^1\chi$, and higher-order chi terms are used to describe a molecule. The $^1\chi$ term is obtained by summing the bonds weighted by the reciprocal square root number of each bond. In the case of propane,

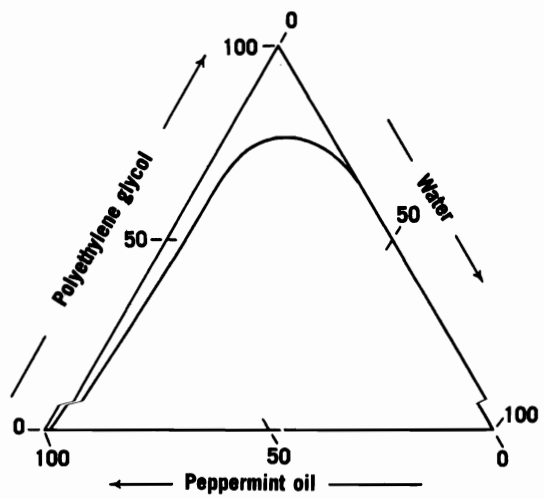


Fig. 10–1. A triangular diagram showing the solubility of peppermint oil in various proportions of water and polyethylene glycol.

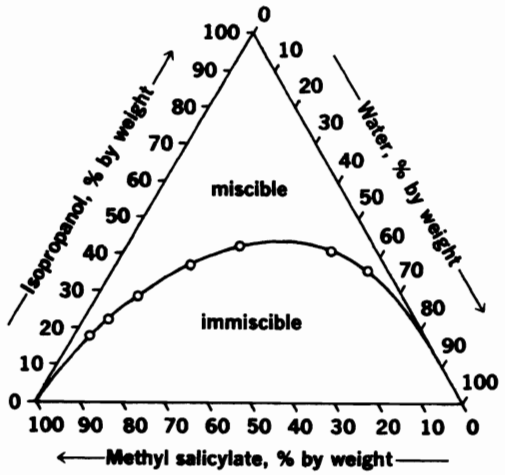
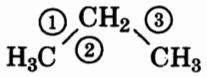


Fig. 10–2. Triangular phase diagram for the three component system, methyl salicylate–isopropanol–water. (From W. G. Gorman and G. D. Hall, J. Pharm. Sci. 53, 1017, 1964, reproduced with permission of the copyright owner.)



disregarding attached hydrogens, carbon 1 is connected through one bond to the central carbon, which is joined to the other carbons by two bonds. The reciprocal square root "valence" is therefore $(1 \cdot 2)^{-1/2} = 0.707$ for the left bond. The right-hand bond has the same reciprocal square root valence, or 0.707. These are summed to yield

$$^1\chi = 0.707 + 0.707 = 1.414$$

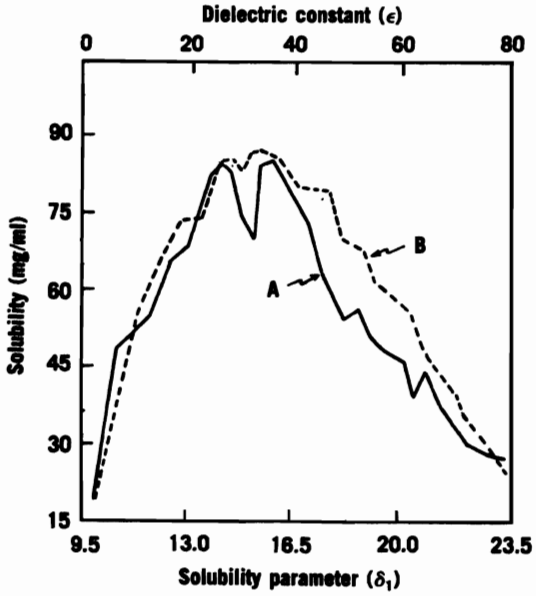


Fig. 10–3. Caffeine in dioxane–water mixtures at 25° C. Solubility profiles were obtained from two studies, *A*[13] and *B*.[34] Solubility in mg/mL is plotted against both dielectric constant (upper scale) and solvent solubility parameter (lower scale). (From A. Martin, A. N. Paruta, and A. Adjei, J. Pharm. Sci. 70, 1115, 1981, reproduced with permission of the copyright owner.)

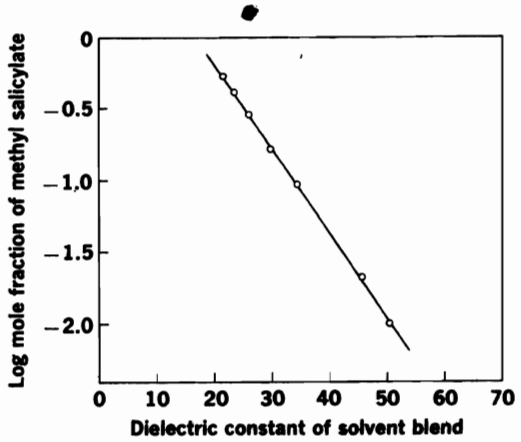
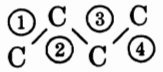


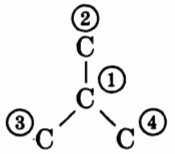
Fig. 10–4. Solubility of methyl salicylate in isopropanol–water blends of differing dielectric constants. (From W. G. Gorman and G. D. Hall, J. Pharm Sci. 53, 1017, 1964, reproduced with permission of the copyright owner.)

for *n*-butane, considering only the carbon atoms and their bonds,



$$^1\chi = (1 \cdot 2)^{-1/2} + (2 \cdot 2)^{-1/2} + (1 \cdot 2)^{-1/2} = 1.914$$

Isobutane,



has a different $^1\chi$ than *n*-butane because of its branching:

$$^1\chi = (1 \cdot 3)^{-1/2} + (1 \cdot 3)^{-1/2} + (1 \cdot 3)^{-1/2} = 1.732$$

For calculating second- and higher-order χ indexes and applications of molecular connectivity in pharmacy, refer to the book by Kier and Hall.[14]

$^1\chi$ may be used to correlate the molal solubilities of aliphatic hydrocarbons, alcohols, and esters in water, using regression analysis (see Chapter 1, p. 15, for regression analysis). The equation found[14] to fit the data for alkanes at 25° C is

$$\ln S = -1.505 - 2.533\ ^1\chi \qquad (10\text{–}8)$$

We learned that the $^1\chi$ value of isobutane was 1.732. Using this value in equation (10–8) yields

$$\ln S = -5.8922;\ S = 2.76 \times 10^{-3} \text{ molal}$$

The experimentally observed solubility of isobutane in water at 25° C is 2.83×10^{-3} molal.

Molecular Surface Area and Solubility. Amidon and associates[15] have published a number of papers dealing with the solubility of liquid nonelectrolytes in polar solvents. They investigated the aqueous solubility of hydrocarbons, alcohols, esters, ketones, ethers, and

carboxylic acids. The method consisted of regression analysis, in which ln (solubility) of the solute is correlated with the total surface area (TSA) of the solute. Excluding olefins, the equation that gave the best correlation with 158 compounds was

$$\log (\text{solubility}) = 0.0168\ (\text{TSA}) + 4.44 \quad (10-9)$$

The TSA of a compound was calculated using a computer program prepared earlier by Hermann.[16,17] Elaborations on the Hermann approach involved dividing the TSA of the solute into *hydrocarbon* and *functional group* surface-area contributions (HYSA and FGSA, respectively).

The following equation was developed by Amidon et al.[15] for calculating molal solubility of hydrocarbons and alcohols in water at 25° C:

$$\ln (\text{solubility}) = -0.0430\ (\text{HYSA}) - 0.0586\ (\text{FGSA}) + 8.003\ (I) + 4.420 \quad (10-10)$$

in which (FGSA) is the surface area for the hydroxyl group. It was found that an indicator variable, I, was needed in equation (10–10) to handle the alcohols. I was given a value of 1 if the compound was an alcohol and 0 if it was a hydrocarbon (no OH groups present).

Example 10–6. Calculate the molar solubility in water at 25° C for *n*-butanol and for cyclohexane using equation (10–10). Determine the percent difference from the observed values. The observed solubilities and the surface areas calculated with the modified computer program of Hermann are found in Table 10–6.

For *n*-butanol:

$$\ln (\text{solubility}) = -0.0430\ (212.9) - 0.0586\ (59.2) + (8.003)\ (1) + 4.420$$

$$\ln (\text{solubility}) = -0.20082$$

Molal solubility = 0.818 (error = 18.7% from the observed value, 1.006)

For cyclohexane:

$$\ln (\text{solubility}) = -0.0430\ (279.1) - 0.586(0) + (8.003)\ (0) + 4.420 = -7.5813$$

Molal solubility = 5.1×10^{-4} (error = 22.8% from the observed value, 6.61×10^{-4})

The method of Amidon et al. may prove applicable for predicting solubilities of complex organic drug molecules that have limited solubility in water.

TABLE 10–6. *Molecular Surface Areas of Alcohols and Hydrocarbons*

	HYSA (angstroms)^2	FGSA (angstroms)^2	Observed Solubility (molal)
n-butanol	212.9	59.2	1.006
Cyclohexanol	240.9	49.6	3.8×10^{-1}
Cyclohexane	279.1	—	6.61×10^{-4}
n-Octane	383	—	5.80×10^{-6}

Key: HYSA = hydrocarbon surface area; FGSA = functional group surface area (OH group in the case of an alcohol).

SOLUBILITY OF SOLIDS IN LIQUIDS

Systems of solids in liquids include the most frequently encountered and probably the most important type of pharmaceutical solutions. The solubility of a solid in a liquid cannot be predicted in a wholly satisfactory manner as yet, except possibly for ideal solutions, because of the complicating factors that must be taken into account.

Pharmaceutical solutions consist of a wide variety of solutes and solvents, as listed in Table 10–2. We shall begin with the ideal solution, proceeding then to regular solutions of nonpolar or moderately polar character and finally to solutions of high polarity, in which solvation and association result in marked deviation from ideal behavior.

In this limited treatment, only the highlights of the derivations are sketched out, and the resulting equations are given without a detailed development of each step in the formulation. It is hoped, however, that the worked examples will show the usefulness of the various equations and that the selected references will lead the interested reader to the original literature where details can be found.

Ideal Solutions. The solubility of a solid in an ideal solution depends on temperature, melting point of the solid, and molar heat of fusion ΔH_f, that is, the heat absorbed when the solid melts. In an ideal solution, the heat of solution is equal to the heat of fusion, which is assumed to be a constant independent of the temperature. Ideal solubility is not affected by the nature of the solvent. The equation derived from thermodynamic considerations for an ideal solution of a solid in a liquid is

$$-\log X_2^i = \frac{\Delta H_f}{2.303R}\left(\frac{T_0 - T}{TT_0}\right) \quad (10-11)$$

in which X_2^i is the ideal solubility of the solute expressed in mole fraction, T_0 is the melting point of the solid solute in absolute degrees, and T is the absolute temperature of the solution.* The superscript ^{i} in the symbol X_2^i refers to an ideal solution, and the subscript $_2$ designates the mole fraction as that of the solute. At temperatures above the melting point, the solute is in the liquid state, and, in an ideal solution, the liquid solute is miscible in all proportions with the solvent. Therefore, equation (10–11) no longer applies when $T > T_0$. The equation is also inadequate at temperatures considerably below the melting point where ΔH_f can no longer be used.

Example 10–7. What is the solubility of naphthalene at 20° C in an ideal solution? The melting point of naphthalene is 80° C, and the molar heat of fusion is 4500 cal/mole.

*Hildebrand and Scott[2] show that calculated results compare better with experimental values if terms involving ΔC_p, the difference in heat capacities of the solid and liquid, are also included in the equation.

$$\log X_2^i = -\frac{4500}{2.303 \times 1.987}\frac{(353 - 293)}{293 \times 353}$$

$$X_2^i = 0.27$$

The mole fraction solubility can be converted to molality (provided the molecular weight M_1 of the solvent is known) by means of the relationship

$$m = \frac{1000X_2}{M_1(1 - X_2)}$$

The value of X_2 in *Example 10–7* may be compared with the results of Scatchard.[18] He found that the mole fraction solubility of naphthalene was 0.24 in benzene, 0.23 in toluene, and 0.21 in carbon tetrachloride at 20° C.

Equation (10–11) can also be written as

$$\log X_2^i = -\frac{\Delta H_f}{2.303R}\frac{1}{T} + \text{constant} \qquad (10\text{–}12)$$

Therefore, a plot of the logarithm of the solubility, expressed in mole fraction, against the reciprocal of the absolute temperature results in a straight line with a slope of $-\Delta H_f/2.303R$ for an ideal solution. By this means, the molar heat of fusion of various drugs may be obtained from their solubility in ideal solutions.

The molar heat of fusion is determined most conveniently in a differential scanning calorimeter (see p. 47). The Drug Standards Laboratory of the United States Pharmacopeial Convention in Washington, D. C., has determined the ΔH_f values for a number of drugs, and these, together with values from other sources, are found in Table 10–7.

Phase Diagrams and the Ideal Solubility Equation.[19] The phase diagram for the system thymol–salol, shown in Figure 2–17 (p. 42), may be constructed with the help of the ideal solubility equation (equations (10–11) and (10–12)). Conversely, if the points along the two lines of Figure 2–17 are obtained experimentally, they may be used together with the ideal solubility equation (equation (10–11) or (10–12)) to calculate the heats of fusion ΔH_f of substances such as salol and thymol, which are completely miscible in the liquid state, immiscible as solids, and form eutectic mixtures. Phase diagrams, such as Figure 2–17, have been used to study matrix-type dosage forms, changes in the solubility of drug mixtures as a function of temperature and composition, and to locate the eutectic point for mixtures of various pharmaceutical excipients.[20–23]

Example 10–8.[24,25] To demonstrate the use of the ideal solubility equation (equation (10–11)), we begin by calculating several points on the phase diagram, Figure 2–17, first taking thymol as the solute and salol as the solvent. This puts us on the right-hand side of the graph. The heat of fusion ΔH_f of thymol is 4126 cal/mole, the melting point is 51.5° C (324.7° K), and the molecular weight is 150.2 g/mole. The melting point of salol is 42.0° C (315.2° K), and its molecular weight is 214.2 g/mole.

(a) Let us calculate the ideal solubilities of thymol, expressed as mole fraction, at 20°, 30°, and 40° C, using the ideal solubility equation (equation (10–11)). Once the mole fraction solubilities are obtained they may be converted to molalities, $m = 1000\ X_2/M_1(1 - X_2)$, and from molalities to weight percent (%[w/w]). The three points may be plotted on the right-hand side of a graph, patterned after Figure 2–17, and a straight line drawn through the points.

The approach taken with thymol as solute and salol as solvent at 40° C (313.2° K) is as follows:

$$\ln X_2 = \frac{-4126}{1.9872}\left(\frac{324.7 - 313.2}{324.7 \cdot 313.2}\right) = 0.235$$

The anti-ln (that is, the exponential, e^x), of $\ln X_2$, −0.235, at 40° C is

$$X_2^{40°} = 0.791 \text{ or } 72.63\% \text{ (w/w)}$$

At 30° and 20° C, the X_2 values are

$$X_2^{30°} = 0.635$$

$$X_2^{20°} = 0.503$$

We now assume that phenyl salicylate (salol), molecular weight 214.2 g/mole, is the solute and thymol is the solvent. It is difficult to find the heat of fusion ΔH_f for salol in the literature; let us work backwards to calculate it. Knowing the melting point of salol, 42° C, and calculating its mole fraction near the temperature (melting point)

TABLE 10–7. *Heats of Fusion for Drugs and Other Molecules

	ΔH_f (cal/mole)
Anthracene	6,897
Benzoic acid	4,302
Butyl *p*-hydroxybenzoate	6,410
Brompheniramine maleate	11,200
Caffeine	5,044
Cannabidiol	4,660
Cetyl alcohol	8,194
Chlorpromazine hydrochloride	6,730
Estradiol cypionate	7,030
Iodine	3,740
Meprobamate	9,340
Methoxyphenamine hydrochloride	6,960
Methyl *p*-aminobenzoate	5,850
Methyl *p*-hydroxybenzoate	5,400
Methyltestosterone	6,140
Myristic acid	10,846
Naphthalene	4,440
Phenanthrene	4,456
Phenylephrine hydrochloride	6,800
Phenytoin	11,300
p-Aminobenzoic acid	5,000
p-Hydroxybenzoic acid	7,510
Protriptyline hydrochloride	6,140
Stearic acid	13,524
Sulfadiazine	9,740
Sulfamethoxazole	7,396
Sulfapyridine	8,930
Sulfisomidine	10,780
Sulfur	4,020
Testolactone	6,760
Testosterone	6,190
Testosterone enanthate	5,260
Testosterone propionate	5,290
Theobromine	9,818
Theophylline	7,097
Thiopental	7,010
Tolbutamide	6,122

*Data from the Drug Standards Laboratory of the U.S. Pharmacopeial Convention (courtesy U.S. Pharmacopeial Drug Research and Testing Laboratories); *Handbook of Chemistry and Physics,* R. C. Weast, Ed., CRC, Cleveland, Ohio, 1975, pp. 717–719; S. H. Yalkowsky, G. L. Flynn and T. G. Slunick, J. Pharm. Sci. **61**, 852, 1972; K. C. James and M. Roberts, J. Pharm. Pharmacol. **20**, 1045, 1968; S. S. Yang and J. K. Guillory, J. Pharm. Sci. **61**, 26, 1972. (See S. S. Yang and J. K. Guillory, J. Pharm. Sci. **61**, 26, 1972, and H. O. Lin and J. K. Guillory, J. Pharm. Sci. **59**, 973, 1970, for the effect of polymorphism on the ΔH_f of sulfonamides.)

for the pure liquid at, say, 35° C, we obtain, with the help of equation (10–11), a good estimate for the heat of fusion of salol. One gets a more accurate value for ΔH_f where the solute, salol, is in high concentration; that is, near the left-hand side of Figure 2–17.

(b) With salol as the solute (left side of the phase diagram) at 35° C (308.2° K), the solution contains 9% (w/w) thymol and 91% (w/w) salol. One converts to mole fraction of salol, using the equation

$$X_2 = \frac{n_2}{n_2 + n_1}$$

The mole n_2 of salol at 35° C is 91 g/214.2 g/mole = 0.4248 mole and the mole n_1 of thymol is 9 g/150.2 g/mole = 0.0599 mole. The mole fraction is therefore

$$X_2 = \frac{0.4248}{0.4248 + 0.0599} = 0.8764$$

$$\ln X_2 = -0.1319 = -\frac{\Delta H_f}{1.9872}\left(\frac{315.2 - 308.2}{315.2 \cdot 308.2}\right)$$

$$\Delta H_f \text{ (salol)} = 3639 \text{ cal/mole}$$

At 35° C the solution should behave nearly ideal, for salol is in the concentration of 91% (w/w), and the ΔH_f obtained should be a reasonable estimate of the heat of fusion of salol.

Nonideal Solutions. The activity of a solute in a solution is expressed as the concentration multiplied by the activity coefficient. When the concentration is given in mole fraction, the activity is expressed as

$$a_2 = X_2\gamma_2 \qquad (10\text{–}13)$$

in which γ_2 on the mole fraction scale is known as the rational activity coefficient (p. 132). Converting to logarithms, we have

$$\log a_2 = \log X_2 + \log \gamma_2 \qquad (10\text{–}14)$$

In an ideal solution, $a_2 = X_2^i$ since $\gamma_2 = 1$, and accordingly the ideal solubility, equation (10–14), may be expressed in terms of activity as

$$-\log a_2 = -\log X_2^i = \frac{\Delta H_f}{2.303RT}\left(\frac{T_0 - T}{T_0}\right) \qquad (10\text{–}15)$$

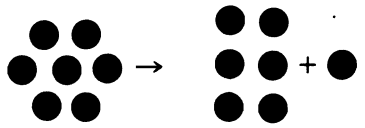
By combining equations (10–14) and (10–15), the mole fraction solubility of a solute in a nonideal solution, expressed in log form, becomes

$$-\log X_2 = \frac{\Delta H_f}{2.303R}\left(\frac{T_0 - T}{T_0\,T}\right) + \log \gamma_2 \qquad (10\text{–}16)$$

Therefore, the mole fraction solubility in various solvents can be expressed as the sum of two terms: the solubility in an ideal solution and the logarithm of the activity coefficient of the solute. As a real solution becomes more ideal, γ_2 approaches unity, and equation (10–16) reduces to equation (10–15). Only rarely, however, does the experimentally determined solubility in real solutions compare favorably with the value calculated by use of the ideal solubility equation. The activity coefficient γ_2, depending on the nature of both the solute and the solvent as well as on the temperature of the solution, must be accounted for before the calculated solubility will correspond well with experimental values.

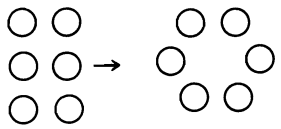
The log γ_2 term of equation (10–16) is obtained by considering the intermolecular forces of attraction that must be overcome, or the work that must be done, in removing a molecule from the solute phase and depositing it in the solvent. This process may be considered as occurring in three steps.[26]

1. The first step involves the removal of a molecule from the solute phase at a definite temperature. The work done in removing a molecule from a solute so that it passes into the vapor state requires breaking the bonds between adjacent molecules. The work involved in breaking the bond between two adjacent molecules is $2w_{22}$, in which the subscript $_{22}$ refers to the interaction between solute molecules. When the molecule escapes from the solute phase, however, the hole it has created closes, and one half of the energy is regained. The gain in potential energy or net work for the process is thus w_{22}, schematically represented as



Solute — Liberation of a molecule from the solute

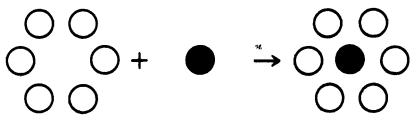
2. The second step involves the creation of a hole in the solvent just large enough to accept the solute molecule. The work required for this step,



Solvent — Creation of a hole in the solvent

is w_{11}, in which the subscript refers to the energy of interaction between solvent molecules.

3. The solute molecule is finally placed in the hole in the solvent,



Solvent — Solute molecule — Solution

and the gain in work or decrease of potential energy in this step is $-w_{12}$. The subscript $_{12}$ stands for the interaction energy of the solute with the solvent. The hole or cavity in the solvent, created in step 2, is now closed, and an additional decrease in energy, $-w_{12}$, occurs, involving net work in this final step of $-2w_{12}$.

The total work as given by this extremely simplified scheme is thus $(w_{22} + w_{11} - 2w_{12})$. The activity coefficient term of the solubility equation, however, has

been shown by Scatchard and by Hildebrand and Wood[18] to be proportional also to the volume of the solute, considered as a supercooled liquid, and to the fraction of the total volume occupied by the solvent. The logarithm of the activity coefficient is given by the more elaborate expression

$$\ln \gamma_2 = (w_{22} + w_{11} - 2w_{12}) \frac{V_2 \Phi_1^2}{RT} \qquad (10-17)$$

in which V_2 is the molar volume or volume per mole of (supercooled) liquid solute and Φ_1 is the volume fraction, or $X_1V_1/(X_1V_1 + X_2V_2)$ of the solvent. R is the gas constant, 1.987 cal/mole deg, and T is the absolute temperature of the solution.

The w terms in equation (10–17) are potential energies or terms representing attractive forces. Since van der Waals forces between molecules follow a geometric mean rule, the term w_{12} can be taken as approximately equal to the *geometric mean* of the solvent and solute terms. That is, the interaction between different molecules is equal to the square root of the product of the attractions among similar molecules, or

$$w_{12} = \sqrt{w_{11}w_{22}} \qquad (10-18)$$

When this substitution is made in equation (10–17), it becomes

$$\ln \gamma_2 = [w_{11} - 2(w_{11}w_{22})^{1/2} + w_{22}] \frac{V_2 \Phi_1^2}{RT} \qquad (10-19)$$

The terms within the brackets are seen to represent a perfect square, and equation (10–19) therefore becomes

$$\ln \gamma_2 = [(w_{11})^{1/2} - (w_{22})^{1/2}]^2 \frac{V_2 \Phi_1^2}{RT} \qquad (10-20)$$

Equation (10–20) can be modified in the following manner. The w terms of equation (10–20) are approximately equal to the a/V^2 term in the van der Waals equation for nonideal gases and liquids (p. 27), and they serve as a measure of the *internal pressures* of the solvent and the solute in nonpolar or moderately polar nonideal solutions. The $(w)^{1/2}$ terms are known as *solubility parameters* and are designated by the symbols δ_1 and δ_2 for solvent and solute respectively. Equation (10–20) is thus written in terms of the common logarithm as

$$\log \gamma_2 = (\delta_1 - \delta_2)^2 \frac{V_2 \Phi_1^2}{2.303RT} \qquad (10-21)$$

In dilute solutions, the volume fraction is nearly unity, and Φ_1^2 may be disregarded as a first approximation. When a rough calculation shows it to be significantly less than 1, a recalculation must be made taking into account the value of Φ_1. this correction will be described in the example to follow.

When the term for $\log \gamma_2$ is substituted in equation (10–16), the mole fraction solubility of a nonpolar or moderately polar solute is obtained as

$$-\log X_2 = \frac{\Delta H_f}{2.303RT}\left(\frac{T_0 - T}{T_0}\right) + \frac{V_2 \Phi_1^2}{2.303RT}(\delta_1 - \delta_2)^2 \qquad (10-22)$$

If R is replaced by 1.987 cal/mole deg and T by 298° K at 25° C, the temperature most frequently employed, we obtain

$$-\log X_2 = \frac{\Delta H_f}{1364}\left(\frac{T_0 - 298}{T_0}\right) + \frac{V_2 \Phi_1^2}{1364}(\delta_1 - \delta_2)^2 \qquad (10-23)$$

The solubility parameters, which express the cohesion between like molecules, may be calculated from heats of vaporization, internal pressures, surface tensions, and other properties, as described by Hildebrand and Scott.[27] The heat of vaporization in conjunction with the molar volume of the species, when available at the desired temperature, probably affords the best means for calculating the solubility parameter. It is roughly the square root of the internal pressure (p. 218) or

$$\delta = \left(\frac{\Delta H_v - RT}{V_l}\right)^{1/2} \qquad (10-24)$$

in which ΔH_v is the heat of vaporization and V_l is the molar volume of the liquid compound at the desired temperature, R is the gas constant, and T is the absolute temperature. If the solute is a solid at this temperature, its molar volume must be obtained at elevated temperature where it is a liquid (i.e., at temperatures above the melting point) and extrapolated to the temperature under consideration. Where this method is not satisfactory for solids, other methods have been devised.[28,29]

Example 10–9. (*a*) Compute the solubility parameter of iodine and then (*b*) determine the mole fraction and molal solubility of iodine in carbon disulfide at 25° C.[30] (*c*) What is the activity coefficient of the solute in this solution? The heat of vaporization of liquid iodine extrapolated to 25° C is 11,493 cal/mole, the average heat of fusion ΔH_f is about 3600 cal at 25° C, the melting point of iodine is 113° C, and its molar volume V_2 is 59 cm³ at 25° C. The solubility parameter of carbon disulfide is 10.

(*a*)

$$\delta = \left(\frac{11{,}493 - 1.987 \times 298.2}{59}\right)^{1/2} = 13.6$$

(Notice that the value in Table 10–8, obtained from solubility data, is somewhat different from the value obtained here.)

(*b*) X_2 is first calculated assuming that Φ_1^2 is unity.

$$-\log X_2 = \frac{3{,}600}{1364}\left(\frac{386 - 298}{386}\right) + \frac{59}{1364}(10.0 - 13.6)^2$$

$$X_2 = 0.0689$$

Now the volume fraction Φ_1 is equal to $V_1(1 - X_2)/[V_1(1 - X_2) + V_2X_2]$ or, for iodine ($V_2 = 59$ cm^3) in carbon disulfide ($V_1 = 60$ cm^3),

$$\Phi_1 = 0.9322$$

Recalculating X_2 under (*b*) with ${\Phi_1}^2$ as $(0.9322)^2$ included in the second right-hand term of the solubility equation gives

$$X_2 = 0.0815$$

After six such replications (iterations) using a hand calculator, the result becomes $X_2 = 0.0845$. This procedure of repeated calculations is called *iteration.*[30] The experimental value for the solubility in carbon disulfide is recorded by Hildebrand and Scott[31] as 0.0546 at 25° C. The ideal mole fraction solubility ${X_2}^i$ of iodine is 0.250 at 25° C.

The calculated mole fraction solubility of iodine in carbon disulfide may be converted to molal concentration by use of the equation

$$m = \frac{1000\,X_2}{(1 - X_2)M_1} = \frac{1000 \times 0.085}{(1 - 0.085)(76.13)} = 1.22 \text{ mole/kg}$$

(*c*) By comparing equations (10–13) and (10–15), it becomes clear that the ideal solubility is related to the actual solubility at a definite temperature by the expression

$$a_2 = {X_2}^i = X_2\gamma_2$$

Therefore, the activity coefficient of the solute is

$$\gamma_2 = {X_2}^i/X_2 = 0.25/0.055 = 4.55$$

Hildebrand and Scott[31] include the solubility parameters for a number of compounds in their book. A table of solubility parameters has also been compiled by Hansen and Beerbower.[32] The approximate values for some representative compounds of pharmaceutical interest are listed in Tables 10–8 and 10–9. $\delta_{(total)}$ is essentially the δ value for solvent and drug referred to in this section. δ_D, δ_P, and δ_H are partial solubility parameters introduced by Hansen and used for an extended theory of solubility, which is not treated here. The parameter δ_D accounts for nonpolar effects, δ_P for polar effects, and δ_H to express the hydrogen bonding nature of the solute or solvent molecules. The sum of the squares of the partial parameters gives the total cohesive energy density ${\delta_{(total)}}^2$,

$${\delta_{(total)}}^2 = {\delta_D}^2 + {\delta_P}^2 + {\delta_H}^2 \qquad (10\text{–}25)$$

Kesselring et al.[33] have determined both total and partial solubility parameters using gas–liquid chromatography.

The more alike are the δ values of two components, the greater is the mutual solubility of the pair. For example, the δ value of phenanthrene is 9.8; for the solvent carbon disulfide, 10; and for normal hexane, 7.3. Therefore, phenanthrene would be expected to be more soluble in CS_2 than in n-C_6H_{14}. When the solubility parameter of the solute is identical to that of the solvent, the cohesive forces of the solute and the solvent are alike as long as hydrogen bonding and other

TABLE 10–8. *Molar Volume and Solubility Parameters for Some Liquid Compounds*,†*

Liquid	V (cm^3/mole)	Solubility Parameter (cal/cm^3)$^{1/2}$			
		δ_D	δ_P	δ_H	$\delta_{(total)}$
n-Butane	101.4	6.9	0	0	6.9
n-Hexane	131.6	7.3	0	0	7.3
n-Octane	163.5	7.6	0	0	7.6
Diethyl ether	104.8	7.1	1.4	2.5	7.7
Cyclohexane	108.7	8.2	0	0.1	8.2
n-Butyl acetate	132.5	7.7	1.8	3.1	8.5
Carbon tetrachloride	97.1	8.7	0	0.3	8.7
Toluene	106.8	8.8	0.7	1.0	8.9
Ethyl acetate	98.5	7.7	2.6	3.5	8.9
Benzene	89.4	9.0	0	1.0	9.1
Chloroform	80.7	8.7	1.5	2.8	9.3
Acetone	74.0	7.6	5.1	3.4	9.8
Acetaldehyde	57.1	7.2	3.9	5.5	9.9
Carbon disulfide	60.0	10.0	0	0.3	10.0
Dioxane	85.7	9.3	0.9	3.6	10.0
1-Octanol	157.7	8.3	1.6	5.8	10.3
Nitrobenzene	102.7	9.8	4.2	2.0	10.9
1-Butanol	91.5	7.8	2.8	7.7	11.3
1-Propanol	75.2	7.8	3.3	8.5	12.0
Dimethylformamide	77.0	8.5	6.7	5.5	12.1
Ethanol	58.5	7.7	4.3	9.5	13.0
Dimethyl sulfoxide	71.3	9.0	8.0	5.0	13.0
Methanol	40.7	7.4	6.0	10.9	14.5
Propylene glycol	73.6	8.2	4.6	11.4	14.8
Ethylene glycol	55.8	8.3	5.4	12.7	16.1
Glycerin	73.3	8.5	5.9	14.3	17.7
Formamide	39.8	8.4	12.8	9.3	17.9
Water	18.0	7.6	7.8	20.7	23.4

*From C. Hansen and A. Beerbower, in *Encyclopedia of Chemical Technology,* Suppl. Vol., 2nd Edition, A. Standen, Ed., Wiley, New York, 1971, pp. 889–910. δ_D, δ_P, and δ_H are partial solubility parameters defined briefly above. $\delta_{(total)}$ is essentially the solvent solubility parameter, δ_1, defined by Hildebrand and used throughout this section.

†It must be cautioned that a number of solvents in this table and throughout the book are not suitable as solvents in medicinal or nutritive products. Dioxane, for example, is both toxic and irritating to the skin.

TABLE 10–9. *Molar Volume and Solubility Parameters of Crystalline Compounds (Tentative Values)**

Solid Compound	V (cm^3/mole)	Solubility Parameter $(cal/cm^3)^{1/2}$			
		δ_D	δ_P	δ_H	$\delta_{(total)}$
Benzoic acid	104	8.9	3.4	4.8	10.7
Caffeine	144	10.1	3.5	9.1	14.1
Methyl paraben	145	9.3	4.4	6.0	11.8
Naphthalene	123	9.4	1.0	1.9	9.6
Phenobarbital	137	10.3	4.8	5.3	12.6
Sulfadiazine	182	9.5	4.8	6.6	12.5
Testosterone propionate	294	9.2	2.9	2.8	10.0
Tolbutamide	229	9.7	2.9	4.1	10.9

*Refer to the footnote in Table 10–8 for a definition of δ_D, δ_P, *and* δ_H. $\delta_{(total)}$ is essentially the solute δ_2 value referred to in this section.

complicating interactions are not involved. Then $\delta_1 - \delta_2 = 0$, and the last term of equation (10–23) becomes zero. The solubility of the solute then depends alone on the ideal solubility term of the equation, involving the heat of fusion, the melting point of the solute, and the temperature of the solution.

James et al.[29] investigated the solubility of testosterone esters in a number of aliphatic straight- and branched-chain alkanes, cyclic and aromatic hydrocarbons, and halogen derivatives. They determined the δ value of testosterone propionate and other esters and arrived at values of 9.5 to 10.0 $(cal/cm^3)^{1/2}$ for testosterone propionate. The Hildebrand solubility theory was used with some success by James and his associates to predict the solubilities of steroidal esters in hydrocarbon solvents.

In the use of solubility parameters, a distinction should also be made between those compounds that form hydrogen bonds and those that do not. The δ values may be used to predict the miscibility of hydrogen-bonding solvents or of non–hydrogen-bonding solvents, but they are not always applicable when members of the two different classes are mixed.

The nonideal solutions to which the Scatchard–Hildebrand equation applies are called *regular solutions*. Regular solutions may be better understood by reference to several properties of ideal solutions. First, the molecules of an ideal solution exhibit complete freedom of motion and randomness of distribution in the solution. Secondly, an ideal solution forms with no change in heat content, that is to say, heat is not absorbed or evolved during the mixing process. Furthermore, there is no change in volume when the components of an ideal solution are mixed. The partial free energy change involved in the transfer of a mole of solute from the solute phase to a saturated solution is written, for an ideal solution, as

$$\overline{\Delta G_2} = RT \ln X_2 \qquad (10\text{–}26)$$

Since the change in heat content ΔH is zero

$$\overline{\Delta G_2} = \overline{\Delta H_2} - T\,\overline{\Delta S_2} = -T\,\overline{\Delta S_2} \qquad (10\text{–}27)$$

and the entropy for the solute in the ideal solution is

$$\overline{\Delta S_2} = -\overline{\Delta G_2}/T = -R \ln X_2 \qquad (10\text{–}28)$$

The molecules of regular solutions, like those of ideal solutions, possess sufficient kinetic energy to prevent ordering and a loss in entropy; and a regular solution, like an ideal solution, exhibits complete randomness. The entropy change in forming a regular solution is given by the same formula as that for an ideal solution,

$$\overline{\Delta S_2} = -R \ln X_2 \qquad (10\text{–}29)$$

On the other hand, owing to cohesion among the solute molecules and among the solvent molecules, regular solutions exhibit positive deviation from Raoult's law. Unlike ideal solutions, they absorb heat when the components are mixed. It can be shown from thermodynamic considerations that the heat change when 1 mole of solute is added to a large quantity of regular solution is equal to $RT \ln \gamma_2$, which may be set equal to the solubility parameter term in the solubility equation (cf. equation (10–21)).

$$\overline{\Delta H_2} = RT \ln \gamma_2 = V_2\Phi_1^2(\delta_1 - \delta_2)^2 \qquad (10\text{–}30)$$

These relationships can be used to derive the solubility expression, equation (10–22) as demonstrated in the following paragraph. For a nonideal solution, X_2 in equation (10–26) must be replaced by the activity a_2 or

$$\overline{\Delta G_2} = RT \ln a_2 \qquad (10\text{–}31)$$

From equations (10–15) and (10–31)

$$-\overline{\Delta G_2} = \frac{\Delta H_f(T_0 - T)}{T_0} \qquad (10\text{–}32)$$

Writing the familiar free energy equation

$$\overline{\Delta G_2} = \overline{\Delta H_2} - T\,\overline{\Delta S_2} \qquad (10\text{–}33)$$

or

$$T\,\overline{\Delta S_2} = -\overline{\Delta G_2} + \overline{\Delta H_2} \qquad (10\text{–}34)$$

gives

$$-RT \ln X_2 = \frac{\Delta H_f(T_0 - T)}{T_0} + V_2\Phi_1^2(\delta_1 - \delta_2)^2 \qquad (10\text{–}35)$$

by the application of equations (10–29), (10–30),

(10–32) and (10–34). Then equation (10–35) may be written as

$$-\log X_2 = \frac{\Delta H_f}{2.303RT}\left(\frac{T_0 - T}{T_0}\right) + \frac{V_2\Phi_1^2}{2.303RT}(\delta_1 - \delta_2)^2$$

which is identical with equation (10–22).

Extended Hildebrand Solubility Approach. A modification of the Scatchard–Hildebrand equation has been developed[34] and is referred to as the *extended Hildebrand solubility approach* (EHS). The extended method allows one to calculate the solubility of polar and nonpolar solutes in solvents ranging from nonpolar hydrocarbons to highly polar solvents such as alcohols, glycols, and water. Although formulated specifically for crystalline solids in liquid solution, the EHS approach should also apply to liquid–liquid and gas–liquid systems.

It is well recognized that the established regular solution theory, represented by equation (10–22), usually provides poor predictions of solubility for drugs and other crystalline solids in polar solvents. Polar systems are quite irregular, involving self-association of solute or solvent, solvation of the solute by the solvent molecules, or complexation of two or more solute species in the solution. The intermolecular attachments consist of hydrogen bonds, charge transfer complexes (Chapter 11), and other types of Lewis acid–base interactions.

The solubility equation used in the EHS approach is

$$-\log X_2 = -\log X_2^i + A(w_{11} + w_{22} - 2W) \qquad (10\text{–}36)$$

in which the last term corresponds to the expression for $\log \gamma_2$, equation (10–17) of Hildebrand and Scatchard. In equation (10–36), A stands for $V_2\Phi_1^2/(2.303RT)$ and W is used for w_{12} from equation (10–17). The negative logarithm of the ideal solubility, $-\log X_2^i$, may be calculated from a knowledge of ΔH_f, T_0, and T as shown in equation (10–15).

Alternatively, it may be obtained from ΔS_f:

$$-\log X_2^i = \frac{\Delta S_f}{R}\log\frac{T_o}{T} \qquad (10\text{–}37)$$

as suggested by Hildebrand et al.[35] ΔS_f, the entropy of fusion at the melting point, is determined using the expression

$$\Delta H_f = T_o \Delta S_f \qquad (10\text{–}38)$$

According to the EHS approach, the term involving the logarithm of the activity coefficient γ_2 is partitioned into two terms, one representing mainly physical or van der Waals forces γ_v and an additional term γ_R representing residual, presumably stronger, forces:

$$\log \gamma_2 = \log \gamma_v + \log \gamma_R \qquad (10\text{–}39)$$

in which

$$\log \gamma_v = A(\delta_1 - \delta_2)^2 = A(\delta_1^2 + \delta_2^2 - 2\delta_1\delta_2) \qquad (10\text{–}40)$$

and

$$\log \gamma_R = A(2\delta_1\delta_2 - 2W) \qquad (10\text{–}41)$$

Equation (10–39) is written, in terms of equations (10–40) and (10–41) as:

$$\log \frac{X_2^i}{X_2} = \log \gamma_2 = A(\delta_1 - \delta_2)^2 + 2A(\delta_1\delta_2 - W)$$

or

$$-\log X_2 = -\log X_2^i + A(\delta_1^2 + \delta_2^2 - 2W) \qquad (10\text{–}42)$$

Investigators[34] have applied the EHS approach to polar and nonpolar solutes in individual solvents as well as mixed solvent systems.

Equation (10–42) differs from equation (10–22) in that the geometric mean is replaced by W. Equation (10–42) ordinarily provides an accurate prediction of the mole fraction solubility of a polar drug in binary solvent systems (i.e., two solvents mixed in various proportions) as demonstrated in *Examples 10–10* and *10–11*. W is obtained for a solute in a particular solvent system by rearranging equation (10–42):

$$\frac{\log (X_2^i/X_2)}{A} = \frac{\log \gamma_2}{A} = \delta_1^2 + \delta_2^2 - 2W$$

$$W = \frac{1}{2}(\delta_1^2 + \delta_2^2 - (\log \gamma_2)/A) \qquad (10\text{–}43)$$

The solubility parameters, δ_1 and δ_2, are known quantities. Log γ_2 is obtained from a knowledge of the drug's ideal solubility, X_2^i, and its mole fraction solubility, X_2, in a particular solvent system. The observed solubilities of caffeine in mixtures of dioxane and water are shown in Figure 10–5 together with the back-calculated solubility curve obtained by use of the

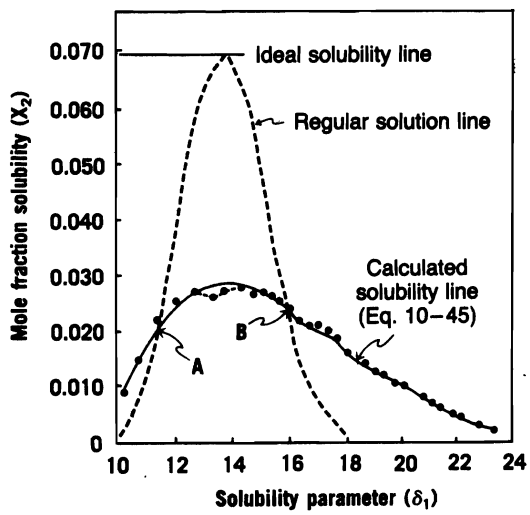


Fig. 10–5. Mole fraction solubility of caffeine at 25° C in dioxane–water mixtures. *A* and *B* are points at which real solubility equals regular solution solubility and W = $\delta_1\delta_2$. Filled circles are experimental solubility points. (From A. Adjei, J. Newburger and A. Martin, J. Pharm. Sci. 69, 659, 1980, reproduced with permission of the copyright owner.)

TABLE 10–10. *Several Observed and Calculated Solubilities of Caffeine in Dioxane–Water Systems at 25° C

Volume % water	δ_1	log X_2	A	W†	$W_{(calc)}$‡	$X_{2(obs)}$	$X_{2(calc)}$§
0	10.01	0.90646	0.10257	140.901	141.120	0.0085	0.0094
20	12.70	0.40443	0.09467	173.729	173.729	0.0270	0.0270
40	15.39	0.41584	0.09269	211.403	211.380	0.0263	0.0261
50	16.73	0.50555	0.09369	232.469	233.465	0.0214	0.0214
60	18.07	0.62665	0.09520	255.191	255.220	0.0162	0.0164
80	20.76	0.94347	0.09837	305.913	305.951	0.0078	0.0080
100	23.45	1.47643	0.10179	362.919	362.343	0.0023	0.0022

*$\delta_2 = 13.8$; $-\log X_2^i = 1.1646$.
†W is calculated from equation (10–43). Its units are cal/cm^3.
‡$W_{(calc)}$ is obtained using the quartic expression (10–45).
§$X_{2(calc)}$ is calculated using equation (10–42) with W replaced by $W_{(calc)}$.

extended Hildebrand approach. The calculations are illustrated in *Example 10–10*, part of the data for which are found in Tables 10–9 and 10–10.

Example 10–10. Compute the value of W for a solution of caffeine in the pure solvent, dioxane ($\delta = 10.01$), in pure water ($\delta = 23.45$), and in a 50:50 volume percent of dioxane and water ($\delta = 16.73$) at 25° C. ΔH_f is 5044 cal/mole, and $T_0 = 512°$ C. According to equation (10–38), $\Delta S_f = 9.85$ cal/mole deg. Using equation (10–37), the logarithm of the ideal mole fraction solubility, $-\log X_2^i$ is found to be 1.16460, or $X_2^i = 0.068454$. The molar volume, V_2, of caffeine is 144 cm^3/mole at 25° C. The volume fractions, ϕ_1, of dioxane, water, and a 50:50 mixture of dioxane and water are 0.985809, 0.982066, and 0.942190, respectively. Using the definition of A, following equation (10–36), one obtains A* for caffeine in dioxane as 0.102570; in water, 0.101793; and in the 50:50 mixture, 0.093694.

The mole fraction solubilities of caffeine in the three solvents at 25° C are found experimentally to be 0.008491 in dioxane, 0.002285 in water, and 0.021372 in the 50:50 mixture of dioxane and water.

Using equation (10–43), one obtains for log γ_2/A for the three solutions

$$\frac{\log (0.068454/0.008491)}{0.102570} = 8.83728 \text{ in dioxane}$$

$$\frac{\log (0.068454/0.002285)}{0.101793} = 14.50505 \text{ in water}$$

and

$$\frac{\log (0.068454/0.021372)}{0.093694} = 5.39580 \text{ in the 50:50 mixture}$$

W values are then obtained again with the help of equation (10–43):

In dioxane:

$$8.83728 = (10.01)^2 + (13.8)^2 - 2W$$
$$W = 140.90141$$

In water:

$$14.50425 = (23.45)^2 + (13.8)^2 - 2W$$
$$W = 362.91913$$

In the 50:50 mixture:

$$5.39574 = (16.73)^2 + (13.8)^2 - 2W$$
$$W = 232.46858$$

The desirability of a theoretic approach is the ability to calculate solubilities of a drug in mixed and pure solvents, using only fundamental physical chemical properties of solute and solvent. Unfortunately, W at present cannot be obtained by a consideration of the molecular characteristics of the species in solution. It has been found, however, that when the experimentally derived W values (as calculated in *Example 10–10*) are regressed against a power series in δ_1, for the various solvents of the mixture, a polynomial equation is obtained that may be used for the accurate back-calculation of solubilities. A power series in the second degree (quadratic) may be used for this purpose. Using the complete set of 30 solubility values (see Table 10–10 for some of these), the quadratic equation is obtained:

$$W_{(calc)} = 79.411400 + 1.868572\delta_1 + 0.435648{\delta_1}^2 \quad (10\text{–}44)$$

The quartic equation is:

$$W_{(calc)} = 15.075279 + 17.627903\delta_1 - 0.966827{\delta_1}^2 + 0.053912{\delta_1}^3 - 0.000758{\delta_1}^4 \quad (10\text{–}45)$$

Using equation (10–44) or (10–45) and a hand calculator, one can readily calculate the solubility of caffeine in any combination of dioxane and water at 25° C.

Example 10–11†. Calculate the solubility of caffeine ($\delta_2 = 13.8$) at 25° C in a 40:60 volume percent mixture of dioxane and water. Use the quadratic expression, equation (10–44), to obtain $W_{(calc)}$.

One first obtains the δ_1 value of the 40:60 mixture of dioxane and water using the equation

$$\delta_1 = \phi_d\delta_d + \phi_w\delta_w$$

in which ϕ_d and ϕ_w are the volume fractions, 0.40 and 0.60, of the solvents dioxane and water and δ_d and δ_w are their solubility parameters.

$$\delta_1 = 0.40(10.01) + 0.60(23.45) = 18.07$$

Then $W_{(calc)}$ is obtained by back-calculation:

$$W_{(calc)} = 79.41140 + 1.86857(18.07) + 0.43565(18.07)^2$$
$$W_{(calc)} = 255.427 \qquad W_{(exp)} = 255.191$$

*A is obtained from a knowledge of $X_{2(obs)}$, and these values are used for convenience in this example. When the solubility is not known, it is necessary to obtain A by use of an iteration (replication) procedure as described on page 225.

†As mentioned in the footnote of Table 10–8, dioxane is externally irritating and internally toxic and cannot be used in drug or food products. It is chosen as a solvent in *Example 10–11* simply because it is miscible with water and has an appropriate solubility parameter. Such agents must be carefully tested for untoward effects before any use is made of them in man or animal.

This value for $W_{(calc)}$ is substituted in equation (10–42) in which $-\log X_2^i$ for caffeine is 1.1646 and A is 0.09520.

$$-\log X_2 = 1.1646 + 0.09520[(18.07)^2 + (13.8)^2 - 2(255.427)]$$

$$-\log X_2 = 1.74635$$

$$X_{2(calc)} = 0.0179 \qquad X_{2(exp)} = 0.0162$$

Some values, calculated as shown in *Examples 10–10* and *10–11*, are found in Table 10–10. The $X_{2(calc)}$ values in Table 10–10 were back-calculated using a quartic expression, equation (10–45), rather than the quadratic equation used in *Example 10–11*, which accounts for the small difference in results.

Solvation and Association in Solutions of Polar Compounds. We saw in equation (10–30) that heat must be absorbed when the solute is mixed with the solvent to form a regular solution. This happens because the squared term $(\delta_1 - \delta_2)^2$ can lead only to positive values (or zero). We can refer back to equation (10–17), however, where we find the term w_{12}, which expresses the interaction of the solute and solvent molecules. If we remove the restriction that this term must follow the rule of the geometric mean given in formula (10–18), we allow $2w_{12}$ to be $> w_{11} + w_{22}$ and ΔH may then become negative. This leads to a negative deviation from Raoult's law and applies when specific interactions, such as hydrogen bonding (p. 213), occur between the solute and the solvent. Such specific combinations of the solvent with the solute are known as *solvation*.

When the interaction occurs between like molecules of one of the components in a solution, the phenomenon is referred to as *association*. This type of interaction is exemplified by the dimerization of benzoic acid in some nonpolar solvents or the interlinking of water molecules by hydrogen bonding. It leads to positive heats of solution and to positive deviations from Raoult's law. The association of water molecules is reflected in a large w_{11} in equation (10–17). When water is mixed with a nonpolar solute, w_{11} is much larger than w_{22}, and w_{12} is small. Such a situation obviously leads to low solubility. The specific interaction effects, known as *solvation* and *association*, cannot be accounted for in a satisfactory way by the Scatchard–Hildebrand formula (equation (10–22)) but rather require a more refined treatment, which is outside the scope of this book.

Solubility and the Heat of Solution. Solubility as a function of temperature for nonelectrolytes, weak electrolytes, or strong electrolytes in highly nonideal solutions can be calculated using the *heat of solution*, ΔH_{soln}, instead of the heat of fusion in an expression analogous to the ideal solubility expression (equation (10–11), p. 221). For nonelectrolytes and weak electrolytes, the following equation is used[36,37]:

$$\ln (c''/c') = \frac{\Delta H_{soln}}{R} \frac{(T'' - T')}{(T'T'')} \qquad (10\text{–}46)$$

For strong electrolytes, R is replaced by νR, in which ν is the number of ions produced in the dissociation of the electrolyte. The terms c' and c'' are concentrations such as molar, molal, mole fraction, grams/liter, or percent. These concentration terms appear in equation (10–46) as ratios, c''/c', so as to cancel the concentration units, as long as the same units are used for both c' and c''. The concentration term c' corresponds to the Kelvin temperature T', and c'' corresponds to T''. ΔH_{soln} is the heat of solution in cal/mole and R is the universal gas constant expressed as 1.9872 cal mole^{-1} deg^{-1}.

Using equation (10–46), the solubility of a solute in a particular solvent can be determined at one temperature if the heat of solution ΔH_{soln} and the solubility at another temperature are known.

Example 10–12. The solubility of urea (molecular weight 60.06 g/mole) in water at 298° K is 1.20 g/g H_2O; the ΔH_{soln} for urea in water at 25° C is 2820 cal/mole. What is the molal solubility of urea at 5° C?

$$\ln (1.20) - \ln c' = \frac{2820}{1.9872}\left(\frac{298 - 278}{298 \cdot 278}\right)$$

$\ln c' = -0.16$ and $c' = 0.85$ g/g H_2O or 850 g/kg H_2O

850 g/kg H_2O ÷ 60.06 g/mole = 14.2 mole/kg H_2O

The experimental solubility of urea on the molal scale is 14.2 mole/kg H_2O.

Solubility of Strong Electrolytes. The effect of temperature on the solubility of some salts in water is shown in Figure 10–6. A rise in temperature increases the solubility of a solid that absorbs heat (*endothermic* process) when it dissolves. This effect conforms with the Le Chatelier principle, which states that a system tends to adjust itself in a manner so as to counteract a stress such as an increase of temperature. Conversely, if the solution process is *exothermic*, that is, if heat is evolved, the temperature of the solution rises and the container feels warm to the touch. The solubility in this case decreases with an elevation of the temperature, again following Le Chatelier's principle. Most solids belong to the class of compounds that absorb heat when they dissolve.

Sodium sulfate exists in the hydrated form, $Na_2SO_4 \cdot 10H_2O$, up to a temperature of about 32° C, the solution process (dissolution) is endothermic, and solu-

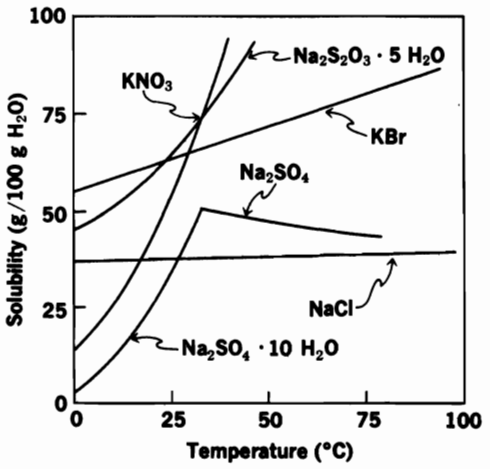


Fig. 10–6. The influence of temperature on the solubility of various salts.

bility increases with temperature. Above this point, the compound exists as the anydrous salt, Na_2SO_4, the dissolution is exothermic, and solubility decreases with an increase of temperature (Fig. 10–6). Sodium chloride does not absorb or evolve an appreciable amount of heat when it dissolves in water; thus, its solubility is not altered much by a change of temperature, and the heat of solution is approximately zero, as observed in Figure 10–6.

These phenomena can be explained in terms of the heat of solution, ΔH. The quantity ΔH is properly known as the *partial* or *differential heat of solution.* It is the heat absorbed per mole when a small quantity of solute is added to a large quantity of solution. It may also be defined as the rate of change of the heat of solution per mole of solute in a solution of any specified concentration. The *total* or *integral heat of solution* is the heat absorbed when 1 mole of solute is dissolved in enough solvent to produce a solution of specified concentration.

The heat of solution of a crystalline substance is the sum of the *heat of sublimation* of the solid, as given by the *crystal lattice energy*, and the *heat of hydration* (solvation) of the ions in solution (Table 10–11).

$$\Delta H \text{ (solution)} = \Delta H_{\text{subl}} + \Delta H_{\text{hyd}} \qquad (10\text{–}47)$$

The lattice energy is the energy required to separate 1 mole of a crystal into its ions in the gaseous state or to vaporize the solid:

$$NaCl_{solid} \rightarrow Na^+_{gas} + Cl^-_{gas}$$

The heat of hydration is the heat liberated when the gaseous ions are hydrated; it is influenced by the radius of an ion, since for ions of the same valence, the smaller the ionic radius, the greater is the electrostatic field surrounding the ion and the larger is the heat of hydration. The hydration process can be represented as

$$Na^+_{gas} + Cl^-_{gas} \xrightarrow{H_2O} Na^+_{aq} + Cl^-_{aq}$$

If the heat of hydration, that is, the heat liberated when the ions are hydrated, is sufficient to provide the energy needed to overcome the lattice forces and thus "pull" the ions away from the crystal, the salt will be soluble. In an ideal solution, no hydration (solvation) occurs, and the heat absorbed is that alone that is required to transform the crystals to the liquid state. For this reason, only the heat of fusion ΔH_f is included in the ideal solubility expression, equation (10–11) on page 221.

The heats of solution and solubilities of some salts are shown in Table 10–11. A positive value of ΔH indicates an absorption of heat; a negative value signifies that heat is evolved. The heat of hydration and the lattice energy of sodium chloride are so similar that the process is only slightly endothermic and the temperature has little effect on the solubility. The large heat of solution of silver chloride (large endothermic value) accounts for the insolubility of the salt in water. This is due to the large lattice energy brought about by the great polarizability of the silver ion (p. 87).

Gibbs' phase rule, page 37, is applied to the solubility of a solid in a liquid in the following manner. Since the pressure is ordinarily fixed at 1 atm and hence need not be specified, the rule becomes

$$\mathbf{F} = C - P + 1$$

A subsaturated solution of sodium chloride in water, for example, consists of a single homogeneous phase and two components, salt and water. The number of degrees of freedom is thus $\mathbf{F} = 2 - 1 + 1 = 2$. This means that two variables, both temperature and composition, must be stated to define the system completely. When the solution is saturated with the solute, sodium chloride, and excess solute is present, two phases exist, and the number of degrees of freedom is $\mathbf{F} = 2 - 2 + 1 = 1$. Hence, the conclusion reached by applying the phase rule is that the solubility of sodium chloride in water has a fixed value at any specified temperature. This statement of course is true not only for this specific system but for solubility in general.

Solubility of Slightly Soluble Electrolytes. When slightly soluble electrolytes are dissolved to form saturated solutions, the solubility is described by a special constant, known as the *solubility product*, K_{sp}, of the compound. The solubility products of a number of substances used in pharmacy are listed in Table 10–12.

TABLE 10–11. ***Heats of Solution and Solubility of Some Chlorides***

Compound	Crystal Energy (kcal/mole)	Heat of Hydration (kcal/mole)	ΔH_{soln}* (kcal/mole) (25° C)	Solubility (g/100 g H_2O) (20° C)
AgCl	207	−192	+15.0	1.5×10^{-4}
LiCl	199	−209	−10.0	78.5
NaCl	184	−183	+1.0	36.0
CsCl	152	−147	+5.0	186.5
KCl	167	−164	+3.0	23.8
KBr	161	−156	+5.0	65.0

*A negative value for ΔH, the heat of solution, indicates an evolution of heat (exothermic), and a positive value indicates an absorption of heat (endothermic) during solution.

TABLE 10–12. *Solubility Products of Some Slightly Soluble Electrolytes in Water*

Substance	Solubility Product K_{sp}	Temperature (°C)
Aluminum hydroxide	7.7×10^{-13}	25
Barium carbonate	8.1×10^{-9}	25
Barium sulfate	1×10^{-10}	25
Calcium carbonate	9×10^{-9}	25
Calcium sulfate	6.1×10^{-5}	20
Ferric hydroxide	1×10^{-36}	18
Ferrous hydroxide	1.6×10^{-14}	18
Lead carbonate	3.3×10^{-14}	18
Lead sulfate	1.1×10^{-8}	18
Magnesium carbonate	2.6×10^{-5}	12
Magnesium hydroxide	1.4×10^{-11}	18
Mercurous chloride	2×10^{-18}	25
Mercurous iodide	1.2×10^{-28}	25
Potassium acid tartrate	3.8×10^{-4}	18
Silver bromide	7.7×10^{-13}	25
Silver chloride	1.25×10^{-10}	25
Silver iodide	1.5×10^{-16}	25
Zinc hydroxide	1.8×10^{-14}	18
Zinc sulfide	1.2×10^{-23}	18

Silver chloride is an example of such a slightly soluble salt. The excess solid in equilibrium with the ions in saturated solution at a specific temperature is represented by the equation

$$AgCl_{solid} \rightleftharpoons Ag^+ + Cl^- \qquad (10\text{–}48)$$

and since the salt dissolves only with difficulty and the ionic strength is low, the equilibrium expression may be written in terms of concentrations instead of activities:

$$\frac{[Ag^+][Cl^-]}{[AgCl_{solid}]} = K \qquad (10\text{–}49)$$

Moreover, since the concentration of the solid phase is essentially constant,

$$[Ag^+][Cl^-] = K_{sp} \qquad (10\text{–}50)$$

The equation is only approximate for sparingly soluble salts, or in the presence of other salts, when activities rather than concentrations should be used. It does not hold for salts that are freely soluble in water such as sodium chloride.

As in the case of other equilibrium expressions, the concentration of each ion is raised to a power equal to the number of ions appearing in the formula. Thus, for aluminum hydroxide, $Al(OH)_3$,

$$Al(OH)_{3\ solid} \rightleftharpoons Al^{3+} + 3OH^-$$

$$[Al^{3+}][OH^-]^3 = K_{sp} \qquad (10\text{–}51)$$

Example 10–13. The measured solubility of silver chloride in water at 20° C is 1.12×10^{-5} mole/liter. This is also the concentration of the silver ion and the chloride ion, since silver chloride, being a strong electrolyte, is nearly completely dissociated. Calculate the solubility product of this salt.

$$K_{sp} = (1.12 \times 10^{-5}) \times (1.12 \times 10^{-5})$$
$$= 1.25 \times 10^{-10}$$

If an ion in common with AgCl, that is, Ag^+ or Cl^-, is added to a solution of silver chloride, the equilibrium is altered. The addition of sodium chloride, for example, increases the concentration of chloride ions so that momentarily

$$[Ag^+][Cl^-] > K_{sp}$$

and some of the AgCl precipitates from the solution until the equilibrium $[Ag^+][Cl^-] = K_{sp}$ is reestablished. Hence, the result of adding a *common ion* is to *reduce* the solubility of a slightly soluble electrolyte, unless, of course, the common ion forms a complex with the salt whereby the net solubility may be increased.

Example 10–14. What is the solubility x of silver chromate in moles/liter in an aqueous solution containing 0.04 *M* silver nitrate? The solubility of silver chromate in water is 8×10^{-5} and its solubility product is 2.0×10^{-12}. The dissociation of silver chromate may be represented as

$$Ag_2CrO_4 \rightleftharpoons 2Ag^+ + CrO_4^=$$

$$K_{sp} = 2.0 \times 10^{-12} = (2x + 0.04)^2 x = 4x^3 + 0.16x^2 + 0.0016x$$

Since the terms in x^3 and x^2 are so small that they may be neglected, the result is

$$x = [Ag_2CrO_4] = \frac{2.0 \times 10^{-12}}{1.6 \times 10^{-3}} = 1.25 \times 10^{-9} \text{ mole/liter}$$

Salts having no ion in common with the slightly soluble electrolyte produce an effect opposite to that of a common ion: at moderate concentration, they *increase* rather than decrease the solubility because they lower the activity coefficient. As mentioned previously, the exact equilibrium expression involves activities. For silver chloride,

$$K_{sp} = a_{Ag^+}a_{Cl^-} \qquad (10\text{–}52)$$

Since activities may be replaced by the product of concentrations and activity coefficients,

$$K_{sp} = [Ag^+][Cl^-]\gamma_{Ag^+}\gamma_{Cl^-} = [Ag^+][Cl^-]\gamma^2_{\pm}$$

$$\frac{K_{sp}}{\gamma^2_{\pm}} = [Ag^+][Cl^-]$$

and

$$\text{Solubility} = [Ag^+] = [Cl^-] = \frac{\sqrt{K_{sp}}}{\gamma_{\pm}} \qquad (10\text{–}53)$$

Example 10–15. Calculate the solubility of silver chloride in a 0.1-*M* solution of ammonium sulfate. The ionic strength of 0.1 *M* $(NH_4)_2SO_4$ is 0.3, and the activity coefficient of a 1:1 electrolyte such as silver chloride at this ionic strength is about 0.70.

$$\text{Solubility} = \frac{\sqrt{1.2 \times 10^{-10}}}{0.70}$$
$$= 1.6 \times 10^{-5} \text{ mole/liter}$$

Therefore, the addition of an electrolyte that does not have an ion in common with AgCl causes an increase in the solubility of silver chloride.

Other useful conclusions may be reached by use of the solubility product principle. If the pharmacist wishes to prevent precipitation of a slightly soluble salt in water,

he may add some substance that will tie up and reduce the concentration of one of the ions. More of the salt will then pass from the undissolved to the dissolved state until the solubility product constant is reached and the equilibrium is reestablished. For example, if the ferric ion in a solution of the slightly soluble base, $Fe(OH)_3$, can be combined by complex formation with sodium citrate, more Fe^{3+} will pass into solution so as to keep K_{sp} constant. In this manner, the solubility of iron compounds is increased by citrates and similar compounds.

Solubility of Weak Electrolytes. Many important drugs belong to the class of weak acids and bases. They react with strong acids and bases and, within definite ranges of pH, exist as ions that are ordinarily soluble in water.

Although carboxylic acids containing more than five carbons are relatively insoluble in water, they react with dilute sodium hydroxide, carbonates, and bicarbonates to form soluble salts. The fatty acids containing more than 10 carbon atoms form soluble soaps with the alkali metals and insoluble soaps with other metal ions. They are soluble in solvents having low dielectric constants; for example, oleic acid ($C_{17}H_{33}COOH$) is insoluble in water but is soluble in alcohol and in ether.

Hydroxy acids, such as tartaric and citric acids, are quite soluble in water since they are solvated through their hydroxyl groups. The potassium and ammonium bitartrates are not very soluble in water, although most alkali metal salts of tartaric acid are soluble. Sodium citrate is used sometimes to dissolve water-insoluble acetylsalicylic acid since the soluble acetylsalicylate ion is formed in the reaction. The citric acid that is produced is also soluble in water, but the practice of dissolving aspirin by this means is questionable since the acetylsalicylate is also hydrolyzed rapidly.

Aromatic acids react with dilute alkalies to form water-soluble salts, but they may be precipitated as the free acids if stronger acidic substances are added to the solution. They may also be precipitated as heavy metal salts should heavy metal ions be added to the solution. Benzoic acid is soluble in sodium hydroxide solution, alcohol, and fixed oils. Salicylic acid is soluble in alkalies and in alcohol. The OH group of salicyclic acid cannot contribute to the solubility since it is involved in an intramolecular hydrogen bond (p. 24).

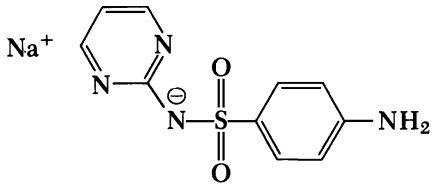
Phenol is weakly acidic and only slightly soluble in water but is quite soluble in dilute sodium hydroxide solution.

$$C_6H_5OH + NaOH \rightarrow C_6H_5O^- + Na^+ + H_2O$$

Phenol is a weaker acid than H_2CO_3 and is thus displaced and precipitated by CO_2 from its dilute alkali solution. For this reason, carbonates and bicarbonates cannot increase the solubility of phenols in water.

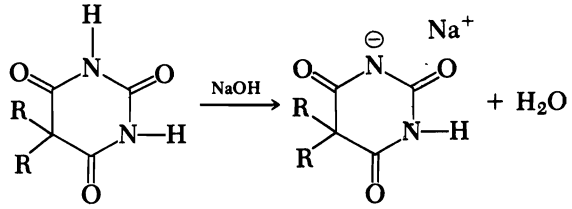
Many organic compounds containing a basic nitrogen atom in the molecule are important in pharmacy. These include the alkaloids, sympathomimetic amines, antihistamines, local anesthetics, and others. Most of these weak electrolytes are not very soluble in water but are soluble in dilute solutions of acids; such compounds as atropine sulfate and tetracaine hydrochloride are formed by reacting the basic compounds with acids. Addition of an alkali to a solution of the salt of these compounds precipitates the free base from solution if the solubility of the base in water is low.

The aliphatic nitrogen of the sulfonamides is sufficiently negative so that these drugs act as slightly soluble weak acids rather than as bases. They form water-soluble salts in alkaline solution by the following mechanism. The oxygens of the sulfonyl ($-SO_2-$) group withdraw electrons, and the resulting electron deficiency of the sulfur atom results in the electrons of the N:H bond being held more closely to the nitrogen atom. The hydrogen therefore is bound less firmly, and, in alkaline solution, the soluble sulfonamide anion is readily formed.



Sulfadiazine anion in a sodium hydroxide solution

The sodium salts of the sulfonamides are precipitated from solution by the addition of a strong acid, or by a salt of a strong acid and a weak base such as ephedrine hydrochloride.



Reaction of barbituric acid derivative with sodium hydroxide to form the anion of the weak acid

The barbiturates, like the sulfonamides, are weak acids because the electronegative oxygen of each acidic carbonyl group tends to withdraw electrons and to create a positive carbon atom. The carbon in turn attracts electrons from the nitrogen group and causes the hydrogen to be held less firmly. Thus, in sodium hydroxide solution, the hydrogen is readily lost, and the molecule exists as a soluble anion of the weak acid. Butler et al.[38] have demonstrated that, in highly alkaline solutions, the second hydrogen ionizes. The pK_1 for phenobarbital is 7.41 and the pK_2 is 11.77. Although the barbiturates are soluble in alkalies, they are precipitated as the free acids when a stronger acid is added and the pH of the solution is lowered.

Calculating the Solubility of Weak Electrolytes as Influenced by pH. From what has been said about the effects of acids and bases on solutions of weak electrolytes, it becomes evident that the solubility of weak electrolytes is strongly influenced by the pH of the solution. For example, a 1% solution of phenobarbital sodium is soluble at pH values high in the alkaline range. The soluble ionic form is converted into molecular phenobarbital as the pH is lowered, and below 8.3, the drug begins to precipitate from solution at room temperature. On the other hand, alkaloidal salts such as atropine sulfate begin to precipitate as the pH is elevated.

To ensure a clear homogeneous solution and maximum therapeutic effectiveness, the preparations should be adjusted to an optimum pH. The pH below which the salt of a weak acid, sodium phenobarbital, for example, begins to precipitate from aqueous solution is readily calculated in the following manner.

Representing the free acid form of phenobarbital as HP and the soluble ionized form as P^-, the equilibria in a saturated solution of this slightly soluble weak electrolyte are

$$HP_{solid} \rightleftharpoons HP_{sol} \qquad (10-54)$$

$$HP_{sol} + H_2O \rightleftharpoons H_3O^+ + P^- \qquad (10-55)$$

Since the concentration of the un-ionized form in solution HP_{sol} is essentially constant, the equilibrium constant for the solution equilibrium, equation (10–54) is

$$S_0 = [HP]_{sol} \qquad (10-56)$$

and the constant for the acid–base equilibrium, equation (10–55), is

$$K_a = \frac{[H_3O^+][P^-]}{[HP]} \qquad (10-57)$$

or

$$[P^-] = K_a \frac{[HP]}{[H_3O^+]} \qquad (10-58)$$

in which the subscript "sol" has been deleted from $[HP]_{sol}$, since no confusion should result from this omission.

The total solubility S of phenobarbital consists of the concentration of the undissociated acid [HP] and the conjugate base or ionized form $[P^-]$:

$$S = [HP] + [P^-] \qquad (10-59)$$

Substituting S_0 for [HP] from equation (10–56) and the expression from equation (10–58) for $[P^-]$ yields

$$S = S_0 + K_a \frac{S_0}{[H_3O^+]} \qquad (10-60)$$

$$S = S_0 \left(1 + \frac{K_a}{[H_3O^+]}\right) \qquad (10-61)$$

Equation (10–61) has been expressed in various forms by Krebs and Speakman[39] Albert,[40] Higuchi,[41] Kostenbauder et al.,[42] and others.

When the electrolyte is weak and does not dissociate appreciably, the solubility of the acid in water or acidic solutions is S_0 = [HP], which, for phenobarbital is approximately 0.005 mole/liter, in other words, 0.12%.

The solubility equation may be written in logarithmic form, beginning with equation (10–60). By rearrangement, we obtain

$$(S - S_0) = K_a \frac{S_0}{[H_3O^+]}$$

$$\log (S - S_0) = \log K_a + \log S_0 - \log [H_3O^+]$$

and finally

$$pH_p = pK_a + \log \frac{S - S_0}{S_0} \qquad (10-62)$$

in which pH_p is the pH below which the drug separates from solution as the undissociated acid.

In pharmaceutical practice, a drug such as phenobarbital is usually added to an aqueous solution in the soluble salt form. Of the initial quantity of salt, sodium phenobarbital, that can be added to a solution of a certain pH, some of it is converted into the free acid HP and some remains in the ionized form P^- (equation (10–59). The amount of salt that can be added initially before the solubility [HP] is exceeded is therefore equal to S. As seen from equation (10–62), pH_p depends on the initial molar concentration S of salt added, the molar solubility of the undissociated acid S_0, and the pK_a. Equation (10–62) has been used to determine the pK_a of sulfonamides and other drugs (see references 49 to 52). Solubility and pH data may also be used to obtain the pK_1 and pK_2 values of dibasic acids as suggested by Zimmerman[43] and by Blanchard et al.[44]

Example 10–16. Below what pH will free phenobarbital begin to separate from a solution having an initial concentration of 1 g of sodium phenobarbital per 100 mL at 25° C? The molar solubility S_0 of phenobarbital is 0.0050 and the pK_a = 7.41 at 25° C. The secondary dissociation of phenobarbital, referred to previously, may ordinarily be disregarded. The molecular weight of sodium phenobarbital is 254.

The molar concentration of salt initially added is

$$\frac{\text{g/liter}}{\text{mol. wt.}} = \frac{10}{254} = 0.039 \text{ mole/liter}$$

$$pH_p = 7.41 + \log \frac{(0.039 - 0.005)}{0.005} = 8.24$$

An analogous derivation may be carried out to obtain the equation for the solubility of a weak base as a function of the pH of a solution. The expression is

$$pH_p = pK_w - pK_b + \log \frac{S_0}{S - S_0} \qquad (10-63)$$

in which S is the concentration of the drug initially added as the salt and S_0 is the molar solubility of the free base in water. Here pH_p is the pH *above* which the

drug begins to precipitate from solution as the free base.

The Influence of Solvents on the Solubility of Drugs. Weak electrolytes may behave like strong electrolytes and like nonelectrolytes in solution. When the solution is of such a pH that the drug is entirely in the ionic form, it behaves as a solution of a strong electrolyte and solubility does not constitute a serious problem. However, when the pH is adjusted to a value at which un-ionized molecules are produced in sufficient concentration to exceed the solubility of this form, precipitation occurs. In this discussion, we are now interested in the solubility of nonelectrolytes and the undissociated molecules of weak electrolytes. The solubility of undissociated phenobarbital in various solvents is discussed here because it has been studied to some extent by pharmaceutical investigators.

Frequently a solute is more soluble in a mixture of solvents than in one solvent alone. This phenomenon is known as *cosolvency*, and the solvents that, in combination, increase the solubility of the solute are called *cosolvents*. Approximately 1 g of phenobarbital is soluble in 1000 mL of water, in 10 mL of alcohol, in 40 mL of chloroform, and in 15 mL of ether at 25° C. The solubility of phenobarbital in water–alcohol–glycerin mixtures is plotted on a semilogarithm grid in Figure 10–7 from the data of Krause and Cross.[45]

By drawing lines parallel to the abscissa in Figure 10–7 at a height equivalent to the required phenobarbital concentration, it is a simple matter to obtain the relative amounts of the various combinations of alcohol, glycerin and water needed to achieve solution. For example, at 22% alcohol, 40% glycerin, and the remainder water (38%), 1.5% *w/v* of phenobarbital is dissolved, as seen by following the vertical and horizontal lines drawn on Figure 10–7.

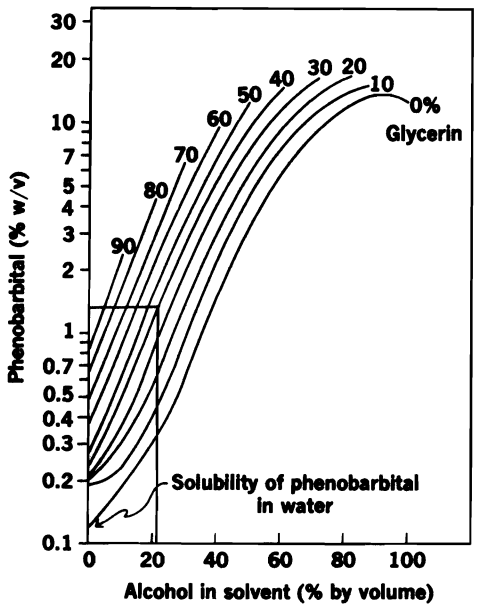


Fig. 10–7. The solubility of phenobarbital in a mixture of water, alcohol, and glycerin at 25° C. The vertical axis is a logarithmic scale representing the solubility of phenobarbital in g/100 mL. (After G. M. Krause and J. M. Cross, J. Am. Pharm. Assoc., Sci. Ed. 40, 137, 1951, reproduced with permission of the copyright owner.)

Combined Effect of pH and Solvents. The solvent affects the solubility of a weak electrolyte in a buffered solution in two ways:

1. The addition of alcohol to a buffered aqueous solution of a weak electrolyte increases the solubility of the un-ionized species by adjusting the polarity of the solvent to a more favorable value.
2. Being less polar than water, alcohol decreases the dissociation of a weak electrolyte, and the solubility of the drug goes down as the dissociation constant is decreased (pK_a is increased).

Stockton and Johnson[46] and Higuchi et al.[47] studied the effect of an increase of alcohol concentration on the dissociation constant of sulfathiazole, and Edmonson and Goyan[48] investigated the effect of alcohol on the solubility of phenobarbital.

Agarwal and Blake[49] and Schwartz et al.[50] determined the solubility of phenytoin as a function of pH and alcohol concentration in various buffer systems and calculated the apparent dissociation constant. Kramer and Flynn[51] examined the solubility of hydrochloride salts of organic bases as a function of pH, temperature, and solvent composition. They described the determination of the pK_a of the salt from the solubility profile at various temperatures and in several solvent systems. Chowhan[52] measured and calculated the solubility of the organic carboxylic acid, naproxen, and its sodium, potassium, calcium, and magnesium salts. The observed solubilities were in excellent agreement with the pH-solubility profiles based on equation (10–62).

The results of Edmonson and Goyan[48] are shown in Figure 10–8, where one observes that the pK_a of phenobarbital, 7.41, is raised to 7.92 in a hydroalcoholic solution containing 30% by volume of alcohol. Furthermore, as can be seen in Figure 10–7 the solubility S_0 of un-ionized phenobarbital is increased from 0.12 g/100 mL or 0.005 *M* in water to 0.64% or 0.0276 *M* in a 30%

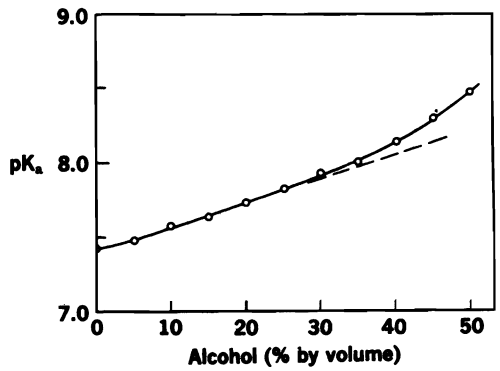


Fig. 10–8. The influence of alcohol concentration on the dissociation constant of phenobarbital. (After T. D. Edmonson and J. E. Goyan, J. Am. Pharm. Assoc., Sci. Ed. 47, 810, 1958, reproduced with permission of the copyright owner.)

alcoholic solution. The calculation of solubility as a function of pH involving these results is illustrated in the following example.

Example 10–17. What is the minimum pH required for the complete solubility of the drug in a stock solution containing 6 g of phenobarbital sodium in 100 mL of a 30% by volume alcoholic solution? From equation (10–62):

$$pH_p = 7.92 + \log \frac{(0.236 - 0.028)}{0.028}$$

$$pH_p = 7.92 + 0.87 = 8.79$$

For comparison, the minimum pH for complete solubility of phenobarbital in an aqueous solution containing no alcohol is computed using equation (10–62).

$$pH_p = 7.41 + \log \frac{(0.236 - 0.005)}{0.005} = 9.07$$

From the calculations of *Example 10–17*, it is seen that although the addition of alcohol increases the pK_a, it also increases the solubility of the un-ionized form of the drug over that found in water sufficiently so that the pH may be reduced somewhat before precipitation occurs.

Equations (10–62) and (10–63) can be made more exact if activities are used instead of concentrations to account for interionic attraction effects. This refinement, however, is seldom required for practical work, in which the values calculated from the approximate equations just given serve as satisfactory estimates.

Influence of Surfactants. Weakly acidic and basic drugs may be brought into solution by the solubilizing action of surface-active agents. Solubilization of drugs in micelles is discussed as a colloidal phenomenon on pages 410 to 414, but it is appropriate here to describe the influence of surface-active agents on the solubility of drugs in quantitative terms along with the solubilizing effects of solvents, such as glycerin and ethanol.

Rippie et al.[53] investigated the micellar solubilization of weak electrolytic drugs by aqueous solutions of the nonionic surfactant polysorbate 80. The terminology of Rippie and associates is used in the following description of the theory.

The total solubility D_T of an acidic drug is expressed as the sum of the concentrations of species in solution:

$$D_T = (D) + (D^-) + [D] + [D^-] \qquad (10–64)$$

in which (D) and (D^-) are nonionized acid and ionized acid, respectively, not in the micelles; $[D]$ and $[D^-]$ are nonionized and ionized acid, respectively, present in the micelles. The drug is considered to partition between the aqueous solution and the surfactant micelles according to the expression

$$K' = \frac{[D]_o}{(D)_o} \qquad (10–65)$$

for the nonionized acid, and

$$K'' = \frac{[D^-]_o}{(D^-)_o} \qquad (10–66)$$

for the ionized acid.

The subscript $_o$ represents concentrations expressed relative to individual phase volumes rather than the total volume of the system. In terms of total volume, equations (10–65) and (10–66) become

$$K' = \frac{[D][1 - (M)]}{(D)(M)} \qquad (10–67)$$

$$K'' = \frac{[D^-][1 - (M)]}{(D^-)(M)} \qquad (10–68)$$

The concentration term, (M), is the volume fraction of surfactant as micelles in solution; the amount in true solution would be small and can be neglected. Now, $1 - (M)$ can be set equal to unity in equations (10–67) and (10–68), yielding

$$[D] = K' (D)(M) \qquad (10–69)$$

$$[D^-] = K'' (D^-)(M) \qquad (10–70)$$

The total drug solubility, D_T^*, in a solution at a definite pH and in the absence of the surfactant ($D_T^* \equiv S$ in equation (10–59)) is defined as

$$D_T^* = (D) + (D^-) \qquad (10–71)$$

The fraction, $(D)/D_T^*$, of un-ionized drug in the aqueous phase is

$$\frac{(D)}{D_T^*} = \frac{(H^+)}{K_a + (H^+)} \qquad (10–72)$$

or

$$D_T^* = (D) \frac{K_a + (H^+)}{(H^+)} \qquad (10–73)$$

Using the relationships just given, Rippie et al.[53] obtained the expression

$$\frac{D_T}{D_T^*} = 1 + (M) \left[\frac{(H^+)K' + K_a K''}{K_a + (H^+)} \right] \qquad (10–74)$$

in which D_T is total drug solubility in the presence of surfactant, according to equation (10–64). With equation (10–74), one may calculate total drug solubility in a solution of a definite pH and having a volume fraction (M) of surfactant present in the form of micelles.

Example 10–18. Calculate the solubility of sulfisoxazole at 25° C in (*a*) a pH 6.0 buffer and (*b*) a pH 6.0 buffer containing 4% by volume (i.e., 0.04 volume fraction) polysorbate 80 (Tween 80). The aqueous solubility of nonionized sulfisoxazole at 25° C is 0.15 g/liter, its $K_a = 7.60 \times 10^{-6}$, and the apparent partition coefficient of the molecular drug, K', and its anion, K'', between polysorbate 80 micelles and water are 79 and 15, respectively. (K' and K'' are dimensionless constants.)

(*a*) From equation (10–73), the total drug solubility at pH 6 in the absence of the surfactant is

$$D_T^* = 0.15 \text{ g/liter} \left[\frac{(7.6 \times 10^{-6}) \text{ moles/liter} + (1.0 \times 10^{-6}) \text{ moles/liter}}{(1.0 \times 10^{-6}) \text{ moles/liter}} \right] = 1.29 \text{ g/liter}$$

(*b*) From equation (10–74), the total solubility of sulfisoxazole in a pH 6 buffer in the presence of 4% Tween 80 is

$$D_T = (1.29)\left\{1 + (0.04) \times \left[\frac{(1 \times 10^{-6})(79) + (7.6 \times 10^{-6})(15)}{(7.6 \times 10^{-6}) + (1 \times 10^{-6})}\right]\right\}$$

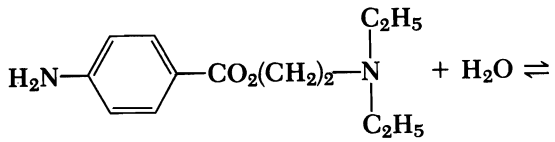
$$D_T = 2.45 \text{ g/liter}$$

The presence of the surfactant has almost doubled the concentration of the drug in solution.

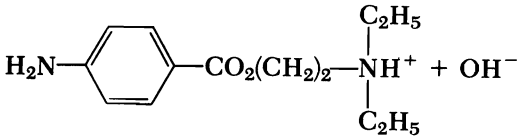
The total solubility of a basic drug corresponding to that for an acidic drug, equation (10–64), in a solution containing a micellar surfactant, is

$$D_T = (D^+) + (D) + [D^+] + [D] \qquad (10\text{–}75)$$

in which D^+ is the cationic acid species and D is the nonionized base. The ionization of a molecular (nonionic) base, procaine, is represented as



(R_3N)
Procaine
(nonionic base)



(R_3NH^+)
Procaine cation
(ionic acid conjugate to
Procaine base) (10–76)

The dissociation equilibrium for this reaction is written

$$K_b = \frac{[R_3NH^+][OH^-]}{[R_3N]} \qquad (10\text{–}77)$$

The dissociation also may be written in terms of the procaine cation to obtain the acid dissociation constant, K_a,

$$R_3NH^+ + H_2O \rightleftharpoons R_3N + H_3O^+ \qquad (10\text{–}78)$$

$$K_a = \frac{[R_3N][H_3O^+]}{[R_3NH^+]} \qquad (10\text{–}79)$$

As noted earlier in the text, the following relationship holds between a molecular base and its cationic acid (also between a molecular acid and its anionic base):

$$K_aK_b = K_w \qquad (10\text{–}80)$$

and

$$pK_a + pK_b = pK_w \qquad (10\text{–}81)$$

For a molecular base such as procaine,

$$(D) = D_T^*\left[\frac{K_a}{K_a + (H^+)}\right] \qquad (10\text{–}82)$$

$$(D^+) = D_T^*\left[\frac{H^+}{K_a + (H^+)}\right] \qquad (10\text{–}83)$$

and

$$\frac{D_T}{D_T^*} = 1 + (M)\left[\frac{K_aK' + (H^+)K''}{K_a + (H^+)}\right] \qquad (10\text{–}84)$$

in which (D) is the free acid not in the micelle, (D^+) is the cationic acid, conjugate to the molecular base, not in the micelle, and the other terms have the same meanings as defined earlier. The expressions permit the calculation of solubilization of a weakly basic drug, such as procaine, in aqueous solutions of a micellar solubilizing agent such as polysorbate 80.

Example 10–19. The aqueous solubility of procaine base at 25° C is 5 g/liter, its K_a is 1.4×10^{-9}, and the apparent partition coefficient for the molecular base is $K' = 30$; for its cationic acid, $K'' = 7.0$. Calculate the solubility of procaine in a pH 7.40 buffer containing 3% (*w/v*) polysorbate 80.

(*a*)

$$D_T^* = (D)\left[\frac{K_a + (H^+)}{K_a}\right] = (5.0)\left[\frac{(1.4 \times 10^{-9}) + (3.98 \times 10^{-8})}{(1.40 \times 10^{-9})}\right]$$

$$= 147.2 \text{ g/liter}$$

(*b*)

$$D_T = 147.2\left\{1 + (0.03) \times \left[\frac{(1.4 \times 10^{-9})(30) + (3.98 \times 10^{-8})(7)}{(1.40 \times 10^{-9}) + (3.98 \times 10^{-8})}\right]\right\}$$

$$= 181.6 \text{ g/liter}$$

What is the fraction of the drug in the aqueous phase and the fraction in the micelles?

$$\frac{\text{Total drug in aqueous phase, } D_T^*}{\text{Total drug in aqueous phase and micelles, } D_T} = \frac{147.2 \text{ g/liter}}{181.6 \text{ g/liter}} = 0.81$$

Thus, the fraction 0.81 of procaine exists in the aqueous phase, and the remainder, 0.19, resides in the micelles. The solubility of procaine is increased by one quarter over that in aqueous buffer owing to the surfactant micelles.

Influence of Complexation in Multicomponent Systems. Many liquid pharmaceutical preparations consist of more than a single drug in solution. Fritz et al.[54] have shown that when several drugs together with pharmaceutical adjuncts interact in solution to form insoluble complexes, simple solubility profiles of individual drugs cannot be used to predict solubilities in mixtures of ingredients. Instead, the specific multicomponent systems must be studied to estimate the complicating effects of species interactions.

Influence of Other Factors on the Solubility of Solids. The size and shape of small particles (those in the micrometer range) also affect solubility. Solubility increases with decreasing particle size according to the approximate equation

$$\log \frac{s}{s_0} = \frac{2\gamma V}{2.303RTr} \qquad (10\text{–}85)$$

in which s is the solubility of the fine particles; s_0 is the solubility of the solid consisting of relatively large particles; γ is the surface tension of the particles, which, for solids, unfortunately, is extremely difficult to obtain; V is the molar volume (volume in cm^3 per mole of particles); r is the final radius of the particles in cm;

R is the gas constant (8.314×10^7 erg/deg mole); and T is the absolute temperature. The equation may be used for solid or liquid particles such as those in suspensions or emulsions. The following example is taken from the book by Hildebrand and Scott.[55]

Example 10–20. A solid is to be comminuted so as to increase its solubility by 10%, i.e., s/s_0 is to become 1.10. What must be the final particle size, assuming that the surface tension of the solid is 100 dynes/cm and the volume per mole is 50 cm^3? The temperature is 27° C.

$$r = \frac{2 \times 100 \times 50}{2.303 \times 8.314 \times 10^7 \times 300 \times 0.0414}$$
$$= 4.2 \times 10^{-6} \text{ cm} = 0.042 \ \mu\text{m}$$

The effects of particle size on the solubility of a solid have been reviewed in some detail by May and Kolthoff,[56] and the interested reader should refer to their report.

The configuration of a molecule and the kind of arrangement in the crystal also has some influence on solubility, and a symmetric particle may be less soluble than an unsymmetric one. This is because solubility depends in part on the work required to separate the particles of the crystalline solute. The molecules of the amino acid α-alanine form a compact crystal with high lattice energy and consequently low solubility. The molecules of α-amino-*n*-butyric acid pack less efficiently in the crystal, partly because of the projecting side chains, and the crystal energy is reduced. Consequently, α-amino-*n*-butyric acid has a solubility of 1.80 moles/liter and α-alanine only 1.66 moles/liter in water at 25° C, although the hydrocarbon chain of α-amino-*n*-butyric acid is the longer of the two compounds.

DISTRIBUTION OF SOLUTES BETWEEN IMMISCIBLE SOLVENTS

If an excess of liquid or solid is added to a mixture of two immiscible liquids, it will distribute itself between the two phases so that each becomes saturated. If the substance is added to the immiscible solvents in an amount insufficient to saturate the solutions, it will still become distributed between the two layers in a definite concentration ratio.

If C_1 and C_2 are the equilibrium concentrations of the substance in solvent$_1$ and solvent$_2$, the equilibrium expression becomes

$$\frac{C_1}{C_2} = K \qquad (10\text{–}86)$$

The equilibrium constant K is known as the *distribution ratio, distribution coefficient,* or *partition coefficient.* Equation (10–86), which is known as the *distribution law,* is strictly applicable only in dilute solutions in which activity coefficients may be neglected.

Example 10–21. When boric acid is distributed between water and amyl alcohol at 25° C, the concentration in water was found to be 0.0510 mole/liter and in amyl alcohol it was found to be 0.0155 mole/liter. What is the distribution coefficient?

$$K = \frac{C_{H_2O}}{C_{alc}} = \frac{0.0510}{0.0155} = 3.29$$

No convention has been established with regard to whether the concentration in the water phase or in the organic phase should be placed in the numerator. Therefore, the result may also be expressed as

$$K = \frac{C_{alc}}{C_{H_2O}} = \frac{0.0155}{0.0510} = 0.304$$

One should always specify in which of these two ways the distribution constant is being expressed.

A knowledge of partition is important to the pharmacist, for the principle is involved in several areas of current pharmaceutical interest. These include preservation of oil–water systems, drug action at nonspecific sites, and the absorption and distribution of drugs throughout the body. Certain aspects of these topics are discussed in the following sections.

Effect on Partition of Ionic Dissociation and Molecular Association. The solute may exist partly or wholly as associated molecules in one of the phases or it may dissociate into ions in either of the liquid phases. The distribution law applies only to the concentration of the species common to both phases, namely, the *monomer* or simple molecules of the solute.

Consider the distribution of benzoic acid between an oil phase and a water phase. When it is neither associated in the oil nor dissociated into ions in the water, equation (10–86) can be used to compute the distribution constant. When association and dissociation occur, however, the situation becomes more complicated. The general case in which benzoic acid associates in the oil phase and dissociates in the aqueous phase is shown schematically in Figure 10–9.

Two cases will be treated. *First,* according to Garrett and Woods,[57] benzoic acid is considered to be distributed between the two phases, peanut oil and water. Although benzoic acid undergoes dimerization (association to form two molecules) in many nonpolar solvents, it does not associate in peanut oil. It ionizes in water to

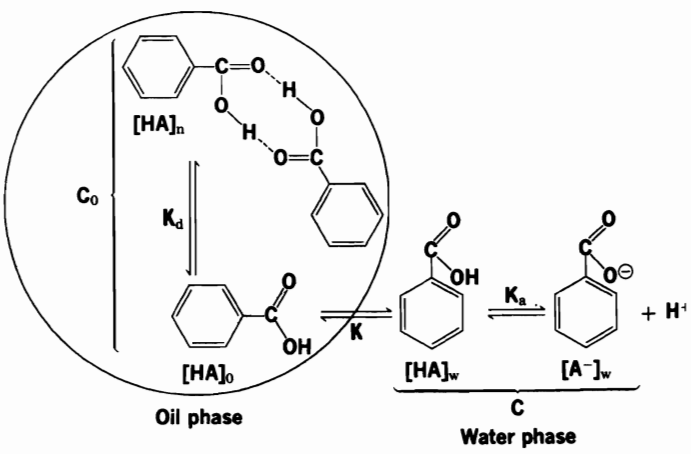


Fig. 10–9. Schematic representation of the distribution of benzoic acid between a water and an oil phase. (The oil phase is depicted as a magnified oil droplet in an oil-in-water emulsion.)

a degree, however, depending on the pH of the solution. Therefore, in Figure 10–9 for the case under consideration, C_o, the total concentration of benzoic acid in the oil phase, is equal to $[HA]_o$, the monomer concentration in the oil phase, since association does not occur in peanut oil.

The species common to both the oil and water phases are the unassociated and undissociated benzoic acid molecules. The distribution is expressed as

$$K = \frac{[HA]_o}{[HA]_w} = \frac{C_o}{[HA]_w} \qquad (10-87)$$

in which K is the *true distribution coefficient* $[HA]_o = C_o$ is the molar concentration of the simple benzoic acid molecules in the oil phase, and $[HA]_w$ is the molar concentration of the undissociated acid in the water phase.

The total acid concentration obtained by analysis of the aqueous phase is

$$C_w = [HA]_w + [A^-]_w \qquad (10-88)$$

and the experimentally observed or *apparent distribution coefficient* is

$$K' = \frac{[HA]_o}{[HA]_w + [A^-]_w} = \frac{C_o}{C_w} \qquad (10-89)$$

As seen in Figure 10–9, the observed distribution coefficient depends on two equilibria: the distribution of the undissociated acid between the immiscible phases as expressed in equation (10–87), and the species distribution of the acid in the aqueous phase, which depends on the hydrogen ion concentration $[H_3O^+]$ and the dissociation constant K_a of the acid.

$$K_a = \frac{[H_3O^+][A^-]_w}{[HA]_w} \qquad (10-90)$$

Association of benzoic acid in peanut oil does not occur, and K_d (the equilibrium constant for dissociation of associated benzoic acid into monomer in the oil phase) may be neglected in this case.

Given these equations and the fact that the concentration C of the acid in the aqueous phase before distribution, assuming equal volumes of the two phases, is*

$$C = C_o + C_w \qquad (10-91)$$

one arrives at the combined result,†

$$\frac{K_a + [H_3O^+]}{C_w} = \frac{K_a}{C} + \frac{K+1}{C}[H_3O^+] \qquad (10-92)$$

Expression (10–92) is a linear equation of the form, $y = a + bx$, and therefore a plot of $(K_a + [H_3O^+])/C_w$ against $[H_3O^+]$ yields a straight line with a slope $b = (K + 1)/C$ and an intercept $a = K_a/C$. The true distribution coefficient K can thus be obtained over the range of hydrogen ion concentration considered. Alternatively, the true distribution constant could be obtained according to equation (10–87) by analysis of the oil phase and of the water phase at a sufficiently low pH (≅2.0) at which the acid would exist completely in the un-ionized form. One of the advantages of equation (10–92), however, is that the oil phase need not be analyzed; only the hydrogen ion concentration and C_w, the total concentration remaining in the aqueous phase at equilibrium, need be determined.

Example 10–22. According to Garrett and Woods,[57] the plot of $(K_a + [H_3O^+])/C_w$ against $[H_3O^+]$ for benzoic acid distributed between equal volumes of peanut oil and a buffered aqueous solution yielded a slope $b = 4.16$ and an intercept $a = 4.22 \times 10^{-5}$. The K_a of benzoic acid is 6.4×10^{-5}. Compute the true partition coefficient, K, and compare it with the value $K = 5.33$ obtained by the authors.

$$b = (K + 1)/C$$

or

$$K = bC - 1$$

*The meaning of C in equation (10–91) is understood readily by considering a simple illustration. Suppose one begins with 1 liter of oil and 1 liter of water, and after benzoic acid has been distributed between the two phases, the concentration C_o of benzoic acid in the oil is 0.01 mole/liter and the concentration C_w of benzoic acid in the aqueous phase is 0.01 mole/liter. Accordingly, there is 0.02 mole/2 liter or 0.01 mole of benzoic acid per liter of total mixture after distribution equilibrium has been attained. Equation (10–91) gives

$$C = C_o + C_w = 0.01 \text{ mole/liter} + 0.01 \text{ mole/liter}$$
$$= 0.02 \text{ mole/liter}$$

The concentration C obviously is not the total concentration of the acid in the mixture at equilibrium but, rather, twice this value. C is therefore seen to be the concentration of benzoic acid in the water phase (or the oil phase) *before* the distribution is carried out.

†Equation (10–92) is obtained as follows. Substituting for $[A^-]_w$ from equation (10–90) into equation (10–89) gives

$$K' = \frac{[HA]_o}{[HA]_w + \dfrac{K_a[HA]_w}{[H_3O^+]}} = \frac{[HA]_o[H_3O^+]}{[HA]_w(K_a + [H_3O^+])} \qquad (a)$$

Then $[HA]_w$ from equation (10–87) is substituted into (*a*) to eliminate $[HA]_o$ from the equation:

$$K' = \frac{[HA]_o[H_3O^+]}{[HA]_o/K(K_a + [H_3O^+])} = \frac{K[H_3O^+]}{K_a + [H_3O^+]} \qquad (b)$$

The apparent distribution constant is eliminated by substituting equation (*b*) into equation (10–89) to give

$$\frac{K[H_3O^+]}{K_a + [H_3O^+]} = \frac{C_o}{C_w}$$

or

$$C_o = \frac{K[H_3O^+]C_w}{K_a + [H_3O^+]} \qquad (c)$$

C_o is eliminated by substituting equation (*c*) into equation (10–91):

$$C = \frac{K[H_3O^+]C_w}{K_a + [H_3O^+]} + C_w$$
$$= \frac{K[H_3O^+]C_w + (K_a + [H_3O^+])C_w}{K_a + [H_3O^+]} \qquad (d)$$

Rearranging equation (*d*) gives the final result:

$$\frac{K_a + [H_3O^+]}{C_w} = \frac{[H_3O^+](K+1) + K_a}{C}$$

Since

$$a = K_a/C \text{ or } C = \frac{K_a}{a}$$

the expression becomes

$$K = \frac{bK_a}{a} - 1 = \frac{bK_a - a}{a}$$

and

$$K = \frac{(4.16 \times 6.4 \times 10^{-5}) - 4.22 \times 10^{-5}}{4.22 \times 10^{-5}} = 5.31$$

Second, let us now consider the case in which the solute is associated in the organic phase and exists as simple molecules in the aqueous phase. If benzoic acid is distributed between benzene and acidified water, it exists mainly as associated molecules in the benzene layer and as undissociated molecules in the aqueous layer.

The equilibrium between simple molecules HA and associated molecules $(HA)_n$ in benzene is

$$\underset{\text{Associated molecules}}{(HA)_n} \rightleftharpoons \underset{\text{Simple molecules}}{n(HA)}$$

and the equilibrium constant expressing the dissociation of associated molecules into simple molecules in this solvent is

$$K_d = \frac{[HA]_o^n}{[(HA)_n]} \tag{10-93}$$

or

$$[HA]_o = \sqrt[n]{K_d}\sqrt[n]{[(HA)_n]} \tag{10-94}$$

Since benzoic acid exists predominantly in the form of double molecules in benzene, C_o may replace $[(HA)_2]$ where C_o is the total molar concentration of the solute in the organic layer. Then equation (10–94) may be written approximately as

$$[HA]_o \cong \text{constant} \times \sqrt{C_o} \tag{10-95}$$

In conformity with the distribution law as given in equation (10–87), the true distribution coefficient is always expressed in terms of simple species common to both phases, that is, in terms of $[HA]_w$ and $[HA]_o$. In the benzene–water system, $[HA]_o$ is given by equation (10–95), and the modified distribution constant becomes

$$K' = \frac{[HA]_o}{[HA]_w} = \frac{\sqrt{C_o}}{[HA]_w} \tag{10-96}$$

The results for the distribution of benzoic acid between benzene and water, as given by Glasstone,[58] are found in Table 10–13.

A third case, involving both association in the organic phase and dissociation in the aqueous phase, might be treated at this point but will be deferred until a later section. It follows directly from the two cases already presented, as will be illustrated in *Example 10–25* dealing with preservative action. Various cases of distribution are treated most adequately by Davies and Hallam.[59]

TABLE 10–13. *Distribution of Benzoic Acid between Benzene and Acidified Water at 6° C

The concentrations are expressed in moles per liter		
$[HA]_w$	C_o	$K' = \sqrt{C_o}/[HA]_w$
0.00329	0.0156	38.0
0.00579	0.0495	38.2
0.00749	0.0835	38.6
0.0114	0.195	38.8

*From S. Glasstone, *Textbook of Physical Chemistry*, Van Nostrand, New York, 1946, p. 738.

Extraction. To determine the efficiency with which one solvent can extract a compound from a second solvent—an operation commonly employed in analytic chemistry and in organic chemistry—we follow Glasstone.[60] Suppose that w grams of a solute are extracted repeatedly from V_1 mL of one solvent with successive portions of V_2 mL of a second solvent, which is immiscible with the first. Let w_1 be the weight of the solute remaining in the original solvent after extracting with the first portion of the other solvent. Then the concentration of solute remaining in the first solvent is (w_1/V_1) g/mL and the concentration of the solute in the extracting solvent is $(w - w_1)/V_2$ g/mL. The distribution coefficient is thus

$$K = \frac{\text{concentration of solute in original solvent}}{\text{concentration of solute in extracting solvent}}$$

$$K = \frac{w_1/V_1}{(w - w_1)V_2} \tag{10-97}$$

or

$$w_1 = w\frac{KV_1}{KV_1 + V_2} \tag{10-98}$$

The process can be repeated, and after n extractions[60]

$$w_n = w\left(\frac{KV_1}{KV_1 + V_2}\right)^n \tag{10-99}$$

By use of this equation, it can be shown that most efficient extraction results when n is large and V_2 is small, in other words, when a large number of extractions are carried out with small portions of extracting liquid. The development just described assumes complete immiscibility of the two liquids. When ether is used to extract organic compounds from water, this is not true; however, the equations provide approximate values that are satisfactory for practical purposes. The presence of other solutes, such as salts, may also affect the results by complexing with the solute or by salting out one of the phases.

Example 10–23. The distribution coefficient for iodine between water and carbon tetrachloride at 25° C is $K = C_{H_2O}/C_{CCl_4} = 0.012$. How many grams of iodine are extracted from a solution in water containing 0.1 g in 50 mL by one extraction with 10 mL of CCl_4? How many grams are extracted by two 5-mL portions of CCl_4?

$$w_1 = 0.10 \times \frac{0.012 \times 50}{(0.012 \times 50) + 10}$$

$$= 0.0057 \text{ g remain or } 0.0943 \text{ g are extracted}$$

$$w_2 = 0.10 \times \left(\frac{0.012 \times 50}{(0.012 \times 50) + 5}\right)^2$$

$$= 0.0011 \text{ g of iodine}$$

Thus, 0.0011 g of iodine remains in the water phase, and the two portions of CCl_4 have extracted 0.0989 g.

Solubility and Partition Coefficients. Hansch et al.[61] observed a relationship between aqueous solubilities of nonelectrolytes and partitioning. Yalkowsky and Valvani[62] obtained an equation to determine the aqueous solubility of liquid or crystalline organic compounds:

$$\log S = -\log K - 1.11 \frac{\Delta S_f (\text{mp} - 25)}{1364} + 0.54 \qquad (10\text{–}100)$$

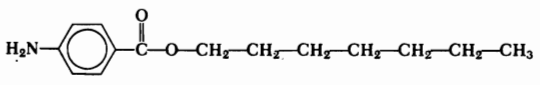
in which S is aqueous solubility in moles/liter, K is the octanol–water partition coefficient, ΔS_f is the molar entropy of fusion, and mp is the melting point of a solid compound on the centigrade scale. For a liquid compound, mp is assigned a value of 25 so that the second right-hand term of equation (10–100) becomes zero.

The entropy of fusion and the partition coefficient may be estimated from the chemical structure of the compound. For rigid molecules, $\Delta S_f = 13.5$ entropy units (eu). For molecules with n greater than five nonhydrogen atoms in a flexible chain,

$$\Delta S_f = 13.5 + 2.5(n - 5) \text{ eu} \qquad (10\text{–}101)$$

Leo et al.[61] have provided partition coefficients for a large number of compounds. When experimental values are not available, group contribution methods (Leo et al.,[61] Rekker[63]) are available for estimating partition coefficients.

Example 10–24. Estimate the molar aqueous solubility of heptyl *p*-aminobenzoate, mp 75° C at 25° C.



It is first necessary to calculate ΔS_f and log K.

There are nine nonhydrogens in the flexible chain (C, O, and seven carbons). Using equation (10–101), we obtain:

$$\Delta S_f = 13.5 + 2.5\,(9 - 5) = 23.5 \text{ eu}$$

For the partition coefficient, Leo et al.[61] give log K of benzoic acid a value of 1.87, the contribution of NH_2 is −1.16, and $CH_2 = 0.50$ or $7 \times 0.50 = 3.50$ for the seven carbon atoms in the chain.

$$\log K \text{ (heptyl } p\text{-aminobenzoate)} = 1.87 - 1.16 + 3.50 = 4.21$$

These values are substituted into equation (10–100):

$$\log S = -4.21 - 1.11\left(\frac{23.5\,(75 - 25)}{1364}\right) + 0.54$$

$$\log S = -4.63$$

$$S_{(\text{calc})} = 2.36 \times 10^{-5}\ M$$

$$S_{(\text{obs})} = 2.51 \times 10^{-5}\ M$$

Preservative Action of Weak Acids in Oil–Water Systems. Solutions of foods, drugs, and cosmetics are subject to deterioration by the enzymes of microorganisms that act as catalysts in decomposition reactions. These enzymes are produced by yeasts, molds, and bacteria, and such microorganisms must be destroyed or inhibited to prevent deterioration. Sterilization and the addition of chemical preservatives are common methods used in pharmacy to preserve drug solutions against attack by various microorganisms. Benzoic acid in the form of its soluble salt, sodium benzoate, is often used for this purpose since it produces no injurious effects in humans when taken internally in small quantities.

Rahn and Conn[64] showed that the preservative or bacteriostatic action of benzoic acid and similar acids is due almost entirely to the undissociated acid and not to the ionic form. These investigators found that the yeast, *Saccharomyces ellipsoideus*, which grows normally at a pH of 2.5 to 7.0 in the presence of strong inorganic acids or salts, ceased to grow in the presence of undissociated benzoic acid when the concentration of the acid reached 25 mg/100 mL. The preservative action of undissociated benzoic acid as compared with the ineffectiveness of the benzoate ion is presumably due to the relative ease with which the un-ionized molecule penetrates living membranes, and conversely, the difficulty with which the ion does so. The undissociated molecule, consisting of a large nonpolar portion, is soluble in the lipoidal membrane of the microorganism and penetrates rapidly.

Bacteria in oil–water systems are generally located in the aqueous phase and at the oil–water interface. Therefore, the efficacy of a weak acid, such as benzoic acid, as a preservative for these systems is largely a result of the concentration of the undissociated acid in the aqueous phase.

To calculate the total concentration of benzoic acid that must be added to preserve an oil–water mixture, we proceed as follows. Let us take the peanut oil–water mixture considered by Garrett and Woods[57] and begin by writing the expression

$$C = qC_o + C_w = q[\text{HA}]_o + [\text{HA}]_w + [\text{A}^-]_w \qquad (10\text{–}102)$$

in which $q = V_o/V_w$, the volume ratio of the two phases, is needed when the volumes are not equal. C is the original concentration of the acid in the water phase before the aqueous solution is equilibrated with peanut oil. C_o is the molar concentration of the simple undissociated molecules in the oil, because the acid does not dimerize or dissociate in the organic phase. C_w, the molar concentration of benzoic acid in water, is equal to the sum of the two terms, $[\text{HA}]_w$ and $[\text{A}^-]_w$, in this ionizing solvent. It is furthermore assumed that concentrations are approximately equal to activities.

The distribution of total benzoic acid among the various species in this system depends upon the distribution coefficient K, the dissociation constant K_a of the acid in the aqueous phase, the phase volume ratio, and the hydrogen ion concentration of the aqueous phase. To account for the first effect, we introduce the term $K = [HA]_o/[HA]_w$ or $[HA]_o = K[HA]_w$ into equation (10–102). We write the dissociation constant, $K_a = [H_3O^+][A^-]_w/[HA]_w$, or the ionic species $[A^-]_w = K_a[HA]_w/[H_3O^+]$, to account for the influence of K_a and $[H_3O^+]$ and substitute it also into equation (10–102). The expression then becomes

$$C = Kq[HA]_w + [HA]_w + K_a[HA]_w/[H_3O^+] \quad (10–103)$$

Factoring out $[HA]_w$, we have

$$C = (Kq + 1 + K_a/[H_3O^+])[HA]_w \quad (10–104)$$

or

$$[HA]_w = \frac{C}{Kq + 1 + K_a/[H_3O^+]} \quad (10–105)$$

Equations (10–104) and (10–105) may be used to calculate the concentration C of total acid that must be added to the entire two-phase system to obtain a final specified concentration $[HA]_w$ of undissociated acid in the aqueous phase buffered at a definite pH or hydrogen ion concentration.[65]

Kazmi and Mitchell[66] and Bean et al.[67] have also proposed calculations for preserving solubilized and emulsified systems that are slightly different from that of Garrett and Woods.

Example 10–25. If benzoic acid is distributed between equal volumes of peanut oil and water, what must be the original concentration in the water phase in order that 0.25 mg/mL of undissociated acid remains in the aqueous phase buffered at a pH of 4.0? The partition coefficient $K = [HA]_o/[HA]_w$ is 5.33 and the dissociation constant of the acid in water is 6.4×10^{-5}. Since the two phases are present in equal amounts, $q = V_o/V_w = 1$. Equation (10–104) is employed.

$$C = \left(5.33 + 1 + \frac{6.4 \times 10^{-5}}{10^{-4}}\right) 0.25$$

$$= 1.74 \text{ mg/mL}$$

In the case in which benzoic acid exists as a dimer in the oil phase, the modified distribution coefficient is $K'' = (1/[HA]_w)\sqrt{C_o}$, therefore equation (10–102) becomes

$$C = K''^2q[HA]_w^2 + [HA]_w + K_a[HA]_w/[H_3O^+] \quad (10–106)$$

and finally

$$C = K''^2q[HA]_w + 1 + (K_a/[H_3O^+])[HA]_w \quad (10–107)$$

Example 10–26. How much undissociated benzoic acid (molecular weight 122 g/mole) remains in the aqueous phase of an emulsion consisting of 100 mL of benzene and 200 mL of water buffered at a pH of 4.2? Is this quantity sufficient to preserve the emulsion? The amount of benzoic acid initially added to the 200 mL of aqueous phase was 0.50 g. The dissociation constant of the acid is 6.4×10^{-5} (pK_a = 4.2), the hydrogen ion concentration of the solution is also 6.4×10^{-5}, and q is $V_o/V_w = 100/200 = 0.5$. The distribution coefficient $K'' = \sqrt{C_o}/[HA]_w \cong 38.5$ as seen in Table 10–13.

$$C = \left\{[(38.5)^2 \times 0.5 \times [HA]_w] + 1 + \frac{6.4 \times 10^{-5}}{6.4 \times 10^{-5}}\right\}[HA]_w$$

$$\frac{0.50 \text{ mole/liter}}{(122)(0.200)} = (741[HA]_w + 2)[HA]_w$$

$$741[HA]_w^2 + 2[HA]_w - 0.0205 = 0$$

$$[HA]_w = \frac{-2 + \sqrt{4 + 60.75}}{1482}$$

$$= 4.079 \times 10^{-3} \text{ mole/liter or } 0.0996 \text{ g/200 mL aqueous phase}$$

Drug Action and Partition Coefficients. At the turn of the century, Meyer and Overton proposed the hypothesis that narcotic action of a nonspecific drug is a function of the distribution coefficient of the compound between a lipoidal medium and water. Later it was concluded that narcosis was a function only of the concentration of the drug in the lipids of the cell. Thus, a wide variety of drugs of different chemical types should produce equal narcotic action at equal concentration in the lipoidal cell substance. Actually, as will be seen shortly, this is a restatement of the theory, first proposed by Ferguson and generally accepted today, that equal degrees of narcotic action should occur at equal thermodynamic activities of the drugs in solution.

The activity of a vapor is obtained approximately by use of the equation (p. 134)

$$\frac{p_{nar}}{p^\circ} = a_{nar} \quad (10–108)$$

If p_{nar} is the partial pressure of a narcotic in solution just necessary to bring about narcosis, and p° is the vapor pressure of the pure liquid, narcosis will occur at a thermodynamic activity of a_{nar}.

Example 10–27. The vapor pressure p° of pure propane is 13 atm and that of butane is 3 atm at 37° C. The partial vapor pressure of propane for narcosis in mice is 0.9 and that for butane is 0.2.[68] Compute the thermodynamic activities of these two compounds required for equinarcotic action.

(*a*) For propane:

$$a_{nar} = \frac{p_{nar}}{p^\circ} = \frac{0.9}{13} = 0.069$$

(*b*) For butane:

$$a_{nar} = \frac{p_{nar}}{p^\circ} = \frac{0.2}{3} = 0.067$$

A still more striking confirmation of the rule that equal degrees of narcosis occur at equal thermodynamic activities (rather than at equal partition coefficients as originally proposed by Meyer and Overton) is shown in Table 10–14. Here it is seen that ethanol, *n*-propanol, and *n*-butanol have distribution coefficients of the same order and all would be expected to show similar narcotic action. Thymol, on the other hand, has a partition coefficient roughly 10,000 times that of the straight-chain alcohols, although its narcotic action is equal to that of the normal alcohols.

TABLE 10–14. *Narcotic Action of Various Compounds*

Substance	Concentration of Compound in Water in Moles/Liter Required for Narcotic Action in Tadpoles	Partition Coefficient of Narcotic Compound $K = \frac{C_{\text{oleyl alcohol}}}{C_{\text{water}}}$	Approximate Activity of Narcotic in Water or Lipoidal Phase ($a_w \cong a_o$)
Ethanol	0.33	0.10	0.033
n-Propanol	0.11	0.35	0.039
n-Butanol	0.03	0.65	0.020
Thymol	0.000047	950	0.045

We can now show that although the distribution coefficients differ, the thermodynamic activities of the compounds are all approximately the same for equal narcotic action. The partition coefficient may be written

$$K = \frac{\text{concentration in organic phase}}{\text{concentration in water phase}} = \frac{a_o/\gamma_o}{a_w/\gamma_w} \quad (10\text{–}109)$$

The student will notice that partition coefficients may be written in terms of concentration rather than activities. Since the activities, a_o and a_w, are equal at equilibrium, K would always equal 1.0. It is the differences in *concentration* we are interested in, and K is therefore defined as expressed in equation (10–109).

When a system is in equilibrium with respect to a compound distributed between two phases, the activities of the solute in the two phases may be taken to be identical, or $a_o = a_w$. Therefore, from (10–109),

$$K = \frac{a/\gamma_o}{a/\gamma_w} = \frac{\gamma_w}{\gamma_o} \quad (10\text{–}110)$$

It can be assumed that the organic solution is approximately ideal so that γ_O is unity. Then, equation (10–110) reduces to

$$K \cong \gamma_w \quad (10\text{–}111)$$

or *the partition coefficient is equal to the activity coefficient* of the compound in the aqueous phase. Finally, when the narcotic concentration in water is multiplied by the activity coefficient, obtained from equation (10–111) in terms of the partition coefficient, the thermodynamic activity for narcosis is obtained:

$$\begin{pmatrix}\text{narcotic concentration} \\ \text{in the aqueous phase}\end{pmatrix} \times (\text{partition coefficient}) = a_{nar} \quad (10\text{–}112)$$

This value for the narcotic in the external phase will also give the thermodynamic activity in the lipoidal or biophase since, as already noted, at equilibrium the activities in the two phases must be the same. The molar concentrations of the narcotics in the external aqueous phase are listed in Table 10–14 together with the oil–water partition coefficients. The thermodynamic activity, calculated according to equation (10–112), is shown in column 4 of Table 10–14. Since the activity coefficients of the drugs in the lipoidal phase are considered to be approximately unity, the *concentrations* in the biophase should be roughly equal to the calculated activities. Therefore, the modified rule of Meyer that isonarcotic action occurs at equal concentrations of the drugs in the lipoidal phase is understandable.

The oil–water partition coefficient is an indication of the lipophilic or hydrophobic character of a drug molecule. Passage of drugs through lipid membranes and interaction with macromolecules at receptor sites sometimes correlate well with the octanol–water partition coefficient of the drug. In the last few sections, the student has been introduced to the distribution of drug molecules between immiscible solvents together with some important applications of partitioning and may wish to pursue the subject further; towards this end, references **69** through **72** provide information on the subject. Three excellent books[73,74,75] on solubility in the pharmaceutical sciences will be of interest to the serious student of the subject.

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*Problems**

10–1. The solubility of sulfamethoxypyridazine (SMP) in a 10% by volume mixture of dioxane and 90% by volume of water is 1.8 mg/mL at 25° C. Calculate **(a)** molarity, **(b)** molality, and **(c)** mole fraction of SMP. The density of the liquid, dioxane, is 1.0313 g/mL, of the solution 1.0086 g/mL, of water 0.9970 g/mL, and of the solvent mixture 1.0082 g/mL. The molecular weight of SMP is 280.32 g/mole, that of dioxane is 88.10, and that of water is 18.015.

Answers: **(a)** 6.421×10^{-3} M; **(b)** 6.378×10^{-3} m; **(c)** $X_2 = 1.251 \times 10^{-4}$

10–2. How many liters of carbon dioxide, reduced to standard conditions of temperature and pressure (25° C and 1 atm, respectively), will dissolve in 1 liter of water at 25° C when the partial pressure of the gas is 0.7 atm?

Answer: 0.53 liter

10–3. Henry's law $p_2 = kX_2$ was discussed in Chapter 5, page 109, and was used in *Problems 5–11, 5–12* and *5–13*. Rather than the Henry's law constant, k, its reciprocal, $\sigma = 1/k$ (pp. 215–216), is sometimes used in problems dealing with the solubility of gases in liquids. What is the solubility of oxygen in water at 25° C and a partial pressure of 610 mm Hg if the reciprocal Henry's law constant, $\sigma = 1/k$, is expressed as σ = concentration (g/liter H_2O)/pressure (mm Hg) = 5.38×10^{-5}?

Answer: 0.0328 g/liter

10–4. Divers ordinarily breathe from tanks of air containing 20% O_2 and 80% N_2. However, He (helium) is less soluble in the blood than N_2 and is now often used to replace N_2.

If the partial pressure of helium in the blood of a diver, using a tank of 20% O_2 and 80% He, is 187.5 mm Hg and the percent of saturation in the red blood cell content is found to be 85.5%, what is the amount of helium that dissolves in the blood? No helium is bound by the hemoglobin of the blood. Express the solubility in moles per kilogram of blood, assuming that the blood behaves as a solvent essentially the same as water. See Table 10–4 for the k value (the Henry's law constant) of helium. Assume that k at 25° C applies with little error at 37° C, the body temperature which is applicable here.

Answer: The concentration of He in the blood at 37° C and a pressure of 187.5 mm Hg is 8.06×10^{-5} moles/kg blood.

10–5. What is the mole fraction solubility of N_2 in water at 25° C and 1 atm pressure? What is the molal solubility? The molecular weight of water is 18.015 g/mole.

Answer: 9.37×10^{-6}, expressed as mole fraction; in molality, the result is 5.20×10^{-4} mole/kg H_2O

10–6. A diver, breathing a mixture of oxygen and helium, descends in a fresh-water lake at sea level to a depth of 30 meters. It is desired that the partial pressure of oxygen at this depth be 0.20 atm.

(a) What is the percent by volume of oxygen in the mixture at this depth? *Hint:* The pressure in atmospheres at a given depth may be computed from the expression: $g\rho h$, where ρ is the density of water, g is the gravity acceleration, and h is the depth (see *Problem 1–10*). Assume that $\rho = 1$ g/cm^3.

(b) At what depth will the diver be subjected to a pressure of 2.5 atmospheres, i.e., 1 atm in air above the lake plus 1.5 atm below the surface of the lake?

(c) At a depth of 50 meters below the surface of the lake what is the pressure in atmospheres? Remember to add on the 1 atm pressure in air above the lake. Incidentally, a diver can withstand a pressure for a short period of time of about 6 atm, corresponding to a depth of about 60 meters.

(d) As stated in Problem 10–4, divers often use a mixture of oxygen, 20% by volume, and helium, 80% by volume. Calculate the mole fraction solubility of helium, He, in water (or in blood where the solubility is essentially the same as in water at 1 atm [in air]) and 25° C. The Henry's law constant for He in water at 25° C is 1.45×10^5 (atm/mole fraction).

(e) At a depth of 30 meters in the lake, the pressure is 3.9 atm and the partial pressure of He is 0.8×3.9 atm or 3.12 atm. The value, 0.8, corresponds to the percentage of He in the gas mixture, 80%. Compute the mole fraction solubility of He in the blood at a partial pressure of 3.12 atm, i.e., at a depth of 30 meters.

(f) Convert the solubility to molality, i.e., moles per kilogram of blood. The blood of an adult consists of approximately 6 kg. Calculate the total moles of He in the blood of the diver at a measured depth in the lake of 30 meters.

(g) Using the ideal gas law, $V_2 = nRT/P$, with R expressed as liter atmosphere per mole degree, and n as the number of moles of He in the blood at a partial pressure P of 3.12 atm, calculate the volume of He in the blood at a depth of 30 meters in the lake. The temperature T is that of the blood, 310° K.

(h) A diver must not surface too quickly, for the sudden decrease in pressure reduces the solubility and releases the gas from the blood as bubbles that may block the blood vessels and cause a painful and possibly life-threatening condition called "bends." What is the volume of He that is suddenly released as bubbles into the bloodstream if the diver surfaces rapidly so as to reduce the He pressure from (2.3 + 1) atm to the surface (1 atm)? For this calculation, one may use the relation, $V_2/V_1 = P_2/P_1$ to obtain the volume of He in the blood at the surface of the lake.

Answers: **(a)** 5.1%; **(b)** 25.85 meter; **(c)** 5.8 atm; **(d)** 5.52×10^{-6}; **(e)** $X_2 = 2.15 \times 10^{-5}$; **(f)** 1.193×10^{-3} mole/kg blood—the total amount is 0.00716 mole He in the blood of an adult; **(g)** 58.4 mL of He in 6 kg of blood; **(h)** 106.5 mL of He released abruptly into the blood as bubbles.

10–7.† According to Chiou and Niazi,[21] succinic acid and griseofulvin form eutectic mixtures (see p. 42). The table here shows the melting temperatures of the mixtures, the compositions of which are given in percent, w/w. The molecular weights of succinic acid and griseofulvin are 118.09 g/mole and 352.8 g/mole, respectively.

Data for *Problem 10–7*

Succinic acid		Griseofulvin	
Temp. (°C)	% (w/w)	Temp. (°C)	% (w/w)
187.2	98	218	99
186.6	96	210	90
183.8	80	200	80
181	65	192	70
177.6	55	—	—
173.3	44	—	—

Plot the phase diagram using temperature in °C against mole fraction (see Fig 2–17, p. 42, for a similar diagram), and from it determine the melting points, T_o, in °C for the two pure components, their heats of fusion, ^oH_f, and the eutectic point of the mixture of succinic acid and griseofulvin.

The ideal solubility expression, equation (10–12), page 222, may be used as a linear regression equation to calculate ΔH_f for both compounds, using the two branches of the plot. The two melting points are obtained from the intercepts on the vertical axes of the

*Problems 10–4 and 10–6 are modified from J. W. Moncrief and W. H. Jones, *Elements of Physical Pharmacy*, Addison-Wesley, Reading, Mass., 1977, p. 122 and R. Chang, *Physical Chemistry with Applications to Biological Systems*, 2nd ed., Macmillan, New York 1977, pp. 23, 24, 175.

†Dr. J. Kieth Guillory suggested this problem and kindly assisted in the preparation of problems from which this one was made.

graph or may be obtained from the two linear regression equations by setting $X_2^i = 1$. The eutectic point is found by extrapolating both lines to their common intersection. To begin the calculations, one should convert °C to °K and % (w/w) to mole fraction.

Answers:

Compound	ΔH_f (cal/mole)	T_o °K (°C)	T_o Literature value
Succinic acid	10,411	460.4 (187.3)	185–187° C
Griseofulvin	13,744	492.3 (219.3)	220° C

The eutectic point, obtained from the intersection of the two lines, corresponds to a mixture of 0.30 griseofulvin and 0.70 succinic acid on the mole fraction scale. The melting point of the eutectic mixture is 173° C.

10–8. At the critical solution temperature of 65.85° C for the phenol–water system, p. 40, the critical composition is 34% by weight of phenol. How many grams of water are dissolved in 1000 g of the solution at this temperature?

Answer: 660 g

10–9. A 200-g mixture of phenol and water at 55° C has a total composition of 20% by weight of phenol. The two liquids have the respective compositions of 13% and 60% phenol. What is the weight in grams of the aqueous layer and of the phenol layer and how many grams of phenol are present in each layer?

Answer: The aqueous layer weighs 170.2 g and contains 22.1 g of phenol; the phenol layer weighs 29.8 g and contains 17.9 g of phenol

10–10. Calculate the Kier–Hall[14] value $^1\chi$ for n-hexane. Using equation (10–8) for the solubility of aliphatic hydrocarbons in water, obtain the molar solubility of n-hexane.

Answer: $^1\chi = 2.914$; $\ln S = 8.886$; $S_{(calc)} = 1.38 \times 10^{-4}$ mole/liter; $S_{(obs)} = 1.11 \times 10^{-4}$ mole/liter

10–11. Using equation (10–10) from Amidon et al.,[15] calculate the molal solubility in water at 25° C of **(a)** cyclohexanol and **(b)** n-octane. Compute the percentage difference of the calculated from the observed solubilities. See Table 10–6 for the HYSA, the FGSA value for the hydroxyl group, and the observed solubilities for the two compounds, cyclohexanol and n-octane.

Answers: **(a)** 0.431 m (−13.4% error); **(b)** 5.85×10^{-6} m (−0.86% error)

10–12. The melting points and molar heat of fusion of three indomethacin polymorphs, I, II, and VII, are found in the table:[76]

Data for *Problem 10–12*

Indomethacin Polymorph	Melting point °C (°K)	ΔH_f cal/mole
I	158 (431)	9550
II	153 (426)	9700
VII	95 (368)	2340

Calculate the ideal mole fraction solubilities at 25° C of the three indomethacin polymorphs, and rank the solubilities in descending order. Is melting point or ΔH_f more useful in ordering the solubilities of the three polymorphs?

Answer: The ideal solubilities, ranked in decreasing order, are

Polymorph	VII	II	I
X_2^i	0.4716	0.0073	0.0069

10–13. Calculate the ideal mole fraction solubility, X_2^i of benzoic acid at 25° C. The melting point of benzoic acid is 122° C (395.15 °K) and the molar heat of fusion is 4139 cal/mole.

Answer: $X_2^i = 0.18$

10–14. The melting points (mp) and heat of fusion for the following three sulfonamides are

Data for *Problem 10–14*

Compound	mp °C (°K)	ΔH_f cal/mole
Sulfamethoxypyridazine	180.4 (453.55)	8110
Sulfameter	211.6 (484.75)	9792
Sulfisomidine	242.2 (515.35)	10781

Calculate the ideal solubilities of these three sulfonamide analogs at 25° C.

Answer:

Compound	Sulfamethoxy-pyridazine	Sulfameter	Sulfisomidine
X_2^i	0.0092	0.0017	0.00047

10–15. In 1893 Schröder[36] measured the solubility of naphthalene in chlorobenzene and obtained the following data for the mole fraction solubility X_2 of naphthalene at a number of temperatures, T, in degrees Kelvin (°K). The δ values (solubility parameter) of naphthalene and chlorobenzene are both 9.6 $(cal/cm^3)^{1/2}$.

Data for *Problem 10–15*

X_2^i	0.840	0.742	0.482	0.392	0.309	0.232
T (°K)	343.5	337.5	317.5	307.5	297.0	285.5

The melting point T_f of naphthalene is 80.2° C (353.4° K). It is assumed that the solubilities X_2 in the table are ideal solubilities, since the δ value of the solvent is equal to that of the solute. This assumption permits the use of equation (10–11) or (10–12) to obtain the heat of fusion and the entropy of fusion from the slope and intercept, respectively, of a plot of $1/T$ (x-axis) ($°K^{-1}$) versus $\ln X_2^i$ (y-axis). The intercept along the vertical $\ln X_2^i$ axis occurs where $1/T$ on the horizontal axis becomes zero, i.e., where T becomes infinite!

(a) Using linear regression, obtain the heat of fusion, ΔH_f, from the slope $\Delta H_f/R$, in which R is the gas constant, 1.9872 cal $mole^{-1}$ deg^{-1}; $\Delta S_f/R$ allows calculation of the entropy of fusion from the integration constant of equation (10–12).

(b) Compare the ΔH_f value obtained from the slope of the regression line with the average ΔH_f obtained from use of equation (10–11), which yields six ΔH_f values.

Answers: **(a)** ΔH_f (from regression) = 4310 cal/mole; $\Delta S_f = 12.18$ cal/(mole deg); **(b)** the average value of ΔH_f from the six values obtained by the use of equation (10–11) is 4382 cal/mole, about 2% larger than the value obtained using equation (10–12). The student's values may differ slightly depending on the rounding off of the decimals.

10–16. Benzoic acid forms an ideal solution in a mixture of 0.7 part of ethanol and 0.3 part of ethyl acetate. The mole fraction solubility at 25° C in this mixture is 0.179. The melting point of benzoic acid is 122.4° C. Calculate the heat of fusion of benzoic acid at 25° C.

Answer: $\Delta H_f = 4144$ cal/mole. The CRC *Handbook of Chemistry and Physics*, 63rd ed., gives ΔH_f of benzoic acid as 4139 cal/mole.

10–17. Compute the mole fraction and the molal solubility of benzoic acid in ethyl acetate at 25° C assuming regular solution behavior. Refer to *Example 10–9* and Wenner[30] for the calculations involved. What is the activity and the activity coefficient of the solute in this solution? The solubility parameter of benzoic acid is 11.3 $(cal/cm^3)^{1/2}$ and the molar volume of the supercooled liquid at 25° C is 104.4 cm^3/mole. The solubility parameter of ethyl acetate may be obtained from its heat of vaporization ΔH_v at 25° C = 97.5 cal/g. The molar volume of ethyl acetate at 25° C is obtained from the molecular weight 88.1 divided by its density at 25° C, 0.90 g/cm^3. The heat of fusion of benzoic acid is 33.9 cal/g and the molecular weight is 122 g/mole. The melting point of benzoic acid is 122° C. For purposes of successive approximations, one may assume that $V_1 = V_2$ so that $\phi_1 \approx 1 - X_2$, although the full equation for ϕ, *Example 10–9*, is ordinarily used.

Answer: $X_2 = 0.082$; $a_2 = X_2^i = 0.18$; $\gamma = 2.21$

10–18. If the mole fraction solubility X_2 of naphthalene in chlorobenzene can be considered as the ideal solubility X_2^i for naphthalene, and if X_2^i is 0.444 for naphthalene in chlorobenzene at 40° C (313° K), a determination of the mole fraction solubility in other solvents at 40° C should allow calculation of the activity coefficient, γ_2, in each solvent. What is γ_2 for naphthalene at 40° C in each of the following solvents?

Data for *Problem 10–18*

Solvent	X_2 (40° C)
Acetone	0.378
Hexane	0.222
Methanol	0.0412
Acetic acid	0.117
Water	1.76×10^{-5}
Chlorobenzene	0.444

Relative to the γ_2 values, what might one conclude about the solubility of naphthalene in these various solvents?

Answers:

Solvent	γ_2 (40° C)
Acetone	1.2
Hexane	2.0
Methanol	10.8
Acetic acid	3.8
Water	2.5×10^4
Chlorobenzene	1.0

10–19. The units of solubility parameter (δ) in the cgs system are $(cal/cm^3)^{1/2}$. **(a)** Obtain a conversion factor to express δ in SI units, $(MPa)^{1/2}$. **(b)** Express the solubility parameter of chloroform, caffeine, tolbutamide, and hydrocortisone in SI units. The solubility parameters in cgs units are 9.3, 14.1, 10.9, and 12.4 $(cal/cm^3)^{1/2}$, respectively.

Answers: **(a)** the conversion factor is 1 $(cal/cm^3)^{1/2}$ = 2.0455 $(MPa)^{1/2}$; **(b)** the δ value for each drug above in SI units is, respectively, 19.0, 28.8, 22.3, and 25.4 $(MPa)^{1/2}$

10–20. The cgs system of units is ordinarily used in this chapter for the calculation of solubilities. However, it is sometimes useful to convert to SI units. For a solution of benzoic acid in water, necessary values are expressed in the cgs units as follows. The molar volume, V_2, for benzoic acid is 104.3 cm^3/mole and for water V_1 = 18.015 cm^3/mole. The heat of fusion of benzoic acid is 4302 cal/mole and the melting point is 395.6° K. The solubility parameters δ_1 and δ_2 for the solvent, water, and the solute, benzoic acid, are, respectively, 23.4 $(cal/cm^3)^{1/2}$ and 11.5 $(cal/cm^3)^{1/2}$. The gas constant R is given in the cgs system as 1.9872 cal deg^{-1} $mole^{-1}$. **(a)** Convert each of these quantities into the SI system of units. **(b)** Compute the mole fraction solubility of benzoic acid in water at 25° C from the Hildebrand equation using the SI units obtained. Assume that $\phi_1 = 1$. Convert the mole fraction to molality. *Hint:* Use the conversion factor obtained in *Problem 10–19* to express the solubility parameters in SI units.

Answers: **(a)** $V_2 = 104.3 \times 10^{-6}$ m^3/mole, $V_1 = 18.015 \times 10^{-6}$ m^3/mole, ΔH_f = 17999.6 J/mole, δ_1 = 47.9 $(MPa)^{1/2}$, δ_2 = 23.5 $(MPa)^{1/2}$; **(b)** $X_2 = 3.04 \times 10^{-3}$, m = 0.169 mole/(kg H_2O).

10–21. The heat of vaporization of the solvent carbon disulfide is 6682 cal/mole and the molar volume is 60.4 cm^3/mole at 25° C. Compute the internal pressure and the solubility parameter of carbon disulfide.

Answer: $P_i \cong 101$ cal/cm^3; $\delta = 10$ $(cal/cm^3)^{1/2}$

10–22. It has been stated in the literature that the a/V^2 term in the van der Waals equation (equations (2–13) and (2–14), pp. 26, 27) is approximately equal to the cohesive energy density, i.e., to the square of the solubility parameter, δ, or $a = \delta^2 V^2$. The CRC *Handbook of Chemistry and Physics*, 63rd ed., page D-195, gives the value of a for n-hexane as 24.39 and a for benzene as 18.00 $liter^2$ atm $mole^{-2}$. Using these handbook values for the van der Waals a—the value for attractive forces between molecules—calculate the solubility parameter δ of n-hexane and of benzene.

The accepted δ values for these two liquids (see Table 10–8) are 7.3 and 9.1 $(cal\ cm^{-3})^{1/2}$, respectively. Do you agree that a/V^2 is a good estimate of δ^2? *Hint:* You will need the conversion factor, 1 liter atm = 24.2179 cal. Express the pressure in atmospheres, the volume in liters, and R as 0.08206 liter atm $mole^{-1}$ deg^{-1}. The molar volume of benzene is 89.4 cm^3 $mole^{-1}$ and the molar volume of n-hexane is 131.6 cm^3 $mole^{-1}$.

Answer: $(a/V^2)^{1/2} \stackrel{?}{=} \delta$(n-hexane) = 5.8 $(cal/cm^3)^{1/2}$; $(a/V^2)^{1/2} \stackrel{?}{=} \delta$(benzene) = 7.4 $(cal/cm^3)^{1/2}$

10–23. Calculate the solute–solvent interaction energy, W_{calc}, for a solution of caffeine in 20% water–80% dioxane (Table 10–10) at 25° C using equation (10–44). With this value for $W_{(calc)}$ and the solubility parameter of the mixed solvent (Table 10–10), calculate the solubility of caffeine in this mixture. The value for A is 0.09467 cm^3/cal, δ_2 (caffeine) = 13.8 $(cal/cm^3)^{1/2}$, and $-\log X_2^i = 1.1646$.

Answer: $W_{(calc)}$ = 173.4079 cal/cm^3; $X_{2(calc)} = 0.024$. The results in Table 10–10, $W_{(calc)}$ = 173.729 cal/cm^3 and $X_{2(calc)} = 0.027$, were obtained using the more accurate quartic expression, equation (10–45).

10–24. (a) What is the $W_{(calc)}$ value for caffeine in a mixture of dioxane and water having a δ_1 value of 17.07 $(cal/cm^3)^{1/2}$? This mixture contains 47.5% by volume of dioxane and 52.5% water. Calculate $W_{(calc)}$ using both the quadratic (equation 10–44) and the quartic (equation 10–45) expressions.

(b) The A value at 25° C is 0.093711 cm^3/cal. The δ_2 value of caffeine is 13.8 $(cal/cm^3)^{1/2}$. The negative log ideal solubility of caffeine at 25° C is $-\log X_2^i = 1.1646$. Calculate the solubility of caffeine in mole fraction and in moles/liter using both $W_{(calc)}$ results (quadratic and quartic) of part (a). The density ρ of the solution is 1.0493 g/cm^3. The molecular weight M_2 of caffeine is 194.19 g/mole, and that of dioxane 88.016 g/mole.

$$\text{Solubility in (moles/liter)} = \frac{1000\ \rho\ (X_2)}{M_1(1 - X_2) + X_2 M_2} \qquad \text{(p. 104)}$$

M_1, the average molecular weight of the solvent at a volume percent of 47.5 dioxane, is given approximately by the use of molecular weights and volume fractions:

M_1 = (88.10 g/mole)(0.475) + (18.015 g/mole)(0.525) ≈ 51.3 g/mole

Partial Answer: Using equation (10–45), $W_{(calc)}$ = 238.06175 cal/cm^3; mole fraction solubility $X_{2(calc)}$ = 0.0200; molar solubility (calculated) = 0.39; molar solubility (experimental) = 0.40 mole/liter.

10–25. Calculate the values of W (equation 10–43), $\delta_1\delta_2$, and the ratio $W/\delta_1\delta_2$ for ketoprofen, an analgesic, in a 70:30 volume percent mixture (δ_1 = 10.32) and a 50:50 volume percent mixture (δ_1 = 11.00) of chloroform–ethanol at 25° C. The ideal solubility of ketoprofen is X_2^i = 0.1516 and its molar volume V_2 = 196 cm^3/mole. The solvent volume fraction ϕ_1 of the two mixtures is 0.6694 and 0.6820, respectively, and the mole fraction solubilities of ketoprofen in the mixtures are X_2 = 0.1848 and X_2 = 0.1622. The solubility parameter of ketoprofen, calculated from the peak solubility value in the chloroform–ethanol mixtures, is δ_2 = 9.8 (cal/cm^3)$^{1/2}$.

Answer:

Mixture	A	W	$\delta_1\delta_2$	$W/\delta_1\delta_2$
70:30	0.0644	101.9389	101.136	1.0079
50:50	0.0668	108.7395	107.800	1.0087

Notice that the use of W instead of $\delta_1\delta_2$ in the Hildebrand equation gives the exact solubility of X_2 = 0.1848. The use of $-2\delta_1\delta_2$ instead of $-2W$ gives a result, X_2 = 0.0813, that is some 56% in error. $W/\delta_1\delta_2$ is nearly unity, viz. 1.0079, which means that W is only slightly different from $\delta_1\delta_2$. Yet, the very small difference causes the use of $-2W$ in the Hildebrand equation to give the exact solubility of ketoprofen in a 70:30 mixture of chloroform and ethanol, and the use of $-2\delta_1\delta_2$ to give a less exact solubility value.

10–26. Calculate the values of A, W, $\delta_1\delta_2$, and $W/\delta_1\delta_2$ for solutions of sulfamethoxypyridazine (SMP) in benzene, δ_1 = 9.07, and in benzyl alcohol, δ_1 = 11.64 (cal/cm^3)$^{1/2}$, at 25° C. The ideal solubility X_2^i of SMP is 9.1411 × 10^{-3}, and its molar volume, V_2, is 172.5 cm^3/mole. The volume fractions ϕ_1 of the solvents benzene and benzyl alcohol are 0.9999 and 0.9757, respectively. The solubility parameter δ_2 of the solute, SMP, is 12.89. The mole fraction solubilities X_2 of SMP in benzene and in benzyl alcohol are 0.0636 × 10^{-3} and 14.744 × 10^{-3} respectively.

Answers:

Solvent	A cm^3/cal	W cal/cm^3	$\delta_1\delta_2$ cal/cm^3	$W/\delta_1\delta_2$
Benzene	0.1264	115.6739	116.9123	0.9894
Benzyl alcohol	0.1204	151.6831	150.0396	1.0110

10–27. The presence of usual components such as sweetening agents in syrup formulas may affect the solubility of preservatives so that changes in temperature yield precipitation and leave the product unprotected. The molar solubility of sorbic acid used as a preservative was studied at 20° C and 37° C as a function of the concentration of glucose.[77]

Data for *Problem 10–27:* Molar Solubility of Sorbic Acid

% Glucose in water	20° C	37° C
0	0.013	0.022
15	0.011	0.019
30	0.009	0.016
45	0.007	0.014
60	0.005	0.011

(a) Plot on the same graph the molar solubility of sorbic acid at 20° C and 37° C (vertical axis) against the percent of glucose in water (horizontal axis) and find a quantitative relationship between these variables. Comment on your results.

(b) The change in the aqueous molar solubility, S, of sorbic acid with addition of glucose is determined by the standard free energy of transfer of sorbic acid from water (w) to the glucose solution (s). Show that these thermodynamic functions, $\Delta G°_{tr}$ and $\Delta H°_{tr}$, can be computed from the following expressions:

$$\Delta G°_{tr} = -RT \ln \frac{S_s}{S_w}$$

and

$$\ln \frac{(S_{s2}/S_{s1})}{(S_{w2}/S_{w1})} = \frac{\Delta H°_{tr}}{R}\left(\frac{T_2 - T_1}{T_1 T_2}\right)$$

(c) As an example, compute $\Delta G°_{tr}$ and $\Delta H°_{tr}$ for the transfer of sorbic acid from water to a 45% solution of glucose at both 20° C and 37° C. Compare your results to the *change in solubility* of sorbic acid from water to 45% glucose at both temperatures. *Hint:* Observe the sign and magnitude of these thermodynamic functions.

Partial Answer: **(c)** $\Delta G°_{tr}$ (20° C) = 360.6 cal/mole; $\Delta G°_{tr}$ (37° C) = 278.6 cal/mole; $\Delta H°_{tr}$ = 1775 cal/mole

10–28. Suppose you traveled to the hypothetical planet Ariston, where the temperature ranged from −100° to 0° C. You were asked to join the scientists at the Ariston National Laboratories to prepare a solution of solid carbon dioxide dissolved in ethanol at −80° C (193° K) to be used in a new rocket engine being developed. The melting point of CO_2 is −56° C and that of ethanol is −114.1° C. At −80° C, the normal room temperature on Ariston, CO_2 exists as a solid and ethanol as a liquid. The boiling point of ethanol is 78.5° C and it re-mains as a liquid from about −114° C to +78.5° C, where it becomes a gas.

(a) Calculate the ideal solubility of solid CO_2 at −80° C. The heat of fusion of CO_2 is 1900 cal/mole.

(b) The density of ethanol at several temperatures is given in the table:

Data for *Problem 10–28*

T (°K)	273.2	283.2	293.2	298.2	303.2
t (°C)	0	10	20	25	30
Density (g/cm^3)	0.80625	0.79788	0.78945	0.78521	0.78097

Regress the density (y values) against t °C (x values) and compute the density and molar volume (cm^3/mole) of ethanol at −80° C. The molecular weight of ethanol is 46.07 gram/mole.

(c) The solubility parameter at temperatures other than 25° C may be determined approximately for a liquid from the densities of the liquid at 25° C and at the new temperature.[78]

$$\delta_{T_1} = \delta_{25°}\left(\frac{\rho_{25°}}{\rho_{T_1}}\right)^{1.25}$$

Use the density of ethanol from the table above (at 25° C) and your result at −80° C, and compute δ for ethanol at −80° C; the δ value for ethanol at 25° C is 12.8 (cal/cm^3)$^{1/2}$.

(d) Estimate the solubility of solid CO_2 in ethanol at −80° C under which conditions it is expected to form a regular solution. The heat of vaporization of CO_2 is 3460 cal/mole. Obtain the solubility parameter at −80° C from this value, knowing that the molar volume at −80° C is V_2 = 38 cm^3/mole. The δ value for CO_2 may be calculated using the expression

$$\delta_{CO_2} = \left(\frac{\Delta H_2^v - RT}{V_2}\right)$$

where ΔH_2^v is the heat of vaporization, R is the gas constant 1.9872 cal/(mole deg), and T is the absolute temperature, 193° K. You will

need the molar volume, V_1, of ethanol and its solubility parameter at −80° C (193° K) (see answers (b) and (c)). You can assume that the volume fraction ϕ_1 of ethanol is 1.00 for the first round of calculations. Then by six or more iteration steps, obtain the more correct solubility (see p. 224, 225).

(e) Once you have calculated the mole fraction solubility of CO_2 in ethanol at −80° C, convert the solubility into units of molality. The molecular weight of CO_2 is 44.01 g/mole.

Answers: **(a)** X_2^i (CO_2, −80° C) = 0.5782; **(b)** ρ (ethanol, −80° C) = 0.87370, V_1 = 52.73 cm^3/mole; **(c)** δ (ethanol, −80° C) = 11.2 $(cal/cm^3)^{1/2}$; δ (CO_2, −80° C) = 9.0 $(cal/cm^3)^{1/2}$; **(d)** X_2 (CO_2, −80° C) = 0.4887 after eight iterations. If ϕ_1 is unity, we obtain the first result of iteration, viz. X_2 = 0.3579; **(e)** molality = 20.7 moles/kg

10–29. The solubility of sodium carbonate, decahydrate, $Na_2CO_3 \cdot 10H_2O$ (washing soda), is 21.52 g/100 g of water at 0° C, and the heat of solution ΔH_{soln} is 13,500 cal/mole. When a substance such as washing soda is added to ice at 0° C, the freezing point of water is lowered and a liquid solution of sodium carbonate is formed at 0° C. Calculate the solubility of sodium carbonate decahydrate at 25° C.

Answer: The solubility of $Na_2CO_3 \cdot 10H_2O$ is 43.13 g/(100 g H_2O) using equation (10–46). Note that Na_2CO_3 contributes three ions in solution, i.e., ν = 3. The experimental value is 50 g/(100 g H_2O) at 25° C, a 14% difference from the calculated value.

10–30. The solubility of $Ba(OH)_2 \cdot 8H_2O$ in water at three temperatures is reported by Daniels and Alberty[79] as follows:

Data for *Problem 10–30*

Temperature (°C)	0.0	10.0	20.0
Molal solubility	0.0974	0.1447	0.227

Use the modification of equation (10–46), that is,

$$\ln m_2 = -\frac{\Delta H_{soln}}{R}\frac{1}{T} + I$$

which provides the heat of solution, ΔH_{soln}, when a graph of the data is plotted with ln m_2 (m_2 is the molality of the solute) on the vertical axis and $1/T$ (T is the absolute temperature) on the horizontal axis. The slope of the line, obtained by linear regression analysis and multiplied by R = 1.9872 cal $mole^{-1}$ deg^{-1}, gives ΔH_{soln} in cal/mole. I in the equation is an integration constant and is the point of intersection on the vertical axis.

Use the equation above to obtain ΔH_{soln}, the heat of solution in the range of 0° C to 20° C and to predict the solubility of barium hydroxide octahydrate at 30° C in water.

Answer: ΔH_{soln} = 6719 cal/mole; calculated molal solubility at 30° C = 0.327 m; experimental solubility[79] = 0.326 m

10–31. If the solubility product of silver chromate is 2×10^{-12} at 25° C, what is the solubility in mole/liter of silver chromate?

Answer: 7.9×10^{-5} mole/liter

10–32. What is the solubility of the electrolyte, magnesium hydroxide, **(a)** in moles/liter and **(b)** in g/100 mL if the solubility product is 1.4×10^{-11}? The molecular weight of $Mg(OH)_2$ is 58.34.

Answers: **(a)** 1.5×10^{-4} mole/liter; **(b)** 8.8×10^{-4} g/dL. The symbol dL stands for deciliter = 100 mL.

10–33. Brequinar sodium dissociates as brequinar$^-$ and Na^+. Its apparent solubility product K'_{sp} = 0.0751. **(a)** Compute the solubility of this compound.[80] **(b)** Compute the solubility product K_{sp}, using the mean activity coefficient, $\gamma_\pm$. **(c)** Compute the solubility after addition of a 0.05-M solution of KCl.

Answers: **(a)** 0.274 mole/liter; **(b)** K_{sp} = 0.0335; **(c)** 0.280 mole/liter

10–34. the crystal lattice energy of AgCl is 207 kcal/mole and its heat of hydration is −192 kcal/mole. **(a)** What is the heat of solution of AgCl in kcal/mole and in kJ/mole **(b)** The solubility of AgCl in water at 10° C is 8.9×10^{-5} g/dL of solution. What is the solubility of AgCl at 25° C? AgCl dissociates into two ionic species in solution.

Answers: **(a)** ΔH_{soln} = 15 kcal/mole (Table 10–11); in kJ/mole; ΔH_{soln} = 62.8; **(b)** 1.74×10^{-4} g/dL of solution. The experimental value is 1.93×10^{-4} % (w/v).

Note: For the strong electrolytes such as NaCl and KBr, which are very soluble in water, the use of equation (10–46) does not give very reasonable results for solubility. As seen in this example, the solubility for a slightly soluble strong electrolyte such as silver chloride at various temperatures is reasonable in comparison with observed values (i.e., within 10%).

10–35. The crystal lattice energies of potassium bromide and potassium chloride are 673 and 699 kJ/mole; their heats of hydration are −651 kJ/mole and −686 kJ/mole, respectively. What is the heat of solution ΔH_{soln} of KBr and of KCl?. Express the results in kJ/mole, then convert to kcal/mole.

Answer: for KBr, ΔH_{soln} = 22 kJ/mole = 5.3 kcal/mole; for KCl, ΔH_{soln} = 13 kJ/mole = 3.1 kcal/mole

10–36. What is the solubility of barium sulfate in a solution having an ionic strength μ of 0.25 and $K_{sp} = 1 \times 10^{-10}$ at 25° C? The activity coefficient for a bi-bivalent salt at this ionic strength is 0.23.

Answer: 4.3×10^{-5} mole/liter

10–37. The solubility of boric acid in an aqueous solvent containing 25% by volume of sorbitol was found by Sciarra et al.[81] to be 2.08 molal at 35° C. The heat of solution of boric acid in this mixed solvent is 3470 cal/mole. Calculate the molal solubility of boric acid at 50° C in this solvent.

Answer: 2.71 molal

10–38. The molar solubility of sulfathiazole in water is 0.002, the pK_a is 7.12, and the molecular weight of sodium sulfathiazole is 304. What is the lowest pH allowable for complete solubility in a 5% solution of the salt?

Answer: pH_p = 9.03

10–39. What is the pH_p of a 2% solution of sodium phenobarbital in a hydroalcoholic solution containing 15% by volume of alcohol? The solubility of phenobarbital in 15% alcohol is 0.22%. The pK_a of phenobarbital in this solution is 7.6. The molecular weight of sodium phenobarbital is 254.22 g/mole and that of phenobarbital is 232.23 g/mole.

Answer: pH_p = 8.5

10–40. Calculate pH_p for a 0.5% solution of cocaine hydrochloride. The molecular weight of the salt is 339.8, and the molar solubility of the base is 5.60×10^{-3}. The pK_b of cocaine is 5.59.

Answer: pH_p = 8.20

10–41. Using data in Figures 10–7 and 10–8, calculate the minimum pH required for complete solubility of sodium phenobarbital in a solution containing 3 g of the drug in 100 mL of a mixed alcohol–water solvent. **(a)** Calculate pH_p, the minimum pH for the drug, in each aqueous solvent consisting of 10%, 20%, 30%, 40%, and 50% by volume of ethanol. **(b)** Plot pH_p versus percent by volume of alcohol in the solvent. The procedure may be checked by comparing the results with the calculations illustrated in *Example 10–17*, page 235. The molecular weight of phenobarbital is 232.23 g/mole and that of sodium phenobarbital is 254.22.

Answer:

% Alcohol	10	20	30	40	50
pH_p	8.73	8.63	8.55	8.02	*

*At about 50% alcohol and above, phenobarbital in a 3g/100 mL solution of the drug will not precipitate no matter how low the pH.

10–42. The molar solubility of codeine, S_o, in water at 25° C is approximately 0.0279 mole/liter; the pK_a of codeine (actually, the conjugate acid of the base, codeine) is 8.21 at 25° C; and the molecular weight of codeine phosphate · $\frac{1}{2}H_2O$ (U.S.P.) is 406.37 dalton.* What

*Recall that the word *dalton* is another term for the units g/mole, i.e., for molecular weight units.

is the highest pH allowable for complete solubility in an aqueous solution of 60 mg of the salt per 5 mL of solution?

Answer: The pH above which the free base precipitates from solution is 9.45.

10–43. A prescription calls for 7 grains (1 gram = 15.432 grains) of phenobarbital in 60 mL of solution. The vehicle consists of 20% by volume of glycerin, 5% by volume of alcohol, and the balance water. From Figure 10–7 it is observed that about 25% by volume of alcohol is required in the solution to dissolve this quantity of phenobarbital. How much U.S.P. alcohol (95% by volume) must be added?

Answer: 13.3 mL

10–44. If a container of pure water is shaken in the air, the water will dissolve atmospheric carbon dioxide until the dissolved gas is in equilibrium with that in the air. At atmospheric pressure the solubility of CO_2 is found to be 1×10^{-5} mole/liter. The dissociation constant K_1 of carbonic acid is approximately equal to 4×10^{-7}. Compute the pH of water saturated with CO_2. *Hint:* $[H_3O^+] = \sqrt{K_1 c}$, in which c is the equilibrium concentration of the gas in water.

Answer: pH = 5.7

10–45. (a) Calculate the solubility at 25° C of sulfisoxazole in an aqueous buffer having a pH of 5.12. (b) Repeat the calculation for the pH 5.12 buffer solution when 3.0% Tween 80 is included in the solution. See *Example 10–18* for K_a, K', and K'', and for the aqueous solubility of nonionized sulfisoxazole at 25° C. (c) Calculate the fraction of sulfisoxazole solubilized in the Tween 80 micelles in this solution.

Answers: (a) 0.30 g/liter; (b) 0.723 g/liter; (c) 0.585

10–46. Calculate the molar solubility of butyl p-hydroxybenzoate (mp 68° C) in water at 25° C using equation (10–100), page 240. The log K for benzoic acid is 1.87; the contribution by an OH group is −1.16 and by a CH_2 group is 0.50, according to Leo et al.[61]

Answer: $\Delta S_f = 16.0$ e.u. $\log K_{(calc)} = 2.71$, $\log S = -2.73$, $S_{(calc)} = 1.86 \times 10^{-3}$ M, $S_{(obs)} = 1.29 \times 10^{-3}$ M

10–47. Pinal and Yalkowsky[62] extended their earlier equations[63] to estimate the aqueous solubility of weak electrolytes. The new equation is

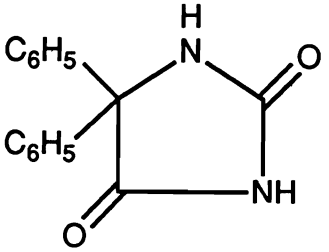
$$\log S = -\frac{\Delta S_f (T_m - T)}{2.303RT} - \log K + \log \alpha + 0.8 \quad (10\text{–}113)$$

where T_m and T are respectively the absolute temperature at the melting point and the temperature at which the experiment is done. The other symbols have the same meaning as in equation (10–100), page 240; α is an ionization term defined as

$$\alpha = \left(1 + \frac{10^{-pK_a}}{10^{-pH}}\right)$$

for monoprotic acids.

(a) Compute the aqueous solubility of phenytoin (a derivative of hydantoin used as an antiepileptic drug) at pH 7.1 and 25° C. The pK_a of phenytoin is 8.30, the melting point is 296.9° C, and the partition coefficient K is 208.9. The entropy of fusion can be calculated according to equation (10–101), page 240, where n is the number of carbons in the longest hydrocarbon chain or flexible ring. Phenytoin has the formula



(b) Compute the partition coefficient in an octanol–water system for pentobarbital using the equation of Yalkowsky et al.[82] (equation (10–113)). The observed solubility of pentobarbital at 33° C and pH 8 is 0.01107 mole/liter. the pK_a is 8.07 and $\Delta S_f = 12.67$ entropy units (e.u.) (i.e., 12.67 cal/mole deg). The melting point is 128.5° C.

Answers: (a) n, the number of carbons in the calculation of ΔS_f is $n = 6$; $\Delta S_f = 16$ e.u.; $\alpha = 1.063$; $\log S = -4.6835$; S, the aqueous solubility of phenytoin, $= 2.07 \times 10^{-5}$ mole/liter; (b) $\log K = 2.16$; $K = 144.5$

10–48. If 0.15 g of succinic acid in 100 mL of ether is shaken with a 10-mL portion of water, how much succinic acid is left in the ether layer? The distribution coefficient K = (conc. in ether)/(conc. in water) = 0.125 at 25° C. How much succinic acid is left in the ether when the phase is extracted with an additional 10 mL of water?

Answer: 0.083 g after first extraction; 0.046 g after second extraction

10–49. How much benzoic acid, $K_a = 6.3 \times 10^{-5}$, will remain undissociated in the aqueous phase of a 50% oil–water emulsion if the initial concentration of benzoic acid in the aqueous phase is 0.5%? The aqueous phase is buffered at pH 5 and the o/w partition coefficient = 5.33. Assume that benzoic acid remains as a monomer in the oil phase.

Answer: 0.396 mg/mL

10–50. Propionic acid is added to the aqueous phase of a 20% oil–water emulsion, and 0.65 mg/mL of free acid remains in the aqueous phase after equilibrium has been attained between the two phases. In a 20% emulsion, $q = V_o/V_w = 20/80 = 0.25$. The aqueous phase is buffered at pH 3.5. Propionic acid is found to dimerize in the oil phase and the distribution constant, $K'' = \sqrt{C}/[HA_w]$, is equal to 15.0. The K_a of propionic acid is 1.4×10^{-5}. Compute the initial concentration C of propionic acid to be introduced into the aqueous phase. The molecular weight of propionic acid is 74.08 g/mole.

Answer: $C = 1.0$ mg/mL

10–51. To determine the *intrinsic partition coefficient* K_{in} of pilocarpine base in a study of transcorneal permeation, the octanol–water aqueous buffer partition coefficient, K_{obs}, was obtained experimentally at various temperatures and pH values (Mitra and Mikkelson[84]). The results are presented in Table 10–15.

TABLE 10–15. ***Observed Partition Coefficients K_{obs} at Various pH's and Temperatures. (Data for Problem 10–51)***

pH	6.25	6.50	6.70	6.85	7.00	7.25
$[H_3O^+]$ ($\times 10^7$)	5.62	3.16	2.00	1.41	1.00	0.56
T (°C)	Observed Partition Coefficients, K_{obs}					
27	0.24	0.38	0.52	0.63	0.72	0.89
30	0.31	0.46	0.62	0.78	0.84	1.06
40	—	0.65	0.88	1.06	1.23	1.49

(a) According to Mitra and Mikkelson,[84] the observed partition coefficient K_{obs} is related to the hydrogen ion concentration of the aqueous phase $[H_3O^+]$ by the expression

$$\frac{1}{K_{obs}} = \frac{1}{K_{in}K_a}[H_3O^+] + \frac{1}{K_{in}}$$

where the intrinsic partition coefficient K_{in} of the free base, pilocarpine is independent of pH. The term K_a is the ionization constant in water of the conjugate acid of pilocarpine, i.e., the pilocarpinium cation. Plot the reciprocal of the observed partition coefficient, $1/K_{obs}$, versus the hydrogen ion concentration, $[H_3O^+]$. Using linear regression analysis obtain the intrinsic partition coefficient, K_{in}, for pilocarpine base between octanol and an aqueous phosphate buffer, and the acidic ionization constant K_a for the pilocarpinium cation at temperatures 27°, 30°, and 40° C. The cation does not partition into octanol.

(b) The intrinsic partition coefficient of pilocarpine base in the logarithmic form ln K_{in} may be expressed in terms of the thermodynamic quantities $\Delta H°$, $\Delta S°$, and $\Delta G°$ using the van't Hoff equation:

$$\ln K_{in} = -\frac{\Delta H°}{R}\frac{1}{T} + \frac{\Delta S°}{R}$$

Regress ln K_{in} against $1/T$, at the three absolute temperatures 27° C = 300.15° K, 30° C = 303.15° K, and 40° C = 313.15° K. Solve for $\Delta H°$ and $\Delta S°$ and obtain $\Delta G°$ at the three temperatures. Interpret the magnitude and the sign of these three thermodynamic quantities as they relate to the partitioning process.

Answers: **(a)**

Temperature (°C)	K_{in}	K_a	pK_a
27	1.324	1.25×10^{-7}	6.90
30	1.433	1.54×10^{-7}	6.81
40	2.106	1.42×10^{-7}	6.85

(b) $\Delta H°$ = 6777 cal/mole = 6.8 kcal/mole; $\Delta S°$ = 23 cal/(mole deg); $\Delta G°$ = −159 cal/mole at 27° C, −228 cal/mole at 30° C, and −460 cal/mole at 40° C

$\Delta H°$ is positive, which mitigates against the partitioning process, yet $\Delta S°$ is sufficiently positive to provide a spontaneous reaction. The negative $\Delta G°$ values corroborate the conclusion that the process is spontaneous (for the solute in its standard state). The large positive $\Delta S°$ value suggests that pilocarpine base is solvated in the aqueous phase in an orderly structure of water, which is broken down to a more random arrangement of drug and solvent in the octanol phase.