THERMODYNAMICS OF PHARMACEUTICAL SYSTEMS

An Introduction for Students of Pharmacy

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SOLUBILITY

10.1. SOLUBILITY AS AN EQUILIBRIUM CONSTANT

The topic of solubility merits special attention because of its great importance in pharmaceutical systems. We can generally anticipate that a drug must be in solution if it is to exert its effect. Typically the type of system we encounter is a pure solid substance (the solute) in contact with a pure liquid (the solvent). We allow equilibrium to be achieved at fixed temperature and pressure, such that at equilibrium the system consists of (excess) pure solid phase and liquid solution of solute dissolved in solvent. According to Gibbs' phase rule, $P = 2$ and $C = 2$, so $F = C - P + 2 = 2$ degrees of freedom. These are the temperature and pressure, which we have specified as fixed. Thus there remain no degrees of freedom; the system is invariant. This means that at fixed temperature and pressure, the concentration of dissolved solute is fixed. We call this invariant dissolved concentration the *equilibrium solubility* of the solute at this pressure and temperature. (We say that the solution is *saturated*.) Our present concern is with how the equilibrium solubility depends on the temperature and on the chemical natures of the solute and the solvent.

Expressed as a reaction, the dissolution process is

$$\text{Pure solute} \rightleftharpoons \text{solute in solution}$$
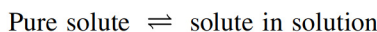
At equilibrium the chemical potentials of the solute in the two phases are equal, or, letting component 1 be the solvent and component 2 the solute

$$\mu_2\,(\text{solid}) = \mu_2\,(\text{soln})$$

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Writing out the chemical potentials gives

$$\mu_2^\circ \,(\text{solid}) + RT \ln a_2 \,(\text{solid}) = \mu_2^\circ \,(\text{soln}) + RT \ln a_2 \,(\text{soln}) \qquad (10.1)$$

where the standard state of the solid is the pure solid, and we will adopt as the standard state of the solute in solution the Henry's law definition on the molar concentration scale. Rearranging Eq. (10.1) leads to

$$\Delta\mu^\circ = -RT \ln \frac{a_2 \,(\text{soln})}{a_2 (\text{solid})} \qquad (10.2)$$

where $\Delta\mu^\circ = \mu_2^\circ \,(\text{soln}) - \mu_2^\circ \,(\text{solid})$. But the solid is in its standard state, so $a_2 \,(\text{solid}) = 1.0$ by definition, and we obtain

$$\Delta\mu^\circ = -RT \ln a_2 \,(\text{soln}) \qquad (10.3)$$

We have seen that $a_2 \,(\text{soln})$ is invariant—it is the activity corresponding to the equilibrium solubility—so comparison of Eq. (10.3) with the fundamental thermodynamic result

$$\Delta G^\circ = -RT \ln K \qquad (10.4)$$

leads to the conclusion that $a_2 \,(\text{soln})$, the activity of the solute in a saturated solution, must have the character of an equilibrium constant. As a consequence, we can evaluate standard free energy, enthalpy, and entropy changes for the solution process in the usual manner (Chapter 4). These quantities are respectively called the *free energy*, *heat*, and *entropy of solution*.

For nonelectrolyte solutes, particularly those of limited solubility, so that the saturated solution is fairly dilute, it will be acceptable to approximate the activity $a_2 \,(\text{soln})$ by the equilibrium solubility concentration. This is usually in molar concentration units, and is often symbolized s.

10.2. THE IDEAL SOLUBILITY

A thermodynamic argument can predict the equilibrium solubility of a nonelectrolyte, provided it dissolves to form an ideal solution. Ideal behavior does not mean that intermolecular interactions are absent. On the contrary, solids and liquids would not exist without the intermolecular forces of interaction. In the present context, ideal behavior means that the energy of interaction between two solvent molecules is identical to that between one solvent and one solute molecule, so that a solvent molecule may be replaced with a solute molecule without altering the intermolecular energies. (This requires that the solvent and solute molecules have the same size, shape, and chemical nature, a demanding set of limitations.)

Quantitatively, an ideal solution can be defined as one having the following properties (Chapter 7):
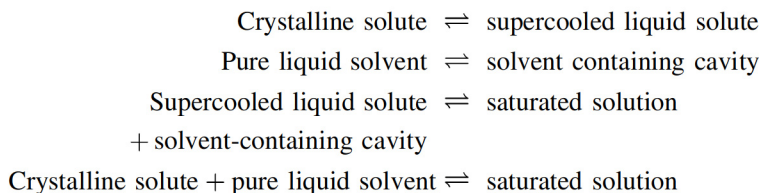
$$\Delta H_{\text{mix}} = 0 \tag{10.5}$$
$$\Delta V_{\text{mix}} = 0 \tag{10.6}$$
$$\Delta S_{\text{mix}} = -R(x_1 \ln x_1 + x_2 \ln x_2) \tag{10.7}$$

According to Eqs. (10.5) and (10.6), there is no heat or volume change on mixing the solute and solvent in an ideal solution, and the entropy change is given by Eq. (10.7). Since $x_1 + x_2 = 1$, the logarithmic terms are necessarily negative, so ΔS_{mix} is positive, and this constitutes the "driving force" for dissolution, because of the relationship $\Delta G = \Delta H - T \Delta S$.

If the entropy of mixing is the driving force for dissolution, what is the "resistance"? It is the solute–solute interaction forces, which, for solids, lead to the "crystal lattice energy." These must be overcome for the solute to dissolve. Now, the free-energy change for the dissolution process is the same no matter what reversible mechanism (path) is taken to pass from the initial state (pure solute) to the final state (saturated solution), so we can divide the process as follows (for a solid solute):

$$\text{Crystalline solute} \rightleftharpoons \text{supercooled liquid solute}$$
$$\text{Pure liquid solvent} \rightleftharpoons \text{solvent containing cavity}$$
$$\text{Supercooled liquid solute} \rightleftharpoons \text{saturated solution}$$
$$+ \text{solvent-containing cavity}$$
$$\text{Crystalline solute} + \text{pure liquid solvent} \rightleftharpoons \text{saturated solution}$$

Since in an ideal solution the solvent–solvent interactions match the solvent–solute interactions, the energy required to create molecule-sized cavities in the solvent is offset by the energy recovered when the solute molecules are inserted into these cavities. The energetic cost of the dissolution process then appears in the first step, the melting of the solid. An equivalent viewpoint (Grant and Higuchi 1990, p. 16) is that the enthalpy of solution is given by

$$\Delta H_{\text{soln}} = \Delta H_{\text{fusion}} + \Delta H_{\text{mix}}$$

But $\Delta H_{\text{mix}} = 0$ for an ideal solution, so $\Delta H_{\text{soln}} = \Delta H_{\text{fusion}}$.

The saturation solubility, we have seen, is an equilibrium constant, so the van't Hoff equation [Eq. (4.29)] is applicable

$$\frac{d \ln x_2}{dT} = \frac{\Delta H_{\text{f}}}{RT^2} \tag{10.8}$$

where the solubility is expressed as the mole fraction simply to maintain consistency with Eq. (10.7), and where ΔH_{f} is the heat of fusion and T is the absolute

temperature. We have seen above why the heat of fusion appears in a solubility expression. (Incidentally, a dissolved solid should be viewed as possessing some of the properties of the liquid state, consistent with the above view that fusion is the first step in the dissolution process.) Now suppose that ΔH_f is independent of temperature, which is equivalent to writing, for the solute from Eq. (1.23):

$$\Delta C_p = C_p^{\text{liq}} - C_p^{\text{solid}} = 0 \tag{10.9}$$

Then integrating Eq. (10.8) from T_m to T gives

$$\ln x_2 = -\frac{\Delta H_f}{R}\left(\frac{T_m - T}{T\,T_m}\right) \tag{10.10}$$

where T_m is the melting temperature and T is the experimental temperature. Equation (10.10) allows us to calculate the ideal solubility.

Example 10.1. The melting point of naphthalene is 80.2°C, and its heat of fusion at the melting point is 4.54 kcal mol^{-1}. What is the ideal solubility of naphthalene at 20°C?

$$\text{Log}\,x_2 = \frac{-4540\,\text{cal mol}^{-1}}{(2.303)(1.987\,\text{cal mol}^{-1}\text{K}^{-1})}\left(\frac{60.2\,\text{K}}{353.35\,\text{K} \times 293.15\,\text{K}}\right)$$

$$= -0.577$$

$$x_2 = 0.265$$

Deviations from ideality will be manifested by discrepancies from the ideal solubility as calculated with Eq. (10.10). Table 10.1 lists equilibrium solubilities for

Table 10.1. Naphthalene solubility at 20°C

Solvent	x_2
(Ideal)	0.265
Chlorobenzene	0.256
Benzene	0.241
Toluene	0.224
Carbon tetrachloride	0.205
Hexane	0.090
Aniline	0.130
Nitrobenzene	0.243
Acetone	0.183
n-Butanol	0.0495
Methanol	0.0180
Acetic acid	0.0456
Water (25°C)	0.0000039

naphthalene in many solvents. Observe that those solvents most chemically like naphthalene, that is, aromatic and nonpolar solvents, show behavior most closely approximating ideal behavior.

At the melting temperature T_m the solid and liquid forms of the solute are in equilibrium, so $\Delta G_f = 0$ and we get $\Delta H_f = T_m \Delta S_f$, giving Eq. (10.11) as an alternative form of Eq. (10.10):

$$\ln x_2 = -\frac{\Delta S_f(T_m - T)}{RT} \tag{10.11}$$

10.3. TEMPERATURE DEPENDENCE OF THE SOLUBILITY

Since ΔH_f is always a positive quantity, Eq. (10.10) predicts that the solubility of a solid will increase with temperature. Moreover, Eq. (10.10) shows that if two solid substances have the same heat of fusion, the one with the higher melting point will have the lower solubility. Conversely, if they have the same melting point, the one with the lower heat of fusion will have the higher solubility. All of these inferences from Eq. (10.10) refer to systems forming ideal solutions, so deviations from the predictions can occur for real systems. Nevertheless, the increase of solubility with temperature is very widely observed for solids. Even the relationship of solubility to melting point can be a useful guide, though confounding phenomena can introduce complications; for example, hydrogen-bonding or other polar interactions may raise both the melting point and the aqueous solubility. The comparison of the temperature dependence of solubility of solids and gases is instructive; see Table 10.2.

Equation (10.10) can be rearranged to Eq. (10.12):

$$\ln x_2 = -\frac{\Delta H_f}{RT} + \frac{\Delta H_f}{RT_m} \tag{10.12}$$

Table 10.2. The contrary effects of temperature on the solubilities of solids and gases

$$\text{Solid} \underset{\Delta H_c}{\overset{\Delta H_f}{\rightleftharpoons}} \text{liquid} \overset{\Delta H_v}{\rightleftharpoons} \text{gas}$$

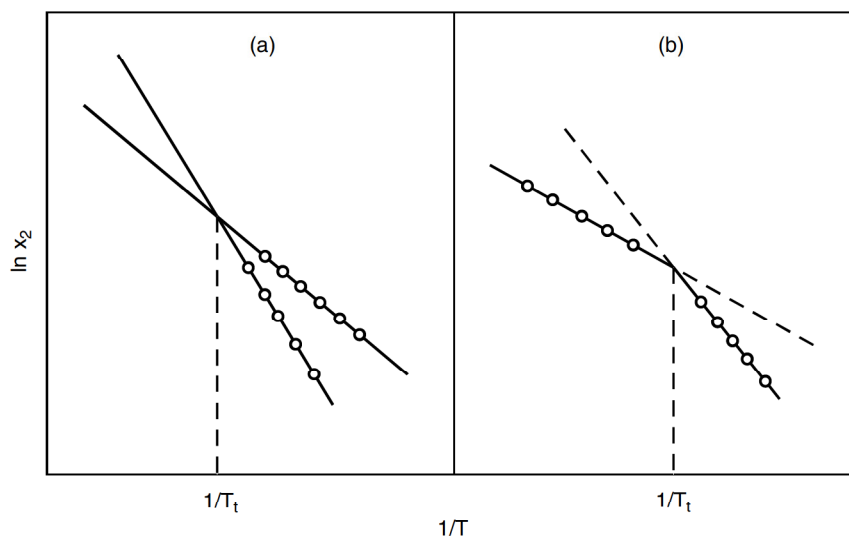| Solids	Gases
Solution is the process of passing from solid to liquid (fusion, ΔH_f)	Solution is the process of passing from gas to liquid (condensation, ΔH_c), which is the reverse of vaporization (ΔH_v)
ΔH_f is *positive*, so x_2 *increases* as T increases	ΔH_v is positive, so ΔH_c is *negative*; thus x_2 *decreases* as T increases

Figure 10.1. Hypothetical solubility van't Hoff plots for polymorphs.

If ΔH_f is essentially constant over the experimental temperature range, Eq. (10.12) predicts that a plot of $\ln x_2$ against $1/T$ will be linear with a slope equal to $-\Delta H_f/R$. The line should terminate at the melting point, where $1/T - 1/T_m$. Often such lines are straight, probably because the usual range of temperatures is small. The slope gives ΔH_f in principle, but in actuality the quantity evaluated from the slope is not precisely ΔH_f because the solution is seldom ideal, and instead the quantity found in this way is termed the *heat of solution*.

Throughout this discussion we have been assuming that the solid phase consists of the pure solid and not a solid solution. Another possible complication arises if the solid substance can exist in two crystalline forms (polymorphs; Chapter 6), which interconvert at transition temperature T_t. The van't Hoff plot can resemble Fig. 10.1a or Fig. 10.1b depending primarily on the kinetics of the transformation. In Fig. 10.1a, the two forms are sufficiently stable that their solubilities can be separately measured at the same temperatures, which are below the transition temperature. Nevertheless, the crystal form having the higher solubility (at a given temperature) is thermodynamically unstable (it is said to be metastable, since its kinetics of transformation permit it to exist for some period during which it acts as if it were stable), and will ultimately be converted to the stable form. Extrapolation of the lines to the transition temperature may be possible. Sulfathiazole in 95% ethanol shows the Fig. 10.1a behavior (Milosovich 1964; Carstensen 1977, p. 7).

In Fig. 10.1b, one form exists in one temperature range, the other form in a temperature range on the other side of T_t. The melting point observed will be that of the higher-melting polymorph. Carbon tetrabromide exemplifies this behavior (Hildebrand et al. 1970, p. 23).

Let us return to the assumption that the change in heat capacities, ΔC_p, is zero, for all the subsequent discussion was based on this assumption. If ΔH_f in fact is a function of temperature, then ΔC_p is not zero. Suppose we make the more reasonable assumption that ΔC_p is a nonzero constant, and write ΔH_f as

$$\Delta H_f = \Delta H_f^m - \Delta C_p(T_m - T) \tag{10.13}$$

where ΔH_f^m is the heat of fusion at T_m. Equation (10.13) is inserted into Eq. (10.8), which can be rearranged and integrated to give Eq. (10.14):

$$\ln x_2^s = \frac{-\Delta H_f^m}{R}\left(\frac{T_m - T}{T\, T_m}\right) + \frac{\Delta C_p}{R}\left(\frac{T_m - T}{T}\right) - \frac{\Delta C_p}{R}\ln\frac{T_m}{T} \tag{10.14}$$

This equation is useful for assessing the error that may be introduced by making the simple assumption $\Delta C_p = 0$. Suppose, for example, that the experimental temperature is 25°C and the melting point is 100°C. Then the last two terms in Eq. (10.14) become equal to $0.25\Delta C_p/R - 0.22\,\Delta C_p/R = 0.03\Delta C_p/R$. Thus considerable compensation can take place, making the approximation $\Delta C_p = 0$ more acceptable than it might have seemed.

Example 10.2. These are solubility data for nitrofurantoin in water (Chen et al. 1976). Analyze the data to obtain the heat of solution.

$t\,(°C)$	$10^6 x_2$
24	6.01
30	8.57
37	13.16
45	18.99

The data are manipulated as required to make the van't Hoff plot according to Eq. (10.12):

$T\,(10^3\,\mathrm{K})$	$\log x_2$
3.37	−5.22
3.30	−5.06
3.23	−4.88
3.14	−4.72

The plot is shown in Fig. 10.2. It is possible that the points describe a curve, but this is uncertain with the data as given, for conceivably the scatter is a consequence of experimental random error. A straight line has therefore been drawn. Its slope is
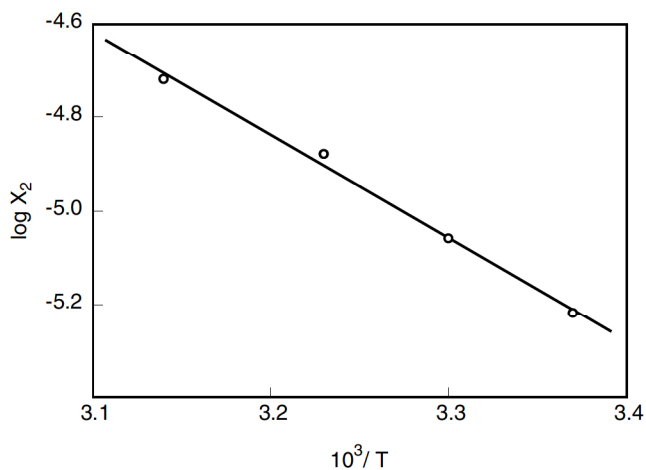
Figure 10.2. van't Hoff plot for nitrofurantoin solubility.

$-2300\,\text{K}$, so we calculate

$$
\begin{aligned}
\Delta H_{\text{soln}} &= (2300\,\text{K})(1.987\,\text{cal mol}^{-1}\,\text{K}^{-1}) \\
&= 4570\,\text{cal mol}^{-1} \\
&= 4.57\,\text{kcal mol}^{-1} \\
&= 19.1\,\text{kJ mol}^{-1}
\end{aligned}
$$

Note that the enthalpy change is labeled ΔH_{soln} to indicate explicitly that this is a heat of solution.

10.4. SOLUBILITY OF SLIGHTLY SOLUBLE SALTS

Many salts exhibit very low solubilities in water. Silver chloride is an example; if aqueous solutions of silver nitrate and sodium chloride are mixed, solid silver chloride precipitates. It is conventional to describe this process as the reverse of the precipitation reaction, namely, as the dissolution of the salt. Let us begin with the simplest case of a $1:1$ sparingly soluble salt MX. The solid crystalline form is ionic. When it dissolves in water the ions dissociate, and no ion pairs are detectable. We therefore write the equilibrium as

$$
\text{MX(s)} \rightleftharpoons \text{M}^+ + \text{X}^- \tag{10.15}
$$

Proceeding as we have done for several earlier processes, we equate the chemical potentials of the solid and the dissolved solute at equilibrium:

$$
\mu(\text{s}) = \mu(\text{soln})
$$

Expanding these gives

$$\mu°(s) + RT \ln a(s) = \mu°_+ + RT \ln a_+ \\ + \mu°_- + RT \ln a_-$$

and collecting terms (and noting that $a(s) = 1$ by our standard state definition),

$$\Delta\mu° = -RT \ln a_+ a_- \qquad (10.16)$$

where $\Delta\mu° = \mu°_+ + \mu°_- - \mu°(s)$. Evidently then [compare with Eq. (10.4)], the product $a_+ a_-$ is an equilibrium constant. By Eq. (8.23a) we see that $a_+ a_- = a_\pm^2$, where $a_\pm$ is the mean ionic activity, and since $a_\pm^2 = \gamma_\pm^2 c_\pm^2$, Eq. (10.16) can be written

$$\Delta\mu° = -RT \ln \gamma_\pm^2 c_\pm^2 \qquad (10.17)$$

If no extraneous ions are present, so that the ionic strength is due solely to the ions from the sparingly soluble salt (and hence is very low), the activity coefficient term is essentially unity. Moreover, the molar concentrations of the cation M^+ and the anion X^- are equal, and each is numerically equal to the equilibrium molar solubility of the salt, which is commonly denoted s. Thus Eq. (10.17) becomes

$$\Delta\mu° = -RT \ln s^2 \qquad (10.18)$$

Equation (10.17) is exact; Eq. (10.18) is usually a reasonable approximation, and both implicitly define the equilibrium constant for Eq. (10.15). This constant is symbolized K_{sp} and is called the *solubility product*. Since solubility products are very small numbers, it is common to state them as pK_{sp}, where $pK_{sp} = -\log K_{sp}$. Table 10.3 lists some pK_{sp} values.

Table 10.3. Solubility products for slightly soluble salts[a]

Salt	pK_{sp}	Salt	pK_{sp}
$BaSO_4$	9.96	$PbCO_3$	13.13
$CaCO_3$	8.54	PbS	27.9
$Ca(OH)_2$	5.26	$MgCO_3$	7.46
$Ca_3(PO_4)_2$	28.7	Hg_2S	47.0
CuI	11.96	HgS (red)	52.4
AuCl	12.7	HgS (black)	51.8
$AuCl_3$	24.5	AgBr	12.30
$Fe(OH)_2$	15.1	AgCl	9.75
$Fe(OH)_3$	37.4	AgI	16.08

[a] In the temperature range 18–25°C; water is the solvent.

Example 10.3. What is the solubility of silver chloride in water? From Table 10.3, $pK_{sp} = 9.75$ for AgCl, so $K_{sp} = 1.78 \times 10^{-10}$. From Eq. (10.18), $K_{sp} = s^2$, so $s = \sqrt{K_{sp}} = 1.33 \times 10^{-5}$ M.

In the general case of the salt whose formula is M_pX_q the solubility product is defined, in accordance with the usual formulation of equilibrium constants:

$$K_{sp} = c_M^p c_X^q \tag{10.19}$$

The quantity that we label s then depends on the stoichiometry.

Example 10.4. What is the molar solubility of ferrous hydroxide?
From Table 10.3, $pK_{sp} = 15.1$, or $K_{sp} = 7.9 \times 10^{-16}$. The dissolution reaction is

$$\mathrm{Fe(OH)_2} \rightleftharpoons \mathrm{Fe^{2+}} + 2\mathrm{OH^-}$$
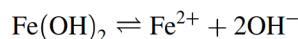
so $K_{sp} = c_{Fe}c_{OH}^2$. (The charges on the subscripts are omitted for clarity.) Since each molecule of Fe $(OH)_2$ that dissolves yields one $\mathrm{Fe^{2+}}$ ion, we define the solubility as the concentration of ferrous ion, or $c_{Fe} = s$. The stoichiometry yields $c_{OH} = 2\,c_{Fe}$, so the result is[1]

$$K_{sp} = s \times (2s)^2 = 4s^3$$

Therefore $s = 5.8 \times 10^{-6}$ M.

Example 10.5. What is the solubility of silver chloride in 0.02 M KCl? Assume activity coefficients are unity.
Again we set $c_{Ag} = s$, the solubility. The solubility product is defined $K_{sp} = c_{Ag}c_{Cl}$; however, the chloride concentration has been augmented by the addition of potassium chloride, so we write $c_{Cl} = 0.02 + s$; that is, the chloride concentration is the sum from two sources, the KCl and the AgCl. We therefore have $K_{sp} = s(0.02 + s)$, which is a quadratic equation that can be solved for s. Before doing that, however, it is worth trying the approximation $c_{Cl} = 0.02$, which involves neglecting the relatively small contribution from dissolution of the AgCl. Thus

$$K_{sp} = 0.02s = 1.78 \times 10^{-10}$$
$$s = 8.9 \times 10^{-9}\,\mathrm{M}$$

First note that the approximation seems well justified. More interestingly, observe that the solubility of silver chloride has been reduced from about 1×10^{-5} M in water (Example 10.3) to about 1×10^{-8} M in 0.02 M KCl. This is an example of the *common ion effect*. The solubility of any slightly soluble salt can be reduced by adding an excess of one of its constituent ions.

The accuracy of such calculations can be improved by making use of the Debye–Hückel equation to estimate the values of mean ionic activity coefficients.

10.5. SOLUBILITIES OF NONELECTROLYTES: FURTHER ISSUES

Salt Effects. In Example 10.5 we encountered one type of salt effect. There is another type of salt effect that is observed when the solubility of a nonelectrolyte is studied as a function of ionic strength (or of the concentration of an added electrolyte). Compare the nonelectrolyte solubility in the absence and presence of added salt. Since the solid solute is present in both cases

$$\mu(\text{solid}) = \mu(c_s = 0) = \mu(c_s)$$

where c_s is the concentration of added salt. Therefore $a(c_s = 0) = a(c_s)$, or

$$s_0\gamma_0 = s\gamma \tag{10.20}$$

where s_0 and s are the solubilities in the two cases. Thus $\gamma/\gamma_0 = s_0/s$; and since $\gamma_0 = 1$ is a reasonable assumption, $\gamma = s_0/s$, and we have a method for measuring nonelectrolyte activity coefficients. Moreover, it is found experimentally that the quantity $\log(s_0/s)$ often varies linearly with c_s, or

$$\text{Log}\frac{s_0}{s} = k_s c_s \tag{10.21}$$

If $s_0/s > 1$, then k_s is positive, and the nonelectrolyte is said to be "salted out"; if $s_0/s < 1$, then k_s is negative, and the solute is "salted in." These are called the "salting-out and salting-in effects," and the constant k_s is known as the Setschenow constant.

Regular Solution Theory. We have seen that an ideal solution has thermodynamic mixing quantities $\Delta H_{\text{mix}} = 0$ and $\Delta S_{\text{mix}} = -R(x_1 \ln x_1 + x_2 \ln x_2)$. A *regular solution* is defined to be one having an ideal entropy of mixing but a nonideal enthalpy of mixing. Recall also that the ideal solubility of a nonelectrolyte (i.e., the solubility when a nonelectrolyte forms an ideal solution) is given by

$$\ln x_2 = \frac{-\Delta H_f}{R}\left(\frac{T_m - T}{T T_m}\right) \tag{10.22}$$

where ΔC_p is assumed to be zero or negligible. The molecular interpretation of an ideal solution is that the energy of interaction of a solute molecule with a solvent molecule is identical with the energy of interaction of two solvent molecules.

The molecular interpretation of regular solution theory is quite different; in regular solution theory the energy of 1–2 interactions (where 1 is the solvent, 2 is the solute) is approximated as the geometric mean of 1–1 and 2–2 interaction energies, or[2]

$$U_{12} = (U_{11}U_{22})^{1/2} \tag{10.23}$$

This approximation results in regular solution theory being applicable mainly to fairly nonpolar systems, that is, nonpolar nonelectrolytes dissolved in nonpolar solvents. For our present interest, the essential result (Hildebrand and Scott 1964, p. 271) of regular solution theory is embodied in Eq. (10.24), which may be compared with Eq. (10.22):

$$\ln x_2 = -\frac{\Delta H_f}{R}\left(\frac{T_m - T}{T\,T_m}\right) - \frac{V_2\varphi_1^2}{RT}(\delta_1 - \delta_2)^2 \tag{10.24}$$

where V_2 is the molar volume of solute and φ_1 is the volume fraction concentration of solvent in the solution. The quantities δ_1 and δ_2 are the *solubility parameters* of the solvent and solute. These are physical properties with the following significance.

The term ΔH_{vap}, the molar heat of vaporization, is the enthalpy required to effect the transformation of one mole of liquid to its vapor state. During this process all the solvent–solvent interactions (which are responsible for the existence of the liquid phase) are overcome. A quantity called the *cohesive energy density* (CED) is defined

$$CED = \frac{\Delta H_{vap} - RT}{V} \tag{10.25}$$

where V is the molar volume of the liquid. We anticipate, and we find, that liquids with strong intermolecular interactions (especially polar "associated" liquids having the potential for strong dipole–dipole and hydrogen-bonding interactions) have larger ced values than do nonpolar liquids. Table 10.4 lists some CED values.

Because of the manner in which CED appears in regular solution theory equations, Hildebrand (Hildebrand et al. 1970; Hildebrand and Scott 1964, p. 271) defined the solubility parameter δ by Eq. (10.26). Table 10.4 also gives δ values.

$$\delta = (CED)^{1/2} \tag{10.26}$$

Referring now to Eq. (10.24), note that if $\delta_1 = \delta_2$, we recover Eq. (10.22) for the ideal solution; in other words, the condition $\delta_1 = \delta_2$ is equivalent to the condition $\Delta H_{mix} = 0$. The greater the difference $\delta_1 - \delta_2$ (or of $\delta_2 - \delta_1$, because the difference is squared), the greater the deviation from ideality, and, as Eq. (10.24) shows, the lower the solubility that is predicted. This provides a guide for experimental design; to achieve maximal solubility according to regular solution theory, strive to equate the solubility parameters of solvent and solute. Since the solute identity is usually established by the nature of the problem, the experimental variable is the solvent identity. Sometimes mixed solvent systems function better than do pure solvents for this reason. For example, a mixture of ether $(\delta = 7.4)$ and ethanol $(\delta = 12.7)$ dissolves nitrocellulose $(\delta = 11.2)$, although neither pure liquid serves as a good solvent for this solute.[3]

Although the cohesive energy density, and therefore the solubility parameter, is a well-defined physical property for any solvent, regular solution theory is limited

Table 10.4. Cohesive energy densities and solubility parameters

Solvent	CED $(\mathrm{cal\ cm^{-3}})$	$\delta(\mathrm{cal^{1/2}\ cm^{-3/2}})$
n-Pentane	50.2	7.0
Cyclohexane	67.2	8.2
1,4-Dioxane	96	10.0
Benzene	84.6	9.2
Diethyl ether	59.9	7.4
Ethyl acetate	83.0	9.1
Acetic acid	102	10.1
n-Butyl alcohol	130.0	11.4
n Propyl alcohol	141.6	11.9
Acetone	95	9.9
Ethanol	168	12.7
Methanol	212	14.5
Acetonitrile	141.6	11.9
Dimethylformamide	146.4	12.1
Ethylene glycol	212	14.6
Glycerol	272	16.5
Dimethylsulfoxide	144	12.0
Water	547.6	23.4

(e.g., by the geometric mean approximation) to solutions of nonpolar substances. It should therefore not be expected to apply quantitatively to polar systems such as aqueous solutions.

Example 10.6. Predict the solubility of naphthalene in n-hexane at 20°C. The solubility parameters are $\delta_1 = 7.3$ and $\delta_2 = 9.9$ (both in $\mathrm{cal^{1/2}\ cm^{-3/2}}$), and the molar volumes are $V_1 = 132\ \mathrm{cm^3\ mol^{-1}}$ and $V_2 = 123\ \mathrm{cm^3\ mol^{-1}}$. See Example 10.1 for additional data.

We use Eq. (10.24), which in Example 10.1 was expressed in terms of log x_2. In that form the first term on the right had the value -0.577, which we need not recalculate. Now we consider the second term. We lack only the quantity φ_1, the volume fraction of solvent. This appears to be a dilemma, because we cannot estimate φ_1 until we know x_2, which is what we want to calculate.

If we anticipate that the solute has a low solubility, it may be acceptable to make the approximation $\varphi_1 = 1$. An alternative is to take the result for an ideal solution (Example 10.1, which gave $x_2 = 0.265$) as a basis for estimating φ_1. We will do the problem in both ways.

(a) Let $\varphi_1 = 1$. Then from eq. (10.24),

$$\mathrm{Log}\ x_2 = -0.577 - \frac{(123\ \mathrm{cm^3})(1)^2(7.3 - 9.9\ \mathrm{cal^{1/2}\ cm^{-3/2}})^2}{(2.303)(1.987\ \mathrm{cal\ mol^{-1}\ K^{-1}})(293.15\ \mathrm{K})}$$

$$= -0.577 - 0.620 = -1.197$$

$$x_2 = 0.064$$

(b) The volume fraction is defined as follows:

$$\varphi_1 = \frac{n_1 V_1}{n_1 V_1 + n_2 V_2} \tag{10.27}$$

Suppose $n_1 + n_2 = 1$; from Example 10.1, $x_2 = 0.265$, or $n_2 = 0.265$ and $n_1 = 0.735$. Using these numbers in Eq. (10.27) gives $\varphi_1 = 0.748$. (Note how close φ_1 is to x_1, because V_1 and V_2 are similar.) Repeating the calculation gives

$$\text{Log } x_2 = -0.577 - 0.335 = -0.912$$
$$x_2 = 0.122$$

We therefore predict that x_2 is between 0.064 and 0.122, and we might take the average as our best estimate. The experimental result (Table 10.1) is $x_2 = 0.090$.

Prediction of Aqueous Solubilities. Water is the preferred solvent for liquid dosage forms because of its biological compatibility, but unfortunately many drugs are poorly soluble in water. To be able to predict the aqueous solubility of compounds, even if only approximately, is a valuable capability because it can guide or reduce experimental effort. Water is a highly polar and structured medium in which nonideal behavior is commonly observed, so we must abandon hope that the ideal solubility prediction of Eq. (10.10) will be useful, and even the regular solution theory [Eq. (10.24)] is ineffectual in solving this problem. Effective approaches may be guided by thermodynamic concepts, but they incorporate much empirical (i.e., experimental) content.

Although the ideal solubility equation will not suffice to predict nonelectrolyte solubility in water, the solute–solute interactions responsible for maintaining the crystal lattice must nevertheless be overcome, so Eq. (10.10) will still be applicable as a means of estimating the solute–solute interaction. What must be done in addition is to take account of the solvent–solvent and solvent–solute interactions, for these will in general not offset each other. In a paper that includes a valuable collection of solubility data, Yalkowsky and Valvani (1980) have developed a very useful method based on this approach. They start with Eq. (10.10), which they transform to Eq. (10.11), repeated here:

$$\ln x_2 = -\frac{\Delta S_f (T_m - T)}{RT} \tag{10.28}$$

They then carry out an analysis of experimental entropies of fusion, reaching these conclusions:

For spherical (or nearly so) molecules: $\Delta S_f = 3.5 \, \text{cal mol}^{-1} \, \text{K}^{-1}$
For rigid molecules: $\Delta S_f = 13.5 \, \text{cal mol}^{-1} \, \text{K}^{-1}$

For molecules having $n > 5$ flexible chain atoms: $\Delta S_f = 13.5 + 2.5$ $(n\ 5)\,\mathrm{cal\,mol^{-1}\,K^{-1}}$

In the following we will use only the result for rigid molecules.

Yalkowsky and Valvani then take the log P value of the solute (where P is the 1-octanol/water partition coefficient) as an empirical measure of the solution phase nonidealities. They combine this with Eq. (10.28), convert to molar concentration, and apply a small statistical adjustment, finally getting Eq. (10.29) for the calculation of rigid nonelectrolyte molar solubility in water at 25°C:

$$\text{Log } c_2 = -0.011(t_m - 25) - \log P + 0.54 \qquad (10.29)$$

where t_m is the solute melting point in centigrade degrees. For liquid nonelectrolytes t_m is set to 25, so the first term vanishes. Log P may be available from experimental studies, but it may have to be estimated by methods cited in Chapter 7.

Yalkowsky and Valvani applied Eq. (10.29) to solubility data on 167 compounds whose solubilities ranged over nine orders of magnitude, finding that the estimated solubilities agreed with the observed solubilities to within 0.5 log unit for all but eight compounds, and in no case was the error greater than a factor of 10. Equation (10.29) is a very practical solution to the problem of predicting aqueous solubilities.

Amidon and Williams (1982) refined the approach of Yalkowsky and Valvani, achieving better accuracy but at the cost of increased complexity in the equation. Grant and Higuchi (1990) describe alternative methods of calculation that are based on different pathways from the initial to the final state.

Equation (10.10) and equations derived from it, such as Eqs. (10.28) and (10.29), contain the difference $(T_m - T)$, showing that a higher melting temperature is reflecting stronger solute–solute interactions in the solid state. As a general but not precise rule, we may anticipate that very polar molecules (or functional groups) will conduce to strong intermolecular interactions by means of electrostatic forces, which for certain groups may include hydrogen bonding. Thus high molecular polarity tends to be associated with high melting temperature, and higher melting temperatures lead to lower solubilities, at least as they are described by Eq. (10.10).

Now consider the special case of water as a solvent. Water is a very polar solvent and is capable of functioning as a hydrogen bond donor and acceptor. Very polar solute molecules will tend to interact strongly with the solvent water; these are the solvent–solute or solvation interactions that increase solubility. But we have seen that highly polar substances tend to have high melting temperatures, so we are led to the tentative conclusion that melting temperature may be an approximate indicator of the extent of solvent–solute interaction. It follows (still arguing in this approximate mode) that the opposing factors of solute–solute (crystal lattice) and solvent–solute (solvation) interactions are both measured by, or at least indicated by, the same quantity, namely, the melting temperature.[4] Thus in some degree we may anticipate that these two factors will compensate each other, with the consequence that the solubility will become essentially independent of the

melting temperature. But then the first term in Eq. (10.29) will (approximately) vanish, leading to a dependence solely on log P.

Correlations of log c with log P are well known (Yalkowsky and Valvani 1980; Grant and Higuchi 1990, Chapter 8). Equations (10.30a) and (10.30b) are such correlations, based on solubility data for compounds having a considerable range of structural features. These equations are to be judged solely by their success in reproducing or predicting solubilities; they are purely empirical.

$$\text{Log } c_2 = -\log P - 1.00 \qquad \text{(for solids)} \qquad (10.30\text{a})$$
$$\text{Log } c_2 = -\log P + 0.27 \qquad \text{(for liquids)} \qquad (10.30\text{b})$$

A comparison of the performance of Eq. (10.29) with Eqs. (10.30) indicates that Eq. (10.29) is slightly superior, but there are some reversals. If the solute melting point is not available, Eq. (10.30a) offers an alternative method of estimation.

Example 10.7. Estimate the aqueous solubility at 25°C of isophthalic acid, for which log $P = 1.73$ and whose melting temperature is 346°C.

With Eq. (10.29), $\log c_2 = -4.72$; with Eq. (10.30a), $\log c_2 = -2.73$. The experimental result is $\log c_2 = -3.40$. Evidently neither Eq. (10.29) nor Eq. (10.30a) yields a fully satisfactory answer in this case. (Although interestingly their average is 3.73, in error by only about a factor of 2 in the solubility c_2.) Obviously there is scope for improved methods of estimation.

Solubility in Mixed Solvents. If the equilibrium solubility of a solute in water is too low to achieve the desired "target" concentration, a preferred approach in many instances is to incorporate an organic solvent in the aqueous solution, in this way increasing the solubility of the solute. This organic solvent (often called the *cosolvent*) must be miscible with water, at least in the proportions used, and if the solution is to be a dosage form, the cosolvent must be physiologically acceptable. These requirements severely limit the cosolvent selection. But beyond this issue is the matter of the optimal cosolvent concentration in the mixed solvent system of water and cosolvent. As in our treatment of aqueous solubility, we seek methods that are rapid and easy to apply, even though approximate in their accuracy, because the calculation will always be followed by laboratory studies to confirm or refine the numerical estimate.

If the solute and solvent molecules in a solution differ greatly in size, plots of various experimental quantities against solvent composition tend to be more symmetrical when solvent composition is given in volume fraction than in mole fraction (Williamson 1967, p. 44). This observation forms the basis of a model proposed by Yalkowsky and Rubino (1985). For these three-component systems, let water be component 1, the cosolvent component 2, and the solute component 3. The molar solubility of solute in water is written $(c_3)_1$ and its molar solubility in pure cosolvent as $(c_3)_2$. In solvent of any composition the solute solubility is written c_3. Then the Yalkowsky–Rubino model becomes

$$\text{Log } c_3 = \varphi_1 \log (c_3)_1 + \varphi_2 \log (c_3)_2 \qquad (10.31)$$

where φ_1 and φ_2 are the volume fractions of water and cosolvent, respectively. Since $\varphi_1 + \varphi_2 = 1$, an equivalent form of Eq. (10.31) is

$$\text{Log}\, c_3 = \varphi_2 [\log (c_3)_2 - \log (c_3)_1] + \log (c_3)_1 \qquad (10.32)$$

This equation predicts that $\log c_3$ will be a linear function of φ_2.

Equation (10.31) is a postulate. It can be described as a linear combination model, or as a weighted average; that is, $\log c_3$ is postulated to be an average of $\log (c_3)_1$ and $\log (c_3)_2$, each of these making a contribution according to (weighted by) its volume fraction.

The procedure for testing and using this model is simple. On a graphical scale of φ_2 one plots $\log (c_3)_1$ at $\varphi_2 = 0.0$ and $\log (c_3)_2$ at $\varphi_2 = 1.0$. These points are connected by a straight line, which is the graphical representation of Eq. (10.32). A test of the model consists of plotting experimental solubilities at intermediate values of φ_2 to learn how well they agree with the straight-line prediction. Alternatively, if (as is usually the case) such data are not available, the model is assumed to be (approximately) valid, and that value of φ_2 is read off the line that will achieve a desired target solubility. It is not necessary to carry this operation out graphically, for by rearrangement of Eq. (10.32) we obtain

$$\varphi_2 = \frac{\log c_3 - \log (c_3)_1}{\log (c_3)_2 - \log (c_3)_1} \qquad (10.33)$$

With this equation the required volume fraction of cosolvent can be calculated, according to this model.

Figure 10.3 shows solubility data for the system water (1)-ethanol (2)-naphthalene (LePree et al. 1994). The straight line connecting the extreme points constitutes the linear combination model, Eq. (10.32); the points are experimental. Obviously the points do not describe a straight line, so in this sense, and for this system, the model does not appear to be valid. On the other hand, as an approximate guide to the dependence of solubility on solvent composition it may be helpful to the experimentalist, and it is in this sense that the model should be judged. It is not a precise description of physicochemical behavior, but rather is a useful tool in formulation development.

Example 10.8. Propose a water/ethanol mixed solvent composition that will dissolve 2.5 mg mL^{-1} of naphthalene. The solubility of naphthalene in water is 2.14×10^{-4} M, and in ethanol it is 0.675 M.

The target concentration of 2.5 mg mL^{-1} is equivalent to 2.5 g L^{-1}. The molecular weight of naphthalene is 128.2, so the molar target concentration c_3 is 0.0195 M, or $\log c_3 = -1.71$. From the given data we have $\log (c_3)_1 = -3.67$ and $\log (c_3)_2 = -0.17$. Applying Eq. (10.33), we obtain

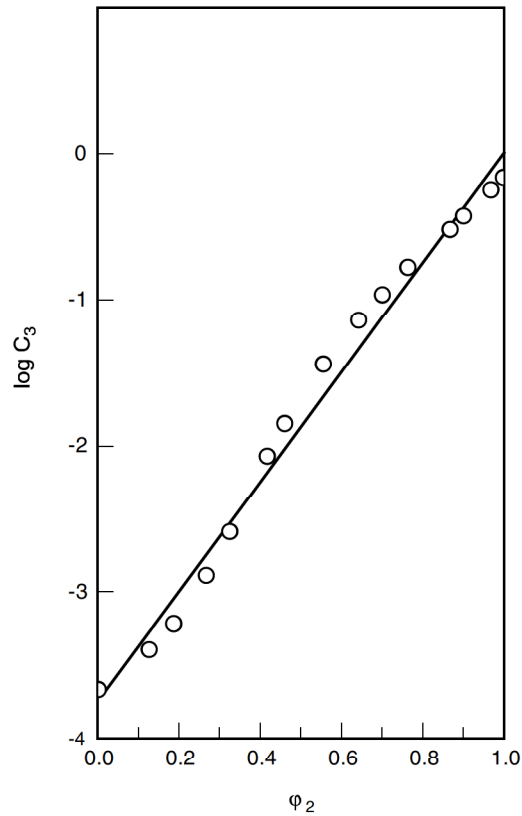$$\varphi_2 = \frac{-1.71 - (-3.67)}{-0.17 - (-3.67)}$$

$$= 0.56$$

Figure 10.3. The linear combination model for naphthalene solubility in aqueous ethanol solutions.

Thus we predict that a volume fraction of 0.56 ethanol will dissolve the target concentration. This result could also have been obtained by reading from the straight line of Fig. 10.3. It is interesting to note, from the experimental points in Fig. 10.3, that a volume fraction $\varphi_2 = 0.51$ will actually dissolve the target concentration.

More accurate models of solvent effects are available, but these require much experimental effort and are computationally more elaborate.

PROBLEMS

10.1. The melting point of benzoic acid is 122.4°C, and its heat of fusion is 4.44 kcal mol^{-1}. Calculate its ideal solubility at 25°C.

10.2. From the data in Example 10.2, convert the mole fraction solubilities to molar solubilities, construct the van't Hoff plot, and evaluate the heat of solution.

10.3. Derive an equation relating the molar solubility of calcium phosphate to its solubility product, and calculate its molar solubility.

10.4. A solution containing NaBr, NaCl, and NaI is titrated with silver nitrate solution. Predict the order in which the silver halides will precipitate.

10.5. Predict the solubility of iodine in carbon tetrachloride at 25°C. The melting point of iodine is 113.6°C, its heat of fusion is 3.71 kcal mol^{-1}, its molar volume is 59 cm^3, and its solubility parameter is 14.1. The solubility parameter of carbon tetrachloride is 8.6.

10.6. Predict the molar solubility of progesterone in water at 25°C. The melting point of progesterone is 131°C and its log P value is 3.87.

10.7. The solubility of naphthalene in water at 25°C is 2.14×10^{-4} M, and its solubility in dimethylsulfoxide (DMSO) is 1.920 M. Estimate the mixed solvent composition required to dissolve 4 mg mL^{-1} of the solute.

NOTES

1. Equations like this one in Example 10.4 are easily solved by a logarithmic technique. We have $7.9 \times 10^{-16} = 4s^3$, or $1.975 \times 10^{-16} = s^3$. Take logarithms of both sides, obtaining $-15.70 = 3 \log s$, or $-5.235 = \log s$. The antilogarithm gives s.
2. The arithmetic mean of two numbers is $(a + b)/2$; their geometric mean is $(ab)^{1/2}$.
3. As a strategy for optimizing solvent selection, evidently this approach requires an estimate of the solubility parameter of the solute. There are several ways to obtain this. One method is suggested by the example; presumably the solubility parameter of the solvent mixture that maximizes solubility is also the solubility parameter of the solute.
4. Polarity is just one factor controlling the melting temperature. Symmetry is another; the more symmetric the molecule, the higher the melting temperature (when comparing "similar" molecules).