Excess Free Energy Approach to the Estimation of Solubility in Mixed Solvent Systems II: Ethanol–Water Mixtures

N. A. WILLIAMS * and G. L. AMIDON *x

Abstract □ The use of the reduced three-suffix solubility equation in characterizing solubility in ethanol–water mixtures is discussed. The equation states that $\ln x_{2,m}^s = \hat{z}_1 \ln x_{2,1}^s + \hat{z}_3 \ln x_{2,3}^s - A_{1\text{-}3}\hat{z}_1\hat{z}_3(2\hat{z}_1 - 1) \cdot (q_2/q_1) + A_{3\text{-}1}2\hat{z}_1^2\hat{z}_3(q_2/q_3) + C_2\hat{z}_1\hat{z}_3$, where $x_{2,1}^s$, $x_{2,3}^s$, and $x_{2,m}^s$ are the mole fraction solubilities of the solute in ethanol (subscript 1), water (subscript 3), and in the mixture (m); $A_{1\text{-}3}$ and $A_{3\text{-}1}$ are solvent–solvent interaction terms; C_2 is a solute–solvent interaction term; and the q- and z-values are molar volumes and solute-free volume fractions, respectively. The contributions of the various terms in the equation to solubility are examined, and the possible use of its derivative in indicating whether a maximum may exist in the solubility profile is discussed. Methods of obtaining the solvent–solvent interaction constant and the ternary constant C_2 are described, and the general effectiveness of the equation in describing solubility is examined. The equation is shown to be applicable to 10 compounds with widely different physical properties and, thus, appears to combine both ease of use and general utility.

Keyphrases □ Solubility—mixed solvent systems, estimation by an excess free energy approach, application to ethanol–water □ Excess free energy—use in estimating solubility in mixed solvent systems, application to ethanol–water □ Mixed solvent systems—estimation of solubility, excess free energy approach, application to ethanol–water

The previous paper (1) described the theoretical aspects of an excess free energy approach to the estimation of solubility in mixed solvent systems. In this report we discuss methods of obtaining the constants in the working equation and their use in characterizing solubility in the ethanol–water system.

THEORETICAL

For a solute (subscript 2) in a mixture of ethanol (subscript 1) and water (subscript 3), the reduced four-suffix solubility equation is:

$$\ln x_{2,m}^s = \hat{z}_1 \ln x_{2,1}^s + \hat{z}_3 \ln x_{2,3}^s - A_{1\text{-}3}\hat{z}_1\hat{z}_3(2\hat{z}_1 - 1)\frac{q_2}{q_1}$$
$$+ A_{3\text{-}1}2\hat{z}_1^2\hat{z}_3\frac{q_2}{q_3} + D_{133}3\hat{z}_1^2\hat{z}_3^2\frac{q_2}{q_3} + C_3\hat{z}_1\hat{z}_3^2\frac{q_2}{q_3} + C_1\hat{z}_1^2\hat{z}_3\frac{q_2}{q_1} \quad \text{(Eq. 1)}$$

The corresponding three-suffix and two-suffix equations are given by Eqs. 2 and 3, respectively:

$$\ln x_{2,m}^s = \hat{z}_1 \ln x_{2,1}^s + \hat{z}_3 \ln x_{2,3}^s - A_{1\text{-}3}\hat{z}_1\hat{z}_3(2\hat{z}_1 - 1)\frac{q_2}{q_1}$$
$$+ A_{3\text{-}1}2\hat{z}_1^2\hat{z}_3\frac{q_2}{q_3} + C_2\hat{z}_1\hat{z}_3 \quad \text{(Eq. 2)}$$

$$\ln x_{2,m}^s = \hat{z}_1 \ln x_{2,1}^s + \hat{z}_3 \ln x_{2,3}^s + A_{1\text{-}3}\hat{z}_1\hat{z}_3\frac{q_2}{q_1} \quad \text{(Eq. 3)}$$

Note that the numerical values of $A_{1\text{-}3}$ and $A_{3\text{-}1}$ differ in Eqs. 1–3 because they are defined differently in the three equations (1). We also note here that Eq. 2 may be rearranged to give:

$$\ln\left(\frac{x_{2,m}^s}{x_{2,3}^s}\right) = \hat{z}_1 \ln\left(\frac{x_{2,1}^s}{x_{2,3}^s}\right) - A_{1\text{-}3}\hat{z}_1\hat{z}_3(2z_1 - 1)\frac{q_2}{q_1} + A_{3\text{-}1}2\hat{z}_1^2\hat{z}_3\frac{q_2}{q_3} + C_2\hat{z}_1\hat{z}_3$$

$$\text{(Eq. 4)}$$

In this report we evaluate the parameters in Eqs. 1–3 and discuss their ability to describe solubility in ethanol–water mixtures.

Evaluation of Interaction Constants—The solvent–solvent inter-

action constants (the A terms) are easily obtained from vapor–liquid equilibrium data. If partial pressure–composition data are available, the constants may be obtained by fitting the excess free energy calculated from such data to whichever n-suffix equation is chosen. As an example consider the three-suffix equation for a binary solvent mixture. The molar excess free energy is given by (2):

$$\frac{g^E}{RT} = \frac{A_{1\text{-}3}}{q_1}[z_1z_3^2(x_1q_1 + x_3q_3)] + \frac{A_{3\text{-}1}}{q_3}[z_1^2z_3(x_1q_1 + x_3q_3)] \quad \text{(Eq. 5)}$$

where

$$A_{1\text{-}3} = q_1(2a_{13} + 3a_{133}), \quad A_{3\text{-}1} = q_3(2a_{13} + 3a_{113}) \quad \text{(Eq. 6)}$$

But

$$\frac{g^E}{RT} = \sum_{\text{solv } i} x_i \ln \gamma_i = x_1 \ln \gamma_1 + x_3 \ln \gamma_3 \quad \text{(Eq. 7)}$$

and

$$\gamma_1 = \frac{p_1}{p_1^0}, \quad \gamma_3 = \frac{p_3}{p_3^0} \quad \text{(Eq. 8)}$$

where p_1 is the partial pressure of component 1 in the mixture of 1 and 3 and p_1^0 is the vapor pressure of pure component 1; p_3 and p_3^0 are defined similarly.

Combining Eqs. 5 and 7 we find:

$$x_1 \ln \gamma_1 + x_3 \ln \gamma_3 = A_{1\text{-}3}\left[\frac{z_1z_3^2(x_1q_1 + x_3q_3)}{q_1}\right]$$
$$+ A_{3\text{-}1}\left[\frac{z_1^2z_3(x_1q_1 + x_3q_3)}{q_3}\right] \quad \text{(Eq. 9)}$$

Equation 9 may be represented as:

$$y = \theta_1\chi_1 + \theta_2\chi_2 \quad \text{(Eq. 10)}$$

where $y = x_1 \ln \gamma_1 + x_3 \ln \gamma_3$, $\theta_1 = A_{1\text{-}3}$, χ_1 is the first term in parentheses,
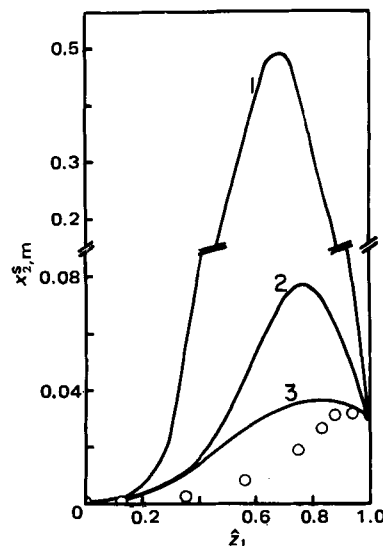

Figure 1—*Solubility profiles of barbital in ethanol calculated from Eqs. 1–3 without any solute–solvent interaction term (i.e., with $C_1 = C_2 = C_3 = 0$). Key: (1) reduced four-suffix solubility equation (Eq. 1); (2) reduced three-suffix solubility equation (Eq. 2); (3) reduced two-suffix solubility equation (Eq. 3); (○) experimental points.*

Figure 2—*Projection of $\langle \hat{z}_1 \rangle$ on to the (C_2/q_2), $(1/q_2)$ ln $(x_{2,1}^s/x_{2,3}^s)$ plane. Key: (a) barbital; (b) acetanilide; (c) phenyl salicylate; (d) stearic acid; (e) o-nitrophenol; (f) antipyrine; (g) phenobarbital; (h) DL-valine; (i) glycine; (j) DL-alanine.*

$\theta_2 = A_{1-3}$, and χ_2 is the second term in parentheses. As shown by Eq. 10, y is a linear function of the parameters θ_1 and θ_2 and, so, A_{1-3} and A_{3-1} can be obtained by linear regression.

The constants for ethanol–water were obtained at 25°C from data in Ref. 5. If only the partial vapor pressure of one component is available, the Gibbs–Duhem relation may be used to calculate the other in the case of a binary system (3). It is usually easier to measure the total vapor pressure over a solvent mixture rather than partial pressures. From the total pressure, the interaction constants may be obtained as follows.

The total pressure P_T over a binary solvent mixture is given by:

$$P_T = p_1 + p_3 = x_1 \gamma_1 p_1^0 + x_3 \gamma_3 p_3^0 \qquad \text{(Eq. 11)}$$

If we differentiate Eq. 5 with respect to n_1, we obtain the expression for ln γ_1 in the solvent mixture:

$$\ln \gamma_1 = A_{1-3}[z_3^2(1 - 2z_1)] + A_{3-1}\left[2z_1 z_3^2 \frac{q_1}{q_3}\right] \qquad \text{(Eq. 12)}$$

Similarly:

$$\ln \gamma_3 = A_{1-3}\left[2z_1^2 z_3 \frac{q_3}{q_1}\right] + A_{3-1}[z_1^2(1 - 2z_3)] \qquad \text{(Eq. 13)}$$

Substituting Eqs. 12 and 13 into Eq. 11, we obtain:

$$P_T = p_1^0 x_1 e^{[A_{1-3}x_1 + A_{3-1}x_2]} + p_3^0 x_3 e^{[A_{1-3}x_3 + A_{3-1}x_4]} \qquad \text{(Eq. 14)}$$

Table I—Solvent–Solvent Interaction Terms

Excess Free Energy Model	Constants	
	Linear Regression	Total Pressure Fit[a]
Four-suffix	$A_{1-3} = 0.9385$	
	$A_{3-1} = 1.387$	
	$D_{13} = 0.6106$	
Three-suffix	$A_{1-3} = 1.216$	1.138
	$A_{3-1} = 0.9093$	0.9047
Two-suffix	$A_{1-3} = 2.215$	

[a] Nonlinear.

where $\chi_1 = z_3^2(1 - 2z_1)$, $\chi_2 = 2z_1 z_3^2(q_1/q_3)$, $\chi_3 = 2z_1^2 z_3(q_3/q_1)$, and $\chi_4 = z_1^2(1 - 2z_3)$.

The parameters may be obtained from Eq. 14 by a total pressure fit using nonlinear regression. This method is more complicated, but it gives similar results to the excess free energy fit (Table I). Where partial pressure data are available, as in the case of ethanol–water, the linear regression fit is the method of choice because of its simplicity and much lower tendency to give non-unique constants than the nonlinear method, whose results sometimes depend on the choice of initial estimates.

Choice of a Working Equation—Figure 1 shows calculated solubility profiles for barbital in ethanol–water mixtures using Eqs. 1, 2, and 3 with the solvent–solvent interaction constants in Table I, but without any ternary solute–solvent interaction terms (i.e., with $C_1 = C_2 = C_3 = 0$). When compared with experimental data (4), it is clearly seen that the reduced four-suffix solubility equation is the worst for predicting solubility. The three-suffix equation does better, but not as well as the two-suffix equation. A comparison of Eqs. 2 and 3, however, shows that while the reduced three-suffix solubility equation has one more constant that is related to, and can be evaluated from, ternary solute–solvent data, the two-suffix equation has none and this severely limits its use. The four-suffix equation has two constants, which may be estimated from ternary solute–solvent data. For the ethanol–water system, the three-suffix equation, with its one constant C_2 estimated from ternary data, satisfactorily predicts the solubilities of compounds in ethanol–water mixtures. This and the fact that it has less parameters than the four-suffix equation has led us to choose the three-suffix equation (Eq. 2) to characterize the solubilities in ethanol–water systems.

Estimation of C_2—The constant C_2, which accounts for the interaction between the solute and the two solvents, was estimated by linear regression from the difference between the reported experimental solubility at 25°C and the calculated solubility (without the C_2 term) at each point in the solvent composition range. The C_2 thus obtained was then used to estimate the solubility over the solvent composition range.

Analysis of Solubility in the Ethanol–Water System—Certain compounds are known to exhibit a maximum in their solubility in some solvent mixtures (4). In this work, we were interested in whether our reduced three-suffix solubility equation for a three-component system predicted a maximum and/or minimum and under what conditions. We used the ethanol–water system as a specific example; the results will therefore be applicable only to a solute in ethanol–water.
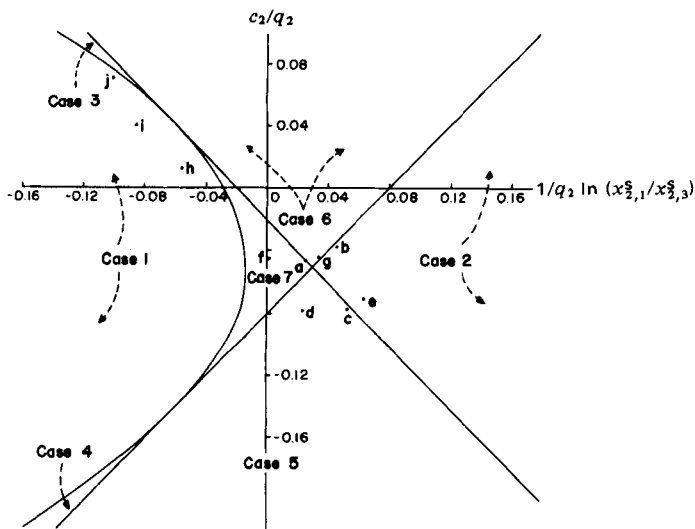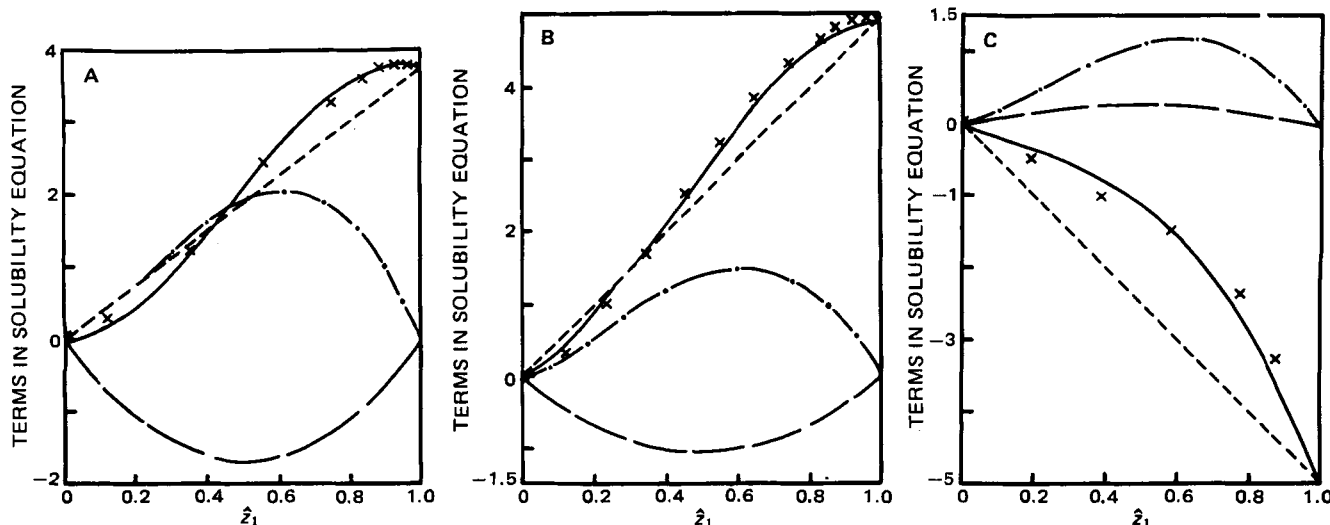

Figure 3—*Solubility profile of barbital (A), acetanilide (B), and DL-valine (C) in ethanol showing contributions from terms in Eq. 4. Key: (- - -) $\hat{z}_1$ ln $(x_{2,1}^s/x_{2,3}^s)$; (- · -) $-A_{1-3}\hat{z}_1\hat{z}_3(2\hat{z}_1 - 1)(q_2/q_1) + A_{3-1}2\hat{z}_1^2\hat{z}_3(q_2/q_3)$; (- -) $C_2\hat{z}_1\hat{z}_3$; (——) calculated ln $(x_{2,m}^s/x_{2,3}^s)$; (X) experimental ln $(x_{2,m}^s/x_{2,3}^s)$.*
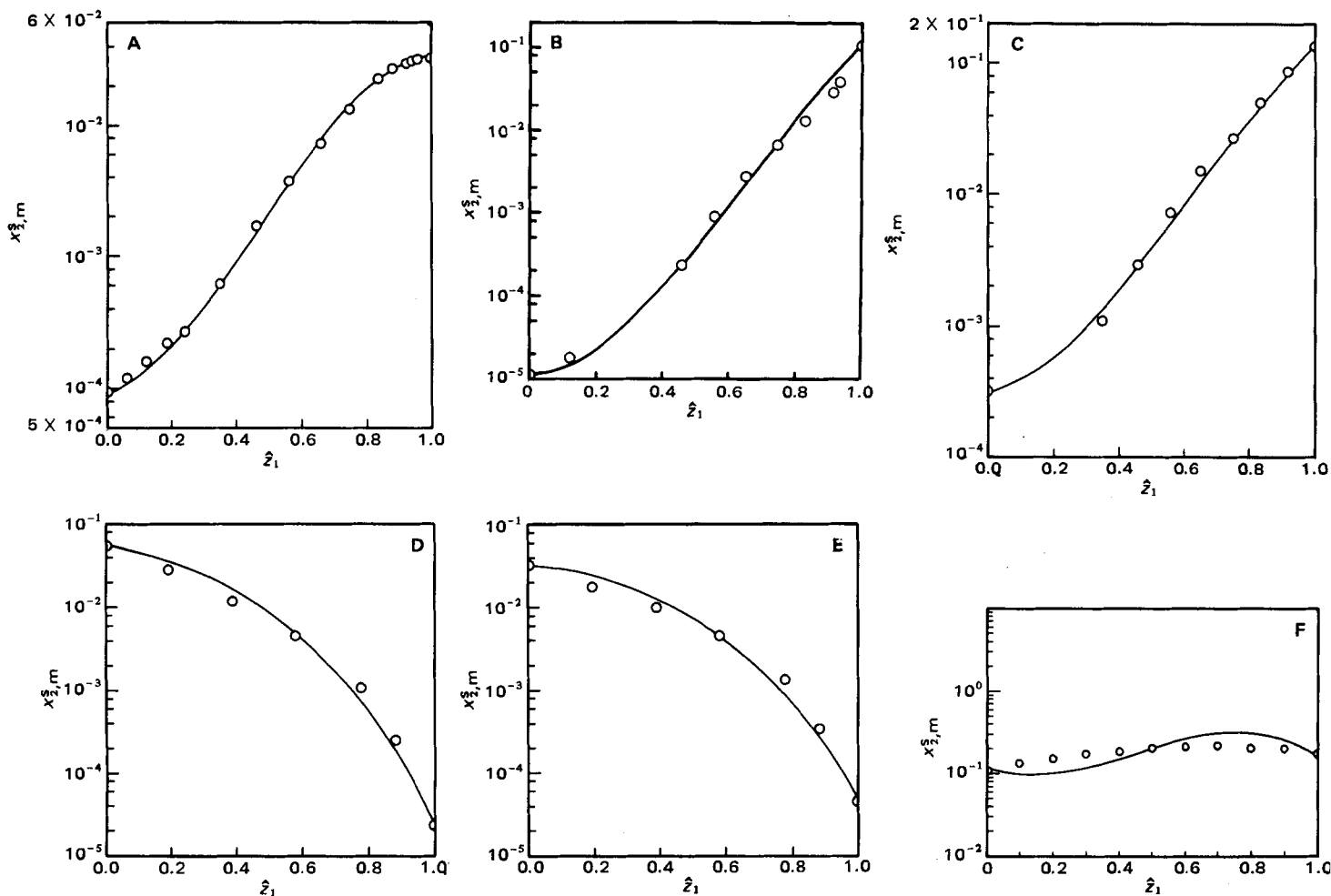
Figure 4—*Solubility profile of phenobarbital (A), pheny salicylate (B), o-nitrophenol (C), glycine (D), DL-alanine (E), and antipyrine (F) in ethanol. Key:* (——) *estimated solubility;* (O) *experimental solubility.*

Differentiating Eq. 2 with respect to $\hat{z}_1$ and equating it to zero yields:

$$\left(\frac{\partial \ln x_{2,m}^s}{\partial \hat{z}_1}\right)_{\hat{z}_3} = 0.1788\langle \hat{z}_1\rangle^2 + \left(\frac{2C_2}{q_2} - 0.0778\right)\langle \hat{z}_1\rangle$$

$$-\left[0.0207 + \frac{1}{q_2}\ln\left(\frac{x_{2,1}^s}{x_{2,3}^s}\right) + \frac{C_2}{q_2}\right] = 0 \quad \text{(Eq. 15)}$$

where the values $A_{1\text{-}3} = 1.216$ and $A_{3\text{-}1} = 0.9093$ obtained from ethanol–water vapor–liquid equilibrium data (5) have been used and the maximum or minimum $\hat{z}_1$ is indicated by $\langle \hat{z}_1\rangle$. Equation 15 can be solved quadratically for $\langle \hat{z}_1\rangle$. Depending on the values of C_2/q_2 and $(1/q_2)\cdot \ln(x_{2,1}^s/x_{2,3}^s)$, the range of possible values for the two roots of $\hat{z}_1$ are given in Table II. Cases 1–4 have no extrema in the 0–1 volume fraction range. Cases 5–6 have one extremum each in the 0–1 range, but without knowing C_2, q_2, and $\ln(x_{2,1}^s/x_{2,3}^s)$, it is impossible to say if it is a maximum or minimum. No solubility profiles exhibiting a minimum have been found in the literature. Case 7 has two extrema which clearly must be a minimum and a maximum; to our knowledge, no such profiles have been found in the literature. The relationship between $\langle \hat{z}_1\rangle$ and the solute-dependent terms mentioned above is illustrated in Fig. 2, where the $\langle \hat{z}_1\rangle$ surface is projected onto the C_2/q_2 *versus* $(1/q_2\cdot\ln(x_{2,1}^s/x_{2,3}^s)$ plane. Theoretically, the question of whether a solute exhibits an extremum in ethanol–water

Table II—Possible Solutions of Eq. 15

Cases	Roots	Remarks
1	Imaginary, Imaginary	No extremum
2	<0, >1	No extremum
3	<0, <0	No extremum
4	>1, >1	No extremum
5	0-1, >1	1 extremum
6	0-1, <0	1 extremum
7	0-1, 0-1	2 extrema

mixtures may be answered by obtaining the above solute-characteristic terms and then locating the area in which they fall in Fig. 2. This will not always be successful since Fig. 2 arises from a purely mathematical treatment; however, it may be useful as a general guide.

RESULTS AND DISCUSSION

Contributions of Various Terms to Solubility—Figure 3 shows a plot of the left-hand side of Eq. 4 against the volume fraction of ethanol for three compounds. Without ethanol, the left-hand side of Eq. 4 is zero because $x_{2,m}^s/x_{2,3}^s = 1$; hence, the curves all start from zero. With water absent, *i.e.*, with $\hat{z}_3 = 0$, only the first term on the right-hand side of Eq. 4 remains, all other terms going to zero as indicated in Fig. 3. If, in a mixture of ethanol and water, we set all the interaction constants equal to zero, then the solubility is given by the dashed straight line. This may be called the ideal mixture solubility since there are no contributing interaction terms. The solvent–solvent interactions contribute to solubility in the manner shown in Fig. 3. They go to zero at each end, as they must. The contribution from these terms usually (but not always) results in a maximum solubility being predicted for the compound without the C_2 term. The C_2 term not only corrects this tendency, but also adjusts the solubility to such an extent as to be able to reproduce the maximum solubility with respect to the value and the volume fraction of ethanol at which it occurs (Fig. 3A). Since C_2 accounts for interactions between solute and solvents, it must necessarily go to zero at both ends of the solvent composition.

Prediction Capabilities of the Reduced Three-Suffix Solubility Equation—Figures 3–5 show the results of using Eq. 2 and the parameters given in Table III to estimate reported solubilities in ethanol–water at 25°C. In the ethanol–barbital–water system in Fig. 3A, the solvent–solvent terms and C_2 make significant contributions to the solubility, but tend to compensate for each other. Since they are unsymmetrical with respect to $\hat{z}_1$, they combine to produce a lower than ideal mixture solubility at low volume fractions of ethanol and a higher than ideal mixture

Table III—Parameters Used to Estimate Solubilities[a] and Partition Coefficients

Compound	Formula	$\ln x^s_{2,1}$	$\ln x^s_{2,3}$	q^b_2	C_2	n	r	s^c	Log (PC) in Octanol–Water[d]	Solubility Data References
Barbital	$C_8H_{12}N_2O_3$	−3.479	−7.240	151.0	−6.76	10	0.999	0.069	0.71	(4)
Acetanilide	C_8H_9NO	−2.294	−7.233	110.9	−4.26	10	1.000	0.095	1.21	(6)
Phenyl salicylate	$C_{13}H_{10}O_3$	−2.266	−11.28	169.8	−13.3	7	0.997	0.315	3	(6)
Stearic acid	$C_{18}H_{36}O_2$	−4.237	−10.75	302.4	−23.8	7	0.993	0.438	6.8[e]	(6)
o-Nitrophenol	$C_6H_5NO_3$	−2.023	−8.037	93.68	−6.67	7	0.997	0.131	1.76	(7)
Antipyrine	$C_{11}H_{12}N_2O$	−1.716	−2.096	175.1	−7.94	9	0.952	0.365	0.26	(8)
Phenobarbital	$C_{12}H_{12}N_2O_3$	−3.450	−9.282	172.0	−7.63	15	1.000	0.062	1.41	(4)
DL-Valine	$C_5H_{11}NO_2$	−9.498	−4.529	89.02	1.15	5	0.996	0.282	−1.14[f]	(9)
Glycine	$C_2H_5NO_2$	−10.68	−2.871	90.66	3.67	5	0.998	0.359	−3.0	(9)
DL-Alanine	$C_3H_7NO_2$	−10.01	−3.433	62.57	4.43	5	0.997	0.367	−2.8	(9)

[a] The solvent–solvent term is $-1.216\hat{z}_1\hat{z}_3(2\hat{z}_1 - 1)(q_2/q_1) + 0.9093\ 2\hat{z}_1^2\hat{z}_3(q_2/q_3)$. [b] $q_1 = 58.68$ (Ref. 11) and $q_3 = 18.07$ (Ref. 12) were used as molar volumes of ethanol and water, respectively; q_2 values were calculated from density data in Ref. 12. [c] s is the standard deviation of the error between $\ln\ (x^s_{2,m})_{obs}$ and $\ln\ (x^s_{2,m})_{est}$. [d] From Ref. 10; some values are averages of reported data. [e] n-Heptane–water; not used in the regression of C_2. [f] 1-Butanol–water; not used in the regression of C_2.

solubility at higher ethanol volume fractions. The maximum in the solubility at $\hat{z}_1 = 0.93$ is also due to the nonsymmetrical contributions of these two terms and the particular values they assume at this point. Figure 3B for acetanilide shows similar contributions from the various terms although there is no maximum; this is due to the lower contribution of the solvent–solvent terms because of a lower q_2. In Fig. 3C, which shows a case where the solubility of the solute (DL-valine) is higher in water than in ethanol, the deviation from the ideal mixture solubility is accounted for largely by the solvent–solvent terms.

Figure 4 shows semilogarithmic plots of solubility profiles for additional compounds. The results for phenobarbital, phenyl salicylate, and o-nitrophenol in Fig. 4A–C are similar to the barbital and acetanilide systems (Fig. 3A and B) previously discussed. Figure 4D and E shows the results for glycine and DL-alanine, which are similar to Fig. 3 for DL-valine.

Figure 5 shows a plot of the terms in Eq. 4 for stearic acid to indicate why a minimum is predicted (although the experimental data from Ref. 6 do not show it). It is seen that the minimum is caused by the large negative value (−3) of the C_2 term compared with the value (+1) of the sum of the solvent–solvent terms.

Figure 4F shows the solubility profile of antipyrine. The solubilities of antipyrine are reported as 620 mg/mL in water and 425 mg/mL in ethanol (8) which, converted to mole fraction solubilities, are 0.123 and 0.180, respectively. These high figures invalidate the assumption (made in the derivation of Eq. 2) that the mole fraction solubility is very small. In addition, the solubility of antipyrine changes very little between the end points. The shallow maximum and minimum in the predicted solubility profile result from the unsymmetric dependence of C_2 and the solvent–solvent terms on volume fraction (see Fig. 3). In summary, Figs. 3–5 show clearly that the reduced three-suffix solubility equation estimates solubilities in ethanol–water systems very well.

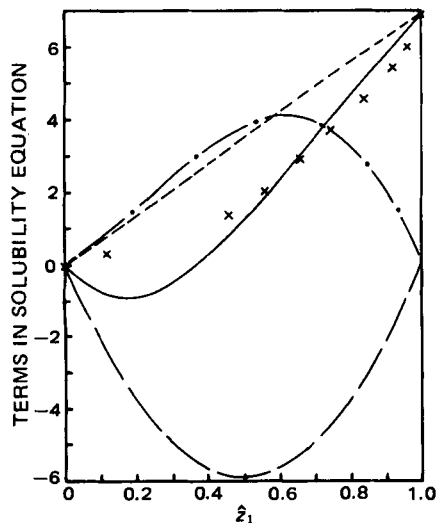In practice, one would have little or no data from which to estimate C_2

as we have done here. In such a case it is still possible to estimate this term by other means requiring the determination of solubility at one or two points in the solvent composition. The significant point, in any case, is that it is possible to obtain the single ternary constant C_2 which, along with the other constants, adequately describes the solubility profile.

Significance of C_2—The solvent–solvent terms, when combined only with ideal mixture solubilities, usually (but not necessarily always) overpredict (as in Fig. 1 and with nonpolar compounds) or underpredict (as with the more polar amino acids in the solubility profiles shown) solubility. Therefore, the C_2 term usually has an opposite sign (but not always; see Fig. 3C) to the sum of the solvent–solvent terms. To determine what influence, if any, the polar or nonpolar nature of the solute has on C_2, we have obtained octanol–water partition coefficients (PC), when available (10), for the solutes whose solubility profiles we examined. There is an excellent trend in which C_2 becomes more negative as the solutes become more nonpolar and more positive as the solutes become more polar (Table III, Fig. 6). The regression equation is:

$$C_2 = -3.96 - 2.66\log\ (PC)$$
$$n = 8,\quad r = 0.946,\quad s = 1.96 \qquad \text{(Eq. 16)}$$

where s is the standard deviation of the error between observed and predicted values of C_2. Equation 16 suggests that it may be possible to estimate C_2 from octanol–water partition coefficients and use the estimated term with the solvent–solvent terms and pure solvent solubilities to estimate the entire solubility profile.

A qualitative interpretation of C_2 is as follows. If the solvents interact in such a manner as to eliminate (i.e., interact "negatively" with) the solute more effectively than would be expected from their interactions with each other (as indicated by the solvent–solvent constants), the predicted solubility without C_2 will tend to be higher than the observed solubility. This may be expected to happen with nonpolar solutes in ethanol–water. To correct this overprediction, C_2 has to be negative to decrease the predicted solubility. Conversely, if the solvents interact in such a manner as to incorporate the solute more effectively than would be expected from their interactions with each other, the predicted solubility will tend to be lower than the observed solubility. This could happen with more polar solutes. C_2 will therefore tend to be more positive in order to increase the solubility.

Prediction of Extrema in Solubility—As was mentioned earlier, it is possible to obtain some idea of whether a solute may exhibit a maxi-
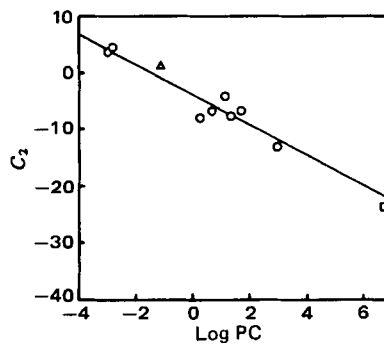

Figure 5—*Solubility profile of stearic acid in ethanol showing contributions from terms in Eq. 4. Key:* (---) $\hat{z}_1\ \ln\ (x^s_{2,1}/x^s_{2,3})$; (-·-) $-A_{1\text{-}3}\hat{z}_1\hat{z}_3(2\hat{z}_1 - 1)(q_2/q_1) + A_{3\text{-}1}2\hat{z}_1^2\hat{z}_3\ (q_2/q_3)$; (- -) $C_2\hat{z}_1\hat{z}_3$; (——) *calculated* $\ln\ (x^s_{2,m}/x^s_{2,3})$; (X) *experimental* $\ln\ (x^s_{2,m}/x^s_{2,3})$.

Figure 6—*Correlation of C_2 with the logarithm of the partition coefficient (octanol–water) where $C_2 = -3.96 - 2.66\ \log\ (PC)$, n = 8, r = 0.946. Key:* (△) *1-butanol–water;* (□) *n-heptane–water.*

mum (or a minimum, although we have not seen this) by computing its C_2/q_2 and $(1/q_2)\cdot\ln(x^s_{2,1}/x^s_{2,3})$ and locating them on Fig. 2. This was done for the solutes listed in Table III, and the values obtained for the above terms were plotted in Fig. 2. It is seen that the amino acids DL-valine, glycine, and DL-alanine fall in the case 1 area where no extrema are predicted (see Table II). They are, therefore, not expected to show any extrema in solubility, and they do not (Figs. 3C and 4D, E). Acetanilide and o-nitrophenol fall in the case 2 area and also show no extrema (Figs. 3B and 4C). Phenyl salicylate and stearic acid fall into case 5 where one extremum is predicted. The literature data we obtained do not show this, although, as expected, the estimated solubility curves in Figs. 4B and 5 indicate a minimum (the minimum in the case of phenyl salicylate is too shallow to be evident on the graph). If indeed these compounds do not show any minimum, the failure of Eq. 15 should not be surprising for reasons indicated earlier. Antipyrine falls into the case 7 area, but the solubility data show only one maximum in Fig. 4F instead of a minimum and maximum as predicted by Eq. 15. Even though the equation predicts a minimum not seen, the fact that it predicts a maximum which is seen makes it useful. Barbital falls in the borderline area between cases 6 and 7, while phenobarbital falls more into case 6 than case 2. The interesting point is that both show well-defined maxima in their solubility profiles in ethanol–water (4). Because the shapes of solubility curves change slightly when solubility is plotted as mole fraction rather than mg/L or mol/L and the fact that the log of the mole fraction solubility is used for most of the plots, the maximum is not pronounced in the case of barbital in Fig. 3A and it is not even evident with phenobarbital in Fig. 4B.

In summary it does seem that Fig. 2 may be of considerable help in indicating when a solute may be expected to show an extremum, usually a maximum, in its solubility in ethanol–water mixtures. Since we have seen no case in which a solute showed an experimental maximum without falling into one of cases 5–7, it may be possible to use a method such as this to a priori rule out possible maxima for solutes in ethanol–water (or other mixed solvent) systems.

CONCLUSIONS

The reduced three-suffix solubility equation (Eq. 2):

$$\ln x^s_{2,m} = \hat{z}_1 \ln x^s_{2,1} + \hat{z}_3 \ln x^s_{2,3} - A_{1\text{-}3}\hat{z}_1\hat{z}_3(2\hat{z}_1 - 1)\frac{q_2}{q_1}$$
$$+ A_{3\text{-}1}2\hat{z}_1^2\hat{z}_3\frac{q_2}{q_3} + C_2\hat{z}_1\hat{z}_3$$

provides a general method for characterizing and estimating solubility in mixed solvent systems. The equation may be partitioned into (a) the ideal mixture solubility described by the first two terms on the right-hand side, (b) solvent–solvent interaction contributions described by the next two terms, and (c) a solute–solvent interaction contribution described by the C_2 term. $A_{1\text{-}3}$ and $A_{3\text{-}1}$ are solvent–solvent interaction constants which, once obtained, are fixed for that particular mixed solvent system. Thus, apart from pure solvent solubilities, the only term needed to estimate the solubility of any solute in ethanol–water is C_2.

All systems investigated in this report were adequately described by Eq. 2, except antipyrine, which was not as well characterized because its high solubility in both solvents invalidates the assumptions made in deriving Eq. 2. The approach is also flexible enough to be appropriately altered. For example, it is possible to use the reduced four-suffix solubility equation (Eq. 1) for a system where the three-suffix equation does not satisfactorily describe the solubility. The method is readily applicable to pharmaceutically important cosolvents such as ethanol, propylene glycol, glycerol, and low-molecular weight polyethylene glycols.

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Excess Free Energy Approach to the Estimation of Solubility in Mixed Solvent Systems III: Ethanol–Propylene Glycol–Water Mixtures

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Abstract ☐ The reduced three-suffix solubility equation derived from the Wohl excess free energy expression is used to describe the solubility of phenobarbital in propylene glycol–water, ethanol–propylene glycol, and ethanol–water–propylene glycol mixtures and the solubility of hydrocortisone in propylene glycol–water mixtures. Solvent–solvent interaction constants were obtained by fitting total vapor pressure versus composition data, obtained at $25 \pm 0.1°C$, to the Wohl excess free energy model for the solvents. The equation describes solubility in these systems satisfactorily except for phenobarbital in ethanol–propylene glycol, where the solubility is fairly high and the assumptions involved in the derivation of the equation do not hold.

Keyphrases ☐ Solubility—mixed solvent systems, estimation by an excess free energy approach, application to binary and ternary mixtures of ethanol, propylene glycol, and water ☐ Excess free energy—use in estimating solubility in mixed solvent systems, application to binary and ternary mixtures of ethanol, propylene glycol, and water ☐ Mixed solvent systems—estimation of solubility, excess free energy approach, application to binary and ternary mixtures of ethanol, propylene glycol, and water

In previous reports, a general equation for describing and estimating solubility in mixed solvent systems was developed (1) and applied to ethanol–water systems (2).

The equation, referred to as the reduced three-suffix solubility equation, was developed from an excess free energy model proposed by Wohl (3).