

mum (or a minimum, although we have not seen this) by computing its  $C_2/q_2$  and  $(1/q_2) \cdot \ln(x_{2,1}^2/x_{2,3}^2)$  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. Barbitol 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 barbitol 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):

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

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.  $A_{1-3}$  and  $A_{3-1}$  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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Received July 22, 1982, from the School of Pharmacy, University of Wisconsin, Madison, WI 53706. Accepted for publication October 22, 1982. \*Present Address: College of Pharmacy, The University of Michigan, Ann Arbor, MI 48109-1065.

**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  $25 \pm 0.1^\circ\text{C}$ , 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).

**Table I—Binary (A Terms) and Ternary ( $G_{134}$ ) Solvent Constants <sup>a</sup>**

System	$A_{1-3}$	$A_{3-1}$	$A_{1-4}$	$A_{4-1}$	$A_{3-4}$	$A_{4-3}$	$G_{134}$
Ethanol-Water	1.138	0.9047					
Ethanol-Propylene Glycol			0.1633	0.5688			
Water-Propylene Glycol					-0.0308	-0.0828	
Ethanol-Water-Propylene Glycol	1.138	0.9047	0.1633	0.5688	-0.0308	-0.0828	-0.1068 mol/cm <sup>3</sup>

<sup>a</sup> Subscript 1 denotes ethanol, subscript 3 denotes water, and subscript 4 denotes propylene glycol.

**THEORETICAL**

For a solute (denoted by subscript 2) in a mixture (subscript m) of two solvents (denoted by subscripts 1 and 3):

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

where  $x_{2,m}^s$  is the mole fraction solubility of the solute in the solvent mixture;  $x_{2,1}^s$  and  $x_{2,3}^s$  are the solute mole fraction solubilities in solvents 1 and 3, respectively;  $A_{1-3}$  and  $A_{3-1}$  are solvent-solvent interaction constants;  $C_2$  is a ternary solute-solvent interaction constant;  $q_1$ ,  $q_2$ , and  $q_3$  are the molar volumes of the first solvent, the solute, and the second solvent, respectively; and  $\hat{z}_1$  and  $\hat{z}_3$  are the solute-free volume fractions of solvents 1 and 3, respectively. Equation 1 may be rearranged to give:

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

For a solute in a ternary solvent mixture (denoted by subscripts 1, 3, and 4), the reduced three-suffix solubility equation is:

$$\ln x_{2,m}^s = \hat{z}_1 \ln x_{2,1}^s + \hat{z}_3 \ln x_{2,3}^s + \hat{z}_4 \ln x_{2,4}^s - A_{1-3} \hat{z}_1 \hat{z}_3 (2\hat{z}_1 + 2\hat{z}_4 - 1) \frac{q_2}{q_1} + A_{3-1} 2\hat{z}_1 \hat{z}_3 (\hat{z}_1 + \hat{z}_4) \frac{q_2}{q_3} - A_{1-4} \hat{z}_1 \hat{z}_4 (2\hat{z}_1 - 1) \frac{q_2}{q_1} + A_{4-1} 2\hat{z}_1^2 \hat{z}_4 \frac{q_2}{q_4} - A_{4-3} \hat{z}_3 \hat{z}_4 (2\hat{z}_4 - 1) \frac{q_2}{q_4} + A_{3-4} 2\hat{z}_3 \hat{z}_4^2 \frac{q_2}{q_3} - G_{134} q_2 \hat{z}_1 \hat{z}_3 \hat{z}_4 + G_{123} q_2 \hat{z}_1 \hat{z}_3 + G_{124} q_2 \hat{z}_1 \hat{z}_4 + G_{234} q_2 \hat{z}_3 \hat{z}_4 - K q_2 \hat{z}_1 \hat{z}_3 \hat{z}_4 \quad (\text{Eq. 3})$$

where  $x_{2,4}^s$  is the solute mole fraction solubility in solvent 4;  $\hat{z}_4$  is the volume fraction of solvent 4;  $A_{1-4}$ ,  $A_{4-1}$ ,  $A_{4-3}$ ,  $A_{3-4}$ , and  $G_{134}$  are solvent-solvent interaction constants;  $G_{123}$  and  $G_{234}$  are ternary solute-solvent interaction constants accounting for the interaction of the solute with solvents 1 and 3, 1 and 4, and 3 and 4, respectively; and  $K$  is a quaternary solute-solvent interaction constant, which accounts for the interaction

of the solute with a mixture of all three solvents. The other terms are as defined in Eq. 1. Examination of Eqs. 1 and 3 shows that Eq. 1 is identical to Eq. 3 with  $\hat{z}_4 = 0$  and  $G_{123} q_2 = C_2$ . The  $q_2$  in  $G_{123} q_2$  arises from the slightly different definitions of  $C_2$  and  $G_{123}$  (1).

Equation 3 shows that the logarithm of the mole fraction solubility of a solute in a ternary solvent mixture  $\ln x_{2,m}^s$  may be described in the following terms:

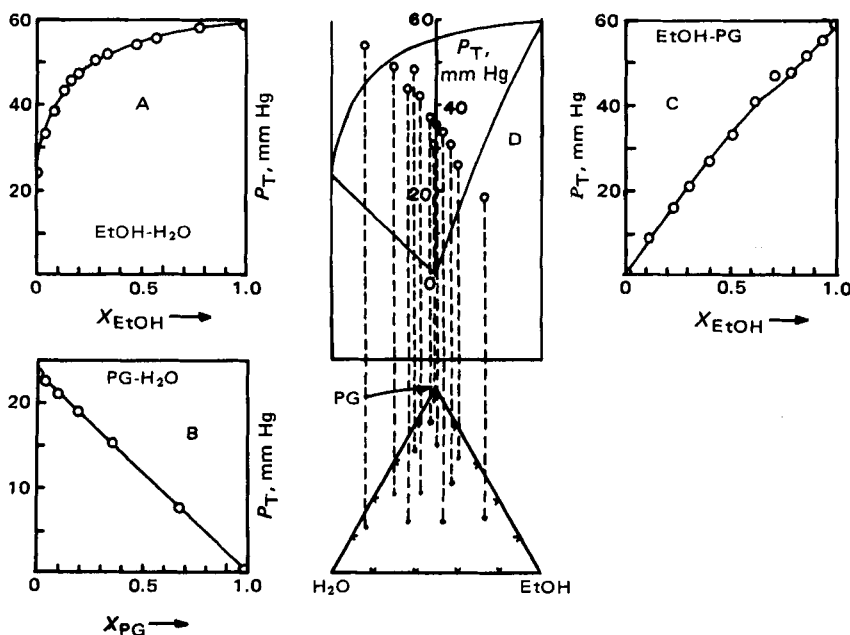
1. The ideal mixture solubility, described by the first three terms which are a volume fraction weighted sum of the logarithm of the pure solvent solubilities.

2. Contributions from binary solvent-solvent interactions between solvents 1 and 3, 1 and 4, 3 and 4, described by the next six terms. Contributions from ternary solvent interactions are described by the  $G_{134}$  term. All the solvent interaction constants ( $A_{1-3}$ ,  $A_{3-1}$ ,  $A_{1-4}$ ,  $A_{4-1}$ ,  $A_{3-4}$ ,  $A_{4-3}$ , and  $G_{134}$ ), once obtained for a ternary solvent system at a particular temperature, are fixed for that solvent system and do not need to be determined again for any solute.

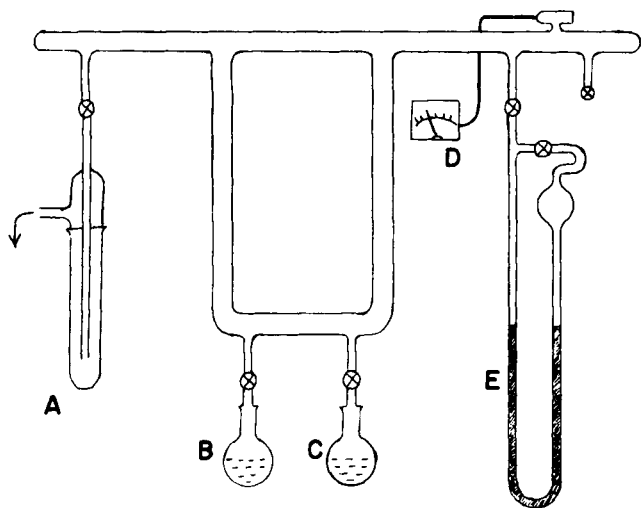
3. Contributions from ternary solute-solvent interactions described by the next three terms. These terms account for the interaction of the solute with two solvents in the absence of the third. For example,  $G_{123} q_2 \hat{z}_1 \hat{z}_3$  (equivalent to  $C_2 \hat{z}_1 \hat{z}_3$  in Eq. 1; see Ref. 1) is the contribution to solubility from the interaction of the solute with a mixture of solvents 1 and 3 only; the constant  $G_{123}$  is determined from solubility data in the absence of solvent 4.

4. Contributions from a quaternary solute-solvent interaction given by the last term. The constant  $K$  describes the interaction of the solute with all three solvents in the mixture. Since  $G_{123}$  and  $G_{124}$  are obtained for the special cases where solvents 4, 3, and 1, respectively, are absent, they, unlike  $K$ , are not new constants to be determined.  $K$ , theoretically, may be obtained from one solubility measurement somewhere in the ternary solvent composition range.

In this report, we measured total vapor pressures over ethanol-propylene glycol (denoted by subscripts 1 and 4, respectively, in Eq. 3) and ethanol-water-propylene glycol (denoted by subscripts 1, 3, and 4, respectively, in Eq. 3) mixtures at 25°C. With these data and reliable vapor pressure data for ethanol-water (4) and propylene glycol-water (5), the binary solvent interaction constants (the A terms) and the ternary solvent interaction constant ( $G_{134}$ ) were obtained. These constants were then used to characterize the solubilities of (a) phenobarbital in propylene glycol-water, ethanol-propylene glycol, and ethanol-water-propylene



**Figure 1—Total vapor pressure  $P_T$  versus mole fraction composition  $x$ . Key: (A) ethanol-water; (B) propylene glycol-water; (C) ethanol-propylene glycol; (D) ethanol-water-propylene glycol; (—) calculated curves; (O) experimental points; (EtOH) ethanol; (H<sub>2</sub>O) water; (PG) propylene glycol.**

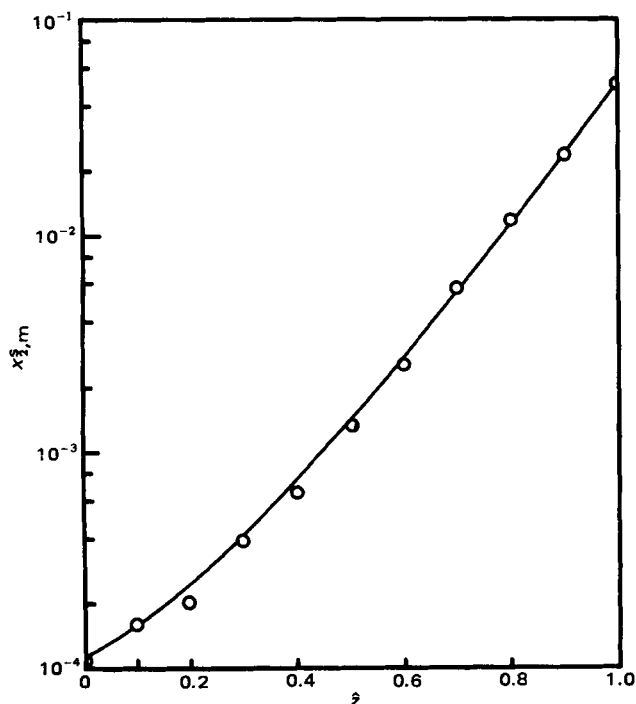


**Figure 2**—Diagram of vapor pressure-measuring apparatus. Key: (A) cold trap; (B, C) flasks containing solvent mixtures; (D) pressure gauge; (E) mercury manometer.

glycol mixtures and (b) hydrocortisone in propylene glycol-water mixtures at 25°C. The solubility of phenobarbital in ethanol-water mixtures has already been described (2).

**Estimation of Binary Solvent Interaction Constants**—Following the method described in the previous paper for the estimation of solvent interaction parameters from total pressure data, the data reported here for ethanol-propylene glycol and those for ethanol-water (4) and propylene glycol-water (5) were reduced to obtain the binary constants. The binary constants, including the ternary constant  $G_{134}$  to be discussed next, are shown in Table I. The experimental vapor pressure-composition data and the calculated curves using the binary solvent interaction constants in Table I are shown in Fig. 1 for three binary systems, ethanol-water, ethanol-propylene glycol, and propylene glycol-water.

**Estimation of Ternary Solvent Interaction Constant  $G_{134}$** —For a ternary solvent mixture such as ethanol-water-propylene glycol, the excess free energy model is given by Eq. 36 of Ref. 1 except that all terms with subscript 2 are omitted. If we rewrite the equation in terms of the A values, multiply by the total number of moles, and differentiate with respect to the number of moles of each of the components, we obtain



**Figure 3**—Solubility profile of phenobarbital in propylene glycol-water mixtures.

**Table II**—Total Vapor Pressure Results for Ethanol-Propylene Glycol

Mole Fraction		Vapor Pressure, mm Hg
Ethanol	Propylene Glycol	
0.0	1.0	0.32
0.1254	0.8746	9.00
0.2258	0.7742	16.43
0.2996	0.7004	21.27
0.3974	0.6026	26.71
0.5135	0.4865	33.12
0.6181	0.3819	40.77
0.7066	0.2934	46.87
0.7864	0.2136	47.28
0.8648	0.1352	51.23
0.9386	0.0614	55.31
1.0	0.0	58.57

expressions for the logarithm of the activity coefficients as already described (2). Thus, for a ternary solvent system:

$$\ln \gamma_1 = z_3^2 \left[ A_{1-3} + 2z_1 \left( A_{3-1} \frac{q_1}{q_3} - A_{1-3} \right) \right] + z_4^2 \left[ A_{1-4} + 2z_1 \left( A_{4-1} \frac{q_1}{q_4} - A_{1-4} \right) \right] + z_3 z_4 \left[ A_{4-1} \frac{q_1}{q_4} + A_{1-3} - A_{3-4} \frac{q_1}{q_3} + 2z_1 \left( A_{3-1} \frac{q_1}{q_3} - A_{1-3} \right) + 2z_3 \left( A_{3-4} \frac{q_1}{q_3} - A_{4-3} \frac{q_1}{q_4} \right) - G_{134} q_1 (1 - 2z_1) \right] \quad (\text{Eq. 4})$$

$$\ln \gamma_3 = z_1^2 \left[ A_{3-1} + 2z_3 \left( A_{1-3} \frac{q_3}{q_1} - A_{3-1} \right) \right] + z_4^2 \left[ A_{3-4} + 2z_3 \left( A_{4-3} \frac{q_3}{q_4} - A_{3-4} \right) \right] + z_4 z_1 \left[ A_{1-3} \frac{q_3}{q_1} + A_{3-4} - A_{4-1} \frac{q_3}{q_4} + 2z_3 \left( A_{4-3} \frac{q_3}{q_4} - A_{3-4} \right) + 2z_4 \left( A_{4-1} \frac{q_3}{q_4} - A_{1-4} \frac{q_3}{q_1} \right) - G_{134} q_3 (1 - 2z_3) \right] \quad (\text{Eq. 5})$$

$$\ln \gamma_4 = z_3^2 \left[ A_{4-3} + 2z_4 \left( A_{3-4} \frac{q_4}{q_3} - A_{4-3} \right) \right] + z_1^2 \left[ A_{4-1} + 2z_4 \left( A_{1-4} \frac{q_4}{q_1} - A_{4-1} \right) \right] + z_1 z_3 \left[ A_{3-4} \frac{q_4}{q_3} + A_{4-1} - A_{1-3} \frac{q_4}{q_1} + 2z_4 \left( A_{1-4} \frac{q_4}{q_1} - A_{4-1} \right) + 2z_1 \left( A_{1-3} \frac{q_4}{q_1} - A_{3-1} \frac{q_4}{q_3} \right) - G_{134} q_4 (1 - 2z_4) \right] \quad (\text{Eq. 6})$$

The total vapor pressure,  $P_T$ , of a ternary solvent system is given by:

$$P_T = x_1 p_1^0 \gamma_1 + x_3 p_3^0 \gamma_3 + x_4 p_4^0 \gamma_4 \quad (\text{Eq. 7})$$

$$P_T = x_1 p_1^0 e^{\ln \gamma_1} + x_3 p_3^0 e^{\ln \gamma_3} + x_4 p_4^0 e^{\ln \gamma_4} \quad (\text{Eq. 8})$$

where  $x_1$ ,  $x_3$ , and  $x_4$  are the mole fraction compositions of solvents 1, 3, and 4 (in this case ethanol, water, and propylene glycol, respectively);  $p_1^0$ ,  $p_3^0$ , and  $p_4^0$  are the pure solvent vapor pressures; and  $\gamma_1$ ,  $\gamma_3$ , and  $\gamma_4$  are the activity coefficients.

**Table III**—Total Vapor Pressure Results for Ethanol-Water-Propylene Glycol

Mole Fraction			Vapor Pressure, mm Hg
Ethanol	Water	Propylene Glycol	
0.1191	0.3033	0.5776	18.44
0.0817	0.6219	0.2964	25.81
0.1857	0.4764	0.3379	30.71
0.0463	0.9265	0.0272	30.73
0.3246	0.2804	0.3950	33.27
0.1359	0.6994	0.1647	35.03
0.1096	0.8259	0.0645	37.03
0.3475	0.4415	0.2110	42.00
0.5003	0.2555	0.2442	43.70
0.2588	0.6638	0.0774	48.42
0.4874	0.4143	0.0983	48.79
0.7188	0.2272	0.0540	53.70

**Table IV—Solute-Solvent Interaction Parameters**

Compound	$q_2^a$	Mixed Solvent System <sup>b</sup>	Solute-Solvent Interaction Constants	$n^c$	$\gamma^c$	$s^{c,d}$
Phenobarbital	172.0	Ethanol-Propylene Glycol	$G_{124}q_2 = -0.092$	9	0.885	0.291
Phenobarbital	172.0	Propylene Glycol-Water	$G_{234}q_2 = -1.80$	9	0.999	0.129
Phenobarbital	172.0	Ethanol-Water	$G_{123}q_2 = -6.74$	9	0.995	0.21
Phenobarbital	172.0	Ethanol-Water-Propylene Glycol	$Kq_2 = 15.3$	20	0.996	0.135
Hydrocortisone	293	Propylene Glycol-Water	$C_2 = 1.44$	4	1.000	0.200

<sup>a</sup>  $q_1 = 58.68$  (Ref. 11),  $q_3 = 18.07$  (Ref. 15), and  $q_4 = 73.69$  (Ref. 14),  $q_2$  was calculated by group contribution from the molar volume of barbital (Ref. 15). <sup>b</sup> Subscript key: 1, ethanol; 2, solute; 3, water; 4, propylene glycol. <sup>c</sup> Linear regression parameters for the estimation of the constants in column 4. <sup>d</sup>  $s$  is the standard deviation of the error between  $\ln(x_{2,m}^{\text{obs}}/x_{2,m}^{\text{est}})$ .

By substituting Eqs. 4-6 into Eq. 8, all seven interaction constants may be obtained by nonlinear regression since  $P_T$ , the mole fractions, and pure solvent-vapor pressures are known. To obtain  $G_{134}$ , the other six constants  $A_{1-3}$ ,  $A_{3-1}$ ,  $A_{1-4}$ ,  $A_{4-1}$ ,  $A_{3-4}$ , and  $A_{4-3}$  were fixed so that only  $G_{134}$  was altered to obtain the best fit. If the six binary constants were allowed to vary, the estimates would become meaningless because of the complexity of the sum of squares surface for seven parameters. With this method,  $G_{134} = -0.1069$  mol/cm<sup>3</sup> was obtained with the A terms as shown in Table I. It should be noted that, while the A terms are dimensionless,  $G_{134}$  has units of reciprocal molar volume because of the way it was defined in Eq. 371 of Ref. 1.

**EXPERIMENTAL**

**Materials**—Absolute ethanol and propylene glycol were used as received. Double-distilled water was used for all aqueous mixtures.

**Method**—All solvent mixtures were made by weighing the appropriate amounts of solvents. To prevent condensation of the solvent vapor on the mercury and in the manifold of the apparatus (Fig. 2), the manometer (E) and the manifold were wrapped with a heating tape kept at  $3 \pm 0.5^\circ\text{C}$  above the temperature of the flask contents (B and C).

The method described here is similar to that used by Verlinde *et al.* (5). The solvent (or solvent mixture) was frozen using liquid nitrogen. The stopcock to the solvent was opened, and the air in the manifold and above the solvent was evacuated by means of a compound-stage vacuum

pump until the pressure gauge (D) indicated a pressure of  $\leq 2 \mu\text{m}$ . The stopcock was then closed, and the solvent was brought to room temperature and stirred by means of a glass-coated magnetic bar in the flask. The solvent was again frozen, the stopcock opened, and the air evacuated. By means of several such freeze-thaw cycles, the dissolved air in the solvent was removed. The process was stopped after the pressure gauge showed no significant increase in pressure on opening the stopcock to the frozen solvent.

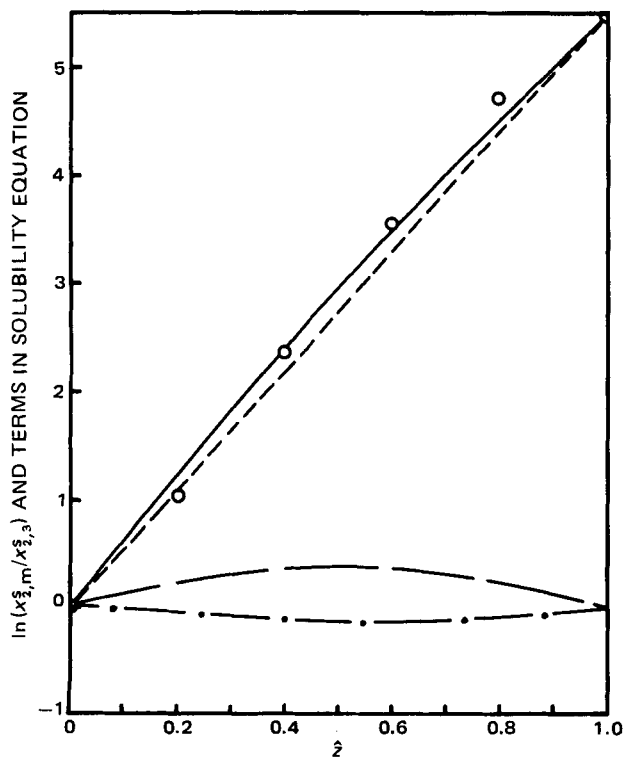
After deaerating the solvent, it was brought to, and kept at,  $25 \pm 0.1^\circ\text{C}$ . The solvent stopcock was opened, the vapor pressure was read by a cathetometer (graduated to 0.05 mm) after the mercury column had stopped moving, and the average was computed.

Two flasks containing two different concentrations of the solvent mixture were used so that deaerating the contents simultaneously saved considerable time. After deaerating, flask B was shut off while the vapor pressure of the contents of flask C was measured. Then flask C was shut off, the system evacuated, and the vapor pressure of the contents of flask B measured. Each averaged vapor pressure reading was corrected for the change in acceleration due to gravity, the change in the density of mercury at  $28^\circ\text{C}$  (temperature of the manometer), and capillary depression (6) using: corrected pressure = (uncorrected pressure)  $(g/g_0) (d_1/d_0) + C_u - C_l$ , where  $g$  is the acceleration due to gravity in Madison ( $980.368 \text{ cm/s}^2$ ) (7);  $g_0 = 980.665 \text{ cm/s}^2$  (6);  $d_1$  is the density of mercury at manometer temperature ( $28^\circ\text{C}$ );  $d_0$  is the density of mercury at  $0^\circ\text{C}$ ;  $C_u$  and  $C_l$  are the capillary depression correction for the upper and lower columns of the manometer, respectively; and  $d_1/d_0 = 0.994939$  (6). The results of four separate measurements with ethanol indicated a relative standard error of  $<1\%$ .

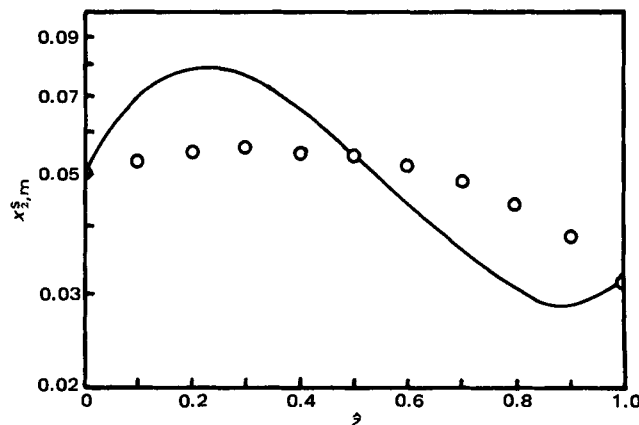
Calculations (using the ideal gas equation  $PV = nRT$ ), with the highest possible partial pressure values showed that with a void volume of  $1324 \pm 7 \text{ cm}^3$  occupied by the solvent or solvent mixture vapor, there was  $<0.6\%$  change between initial and equilibrium weight fractions of the components. There was, therefore, no need to use equilibrium weight/mole fraction values.

**RESULTS**

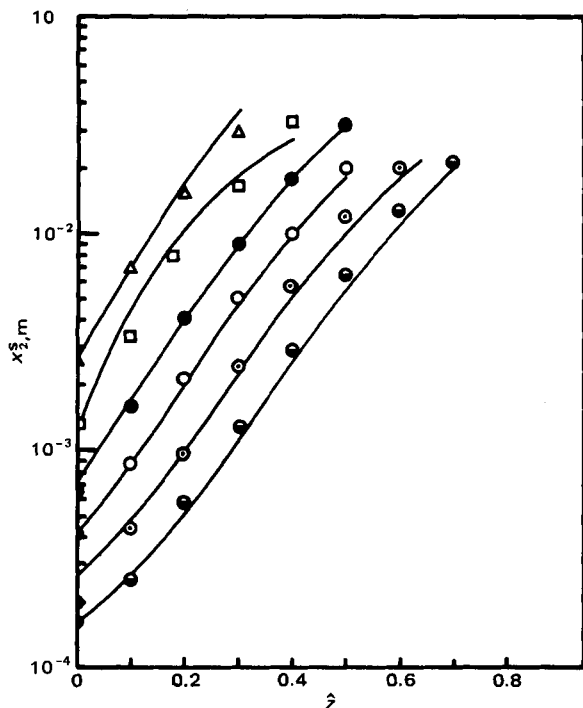
**Vapor Pressure Results**—Corrected total vapor pressure readings at different solvent compositions are given in Tables II and III for ethanol-propylene glycol and ethanol-water-propylene glycol mixtures. For ethanol-water mixtures, partial vapor pressure readings that had been



**Figure 4**—Solubility profile of hydrocortisone in water-propylene glycol mixtures (showing contributions from terms in Eq. 4). Key: (---)  $z_1 \ln(x_{2,1}^{\text{obs}}/x_{2,3}^{\text{obs}})$ ; (-·-·-)  $-A_{1-3}z_1z_3(2z_1 - 1)q_2/q_1 + A_{3-1}z_1^2z_3q_2/q_3$ ; (—)  $C_2z_1z_3$ ; (—) estimated  $\ln(x_{2,m}^{\text{obs}}/x_{2,m}^{\text{est}})$ ; (O) experimental  $\ln(x_{2,m}^{\text{obs}}/x_{2,m}^{\text{est}})$ .



**Figure 5**—Solubility profile of phenobarbital in ethanol-propylene glycol mixtures. Key: (—) estimated solubility; (O) experimental solubility.



**Figure 6**—Solubility profiles of phenobarbital in ethanol-water at designated volume fractions of propylene glycol. Lines represent estimated solubilities and points are the experimental solubilities. Volume fractions of propylene glycol: (●) 0.1; (○) 0.2; (○) 0.3; (●) 0.4; (□) 0.5; (Δ) 0.6.

tested for thermodynamic consistency (8) were taken from Ref. 4. For propylene glycol-water mixtures, total vapor pressure results from Ref. 5 were used after being checked with the apparatus described above.

Figure 1A-C shows the experimental points for the three binary systems. Figure 1D combines all three cases and the ternary mixture vapor pressures. The resulting vapor pressure surface is plotted above a triangular plane each of whose apices represent a pure solvent.

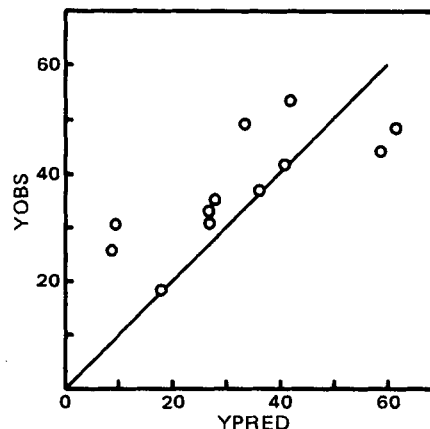
**Solubility in Ethanol-Water-Propylene Glycol Mixtures**—Figures 3 and 4 show the estimated and experimental solubility profiles of phenobarbital (9) and hydrocortisone (10) in propylene glycol-water mixtures obtained by methods described in the previous paper (2). In summary, the ternary solute-solvent interaction constant for this system,  $G_{234}$ , is estimated from differences between experimental solubilities and solubilities calculated with  $G_{234} = 0$ . The binary solvent-solvent interaction constants needed in this case are  $A_{3-4}$  and  $A_{4-3}$ , whose values are given in Table I. With regard to Eq. 4, it means that one sets  $\xi_1 = 0$ .

Figure 5 shows the estimated and experimental solubility profile of phenobarbital in ethanol-propylene glycol mixtures (9), and Fig. 6 shows the same compound in a mixture of all three solvents (9). In this case,  $K$ , the quaternary solute-solvent constant, was estimated from differences between experimental solubilities in mixtures of the three solvents and solubilities calculated from all the terms in Eq. 4 without the  $K$  term.  $G_{123}$ ,  $G_{234}$ , and  $G_{124}$  were already known from the solubilities of phenobarbital in mixtures of ethanol-water, water-propylene glycol, and ethanol-propylene glycol, respectively. All ternary and quaternary solute-solvent interaction constants estimated are shown in Table IV.

## DISCUSSION

**Vapor Pressure Fit by Excess Free Energy Model**—As shown in Fig. 1A-C, the three-suffix excess free energy model accurately predicts total vapor pressures for the three binary systems described here. This indicates that it is very reliable for obtaining binary solvent interaction constants which adequately represent interactions between the solvents. It is interesting to note that in Fig. 1B, the total vapor pressure over propylene glycol-water mixtures can be described by a straight line, which implies that the solvent mixture follows Raoult's Law for ideal mixtures. Raoult's Law states that the total vapor pressure,  $P_T$ , over an ideal mixture of solvents may be expressed as:

$$P_T = \sum_i x_i p_i^0 \quad (\text{Eq. 9})$$



**Figure 7**—Observed (YOBS) versus predicted (YPRED) vapor pressures for ethanol-water-propylene glycol mixtures;  $n = 12$ ,  $r = 0.765$ ,  $s = 11.1$ .

where  $x_i$  represents the mole fraction of each component  $i$  and  $p_i^0$  is the pure vapor pressure of component  $i$ . In systems where Raoult's Law holds, the excess free energy of mixing is zero. The implications of this observation as it concerns solubility in propylene glycol-water mixtures will be discussed in the next section. The vapor pressure curve for ethanol-propylene glycol (Fig. 1C) follows that of a typical solute (with a relatively low vapor pressure) in a solvent. At high concentrations of ethanol, the total vapor pressure is practically equal to the partial pressure of ethanol, which, as expected, converges to the Raoult's Law line as the mole fraction of ethanol in the mixture approaches 1.

For the mixture of all three solvents, predicted vapor pressures (Fig. 7) were not as good as for the binary systems (Fig. 1), but if one considers the complexity of the ternary system, the fit is satisfactory. A better fit may be obtained by using the four-suffix excess free energy model (3), but the number of solvent constants to be estimated (12, see Ref. 3) becomes inconveniently high. Another excess free energy model which has been shown to better describe ternary vapor-liquid equilibrium data is the nonrandom two liquid (NRTL) model (12). However, we have not examined this model at this time for possible application to solid-solvent systems.

**Estimation of Solubility in Ethanol-Water-Propylene Glycol Mixtures**—As was mentioned above, the propylene glycol-water system is close to ideal in the Raoult's Law sense. This is also indicated by the binary solvent interaction constants ( $A$  terms) which are quite small in magnitude (Table I). Consequently, the solubility of a compound in their mixture should be approximately equal to the ideal mixture solubility discussed earlier if there is little interaction between the solute and mixed solvent. This is borne out by Figs. 3 and 4, in which the experimental solubility is close to a straight line between the two end points. This provides a rationale for the observation that the logarithm of the solubility of some compounds, e.g., alkyl *p*-aminobenzoates (13), in propylene glycol-water mixtures increases linearly with the volume fraction of propylene glycol in the mixture.

Figure 4 shows the contributions of the various terms in Eq. 2 to the solubility of hydrocortisone in propylene glycol-water mixtures. Equation 2 is written for solvents 1 and 3. It may be applied to propylene glycol-water mixtures by temporarily designating propylene glycol as solvent 1. If we temporarily make this change, then we can refer to the ternary solute-solvent constant  $C_2$  in Eq. 2 instead of  $G_{234}q_2$  in Eq. 3. As seen in Fig. 4, the solvent interaction contribution (the sum of the  $A$  terms) is always close to zero and has no significant deviation from the ideal mixture solubility. The magnitude of the sum of the  $A$  terms in Eq. 2 is influenced by the ratio of the solute to solvent molar volumes  $q_2/q_1$  and  $q_2/q_3$ . If we temporarily label propylene glycol "1" (water is still "3"), then since the molar volumes of hydrocortisone, propylene glycol, and water are 293 (10), 73.69 (14), and 18.07  $\text{cm}^3/\text{mol}$  (15), respectively,  $q_2/q_1 = 3.98$  and  $q_2/q_3 = 16.2$ . These ratios are about as high as they can get for many solutes. Therefore, the fact that the solvent interaction contribution is very small for hydrocortisone indicates that it is likely to be even smaller for many other solutes in this binary solvent mixture. One can conclude from these results that for propylene glycol-water systems, only the interaction between the solute and solvent mixture (estimated by  $C_2$ ) contributes significantly to the deviation of the solubility profile from that estimated by using only the ideal mixture solubility terms.

The solubility of phenobarbital in ethanol-propylene glycol mixtures is not well described by Eq. 1, as seen in Fig. 5. However, if one takes into account that Fig. 5 is drawn on an expanded scale compared with, for example, Fig. 3, then the estimation is not overwhelmingly poor. The equation predicts a maximum and a minimum, whereas only the maximum is seen experimentally. The comparatively poor characterization of solubility in this case [as in the case of antipyrine in ethanol-water discussed previously (2)] is most likely due to the fairly high solubility of the drug in each of the solvents (149.5 mg/mL in propylene glycol and 117.9 mg/mL in ethanol) (9). These values are 0.051 and 0.032, respectively, in mole fraction units.

Figure 6 shows the estimated and experimental (9) solubility profiles of phenobarbital in ethanol-water-propylene glycol mixtures. The fit is remarkably good. One could argue that the curves could be well approximated by straight lines so that the effectiveness of Eq. 3 is not really demonstrated by Fig. 6. If the points are fitted to straight lines, two parameters would be required for each line. In this approach, however, only one parameter (K) is required to generate all the curves in Fig. 6, since the solvent-solvent constants (the A terms and  $G_{134}$  in Eq. 3) and the ternary solute-solvent constants ( $G_{123}$ ,  $G_{124}$ , and  $G_{234}$  in Eq. 3) are known (Tables I and IV). Thus, this approach is more flexible and requires fewer empirically adjusted parameters (compared with the straight line fit just discussed, for example) to describe solubility in a ternary solvent system.

As was pointed out earlier, the binary solvent interaction contributions from propylene glycol-water are quite small. It is, therefore, possible to drop these terms (*i.e.*, set  $A_{3,4} = A_{4,3} = 0$ ) from Eq. 3 for mixtures of ethanol-water-propylene glycol without any significant loss in estimation capabilities.

### CONCLUSION

The reduced three-suffix solubility equation for decreasing solubility in binary and ternary solvent mixtures has previously been shown to be quite successful for ethanol-water systems (2). In this report, its applicability to other binary systems and a ternary system is further demonstrated. Our results indicate that the solubility of compounds in propylene glycol-water systems may be described in terms of the volume fraction weighted sum of the pure solvent solubilities and a ternary solute-solvent interaction term, *i.e.*, solvent-solvent interaction terms make negligible contributions to the total solubility. This finding provides a rational explanation for the observation that the logarithms of the solubilities of a number of compounds in propylene glycol-water mixtures are a linear function of the volume fraction of the former.

Estimation of solubility in a ternary solvent system requires more terms than in a binary solvent system, which is not unexpected considering that the former is complicated. However, in both systems only one unknown parameter needs to be estimated from mixed solvent solubility data. For instance, to describe the solubility of phenobarbital in ethanol-water, ethanol-propylene glycol, and propylene glycol-water, we may use Eq. 1 or 3. To use Eq. 3 for ethanol-water, we set  $\hat{z}_4 = 0$  and estimate  $G_{123}$  as already described; for ethanol-propylene glycol we set  $\hat{z}_3 = 0$  and estimate

$G_{124}$ ; and for propylene glycol-water, we set  $\hat{z}_1 = 0$  and estimate  $G_{234}$ . To describe the solubility of phenobarbital in ternary mixtures of these solvents, the only known term to estimate in Eq. 3 is the quaternary solute-solvent constant K since the A terms and  $G_{134}$  are fixed for the solvent system and  $G_{123}$ ,  $G_{124}$ , and  $G_{234}$  are fixed for the solute in this solvent system. With the estimated K, the entire solubility profile of phenobarbital in a mixture of these three solvents was described very well. It appears, then, that this approach is reasonably flexible and general while requiring relatively few empirically adjusted solute-solvent parameters.

The only apparent limitation of the reduced three-suffix solubility equation thus far is in describing relatively high solubilities. Bearing in mind that the equation was developed with the assumption that the solubility of the solute is very small, it is not surprising that the equation does not do well for compounds that are fairly to highly soluble in both (or all) of the pure solvents used. From a pharmaceutical point of view, a compound with appreciably high solubility in water does not need a cosolvent. Therefore, it seems that the equation is well suited for the systems for which it was derived: compounds whose very low solubility in water (or another solvent) necessitate the addition of a second solvent or solvents to increase their solubility.

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