# AN EXCESS FREE ENERGY APPROACH TO THE ESTIMATION OF SOLUBILITY IN MIXED SOLVENT SYSTEMS

BY

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To

Iyabo and Foluso

Glad to have you

and

To the memory of

Tolulope and 'Leke

Wish you were here too.

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Under the supervision of Associate Professor Gordon L. Amidon

A general equation for characterizing and estimating the solubility of organic compounds in binary and ternary solvent systems was developed from an excess free energy model. The equation, known as the reduced 3-suffix solubility equation, for a solute (denoted by subscript 2) in a binary (denoted by subscripts 1 and 3) solvent mixture m is

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

where $x^s_{2,1}$, $x^s_{2,3}$ and $x^s_{2,m}$ are the mole fraction solubilities of the solute in solvents 1, 3 and the mixture, respectively; $A_{1-3}$ and $A_{3-1}$ are solvent-solvent interaction constants; $C_2$ is a ternary solute-solvent interaction constant; the q's are the molar volumes and $\hat{z}_1$ and $\hat{z}_3$ are solute-free volume fractions.

The solvent-solvent interaction constants (A's) are estimated from vapor liquid equilibrium data. Once obtained at a particular temperature, they are fixed for that solvent

system regardless of the solute in question. The ternary constant $C_2$ is estimated in principle, from an experimentally determined solubility at a point in the solvent composition range. Thus, the only additional data needed to completely describe the solubility profile are the pure solvent solubilities.

Total vapor pressure measurements were made or taken from the literature for ethanol-water, ethanol-propylene glycol, propylene glycol-water and ethanol-water-propylene glycol mixtures. The solvent constants were then obtained by fitting the data to the applicable excess free energy model. Attempts to describe literature solubility data in these mixed solvent systems with the reduced 3-suffix solubility equation were very successful in general. The equation was not as successful where solubilities were high because such conditions invalidated the approximations made in its derivation.

The generality and flexibility of this approach make it easily adjustable for other systems which may not be well-characterized by the reduced 3-suffix equation.

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# I. GENERAL INTRODUCTION

The estimation of the solubility of solids, gases and liquids (to a lesser extent) in pure and mixed solvents is a problem that has been of interest to physical chemists, chemical engineers and pharmaceutical scientists. While solubility predictions for gases and liquids have been investigated mostly by chemical engineers, solids have been treated mainly by physical chemists and even among these, the systems dealt with have been mostly non-polar systems for which fundamental equations may be developed. Examples are:

(i) The ideal solubility equation (1)

$$\log \frac{1}{X_2} = \frac{\Delta h^f}{RT}\left[1 - \frac{T}{T_t}\right] - \frac{\Delta C_p}{R}\left(\frac{T_t - T}{T}\right) + \frac{\Delta C_p}{R} \ln \frac{T_t}{T} \qquad (1)$$

where R is the gas constant and T is the temperature of interest (in degrees Kelvin). Equation 1 expresses the mole fraction solubility $X_2$ of a solid in terms of its heat of fusion $\Delta h^f$, its triple point temperature ($T_t$), usually approximated by its normal melting point, and the difference in heat capacities of the crystalline and melted solid $\Delta C_p$. Very few solid/liquid systems adhere to this equation because it neglects all interactions between solute and solvent.

(ii) The regular solution equation (2)

$$RT \ln \gamma_2 = v_2 \phi_1^2 [\delta_1 - \delta_2]^2 \qquad (2)$$

where R and T are as defined in equation 1, $v_2$ is the molar volume of the solute, $\gamma_2$ is the activity coefficient of the solute, $\phi_1$ is the volume fraction of the solvent, and $\delta_1$ and $\delta_2$ are the solvent and solute solubility parameters respectively. The regular solution equation takes into account interactions between the solute and solvent but treats only dispersion forces. This gives rise to the activity coefficient expression which is then usually added to the ideal solubility equation (see Appendix A). This combination usually describes the solubility of strictly non-polar solids in strictly non-polar solvents satisfactorily (2). However since many compounds and solvents of interest are polar to a small or large extent, the equation often fails. This has led various investigators to modify the regular solution equation by introducing corrections for dipole and hydrogen bonding interactions (3-6). One of these approaches will be discussed shortly in relation to mixed solvents.

Another large group of scientists interested in the solubility of solids are the pharmaceutical scientists and the reason for this is clear; most therapeutically effective

drugs are crystalline solids. In the formulation of these drugs for delivery to the patient, their solubility in the vehicle(s) is often of crucial importance. If the drug is not readily soluble in water, organic solvents, called co-solvents, are often added to increase the solubility. Examples of such co-solvents are ethanol, glycerin, propylene glycol and the low molecular weight polyethylene glycols. The need to mix solvents in general in order to influence the solubility of a solute generates the need to characterize solubility in a mixture of solvents. If solubility can be characterized well, then it may be predicted accurately enough to reduce experimental work and limit determinations only to particular solvent compositions of interest.

Since virtually all of the co-solvents of interest in pharmaceutics are polar to some extent, the regular solution theory generally fails to describe solubility in these solvents satisfactorily. Attempts to avoid this problem have led workers in this field to use purely empirical equations (8), modified forms of the regular solution theory (5,6), or a semi-empirical approach which incorporates some polarity related term like interfacial tension (7).

As an example, Moustafa and co-workers (8) used an empirical approach to describe the solubility of phenobarbital in propylene glycol-water-glycerin mixtures. They use

the equation

$$\log S_t = \log S_o + \alpha_1 f_1 + \alpha_2 f_2 + \beta f_1^2 f_2$$

where

$S_t$ = estimated solubility of phenobarbital

$S_o$ = solubility of phenobarbital in water

$f_1$, $f_2$ = volume fractions of glycerin, propylene glycol, respectively

$\alpha_1$, $\alpha_2$ = constants obtained for glycerin, propylene glycol, respectively

$\beta$ = constant obtained by fitting experimental data to equation

While equations of this type are useful, they are by their nature, restricted to, and only useful for, the particular solute-solvent systems for which they were formulated. Also, the constants often have little physical meaning.

Recently Martin and co-workers (5,6) have attempted to use an extended form of the regular solution equation for the solubility of solids to estimate solubility in pure and mixed solvents. This is accomplished in effect by adding a term, W, to the expression for the regular solution activity coefficient to account for non-dispersion type solute-solvent interactions. W is then estimated from differences between experimental and calculated solubilities using the

regular solution equation. While their method is an improvement over the purely empirical approach, it does have a few disadvantages. For instance, it requires obtaining the heat of fusion, melting point, molar volume and solubility parameter of the solute, and the solubility parameter of the solvent or solvent mixture. Where these data are not readily available the experimental labor involved in determining them may be such as to frustrate the ultimate aim of the approach: to estimate solubility with the minimum number of experiments. As the authors have also pointed out (5), the correction term, W, is difficult to determine independently and the solubility parameter of the solute may assume a different value in a different solvent system (although this does not seriously affect the results) (6).

## Objectives

In this work we have attempted to develop a general equation which describes the solubility of compounds in mixed solvents and which is applicable in principle to virtually any solute-mixed solvent where the solubility is not high. The approach should have a rational basis with terms which have some physical meaning even if they are estimated empirically. The equation should also achieve a balance between complexity and effectiveness, i.e., it should be as simple as it can be and yet satisfactorily describe

solubility in binary and ternary solvent mixtures.

We have made use of an excess free energy model because the change of the excess free energy with composition can be related to the activity coefficients of the components which account for non-idealities in a mixture. Excess free energy models have been used extensively to fit activity coefficient data (9) and applied to the estimation of gas solubilities in mixed solvents (10,11).

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# II.

# An Excess Free Energy Approach to the Estimation of Solubility in Mixed Solvent Systems: I

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## Abstract

An approach is developed by which the solubility of an organic compound in mixed solvents may be estimated. In this approach, an expression for the excess Gibbs free energy of mixing for multi-component solvent systems is used to obtain parameters characteristic of the interaction between the solvents. A fairly simple equation which predicts the solubility of a solute in e.g. a binary solvent system over the entire solvent composition range is then derived. The equation may be partitioned into terms which contain (a) pure solvent solubilities, (b) solvent-solvent interaction contributions, and (c) contributions from the solute-mixed solvent interactions. The data required are the molar volume of the solute, the pure solvent solubilities and theoretically, one experimentally determined solubility in a solvent mixture. The equation can be easily extended for three or more mixed solvent systems.

For pharmaceutical purposes, it is often necessary to dissolve a non-polar or slightly polar drug in a mixture of water and one or more co-solvents such as ethanol, glycerin, propylene glycol and low molecular weight polyethylene glycols in order to increase its solubility. It is also often desirable to know if and where a maximum exists in the solubility profile of the drug in the mixture of solvents. Apart from determining such a profile experimentally over the whole solvent composition range, no general method exists at present which can, with a minimum of experiments, describe completely the solubility in the solvent mixture. Typical approaches to the estimation of solubility in mixed solvents merely express solubility in terms of a power series in mole or volume fraction multiplied by arbitrary numbers which have little physical meaning (1). Such equations although useful are, by their nature, restricted to, and only useful for, the particular solute-solvent systems for which they were formulated.

Recently Martin and co-workers (2-5) have attempted to use an extended form of the regular solution equation for the solubility of solids to estimate solubility in pure and mixed solvents. This is accomplished in effect by adding a term, W, to the expression for the regular solution activity coefficient to account for non-dispersion type solute-solvent interactions. W is then estimated from differences between experimental and calculated solubilities using the regular solution equation. While their method is an improvement over the purely empirical approach, it does have a few disadvantages. For instance, it

requires obtaining the heat of fusion, melting point, molar volume and solubility parameter of the solute, and the solubility parameter of the solvent or solvent mixture. Where these data are not readily available the experimental labor involved in determining them may be such as to frustrate the ultimate aim of the approach: to estimate solubility with the minimum number of experiments. As the authors have also pointed out (2), the correction term, W, is difficult to determine independently and the solubility parameter of the solute may assume a different value in a different solvent system (although this does not seriously affect the results) (4).

This paper presents the theoretical aspects of a method based on an excess free energy model which can be used to characterize the solubility of compounds in binary and ternary solvent systems. The method is general and is applicable in principle to virtually any solute-mixed solvent system as long as the solubility is not high. The data required are the molar volume of the solute, the pure solvent solubilities and theoretically, one experimentally determined solubility in a solvent mixture. The last item is required for estimating $C_2$, a ternary interaction term. Although $C_2$ is estimated empirically, unlike W, it results logically from the development of the excess free energy model for the system. A subsequent paper (6) will discuss the usefulness of this approach in describing experimental data from the literature.

Theory

For a solute in solution in equilibrium with its solid phase,

$$f_2^{soln} = f_2^{pure} \tag{1}$$

where $f_2^{soln}$ is the fugacity of the solute in solution and $f_2^{pure}$ is the fugacity of the pure solid. The fugacity of the solute in solution may be expressed as (9)

$$f_2^{soln} = x_2 \gamma_2 f_2^{o} \tag{2}$$

where $x_2$ is the mole fraction concentration of the solute, $\gamma_2$ is the symmetric convention activity coefficient and $f_2^{o}$ is the fugacity of the hypothetical pure liquid at the same temperature and pressure as the solution (as is shown later, $f_2^{o}$ drops out of the equation and so its evaluation does not present a problem).

The symmetric convention activity coefficient $\gamma_2$ has the property that $\gamma_2 \to 1$ as $x_2 \to 1$ while the unsymmetric convention activity coefficient (which we denote as $\gamma_2^*$) has the property that $\gamma_2^* \to 1$ as $x_2 \to 0$. The relationship between the two activity coefficients has been derived by Prigogine and Defay (8). They show that

$$\frac{\gamma_2}{\gamma_2^*} = \lim_{x_2 \to 0} \gamma_2 \tag{3}$$

If $x_2$ approaches zero, $\gamma_2^*$ is approximately equal to 1 and equation 3 becomes

$$\gamma_2 \approx \lim_{x_2 \to 0} \gamma_2 \tag{4}$$

This situation is described by Henry's Law which may be written as

$$\lim_{x_2 \to 0} \frac{f_2^{soln}}{x_2} = H_2 \tag{5}$$

where $H_2$ is Henry's Law constant.

If we assume that the mole fraction solubility is sufficiently small such that Henry's Law holds up to the solubility limit, we can write

$$f_2^{soln} = f_2^{pure} = H_2 x_2^s \tag{6}$$

where $X_2^s$ is the mole fraction solubility. In many cases of interest, the mole fraction solubility of the drug or chemical in question is low enough even in the pure co-solvent to justify such an assumption.

Comparison of equations 2 and 5 shows that

$$\lim_{x_2 \to 0} \gamma_2 = \frac{H_2}{f_2^o} \tag{7}$$

If we take the logarithm of equation 7 and then write the expression for the solute in say solvents 1 and 3 separately, we obtain for solvent 1

$$\lim_{x_2 \to 0} \ln\gamma_{2,1} = \ln \frac{H_{2,1}}{f_2^{o}} \tag{8a}$$

and for solvent 3

$$\lim_{x_2 \to 0} \ln\gamma_{2,3} = \ln \frac{H_{2,3}}{f_2^{o}} \tag{8b}$$

We note here that subscript 2 is used for the solute while subscripts 1, 3, 4, etc. are used for the pure solvents. For a binary mixture denoted by subscript "m", of say solvents 1 and 3, equation 7 becomes

$$\lim_{x_2 \to 0} \ln\gamma_{2,m} = \ln \frac{H_{2,m}}{f_2^{o}} \tag{8c}$$

If we take the logarithm of equations 1, 2 and 4 and combine them, we obtain, at the solubility limit

$$\ln x_2^{s} = \ln \left( \frac{f_2^{pure}}{f_2^{o}} \right) - \lim_{x_2 \to 0} \ln\gamma_2 \tag{9}$$

Substituting the expressions for $\ln\gamma_2$ in equations 8a-8c we obtain, for solvent 1,

$$\ln x_{2,1}^{s} = \ln \frac{f_2^{pure}}{H_{2,1}} \tag{10a}$$

for solvent 2

$$\ln x^{s}_{2,3} = \ln \frac{f_2^{pure}}{H_{2,3}} \tag{10b}$$

and for a mixture of 1 and 3

$$\ln x^{s}_{2,m} = \ln \frac{f_2^{pure}}{H_{2,m}} \tag{10c}$$

We now define the volume fraction $z_i$ of any component "i" in the mixture as

$$z_i = \frac{x_i q_i}{\sum_i x_i q_i} \tag{11}$$

where $q_i$ is the molar volume of component "i". If we let $x_2$ approach zero, $z_2$ also approaches zero and $z_1$ and $z_3$ become solute-free volume fractions i.e.,

$$\hat{z}_1 + \hat{z}_3 = 1 \tag{12}$$

where the symbol "^" denotes solute-free terms. From equation 6 we can write

$$\ln f_2^{pure} = \ln x^{s}_{2,1} + \ln H_{2,1} \tag{13a}$$

and

$$\ln f_2^{pure} = \ln x^s_{2,3} + \ln H_{2,3} \tag{13b}$$

If we multiply equation 13a by $\hat{z}_1$, 13b by $\hat{z}_3$ and add them we obtain

$$\ln f_2^{pure} = \hat{z}_1(\ln x^s_{2,1} + \ln H_{2,1}) + \hat{z}_3(\ln x^s_{2,3} + \ln H_{2,3}) \tag{14}$$

and equation 14 substituted into equation 10c gives

$$\ln x^s_{2,m} = \hat{z}_1 \ln x^s_{2,1} + \hat{z}_3 \ln x^s_{2,3} - (\ln H_{2,m} - \hat{z}_1 \ln H_{2,1} - \hat{z}_3 \ln H_{2,3}) \tag{15}$$

Equation 15 shows that the solubility of a compound in a binary solvent mixture is a volume fraction weighted sum of the two pure solvent solubilities plus what can be termed an excess Henry's Law constant $H_2^{Ex}$. In general, we may write

$$\ln x^s_{2,m} = \sum_{\text{solvents } i} \hat{z}_1 \ln x^s_{2,1} - \ln H_2^{Ex} \tag{16}$$

$$\ln H_2^{Ex} = \ln H_{2,m} - \sum_{\text{solvents } i} \hat{z}_1 \ln H_{2,i} \tag{17}$$

In order for equations 15-17 to be useful, an expression for $\ln H_2^{Ex}$ must be developed. To obtain such an expression for $\ln H_2^{Ex}$, we have employed an excess free energy model proposed by Wohl (7) which we now present.

Excess Free Energy Model

The total free energy G of a homogeneous system consisting of r components may be written as

$$G = \sum_{i=1}^{r} n_i g_i^{o} + RT \sum_{i=1}^{r} n_i \ln x_i + \left( \sum_{i=1}^{r} n_i \right) g^{E} \qquad (18)$$

In equation 18, $n_i$ represents the number of moles of the $i^{th}$ component, $x_i$ is the mole fraction of the $i^{th}$ component, and $g^E$ is the excess free energy per mole. The first term represents the free energies of each of the pure components ($g_i^o$ being the free energy per mole of pure component i). The second term is the free energy of ideal mixing and the third term represents the excess free energy arising from non-idealities in the mixing. The partial molar free energy of say component j at constant temperature, pressure and composition is given by

$$\left( \frac{\partial G}{\partial n_j} \right)_{T,P,n_{i \neq j}} = g_j = g_j^{o} + RT \ln x_j + RT \ln \gamma_j \qquad (19)$$

where

$$\ln \gamma_j = \left[ \frac{\partial \left[ \sum_{i=1}^{r} n_i \frac{g^E}{RT} \right]}{\partial n_j} \right]_{T,P,n_{i \neq j}} \qquad (20)$$

In 1946, Wohl (7) proposed a general method for expressing the excess free energies of mixtures in terms of increasing powers of the

volume fractions, z, of the components. Thus the excess free energy of a ternary system may be expressed as

$$\frac{g^E}{RT(x_1q_1 + x_2q_2 + x_3q_3)} = 2a_{12}z_1z_2 + 2a_{13}z_1z_3 + 2a_{23}z_2z_3$$
$$+ 3a_{112}z_1^2z_2 + 3a_{122}z_1z_2^2 + 3a_{113}z_1^2z_3 + 3a_{133}z_1z_3^2$$
$$+ 3a_{223}z_2^2z_3 + 3a_{233}z_2z_3^2 + 6a_{123}z_1z_2z_3 + 4a_{1112}z_1^3z_2$$
$$+ 6a_{1122}z_1^2z_2^2 + 4a_{1222}z_1z_2^3 + 4a_{1113}z_1^3z_3 + 6a_{1133}z_1^2z_3^2$$
$$+ 4a_{1333}z_1z_3^3 + 4a_{2223}z_2^3z_3 + 6a_{2233}z_2^2z_3^2 + 4a_{2333}z_2z_3^3$$
$$+ 12a_{1123}z_1^2z_2z_3 + 12a_{1223}z_1z_2^2z_3 + 12a_{1233}z_1z_2z_3^2 \qquad (21)$$

where

$$z_1 = \frac{x_1q_1}{x_1q_1 + x_2q_2 + x_3q_3} \quad \text{etc.} \qquad \text{(see equation 11)}$$

The q's are usually considered a measure of the sizes of the molecules. In this report we have used molar volumes for the q's and Wohl used the term "four-suffix q-equation" in describing equation 21 to distinguish it from Margules-type equations which assume that all the molecules are of equal size. The "four" refers to the largest number of subscripts on an "a" term in the equation. As an example $a_{12}$ is a constant which represents the interaction between one molecule of component 1 and another of component 2. Also, as Prausnitz (9) has pointed out, the probability

that any pair of two molecules consists of one molecule each of components 1 and 2 is given by $2z_1z_2$. Similarly $a_{1133}$ is the interaction parameter for four interacting molecules two of which are made up of components 1 and 3 respectively and $6z_1^2z_3^2$ is the probability that any four neighboring molecules consist of two molecules each of components 1 and 3. Although the "a's" may be regarded in a rough sense as similar to virial coefficients, they do not have a rigorous theoretical basis (9). Their importance lies in the fact that they are physically meaningful parameters.

Higher- or lower-suffix q-equations may also be written for the excess free energy depending on the degree of complexity required. A three-suffix equation contains only the first ten terms on the right hand side of equation 21 and a two-suffix equation contains only the first three terms.

Wohl (7) defined

$$A_{2\text{-}1} = q_2(2a_{12} + 3a_{112} + 4a_{1112}) \tag{22a}$$

$$A_{1\text{-}2} = q_1(2a_{12} + 3a_{122} + 4a_{1222}) \tag{22b}$$

$$A_{3\text{-}1} = q_3(2a_{13} + 3a_{113} + 4a_{1113}) \tag{22c}$$

$$A_{1\text{-}3} = q_1(2a_{13} + 3a_{133} + 4a_{1333}) \tag{22d}$$

$$A_{3\text{-}2} = q_3(2a_{23} + 3a_{223} + 4a_{2223}) \tag{22e}$$

$$A_{2\text{-}3} = q_2(2a_{23} + 3a_{233} + 4a_{2333}) \tag{22f}$$

$$C_1 = q_1[(3a_{112} + 3a_{133} + 3a_{223} - 6a_{123}) + 4a_{1112} + 6a_{1122} - 4a_{1222} + 6a_{1133} + 4a_{2223} - 12a_{1123}] \tag{22g}$$

$$C_2 = q_2[(3a_{112} + 3a_{133} + 3a_{223} - 6a_{123}) + 4a_{2223} + 6a_{2233} - 4a_{2333} + 6a_{1122} + 4a_{1333} - 12a_{1223}] \quad (22h)$$

$$C_3 = q_3[(3a_{112} + 3a_{133} + 3a_{223} - 6a_{123}) + 4a_{1333} + 6a_{1133} - 4a_{1113} + 6a_{2233} + 4a_{1112} - 12a_{1233}] \quad (22i)$$

$$D_{12} = q_1[4a_{1112} + 4a_{1222} - 6a_{1122}] \quad (22j)$$

$$D_{13} = q_3[4a_{1333} + 4a_{1113} - 6a_{1133}] \quad (22k)$$

$$D_{23} = q_2[4a_{2223} + 4a_{2333} - 6a_{2233}] \quad (22l)$$

If we introduce equations 22a-22l into equation 21 and differentiate the total excess free energy with respect to $n_2$, equation 23 is obtained.

$$\left[\frac{\partial n_T \frac{gE}{RT}}{\partial n_2}\right]_{T,P,n_1,n_3} = \ln \gamma_{2,m} = z_3^2\left[A_{2-3} + 2z_2(A_{3-2}\frac{q_2}{q_3} - A_{2-3} - D_{23}) + 3z_2^2 D_{23}\right]$$
$$+ z_1^2\left[A_{2-1} + 2z_2(A_{1-2}\frac{q_2}{q_1} - A_{2-1} - D_{12}\frac{q_2}{q_1}) + 3z_2^2 D_{12}\frac{q_2}{q_1}\right]$$
$$+ z_1 z_3\left[A_{3-2}\frac{q_2}{q_3} + A_{2-1} - A_{1-3}\frac{q_2}{q_1} + 2z_2(A_{1-2}\frac{q_2}{q_1} - A_{2-1})\right.$$
$$+ 2z_1(A_{1-3}\frac{q_2}{q_1} - A_{3-1}\frac{q_2}{q_3}) - 3z_1 z_3 D_{13}\frac{q_2}{q_3} - C_2 z_2(2-3z_2)$$
$$\left.-C_3\frac{q_2}{q_3}z_3(1-3z_2) - C_1\frac{q_2}{q_1}z_1(1-3z_2)\right] \quad (23)$$

where $n_T$ is the total number of moles.

Since, in our convention, subscripts 1, 2 and 3 represent one solvent, the solute and the other solvent respectively in the mixture, m, $\gamma_{2,m}$ is the activity coefficient of a solute in a mixture of two solvents in which the solute is dissolved. If desired, the activity coefficients of each of the solvents may be obtained by appropriately interchanging the subscripts (7) but they are not needed in this analysis.

For the purpose of our analysis equation 23 may be simplified by making the following approximations.

$$^{3}a_{122} \approx {}^{3}a_{112},\ {}^{4}a_{1222} \approx {}^{4}a_{1112} \tag{24a}$$

$$^{3}a_{233} \approx {}^{3}a_{223},\ {}^{4}a_{2333} \approx {}^{4}a_{2223} \tag{24b}$$

With these approximations,

$$\frac{A_{1\text{-}2}}{A_{2\text{-}1}} = \frac{q_1}{q_2} \quad \text{and} \quad \frac{A_{2\text{-}3}}{A_{3\text{-}2}} = \frac{q_2}{q_3} \tag{25}$$

Equations 24a and 24b imply that we are neglecting 3- (or more) body interactions between the solute and each of the solvents. This approximation seems reasonable in view of the fact that we are dealing in most cases with low concentrations of solute. If we apply the same approximation to solvent-solvent interactions, equation 23 reduces to the van Laar equations which have been used to fit activity coefficient data with some success.

Substituting equation 25 into equation 23 and letting $x_2$ (and hence $z_2$) approach zero we obtain

$$\lim_{x_2 \to 0} \ln \gamma_{2,m} = A_{2-3}\hat{z}_3 + A_{2-1}\hat{z}_1 + A_{1-3}\hat{z}_1\hat{z}_3(2\hat{z}_1-1)\frac{q_2}{q_1}$$
$$- A_{3-1}2\hat{z}_1^2\hat{z}_3\frac{q_2}{q_3} - D_{13}3\hat{z}_1^2\hat{z}_3^2\frac{q_2}{q_3} - C_3\hat{z}_1\hat{z}_3^2\frac{q_2}{q_3} - C_1\hat{z}_1^2\hat{z}_3\frac{q_2}{q_1} \qquad (26)$$

where $A_{2-3}$ is the constant arising from the interaction of the solute with pure solvent 3 and $A_{2-1}$ is the corresponding constant for the solute and pure solvent 1.

Comparison of equations 8a and 8b with the first two terms in equation 26 shows that

$$\lim_{x_2 \to 0} \ln \gamma_{2,1} = \ln \frac{H_{2,1}}{f_2^o} = A_{2-1} \qquad (27a)$$

and

$$\lim_{x_2 \to 0} \ln \gamma_{2,3} = \ln \frac{H_{2,3}}{f_2^o} = A_{2-3} \qquad (27b)$$

Substituting equations 8c, 27a and 27b into equation 26 we obtain

$$\ln H_{2,m} = \hat{z}_1 \ln H_{2,1} + \hat{z}_3 \ln H_{2,3} + A_{1-3}\frac{q_2}{q_1}\hat{z}_1\hat{z}_3(2\hat{z}_1-1)$$
$$-A_{3-1}\frac{q_2}{q_3}2\hat{z}_1^2\hat{z}_3 - D_{13}\frac{q_2}{q_3}3\hat{z}_1^2\hat{z}_3^2 - C_3\frac{q_2}{q_3}\hat{z}_1\hat{z}_3^2 - C_1\frac{q_2}{q_1}\hat{z}_1^2\hat{z}_3 \qquad (28)$$

Note that $f_2^o$ does not appear in equation 28. It drops out since $\hat{z}_1$ +

$\hat{z}_3 = 1$. If we substitute equation 28 into equation 15, we obtain the final equation

$$\ln x^s_{2,m} = \hat{z}_1 \ln x^s_{2,1} + \hat{z}_3 \ln x^s_{2,3} - A_{1-3}\,\hat{z}_1\hat{z}_3(2\hat{z}_1-1)\,\frac{q_2}{q_1}$$
$$+ A_{3-1}\,2\hat{z}_1{}^2\hat{z}_3\,\frac{q_2}{q_3} + D_{13}\,3\hat{z}_1{}^2\hat{z}_3{}^2\,\frac{q_2}{q_3} + C_3\hat{z}_1\hat{z}_3{}^2\,\frac{q_2}{q_3} + C_1\hat{z}_1{}^2\hat{z}_3\,\frac{q_2}{q_1} \qquad (29)$$

The above equation will be referred to as the reduced 4-suffix solubility equation since it was derived from the 4-suffix excess free energy expression. Other solubility equations to be derived later will be referred to in a similar manner. Equation 29 expresses the mole fraction solubility $x^s_{2,m}$ of the solute in the mixed solvent in terms of (a) the pure solvent solubilities given by the first two terms (b) contributions from solvent-solvent interactions given by the next three terms and (c) contributions from the interaction between the solute and the solvent mixture described by the last two terms. The data needed for the estimation of the solubility in equation 29 are

(i) the pure solvent solubilities $x^s_{2,1}$ and $x^s_{2,3}$,

(ii) the binary solvent data (usually vapor pressure as a function of composition) from which solvent-solvent interaction constants $A_{1-3}$, $A_{3-1}$ and $D_{13}$ may be obtained,

(iii) the molar volumes of the pure compounds and,

(iv) two ternary experimental points (obtained from the solubility of the solute in the solvent mixture at two different compositions) from which $C_1$ and $C_3$ are calculated. It

is important to note that the solvent-solvent interaction constants, once obtained at a particular temperature are fixed for the solvent system at that temperature.

Corresponding 2- and 3-suffix equations may also be written for the system described by equation 23. The 3-suffix equation is obtained by setting the D's equal to zero or in other words by neglecting four-body interactions. If this is done, then

$$C_2 = C_1 \frac{q_2}{q_1} \text{ and } C_3 = C_1 \frac{q_3}{q_1} \tag{30}$$

and equation 23 becomes

$$\begin{aligned} \ln \gamma_{2,m} = {} & z_3^2\left[A_{2-3} + 2z_2\left(A_{3-2}\frac{q_2}{q_3} - A_{2-3}\right)\right] + z_1^2\left[A_{2-1} + 2z_2\left(A_{1-2}\frac{q_2}{q_1} - A_{2-1}\right)\right] \\ & + z_1 z_3\left[A_{3-2}\frac{q_2}{q_3} + A_{2-1} - A_{1-3}\frac{q_2}{q_1} + 2z_2\left(A_{1-2}\frac{q_2}{q_1} - A_{2-1}\right)\right. \\ & \left. + 2z_1\left(A_{1-3}\frac{q_2}{q_1} - A_{3-1}\frac{q_2}{q_3}\right) - C_2(1-2z_2)\right] \end{aligned} \tag{31}$$

where $C_2 = q_2[3a_{112} + 3a_{133} + 3a_{223} - 6a_{123}]$ and the A's are as defined in equations 22a-22f without four-body interaction terms. Following the same treatment given in equations 23 to 29 we arrive at the reduced 3-suffix solubility equation.

$$\begin{aligned} \ln x^s_{2,m} = {} & \hat{z}_1 \ln x^s_{2,1} + \hat{z}_3 \ln x^s_{2,3} - A_{1-3}\,\hat{z}_1\hat{z}_3(2\hat{z}_1 - 1)\frac{q_2}{q_1} \\ & + A_{3-1}\,2\hat{z}_1^2\hat{z}_3\,\frac{q_2}{q_3} + C_2\hat{z}_1\hat{z}_3 \end{aligned} \tag{32}$$

Equation 32 shows that only one constant, $C_2$, needs to be obtained from ternary data and theoretically, only one point in the ternary system is needed.

The 2-suffix equation is obtained by neglecting 3- and 4-body interactions. Then equation 23 becomes

$$\ln \gamma_{2,m} = z_3^2 A_{2-3} + z_1^2 A_{2-1} + z_1 z_3 \left( A_{2-3} + A_{2-1} - A_{1-3} \frac{A_{2-1}}{A_{1-2}} \right) \quad (33)$$

where

$$A_{1-2} = 2a_{12} q_1, \; A_{2-1} = 2a_{12} q_2 \quad (34a)$$

$$A_{1-3} = 2a_{13} q_1, \; A_{3-1} = 2a_{13} q_3 \quad (34b)$$

$$A_{2-3} = 2a_{23} q_2, \; A_{3-2} = 2a_{23} q_3 \quad (34c)$$

Again, following the same treatment given in equations 23 to 29 (excepting that it is not necessary to make the van Laar-type approximation mentioned earlier because it is already implied in equation 34), equation 33 leads to the reduced 2-suffix solubility equation

$$\ln x^s_{2,m} = \hat{z}_1 \ln x^s_{2,1} + \hat{z}_3 \ln x^s_{2,3} + A_{1-3} \hat{z}_1 \hat{z}_3 \frac{q_2}{q_1} \quad (35)$$

Examination of equation 35 shows that unlike the reduced 3- and 4-suffix solubility equations, it contains no constant to be estimated from ternary data. This, combined with the fact that the reduced 3-suffix solubility equation with its fewer parameters (compared to the corres-

ponding 4-suffix equation) satisfactorily describes the data used (6) has led us to choose equation 32 as our working equation for a 3-component system. The estimation of the constants in equation 32 and its usefulness in describing solubility in ethanol-water systems are discussed in the following paper.

4-component systems

For a 4-component system, the 3-suffix excess free energy expression is given by

$$\frac{g^E}{RT\left(x_1 + x_2\frac{q_2}{q_1} + x_3\frac{q_3}{q_1} + x_4\frac{q_4}{q_1}\right)} = q_1\Big[2a_{12}z_1z_2 + 2a_{13}z_1z_3 + 2a_{14}z_1z_4 + 2a_{23}z_2z_3 + 2a_{34}z_3z_4 + 2a_{24}z_2z_4 + 3a_{112}z_1^2z_2 + 3a_{122}z_1z_2^2 + 3a_{113}z_1^2z_3 + 3a_{133}z_1z_3^2 + 3a_{114}z_1^2z_4 + 3a_{144}z_1z_4^2 + 3a_{223}z_2^2z_3 + 3a_{233}z_2z_3^2 + 3a_{224}z_2^2z_4 + 3a_{244}z_2z_4^2 + 3a_{334}z_3^2z_4 + 3a_{344}z_3z_4^2 + 6a_{123}z_1z_2z_3 + 6a_{124}z_1z_2z_4 + 6a_{234}z_2z_3z_4 + 6a_{134}z_1z_3z_4 + 24a_{1234}z_1z_2z_3z_4\Big] \quad (36)$$

With the following definitions:

$$A_{1-4} = q_1(2a_{14} + 3a_{144}) \quad (37a)$$

$$A_{4-1} = q_4(2a_{14} + 3a_{114}) \quad (37b)$$

$$A_{3-4} = q_3(2a_{34} + 3a_{344}) \quad (37c)$$

$$A_{4-3} = q_4(2a_{34} + 3a_{334}) \tag{37d}$$

$$A_{2-4} = q_2(2a_{24} + 3a_{244}) \tag{37e}$$

$$A_{4-2} = q_4(2a_{24} + 3a_{224}) \tag{37f}$$

$$G_{123} = 3a_{112} + 3a_{133} + 3a_{223} - 6a_{123} \tag{37g}$$

$$G_{234} = 3a_{223} + 3a_{334} + 3a_{244} - 6a_{234} \tag{37h}$$

$$G_{134} = 3a_{144} + 3a_{113} + 3a_{334} - 6a_{134} \tag{37i}$$

$$G_{124} = 3a_{112} + 3a_{224} + 3a_{144} - 6a_{124} \tag{37j}$$

$$K = 24a_{1234} \tag{37k}$$

equation 36 becomes

$$\frac{g^E}{RT\left(x_1 + x_2\frac{q_2}{q_1} + x_3\frac{q_3}{q_1} + x_4\frac{q_4}{a_1}\right)} = z_1z_2(A_{2-1}\, z_1\frac{q_1}{q_2} + A_{1-2}\, z_2)$$
$$+ z_1z_3(A_{3-1}\, z_1\frac{q_1}{q_3} + A_{1-3}\, z_3) + z_1z_4(A_{4-1}\, z_1\frac{q_1}{q_4} + A_{1-4}\, z_4)$$
$$+ z_2z_3\left(A_{3-2}\, z_2\frac{q_1}{q_3} + A_{2-3}\, z_3\frac{q_1}{q_2}\right) + z_2z_4\left(A_{4-2}\frac{q_1}{q_4} + A_{2-4}\, z_4\frac{q_1}{q_2}\right)$$
$$+ z_3z_4\left(A_{4-3}\, z_3\frac{q_1}{q_4} + A_{3-4}\, z_4\frac{q_1}{q_3}\right) + z_1z_2z_3(A_{2-1}\frac{q_1}{q_2} + A_{3-2}\frac{q_1}{q_3}$$
$$+ A_{1-3} - G_{123}\, q_1) + z_1z_2z_4(A_{2-1}\frac{q_1}{q_2} + A_{4-2}\frac{q_1}{q_4} + A_{1-4}$$
$$- G_{124}\, q_1) + z_2z_3z_4(A_{3-2}\frac{q_1}{q_3} + A_{4-3}\frac{q_1}{q_4} + A_{2-4}\frac{q_1}{q_2} - G_{234}\, q_1)$$
$$+ z_1z_3z_4(A_{1-4} + A_{3-1}\frac{q_1}{q_3} + A_{4-3}\frac{q_1}{q_4} - G_{134}\, q_1) + Kz_1z_2z_3z_4\, q_1 \tag{38}$$

where $A_{1-2}$, $A_{2-1}$, $A_{1-3}$, $A_{3-1}$, $A_{2-3}$ and $A_{3-2}$ are as defined eariler in equations 22a-22f but without the 4-body interaction terms. If we

consider this system as a solute (denoted by subscript 2) in a mixture of three solvents (denoted by subscripts 1, 3, 4) then an approach similar to that given in equations 23 to 29 yields the reduced 3-suffix solubility equation for a 4-component system:

$$\ln x^s_{2,m} = \hat{z}_1 \ln x^s_{2,1} + \hat{z}_3 \ln x^s_{2,3} + \hat{z}_4 \ln x^s_{2,4} - A_{1-3}\, \hat{z}_1\hat{z}_3(2\hat{z}_1+2\hat{z}_4-1)\, \frac{q_2}{q_1}$$
$$+ A_{3-1}\, 2\hat{z}_1\hat{z}_3(\hat{z}_1+\hat{z}_4)\, \frac{q_2}{q_3} - A_{1-4}\, \hat{z}_1\hat{z}_4(2\hat{z}_1-1)\, \frac{q_2}{q_1} + A_{4-1}\, 2\hat{z}_1{}^2\hat{z}_4\, \frac{q_2}{q_4}$$
$$- A_{4-3}\, \hat{z}_3\hat{z}_4(2\hat{z}_4-1)\, \frac{q_2}{q_4} + A_{3-4}\, 2\hat{z}_3\hat{z}_4{}^2\, \frac{q_2}{q_3} + G_{123}\, q_2\, \hat{z}_1\hat{z}_3$$
$$+ G_{124}\, q_2\, \hat{z}_1\hat{z}_4 + G_{234}\, q_2\, \hat{z}_3\hat{z}_4 - G_{134}\, q_2\, \hat{z}_1\hat{z}_3\hat{z}_4 - K\, q_2\, \hat{z}_1\hat{z}_3\hat{z}_4 \quad (39)$$

Equation 39 shows that only one constant, K, need be obtained from a quaternary system. The A's and $G_{134}$ are obtained from solvent vapor pressure-composition data. If we let $\hat{z}_4$ equal zero, equation 39 reduces to equation 32 with $C_2 = G_{123}\, q_2$. Thus $G_{123}$, $G_{124}$ and $G_{234}$ are estimated from solubility data at points where solvent 4, solvent 3 and solvent 1 respectively are absent. They are therefore not new parameters in the sense that K is. It is important to note that even with the more complex 4-component system, we need to estimate only one quaternary constant to describe the system. It is clear that if equation 39 is used for predictive purposes (for systems in which it is valid) the experimental labor saved is substantial. The same consideration holds to a lesser degree for equation 32.

Discussion

The reduced 3-suffix solubility equation for a solute in a mixture of two solvents (equation 32) describes solubility in terms of pure-solvent solubilities, contributions from solvent-solvent interactions and from solute-binary solvent interactions. The advantages of this approach over present ones are its generality and flexibility. Once the solvent-solvent interaction constants are obtained they are fixed for that solvent system (provided one operates at or close to the temperature at which they were determined, usually 25°C). Thus the only constant which needs to be determined (we assume that the solubility of the solute in each solvent is known) in order to completely describe the solubility is the ternary constant $C_2$. For a solute in a mixture of three solvents (4-component system), only one quaternary constant (K in equation 39) is again needed to describe the solubility. The ternary constants $G_{124}$, $G_{234}$ and $G_{123}$ are obtained in practice in the absence of solvents 3, 1 and 4 respectively.

The essential aspects of this treatment are presented in Table I. In summary, it consists of

(i) starting with the described n-suffix excess free energy model for the number of components involved,

(ii) making simplifying assumptions concerning the solute-solvent interactions while,

(iii) keeping the solvent-solvent interaction terms as detailed as necessary.

Table I: Summary of Equations (symbols defined in text)

| Excess Free Energy Models | Starting Equation: $\frac{g^E}{RT}$ | $\ln \gamma_{2,m} = \left[\frac{\partial n_T \frac{g^E}{RT}}{\partial n_2}\right]_{T,P,n_1,n_3}$ | Simplifications | Final Equation |
|---|---|---|---|---|
| 4-suffix | $(x_1q_1+x_2q_2+x_3q_3)[2a_{12}z_1z_2$<br>$+2a_{13}z_1z_3+2a_{23}z_2z_3$<br>$+3a_{112}z_1^2z_2+3a_{122}z_1z_2^2$<br>$+3a_{113}z_1^2z_3+3a_{133}z_1z_3^2$<br>$+3a_{223}z_2^2z_3+3a_{233}z_2z_3^2$<br>$+6a_{123}z_1z_2z_3+4a_{1112}z_1^3z_2$<br>$+6a_{1122}z_1^2z_2^2+4a_{1222}z_1z_2^3$<br>$+4a_{1113}z_1^3z_3+6a_{1133}z_1^2z_3^2$<br>$+4a_{1333}z_1z_3^3+4a_{2223}z_2^3z_3$<br>$+6a_{2233}z_2^2z_3^2+4a_{2333}z_2z_3^3$<br>$+12a_{1123}z_1^2z_2z_3+12a_{1223}z_1z_2^2z_3$<br>$+12a_{1233}z_1z_2z_3^2$ | $z_3^2[A_{2-3}+2z_2(A_{3-2}\ q_2/q_3-A_{2-3}$<br>$-D_{23})+3z_2^2D_{23}]+z_1^2[A_{2-1}+2z_2$<br>$(A_{1-2}\ q_2/q_1-A_{2-1}-D_{12}\ q_2/q_1)$<br>$+3z_2^2D_{12}\ q_2/q_1]+z_1z_3[A_{3-2}$<br>$q_2/q_3+A_{2-1}-A_{1-3}\ q_2/q_1+2z_2$<br>$(A_{1-2}\ q_2/q_1-A_{2-1})+2z_1(A_{1-3}$<br>$q_2/q_1-A_{3-1}\ q_2/q_3)-3z_1z_3D_{13}$<br>$q_2/q_3-C_2z_2(2-3z_2)-C_3\ q_2/q_3$<br>$z_3(1-3z_2)-C_1\ q_2/q_1z_1(1-3z_2)]$ | 1. $3a_{112}=3a_{122}$<br>$3a_{233}=3a_{223}$<br>$4a_{1112}=4a_{1222}$<br>$4a_{2333}=4a_{2223}$<br>Then $\frac{A_{1-2}}{A_{2-1}}=\frac{q_1}{q_2}$<br>and $\frac{A_{2-3}}{A_{3-2}}=\frac{q_2}{q_3}$<br>2. Let $x_2\to 0$<br>3. limit $\ln\gamma_{2,1}=\ln\frac{H_{2,1}}{f_2^0}$<br>$x_2\to 0$<br>$=A_{2-1}$<br>and<br>limit $\ln\gamma_{2,3}=\ln\frac{H_{2,3}}{f_2^0}$<br>$x_2\to 0$<br>$=A_{2-3}$ | $\ln x^S_{2,m}=\hat{z}_1\ln x^S_{2,1}$<br>$+\hat{z}_3\ln x^S_{2,3}-A_{1-3}\hat{z}_1\hat{z}_3$<br>$(2\hat{z}_1-1)\ q_2/q_1+$<br>$A_{3-1}2\hat{z}_1^2\hat{z}_3\ q_2/q_3$<br>$+D_{13}3\hat{z}_1^2\hat{z}_1^2\ q_2/q_3$<br>$+C_3\hat{z}_1\hat{z}_3^2\ q_2/q_3$<br>$+C_1\hat{z}_1^2\hat{z}_3\ q_2/q_1$ |

| | | | | |
|---|---|---|---|---|
| 3-suffix | Above equation with<br>$a_{1112} = a_{1122} = a_{1222} =$<br>$a_{1113} = a_{1133} = a_{1333} =$<br>$a_{2223} = a_{2233} = a_{2333} =$<br>$a_{1123} = a_{1223} = a_{1233} = 0$ | $z_3[A_{2-3}+2z_2(A_{3-2}\ q_2/q_3-A_{2-3})]$<br>$+z_1^2[A_{2-1}+2z_2(A_{1-2}\ q_2/q_1-A_{2-1})]$<br>$+z_1z_3[A_{3-2}\ q_2/q_3+A_{2-1}-A_{1-3}\ q_2/q_1$<br>$+2z_2(A_{1-2}\ q_2/q_1-A_{2-1})+2z_1(A_{1-3}$<br>$q_2/q_1\ -A_{3-1}\ q_2/q_3)-C_2(1-2z_2)]$ | 1. $3a_{112}=3a_{122}$<br>$3a_{233}=3a_{223}$<br>Then<br>$\frac{A_{1-2}}{A_{2-1}} = \frac{q_1}{q_2}$<br>and<br>$\frac{A_{2-3}}{A_{3-2}} = \frac{q_2}{q_3}$<br>2. Same as in 2 above<br>3. Same as in 3 above | $\ln x^s_{2,m}=\hat{z}_1 \ln x^s_{2,1}$<br>$+\hat{z}_3 \ln x^s_{2,3}-A_{1-3}$<br>$\hat{z}_1\hat{z}_3(2\hat{z}_1-1)\ q_2/q_1$<br>$+A_{3-1}2\hat{z}_1^2\hat{z}_3\ q_2/q_3$<br>$+C_2\hat{z}_1\hat{z}_3$ |
| 2-suffix | Top equation with<br>$a_{112}=a_{122}=a_{113}=a_{133}=a_{223}$<br>$a_{233}=a_{123}$ ... etc. = 0 | $z_3^2A_{2-3}+z_1^2A_{2-1}+z_1z_3(A_{2-3}$<br>$+A_{2-1}-A_{1-3}\frac{A_{2-1}}{A_{1-2}})$<br>Note that "A's" here are defined differently (see text) | Same as in 2 and 3 above | $\ln x^s_{2,m}=\hat{z}_1 \ln x^s_{2,1}$<br>$+\hat{z}_3 \ln x^s_{2,3}+A_{1-3}\hat{z}_1\hat{z}_3$<br>$q_2/q_1$ |

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# III.

# AN EXCESS FREE ENERGY APPROACH TO THE ESTIMATION OF SOLUBILITY IN MIXED SOLVENT SYSTEMS II. ETHANOL-WATER MIXTURES

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## Abstract

The use of the reduced 3-suffix solubility equation in characterizing solubility in ethanol-water mixtures is discussed. The equation states:

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

$$+ A_{3-1}\, 2\hat{z}_1 \hat{z}_3\, \frac{q_2}{q_3} + C_2 \hat{z}_1 \hat{z}_3$$

where $x^{s}_{2,1}$, $x^{s}_{2,3}$ and $x^{s}_{2,m}$ are the mole fraction solubilities of the solute in ethanol (subscript 1), water (subscript 3) and in the mixture m; $A_{1-3}$ and $A_{3-1}$ are solvent-solvent interaction terms; $C_2$ is a solute-solvent interaction term, and the q's and $\hat{z}$'s 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 constants 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 ten compounds with widely different physical properties and thus appears to combine both ease of use and general utility.

In the previous paper (1), we 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.

For a solute (subscript 2) in a mixture of ethanol (subscript 1) and water (subscript 3) the reduced 4-suffix solubility equation is

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

$$+ A_{3-1}\, 2\hat{z}_1 {}^{2}\hat{z}_3\, \frac{q_2}{q_3} + D_{13}\, 3\hat{z}_1 {}^{2}\hat{z}_3 {}^{2}\, \frac{q_2}{q_3} + C_3\, \hat{z}_1 \hat{z}_3 {}^{2}\, \frac{q_2}{q_3}$$

$$+ C_1\, \hat{z}_1 {}^{2}\hat{z}_3\, \frac{q_2}{q_1} \qquad (1)$$

The corresponding 3-suffix and 2-suffix equations are given by equations 2 and 3 respectively.

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

$$+ A_{3-1}\, 2\hat{z}_1 {}^{2}\hat{z}_3\, \frac{q_2}{q_3} + C_2\, \hat{z}_1 \hat{z}_3 \qquad (2)$$

$$\ln x^{s}_{2,m} = \hat{z}_1 \ln x^{s}_{2,1} + \hat{z}_3 \ln x^{s}_{2,3} + A_{1-3}\, \hat{z}_1 \hat{z}_3\, \frac{q_2}{q_1} \qquad (3)$$

Note that the numerical values of $A_{1-3}$ and $A_{3-1}$ differ in equations 1, 2 and 3 because they are defined differently in the three equations (see reference 1). We also note here that equation 2 may be rearranged to give

$$\ln\left(\frac{x^s_{2,m}}{x^2_{2,3}}\right) = \hat{z}_1 \ln\left(\frac{x^s_{2,1}}{x^s_{2,3}}\right) - A_{1-3}\hat{z}_1\hat{z}_3(2\hat{z}_1 - 1)\frac{q_2}{q_1} + A_{3-1}\,2\hat{z}_1^2\hat{z}_3\frac{q_2}{q_3} + C_2\hat{z}_1\hat{z}_3 \qquad (4)$$

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

## Evaluation of interaction constants

The solvent-solvent interaction constants (the A's) 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 3-suffix equation for a binary solvent mixture. The molar excess free energy is given by (2)

$$\frac{g^E}{RT} = \frac{A_{1-3}}{q_1}\left[z_1 z_3^2(x_1q_1 + x_3q_3)\right] + \frac{A_{3-1}}{q_3}\left[z_1^2 z_3(x_1q_1 + x_3q_3)\right] \qquad (5)$$

where

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

But

$$\frac{g^E}{RT} = \sum_{\text{solvents } i} x_1 \ln\gamma_i = x_1 \ln\gamma_1 + x_3 \ln\gamma_3 \tag{7}$$

and

$$\gamma_1 = \frac{p_1}{p_1^{\,o}},\ \gamma_3 = \frac{p_3}{p_3^{\,o}} \tag{8}$$

where $p_1$ = the partial pressure of component 1 in the mixture of 1 and 3 and $p_1^{\,o}$ = the vapor pressure of pure component 1; $p_3$ and $p_3^{\,o}$ are defined similarly.

Combining equations 5 and 7 we find

$$x_1 \ln\gamma_1 + x_3 \ln\gamma_3 = A_{1-3}\left[\frac{z_1 z_3^{\,2}(x_1 q_1 + x_3 q_3)}{q_1}\right] + A_{3-1}\left[\frac{z_1^{\,2} z_3 (x_1 q_1 + x_3 q_3)}{q_3}\right] \tag{9}$$

Equation 9 may be represented as

$$y = \theta_1 x_1 + \theta_2 x_2 \tag{10}$$

where $y = x_1 \ln\gamma_1 + x_3 \ln\gamma_3$, $\theta_1 = A_{1-3}$, $x_1$ = 1st term in parenthesis, $\theta_2 = A_{3-1}$, $x_2$ = 2nd term in parenthesis.

As shown by equation 10, $y$ is a linear function of the parameters $\theta_1$ and $\theta_2$ 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 reference 9 as described below.

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

$$P_T = p_1 + p_3 = x_1\gamma_1 p_1^{\,o} + x_3\gamma_3 p_3^{\,o} \tag{11}$$

If we differentiate equation 5 with respect to $n_1$ we obtain the expression for $\ln\gamma_1$ in the solvent mixture.

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

Similarly,

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

Substituting equations 12 and 13 into equation 11 we obtain

$$P_T = p_1^{\,o}x_1 e^{\left[A_{1\text{-}3}x_1 + A_{3\text{-}1}x_2\right]} + p_3^{\,o}x_3 e^{\left[A_{1\text{-}3}x_3 + A_{3\text{-}1}x_4\right]} \tag{14}$$

where

$$x_1 = z_3^2(1 - 2z_1),\ x_2 = 2z_1z_3^2\frac{q_1}{q_3}$$
$$x_3 = 2z_1^2z_3\frac{q_3}{q_1},\ x_4 = z_1^2(1 - 2z_3)$$

The parameters may be obtained from equation 14 by a total pressure fit using non-linear regression. This method is more complicated but it gives similar results to the excess free energy fit (see 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 a much lower tendency to give non-unique constants, rather than the non-linear method whose results sometimes depend on the choice of initial estimates.

Choice of working equation

Figure 1 shows calculated solubility profiles of barbital in ethanol-water mixtures using equations 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 to the experimental data (from reference 4) it is clearly seen that the reduced 4-suffix solubility equation does worst in predicting solubility. The 3-suffix equation does better but not as well as the 2-suffix equation. A comparison of equations 2 and 3 however shows that while the reduced 3-suffix solubility equation has one more constant that is related to, and can be evaluated from, ternary solute-solvent data, the 2-suffix equation has none and this severely limits its use. The 4-

Fig. 1: Solubility profiles of barbital calculated from equations 1-3 without any solute-solvent interaction term (i.e., with $C_1 = C_2 = C_3 = 0$).

1: Reduced 4-suffix solubility equation (equation 1)

2: Reduced 3-suffix solubility equation (equation 2)

3: Reduced 2-suffix solubility equation (equation 3)

0: Experimental points

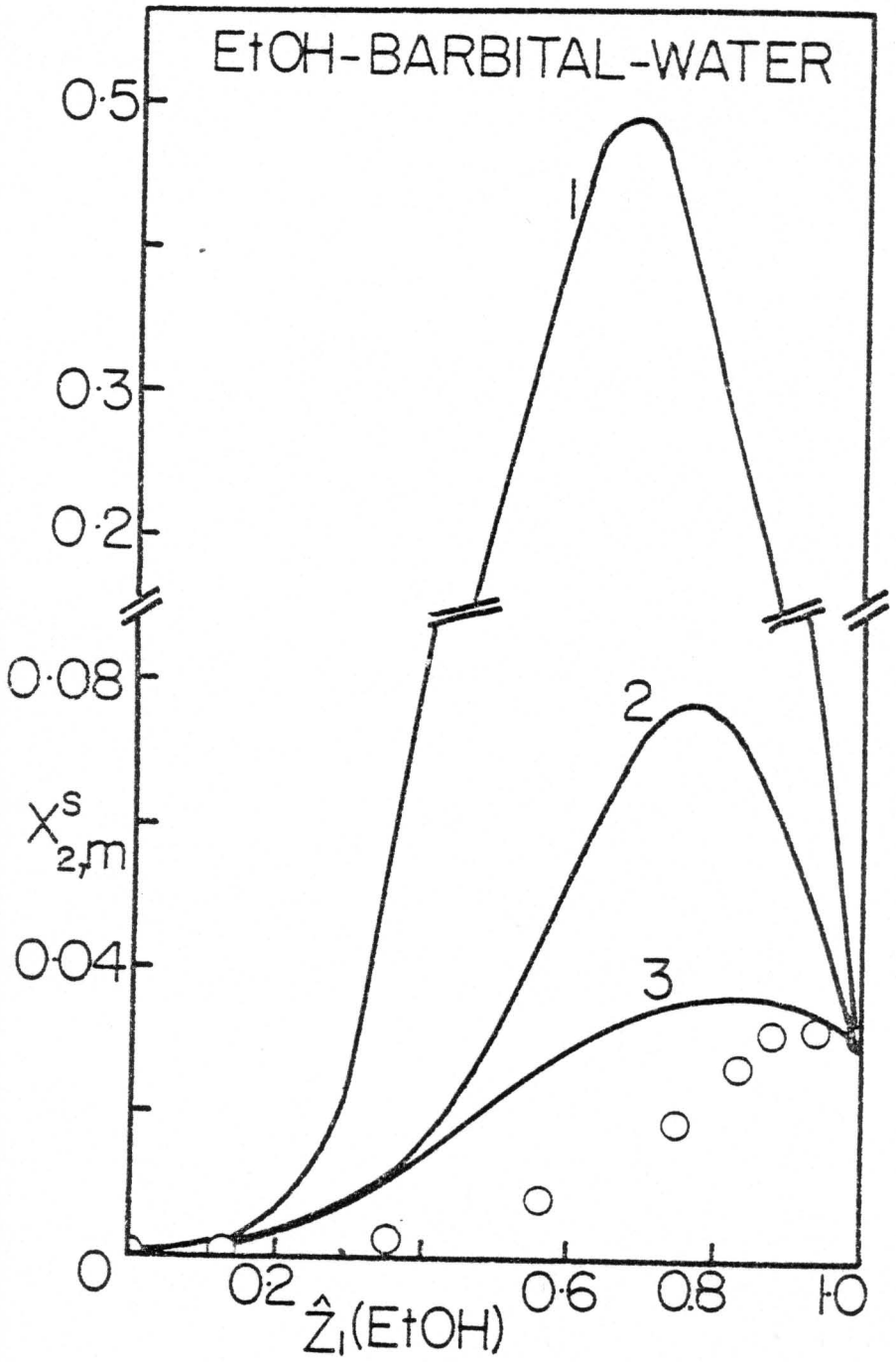

EtOH-BARBITAL-WATER
0·5
0·3
0·2
0·08
0·04
0
$X^s_{2,m}$
1
2
3
0·2
0·6
0·8
1·0
$\hat{Z}_1$(EtOH)

Table I: Solvent-solvent interaction terms

| Excess Free Energy Model | Constants (from linear regression) | Constants from total pressure (non-linear) fit |
|---|---|---|
| 4-suffix | $A_{1-3} = 0.9385$ | |
| | $A_{3-1} = 1.387$ | |
| | $D_{13} = 0.6106$ | |
| 3-suffix | $A_{1-3} = 1.216$ | 1.138 |
| | $A_{3-1} = 0.9093$ | 0.9047 |
| 2-suffix | $A_{1-3} = 2.215$ | |

suffix equation has two constants which may be estimated from ternary solute-solvent data. For the ethanol-water system shown in Figures 3-12, the 3-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 4-suffix equation has led us to choose the 3-suffix equation (equation 2) in characterizing 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 are interested in whether our reduced 3-suffix solubility equation for a three-component system predicts a maximum and/or minimum and under what conditions. We use the ethanol-water system as a specific example. The results will therefore be applicable only to a solute in ethanol-water.

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

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

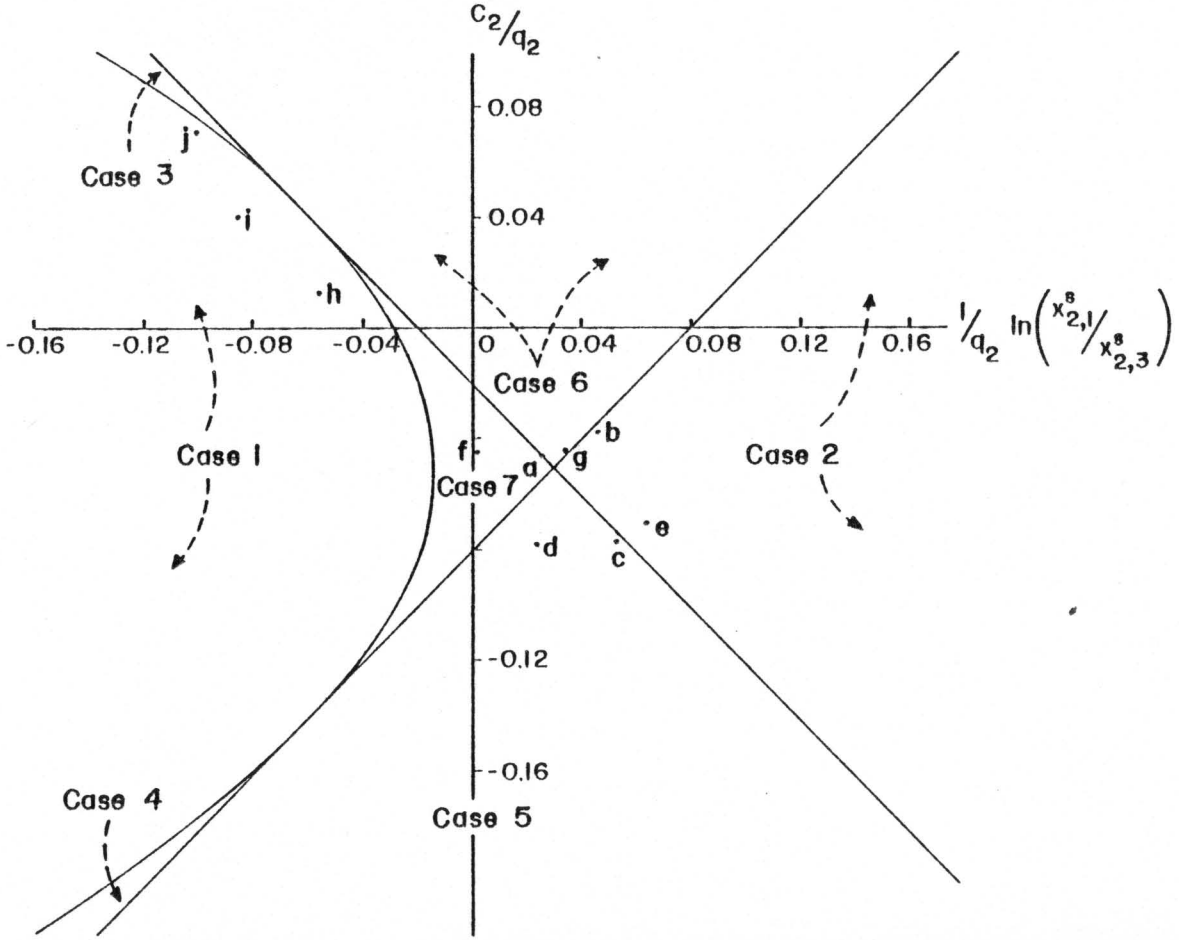
$$- \left(0.0207 + \frac{1}{q_2}\ln\left(\frac{x^s_{2,1}}{x^s_{2,3}}\right) + \frac{C_2}{q_2}\right) = 0 \qquad (15)$$

where the values $A_{1-3} = 1.216$ and $A_{3-1} = 0.9093$ obtained from ethanol-water vapor liquid equilibrium data (9) have been used and the maximum or minimum $\hat{z}_1$ indicated by $\langle\hat{z}_1\rangle$. Equation 15 can be solved quadratically for $\langle\hat{z}_1\rangle$. Depending on the values of $\frac{C_2}{q_2}$ and $\frac{1}{q_2}\ln\left(\frac{x^s_{2,1}}{x^s_{2,3}}\right)$, 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 do have one extremum each in the 0-1 range but without knowing $C_2$, $q_2$ and $\ln\left(\frac{x^s_{2,1}}{x^s_{2,3}}\right)$ 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 Figure 2 where the $\langle\hat{z}_1\rangle$ surface is projected onto the $\frac{C_2}{q_2}$ versus $\frac{1}{q_2}\ln\left(\frac{x^s_{2,1}}{x^s_{2,3}}\right)$ plane. Theoretically the question of whether a solute exhibits an extremum in ethanol-water mix-

Table II: Possible solutions of equation 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 |

Fig. 2: Graph showing projection of $\langle \hat{z}_1 \rangle$ on to the $\frac{C_2}{q_2}, \frac{1}{q_2} \ln \left( \frac{x^s_{2,1}}{x^s_{2,3}} \right)$ plane. See Tables II and IV for explanation of symbols and text for discussion.


$c_2/q_2$
0.08
0.04
-0.12
-0.16
-0.16
-0.12
-0.08
-0.04
0
0.04
0.08
0.12
0.16
$1/q_2 \ln\left(x^s_{2,1}/x^s_{2,3}\right)$
Case 1
Case 2
Case 3
Case 4
Case 5
Case 6
Case 7
a
b
c
d
e
f
g
h
i
j

tures may be answered by obtaining the above solute-characteristic terms and then locating the area they fall in Figure 2. This will not always be successful since Figure 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

Figures 3-5 show a plot of the left hand side of equation 4 against the volume fraction of ethanol for three compounds. Without any ethanol, the left hand side of equation 4 is zero because $\frac{x_{2,m}^{s}}{x_{2,3}} = 1$; 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 equation 4 remains, all other terms going to zero as indicated in Figures 3-5. 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 Figures 3-5. 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 (see Figure 3). Since $C_2$

Fig. 3: Solubility profile of barbital showing contributions from terms in equation 4.

----- : $\hat{z}_1 \ln \left( \frac{x^s_{2,1}}{x^s_{2,3}} \right)$

—·— : $-A_{1\text{-}3} \hat{z}_1 \hat{z}_3 (2\hat{z}_1 - 1) \frac{q_2}{q_1} + A_{3\text{-}1} 2\hat{z}_1^2 \hat{z}_3 \frac{q_2}{q_3}$

— — : $C_2 \hat{z}_1 \hat{z}_3$

——— : calculated $\ln \left( \frac{x^s_{2,m}}{x^s_{2,3}} \right)$

x : experimental $\ln \left( \frac{x^s_{2,m}}{x^s_{2,3}} \right)$

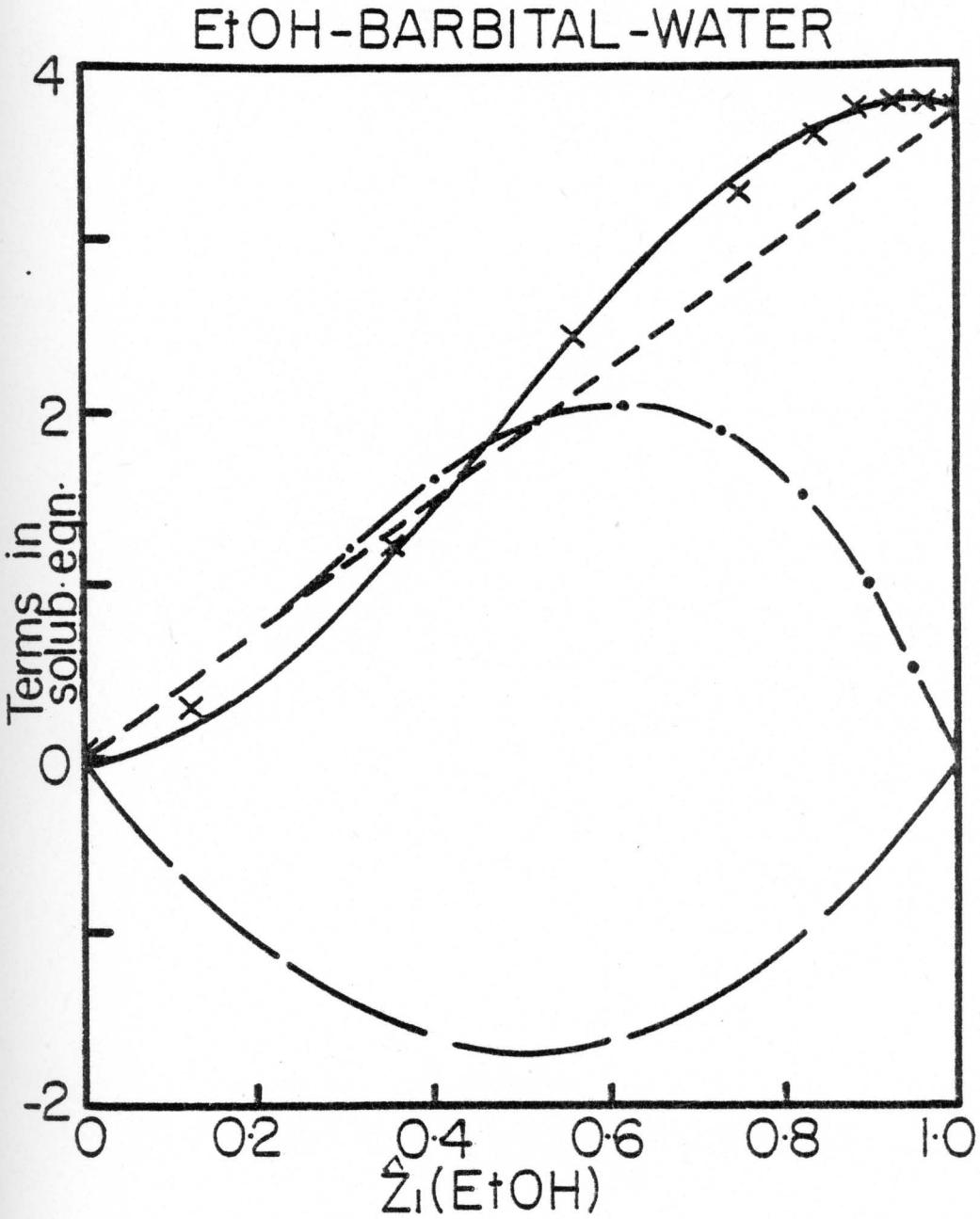

EtOH-BARBITAL-WATER
4
2
0
-2
Terms in solub. eqn.
0
0·2
0·4
0·6
0·8
1·0
$\hat{Z}_1$(EtOH)

Fig. 4: Solubility profile of acetanilide showing contributions from terms in equation 4.

-----: $\hat{z}_1 \ln \left( \frac{x^s_{2,1}}{x^s_{2,3}} \right)$

—·—: $-A_{1-3}\hat{z}_1\hat{z}_3(2\hat{z}_1 - 1)\frac{q_2}{q_1} + A_{3-1}2\hat{z}_1{}^2\hat{z}_3 \frac{q_2}{q_3}$

— —: $C_2\hat{z}_1\hat{z}_3$

———: calculated $\ln \left( \frac{x^s_{2,m}}{x^s_{2,3}} \right)$

x: experimental $\ln \left( \frac{x^s_{2,m}}{x^s_{2,3}} \right)$

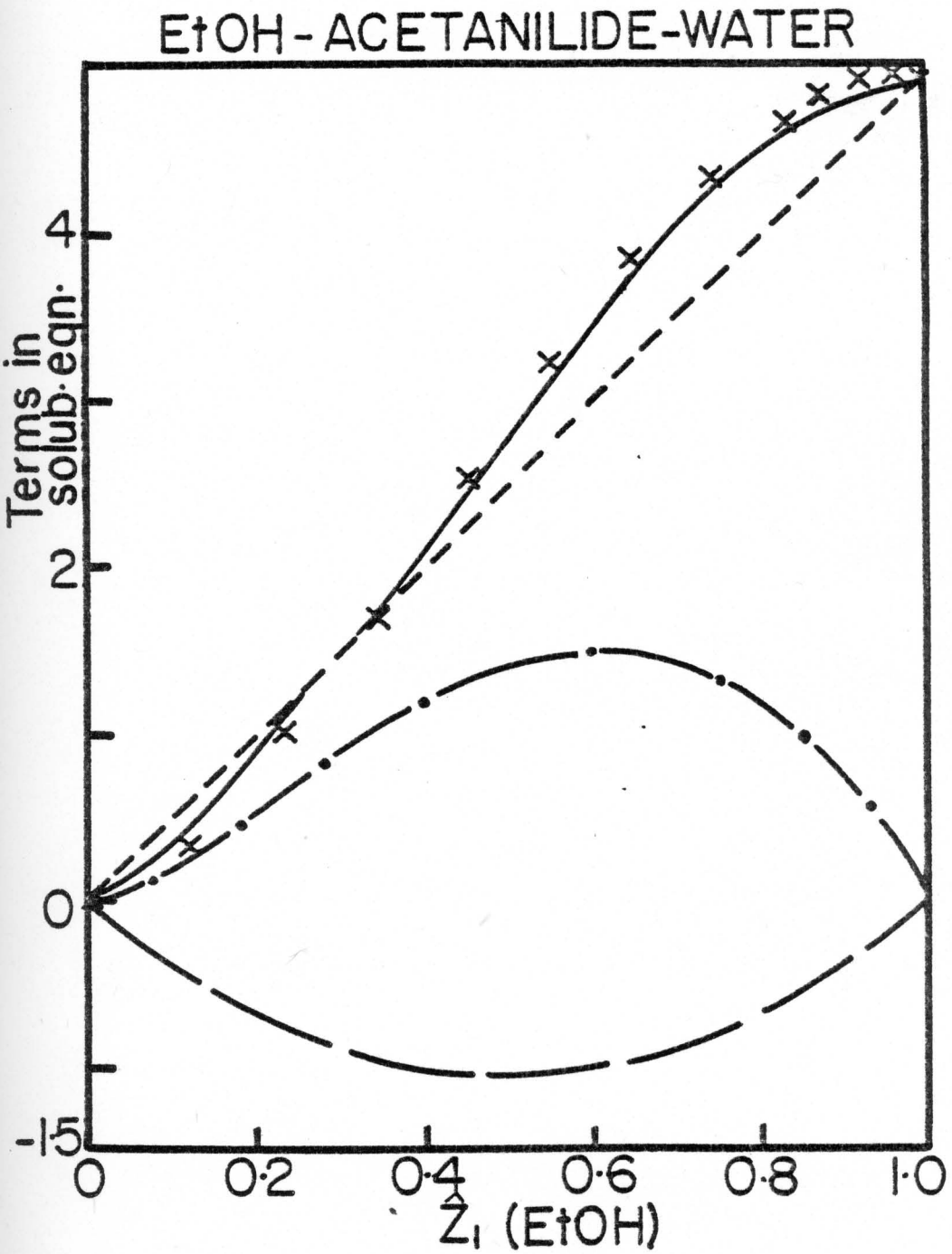

EtOH - ACETANILIDE-WATER
Terms in solub. eqn.
4
2
0
-1·5
0
0·2
0·4
0·6
0·8
1·0
$Z_1$ (EtOH)

Fig. 5: Solubility profile of DL-valine showing contributions from terms in equation 4.

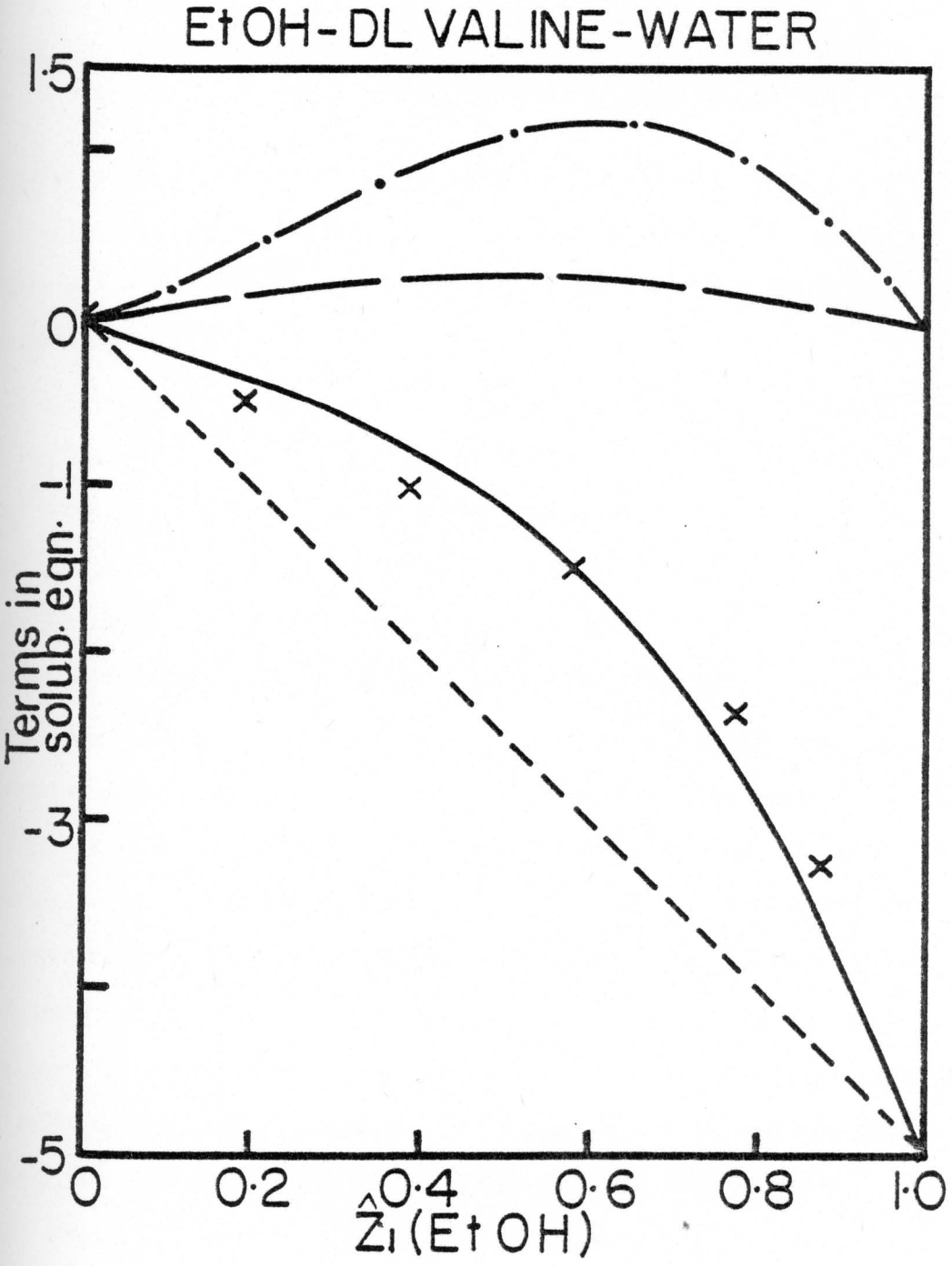
-----: $\hat{z}_1 \ln\left(\frac{x^s_{2,1}}{x^2_{2,3}}\right)$

—·—: $-A_{1-3}\hat{z}_1\hat{z}_3(2\hat{z}_1 - 1)\frac{q_2}{q_1} + A_{3-1}2\hat{z}_1{}^2\hat{z}_3\frac{q_2}{q_3}$

— —: $C_2\hat{z}_1\hat{z}_3$

———: calculated $\ln\left(\frac{x^s_{2,m}}{x^s_{2,3}}\right)$

x: experimental $\ln\left(\frac{x^s_{2,m}}{x^s_{2,3}}\right)$


EtOH-DL VALINE-WATER
1·5
0
-5
0
0·2
0·4
0·6
0·8
1·0
Terms in solub. eqn.
$\hat{Z}_1$ (EtOH)

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 3-suffix solubility equation

Figures 3-12 show the results of using equation 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 Figure 3, 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" solubility at higher ethanol volume fractions. The maximum in the solubility at $\hat{z}_1 = 0.93$ is also due to the non-symmetrical contributions of these two terms and the particular values they assume at this point. Figure 4 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 Figure 5, 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.

Figs. 6-10 and 12 show semi-log plots of solubility profiles for additional compounds. The results for phenobarbital, phenylsalicylate

Table III: Parameters used to estimate solubilities in Figures 3-12[a]

| Compound | $\ln x^{s}_{2,1}$[b] | $\ln x^{s}_{2,3}$[b] | $q_2$[c] | $C_2$ | n | r | s[d] |
|---|---|---|---|---|---|---|---|
| Barbital | - 3.479 | - 7.240 | 151.0 | - 6.76 | 10 | 0.999 | 0.069 |
| Acetanilide | - 2.294 | - 7.233 | 110.9 | - 4.26 | 10 | 1.000 | 0.095 |
| Phenylsalicylate | - 2.266 | -11.28 | 169.8 | -13.3 | 7 | 0.997 | 0.315 |
| Stearic Acid | - 4.237 | -10.75 | 302.4 | -23.8 | 7 | 0.993 | 0.438 |
| O-nitrophenol | - 2.023 | - 8.037 | 93.68 | - 6.67 | 7 | 0.997 | 0.131 |
| Antipyrine | - 1.716 | - 2.096 | 175.1 | - 7.94 | 9 | 0.952 | 0.365 |
| Phenobarbital | - 3.450 | - 9.282 | 172.0 | - 7.63 | 15 | 1.000 | 0.062 |
| DL-valine | - 9.498 | - 4.529 | 89.02 | + 1.15 | 5 | 0.996 | 0.282 |
| Glycine | -10.68 | - 2.871 | 90.66 | + 3.67 | 5 | 0.998 | 0.359 |
| DL-alanine | -10.01 | - 3.433 | 62.57 | + 4.43 | 5 | 0.997 | 0.367 |

(a) The solvent-solvent term is

$$-1.216\ \hat{z}_1\hat{z}_3(2\hat{z}_1 - 1)\frac{q_2}{q_1} + 0.9093\ 2\hat{z}_1^2\hat{z}_3\frac{q_2}{q_3}$$

(b) See Table IV for references for solubility data.

(c) $q_1 = 58.68$ (ref. 11) and $q_3 = 18.07$ (ref. 12) were used as molar volumes of ethanol and water respectively; $q_2$'s were calculated from density data in ref. 12.

(d) s is the standard deviation of the error between $\ln(x^{s}_{2,m})_{\text{observed}}$ and $\ln(x^{s}_{2,m})_{\text{estimated}}$.

and o-nitrophenol in Figures 6-8 are similar to the barbital and acetanilide systems (Figures 3 and 4) previously discussed. Figures 9 and 10 show results for glycine and DL-alanine which are similar to Figure 5 for DL-valine.

Figure 11 shows a plot of the terms in equation 4 for stearic acid to indicate why a minimum is predicted (although the experimental data from reference 5 do not show it). It is seen that the minimum is caused by the large negative value (-3) of the $C_2$ term compared to the value (+1) of the sum of the solvent-solvent terms.

Figure 12 shows the solubility profile of antipyrine. The solubility of antipyrine in water is reported as 620 mg/ml and 425 mg/ml in ethanol (7) which, converted to mole fraction solubilities, are 0.123 and 0.180 respectively. These high figures invalidate the assumption (made in the derivation of equation 2) that the mole fraction solubility is very small. In addition, antipyrine's solubility 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 Figs. 3-5). In summary, Figures 3-12 show clearly that the reduced 3-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 it by other means requiring the determination of solubility at one or two points in the solvent composition. The significant point, in

Fig. 6: Solubility profile of phenobarbital

-: estimated solubility

o: experimental solubility

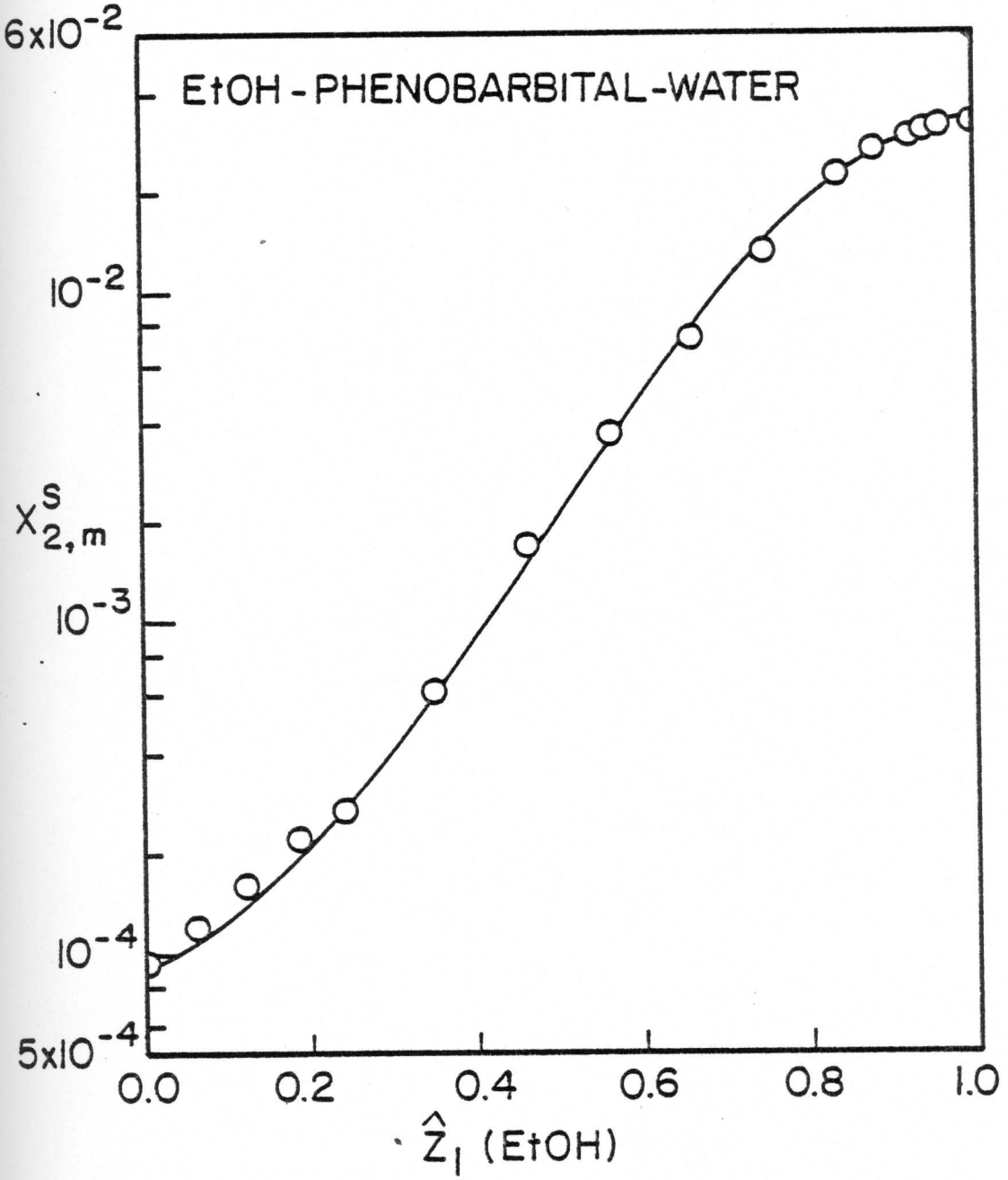

EtOH - PHENOBARBITAL-WATER
6x10-2
10-2
10-3
10-4
5x10-4
X2,m S
0.0
0.2
0.4
0.6
0.8
1.0
Ẑ1 (EtOH)

Fig. 7: Solubility profile of phenysalicylate

-: estimated solubility

o: experimental solubility

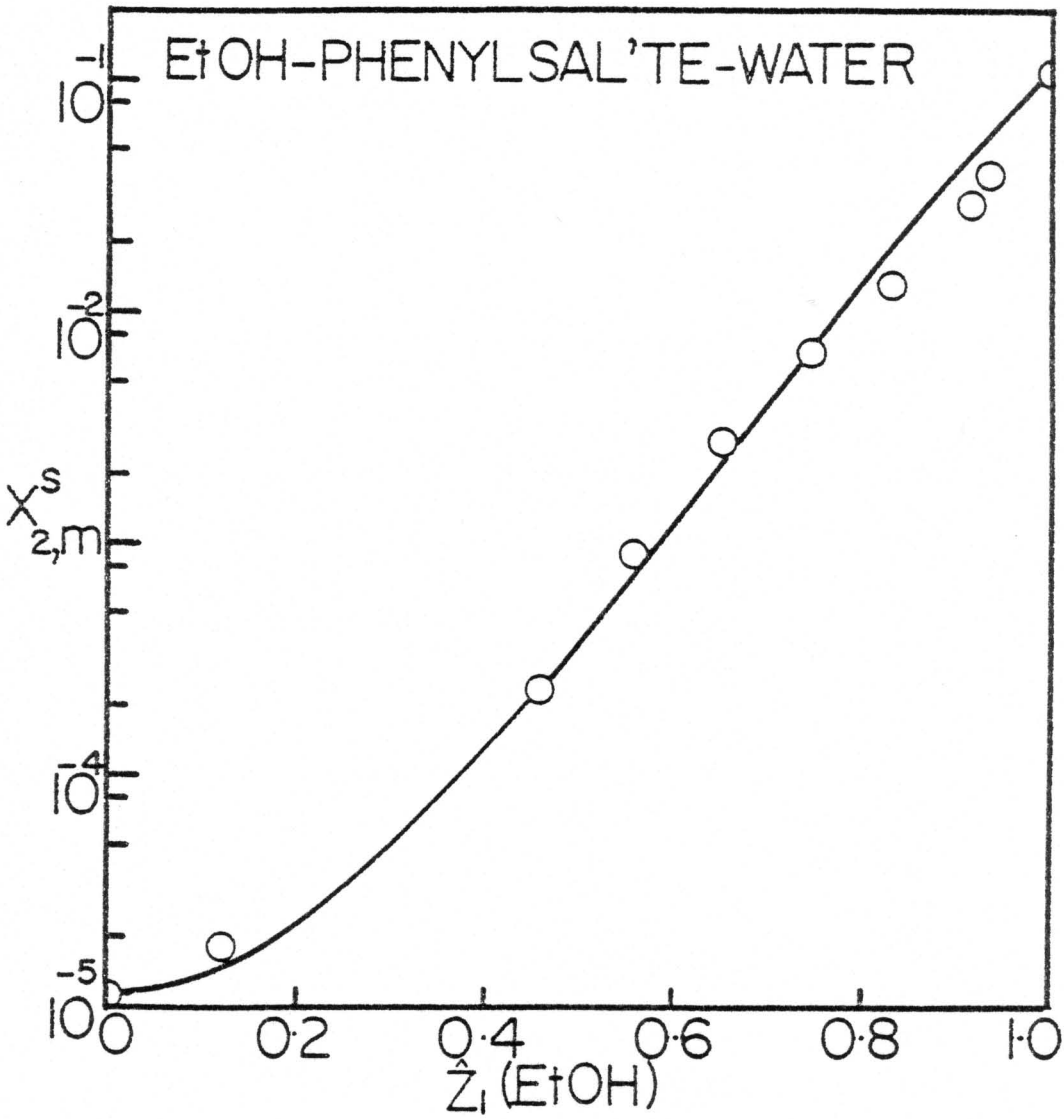

EtOH-PHENYLSAL'TE-WATER
$10^{-1}$
$10^{-2}$
$10^{-4}$
$10^{-5}$
$X^{s}_{2,m}$
0
0·2
0·4
0·6
0·8
1·0
$\hat{Z}_1$ (EtOH)

Fig. 8: Solubility profile of O-nitrophenol

-: estimated solubility

o: experimental solubility

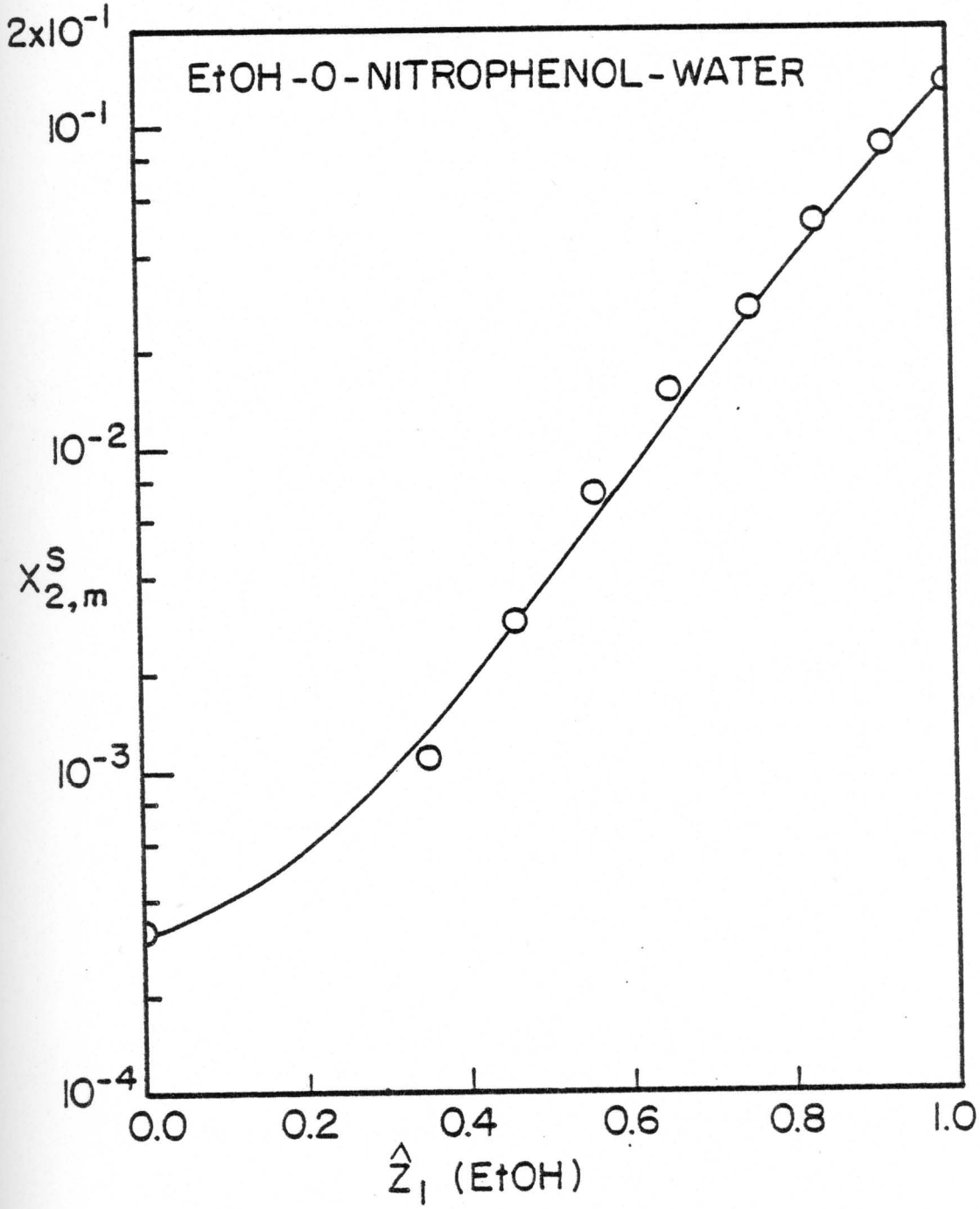

EtOH - O - NITROPHENOL - WATER
2x10⁻¹
10⁻¹
10⁻²
10⁻³
10⁻⁴
X^S_2,m
0.0
0.2
0.4
0.6
0.8
1.0
Ẑ₁ (EtOH)

Fig. 9: Solubility profile of glycine

-: estimated solubility

o: experimental solubility

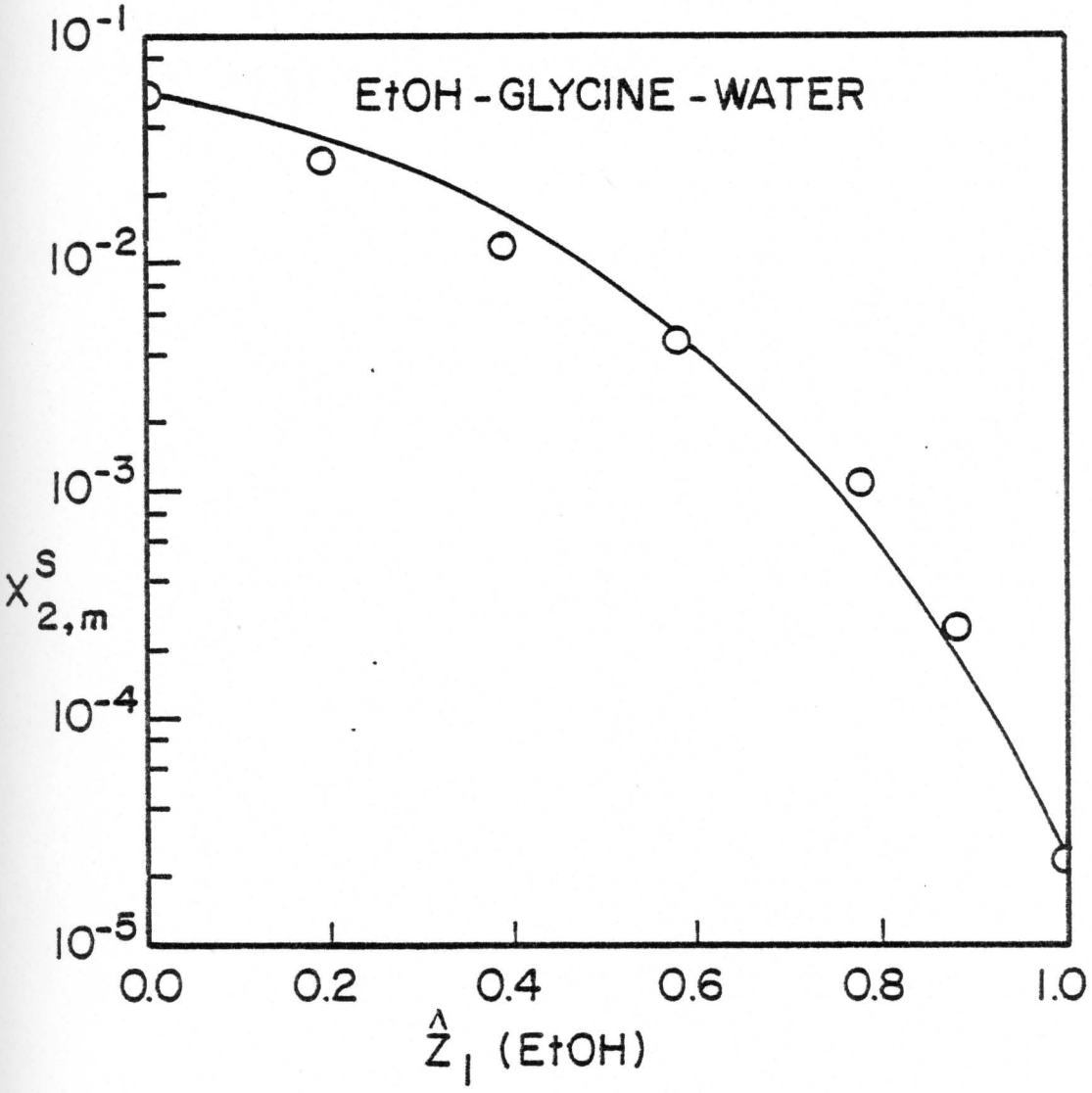

EtOH - GLYCINE - WATER
$10^{-1}$
$10^{-2}$
$10^{-3}$
$10^{-4}$
$10^{-5}$
$X^{S}_{2,m}$
0.0
0.2
0.4
0.6
0.8
1.0
$\hat{Z}_1$ (EtOH)

Fig. 10: Solubility profile of DL-alanine

-: estimated solubility

o: experimental solubility

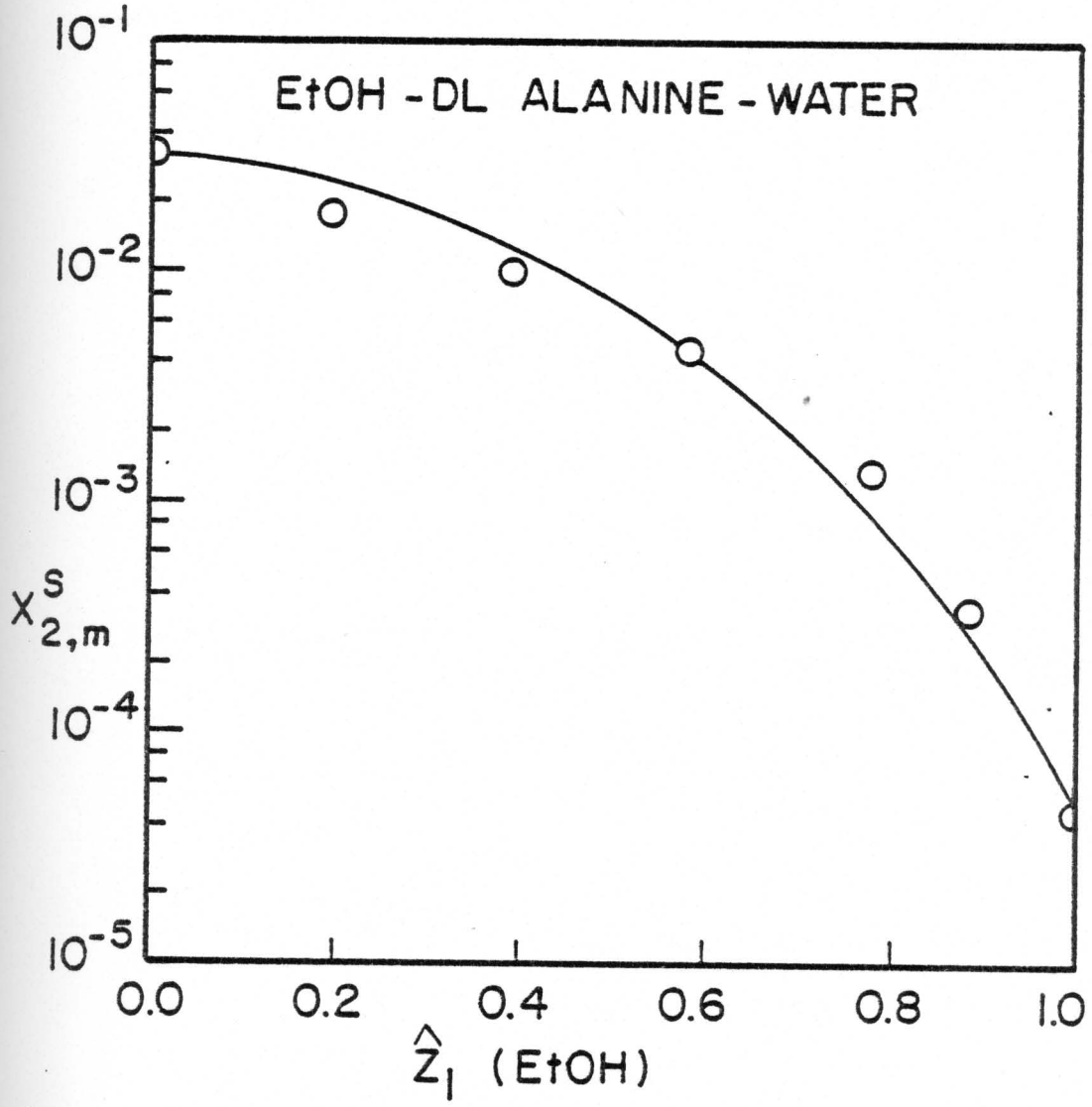

EtOH - DL ALANINE - WATER
$10^{-1}$
$10^{-2}$
$10^{-3}$
$10^{-4}$
$10^{-5}$
$X^{S}_{2,m}$
0.0
0.2
0.4
0.6
0.8
1.0
$\hat{Z}_1$ (EtOH)

Fig. 11: Solubility profile of stearic acid showing contributions from terms in equation 4.

-----: $\hat{z}_1 \ln \frac{x^s_{2,1}}{x^s_{2,3}}$

—·—: $-A_{1-3}\hat{z}_1\hat{z}_3(2\hat{z}_1 - 1)\frac{q_2}{q_1} + A_{3-1}2\hat{z}_1{}^2\hat{z}_3 \frac{q_2}{q_3}$

— —: $C_2\hat{z}_1\hat{z}_3$

———: calculated $\ln \frac{x^s_{2,m}}{x^s_{2,3}}$

x: experimental $\ln \frac{x^s_{2,m}}{x^s_{2,3}}$

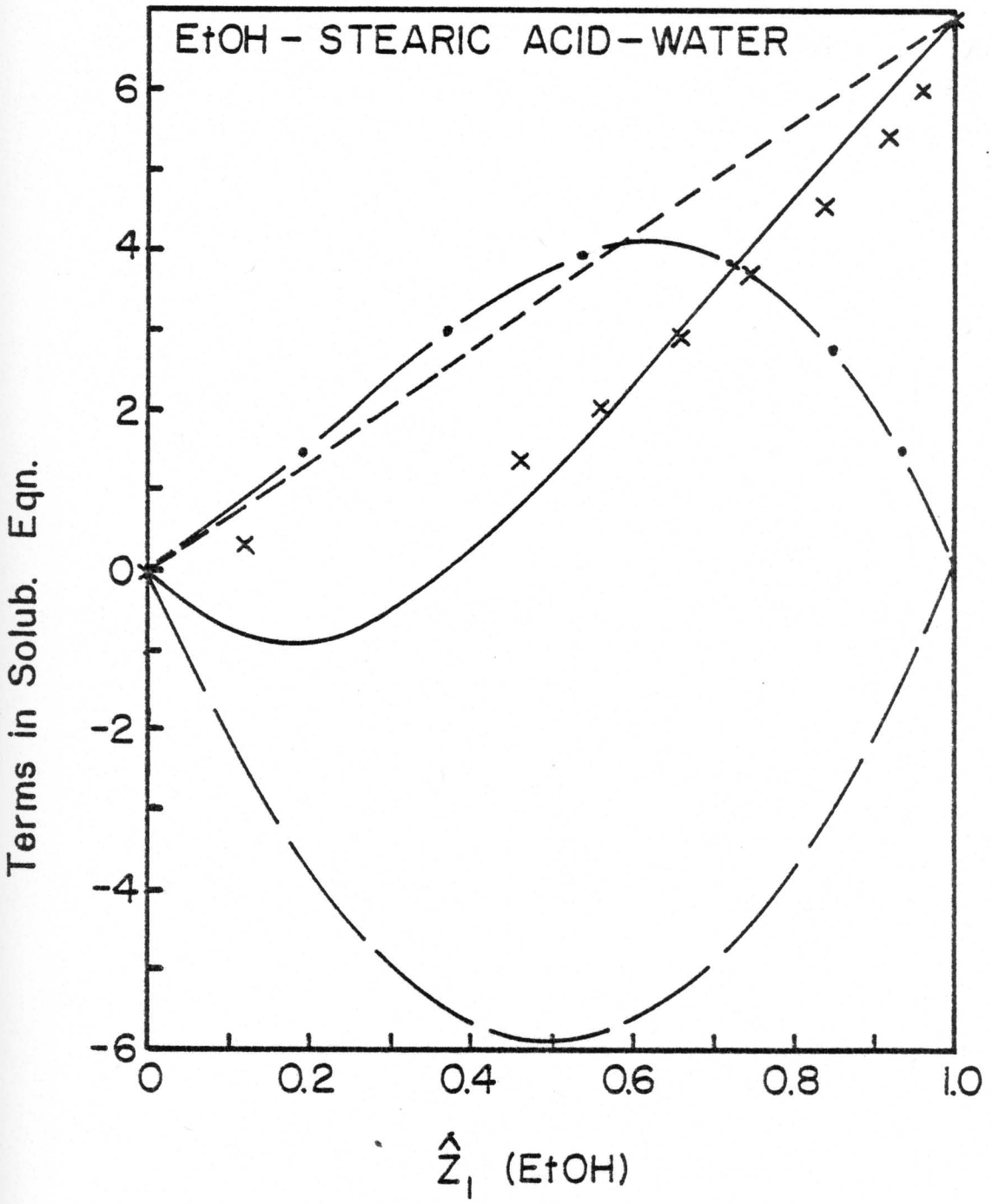
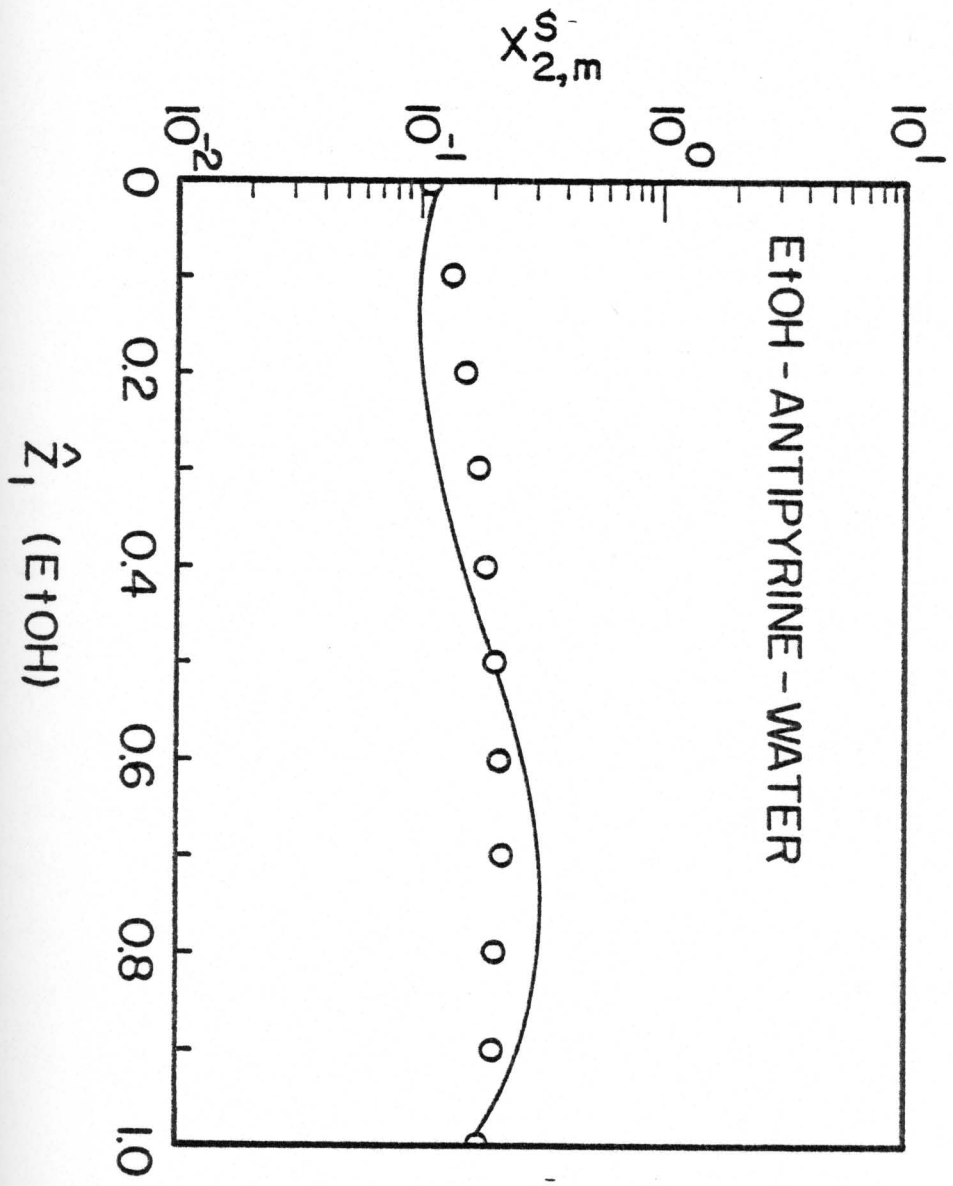

EtOH - STEARIC ACID - WATER
Terms in Solub. Eqn.
6
4
2
0
-2
-4
-6
0
0.2
0.4
0.6
0.8
1.0
$\hat{Z}_1$ (EtOH)

Fig. 12: Solubility profile of antipyrine

-: estimated solubility

o: experimental solubility


$X^{S}_{2,m}$
$10^{1}$
$10^{0}$
$10^{-1}$
$10^{-2}$
EtOH - ANTIPYRINE - WATER
0
0.2
0.4
0.6
0.8
1.0
$\hat{Z}_1$ (EtOH)

any case, is that it is possible to obtain a 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) over-predict (as in Figure 1 and with non-polar compounds) or under-predict (as with the more polar amino acids in the solubility profiles shown) solubility. Therefore the $C_2$ term has an opposite sign (but not always; see Figure 5) to the sum of the solvent-solvent terms. In order to determine what influence, if any, the polar or non-polar nature of the solute has on $C_2$ we have obtained octanol-water partition coefficients (PC), where available (10), for the solutes whose solubility profiles we examined. Table IV and Figure 13 show that there is an excellent trend in which $C_2$ becomes more negative as the solutes become more non-polar and more positive as the solutes become more polar. The regression equation is

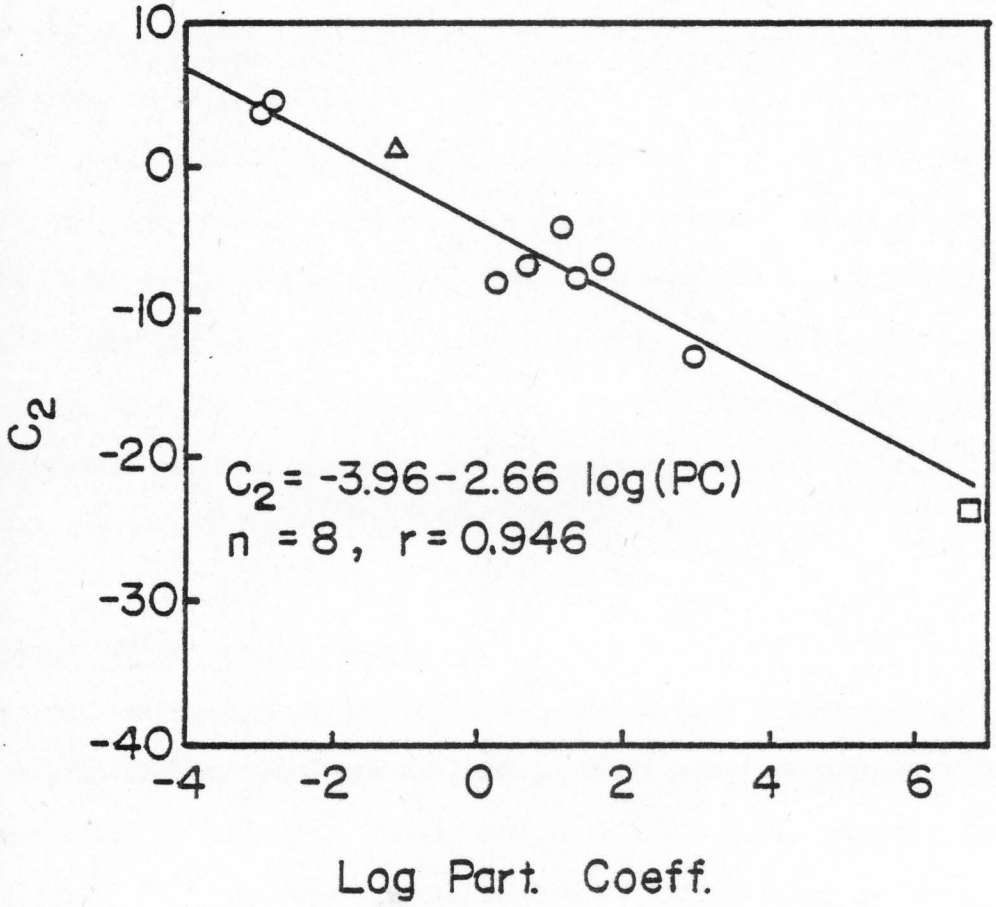
$$C_2 = - 3.96 - 2.66 \log (PC) \qquad (16)$$

$n = 8$, $r = 0.946$, $s = 1.96$ ($s$ 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 it, along with the solvent-solvent terms

Fig. 13: Graph showing correlation of $C_2$ with log partition coefficient (octanol/water).

△ : n-butanol/water

□ : n-heptane/water


10
0
-10
-20
-30
-40
-4
-2
0
2
4
6
$C_2$
$C_2$ = -3.96-2.66 log(PC)
n = 8, r = 0.946
Log Part. Coeff.

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 the $C_2$ will tend to be higher than the observed solubility. This may be expected to happen with non-polar solutes in ethanol-water. In order to correct this over-prediction, $C_2$ 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 extremum in solubility

As was mentioned earlier, it is possible to obtain some idea of whether a solute may exhibit a maximum (or a minimum, although we have not seen this) by computing its $\frac{C_2}{q_2}$ and $\frac{1}{q_2} \ln\left(\frac{x^s_{2,1}}{x^s_{2,3}}\right)$ and locating them on Figure 2. This was done for the solutes listed in Table IV, the values obtained for the above terms were plotted in Figure 2 and labelled with letters representing the solutes in Table IV. It is seen

Table IV: Values of $C_2$ and partition coefficient

| Compound | Formula | $C_2$ | log octanol-water part. coeff.[1] | Solubility data References |
|---|---|---|---|---|
| Barbital (a) | $C_8H_{12}N_2O_3$ | - 6.76 | 0.71 | 4 |
| Acetanilide (b) | $C_8H_9NO$ | - 4.26 | 1.21 | 5 |
| Phenylsalicylate (c) | $C_{13}H_{10}O_3$ | -13.3 | 3 | 5 |
| Stearic acid (d) | $C_{18}H_{36}O_2$ | -23.8 | 6.8[2] | 5 |
| O-nitrophenol (e) | $C_6H_5NO_3$ | - 6.67 | 1.76 | 6 |
| Antipyrine (f) | $C_{11}H_{12}N_2O$ | - 7.94 | 0.26 | 7 |
| Phenobarbital (g) | $C_{12}H_{12}N_2O_3$ | - 7.63 | 1.41 | 4 |
| DL-valine (h) | $C_5H_{11}NO_2$ | + 1.15 | -1.14[3] | 8 |
| Glycine (i) | $C_2H_5NO_2$ | + 3.67 | -3.0 | 8 |
| DL-alanine (j) | $C_3H_7NO_2$ | + 4.43 | -2.8 | 8 |

1: From reference 10. Some values are averages of reported data.

2: n-heptane/water; not used in the regression of $C_2$

3: n-butanol/water; not used in the regression of $C_2$

that the amino acids DL-valine, glycine and DL-alanine labelled h, i, j respectively 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, as seen in Figures 5, 9 and 10. Acetanilide (b) and o-nitrophenol (e) fall in the case 2 area and also show no extrema (see Figures 4 and 8). Phenylsalicylate (c) and stearic acid (d) 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 Figures 7 and 11 indicate a minimum (the minimum in the case of phenylsalicylate is too shallow to be evident on the graph). If indeed these compounds do not show any minimum, the failure of equation 15 should not be surprising for reasons indicated earlier.

Antipyrine (f) falls into the case 7 area but the solubility data show only one maximum in Figure 12 instead of a minimum and maximum as predicted by equation 15. Even though the equation predicts a minimum not seen, the fact that it predicts a maximum which is seen makes it useful. Barbital (a) falls in the borderline area between cases 6 and 7 while phenobarbital (g) 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/liter or moles/liter 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 Figure 3 and it is not even

evident with phenobarbital in Figure 6. In summary it does seem that Figure 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.

## Summary and Conclusions

The reduced 3-suffix solubility equation

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

$$+ A_{3-1}\, 2\hat{z}_1^2 \hat{z}_3 \frac{q_2}{q_3} + C_2 \hat{z}_1 \hat{z}_3 \qquad (2)$$

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 equation 2, except antipyrine which was not as well characterized because its high solubility in both solvents invalidates the assumptions made in deriving equation 2. The approach is also flexible enough to be appropriately altered. For example, it is possible to use the reduced 4-suffix solubility equation (equation 1) for a system where the 3-suffix equation does not satisfactorily describe the solubility. The method finds ready application with pharmaceutically important co-solvents such as ethanol, propylene glycol, glycerin and low molecular weight polyethylene glycols.

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# IV.

# AN 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 3-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 quite 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.

## INTRODUCTION

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 3-suffix solubility equation, was developed from an excess free energy model proposed by Wohl (8) and is given below. For a solute (denoted by subscript 2) in a mixture m, of two solvents (denoted by subscripts 1 and 3)

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

where $x^s_{2,m}$ is the mole fraction solubility of the solute in the solvent mixture; $x^s_{2,1}$ and $x^s_{2,3}$ 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

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

$$+ A_{3\text{-}1} 2\hat{z}_1 \hat{2z}_3 \frac{q_2}{q_1} + C_2 \hat{z}_1 \hat{z}_3 \qquad (2)$$

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

$$\ln x^s_{2,m} = \hat{z}_1 \ln x^s_{2,1} + \hat{z}_3 \ln x^s_{2,3} + \hat{z}_4 \ln x^s_{2,4} - A_{1\text{-}3} \hat{z}_1 \hat{z}_3 (2\hat{z}_1 + 2\hat{z}_4 - 1) \frac{q_2}{q_1}$$

$$+ A_{3\text{-}1} 2\hat{z}_1 \hat{z}_3 (\hat{z}_1 + \hat{z}_4) \frac{q_2}{q_3} - A_{1\text{-}4} \hat{z}_1 \hat{z}_4 (2\hat{z}_1 - 1) \frac{q_2}{q_1} + A_{4\text{-}1} 2\hat{z}_1 \hat{2z}_4 \frac{q_2}{q_4}$$

$$- A_{4\text{-}3} \hat{z}_3 \hat{z}_4 (2\hat{z}_4 - 1) \frac{q_2}{q_4} + A_{3\text{-}4} 2\hat{z}_3 \hat{z}_4^2 \frac{q_2}{q_3} - G_{134} q_2 \hat{z}_1 \hat{z}_3 \hat{z}_4$$

$$+ G_{123} q_2 \hat{z}_1 \hat{z}_3 + G_{124} q_2 \hat{z}_1 \hat{z}_4 + G_{234} q_2 \hat{z}_3 \hat{z}_4 - K q_2 \hat{z}_1 \hat{z}_3 \hat{z}_4 \qquad (3)$$

where $x^s_{2,4}$ is the solute mole fraction solubility in solvent 4; $\hat{z}_4$ is the volume fraction of solvent 4; $A_{1\text{-}4}$, $A_{4\text{-}1}$, $A_{4\text{-}3}$, $A_{3\text{-}4}$ and $G_{134}$ are solvent-solvent interaction constants; $G_{123}$, $G_{234}$ 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 equation 1.

Examination of equations 1 and 3 shows that equation 1 is identical with equation 3 with $\hat{z}_4 = 0$ and $G_{123}q_2 = C_2$. The $q_2$ in front of $G_{123}$ arises from the slightly different definitions of $C_2$ and $G_{123}$ (see reference 1).

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

(i) 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.

(ii) 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 namely $A_{1-3}$, $A_{3-1}$, $A_{1-4}$, $A_{4-1}$, $A_{3-4}$, $A_{4-3}$, and $G_{134}$ once obtained for a ternary solvent system at a particular termperature, are fixed for that solvent system and do not need to be determined again for any solute.

(iii) 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 equation 1; see reference 1) is the contribution to solubility from the interaction of the solute with a mixture of solvents 1 and 3 only and the constant $G_{123}$ is determined from solubility data in the absence of solvent 4.

(iv) 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 $G_{123}$, $G_{124}$ are obtained for the special cases where solvents 4, 3 and 1 respectively are absent, they are not new constants to be determined in the sense that K is. 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(1)-propylene glycol(4) (denoted by subscripts 1 and 4 respectively in equation 3) and ethanol(1)-water(3)-propylene glycol(4) (denoted by subscripts 1, 3 and 4 respectively in equation 3) mixtures at 25°C. With these data and reliable vapor pressure data for ethanol(1)-water(3) (reference 3) and propylene glycol(4)-water(3) (reference 4), the binary solvent interaction constants (the A's) 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 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 previously in reference 2 for the estimation of solvent interaction parameters from total pressure data,

the data reported here for ethanol-propylene glycol and those for ethanol-water (reference 3) and propylene glycol-water (reference 4) were reduced to obtain the binary constants. As indicated earlier, 1 represents ethanol; 3, water; and 4, propylene glycol. The binary constants, including the ternary constant $G_{134}$ to be discussed next, are shown in Table III. The experimental vapor pressure-composition data and the calculated curves using the binary solvent interaction constants in Table III are shown in Figure 2 for the 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(1)-water(3)-propylene glycol(4), the excess free energy model is given by equation 36 of reference 1 except that all terms with subscript 2 are omitted. If we rewrite the equation in terms of A's, multiply it by the total number of moles and differentiate it with respect to the number of moles of each of the components, we obtain expressions for the logarithm of the activity coefficients as already described (2). Thus, for a ternary solvent system,

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

$$+ z_4^2 \left[ A_{1-4} + 2z_1\left(A_{4-1}\frac{q_1}{q_4} - A_{1-4}\right)\right]$$

$$+ z_3 z_4 \left[ A_{4-1} \frac{q_1}{q_4} + A_{1-3} - A_{3-4} \frac{q_1}{q_3} + 2z_1 \left( A_{3-1} \frac{q_1}{q_3} - A_{1-3} \right) \right.$$

$$\left. + 2z_3 \left( A_{3-4} \frac{q_1}{q_3} - A_{4-3} \frac{q_1}{q_4} \right) - G_{134} q_1 (1-2z_1) \right] \qquad (4)$$

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

$$+ z_4^2 \left[ A_{3-4} + 2z_3 \left( A_{4-3} \frac{q_3}{q_4} - A_{3-4} \right) \right] + z_4 z_1 \left[ A_{1-3} \frac{q_3}{q_1} \right.$$

$$+ A_{3-4} - A_{4-1} \frac{q_3}{q_4} + 2z_3 \left( A_{4-3} \frac{q_3}{q_4} - A_{3-4} \right)$$

$$\left. + 2z_4 \left( A_{4-1} \frac{q_3}{q_4} - A_{1-4} \frac{q_3}{q_1} \right) - G_{134} q_3 (1-2z_3) \right] \qquad (5)$$

$$\ln \gamma_4 = z_3^2 \left[ A_{4-3} + 2z_4 \left( A_{3-4} \frac{q_4}{q_3} - A_{4-3} \right) \right]$$

$$+ z_1^2 \left[ A_{4-1} + 2z_4 \left( A_{1-4} \frac{q_4}{q_1} - A_{4-1} \right) \right]$$

$$+ z_1 z_3 \left[ A_{3-4} \frac{q_4}{q_3} + A_{4-1} - A_{1-3} \frac{q_4}{q_1} + 2z_4 \left( A_{1-4} \frac{q_4}{q_1} - A_{4-1} \right) \right.$$

$$\left. + 2z_1 \left( A_{1-3} \frac{q_4}{q_1} - A_{3-1} \frac{q_4}{q_3} \right) - G_{134} q_4 (1-2z_4) \right] \qquad (6)$$

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

$$P_T = x_1 p_1^0 \gamma_1 + x_3 p_3^0 \gamma_3 + x_4 p_4^0 \gamma_4 \qquad (7)$$

$$= x_1 p_1^{\circ} e^{-\ln\gamma_1} + x_3 p_3^{\circ} e^{\ln\gamma_3} + x_4 p_4^{\circ} e^{\ln\gamma_4} \qquad (8)$$

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); $p_1^{\circ}$, $p_3^{\circ}$ and $p_4^{\circ}$ are the pure solvent vapor pressures and $\gamma_1$, $\gamma_3$ and $\gamma_4$ are the activity coefficients.

By substituting equations 4-6 into equation 8, all seven interaction constants may be obtained by non-linear regression since $P_T$, the mole fractions and pure solvent-vapor pressures are known. In order 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,

$$G_{134} = -0.1069 \text{ mol/cm}^3$$

was obtained with the A's an shown in Table III. It should be noted that, while the A's are dimensionless, $G_{134}$ has units of reciprocal molar volume because of the way it was defined in equation 37i of reference 1.

## EXPERIMENTAL

### Materials

Absolute ethanol (U.S. Industrial Chemicals Co.) and propylene glycol (J.T. Baker Chemical Co.) 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.

In order to prevent condensation of the solvent vapor on the mercury and in the manifold of the apparatus (see Figure 1), the manometer E, and the manifold were wrapped with a heating tape kept at 3 ± 0.5°C above the temperature of the flask contents, B and C.

The method described here is similar to that used by Verlinde et al (4). The solvent (or solvent mixture) was frozen by means of liquid nitrogen. The stopcock to the solvent was opened and the air in the manifold and above the solvent evacuated by means of a Marvac compound stage vacuum pump until the pressure gauge D (Granville-Phillips Co.) indicated a pressure of 2 microns or less. The stopcock was then closed, the solvent 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 degassing the solvent, it was brought to, and kept at, 25 ± 0.1°C. The solvent stopcock was opened and the vapor pressure read by a

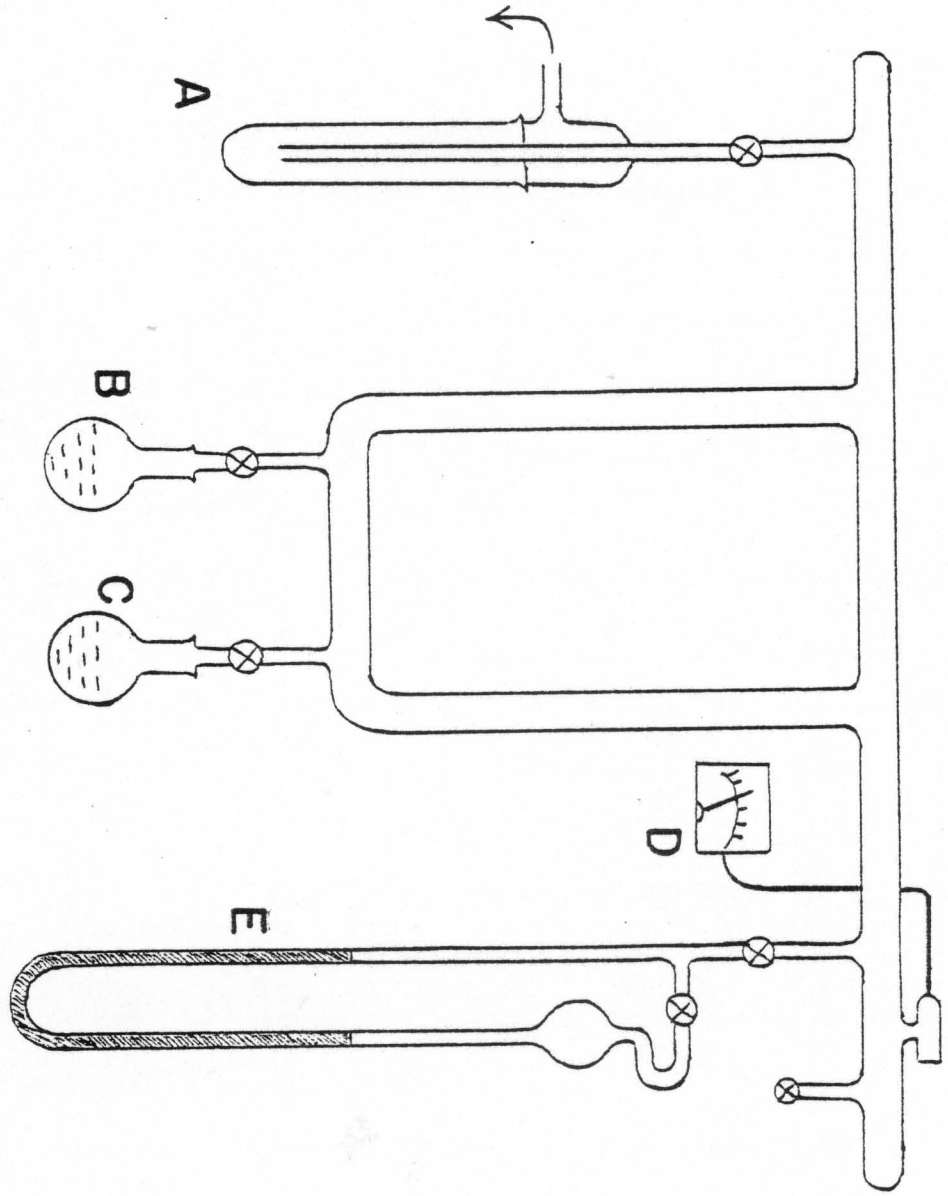
Fig. 1: Diagram of vapor pressure measuring apparatus.

A: Cold trap

B, C: Flasks containing solvent mixtures

D: Pressure gauge

E: Mercury manometer


A
B
C
D
E

cathetometer (graduated to 0.05 mm) after the mercury column had stopped moving. The cathetometer readings were taken and the average computed.

Two flasks, B and C, containing two different concentrations of the solvent mixture, were used so that degassing the contents simultaneously saved considerable time. After degassing, 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°C (temperature of manometer) and capillary depression as follows (see reference 5).

Corrected pressure = (uncorrected pressure) (g/go) (dt/do) + $C_u$ - $C_l$ where

$g$ = acceleration due to gravity in Madison (980.368 cm/sec$^2$) (reference 6)

$g_o$ = 980.665 cm/sec$^2$ (reference 5)

$d_t$ = density of mercury at manometer temperature (28°C)

$d_o$ = density of mercury at 0°C

$C_u$ = capillary depression correction for upper column of manometer

$C_l$ = capillary depression correction for lower column of manometer

$d_t/d_o$ = 0.994939 (reference 5)

The results of four separate measurements with ethanol indicated a relative standard error of less than 1 percent.

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 $cm^3$ occupied by the solvent or solvent mixture vapor, there was less than 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 I and II for ethanol-propylene glycol mixtures and ethanol-water-propylene glycol mixtures. For ethanol-water mixtures, partial vapor presure readings which had been tested for thermodynamic consistency (7) were taken from reference 3. For propylene glycol-water mixtures, total vapor pressure results from reference 4 were used after being checked with the apparatus described above.

Figure 2 A-C shows the experimental points for the three binary systems. Figure 2 D 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 represents a pure solvent.

### Solubility in ethanol-water-propylene glycol mixtures

TABLE 1: Total Vapor Pressure Results for Ethanol-Propylene Glycol (PG)

| Mole Fraction of Ethanol | Mole Fraction of PG | Vapor Pressure (mmHg) |
|---|---|---|
| 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 |

TABLE II: Total Vapor Pressure Results for Ethanol-Water-Propylene Glycol (PG)

| Mole Fraction of Ethanol | Water | PG | Vapor Pressure (mmHg) |
|---|---|---|---|
| 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 |

Fig. 2: Total vapor pressure $P_T$ versus mole fraction composition X for

A: Ethanol (EtOH)-water ($H_2O$)

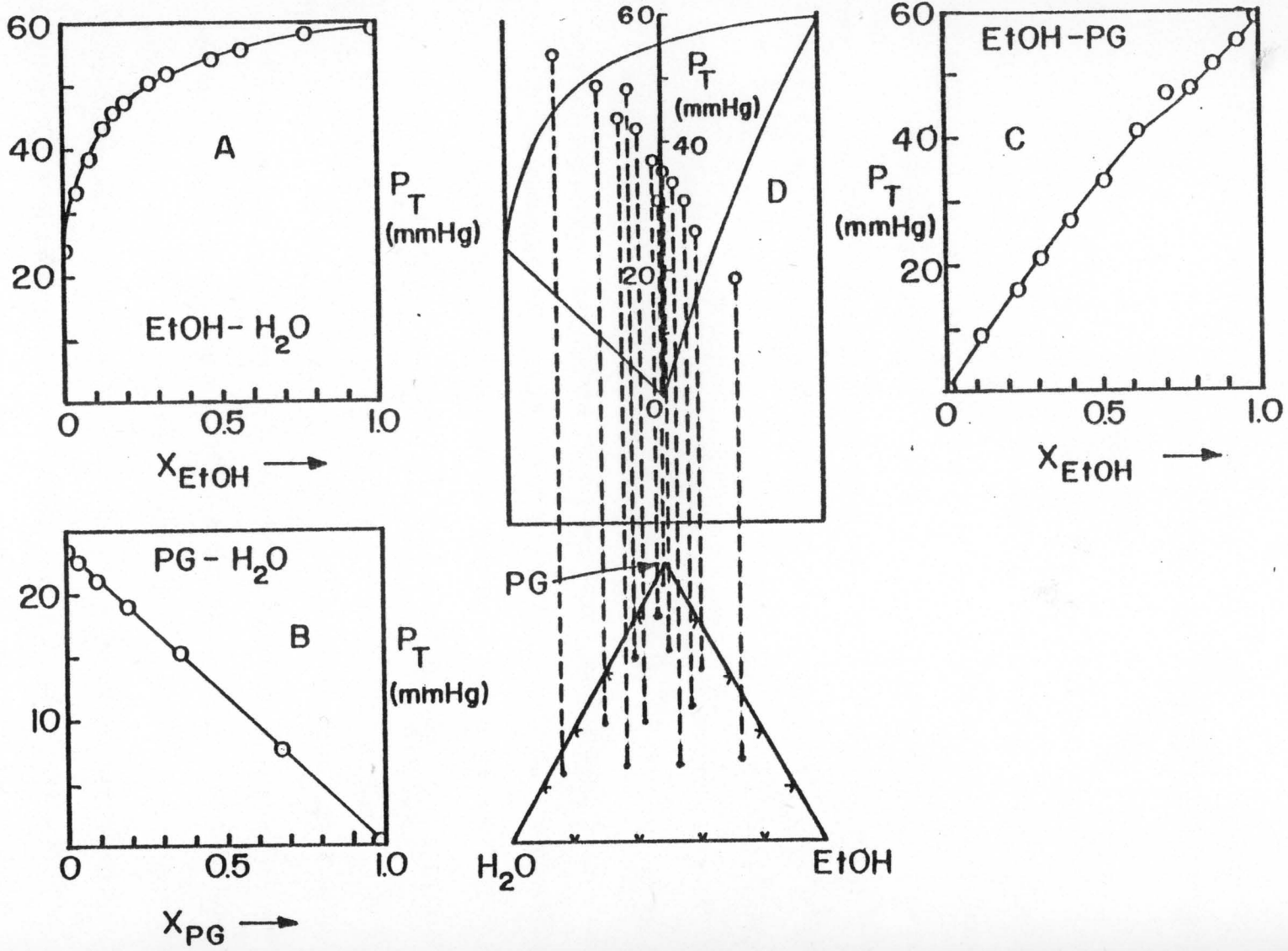
B: Propylene glycol (PG)-water

C: Ethanol-PG

D: Ethanol-water-propylene glycol

———: Calculated curves

○: Experimental points


60
40
20
A
EtOH- $H_2O$
$P_T$ (mmHg)
0
0.5
1.0
$X_{EtOH}$
PG - $H_2O$
20
10
B
$P_T$ (mmHg)
0
0.5
1.0
$X_{PG}$
60
$P_T$ (mmHg)
40
20
0
D
PG
$H_2O$
EtOH
60
EtOH-PG
40
C
$P_T$ (mmHg)
20
0
0.5
1.0
$X_{EtOH}$

Figures 4-5 show the estimated and experimental solubility profiles of phenobarbital (from reference 9) and hydrocortisone (from reference 10) in propylene glycol(4)-water(3)-mixtures obtained by methods already described in reference 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 III. With regard to equation 4, it means that one sets $\hat{z}_1 = 0$.

Figure 6 shows the estimated and experimental solubility profile of phenobarbital in ethanol (1) - propylene glycol (4) mixtures (from reference 9) and Figure 7 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 equation 4 without the K term. $G_{123}$, $G_{234}$ and $G_{124}$ were already known from the solubilities of phenobarbital in mixtures of ethanol(1)-water(3), water(3)-propylene glycol(4) and ethanol(1)-propylene glycol(4) 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 Figure 2, A, B and C, the 3-suffix excess free energy model very 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 in Figure 2B, that 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

$$P_T = \sum_i x_i p_i^0 \qquad (9)$$

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 described in the next section. The vapor pressure curve for ethanol-propylene glycol (Figure 2C) 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.

TABLE III: Binary (A's) and Ternary ($G_{134}$) Solvent Constants

| System | $A_{1-3}$ | $A_{3-1}$ | $A_{1-4}$ | $A_{4-1}$ | $A_{3-4}$ | $A_{4-3}$ | $G_{134}$ |
|---|---|---|---|---|---|---|---|
| Ethanol(1)-Water(3) | 1.138 | 0.9047 | | | | | |
| Ethanol(1)-PG[a](4) | | | 0.1633 | 0.5688 | | | |
| Water(3)-PG(4) | | | | | -0.0308 | -0.0828 | |
| Ethanol(1)-Water(3)-PG(4) | 1.138 | 0.9047 | 0.1633 | 0.5688 | -0.0308 | -0.0828 | -0.1069 mol/cm$^3$ |

[a] PG = Propylene glycol

For the mixture of all three solvents, predicted vapor pressures (see Figure 3) were not as good as for the binary systems (Figure 2) but if one considers the complexity of the ternary system, the fit is satisfactory. A better fit may be obtained by using the 4-suffix excess free energy model (8) but the number of solvent constants to be estimated (twelve, see reference 8) becomes inconveniently high. Another excess free energy model which has been shown to better describe ternary vapor-liquid equilibrium data is the non-random two liquid (NRTL) model (12). However, we have not examined it 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's) which are quite small in magnitude (see Table III). 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 Figures 4 and 5 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.

Fig. 3: Observed (YOBS) versus predicted (YPRED) vapor pressures for ethanol-water-propylene glycol mixtures.

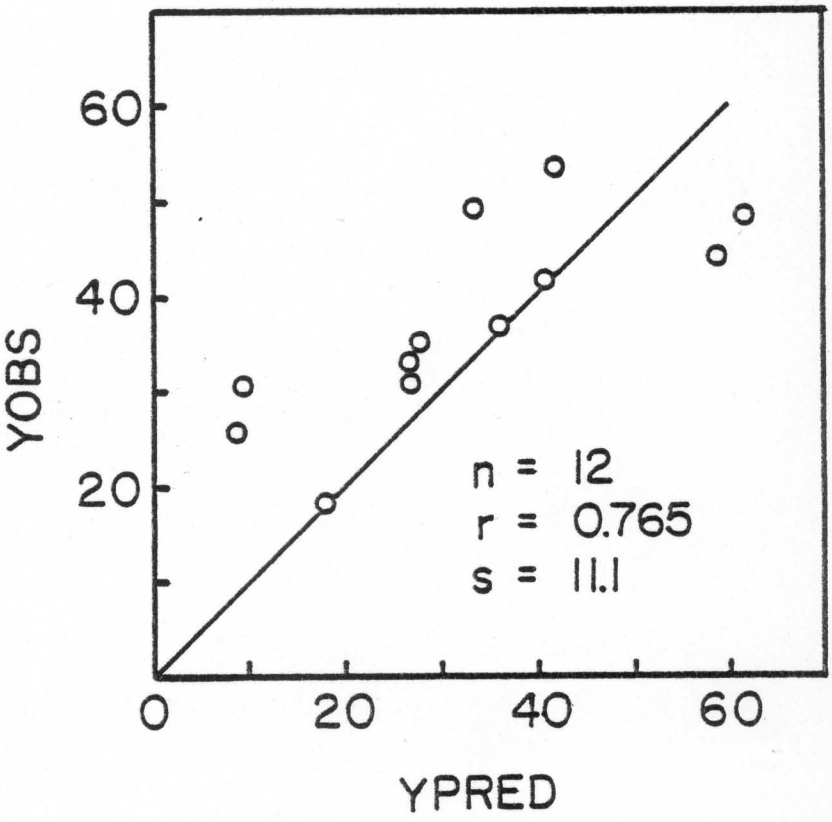

60
40
20
YOBS
n = 12
r = 0.765
s = 11.1
0
20
40
60
YPRED

Fig. 4: Solubility profile of phenobarbital in propylene glycol (PG)-water mixtures.

-: Estimated solubility

o: Experimental solubility

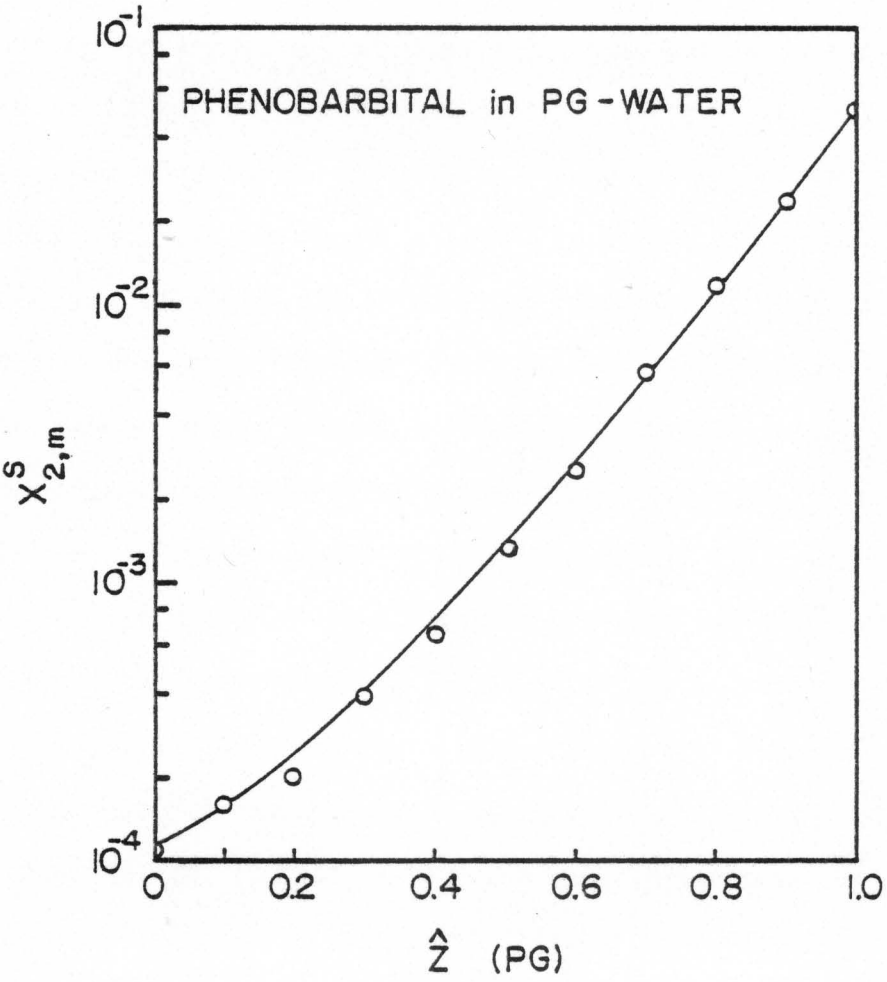

PHENOBARBITAL in PG-WATER
$10^{-1}$
$10^{-2}$
$10^{-3}$
$10^{-4}$
$X^{S}_{2,m}$
0
0.2
0.4
0.6
0.8
1.0
$\hat{Z}$ (PG)

Figure 5 shows the contributions of the various terms in equation 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(4)-water(3) 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 equation 2 instead of $G_{234}q_2$ in equation 3. As seen in Figure 5, the solvent interaction contribution (the sum of the A terms) is always close to zero and has no significant effect on the solubility. The $C_2$ term is responsible for the positive deviation from the "ideal mixture" solubility. The magnitude of the sum of the A terms in equation 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 (reference 10), 73.69 (reference 14) and 18.07 $cm^3$/mole (reference 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.

Fig. 5: Solubility profile of hydrocortisone (showing contributions from terms in equation 4) in PG(1)-water(3) mixtures

-----: $\hat{z}_1 \ln\left(\frac{x^s_{2,1}}{x^s_{2,3}}\right)$

—·—·—: $-A_{1\text{-}3}\hat{z}_1\hat{z}_3(2\hat{z}_1 - 1)\frac{q_2}{q_1} + A_{3\text{-}1}2\hat{z}_1{}^2\hat{z}_3\frac{q_2}{q_3}$

— —: $C_2\hat{z}_1\hat{z}_3$

———: Estimated $\ln\left(\frac{x^s_{2,m}}{x^s_{2,3}}\right)$

o: Experimental $\ln\left(\frac{x^s_{2,m}}{x^s_{2,3}}\right)$

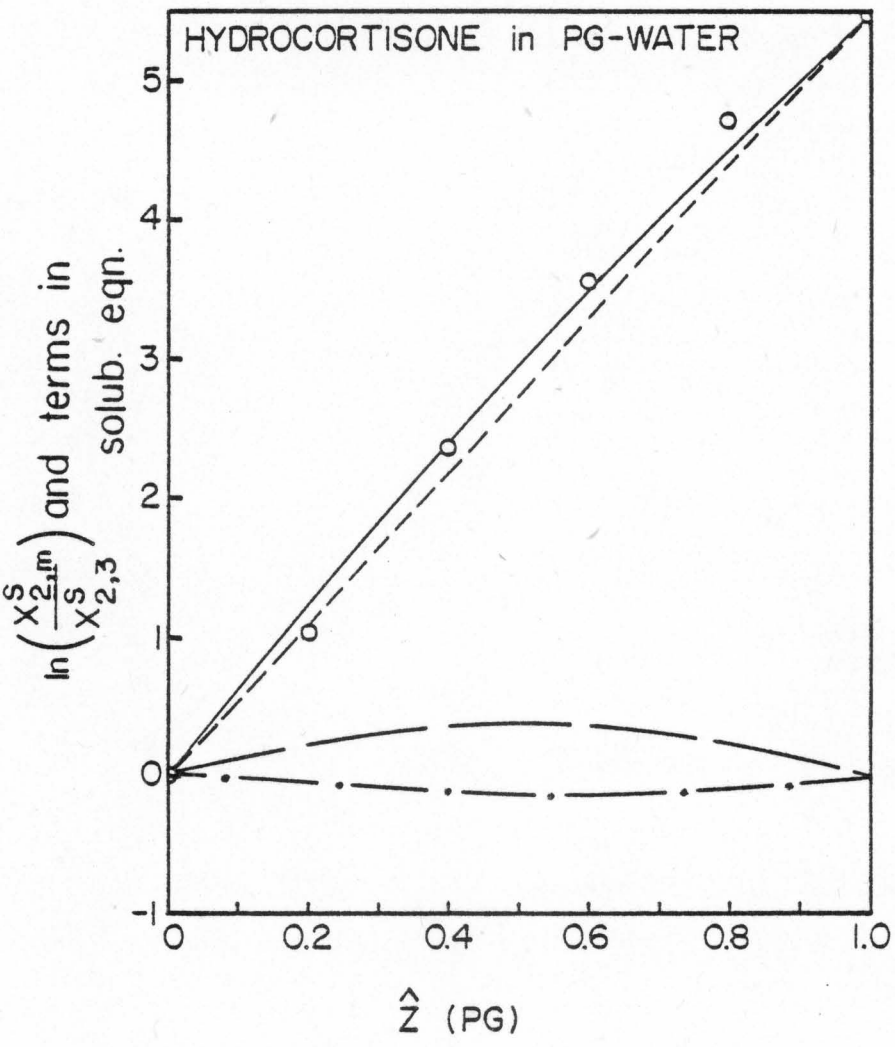
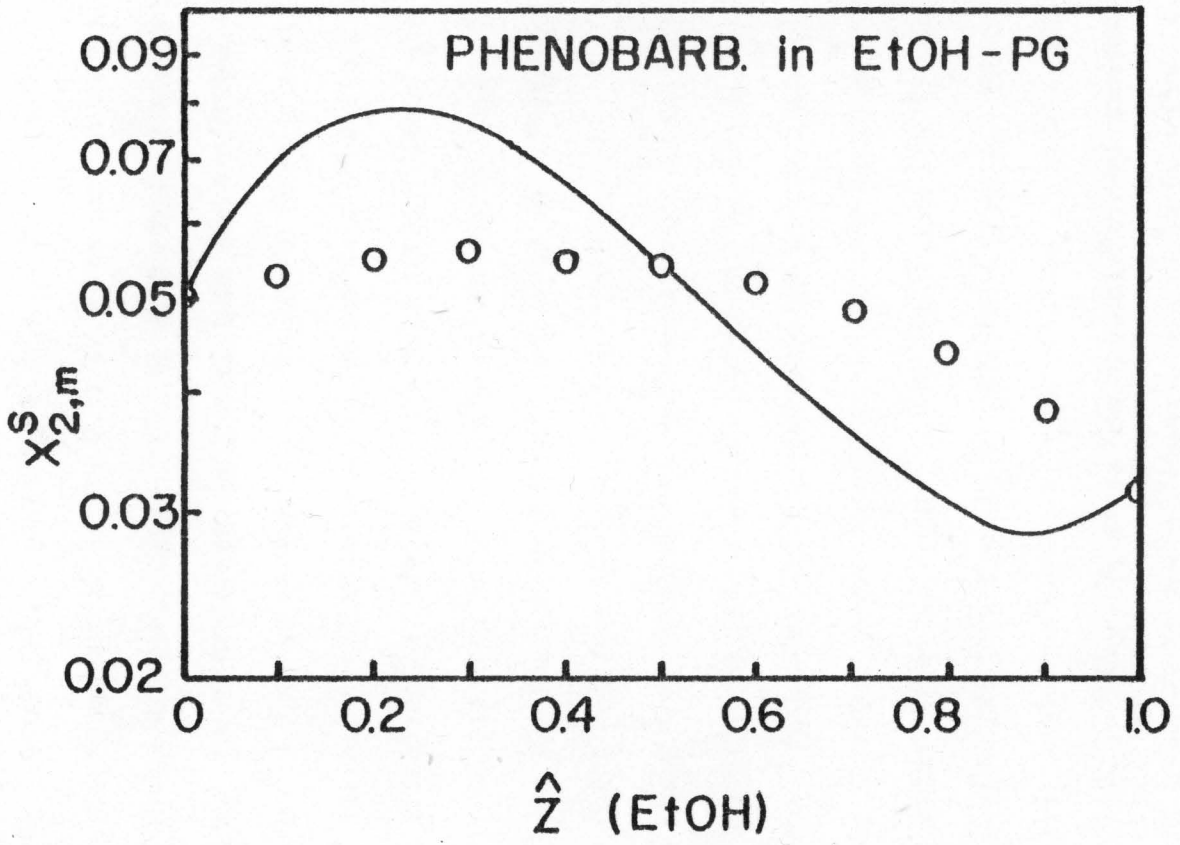

HYDROCORTISONE in PG-WATER
$\ln\left(\frac{X^S_{2,m}}{X^S_{2,3}}\right)$ and terms in solub. eqn.
5
4
3
2
1
0
-1
0
0.2
0.4
0.6
0.8
1.0
$\hat{Z}$ (PG)

Fig. 6: Solubility profile of phenobarbital in ethanol-propylene glycol (PG) mixtures.

-: Estimated solubility

o: Experimental solubility


PHENOBARB. in EtOH-PG
0.09
0.07
0.05
0.03
0.02
$X^S_{2,m}$
0
0.2
0.4
0.6
0.8
1.0
$\hat{Z}$ (EtOH)

The solubility of phenobarbital in ethanol-propylene glycol mixtures is not well described by equation 1 as seen in Figure 6. However, if one takes into account that Figure 6 is drawn on an expanded scale compared to, for example, Figure 4, 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 in reference 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, reference 9). These values are 0.051 and 0.032 respectively in mole fraction units.

Figure 7 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 equation 3 is not really demonstrated by Figure 7. 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 in effect, to generate all the curves in Figure 7, since the solvent-solvent constants (the A's and $G_{134}$ in equation 3) and the ternary solute-solvent constants ($G_{123}$, $G_{124}$, and $G_{234}$ in equation 3) are known (see Tables III and IV). Thus, this approach is more flexible and requires fewer empirically adjusted parameters (compared to, for example, the straight line fit just discussed) to describe solubility in a ternary solvent system.

TABLE IV: Solute-Solvent Interaction Parameters

| Compound | $q_2$[a] | Mixed Solvent System | Solute-solvent Interaction Constants | n[c] | $\gamma$[c] | s[c,d] |
|---|---|---|---|---|---|---|
| Phenobarbital | 172.0 | Ethanol(1)-PG[b](4) | $G_{124}q_2 = -0.092$ | 9 | 0.885 | 0.291 |
| Phenobarbital | 172.0 | PG(4)-Water(3) | $G_{234}q_2 = -1.80$ | 9 | 0.999 | 0.129 |
| Phenobarbital | 172.0 | Ethanol(1)-Water(3) | $G_{123}q_2 = -6.74$ | 9 | 0.995 | 0.21 |
| Phenobarbital | 172.0 | Ethanol(1)-Water(3)-PG(4) | $Kq_2 = +15.3$ | 20 | 0.996 | 0.135 |
| Hydrocortisone | 293 | PG(1)-Water(3) | $C_2 = +1.44$ | 4 | 1.000 | 0.200 |

a: $q_1 = 58.68$ (reference 11), $q_3 = 18.07$ (reference 15) and $q_4 = 73.69$ (reference 14)
$q_2$ was calculated by group contribution from the molar volume of barbital (reference 15)

b: PG = Propylene glycol

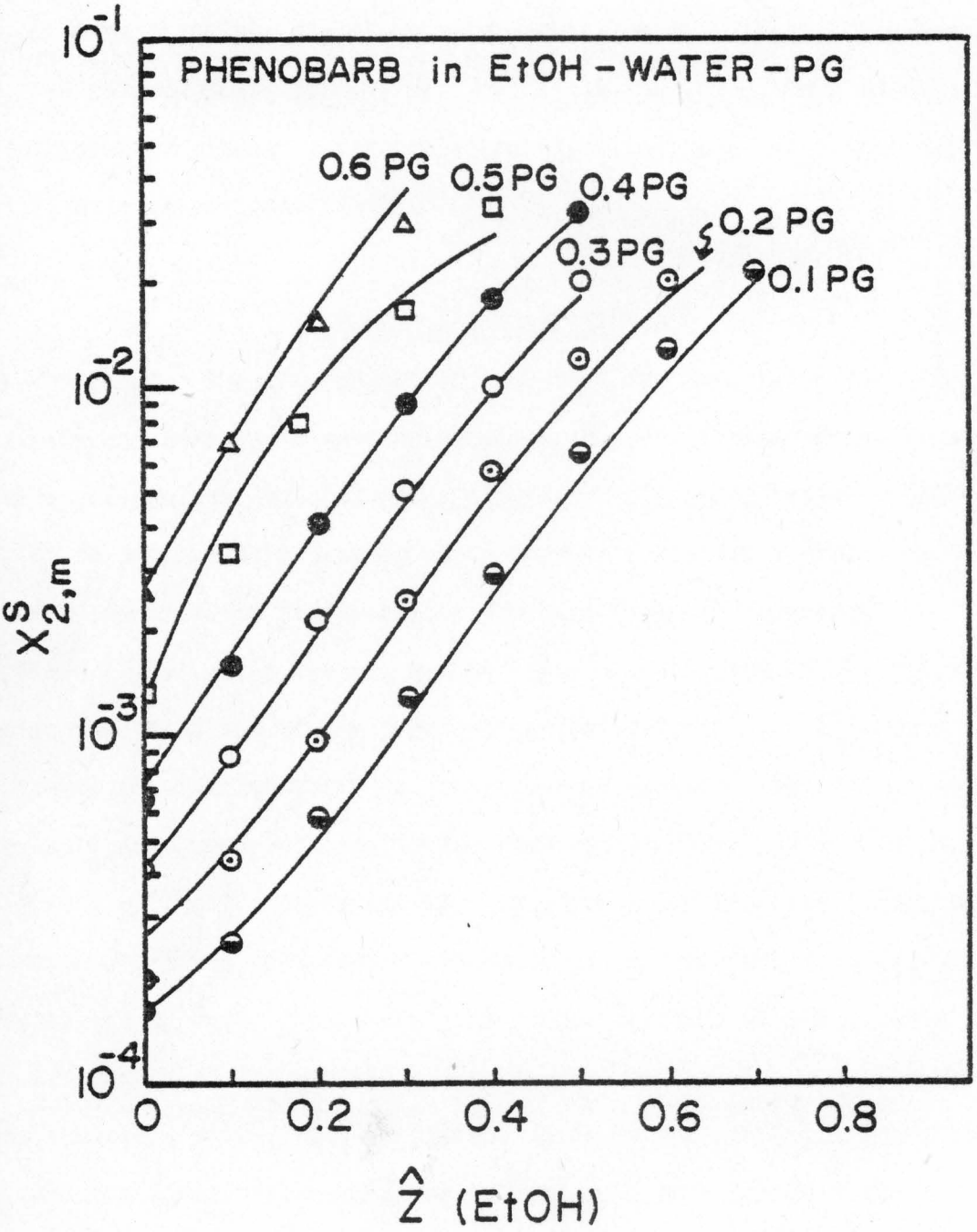
c: Linear regression parameters for the estimation of the constants in column 4

d: s is the standard deviation of the error between $\ln(x_{2,m}^{s})_{observed}$ and $\ln(x_{2,m}^{s})$ estimated

Fig. 7: Solubility profiles of phenobarbital in ethanol-water at designated volume fractions of propylene glycol (PG).

——: Estimated solubility

●, o, △, etc: Experimental solubility


PHENOBARB in EtOH - WATER - PG
0.6 PG
0.5 PG
0.4 PG
0.3 PG
0.2 PG
0.1 PG
$10^{-1}$
$10^{-2}$
$10^{-3}$
$10^{-4}$
$X^{S}_{2,m}$
0
0.2
0.4
0.6
0.8
$\hat{Z}$ (EtOH)

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 equation 3 for mixtures of ethanol-water-propylene glycol without any significant loss in estimation capabilities.

## SUMMARY AND CONCLUSION

The reduced 3-suffix solubility equation for describing solubility in binary and ternary solvent mixtures has previously been shown to be quite successful for ethanol-water systems. 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 phenobarbital's solubility in (a)

ethanol(1)-water(3), (b) ethanol(1)-propylene glycol(4) and (c) propylene glycol(4)-water(3), we may use equation 1 or equation 3. To use equation 3 for system (a) we set $\hat{z}_4 = 0$ and estimate $G_{123}$ as already described; for system (b) we set $\hat{z}_3 = 0$ and estimate $G_{124}$, and for (c) we set $\hat{z}_1 = 0$ and estimate $G_{234}$. To describe phenobarbital's solubility in ternary mixtures of these solvents, the only unknown term we need to estimate in equation 3 is the quaternary solute-solvent constant K since the A's 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 3-suffix solubility equation thus far is in describing fairly high to high solubilities. Bearing in mind the fact 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 which 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 say water does not need a co-solvent. It therefore 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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# V. GENERAL SUMMARY AND CONCLUSION

The reduced 3-suffix solubility equation for the estimation of solubility in mixed solvents arises from the Wohl excess free energy model. Differentiating the excess free energy equation with respect to the mole number of each of the components gives activity coefficient expressions for each of these components. By making appropriate simplifications in the activity coefficient equation for the solute, certain constants are related to Henry's Law constants of the solute in the solvents. This enables one to express Henry's Law constants of the solute in the solvents in terms of an equation containing solvent-solvent and solute-solvent interaction parameters. By combining this equation and a general equation expressing the solubility of the solute in the solvent mixture in terms of the pure solvent solubilities and Henry's Law constants of the solute in the solvents, the final equation is obtained. If necessary, the solvent-solvent interaction terms may be made more complex (by including more interaction terms in the excess free energy model) while still keeping the solute-solvent terms simple. This increases the flexibility of the system.

The final working equation is a general and systematic equation which expresses the solubility of a solute in a solvent mixture in terms of (i) the volume fraction weighted

sum of the pure solvent solubilities or "ideal mixture solubility", (ii) solvent-solvent interaction terms which increase or decrease the "ideal mixture solubility" and (iii) a ternary solute-solvent term which accounts for interactions between the solute and mixed solvent. The solvent-solvent interaction terms are obtained from vapor liquid equilibrium data while the ternary term is estimated in principle, from an experimentally determined solubility at a point in the solvent composition range.

Attempts to describe literature solubility data in mixed solvents with the reduced 3-suffix solubility equation were very successful. The equation was not as successful where solubilities were high, which is not surprising in view of the approximations made. Apart from this drawback, the equation seems to describe solubility in binary and ternary solvents quite satisfactorily with terms which have some physical meaning. The generality and flexibility of this approach make it easily adjustable for other systems which may not be well-characterized by the 3-suffix equation.

Future work in this area may involve the application of this equation or approach to the description of the solubility of poorly soluble gases and liquids in mixed solvents. Also, solvent-interaction constants for aqueous mixtures of other co-solvents like glycerin and low

molecular weight polyethylene glycols will need to be obtained in order to estimate solubility in these systems. More investigation into the physical significance of the ternary term $C_2$ needs to be done. With more data on $C_2$ and partition coefficients (or some other polarity measure) it should be possible to establish what is now only a tentative conclusion: that a correlation exists between $C_2$ and the partition coefficient of the solute.

# APPENDIX A:

# A Solubility Equation for Non-Electrolytes in Water.

# A Solubility Equation for Non-Electrolytes in Water

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## ABSTRACT

A solubility equation is developed based on the steps: solid → super cooled liquid → octanol → water. Estimating the Standard Gibbs energy change for each step gives the following result:

$$\log C_{2,w}^{s} = 0.80 - 7.3 \times 10^{-4}[\Delta S^{f}(T_m - 298)] - 7.3 \times 10^{-4}[V_2(10.3-\delta_2)^2] - \log PC$$

Where $C_{2,w}^{s}$ is the molar aqueous solubility of the solute, $\Delta S^{f}$ is entropy of fusion, $T_m$ its melting point, $V_2$ its molar volume, $\delta_2$ its solubility parameter and PC its octanol-water partition coefficient. Comparison of this equation with a regression equation based on experimental data shows the derived result above to be nearly as good as the regression equation. The equation appears to provide good aqueous solubility estimates for solids and liquids.

## INTRODUCTION

Recent reports (Yalkowsky and Valvani, 1980; Valvani et al., 1981) have developed an approach to estimating the aqueous solubility of non-electrolytes which appears to be remarkably successful. The development of the approach was based on both molecular and thermodynamic considerations. In this report we present a more complete thermodynamic framework for this approach based on the following steps:

$$\text{solid} \xrightarrow{\Delta g_1^o} \text{super cooled liquid}$$

$$\text{super cooled liquid} \xrightarrow{\Delta g_2^o} \text{octanol solution } (X_{2,oct}^s)$$

$$\text{octanol solution } (X_{2,oct}^s) \xrightarrow{\Delta g_3^o} \text{aqueous solution } (X_{2,w}^s)$$

---

$$\text{solid} \xrightarrow{\Delta g_T^o} \text{aqueous solution } (X_{2,w}^s)$$

SCHEME I

The resulting equation is slightly more general than the previously presented equations. Perhaps of more significance is the fact that if the observed solubility differs considerably from the estimated value,

experimental determination of Gibbs energy for each step in Scheme I can be made and the factors responsible for the deviation determined.

## THEORETICAL

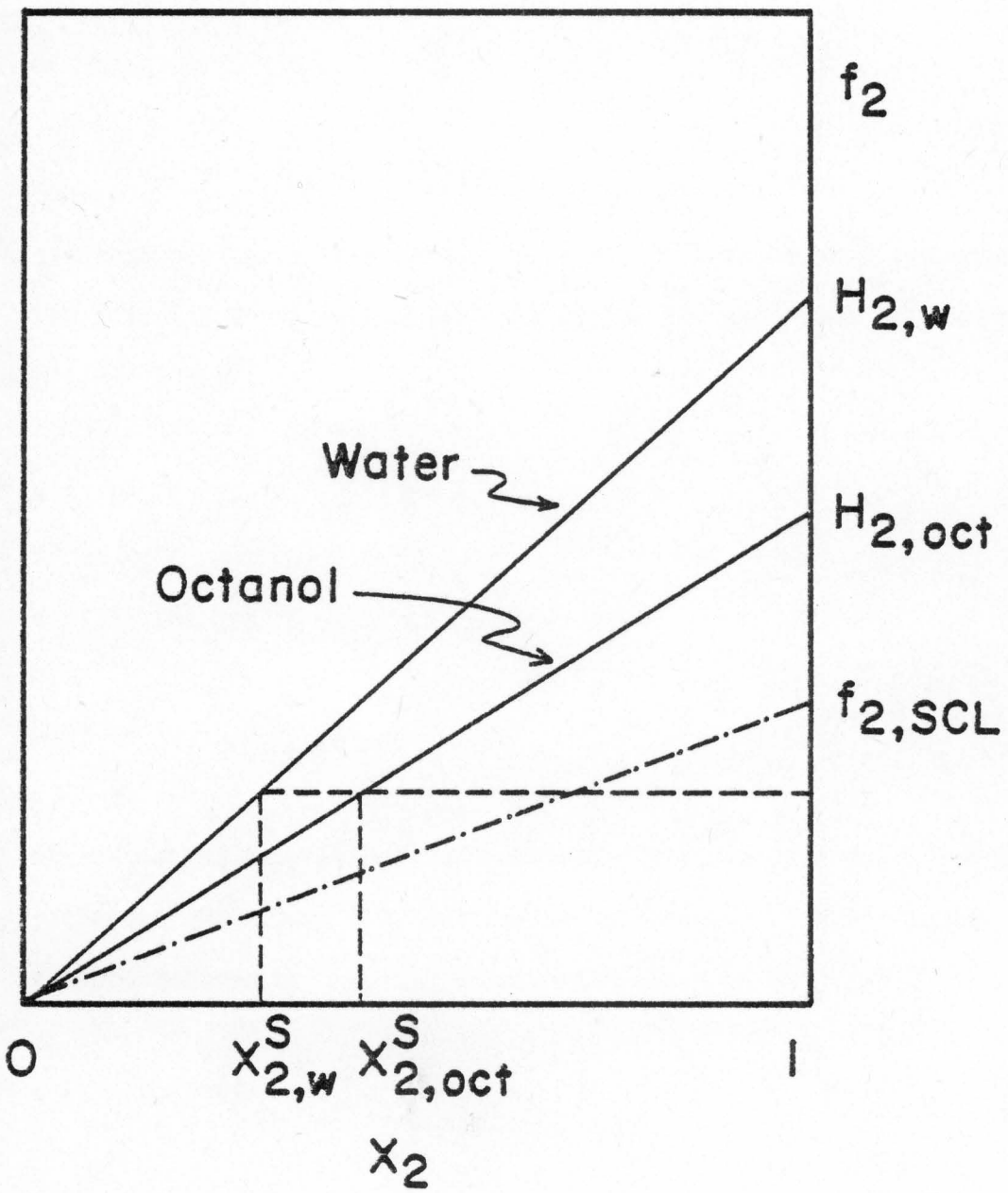
From Scheme I

$$\Delta g_T^o = \Delta g_1^o + \Delta g_2^o + \Delta g_3^o \qquad (1)$$

where $\Delta g^o$ is the Standard Gibbs energy change per mole. Consequently, estimation of the free energy change associated with each step will give $\Delta g_T^o$ and hence the solubility estimate. The equations used to estimate the free energy change associated with each step are generally available in the literature. We give only the brief discussion that follows: Figure 1 presents a hypothetical composite graph of the fugacity vs. composition. In figure 1, $X_2$ represents the solute mole fraction concentration in water or octanol as the solvent, $f_{2,solid}$ and $f_{2,scl}$ the fugacities of the pure solid and (hypothetical) super cooled liquid solute, $H_{2,oct}$ and $H_{2,w}$ the Henry's law constants for the solute in octanol and water respectively, $X_{2,w}^s$ and $X_{2,oct}^s$ represent the solubility of the solute in water and octanol. The Henry's law constants are given by

$$H_{2,w} = f_{2,solid}/X_{2,w}^s \qquad (2)$$

Fig. 1: Fugacity ($f_2$) versus composition diagram.


$f_2$
$H_{2,w}$
Water
$H_{2,oct}$
Octanol
$f_{2,SCL}$
0
$x^S_{2,w}$
$x^S_{2,oct}$
1
$x_2$

$$H_{2,oct} = f_{2,solid}/X^{s}_{2,oct} \quad (3)$$

Henry's law for the solute

$$f_2 = H_2 X_2 \quad (4)$$

is assumed to hold up to the solubility limit in both octanol and water.

The Standard Gibbs energy per mole change for each step in scheme I (see Figure 1) are:

$$\Delta g^{o}_{1} = RT \ln (f_{2,scl}/f_{2,solid}) \quad (5)$$

$$\Delta g^{o}_{2} = RT \ln (H_{2,oct}/f_{2,scl}) \quad (6)$$

$$\Delta g^{o}_{3} = RT \ln (H_{2,w}/H_{2,oct}) \quad (7)$$

Approximating expressions for estimating the standard molar Gibbs energy changes (equations 5-7) can now be introduced. The first step may be approximateed by

$$\Delta g^{o} = \Delta h^{f} (1-T/Tm) \quad (8)$$

where $\Delta h^f$ is the molar heat of fusion of the solute,[1] $T_m$ the melting point (°K) and T the temperature of interest (usually 298°K). The above equation is the ideal solubility equation if we assume that the difference in the heat capacities of the supercooled liquid and crystalline forms of the solute is negligible. This has been shown to be a reasonable approximation (Yalkowsky and Valvani, 1980) when describing the aqueous solubility of a large number of organic non-electrolytes.

The second step (supercooled liquid solute → solute in octanol) is a mixing process which may be estimated by the well-known regular solution theory (Hildebrand et al., 1970) since only relatively non-polar substances are involved. Thus equation 6 may be written as

$$\Delta g_2^o = V_2 \phi_{oct}^2 (\delta_{oct} - \delta_2)^2 \qquad (9)$$

where $V_2$ is the solute molar volume, $\phi_{oct}$ the volume fraction of octanol in the solution (usually it is assumed that $\phi_{oct} = 1$) and $\delta_{oct}$ and $\delta_2$ one, respectively, the octanol and solute solubility parameters.

The third step (solute in octanol → solute in water) involves the distribution of the solute between octanol and water and hence may be estimated by

$$\Delta g_3^o = RT \ln (PC_x) \qquad (10)$$

---

1. Note that step one (equation 8) is only needed for solids.

where $PC_x$ is the octanol-water partition coefficient of the solute on a mole fraction basis. We assume here that $PC_x$ is concentration independent which is not unreasonable when one is dealing with non-electrolytes of low solubility.

Equations 1, 8, 9, and 10 combine to give

$$\Delta g_T^o = \Delta h^f(1-T/T_m) + V_2\phi_{oct}^2(\delta_{oct} - \delta_2)^2 + RT \ln_x(PC_x) \quad (11)$$

Since

$$\Delta g_T^o = RT \ln (H_{2,w}/f_{2,solid}) \quad (12)$$

$$= -RT \ln X_{2,w}^s \quad (13)$$

From equation 2 and figure 1, combining equations 13 and 11 gives an expression for the mole fraction solubility of solute, $X_{2,w}^s$, in water

$$\ln X_{2,w}^s = \frac{-\Delta h^f}{RT}(1-T/T_m) - \frac{V_2 \phi_{oct}^2(\delta_{oct}-\delta_2)^2}{RT} - \ln PC_x \quad (14)$$

Using $T = 298°K$, $\phi_{oct} = 1$, $\Delta S^f = \Delta h^f / T_m$, $\delta_{oct} = 10.3$ and the fact that the commonly used molar partition coefficient, PC, is related approximately to $PC_x$ by the equation

$$\log PC_x = \log PC + 0.94 \quad (15)$$

$$\log X^{s}_{2,w} = -0.94 - 7.3 \times 10^{-4}[\Delta S^{f}(T_m-298)] - 7.3 \times 10^{-4}[V_2(10.3-\delta_2)^2] - \log PC \quad (16)$$

The molar solubility $C^{s}_{2,w}$ is given by (approximately)

$$\log C^{s}_{2,w} = \log X^{s}_{2,w} + 1.74 \quad (17)$$

Thus, the molar solubility equation is

$$\text{Log } C^{s}_{2,w} = 0.80 - 7.3 \times 10^{-4}[\Delta S^{f}(T_m-298)]-7.3 \times 10^{-4}[V_2(10.3-\delta_2)^2] - \log PC \quad (18)$$

## RESULTS AND DISCUSSION

Equations 16 and 18 are identical with equations 26 and 29 of Yalkowsky and Valvani (1980), except for the inclusion of the solubility parameter term. Regression analysis on rigid compounds gave (Yalkowsky and Valvani, 1980)

$$\log C^{s}_{2,w} = -1.05 \log PC - 0.012\ MP + 0.87 \quad (19)$$

For rigid molecules ($\Delta S^{f}$ = 13.5 eu) equation 18 gives

$$\text{Log } C^{s}_{2,w} = 0.80-0.0099\ (MP-25)-7.3 \times 10^{-4}[V_2(10.3-\delta_2)^2]-\log PC \quad (20)$$

where MP is the melting point in °C and the temperature of interest is 25°C. Assuming $\delta_2$ = 10.3 for all compounds gives

$$\log C^s_{2,w} = 1.05 - 0.0099\ MP - \log PC \qquad (21)$$

Equations 21 and 19 are remarkably close. Note that the solubility parameter term in equation 20 is always negative (i.e. lowers solubility). Neglecting this term is the likely reason for the coefficients of the log PC and MP terms being more negative in equation 19 than expected from equations 20 or 21. Since equation 19 provided a remarkably good fit to the data (Yalkowsky and Valvani, 1980) it is expected that equation 20 should also.

For liquids, the regression result is (Yalkowsky and Valvani, 1980)

$$\log X^s_{2,w} = -1.08 \log PC - 1.04 \qquad (22)$$

and equation 16 gives

$$\log X^s_{2,w} = -\log PC - 0.94 \qquad (23)$$

assuming $\delta_2$ = 10.3. As expected, the agreement between equations 22 and 23 is excellent.

To further assess the quality of equations 16 and 18, we present in Table 1, the experimental and calculated (equation 18) solubilities for liquids at room temperature, using literature data for all required parameters ($V_2$, $\delta_2$ and log PC) Table 2 contains the results for solids and Table 3 gives the experimental data used for the solubility estimate of the solids. Figure 2 presents a graph of the error, log $C^s_{2,w}$ (observed) - log $C^s_{2,w}$ (predicted) versus log PC for both equation 18 of this work and the regression equation of Yalkowsky and Valvani (1980) (equation 19) for liquids. The standard error of the estimate using equation 18 is 0.51 while that using the regression equation is 0.46. These results indicate that the derived equation (equation 18) does nearly as well as the regression equation. The error terms in Figure 2 are comparable in all cases. There is a slight trend evident in Figure 2 for the error term to increase with increasing partition coefficient, but the trend is similar for both approaches. The error term for the solid compounds is also presented in Figure 2. The result for the solids appears to be similar to that for liquids.

The individual terms in equation 18 are given in Tables 1 and 2. For both liquids and solids the log PC term is the dominating term. For solids the entropy of fusion term (ideal solubility based on $\Delta Cp = 0$) also makes a substantial contribution. The solubility parameter term is usually small. Consequently the assumption of ideal solubility (made by Yalkowsky and Valvani, 1980) of all compounds in octanol ($\delta_2 = \delta_{oct} =$

Table 1: Solubility Estimates for Liquids

(a): From Valvani et al. (1981)

(b): From Hoy (1970)

Table 1: Solubility Estimates for Liquids

| Compound | log PC[a] | $V_2$[b] | $\delta_2$[b] | $7.3 \times 10^{-4} V_2(10.3-\delta_2)^2$ | log $C^s_{2,w}$ Calculated | log $C^s_{2,w}$ Experimental[a] |
|---|---|---|---|---|---|---|
| Carbon tetrachloride $CCl_4$ | 2.83 | 97.10 | 8.55 | 0.2171 | -2.25 | -2.22 |
| Chloroform $CHCl_3$ | 1.96 | 80.64 | 9.16 | 0.0765 | -1.24 | -1.12 |
| Dichloromethane $CH_2Cl_2$ | 1.25 | 64.51 | 9.88 | 0.0083 | -0.46 | -0.66 |
| Acrylonitrile $C_3H_3N$ | -0 .92 | 66.28 | 10.56 | 0.0033 | 1.72 | 0.15 |
| Methyl acetate $C_3H_6O_2$ | 0.18 | 79.88 | 9.46 | 0.0412 | 0.58 | 0.61 |
| Chloropropane $C_3H_7Cl$ | 2.04 | 88.74 | 8.39 | 0.2363 | -1.48 | -1.46 |
| Ethyl acetate $C_4H_8O_2$ | 0.70 | 99.53 | 8.91 | 0.1404 | -0.04 | -0.06 |
| 2-butanol $C_4H_{10}O$ | 0.61 | 92.41 | 11.08 | 0.0410 | 0.15 | 0.39 |
| 1-pentanol $C_5H_{12}O$ | 1.48 | 108.7 | 11.12 | 0.0534 | -0.73 | -0.60 |
| 3-pentanol $C_5H_{12}O$ | 1.21 | 108.0 | 10.16 | 0.0015 | -0.41 | -0.24 |
| 1,2-dichlorobenzene $C_6H_4Cl_2$ | 3.38 | 113.1 | 10.04 | 0.0056 | -2.59 | -3.13 |
| Benzene $C_6H_6$ | 2.01 | 89.41 | 9.16 | 0.0848 | -1.65 | -1.29 |
| Cyclohexanone $C_6H_{10}O$ | 0.81 | 104.2 | 10.42 | 0.0011 | -0.01 | -0.05 |
| Cyclohexane $C_6H_{12}$ | 3.44 | 108.8 | 8.19 | 0.3535 | -2.99 | -3.07 |
| 2-hexanone $C_6H_{12}O$ | 1.38 | 124.2 | 8.63 | 0.2528 | -0.83 | -0.84 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Hexanoic Acid $C_6H_{12}O_2$ | 1.90 | 125.9 | 11.68 | 0.1750 | -1.27 | -1.07 |
| 2,2-dimethylbutane $C_6H_{14}$ | 3.82 | 133.7 | 6.71 | 1.258 | -4.28 | -3.61 |
| 2,3-dimethylbutane $C_6H_{14}$ | 3.85 | 131.1 | 6.97 | 1.062 | -4.11 | -3.62 |
| 3,3-dimethyl 2-butanol $C_6H_{14}O$ | 1.48 | 125.4 | 9.51 | 0.0572 | -0.74 | -0.65 |
| Dipropylamine $C_6H_{15}N$ | 1.70 | 138.2 | 7.97 | 0.5475 | -1.45 | -0.54 |
| Triethylamine $C_6H_{15}N$ | 1.45 | 139.9 | 7.42 | 0.8473 | -1.50 | -0.83 |
| Benzyl alcohol $C_7H_8O$ | 1.02 | 103.8 | 12.05 | 0.2321 | -0.45 | -0.45 |
| Methyl benzoate $C_8H_8O_2$ | 2.12 | 125.9 | 10.19 | 0.0011 | -1.32 | -1.81 |
| Ethyl benzene $C_8H_{10}$ | 3.15 | 123.1 | 8.84 | 0.1916 | -2.54 | -2.81 |
| Dibutylamine $C_8H_{19}N$ | 2.75 | 170.7 | 8.15 | 0.5758 | -2.53 | -1.44 |
| Ethyl benzoate $C_9H_{10}O_2$ | 2.64 | 144.2 | 9.75 | 0.0318 | -1.87 | -2.22 |
| n-Propyl benzene $C_9H_{12}$ | 3.63 | 140.1 | 8.64 | 0.2818 | -3.11 | -3.14 |
| Isopropyl benzene $C_9H_{12}$ | 3.66 | 140.2 | 8.60 | 0.2958 | -3.16 | -3.33 |
| 1,3,5-trimethylbenzene $C_9H_{12}$ | 3.42 | 139.6 | 8.88 | 0.2054 | -2.83 | -3.25 |
| Diphenylether $C_{12}H_{12}O$ | 4.28 | 160.4 | 10.10 | 0.0047 | -3.48 | -2.60 |
| 1-dodecanol $C_{12}H_{26}O$ | 5.13 | 224.6 | 9.78 | 0.0443 | -4.37 | -4.80 |
| Diphenyl methane $C_{13}H_{12}$ | 4.14 | 167.9 | 9.57 | 0.0653 | -3.40 | -4.07 |

Table 2: Solubility Estimates for Solids

(a): From Hansch and Leo (1979)

(b): From Yalkowsky and Valvani (1980)

(c): From Seidell (1941)

Table 2: Solubility Estimates for Solids

| Compound | $7.3 \times 10^{-4}[\Delta S^f(T_m-298)]$ | log PC[a] | $7.3 \times 10^{-4}\ V_2(10.3 - \delta_2)^2$ | log $C^s_{2,w}$ | |
|---|---|---|---|---|---|
| | | | | Calculated | Experimental |
| p-Dichlorobenzene $C_6H_4Cl_2$ | 0.269 | 3.39 | 0.030 | -2.89 | -3.21[b] |
| Benzoic Acid $C_7H_6O_2$ | 0.744 | 2.0 | 0.426 | -2.37 | -1.55[c] |
| Phenylacetic Acid $C_8H_8O_2$ | 0.374 | 1.46 | 0.041 | -1.07 | -0.896[c] |
| Naphthalene $C_{10}H_8$ | 0.513 | 3.30 | 0.000 | -3.01 | -3.61[b] |
| 2-naphthol $C_{10}H_8O$ | 0.801 | 2.86 | 0.035 | -2.89 | -2.29[c] |
| Anthracene $C_{14}H_{10}$ | 1.97 | 4.45 | 0.025 | -5.65 | -6.19[b] |
| Phenanthrene $C_{14}H_{10}$ | 0.628 | 4.46 | 0.362 | -4.65 | -5.11[b] |

Fig. 2: Graph of Log $C^{s}_{2,w}$ (observed) - Log $C^{s}_{2,w}$ (predicted) versus log partition coefficient.

Open bars  , obtained from data in Valvani, Yalkowsky and Roseman (1981)

Closed bars  , this work

 , solids.

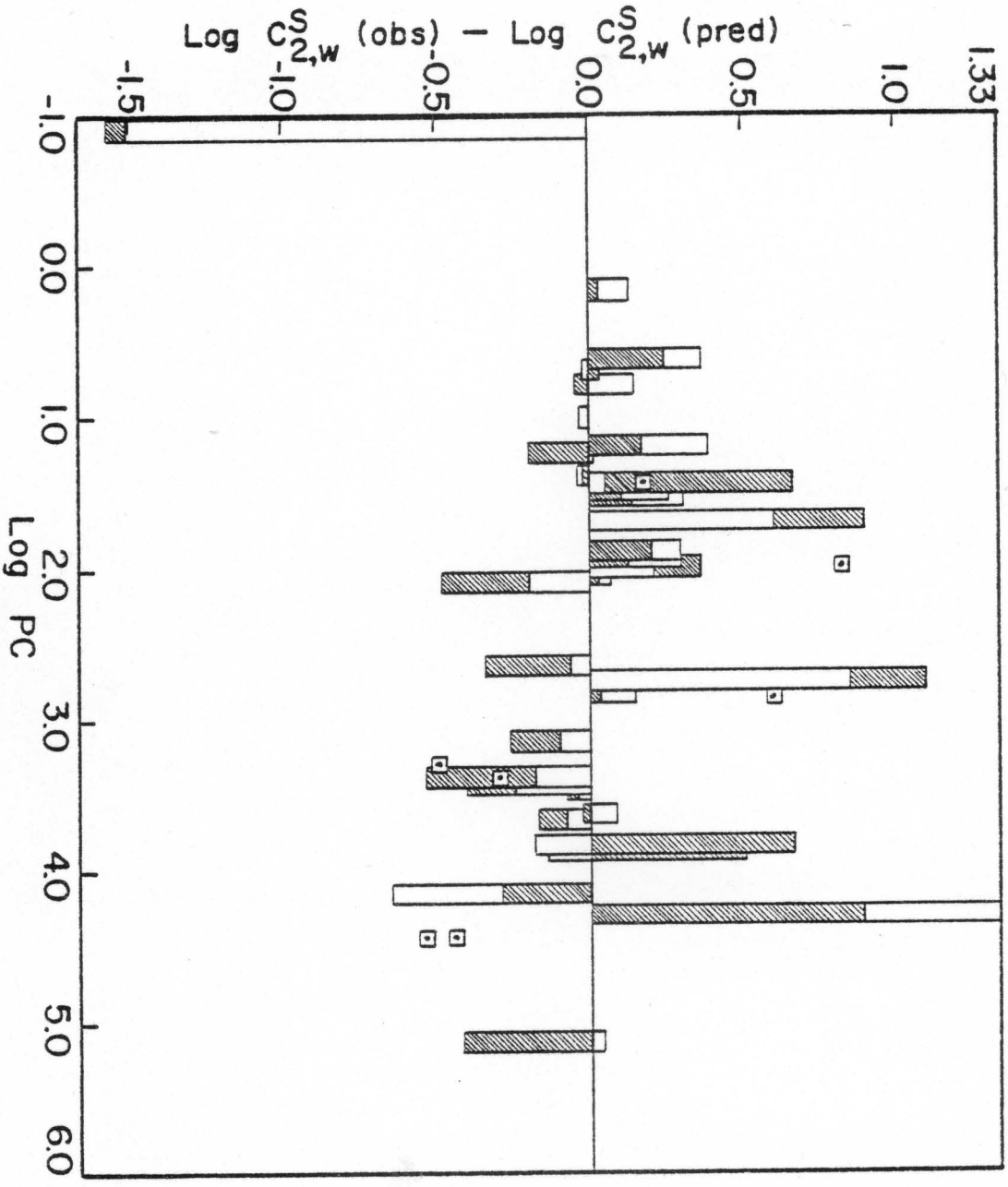

Log $C^{S}_{2,w}$ (obs) − Log $C^{S}_{2,w}$ (pred)
-1.5
-1.0
-0.5
0.0
0.5
1.0
1.33
-1.0
0.0
1.0
2.0
3.0
4.0
5.0
6.0
Log PC

Table 3: Literature Data for Solids

(a): From Handbook of Physics and Chemistry, $54^{th}$ Ed., C.R.C. Press, 1974.

(b): Calculated from enthalpies of vaporization obtained from Dreisbach (1955).

(c): Calculated from enthalpies of vaporization obtained from vapor pressure data in ref. (a) above.

Table 3: Literature Data for Solids

| Compound | $\Delta S^f$(e.u)[a] | $T_m$(°K)[a] | $V_2$[a] | $\delta_2$ |
|---|---|---|---|---|
| p-Dichlorobenzene | 13.1 | 326.1 | 117.8 | 9.71[b] |
| Benzoic Acid | 10.47 | 395.4 | 96.47 | 12.76[c] |
| Phenylacetic Acid | 9.91 | 349.7 | 124.8 | 10.97[c] |
| Naphthalene | 12.72 | 353.2 | 126.1 | 10.24[b] |
| 2-naphthol | 11.47 | 393.6 | 112.7 | 10.95[c] |
| Anthracene | 14.09 | 489.5 | 138.9 | 10.80[c] |
| Phenanthrene | 12.07 | 369.3 | 181.9 | 8.65[c] |

10.3 in equation 18) appears to be a reasonable approximation to make especially when the required data is not available.

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# APPENDIX B:

## Program and Typical Output for Estimating Binary Solvent Interaction Constants from Total Vapor Pressure-Composition Data.

```
      PARAMETER
     1 NEXPD=50,
     2 NVAR=2,
     3 NPD=2,
     4 NRØBS=NEXPD,
     5 NRPRD=NEXPD,
     6 NS=(17+NEXPD*NVAR)*NPD+2*NRPRD*NVAR+2*(NPD+1)*(NPD+2)+1
      REAL  THINT(NPD), THFIN(NPD), YØBS(NRØBS,NVAR), YPRD(NRØBS,NVAR),
     1 S(NS), TØL(4), X(NEXPD), BNDLØ(NPD), BNDHI(NPD), NAMES(NPD),
     2 DIFF(NPD), FIX(NPD), WTS(NRØBS,NVAR), Z(NEXPD)
      INTEGER  ITEMS(12), INFØ(7), IDENT(13), NEXP
      CØMMØN/ MØLE / X
      CØMMØN  P10,P30,Q1,Q3,Z
      DATA  FIX/2*1.0/
      DATA  DIFF/2*0.005/
      DATA  BNDLØ/2*-1.0E+1 /
      DATA  BNDHI/2*+1.0E+1/
      DATA  NAMES/6H A13  ,6H A31  /
      DATA  TØL/1.5E-6, 1.0E-9, 0.0, 1.0E-16/
      DATA  INFØ/1, 10, 5*1/
      DATA  ITEMS/1, NVAR, 2, NRØBS, NRPRD, NRØBS, 'MARQ', 'ALL',
     1      'NREG', 'CENT', 'REL', 50 /
      READ(-,40) (IDENT(I), I=1,13)
 40   FØRMAT(13A6)
      READ(-,-) P10, P30
      READ(-,-)Q1, Q3
      READ(-,-) A13, A31
      THINT(1)=A13
      THINT(2)=A31
      READ(-,-) NEXP
      ITEMS(1)=NEXP
      READ(-,-) (YØBS(I,1), X(I), I=1,NEXP)
      DØ 50 I=1,NEXP
      WTS(I,1)=(1/(YØBS(I,1)))**2
      WRITE(-,-) WTS(I,1)
 50   CØNTINUE
      WRITE(-,60) P10, P30
 60   FØRMAT(1X, 'P10=', F10.4,   'P30=',F10.4)
      WRITE(-,61) Q1, Q3
 61   FØRMAT(1X, 'Q1=',F10.4, 'Q3=', F10.4)
      WRITE(-,62) A13, A31
 62   FØRMAT(10X, 'A13=',F10.5, 'A31=',F10.5)
      WRITE(-,63) NEXP
 63   FØRMAT(1X, 'NUMBER ØF MØLE FRACTIØNS=', I3)
      WRITE(-,64) (YØBS(I,1), X(I), I=1,NEXP)
 64   FØRMAT('1',5X, 'TØTAL PRESSURE', 5X, 'MØLE FRACTIØN' /
     1          5X, F10.4, 10X, F10.5)
      EXTERNAL F, DERIV
      CALL NREG(THINT,NAMES,BNDLØ,BNDHI,FIX,DIFF,THFIN,YØBS,
     1   YPRD,WTS,F,'NØNE',ITEMS,TØL,INFØ,IDENT,S)
      END
*** TØP ØF FILE ***
```

```
      SUBROUTINE F(TH,Y,NEXP,NVAR,NP,NRPRD)
      DIMENSION TH(1),Y(NRPRD,NVAR),X(1),Z(1)
      COMMON/ MOLE /X
      COMMON P10,P30,Q1,Q3,Z
      A13=TH(1)
      A31=TH(2)
C     WRITE(-,-)  (X(I), I=1,NEXP)
C     WRITE(-,-) P10,  P30,    Q1,  Q3
      DO 200 I=1,NEXP
         X11=X(I)
         X3=1.0-X11
         Z1=X11*Q1/(X11*Q1+X3*Q3)
         Z3=1.0-Z1
         G1=A13*Z3*Z3*(1.0-2.0*Z1) + A31*2.0*Z1*Z3*Z3*Q1/Q3
         G3=A31*Z1*Z1*(1.0-2.0*Z3) + A13*2.0*Z3*Z1*Z1*Q3/Q1
C     WRITE(-,-) X11,X3,Z1,Z3
C     WRITE(-,-) G1,  G3
         Y(I,1)=EXP(G1)*P10*X11 + EXP(G3)*P30*X3
 200  CONTINUE
      RETURN
      END
*** TOP OF FILE ***
```

```
      1.2346E-02
      3.7045E-03
      2.2104E-03
      1.4017E-03
      9.1163E-04
      6.0161E-04
      4.5521E-04
      4.4735E-04
      3.8102E-04
      3.2638E-04
P10=    53.5700P30=      .3200
01=    58.6300Q3=    73.6900
          A13=    1.50000A31=     .60000
NUMBER OF MOLE FRACTIONS= 10

      TOTAL PRESSURE      MOLE FRACTION
        9.0000                .12540

      TOTAL PRESSURE      MOLE FRACTION
        16.4300               .22530

      TOTAL PRESSURE      MOLE FRACTION
        21.2700               .29960

      TOTAL PRESSURE      MOLE FRACTION
        26.7100               .39740

      TOTAL PRESSURE      MOLE FRACTION
        33.1200               .51350

      TOTAL PRESSURE      MOLE FRACTION
        40.7700               .61310

      TOTAL PRESSURE      MOLE FRACTION
        46.8700               .70660

      TOTAL PRESSURE      MOLE FRACTION
        47.2800               .73640

      TOTAL PRESSURE      MOLE FRACTION
        51.2300               .86430

      TOTAL PRESSURE      MOLE FRACTION
        55.3100               .93860

MADISON ACADEMIC COMPUTING CENTER - SUBROUTINE NREG                    04/20/82     TRANSMITTAL NO.  Y52106     CALL  1
   PAGE   1
ETHANOL
```

## SUMMARY ØF THE DATA

### ITEMS

ITEMS(1): NEXP = 10 NUMBER ØF EXPERIMENTS
ITEMS(2): NVAR = 2 NUMBER ØF VARIABLES
ITEMS(3): NP = 2 NUMBER ØF PARAMETERS
VES

ITEMS(4): NRØWS = 50 ROW DIMENSIØN ØF ARRAY YØBS
ITEMS(5): NRPRD = 50 RØW DIMENSIØN ØF ARRAY YPRD
ITEMS(6): NRWTS = 50 RØW DIMENSIØN ØF ARRAY WTS
TIØNS

ITEMS(7): METHØD = 'MARQ' MARQUARDT'S METHØD
ITEMS(8): KWTS = 'ALL' WEIGHTING BY ØBSERVATIØN
ITEMS(9): KDERIV = 'NREG' NREG CALCULATED DERIVATI

ITEMS(10): KSYM = 'CENT' CENTRAL DIFFERENCES
ITEMS(11): KDIFF = 'REL' RELATIVE DIFFERENCES

ITEMS(12): MAXIT = 50 LIMIT ØN NUMBER ØF ITERA

### TØLERANCES

TØL(1) = 1.5000000-06 REL. CHANGE IN A PARAMETER
TØL(2) = 1.0000000-09 REL. CHANGE IN SUM ØF SQUARES
TØL(3) = 0.0000000 RATIØ TØ INITIAL SUM ØF SQUARES
TØL(4) = 1.0000000-16 PIVØT TØLERANCE

### SUNDRIES

NUMBER ØF ACTIVE PARAMETERS = 2
NUMBER ØF CELLS ØF SCRATCH REQUIRED = 299

### PARAMETERS

| NØ. | NAME | INITIAL VALUE | PRØJECTIØN FØR DERIV. ESTIMATE | LØWER BØUND | UPPER BØUND |
|---|---|---|---|---|---|
| 1 | A13 | 1.5000000+00 | 5.0000000-03 | -1.0000000+01 | 1.0000000+01 |
| 2 | A31 | 5.9999999-01 | 5.0000000-03 | -1.0000000+01 | 1.0000000+01 |

## SINGULAR VALUES AND VECTØRS AT INITIAL PØINT

SING. VALUES 1.7659621+00 4.6272034-01

PAR. 1 A13 -.9519605 .3062207
2 A31 -.3062207 -.9519605

SETUP TIME = .041 SECØNDS

## THE ITERATIØNS

| ITERATIØN NØ. 1 | | | BASE PØINT | | TEST PØINT |
|---|---|---|---|---|---|
| SUM ØF SQUARES | | | 2.5414972+00 | | 1.3620503-01 |
| L | | | 0 | | 0 |
| LAMBDA | | | 0.0000000 | | 0.0000000 |
| GAMMA | | | 1.0000000+00 | | 1.0000000+00 |
| ANGLE IN DEGREES | | | .0000 | | 5.0993 |
| MAX. PIVØT REDUCTIØN | | | 1.0000000+00 | | 4.8224743-01 |
| PAR. | 1 | A13 | 1.5000000+00 | | 6.1700776-01 |
| | 2 | A31 | 5.9999999-01 | S | 4.0658491-01 |

CUMULATIVE NØ. ØF FUNCTIØN CALLS = 2 ITERATIØN TIME = .018 SECØNDS CUMULATIVE TIME = .059 SECØNDS

## THE LAST ITERATIØN

| ITERATIØN NØ. 6 | | | BASE PØINT | | TEST PØINT |
|---|---|---|---|---|---|
| SUM ØF SQUARES | | | 6.4334164-03 | | 6.4334156-03 |
| L | | | 1 | | 0 |
| LAMBDA | | | 1.5640612-01 | | 0.0000000 |
| GAMMA | | | 1.0000000+00 | | 1.0000000+00 |
| ANGLE IN DEGREES | | | 30.3513 | | 43.6909 |
| MAX. PIVØT REDUCTIØN | | | 1.2427103+00 | | 6.4135926-01 |
| PAR. | 1 | A13 | S 1.6327188-01 | S | 1.6327189-01 |
| | 2 | A31 | 5.6332760-01 | | 5.6332732-01 |

CUMULATIVE NØ. ØF FUNCTIØN CALLS = 8 ITERATIØN TIME = .012 SECØNDS CUMULATIVE TIME = .121 SECØNDS

ITERATIØN TERMINATES:
MAX. RELATIVE CHANGE IN A PARAMETER .LT. TØL(1) = 1.5000000-06



## FINAL PARAMETER VALUES

| | | | FINAL VALUE | SUM ØF SQUARES = 6.4334157-03 |
|---|---|---|---|---|
| AR. | 1 | A13 | 1.6327189-01 | |
| | 2 | A31 | 5.6332732-01 | |

## ITERATIØN SUMMARY

| ITER NØ. | TIME IN SECØNDS | SUM ØF SQUARES | L | LAMBDA | GAMMA | ANGLE | NØ. PIVØT FAILURES | NØ. BØUNDS FAILURES | MAX. PIVØT REDUCTIØN |
|---|---|---|---|---|---|---|---|---|---|
| 0 | .000 | 2.5414972+00 | 0 | 0.0000000 | 1.0000000+00 | .0000 | 0 | 0 | 1.0000000+00 |
| 1 | .018 | 1.3620503-01 | 0 | 0.0000000 | 1.0000000+00 | 5.0993 | 0 | 0 | 4.3224743-01 |
| 2 | .019 | 7.6263520-03 | 0 | 0.0000000 | 1.0000000+00 | 34.9776 | 0 | 0 | 5.9321190-01 |
| 3 | .008 | 6.4335989-03 | 0 | 0.0000000 | 1.0000000+00 | 34.7799 | 0 | 0 | 6.3699862-01 |
| 4 | .007 | 6.4334167-03 | 0 | 0.0000000 | 1.0000000+00 | 27.1777 | 0 | 0 | 6.4179967-01 |
| 5 | .016 | 6.4334164-03 | 1 | 1.5640612-01 | 1.0000000+00 | 30.3513 | 0 | 0 | 1.2427103+00 |
| 6 | .012 | 6.4334156-03 | 0 | 0.0000000 | 1.0000000+00 | 43.6909 | 0 | 0 | 6.4185926-01 |

## SINGULAR VALUES AND VECTØRS AT TERMINAL PØINT

| | | | | |
|---|---|---|---|---|
| SING. VALUES | | | 3.7268750-01 | 3.7320502-01 |
| PAR. | 1 | A13 | -.9009461 | .4339310 |
| | 2 | A31 | -.4339310 | -.9009461 |

## NØRMALIZING ELEMENTS AND CØRRELATIØN MATRIX

| PARAMETER NØ. | | | 1 | 2 |
|---|---|---|---|---|
| NØRM. ELTS. | | | 1.5549003+00 | 2.4647543+00 |
| PAR. | 1 | A13 | 1.0000000 | |
| | 2 | A31 | -.5934549 | 1.0000000 |



## CØNFIDENCE LIMITS ØN LINEAR HYPØTHESIS

| | | | LØWER LIMIT | FINAL VALUE | UPPER LIMIT |
|---|---|---|---|---|---|
| PAR. | 1 | A13 | 1.0443003-01 | 1.6327139-01 | 2.2206376-01 |
| | 2 | A31 | 4.7563326-01 | 5.6332732-01 | 6.6202139-01 |

EXPLØRATIØN

| NEAR EST. ØF M ØF SQUARES | | | LØWER TEST | SUM ØF SQUARES | LINEAR EST. ØF SUM ØF SQUARES | UPPER TEST | SUM ØF SQUARES | LI SU |
|---|---|---|---|---|---|---|---|---|
| PAR. .5726263-03 | 1 | A13 | 1.4857393-01 | 6.5713995-03 | 6.5726263-03 | 1.7796936-01 | 6.5735415-03 | 6 |
| .5726263-03 | 2 | A31 | 5.4552831-01 | 6.5723427-03 | 6.5726263-03 | 5.9212534-01 | 6.5736404-03 | 6 |

MADISØN ACADEMIC CØMPUTING CENTER - SUBRØUTINE NREG 04/20/32 TRANSMITTAL NØ. Y52106 CALL 1

PAGE 5

ETHANØL

FINAL FUNCTIØN VALUES AND RESIDUALS

WEIGHTED RØØT MEAN SQUARE RESIDUAL = 1.3905343-02 NØ. DEGREES ØF FREEDØM = 18

THIS IS THE SCALE UNIT IN THE GRAPH ØF THE WEIGHTED RESIDUALS.

| EXPT. NØ. | VAR. NØ. | PREDICTIØN | ØBSERVATIØN | RESIDUAL | WEIGHTED RES. | GRAPH ØF WEIGHTED RESIDUAL -2 -1 0 +1 |
|---|---|---|---|---|---|---|
| 1 | 1 | 9.0670960+00 | 9.0000000+00 | -6.7095995-02 | -7.4551105-03 | ***** |
| 2 | 1 | 1.6072644+01 | 1.6430000+01 | 3.5735617-01 | 2.1736742-02 | ********** |
| 3 | 1 | 2.1031017+01 | 2.1270000+01 | 1.3393296-01 | 8.3849536-03 | ****** |
| 4 | 1 | 2.7399042+01 | 2.6710000+01 | -6.8904233-01 | -2.5797167-02 | ********** |
| 5 | 1 | 3.4236205+01 | 3.3120000+01 | -1.1662054+00 | -3.5211516-02 | ********** |
| 6 | 1 | 3.9830367+01 | 4.0770000+01 | 8.3963313-01 | 2.1320779-02 | ********** |
| 7 | 1 | 4.4224616+01 | 4.4670000+01 | 2.6453343+00 | 5.6440335-02 | ********** |
| ********** | | | | | | ********* |
| 8 | 1 | 4.7952353+01 | 4.7230000+01 | -6.7235351-01 | -1.4220781-02 | ***** |
| 9 | 1 | 5.1601669+01 | 5.1230000+01 | -3.7166929-01 | -7.2549149-03 | ** |
| 10 | 1 | 5.5226055+01 | 5.5310000+01 | 8.3945274-02 | 1.5177233-03 | * |
| 1 | 2 | 0.0000000 | 0.0000000 | 0.0000000 | 0.0000000 | * |
| 2 | 2 | 0.0000000 | 0.0000000 | 0.0000000 | 0.0000000 | * |
| 3 | 2 | 0.0000000 | 0.0000000 | 0.0000000 | 0.0000000 | * |
| 4 | 2 | 0.0000000 | 0.0000000 | 0.0000000 | 0.0000000 | * |
| 5 | 2 | 0.0000000 | 0.0000000 | 0.0000000 | 0.0000000 | * |
| 6 | 2 | 0.0000000 | 0.0000000 | 0.0000000 | 0.0000000 | * |
| 7 | 2 | 0.0000000 | 0.0000000 | 0.0000000 | 0.0000000 | * |
| 8 | 2 | 0.0000000 | 0.0000000 | 0.0000000 | 0.0000000 | * |
| 9 | 2 | 0.0000000 | 0.0000000 | 0.0000000 | 0.0000000 | * |
| 10 | 2 | 0.0000000 | 0.0000000 | 0.0000000 | 0.0000000 | * |

TIME SINCE END ØF THE LAST ITERATIØN = .121 SECØNDS TØTAL TIME = .242 SECØNDS

# APPENDIX C:

## Program and Typical Output for Estimating Ternary Solvent Interaction Constants from Total Vapor Pressure-Composition Data.

```
      PARAMETER
     1 NEXPD=50,
     2 NVAR=3,
     3 NPD=7,
     4 NRØBS=NEXPD,
     5 NRPRD=NEXPD,
     6 NS=(17+NEXPD*NVAR)*NPD+2*NRPRD*NVAR+2*(NPD+1)*(NPD+2)+1
       REAL  THINT(NPD), THFIN(NPD), YØBS(NRØBS,NVAR), YPRD(NRØBS,NVAR),
     1 S(NS), TØL(4), X(NEXPD,NVAR), BNDLØ(NPD), BNDHI(NPD), NAMES(NPD),
     2 DIFF(NPD), FIX(NPD), WTS(NRØBS,NVAR), ZØNEXPD)
       INTEGER  ITEMS(12), INFØ(7), IDENT(13), NEXP
       CØMMØN/ MØLE / X
       CØMMØN  P10,P30,P40,Q1,Q3,Q4,Z
       DATA FIX/6*0,1/
       DATA DIFF/7*0.005/
       DATA BNDLØ/7* -1.0E+2/
       DATA BNDHI/7* +1.0E+2/
       DATA TØL/1.5E-6,1.0E-9,0.0,1.0E-16/
       DATA NAMES/6H A13   ,6H A31   ,6H A14   ,6H A41   ,
     1  6H A34   ,6H A43   ,6H G134   /
       DATA INFØ/1,  10,  5*1/
       DATA ITEMS/1,NVAR,7,NRØBS,NRPRD,NRØBS,'MARQ','ALL',
     1 'NREG','CENT','REL',50/
       READ(-,40) (IDENT(I), I=1,13)
  40   FØRMAT(13A6)
       READ(-,-) P10,P30, P40
       READ(-,-) Q1,Q3,Q4
       READ(-,-) A13,A31
       READ(-,-) A14,A41
       READ(-,-) A34,A43,G134
       THINT(1)=A13
       THINT(2)=A31
       THINT(3)=A14
       THINT(4)=A41
       THINT(5)=A34
       THINT(6)=A43
       THINT(7)=G134
       READ(-,-) NEXP
       ITEMS(1)=NEXP
       READ(-,-) (YØBS(I,1), X(I,1),X(I,2),X(I,3), I=1,NEXP)
       DØ 50 I=1,NEXP
       WTS(I,1)=(1/(YØBS(I,1)))**2
       WRITE(-,-) WTS(I,1)
  50   CØNTINUE
       WRITE(-,60) P10,P30,P40
  60   FØRMAT(1X, 'P10=',F10.4, 'P30=',F10.4, 'P40=',F10.4)
       WRITE(-,61) Q1,   Q3,   Q4
  61   FØRMAT(1X,'Q1=',F10.4, 'Q3=',F10.4,  'Q4=',F10.4)
       WRITE(-,62) A13,A31,A14,A41,A34,A43,G134
  62   FØRMAT(10X,'A13=',F10.5, 'A31=',F10.5, 'A14=',F10.5,
     1 'A41=',F10.5, 'A34=',F10.5, 'A43=',F10.5, 'G134=',F10.5)
       WRITE(-,63) NEXP
  63   FØRMAT(1X,'NUMBER ØF PØINTS=',I3)
       WRITE(-,64)
  64   FØRMAT ('1',5X,'TØTAL PRESS', 5X, 'MØLE FRACTIØNS 1,3,4,')
       WRITE(-,65) (YØBS(I,1),X(I,1),X(I,2),X(I,3), I=1,NEXP)
  65   FØRMAT(10X,F10.4, 10X,F10.5, 3X,F10.5,3X,F10.5)
       EXTERNAL F,DERIV
       CALL NREG(THINT,NAMES,BNDLØ,BNDHI,FIX,DIFF,THFIN,YØBS,YPRD,
     1 WTS,F,'NØNE',ITEMS,TØL,INFØ,IDENT,S)
       END
```

```
      SUBRØUTINE F(TH,Y,NEXP,NVAR,NP,NRPRD)
      DIMENSIØN TH(1),Y(NRPRD,NVAR),X(1,1),Z(1)
      CØMMØN/ MØLE /X
      CØMMØN P10,P30,P40,Q1,Q3,Q4,Z
      A13=TH(1)
      A31=TH(2)
      A14=TH(3)
      A41=TH(4)
      A34=TH(5)
      A43=TH(6)
      G134=TH(7)
C     WRITE(-,-) (X(I,1), X(I,2), X(I,3), I=1,NEXP)
C     WRITE(-,-) P10,   P30,   P40
C     WRITE(-,-) Q1,      Q3,      Q4
      DØ 80 I=1,NEXP
       X11=X(I,1)
       X3=X(I,2)
       X4=X(I,3)
       Z1=X11*Q1/(X11*Q1 + X3*Q3 + X4*Q4)
       Z3=X3*Q3/(X11*Q1 + X3*Q3 + X4*Q4)
       Z4=1.0-Z1-Z3
       G1=  Z3*Z3*(A13 + 2.0*Z1*(A31*Q1/Q3 - A13))
     1      + Z4*Z4*(A14 + 2.0*Z1*(A41*Q1/Q4 - A14))
     2    + Z3*Z4*(A41*Q1/Q4+A13-A34*Q1/Q3+2.0*Z1*(A31*Q1/Q3-A13)
     3      + 2.0*Z3*(A34*Q1/Q3 - A43*Q1/Q4) - G134*Q1*(1.0-2.0*Z1))
       G3=  Z1*Z1*(A31 + 2.0*Z3*(A13*Q3/Q1 - A31))
     1      + Z4*Z4*(A34 + 2.0*Z3*(A43*Q3/Q4 - A34))
     2    + Z1*Z4*(A13*Q3/Q1+A34-A41*Q3/Q4+2.0*Z3*(A43*Q3/Q4-A34)
     3      + 2.0*Z4*(A41*Q3/Q4 - A14*Q3/Q1) - G134*Q3*(1.0-2.0*Z3))
       G4=  Z3*Z3*(A43 + 2.0*Z4*(A34*Q4/Q3 - A43))
     1      + Z1*Z1*(A41 + 2.0*Z4*(A14*Q4/Q1 - A41))
     2      + Z1*Z3*(A34*Q4/Q3 + A41 - A13*Q4/Q1+2.0*Z4*(A14*Q4/Q1-A41)
     3      + 2.0*Z1*(A13*Q4/Q1 - A31*Q4/Q3) - G134*Q4*(1.0-2.0*Z4))
C     WRITE(-,-) X11,   X3,   X4
C     WRITE(-,-) Z1,   Z3,   Z4
C     WRITE(-,-) G1,   G3,   G4
      Y(I,1)= EXP(G1)*P10*X11 + EXP(G3)*P30*X3 + EXP(G4)*P40*X4
 80   CØNTINUE
      RETURN
      END
*** TØP ØF FILE ***
```

```
      2.9409E-03
      1.5011E-03
      1.0603E-03
      1.0589E-03
      9.0343E-04
      8.1493E-04
      7.2923E-04
      5.6639E-04
      5.2365E-04
      4.2653E-04
      4.2009E-04
      3.4673E-04
 P10=    58.5700P30=      .3200P40=    23.7500
 Q1=     58.630003=    73.690004=    18.0700
          A13=     .16330A31=     .56830A14=    1.13800A41=     .90470A34=    -.03080A43=    -.05280G134=     .50000
 NUMBER ØF PØINTS= 12

      TØTAL PRESS      MØLE FRACTIØNS 1,3,4,
            18.4400              .11910        .30330        .57760
            25.8100              .08170        .62190        .29640
            30.7100              .18570        .47640        .33790
            30.7300              .04630        .92650        .02720
            33.2700              .32460        .28040        .39500
            35.0300              .13590        .69940        .16470
            37.0300              .10960        .82590        .06450
            42.0000              .34750        .44150        .21100
            43.7000              .50030        .25550        .24420
            48.4200              .25380        .66830        .07740
            48.7900              .43740        .41430        .09330
            53.7000              .71830        .22720        .05400

 MADISØN ACADEMIC CØMPUTING CENTER - SUBRØUTINE NREG                    04/20/82     TRANSMITTAL NØ.  Y52106     CALL  1
   PAGE   1
 ETHANØL(1)-WATER(3)-PG(4) TØTAL PRESS DATA 25C 0-EQTN 3S

                                S U M M A R Y   Ø F   T H E   D A T A

                                                ITEMS

   ITEMS(1): NEXP   =   12  NUMBER ØF EXPERIMENTS
   ITEMS(2): NVAR   =    3  NUMBER ØF VARIABLES
   ITEMS(3): NP     =    7  NUMBER ØF PARAMETERS
 VES

   ITEMS(4): NRØBS  =   50  RØW DIMENSIØN ØF ARRAY YØBS
   ITEMS(5): NRPRD  =   50  RØW DIMENSIØN ØF ARRAY YPRD
   ITEMS(6): NRWTS  =   50  RØW DIMENSIØN ØF ARRAY WTS
 TIØNS

   ITEMS(7): METHØD = 'MARQ'    MARQUARDT'S METHØD
   ITEMS(8): KWTS   = 'ALL'     WEIGHTING BY ØBSERVATIØN
   ITEMS(9): KDERIV = 'NREG'    NREG CALCULATED DERIVATI

   ITEMS(10): KSYM  = 'CENT'    CENTRAL DIFFERENCES
   ITEMS(11): KDIFF = 'REL'     RELATIVE DIFFERENCES

   ITEMS(12): MAXIT =     50    LIMIT ØN NUMBER ØF ITERA

                    TØLERANCES                                  SUNDRIES

   TØL(1) =  1.5000000-06  REL. CHANGE IN A PARAMETER          NUMBER ØF ACTIVE PARAMETERS =    1
   TØL(2) =  1.0000000-09  REL. CHANGE IN SUM ØF SQUARES       NUMBER ØF CELLS ØF SCRATCH REQUIRED =   816
   TØL(3) =  0.0000000     RATIØ TØ INITIAL SUM ØF SQUARES
   TØL(4) =  1.0000000-16  PIVØT TØLERANCE
```

PARAMETERS

| | NØ. | NAME | INITIAL VALUE | PRØPØRTIØN FØP DERIV. ESTIMATE | LØWER BØUND | UPPER BØUND |
|---|---|---|---|---|---|---|
| F | 1 | A13 | 1.6330000-01 | 5.0000000-03 | -1.0000000+02 | 1.0000000+02 |
| F | 2 | A31 | 5.6379999-01 | 5.0000000-03 | -1.0000000+02 | 1.0000000+02 |
| F | 3 | A14 | 1.1330000+00 | 5.0000000-03 | -1.0000000+02 | 1.0000000+02 |
| F | 4 | A41 | 9.0470000-01 | 5.0000000-03 | -1.0000000+02 | 1.0000000+02 |
| F | 5 | A34 | -3.0300000-02 | 5.0000000-03 | -1.0000000+02 | 1.0000000+02 |
| F | 6 | A43 | -8.2300000-02 | 5.0000000-03 | -1.0000000+02 | 1.0000000+02 |
| | 7 | G134 | 5.0000000-01 | 5.0000000-03 | -1.0000000+02 | 1.0000000+02 |

MADISØN ACADEMIC CØMPUTING CENTER - SUBRØUTINE NREG 04/20/32 TRANSMITTAL NØ. Y52106 CALL 1
PAGE 2
ETHANØL(1)-WATER(3)-PG(4) TØTAL PRESS DATA 25C Ø-EQTN 3S

S I N G U L A R V A L U E S A N D V E C T Ø R S A T I N I T I A L P Ø I N T

SING. VALUES 1.1283550+00

| | | | |
|---|---|---|---|
| PAR. | F 1 | A13 | *** |
| | F 2 | A31 | *** |
| | F 3 | A14 | *** |
| | F 4 | A41 | *** |
| | F 5 | A34 | *** |
| | F 6 | A43 | *** |
| | 7 | G134 | 1.0000000 |

SETUP TIME = .050 SECØNDS

MADISØN ACADEMIC CØMPUTING CENTER - SUBRØUTINE NREG 04/20/32 TRANSMITTAL NØ. Y52106 CALL 1
PAGE 3
ETHANØL(1)-WATER(3)-PG(4) TØTAL PRESS DATA 25C Ø-EQTN 3S

T H E I T E R A T I Ø N S

| ITERATIØN NØ. 1 | | BASE PØINT | TEST PØINT | TEST PØINT |
|---|---|---|---|---|
| SUM ØF SQUARES | | 3.7675942+00 | 1.4067415+03 | 1.5214919+00 |
| L | | 0 | 0 | 0 |
| LAMBDA | | 0.0000000 | 0.0000000 | 0.0000000 |
| GAMMA | | 1.0000000+00 | 1.0000000+00 | 5.0000000-01 |
| ANGLE IN DEGREES | | .0000 | .0000 | .0000 |
| MAX. PIVØT REDUCTIØN | | 1.0000000+00 | 1.0000000+00 | 1.0000000+00 |
| PAR. | 1 A13 | F 1.6330000-01 | F 1.6330000-01 | F 1.6330000-01 |
| | 2 A31 | F 5.6379999-01 | F 5.6379999-01 | F 5.6879999-01 |
| | 3 A14 | F 1.1330000+00 | F 1.1330000+00 | F 1.1330000+00 |
| | 4 A41 | F 9.0470000-01 | F 9.0470000-01 | F 9.0470000-01 |
| | 5 A34 | F -3.0300000-02 | F -3.0300000-02 | F -3.0300000-02 |
| | 6 A43 | F -8.2300000-02 | F -8.2300000-02 | F -8.2300000-02 |
| | 7 G134 | 5.0000000-01 | S -8.4390612-01 | S -1.7195306-01 |

CUMULATIVE NØ. ØF FUNCTIØN CALLS = 3 ITERATIØN TIME = .036 SECØNDS CUMULATIVE TIME = .086 SECØNDS

## THE LAST ITERATION

| | | | | | | |
|---|---|---|---|---|---|---|
| ITERATION NO. | 5 | | BASE POINT | | TEST POINT | |
| SUM OF SQUARES | | | 1.3441713+00 | | 1.3441713+00 | |
| L | | | 0 | | 0 | |
| LAMBDA | | | 0.0000000 | | 0.0000000 | |
| GAMMA | | | 5.0000000-01 | | 1.5625000=02 | |
| ANGLE IN DEGREES | | | .0000 | | .0000 | |
| MAX. PIVOT REDUCTION | | | 1.0000000+00 | | 1.0000000+00 | |
| PAR. | 1 | A13 | F 1.6330000-01 | | F 1.6330000-01 | |
| | 2 | A31 | F 5.6379999-01 | | F 5.6379999-01 | |
| | 3 | A14 | F 1.1380000+00 | | F 1.1380000+00 | |
| | 4 | A41 | F 9.0470000-01 | | F 9.0470000-01 | |
| | 5 | A34 | F -3.0800000-02 | | F -3.0800000-02 | |
| | 6 | A43 | F -8.2800000-02 | | F -8.2800000-02 | |
| | 7 | G134 | S -1.0692234-01 | | S -1.0692246-01 | |

CUMULATIVE NO. OF FUNCTION CALLS = 14 ITERATION TIME = .043 SECONDS CUMULATIVE TIME = .
221 SECONDS

ITERATION TERMINATES:
MAX. RELATIVE CHANGE IN A PARAMETER .LT. TOL(1) = 1.5000000-06

MADISON ACADEMIC COMPUTING CENTER - SUBROUTINE NREG 04/20/82 TRANSMITTAL NO. Y52106 CALL 1
PAGE 4
ETHANOL(1)-WATER(3)-PG(4) TOTAL PRESS DATA 25C 0-EOTN 3S

## FINAL PARAMETER VALUES

| | | | | FINAL VALUE | SUM OF SQUARES = 1.3441713+00 |
|---|---|---|---|---|---|
| AR. | F | 1 | A13 | 1.6330000-01 | |
| | F | 2 | A31 | 5.6379999-01 | |
| | F | 3 | A14 | 1.1380000+00 | |
| | F | 4 | A41 | 9.0470000-01 | |
| | F | 5 | A34 | -3.0800000-02 | |
| | F | 6 | A43 | -8.2800000-02 | |
| | | 7 | G134 | -1.0692234-01 | |

## ITERATIØN SUMMARY

| ITER NØ. | SUM ØF SQUARES | L | LAMBDA | GAMMA | ANGLE | NØ. PIVØT FAILURES | NØ. BØUNDS FAILURES | MAX. PIVØT REDUCTIØN | TIME IN SECØNDS |
|---|---|---|---|---|---|---|---|---|---|
| 0 | 3.7675942+00 | 0 | 0.0000000 | 1.0000000+00 | .0000 | 0 | 0 | 1.0000000+00 | .000 |
| 1 | 1.5214919+00 | 0 | 0.0000000 | 5.0000000-01 | .0000 | 0 | 0 | 1.0000000+00 | .036 |
| 2 | 1.3453247+00 | 0 | 0.0000000 | 1.0000000+00 | .0000 | 0 | 0 | 1.0000000+00 | .049 |
| 3 | 1.3441718+00 | 0 | 0.0000000 | 1.0000000+00 | .0070 | 0 | 0 | 1.0000000+00 | .021 |
| 4 | 1.3441718+00 | 0 | 0.0000000 | 5.0000000-01 | .0000 | 0 | 0 | 1.0000000+00 | .022 |
| 5 | 1.3441718+00 | 0 | 0.0000000 | 1.5625000-02 | .0000 | 0 | 0 | 1.0000000+00 | .043 |

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## SINGULAR VALUES AND VECTØRS AT TERMINAL PØINT

SING. VALUES 5.6626706+00

| | | | | |
|---|---|---|---|---|
| PAR. | F | 1 | A13 | *** |
| | F | 2 | A31 | *** |
| | F | 3 | A14 | *** |
| | F | 4 | A41 | *** |
| | F | 5 | A34 | *** |
| | F | 6 | A43 | *** |
| | | 7 | G134 | 1.0000000 |

## NØRMALIZING ELEMENTS AND CØRRELATIØN MATRIX

| PARAMETER NØ. | | | | 1 | 2 | 3 | 4 | 5 | 6 |
|---|---|---|---|---|---|---|---|---|---|
| NØRM. ELTS. | | | | *** | *** | *** | *** | *** | *** |
| PAR. | F | 1 | A13 | *** | | | | | |
| | F | 2 | A31 | *** | *** | | | | |
| | F | 3 | A14 | *** | *** | *** | | | |
| | F | 4 | A41 | *** | *** | *** | *** | | |
| | F | 5 | A34 | *** | *** | *** | *** | *** | |
| | F | 6 | A43 | *** | *** | *** | *** | *** | *** |
| | | 7 | G134 | *** | *** | *** | *** | *** | *** |

PARAMETER NØ. 7

NØRM. ELTS. 1.7659512-01

PAR. 7 G134 1.0000000

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C Ø N F I D E N C E L I M I T S Ø N L I N E A R H Y P Ø T H E S I S

| | | | LØWER LIMIT | FINAL VALUE | UPPER LIMIT |
|---|---|---|---|---|---|
| PAR. | F 1 | A13 | *** | 1.6330000-01 | *** |
| | F 2 | A31 | *** | 5.6379999-01 | *** |
| | F 3 | A14 | *** | 1.1380000+00 | *** |
| | F 4 | A41 | *** | 9.0470000-01 | *** |
| | F 5 | A34 | *** | -3.0300000-02 | *** |
| | F 6 | A43 | *** | -8.2300000-02 | *** |
| | 7 | G134 | -1.7613764-01 | -1.0692234-01 | -3.7707053-02 |

E X P L Ø R A T I Ø N

| | | | LØWER TEST | SUM ØF SQUARES | LINEAR EST. ØF SUM ØF SQUARES | UPPER TEST | SUM ØF SQUARES | LI SU |
|---|---|---|---|---|---|---|---|---|
| NEAR EST. ØF M ØF SQUARES | | | | | | | | |
| PAR. | F 1 | A13 | 1.6330000-01 | *** | *** | 1.6330000-01 | *** | |
| *** | | | | | | | | |
| | F 2 | A31 | 5.6379999-01 | *** | *** | 5.6379999-01 | *** | |
| *** | | | | | | | | |
| | F 3 | A14 | 1.1380000+00 | *** | *** | 1.1380000+00 | *** | |
| *** | | | | | | | | |
| | F 4 | A41 | 9.0470000-01 | *** | *** | 9.0470000-01 | *** | |
| *** | | | | | | | | |
| | F 5 | A34 | -3.0300000-02 | *** | *** | -3.0300000-02 | *** | |
| *** | | | | | | | | |
| | F 6 | A43 | -8.2300000-02 | *** | *** | -8.2300000-02 | *** | |
| *** | | | | | | | | |
| | 7 | G134 | -1.2422617-01 | 1.3545725+00 | 1.3537730+00 | -8.9618522-02 | 1.3533301+00 | 1 |
| .3537730+00 | | | | | | | | |

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## FINAL FUNCTION VALUES AND RESIDUALS

WEIGHTED ROOT MEAN SQUARE RESIDUAL = 1.9597170-01 NO. DEGREES OF FREEDOM = 35
THIS IS THE SCALE UNIT IN THE GRAPH OF THE WEIGHTED RESIDUALS.

| EXPT. NO. | VAR. NO. | PREDICTION | OBSERVATION | RESIDUAL | WEIGHTED RES. | GRAPH OF WEIGHTED RESIDUAL -2 -1 0 +1 |
|---|---|---|---|---|---|---|
| 1 | 1 | 1.8041080+01 | 1.8440000+01 | 3.9891953-01 | 2.1633333-02 | ** |
| 2 | 1 | 8.6913634+00 | 2.5810000+01 | 1.7118132+01 | 6.6323640-01 | ********** |
| 3 | 1 | 2.6340721+01 | 3.0710000+01 | 3.3692789+00 | 1.2599410-01 | ******* |
| 4 | 1 | 9.6070700+00 | 3.0730000+01 | 2.1122930+01 | 6.8737162-01 | ********** |
| 5 | 1 | 2.6970965+01 | 3.3270000+01 | 6.2990351+00 | 1.8933073-01 | ********** |
| 6 | 1 | 2.7383122+01 | 3.5030000+01 | 7.1468778+00 | 2.0402163-01 | ********** |
| 7 | 1 | 3.6542600+01 | 3.7030000+01 | 4.8740005-01 | 1.3162302-02 | ** |
| 8 | 1 | 4.0791023+01 | 4.2000000+01 | 1.2039772+00 | 2.8735171-02 | ** |
| 9 | 1 | 5.8909698+01 | 4.3700000+01 | -1.5209698+01 | -3.4804301-01 | ********** |
| 10 | 1 | 6.1378249+01 | 4.8420000+01 | -1.2958249+01 | -2.6762133-01 | ********** |
| 11 | 1 | 3.3549562+01 | 4.3790000+01 | 1.0240438+01 | 3.1236307-01 | ********** |
| 12 | 1 | 4.2100115+01 | 5.3700000+01 | 1.1599885+01 | 2.1601275-01 | ********** |
| 1 | 2 | 0.0000000 | 0.0000000 | 0.0000000 | 0.0000000 | * |
| 2 | 2 | 0.0000000 | 0.0000000 | 0.0000000 | 0.0000000 | * |
| 3 | 2 | 0.0000000 | 0.0000000 | 0.0000000 | 0.0000000 | * |
| 4 | 2 | 0.0000000 | 0.0000000 | 0.0000000 | 0.0000000 | * |
| 5 | 2 | 0.0000000 | 0.0000000 | 0.0000000 | 0.0000000 | * |
| 6 | 2 | 0.0000000 | 0.0000000 | 0.0000000 | 0.0000000 | * |
| 7 | 2 | 0.0000000 | 0.0000000 | 0.0000000 | 0.0000000 | * |
| 8 | 2 | 0.0000000 | 0.0000000 | 0.0000000 | 0.0000000 | * |
| 9 | 2 | 0.0000000 | 0.0000000 | 0.0000000 | 0.0000000 | * |
| 10 | 2 | 0.0000000 | 0.0000000 | 0.0000000 | 0.0000000 | * |
| 11 | 2 | 0.0000000 | 0.0000000 | 0.0000000 | 0.0000000 | * |
| 12 | 2 | 0.0000000 | 0.0000000 | 0.0000000 | 0.0000000 | * |
| 1 | 3 | 0.0000000 | 0.0000000 | 0.0000000 | 0.0000000 | * |
| 2 | 3 | 0.0000000 | 0.0000000 | 0.0000000 | 0.0000000 | * |
| 3 | 3 | 0.0000000 | 0.0000000 | 0.0000000 | 0.0000000 | * |
| 4 | 3 | 0.0000000 | 0.0000000 | 0.0000000 | 0.0000000 | * |
| 5 | 3 | 0.0000000 | 0.0000000 | 0.0000000 | 0.0000000 | * |
| 6 | 3 | 0.0000000 | 0.0000000 | 0.0000000 | 0.0000000 | * |
| 7 | 3 | 0.0000000 | 0.0000000 | 0.0000000 | 0.0000000 | * |
| 8 | 3 | 0.0000000 | 0.0000000 | 0.0000000 | 0.0000000 | * |
| 9 | 3 | 0.0000000 | 0.0000000 | 0.0000000 | 0.0000000 | * |
| 10 | 3 | 0.0000000 | 0.0000000 | 0.0000000 | 0.0000000 | * |
| 11 | 3 | 0.0000000 | 0.0000000 | 0.0000000 | 0.0000000 | * |
| 12 | 3 | 0.0000000 | 0.0000000 | 0.0000000 | 0.0000000 | * |

TIME SINCE END OF THE LAST ITERATION = .181 SECONDS TOTAL TIME = .402 SECONDS