

## RESEARCH ARTICLES

### Extended Hildebrand Solubility Approach: Solubility of Theophylline in Polar Binary Solvents

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**Abstract** □ A quantitative approach is presented for predicting solubilities of crystalline compounds in binary solvent systems. The solubility of theophylline in mixed solvents consisting of dioxane and water was determined at  $25 \pm 0.1^\circ$ . The solubilities across this range of polar solvents were back-calculated using a technique involving an interaction energy term,  $W$ . This parameter is regressed against a polynomial expression in  $\delta_1$ , the solubility parameter for the mixed solvents. Except for the end-points, solubilities were predicted within <12% and with considerably better accuracy in most cases. The new approach modifies the well-known Hildebrand solubility equation to make it applicable to polar systems. Although the method may be used with solutes in pure solvents, its greatest application appears to be the prediction of drug solubility in binary solvent mixtures.

**Keyphrases** □ Theophylline—solubility in polar binary solvents □ Solvent systems—solubility of theophylline in polar binary solvents

Solubility data on drugs and pharmaceutical adjuncts in mixed solvents have wide application in the drug sciences. Knowledge of interactive forces between solutes and solvents are of considerable theoretical and practical interest throughout the physical and biological sciences.

#### BACKGROUND

The term regular solution was introduced by Hildebrand (1) to describe solutions showing random molecular distribution and orientation as found in ideal solutions. There is no entropy change, but heat is absorbed when the components of a regular solution are mixed. Although these solutions are not ideal, they yield curves of log solubility versus  $1/T$  that are quite regular. Other kinds of solutions, those that involve solvation or association, produce irregular solubility curves. Modifications of the Hildebrand approach for irregular solutions have been reported in the field of solution technology by various investigators (2-8).

The Hildebrand-Scatchard equation for the solubility of solids in a regular solution may be written as (9-13):

$$-\log X_2 = \frac{\Delta S_m^f}{R} \log \frac{T_m}{T} + \frac{V_2 \phi_1^2}{2.303RT} (\delta_1 - \delta_2)^2 \quad (\text{Eq. 1})$$

where  $X_2$  is the mole fraction solubility of the solute or drug (represented by subscript 2);  $\Delta S_m^f$  is the entropy of fusion of the crystalline drug at its melting point,  $T_m$ , on the Kelvin scale;  $T$  is the temperature in degrees

Kelvin at which the solubility is determined;  $R$  is the molar gas constant;  $V_2$  is the molar volume of the drug;  $\phi_1$  is the volume fraction of the solvent (represented by subscript 1);  $\delta_2$  is the solubility parameter of the solute; and  $\delta_1$  is the solubility parameter of the solvent or mixed solvent. Solubility parameters also are referred to as delta values. The first right-hand term of Eq. 1 frequently is written as  $(\Delta H_m^f/2.303RT)(1/T - 1/T_m)$ , but the  $\Delta S_m^f$  term of Eq. 1 is more correct, as will be discussed later.

The solubility parameter or delta value of the solvent,  $\delta_1$ , is obtained as suggested by Hildebrand and Scott (10) using the relationship:

$$\delta_1 = \left( \frac{\Delta E_1^v}{V_1} \right)^{1/2} = \left( \frac{\Delta H_1^v - RT}{V_1} \right)^{1/2} \quad (\text{Eq. 2})$$

where  $\Delta E_1^v$  is the molar energy of vaporization,  $\Delta H_1^v$  is the heat of vaporization, and  $V_1$  is the molar volume of the solvent. The square of  $\delta_1$ , or  $\Delta E_1^v/V_1$ , is called the cohesive energy density of the solvent. Other methods for obtaining  $\delta_1$  were given by Hildebrand and Scott (10).

The solubility parameter of a solid compound is difficult to obtain, and few values are recorded in the literature. The  $\delta^2$  value for iodine is ~14.1 (10), and the value for naphthalene, phenanthrene, and anthracene is ~9.8. Several investigators (12, 14) estimated the solubility parameters of benzoic acid and some *p*-hydroxybenzoic acid esters from the peak values obtained from a plot of mole fraction solubility versus delta values of solvents. The parameter for benzoic acid also was determined from the solubility data in hexane and was found to be 11.5. The solubility parameters for barbiturates have been determined (15, 16). Yalkowsky *et al.* (17) obtained the solubility parameters for *p*-aminobenzoate esters from their solubility in hexane. For example, the value for the ethyl ester was 12.05. James *et al.* (18) reported solubility parameters for some testosterone esters and related compounds.

The first term on the right side of Eq. 1, the ideal solubility term, is for the dissociation of the crystal lattice of a solid compound, rendering it in the liquid form. In the presence of solvents that form nearly ideal solutions, the second right-hand quantity, the regular solution term, is nearly zero and may be omitted.

The regular solution term, involving solubility parameters, is an activity coefficient,  $\log \alpha_v$ , used to represent nonideality due to the interaction of solute and solvent molecules in a regular solution where only nonpolar and weak polar forces exist:

$$\log \alpha_v = A(\delta_1 - \delta_2)^2 \quad (\text{Eq. 3})$$

where  $A$  represents  $V_2 \phi_1^2/2.303RT$  and the subscript  $v$  stands for van der Waals forces.

Following the suggestion by Crowley *et al.* (8), Hansen (5, 6) introduced a three-dimensional system of solubility parameters. The energy of va-

porization in Eq. 2 was assumed to be an additive quantity composed of three energies representing London dispersion forces ( $\Delta E_d^v$ ), polar forces ( $\Delta E_p^v$ ), and hydrogen bonding ( $\Delta E_h^v$ ) in the solvent. Dividing each term by the molar volume of the solvent ( $V_1$ ), the total cohesive energy density was obtained:

$$\frac{\Delta E^v}{V_1} = \frac{\Delta E_d^v}{V_1} + \frac{\Delta E_p^v}{V_1} + \frac{\Delta E_h^v}{V_1} \quad (\text{Eq. 4})$$

or, in terms of delta values:

$$\delta^2 = \delta_d^2 + \delta_p^2 + \delta_h^2 \quad (\text{Eq. 5})$$

where  $\delta^2$  is the total cohesive energy density for the liquid. Values for  $\delta_d$  were determined by reference to a corresponding hydrocarbon called a homomorph, and  $\delta_p$  and  $\delta_h$  were estimated by empirical methods. Hoy *et al.* (19) developed extensive tables of three-dimensional delta values, which differ somewhat from the values of Hansen (5, 6). Hansen noted that there is yet no theoretical basis for the new three-dimensional solubility parameters, and he used them empirically to interpret the solubility of polymers and other solutes employed in industry and commerce.

Weimer and Prausnitz (20) calculated polar and nonpolar solubility parameters using the homomorph concept, and Blanks and Prausnitz (7) applied these values to the study of polymer solubility in polar solvents. These investigators did not consider hydrogen bonding systems.

$$\Delta H_m^f = \Delta H_m^f (\text{standard}) \times \text{standard weight} \times \text{sample peak area} \times \frac{\text{instrument range for sample} \times \text{sample mol. wt.}}{\text{instrument range for standard} \times \text{sample weight} \times \text{standard mol. wt.} \times \text{standard peak area}} \quad (\text{Eq. 11})$$

The method presented here<sup>1</sup> allows calculation of the solubility of polar and nonpolar solutes in solvents ranging from nonpolar (hexane) to aprotic polar (*e.g.*, *N,N*-dimethylformamide) and highly polar protic solvents such as alcohols, acids, and water. Although formulated specifically in terms of the solubility of a nonelectrolytic solid in liquid solution, the technique should apply as well to liquid-liquid and other equilibrium systems.

Equation 1 ordinarily provides a poor prediction for the solubility of a drug or other crystalline compound in a polar solvent. These solutions are quite irregular, often involving self-association or solvation. The logarithm of the activity coefficient, calculated using Eq. 3, accounts for the nonideality of solutions resulting from the interaction of solute and solvent molecules of the physical or van der Waals type. Several investigators, including Hildebrand, have cautioned that expressions in the form of Eq. 3 are not good representations of nonideality in solutions of polymers and various polar and semipolar compounds in polar and hydrogen bonding solvents. For irregular solutions, a total activity coefficient,  $\alpha_2$ , must be written consisting of the term (Eq. 3) representing physical or van der Waals forces and an additional term,  $\log \alpha_R$ , representing residual, presumably stronger, forces:

$$\log \alpha_2 = \log \alpha_v + \log \alpha_R \quad (\text{Eq. 6})$$

The total activity coefficient may be written as:

$$\log \alpha_2 = A(\delta_1^2 + \delta_2^2 - 2W) \quad (\text{Eq. 7})$$

where  $W$  is the interaction energy between the solute and solvent in an irregular solution.

Employing Eqs. 3, 6, and 7, one obtains for the residual term:

$$\log \alpha_R = 2A(\delta_1\delta_2 - W) \quad (\text{Eq. 8})$$

The logarithm of the total activity coefficient may be written for irregular solutions as:

$$\log \alpha_2 = A(\delta_1 - \delta_2)^2 + 2A(\delta_1\delta_2 - W) \quad (\text{Eq. 9})$$

and the modified Hildebrand solubility equation becomes:

$$-\log X_2 = \frac{\Delta S_m^f}{R} \log \frac{T_m}{T} + A(\delta_1^2 + \delta_2^2 - 2W) \quad (\text{Eq. 10})$$

## EXPERIMENTAL

**Materials**—Anhydrous theophylline<sup>2</sup> and *p*-dioxane<sup>3</sup> were obtained commercially.

<sup>1</sup> The first report in this series is Ref. 21. It provides a sample calculation for the method described here and in subsequent papers.

<sup>2</sup> Knoll Chemicals.

<sup>3</sup> Mallinckrodt Chemical Works.

**Solubility Determination**—The solubility of theophylline ( $\delta^2 = 14.0$ ) was determined in mixed solvents consisting of dioxane ( $\delta_{1a} = 10.01$ ) and water ( $\delta_{1b} = 23.45$ ). Glass-distilled deionized water was used to prepare mixtures with dioxane in concentrations of 0–100% by volume of dioxane. About 10 ml of the mixture was introduced into screw-capped vials containing excess theophylline. The vials were agitated for 96 hr in a shaker bath maintained at  $25 \pm 0.1^\circ$ . Preliminary studies showed that this period was sufficient to ensure saturation at  $25^\circ$ .

After equilibrium was attained, vials were removed for analysis. The solutions were filtered, and aliquots were placed in volumetric flasks and brought to the final volume with the solvent mixture in which the drug was originally dissolved. The solutions were analyzed in a spectrophotometer<sup>4</sup> at 273.4 nm. Three samples were withdrawn from four separate vials and measured at each mixed solvent concentration. The standard error for the analysis of individual samples was  $< \pm 0.7 \mu\text{g/ml}$ .

The densities of the solvent mixtures and the filtrates of the saturated solutions of theophylline were determined in triplicate at  $25 \pm 0.1^\circ$  using a pycnometer.

**Heat of Fusion**—The heat of fusion of crystalline theophylline was determined experimentally in a differential scanning calorimeter<sup>5,6</sup>. Thermograms were run at 100 psi to retard sublimation, and the heat of fusion was determined from the area under the curve, using indium metal as a standard. The equation employed in calculating the heats of fusion from differential scanning calorimetry is:

To obtain the ideal solubility,  $X_2^i$ , Hildebrand *et al.* (22) showed that entropy of fusion,  $\Delta S_m^f$ , can replace heat of fusion to take into account the molar heat capacity change,  $\Delta C_p$ , in going from a solid to a liquid solute. The equation for calculating the ideal solubility employing  $\Delta S_m^f$  is (22):

$$\log X_2^i \cong \frac{\Delta S_m^f}{R} \log \frac{T}{T_m} \quad (\text{Eq. 12})$$

The entropy of fusion is obtained by plotting  $\log X_2$  versus  $\log T$  under ideal solution conditions. With solubility data,  $X_2$ , at three or four temperatures, a linear plot with a slope proportional to  $\Delta S_m^f$  is obtained. However, the  $\Delta H_m^f$  and  $T_m$  values may be determined more conveniently using a differential scanning calorimeter (23). Once these values are obtained,  $\Delta S_m^f$  is calculated from:

$$\Delta S_m^f = \frac{\Delta H_m^f}{T_m} \quad (\text{Eq. 13})$$

**Solubility Parameter of Mixed Solvents**—The solubility parameter,  $\delta_1$ , for a mixture of two solvents, *a* and *b*, is calculated (24, 25) using the expression:

$$\delta_1 = \frac{\phi_a \delta_a + \phi_b \delta_b}{\phi_a + \phi_b} \quad (\text{Eq. 14})$$

where:

$$\phi_1 = \phi_a + \phi_b \quad (\text{Eq. 15})$$

in which  $\phi_1$  is the total volume fraction of the two solvents and  $\delta_1$ , the solubility parameter of solvents *a* and *b*, is averaged in terms of volume fractions.

**Volume Fraction and Mean Molar Volume in Mixed Solvents**—The total volume fraction,  $\phi_1$ , of the solvent mixture is calculated using the expression:

$$\phi_1 = \frac{(1 - X_2)V_1}{(1 - X_2)V_1 + X_2V_2} \quad (\text{Eq. 16})$$

where  $X_2$  is the mole fraction solubility of the drug in the mixed solvent and  $V_1$  is the mean molar volume of the binary solvent. For each mixed solvent composed of solvents *a* and *b* in various proportions:

$$V_1 = \frac{X_a M_a + (1 - X_a) M_b}{\rho_1} \quad (\text{Eq. 17})$$

where  $X_i$  and  $M_i$  are the mole fraction and molecular weight of the par-

<sup>4</sup> Model 25 spectrophotometer, Beckman.

<sup>5</sup> Model 1B, Perkin-Elmer.

<sup>6</sup> L. T. Grady of the United States Pharmacopeia Laboratories, Rockville, Md., and S. H. Yalkowsky, The Upjohn Co., Kalamazoo, Mich., provided independent measurements of theophylline, theobromine, and caffeine in their laboratories.

**Table I—Mole Fraction Solubility of Theophylline in Dioxane–Water Mixtures at 25°**

Dioxane, %	$V_1$	$\delta_1$	Solution Density	$\phi_1$	$X_2$ (obs.) <sup>a</sup>	A	Log $\alpha_2$	Log $\alpha_v$	Log $\alpha_R$	W (Eq. 7)
0	18.063	23.45	0.9988	0.99493	0.0007414	0.08997	1.40772	8.03426	-6.62654	365.128
5	21.577	22.78	0.9988	0.99390	0.0010668	0.08978	1.24969	6.92101	-5.67132	350.504
10	24.880	22.11	1.0058	0.99228	0.0015583	0.09849	1.08512	5.88581	-4.80069	336.363
15	28.232	21.43	1.0105	0.99082	0.0021046	0.08922	0.95460	4.92565	-3.97105	322.273
20	31.566	20.76	1.0148	0.98916	0.0027831	0.08925	0.83325	4.06366	-3.23041	308.804
25	34.875	20.09	1.0190	0.98761	0.0035158	0.08865	0.73175	3.28777	-2.55602	295.677
30	38.158	19.42	1.0232	0.98494	0.0046818	0.08817	0.60736	2.59010	-1.98274	283.124
35	41.450	18.75	1.0265	0.98320	0.0056783	0.08786	0.52356	1.98230	-1.45874	270.802
40	44.713	18.07	1.0300	0.98168	0.0066856	0.08759	0.45263	1.45084	-0.99821	258.679
45	48.018	17.40	1.0321	0.97877	0.0083295	0.08707	0.35716	1.00650	-0.64934	247.329
55	54.589	16.06	1.0362	0.97438	0.0114449	0.08629	0.21916	0.36617	-0.14701	225.692
60	57.907	15.39	1.0374	0.97352	0.0125411	0.08614	0.17944	0.16642	0.01302	215.384
62	59.228	15.12	1.0379	0.97287	0.0131436	0.08602	0.15906	0.10791	0.05115	211.383
66	64.630	14.58	1.0379	0.97277	0.0143803	0.08600	0.12001	0.02893	0.09108	203.590
70	64.630	14.04	1.0379	0.97293	0.0142926	0.08603	0.12266	0.00014	0.12252	195.848
75	68.011	13.37	1.0379	0.97428	0.0142711	0.08627	0.12332	0.03424	0.08908	186.664
77	69.385	13.10	1.0375	0.97480	0.0142592	0.08636	0.12368	0.06995	0.05373	183.089
80	71.464	12.70	1.0368	0.97617	0.0138736	0.08661	0.13559	0.14636	-0.01077	177.862
85	74.956	12.03	1.0352	0.97816	0.0331770	0.08696	0.15334	0.33748	-0.18414	169.479
90	78.459	11.35	1.0367	0.98162	0.0117074	0.08758	0.20931	0.61500	-0.40569	161.216
100	85.663	10.01	1.0286	0.99625	0.0025959	0.09020	0.86349	1.43607	-0.57258	143.314

<sup>a</sup> Mole fraction solubilities are obtained at best to five figures following the decimal point. Two additional positions have been retained to provide four to six significant figures and thus facilitate comparison with calculated solubility values and to compute percentage differences.

ticular solvent in the mixture, respectively, and  $\rho_1$  is the density of the solvent mixture at the experimental temperature.

**Molar Volume and Solubility Parameter for Solute**—The molar volume of theophylline taken as a supercooled liquid at 25° is calculated using the group contribution approach of Fedors (26). The solubility parameter,  $\delta_2$ , for theophylline is obtained at the peak solubility where the  $\delta_1$  value of the solvent should equal  $\delta_2$  as required by Eq. 1. This principle was discussed previously (12). The  $\delta_2$  value of theophylline also may be calculated by the Fedors method (26).

**Calculations of Ideal Solubility, Activity Coefficients, and W**—The method begins with a calculation of the ideal solubility,  $X_2^i$ , of theophylline, employing the first right-hand term of Eq. 1 or 10. The logarithmic ideal solubility, together with the logarithm of the experimentally determined solubility, yields the logarithm of the solute activity coefficient:

$$\log X_2^i - \log X_2 = \log \alpha_2 \quad (\text{Eq. 18})$$

Log  $\alpha_v$  is obtained from the application of Eq. 3, and log  $\alpha_R$  is obtained from Eq. 6 or 8. Values for W, the solute–solvent interaction energy, are calculated with Eq. 7.

## RESULTS AND DISCUSSION

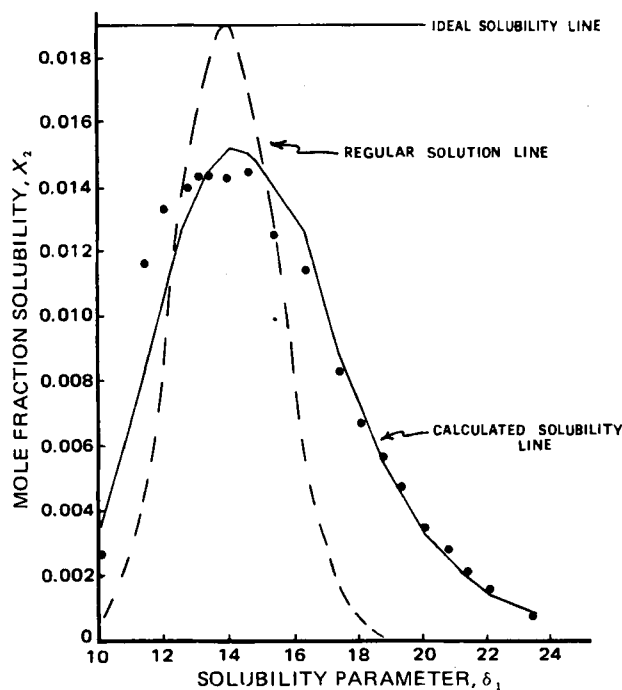
The experimentally determined solubilities of theophylline at 25° in dioxane–water mixtures are found in Table I together with the composition and densities of the solutions. The densities of solutions are included in reporting solubility data to allow conversion from mole fractions to molar concentrations, to assist in obtaining partial molar volumes, and to permit the calculation of other quantities. The calculated log  $\alpha_2$ , log  $\alpha_v$ , log  $\alpha_R$ , and W values also are found in Table I.

By employing the procedure described under *Experimental* to yield ideal solubility, a  $\Delta H_m^i$  value of 7097 cal/mole<sup>7</sup> and  $T_m$  value of 547.7°K were obtained. Then  $\Delta S_m^i$  was calculated using Eq. 13 to yield a value of 12.96 cal/mole/degree and a mole fraction ideal solubility for theophylline of 0.01896 (log  $X_2^i = -1.7222$ ). The molar volume of theophylline is 124.

The experimental solubilities, expressed as mole fractions, are plotted in Fig. 1 against the solubility parameter,  $\delta_1$ , of the various mixed solvents. Also shown in Fig. 1 is the ideal solubility level (horizontal line at a mole fraction of 0.01896). The regular solution line of Fig. 1 is a curve expressing solubilities of theophylline, with the assumption that the mixtures follow regular solution theory. The solubility of theophylline ( $\delta_2 = 14.0$ ) in pure dioxane ( $\delta_1 = 10.01$ ), in pure water ( $\delta_1 = 23.45$ ), and in the binary solutions composed of these two solvents did not approach the level of ideality, namely  $X_2 = 0.019$ , and did not coincide with regular solution behavior except where the experimental curve, by chance, crossed the regular solution line.

The original Hildebrand equation for regular solution behavior cannot be used to represent solubility in these polar solvents. However, Eq. 10, which involves the interaction term, W, does reproduce exactly the solubility of theophylline in dioxane, water, and the mixed solvent systems. Figure 1 shows that the peak solubility, although lower than ideal, occurred at a  $\delta_1$  value of ~14.0, which was taken as the  $\delta_2$  value of theophylline. The Fedors method (26) of calculating  $\delta$  values from molecular group and fragment constants gives essentially the same value (14.1).

When solubility was plotted as moles per liter instead of as mole fraction concentration, a slightly different shape than the curve of Fig. 1 was obtained. Peaks and valleys were not obtained in the curve of theophylline in dioxane–water mixture as reported by Paruta *et al.* (27). However, two small plateaus were found. These plateaus possibly were overlooked because the solubility measurements were not spaced as closely in the solvent composition as in the results of Paruta *et al.* Ongoing work in this laboratory with caffeine in dioxane–water has reproduced the two-peak maximum reported by Paruta *et al.* (27).



**Figure 1**—Solubility of theophylline in dioxane, water, and dioxane–water mixtures at 25°. Key: ● experimental solubilities; and — back-calculated solubilities from Eq. 10.

<sup>7</sup> L. T. Grady and W. H. Yalkowsky (personal communications) obtained values of  $\Delta H_m^i$  varying between 5940 and 7225 cal/mole.

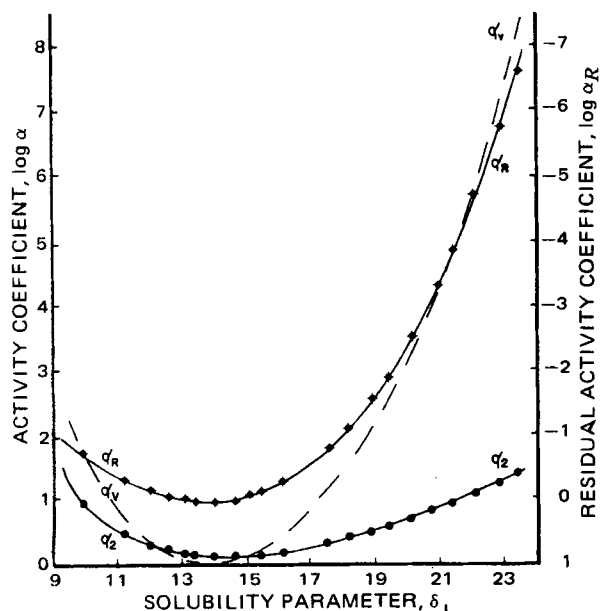
**Table II—Calculated Solubilities of Theophylline in Dioxane–Water Systems at 25°**

Dioxane, %	$\delta_1$	$W^a$	$\text{Log } \alpha_2/A^b$	$X_2$ (calc.)	$X_2$ (obs.) - $X_2$ (calc.) Difference
0	23.45	365.501	14.901	0.0008654	0.00012 (16.2%)
5	22.78	350.581	13.766	0.0011013	0.00003 (2.8%)
10	22.11	336.158	12.536	0.0014321	0.00013 (8.3%)
15	21.43	322.012	11.221	0.0018904	0.00021 (10.0%)
20	20.76	308.544	9.891	0.0025018	0.00028 (10.1%)
25	20.09	295.527	8.554	0.0033073	0.00021 (6.0%)
30	19.42	282.947	7.241	0.0043582	0.00032 (6.8%)
35	18.75	270.790	5.982	0.0056522	0.00003 (0.5%)
40	18.07	258.868	4.788	0.0072174	0.00053 (7.9%)
45	17.40	247.517	3.726	0.0089824	0.00065 (7.8%)
55	16.06	225.934	2.056	0.0126004	0.00116 (10.1%)
60	15.39	215.672	1.508	0.0140577	0.00152 (12.1%)
62	15.12	211.632	1.350	0.0145088	0.00137 (10.4%)
66	14.58	203.711	1.155	0.0150804	0.00070 (4.9%)
70	14.04	195.994	1.133	0.0151452	0.00085 (5.9%)
75	13.37	186.694	1.369	0.0144424	0.00017 (1.2%)
77	13.10	183.028	1.553	0.0139202	0.00034 (2.4%)
80	12.70	177.683	1.925	0.0129147	0.00096 (6.9%)
85	12.03	168.946	2.829	0.0107594	0.00256 (19.2%)
90	11.35	160.345	4.133	0.0082377	0.00347 (29.6%)
100	10.01	144.118	7.962	0.0036262	0.00103 (39.7%)

<sup>a</sup> Back-calculated by Eq. 19. <sup>b</sup> Back-calculated by Eq. 21.

Figure 2 shows the three activity coefficients,  $\log \alpha_v$ ,  $\log \alpha_R$ , and  $\log \alpha_2$ , which represent the van der Waals interactions between the solute and solvent, the residual term that accounts for stronger interactions, and the total solute activity coefficient, respectively. As expressed by Eq. 6,  $\log \alpha_2$  is the sum of  $\log \alpha_v$  and  $\log \alpha_R$ . As noted in Fig. 2,  $\log \alpha_v$  is plotted using a positive vertical axis (left side), while  $\log \alpha_R$  is plotted with reference to a negative (right) axis. The positive and negative values almost balance each other so that their composite values, represented by  $\log \alpha_2$ , yield only a moderately bowed curve across the range of  $\delta_1$  values (horizontal axis). This result demonstrates that the nonregularity in mixed solvents is not large and, when contrasted to individual solvents, provides a greater possibility of predicting solubilities by back-calculation as described.

The usefulness of a theoretical approach is the ability to calculate solubilities of a drug in mixed or pure solvents, using only fundamental physicochemical properties of the solute and solvent. Unfortunately,  $W$  is not a property that is readily and accurately back-calculated by independent means. The method could be useful for predicting solubilities, however, if a procedure were found for estimating  $W$  in this range of mixed solvents. Then, with Eq. 10, the solubility of theophylline could



**Figure 2—Values for theophylline activity coefficients,  $\log \alpha_v$ ,  $\log \alpha_R$ , and  $\log \alpha_2$ , over the range of solubility parameter values of the mixed dioxane–water solvent system.  $\log \alpha_v$  and  $\log \alpha_2$  are plotted with reference to the vertical axis on the left side of the figure;  $\log \alpha_R$  is plotted with reference to the right side.**

be estimated in pure dioxane, pure water, and mixed dioxane–water solvents for which the  $\delta_1$  values were known.

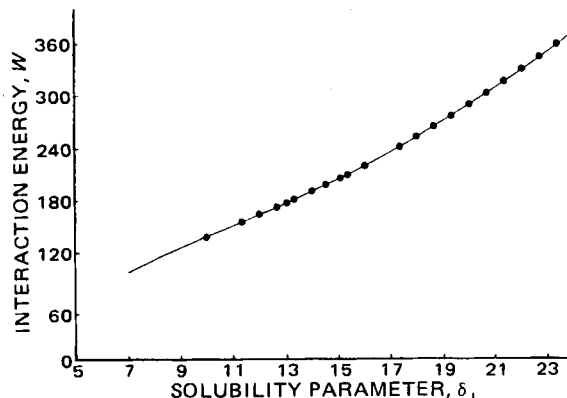
When  $W$  values, obtained from Eq. 7, are plotted against  $\delta_1$ , a curved line results, as shown in Fig. 3 for theophylline in dioxane–water. This curve suggests that  $W$  should be regressed against a polynomial in  $\delta_1$  for as many solutions for which accurate experimental solubilities are available. With the data of Table I, the following third-degree (cubic) equation was obtained:

$$W = 42.121367 + 9.424012\delta_1 - 0.005242\delta_1^2 + 0.008163\delta_1^3 \quad (\text{Eq. 19})$$

The  $W$  values calculated by the cubic expression (Eq. 19) are shown in Table II and are comparable to the original  $W$  values (Table I) calculated by Eq. 7. The  $W$  values obtained from the cubic polynomial are substituted into Eq. 10 to predict the solubility of theophylline in mixed solvents. The back-calculated solubilities are recorded in Table II.

The solid line, passing through the experimental points in Fig. 1, was obtained by this procedure. The solubilities are faithfully reproduced for solvent mixtures of high  $\delta_1$  values. At the peak of the curve, the experimental points fall below the solubility predicted by the theoretical line, but the error is not great (<~12%). Solubilities represented by the points to the left of the peak values are reproduced less well than to the right of the peak. The solubilities of theophylline in pure dioxane and in pure water are predicted within an error of <40% by this method. Solubilities in these pure solvents are quite small, and this percentage error is not excessive.

The drug solubility obtained by this method is expressed in mole fraction concentration. It can be converted to molal concentration or to grams of solute per gram of solvent. Since the various solution densities are known (Table I), solubility also may be expressed in molarity or in



**Figure 3—Tracing of a computer plot (Eq. 19) of  $W$  values against the solubility parameter,  $\delta_1$ , for theophylline solutions in dioxane–water mixtures. Points represent  $W$  values calculated from experimental solubility data using Eq. 7.**

grams of solute per liter or per milliliter of solution.

The interaction value,  $W$ , may be bypassed and  $\log \alpha_2/A$  may be back-calculated directly. The removal of  $W$  occurs by observing from Eq. 7 that:

$$2W = \delta_1^2 + \delta_2^2 - \log \alpha_2/A \quad (\text{Eq. 20})$$

Substituting Eq. 20 for  $W$  in Eq. 19 yields:

$$\log \alpha_2/A = 111.757266 - 18.848024\delta_1 + 1.010484\delta_1^2 - 0.016327\delta_1^3 \quad (\text{Eq. 21})$$

Equations 19 and 21 are analogous and yield identical results except for rounding-off errors. The back-calculated  $\log \alpha_2$  values are found in Table II and may be compared with the original values obtained from experimental solubilities found in Table I.

This method for adapting the Hildebrand approach to polar systems has advantages and drawbacks, and certain precautions should be taken in its use. The best  $\delta_1$  values should be used for pure solvents and should be accurate to two decimal points where possible. Bagley *et al.* (28) and Nisbet (29) discussed methods for obtaining accurate solvent delta values.

Solute delta values,  $\delta_2$ , and molar volumes,  $V_2$ , for solids ordinarily are not recorded in the literature and are difficult to determine. An interesting result of the new approach is that solubility predictions do not depend on the choice of  $\delta$  or  $V$  of the solute. Whatever values for these quantities were used originally to obtain the  $W$  values will, of course, remain unchanged in the back-calculation and will not affect the accuracy of solubility predictions. However, the investigator must make every effort to obtain reasonable values for  $\delta_2$  and  $V_2$  and to employ the same values each time a solubility analysis is conducted for a particular solute. The best possible  $\delta_2$  and  $V_2$  values must be estimated and used uniformly from one laboratory to another if consistent and reproducible data are to be recorded in the literature.

## CONCLUSION

The present technique is an extension of the Hildebrand method for expressing the solubility of solids in liquid solvents. It should also find use in related equilibria studies. The new method extends the Hildebrand approach from regular solutions, where van der Waals forces predominate, to irregular systems involving stronger solute-solvent interactions such as hydrogen bonding and other acid-base interactions.

The method is not a new physical theory but rather is a technique partly based on polynomial regression for back-calculating solubilities of drugs and other solutes in polar and nonpolar liquids. In a previous report (21) and in cases to be treated later, the procedure may be used to reproduce solubilities of drugs in a range of pure solvents, most satisfactorily in a particular class of solvents; however, it appears to be considerably more successful in predicting solubilities in mixed solvent systems.

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