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Expanded Solubility Parameter Approach I: Naphthalene and Benzoic Acid in Individual Solvents

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Abstract □ An expanded solubility parameter system was tested in conjunction with the extended Hansen solubility approach and the UNIFAC method to calculate the solubilities of naphthalene and benzoic acid in polar and nonpolar solvents. The expanded parameter system is characterized by δ_d for the dispersion force, δ_p for dipolar forces, a basic or electron-donor parameter, δ_b, and an acidic or electron-acceptor parameter δ_a. The correlation between the calculated and observed solubilities of benzoic acid was increased by use of the four-parameter system. An indicator variable was required to bring the solubilities into line in strongly dipolar solvents such as N,N-dimethylformamide. For naphthalene, use of the four-parameter approach proved not to be an improvement over the three-parameter extended Hansen solubility approach. The UNIFAC method was not successful in calculating solubilities of benzoic acid in the 40 polar and nonpolar solvents. A triangular plot of the three Hansen parameters for benzoic acid, *p*-hydroxybenzoic acid, and methyl *p*-hydroxybenzoate illustrated the contributions of dispersion, dipolar, and Lewis acid–base (hydrogen bonding) interaction forces among the three benzoic acid compounds and the various classes of solvents. A multiple regression procedure for calculating the four partial solubility parameters of drug solutes was developed.

Keyphrases □ Solubility parameters, expanded—individual solvents, four-parameter extended Hansen approach, UNIFAC, naphthalene, benzoic acid □ Extended Hansen approach—solubility of naphthalene and benzoic acid in individual solvents, four-parameter system, UNIFAC □ Benzoic acid—model drug, solubility in individual solvents, four-parameter extended Hansen approach, UNIFAC

Recently (1) the solubility of naphthalene was investigated in individual solvents. A new technique, the extended Hansen solubility approach, was compared with the universal functional group activity coefficient (UNIFAC) method (2) and the extended Hildebrand solubility approach (3). The present study was undertaken to investigate the extended Hansen method in more detail and to expand the number of partial solubility parameters from three in the original Hansen approach to four to account for Lewis acid–base (electron acceptor and donor) properties.

Naphthalene was studied in 26 solvents at 40°C and benzoic acid in 40 solvents at 25°C. Naphthalene data were obtained from the literature (1), and benzoic acid data were generated in this laboratory. Both three- and four-pa-

rameter solubility systems were used to correlate the solubilities for naphthalene and benzoic acid.

THEORETICAL

Extended Hansen Solubility Approach—The extended Hansen method (1) was successful in predicting the solubilities of naphthalene in individual solvents. Naphthalene is a good model to begin the study of nonpolar compounds in single solvents; however, it is a poor prototype of a drug molecule. Although naphthalene provides π-electrons for solute–solvent interaction, its lack of functional groups and side chains makes it considerably less irregular than molecules typically encountered in the pharmaceutical sciences. Benzoic acid, with its behavior in water and other polar solvents, provides a considerably better model of a drug.

The extended Hansen solubility equation is written:

$$\log \frac{X_2^i}{X_2} = \log \alpha_2 = C_0 A + C_1 A(\delta_{1d} - \delta_{2d})^2 + C_2 A(\delta_{1p} - \delta_{2p})^2 + C_3 A(\delta_{1h} - \delta_{2h})^2 \quad \text{(Eq. 1)}$$

where X_2^i is the solute ideal mole fraction solubility, X_2 is the observed solute mole fraction solubility, α_2 is the activity coefficient of the solute, and C_i (where $i = 0,1,2,3$) are regression coefficients obtained from regression analysis. δ_{jd} is the partial solubility parameter representing London dispersion forces, δ_{jp} is the Keesom dipolar solubility parameter, and δ_{jh} is a term for generalized electron-transfer bonding which includes hydrogen bonding and other Lewis acid–base interactions; j is 1 for solvent and 2 for solute. These parameters are always taken at 25°C, regardless of use. A is a term from regular solution theory (4):

$$A = \frac{V_2 \phi_1^2}{2.303RT} \quad \text{(Eq. 2)}$$

where V_2 is the molar volume of the solid solute taken as a hypothetical supercooled liquid at 25°C, ϕ_1 is the volume fraction of the solvent, R is the molar gas constant, and T is the absolute temperature. The volume fraction of the solvent is defined as:

$$\phi_1 = \frac{(1 - X_2)V_1}{(1 - X_2)V_1 + X_2V_2} \quad \text{(Eq. 3)}$$

where V_1 is the molar volume of the solvent.

The partial solubility parameters, δ_{1d}, δ_{1p} and δ_{1h} for the solvents are found in the literature (5). Solubility parameters for solid solutes are seldom reported because organic compounds may decompose near their melting points and because of the low vapor pressures of these compounds. The properties of the solid phase cannot be used since the state

of a solute is essentially that of the liquid phase, even if highly super-cooled. Hansen and Beerbower (5) provide a group contribution method by which the partial solubility parameters can be estimated. A recent method based on multiple regression has been suggested to obtain partial solubility parameters for crystalline solid compounds (6).

For a given solute, δ_{2d}, δ_{2p}, and δ_{2h} are constants; therefore, $(\log \alpha_2)/A$ values are regressed only on δ_{1d}, δ_{1d}^2, δ_{1p}, δ_{1p}^2, δ_{1h}, and δ_{1h}^2, according to an expression obtained by expanding Eq. 1:

$$\frac{\log \alpha_2}{A} = C_1\delta_{1d}^2 + (-2C_1\delta_{2d})\delta_{1d} + C_2\delta_{1p}^2 + (-2C_2\delta_{2p})\delta_{1p}$$
$$+ C_3\delta_{1h}^2 + (-2C_3\delta_{2h})\delta_{1h} + (C_0 + C_1\delta_{2d}^2 + C_2\delta_{2p}^2 + C_3\delta_{2h}^2) \quad \text{(Eq. 4)}$$

According to the model:

$$\frac{\log \alpha_2}{A} = D_1\delta_{1d}^2 + D_2\delta_{1d} + D_3\delta_{1p}^2 + D_4\delta_{1p} + D_5\delta_{1h}^2$$
$$+ D_6\delta_{1h} + D_0 \quad \text{(Eq. 5)}$$

where D_0 represents the last term of Eq. 4, made up exclusively of constants. This procedure eliminates the need for solubility parameters of the solute in the regression equation.

Expanded Parameter Approach—Karger et al. (7, 8) proposed five specific solubility parameters for solvents and adsorbents: dispersion, δ_d; induction, δ_{in}; orientation, δ_o; and δ_a and δ_b for acid and base effects, respectively. The authors used this expanded set of parameters to estimate selectivity in chromatography. According to their method, the dispersion solubility parameter is determined (9) from the refractive index fraction, $X = (n^2 - 1)/(n^2 - 2)$ and the expression:

$$\delta_d = -2.24 + 53X - 58X^2 + 22X^3 \quad \text{(Eq. 6)}$$

The orientation parameter (δ_o) is obtainable, in principle, from the dipole moment and molar volume of the substance. It can be calculated using the equation:

$$\delta_o^2 = (\delta_T^2 - \delta_d^2)/(1 + 0.0014\delta_d V) \quad \text{(Eq. 7)}$$

where δ_T is the total solubility parameter obtained from the energy of vaporization (4). The induction solubility parameter is obtained from the orientation parameter and molar volume:

$$\delta_{in} = 0.0007\delta_o^2 V \quad \text{(Eq. 8)}$$

For hydrogen bonding or acid–base effects, the $\delta_a\delta_b$ parameters of alcohols are obtained from:

$$\Delta H_{hb} = C^*V\delta_a\delta_b \quad \text{(Eq. 9)}$$

where ΔH_{hb} is the heat of hydrogen bonding, taken as 5200 cal/mol, and C^* is a proportionality constant. For alcohols C^* has a value of 1.8. With the assumption of equal values of δ_a and δ_b for all alcohols, it is possible to determine the acid and base parameters for other compounds via heats of hydrogen bonding. The expansion of Hansen solubility parameters as proposed here divides the electron transfer solubility parameter, δ_h, to yield acidic, δ_a, and basic, δ_b, solubility parameters in order to quantify electron-donor and -acceptor properties.

The detailed procedures employed in the current study for obtaining the partial solubility parameters of the solvents are as follows.

Dispersion Solubility Parameter, δ_d—The δ_d values proposed by Karger et al. (7, 8) are almost the same as Hansen's δ_d values (5). Since Hansen's δ_d has been refined over a long period of time, based on solubility data, the δ_d values of the solvents used in the current study are those provided by Hansen and Beerbower (5) with a few corrections.

Polar Solubility Parameter, δ_p—The polar parameter, δ_p, was calculated using the modified Boettcher equation (5, 10–12):

$$\delta_p^2 = \frac{12{,}108}{V^2} \cdot \frac{\epsilon - 1}{2\epsilon + n_D^2} (n_D^2 + 2)\mu^2 \quad \text{(Eq. 10)}$$

where V is the molar volume of the compound, ϵ is the dielectric constant, n_D is the refractive index for the D line of sodium, and μ is the dipole moment expressed in units of 10^{-18} esu·cm (Debye units). The δ_p values of the solvents in this study were obtained from Hansen and Beerbower (5).

Basic Solubility Parameter, δ_b—Recently Kamlet et al. (13) used spectrometric methods to obtain three solvatochromic parameters, π^*, α, and β. The α-scale of the solvent provided a measure of proton-donor capacity, and the β-scale quantified the ability of the solvent to accept a proton. Kamlet et al. have prepared an extensive table of β-values for solvents, and Karger et al. (7, 8) provided a limited number of δ_a and δ_b

values for solvents. It was found in the current work that a linear relationship exists between the δ_b-value of Karger et al. and the β-value of Kamlet et al.:

$$V^{1/2}\delta_b = 60.1\beta + 2.45$$
$$n = 22, r^2 = 0.918 \quad \text{(Eq. 11)}$$

The β-value provided by Kamlet et al. (13) in Eq. 11 yields δ_b of the solvent. For example, the β-value of dimethyl sulfoxide is 0.76 (13) and $V = 71.3$ (Table I): $V^{1/2}\delta_b = (60.1)(0.76) + 2.45$; $(71.3)^{1/2}\delta_b = 48.13$. Therefore, $\delta_b = (48.13)/(8.44) = 5.7$. Table I lists δ_b-values for the solvents. Solvents for which Kamlet et al. did not list β-values were evaluated by comparison with the extensive compilation of basicity and acidity parameters by Griffiths and Pugh (14). Some partial parameters were adjusted based on solubility data.

Acidic Solubility Parameter, δ_a—The α-values given by Kamlet et al. are less accurate than β-values, as noted by the authors (13). However, since δ_T, δ_d, δ_p, and δ_b are known, δ_a can be obtained using the following equation:

$$2\delta_a\delta_b = \delta_T^2 - \delta_d^2 - \delta_p^2 = \delta_h^2 \quad \text{(Eq. 12)}$$

For dimethyl sulfoxide, $\delta_b = 5.7$ as given above; $\delta_T = 13.04$, $\delta_d = 9.0$, and $\delta_p = 8.0$ are obtained from Table I. One gets δ_a for dimethyl sulfoxide by substituting these values into Eq. 12: $2\delta_a\delta_b = (13.04)^2 - (9.0)^2 - (8.0)^2 = 25.04$; $\delta_a = (25.04)/(2 \times 5.7) = 2.2$. The δ_a-values for the solvents are found in Table I.

Regression Approach Using Expanded Solubility Parameters—The solubility of a compound in a liquid solvent can be expressed as (7, 8):

$$\frac{\log \alpha_2}{A} = (\delta_{1d} - \delta_{2d})^2 + (\delta_{1o} - \delta_{2o})^2 + 2(\delta_{1d} - \delta_{2d})(\delta_{1in} - \delta_{2in})$$
$$+ 2(\delta_{1a} - \delta_{2a})(\delta_{1b} - \delta_{2b}) \quad \text{(Eq. 13)}$$

where δ_{1d}, δ_{2d}, δ_{1o}, δ_{2o}, δ_{1a}, δ_{2a}, δ_{1b}, and δ_{2b} have already been defined. Since δ_p and δ_o are both contributed from the dipolar property of the compound, δ_p-values were used instead of δ_o in the present study. The induction solubility parameter, δ_{in}, a product term of δ_o and V, was found to be insignificant in improving the predicted solubilities[1] and was deleted. Equation 13 can then be transformed to:

$$\frac{\log \alpha_2}{A} = (\delta_{1d} - \delta_{2d})^2 + (\delta_{1p} - \delta_{2p})^2 + 2(\delta_{1a} - \delta_{2a})(\delta_{1b} - \delta_{2b})$$
$$\text{(Eq. 14)}$$

The solubility of one compound in various single solvents can be predicted by expanding Eq. 14:

$$\frac{\log \alpha_2}{A} = \delta_{1d}^2 - 2\delta_{1d}\delta_{2d} + \delta_{2d}^2 + \delta_{1p}^2 - 2\delta_{1p}\delta_{2p} + \delta_{2p}^2$$
$$+ 2\delta_{1a}\delta_{1b} - 2\delta_{1a}\delta_{2b} - 2\delta_{2a}\delta_{1b} + 2\delta_{2a}\delta_{2b} \quad \text{(Eq. 15)}$$

where δ_{2d}, δ_{2p}, δ_{2a}, and δ_{2b} are now the solubility parameters of the solute, which obviously are constant for a particular solute dissolved in a series of different solvents. Therefore, the solubilities are simply estimated by regressing $(\log \alpha_2)/A$ against δ_{1d}^2, δ_{1d}, δ_{1p}^2, δ_{1p}, $\delta_{1a}\delta_{1b}$, δ_{1a}, and δ_{1b} using the model suggested by Eq. 15:

$$\frac{\log \alpha_2}{A} = C_0 + C_1\delta_{1d}^2 + C_2\delta_{1d} + C_3\delta_{1p}^2 + C_4\delta_{1p} + C_5\delta_{1a}\delta_{1b}$$
$$+ C_6\delta_{1a} + C_7\delta_{1b} \quad \text{(Eq. 16)}$$

where $C_0, C_1, \ldots$ are the coefficients of the regression equation.

EXPERIMENTAL

Materials—The solubility of benzoic acid[2] in a number of solvents was compared with literature values, and the UV spectra of the various solutions were measured. The solvents were spectrophotometric or ACS grade or redistilled before used and are listed in Table I. The solubility data for naphthalene was obtained from the literature (1).

Heat of Fusion and Molar Volume—The heat of fusion of benzoic acid, determined by differential scanning calorimetry[3], was found to be

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[1] P. L. Wu and A. Martin, unpublished data.
[2] Matheson Coleman Bell, Norwood, OH 45212.
[3] Perkin-Elmer DSC Model 1B, Norwalk, Conn.

Table I—Solubility Parameters and Molar Volumes of Commonly Used Solvents

| No. | Solvent | Molar Volume (V_1) | Solubility Parameter | | | | |
			Dispersion (δ_d)	Dipolar (δ_p)	Hydrogen Bonding (δ_h)	Acidic (δ_a)	Basic (δ_b)	Total (δ_T)
1	Pentane	116.1	7.1	0.0	0.0	0.0	0.0	7.10
2	Hexane	131.6	7.3	0.0	0.0	0.0	0.0	7.30
3	Heptane	147.5	7.5	0.0	0.0	0.0	0.0	7.50
4	Nonane	179.7	7.7	0.0	0.0	0.0	0.0	7.70
5	Decane	195.9	7.7	0.0	0.0	0.0	0.0	7.70
6	Cyclohexane	108.8	8.2	0.0	0.0	0.0	0.0	8.20
7	Benzene	89.4	9.0	0.5	1.0	0.7	0.7	9.07
8	Toluene	106.9	8.8	0.7	1.0	0.8	0.6	8.88
9	Chlorobenzene	102.2	9.3	2.1	1.0	1.0	0.5	9.59
10	Ethylene dichloride	79.4	9.3	3.6	2.0	2.0	1.0	10.17
11	Ethylidene chloride	84.8	8.1	4.0	0.2	0.2	0.1	9.04
12	Chloroform	80.8	8.7	1.5	2.8	3.0	1.3	9.26
13	Carbon tetrachloride	97.1	8.7	0.0	0.3	0.05	0.9	8.71
14	Ethylene dibromide	87.0	9.3[a]	1.7	4.2	11.2	0.8	10.36
15	Ethylidene bromide	92.9	9.0[a]	2.5[a]	3.2[a]	10.0	0.5	9.86
16	Diethyl ether	104.8	7.1	1.4	2.5	0.5	6.3	7.66
17	Dipropyl ether	139.4	7.3	1.1	2.0	0.4	5.0	7.65
18	Dibutyl ether	170.4	7.6	0.8	1.5	0.3	3.9	7.79
19	Ethyl acetate	98.5	7.4	2.6	4.5	5.3	1.9	9.04
20	Propyl acetate	115.7	7.7	2.1	3.3	3.6	1.5	8.63
21	Butyl acetate	132.6	7.7	1.8	3.1	2.8	1.7	8.49
22	Hexyl acetate	164.5	7.8	1.5	2.9	1.9	2.2	8.45
23	Carbon disulfide	60.0	10.0	0.0	0.3	0.2	0.2	10.00
24	Acetone	74.0	7.6	5.1	3.4	2.4	2.4	9.76
25	Dioxane	85.7	9.3	0.9	3.6	1.0	6.5	10.01
26	Aniline	91.5	9.5	2.5	5.0	1.9	6.5	11.01
27	Nitrobenzene	102.7	9.8	4.2	2.0	2.0	1.0	10.85
28	Acetophenone	117.4	9.6	4.2	1.8	1.1	1.5	10.63
29	Benzyl alcohol	103.9	9.0	3.1	6.7	5.9	3.8	11.64
30	Cyclohexanol	106.0	8.5	2.0	6.6	7.3	3.0	10.96
31	Methyl alcohol	40.7	7.4	6.0	10.9	8.4	7.1	14.49
32	Ethyl alcohol	58.7	7.7	4.3	9.5	8.3	5.5	12.96
33	Propyl alcohol	75.1	7.8	3.3	8.5	7.5	4.8	11.99
34	Isopropyl alcohol	76.9	7.7	3.0	8.0	7.1	4.5	11.50
35	Butyl alcohol	92.0	7.8	2.8	7.7	6.4	4.6	11.29
36	Isobutyl alcohol	92.4	7.4	2.8	7.8	6.0	5.1	11.13
37	sec-Butyl alcohol	92.5	7.7	2.8	7.1	6.6	3.8	10.83
38	tert-Butyl alcohol	94.3	7.3	2.5	6.8	9.6	2.4	10.28
39	1-Pentanol	108.6	7.8	2.2	6.8	5.4	4.3	10.59
40	1-Hexanol	125.2	8.0	2.1	6.3	5.7	3.5	10.41
41	1-Heptanol	141.9	8.1	2.0	6.0	5.3	3.4	10.28
42	1-Octanol	158.4	8.3	1.6	5.8	5.2	3.2	10.23
43	Ethylene Glycol	55.9	8.3	5.4	12.6	17.9	4.4	15.99
44	1,2-Propanediol	73.7	8.2	4.6	11.4	14.1	4.6	14.77
45	1,3-Propanediol	72.5	8.1	5.3	12.7	10.9	7.4	15.97
46	Glycerol	73.2	8.5	5.9	14.3	20.0	5.1	17.64
47	1,4-Butanediol	88.6	8.2	8.1	11.6	18.2	3.7	16.36
48	Acetic acid	57.6	7.1	3.9	6.6	7.0	3.1	10.44
49	Propionic acid	75.0	7.2	3.8	6.0	6.0	3.0	10.11
50	Butyric acid	91.9	7.3	2.0	5.2	6.4	2.1	9.17
51	Dimethyl sulfoxide	71.3	9.0	8.0	5.0	2.2	5.7	13.04
52	Pyridine	80.9	9.3	4.3	3.0	1.4	3.2	10.67
53	Formamide	39.9	8.4	12.8	9.3	5.7	7.6	17.92
54	N-Methylformamide	59.1	8.4	10.1	6.1	4.8	3.9	14.49
55	N,N-Dimethylformamide	77.4	8.5	6.7	5.5	3.4	4.4	12.13
56	N,N-Diethylformamide	112.0	8.2	5.6	4.3	2.7	3.4	10.81
57	N,N-Dimethylacetamide	93.0	8.2	5.6	5.0	2.9	4.3	11.11
58	N,N-Diethylacetamide	126.6	8.2	4.1	3.7	2.1	3.2	9.87
59	Water	18.1	7.6	7.8	20.7	6.7	32.0	23.40

[a] Values recalculated.

4326 cal/mol (average of six measurements). The molar volume of supercooled benzoic acid at 25°C was taken as 104.3 cm³/mol (15). The molar volumes of the solvents were obtained from the literature (16).

Ideal Solubility and Activity Coefficient—The ideal solubility of benzoic acid can be calculated from the heat of fusion of the solute and heat capacities of the solid and its supercooled liquid (17):

$$\log X_2^i = -\frac{\Delta H_m^f}{4.575}\left(\frac{T_m - T}{T_m T}\right) + \frac{\Delta C_p}{4.575}\left(\frac{T_m - T}{T}\right) - \frac{\Delta C_p}{1.987}\log\frac{T_m}{T}$$

(Eq. 17)

The ideal solubility of benzoic acid was calculated using the following data: $\Delta H_m^f = 4326$ cal/mol, $T_m = 395.45$ K, $T = 298.15$ K, and $\Delta C_p = C_p^l - C_p^s = 13.83$ cal/mol·deg (18). These quantities result in the following

ideal solubility values at 25°C: $\log X_2^i = -0.6475$ or $X_2^i = 0.2251$. The activity coefficient is calculated from:

$$\log \alpha_2 = \log X_2^i - \log X_2 = \log\frac{X_2^i}{X_2}$$

(Eq. 18)

Solubility Determination—The solubility of benzoic acid was determined in individual solvents at 25°C. A suitable amount of an individual solvent was introduced into screw-capped vials containing an excess amount of the solute. After being sealed with several turns of plastic tape, the vials were submerged in water at 25 ± 0.2°C and were shaken at 100 cycles/min for 24 h in a constant-temperature bath[4]. Preliminary studies showed that this time period was sufficient to assure saturation at 25°C.
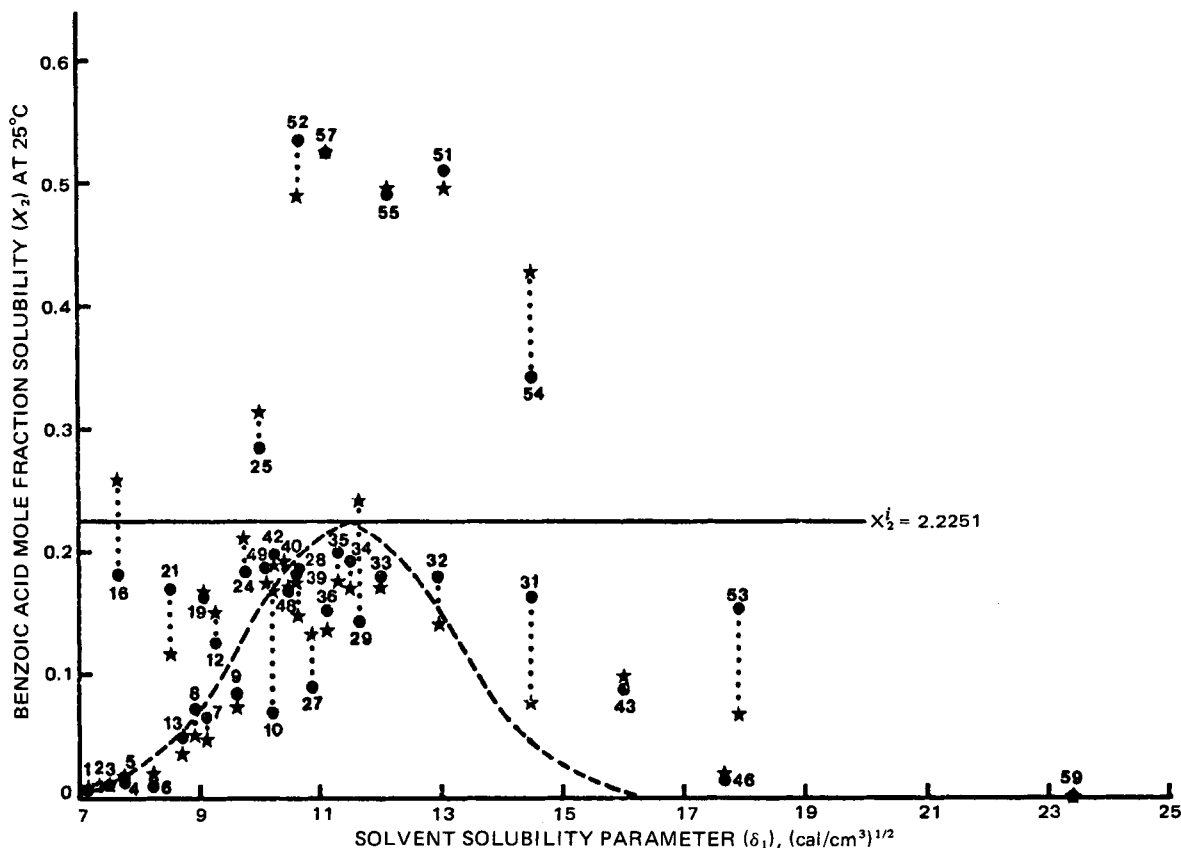
[4] Blue-M Electric Co., Blue Island, Ill.

Figure 1—*Solubility profile of benzoic acid in individual solvents at 25°C. See Table I for solvent numbers. Key: (- - -) regular solution curve; (——) ideal solubility line, $X_2 = 0.2251$; (●) experimental solubilities; (★) solubilities calculated using Eq. 28.*

After equilibrium had been attained, each vial was removed, wiped dry, and analyzed. The solutions were transferred to a syringe and filtered using a filter[5] of pore size <1 μm. After suitable dilution, the solutions were assayed using a spectrophotometer[6] set at the λ_{max} of the solute. The solubility was determined at least six times for each solvent, and the average value was taken. The experimental variation in solubility was $<3\%$ in replicate samples and was consistent with an acid–base titration method (19). The densities of the saturated solutions were determined with a calibrated pycnometer at 25°C.

RESULTS AND DISCUSSION

Three-Parameter Solubility System—(Log α_2)/A for naphthalene solubility in 26 solvents at 40°C was regressed against the Hansen solvent parameters (Table I, Eq. 5) to yield:

$$\frac{\log \alpha_2}{A} = 0.6214\delta_{1d}^2 - 12.70\delta_{1d} - 0.1240\delta_{1p}^2 + 0.5383\delta_{1p}$$

$$+ 0.1292\delta_{1h}^2 - 0.2242\delta_{1h} + 64.62$$

$$n = 26, s = 1.37, r^2 = 0.986, F = 231, F(6,19,0.01) = 3.94 \quad (Eq. 19)$$

This regression equation is slightly different from the one reported earlier (6) due to recalculation of the solubility parameters of ethylene dibromide and ethylidene bromide.

To predict the solubility of naphthalene at 40°C in acetone, the calculation is made as follows. The partial solubility parameters for acetone are $\delta_{1d} = 7.6$, $\delta_{1p} = 5.1$, and $\delta_{1h} = 3.4$. Substituting these values in Eq. 19 yields (log α_2)/A = 4.24. The A-value is then calculated using Eq. 2 with $V_2 = 123$, $V_1 = 74.0$, $R = 1.987$, $T = 313.15$ K, and $X_2^i = 0.466$. The volume fraction of the solvent, ϕ_1, is unknown since it depends on the value of X_2 (Eq. 3). Hence, A is found by an iteration procedure (20), beginning with a value of 1 for ϕ_1 and iterating until X_2 or ϕ_1 no longer changes by more than some small desired value, e.g., 0.0001. In the present example, the steps of the iteration are shown in Table II. The iteration yielded X_2 (calc.) = 0.379, a result that compares favorably with X_2 (obs.) = 0.378, and provides a predicted value within a 1% error relative to the observed

mole fraction solubility. The back-calculated solubilities of naphthalene, using Eq. 19, are listed in Table III. They are within 30% error of the observed values, except for those in aniline (31%), isopropyl alcohol (38%), and acetic acid (68%). The residuals and percentage errors are also given in Table III. Thirty percent error is taken in this work as a criterion of acceptability. A maximum value of 15% would be highly desirable, but is unrealistic at this stage of development of the methods.

The mole fraction solubilities of benzoic acid in 40 solvents at 25°C are listed in Table IV. A mole fraction solubility profile of benzoic acid is plotted on the total solubility parameter scale in Fig. 1. The data points for observed solubilities are shown as filled circles, joined to the calculated values (stars) by dotted lines.

When benzoic acid is dissolved in a nonpolar solvent, it tends to self-associate, even at high dilution, through intermolecular hydrogen bonds and other attraction forces. In benzene at 25°C, benzoic acid forms dimers and trimers (21), in carbon tetrachloride it exists as dimers, and in alcohols it remains as the monomer (22). The degree of self-association of dissolved benzoic acid and the percentages of monomeric, dimeric, trimeric, and polymeric forms are not currently known for most solvents. Benzoic acid is therefore treated in this study as if it behaved as a monomer in all solvents, and the mole fraction solubility is calculated based on the monomeric form.

(Log α_2)/A of benzoic acid in 40 solvents at 25°C was regressed against

Table II—Iteration Procedure for Calculating the Solubility of Naphthalene in Acetone at 40°C Using Eq. 19

Step	ϕ_1	A	log α_2	X_2
1	1	0.08583	0.36394	0.20158
2	0.70440	0.04259	0.18058	0.30747
3	0.57538	0.02842	0.12049	0.35310
4	0.52431	0.02360	0.10005	0.37012
5	0.50590	0.02197	0.09314	0.37605
6	0.49956	0.02142	0.09082	0.37806
7	0.49742	0.02124	0.09005	0.37874
8	0.49670	0.02118	0.08979	0.37897
9	0.49646	0.02116	0.08970	0.37904
10	0.49637	0.02115	0.08967	0.37907
11	0.49635	0.02115	0.08966	0.37908

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[5] Filter paper, Glass Fiber, Whatman Grade GF/F.
[6] Beckman, Model 25.

Table III—Back-Calculated Solubilities of Naphthalene in Solvents at 40°C Using Three- and Four-Parameter Systems

		Mole Fraction Solubility (X_2)	Equation 29			Equation 19		
No.	Solvent		X_2 (Calc.)	Residual	Error, %	X_2 (Calc.)	Residual	Error, %
2	Hexane	0.222	0.266	−0.044	−19.8	0.269	−0.047	−21.2
7	Benzene	0.428	0.446	−0.018	− 4.2	0.450	−0.022	− 5.1
8	Toluene	0.422	0.432	−0.010	− 2.4	0.436	−0.014	− 3.3
9	Chlorobenzene	0.444	0.453	−0.009	− 2.0	0.449	−0.005	− 1.1
10	Ethylene dichloride	0.452	0.455	−0.003	− 0.7	0.455	−0.003	− 0.7
11	Ethylidene chloride	0.437	0.416	0.021	4.8	0.409	0.028	6.4
12	Chloroform	0.467	0.419	0.048	10.3	0.426	0.041	8.8
13	Carbon tetrachloride	0.395	0.431	−0.036	− 9.1	0.441	−0.046	−11.6
14	Ethylene dibromide	0.439	0.442	−0.003	− 0.7	0.419	0.020	4.6
15	Ethylidene bromide	0.456	0.447	0.009	2.0	0.425	0.031	6.8
23	Carbon disulfide	0.494	0.473	0.021	4.3	0.469	0.025	5.1
24	Acetone	0.378	0.351	0.027	7.1	0.379	−0.001	− 0.3
26	Aniline	0.306	0.321	−0.015	− 4.9	0.402	−0.096	−31.4
27	Nitrobenzene	0.432	0.469	−0.037	− 8.6	0.466	−0.034	− 7.9
30	Cyclohexanol	0.232	0.241	−0.009	− 3.9	0.237	−0.005	− 2.2
31	Methyl alcohol	0.0412	0.0372	0.0040	9.7	0.0320	0.0092	22.3
32	Ethyl alcohol	0.0726	0.0686	0.0040	5.5	0.0599	0.0127	17.5
33	Propyl alcohol	0.0944	0.0930	0.0014	1.5	0.0910	0.0034	3.6
34	Isopropyl alcohol	0.0764	0.1023	−0.0259	−33.9	0.1051	−0.0287	−37.6
35	Butyl alcohol	0.116	0.104	0.012	10.3	0.114	0.002	1.7
36	Isobutyl alcohol	0.0925	0.0640	0.0285	30.8	0.0746	0.0179	19.4
37	sec-Butyl alcohol	0.1122	0.1284	−0.0162	−14.4	0.1364	−0.0242	−21.6
38	tert-Butyl alcohol	0.1009	0.1220	−0.0211	−20.9	0.1049	−0.0040	− 4.0
48	Acetic acid	0.117	0.192	−0.075	−64.1	0.197	−0.080	−68.4
50	Butyric acid	0.251	0.180	0.071	28.3	0.186	0.065	25.9
59	Water	1.76×10^{-5}	1.75×10^{-5}	1.0×10^{-7}	0.5	1.81×10^{-5}	5.0×10^{-5}	2.8

the Hansen parameters (Table I) to produce the regression equation:

$$\frac{\log \alpha_2}{A} = 5.498\delta_{1d}^2 - 92.79\delta_{1d} + 0.4686\delta_{1p}^2 - 7.397\delta_{1p}$$
$$+ 0.1597\delta_{1h}^2 - 0.6623\delta_{1h} + 403.17$$
$$n = 40, s = 7.47, r^2 = 0.71, F = 13.7, F(6,33,0.01) = 3.40 \quad \text{(Eq. 20)}$$

It has subsequently been found that a root-finder method (23) is more satisfactory than simple iteration, and this technique is now used in place of iteration in the extended Hansen solubility approach. Since the right-hand side of Eq. 20 is a function of the three partial parameters, which together constitute δ_1, it can be designated as $f(\delta_1)$. Combining this with Eqs. 2, 3, and 18, one obtains:

$$f(X_2) = (\log X_2^i - \log X_2)(2.303RT)[V_1(1 - X_2) + V_2 X_2]^2$$
$$- V_2[V_1(1 - X_2)]^2 f(\delta_1) = 0 \quad \text{(Eq. 21)}$$

X_2 can be found by a trial and error method. For ethyl acetate ($\delta_{1d} = 7.4$, $\delta_{1p} = 2.6$, and $\delta_{1h} = 4.5$) one may substitute these partial solubility parameters into Eq. 20 and obtain $f(\delta_1) = 1.7836$. The mole fraction solubility of benzoic acid in ethyl acetate can then be estimated from Eq. 21 using $V_1 = 98.5$, $V_2 = 104.3$, $T = 298.15$ K, and $\log X_2^i = -0.6475$. Table V lists the values of X_2 found during the trial and error procedure, which can easily be accomplished by use of a programmable calculator. The root-finder subroutine ZBRENT found in The International Mathematics and Statistics Library (IMSL) (23) can be run on an electronic computer[7] to obtain the calculated solubilities. It was observed that 24 of the 40 solubilities were within 30% error of the experimental result. The calculated solubilities (Eq. 20) for benzoic acid at 25°C are found in Table IV.

Estimating the Partial Solubility Parameters of Benzoic Acid—Using the extended Hansen three-parameter system as previously reported for naphthalene (6), the regression equation obtained for benzoic acid can be transformed to a form that yields the partial solubility parameters of the solute. The steps are as follows:

$$\frac{\log \alpha_2}{A} = 5.489(\delta_{1d}^2 - 16.877\delta_{1d}) + 0.4686(\delta_{1p}^2 - 15.785\delta_{1p})$$
$$+ 0.1597(\delta_{1h}^2 - 4.147\delta_{1h}) + 403.17 \quad \text{(Eq. 22)}$$

$$\frac{\log \alpha_2}{A} = 5.489(\delta_{1d}^2 - 16.877\delta_{1d} + 71.208)$$
$$+ 0.4686(\delta_{1p}^2 - 15.785\delta_{1p} + 62.292)$$
$$+ 0.1597(\delta_{1h}^2 - 4.147\delta_{1h} + 4.299) - (5.489)(71.208)$$
$$- (0.4686)(62.292) - (0.1597)(4.299) + 403.17 \quad \text{(Eq. 23)}$$

Therefore, $71.208 = \delta_{2d}^2$ and $(71.208)^{1/2} = 8.44 = \delta_{2d}$; likewise for δ_{2p} and δ_{2h}:

$$\frac{\log \alpha_2}{A} = 5.498(\delta_{1d} - 8.44)^2 + 0.4686(\delta_{1d} - 7.89)^2$$
$$+ 0.1597(\delta_{1h} - 2.07)^2 - 18.27 \quad \text{(Eq. 24)}$$

The partial solubility parameters, $\delta_{2d} = 8.44$, $\delta_{2p} = 7.89$, and $\delta_{2h} = 2.07$, have thus been obtained by a regression method involving only solvent partial solubility parameters, together with experimental data from which $(\log \alpha_2)/A$ is calculated. The total solubility parameter, δ_T, for benzoic acid by this method is:

$$\delta_T^2 = \delta_{2d}^2 + \delta_{2p}^2 + \delta_{2h}^2 = (8.44)^2 + (7.89)^2 + (2.07)^2 = 137.77$$
$$\delta_T = (137.77)^{1/2} = 11.74 \quad \text{(Eq. 25)}$$

This value compares favorably with $\delta_2 = 11.5$ given in the literature (15). An earlier publication (5) gave $\delta_{2d} = 8.9$, $\delta_{2p} = 3.4$, and $\delta_{2h} = 4.8$, from which $\delta_2 = 10.7$. These values appeared to be quite low, so they were recalculated in 1974[8] to be $\delta_{2d} = 10.5$, $\delta_{2p} = 2.8$, and $\delta_{2h} = 4.8$, from which $\delta_2 = 11.9$, in good agreement with δ_2 calculated by Eq. 25.

Agreement with the partial parameters of Eq. 25 is less satisfactory, partly because C_1 was allowed to have any value that the computer found gave the best fit to the solubilities in Table IV. That resulted in $C_1 = 5.489$, which is contrary to both theory and experience with London (dispersion) forces. Though they are omnidirectional and universal, they can interact only once with each nearest neighbor, so that any value of C_1 other than 1.000 must be an artifact. Trial runs with the computer constrained in that way show that the loss of accuracy in predicting solubility is not serious. It will be necessary to continue with this approach at a later time.

Graphical Solubility Relationships: Triangular Diagrams—To demonstrate graphically the effects of solvents, Teas (24) expressed the three solubility parameters of Hansen as functions:

$$f_d = \frac{\delta_d}{\delta_d + \delta_p + \delta_h}; \quad f_p = \frac{\delta_p}{\delta_d + \delta_p + \delta_h}; \quad f_h = \frac{\delta_h}{\delta_d + \delta_p + \delta_h} \quad \text{(Eq. 26)}$$

These functional values are plotted along the three axes of the triangular graphs in Fig. 2. The points for the solvents, numbered according to the listing in Table I, are then entered on each triangular graph. Solvents with high solvencies (mole fraction solubilities >0.150) for benzoic acid are plotted as filled circles, and those with low solvencies are plotted as open squares. A boundary line has been drawn around the solvents in Fig. 2A with solvencies for benzoic acid greater than $X_2 = 0.150$. Triangular solubility plots for p-hydroxybenzoic acid and for methyl p-hydroxy-

[7] University of Texas Cyber Computer System.

[8] Unpublished data.

Table IV—Calculated Solubilities of Benzoic Acid in Individual Solvents at 25°C

No.	Solvent	Mole Fraction Solubility (X_2)	UNIFAC			Equation 20			Equation 27			Equation 28		
			X_2 (Calc.)	Residual	Error, %	X_2 (Calc.)	Residual	Error, %	X_2 (Calc.)	Residual	Error, %	X_2 (Calc.)	Residual	Error, %
1	Pentane	0.0059	0.0100	-0.0041	-64.5	0.0053	0.0006	10.2	0.0024	0.0035	59.3	0.0078	-0.0019	-32.2
2	Hexane	0.0095	0.0101	-0.0006	-6.3	0.0086	0.0009	9.5	0.0045	0.0050	52.6	0.0097	-0.0002	-2.1
3	Heptane	0.0117	0.0103	0.0014	12.0	0.0130	-0.0013	-11.1	0.0075	0.0042	35.9	0.0118	-0.0001	-0.9
4	Nonane	0.0141	0.0109	0.0032	22.7	0.0180	-0.0039	-27.7	0.0115	0.0026	18.4	0.0138	0.0003	2.1
5	Decane	0.0154	0.0114	0.0040	26.0	0.0179	-0.0025	-16.2	0.0114	0.0040	26.0	0.0138	0.0016	10.4
6	Cyclohexane	0.0102	0.0112	-0.0010	-9.8	0.0310	-0.0208	-203.9	0.0220	-0.0118	-115.7	0.0191	-0.0089	-87.3
7	Benzene	0.0689	0.0623	0.0066	9.6	0.0532	0.0157	22.8	0.0459	0.0230	33.4	0.0476	0.0213	30.9
8	Toluene	0.0734	0.0407	0.0327	44.6	0.0798	-0.0064	-8.7	0.0707	0.0027	3.7	0.0512	0.0222	30.2
9	Chlorobenzene	0.0862	0.0747	0.0115	13.3	0.1832	-0.0970	-112.5	0.1265	-0.0403	-46.8	0.0762	0.0100	11.6
10	Ethylene dichloride	0.0695	0.1334	-0.0639	-91.9	0.3242	-0.2547	-366.5	0.2932	-0.2237	-321.9	0.1676	-0.0981	-141.2
12	Chloroform	0.1283	0.0038	0.1245	97.0	0.1954	-0.0671	-52.3	0.2185	-0.0902	-70.3	0.1537	-0.0254	-19.8
13	Carbon tetrachloride	0.0494	0.0178	0.0316	64.0	0.0322	0.0172	34.8	0.0352	0.0142	28.7	0.0356	0.0138	27.9
16	Diethyl ether	0.1837	0.0832	0.1005	54.7	0.0346	0.1491	81.6	0.2123	-0.0286	-15.6	0.2602	-0.0765	-41.6
19	Ethyl acetate	0.1649	0.1251	0.0398	24.1	0.1835	-0.0186	-11.3	0.1879	-0.0230	-13.9	0.1688	-0.0039	-2.4
21	Butyl acetate	0.1699	0.0937	0.0762	44.8	0.1655	0.0044	2.6	0.1874	-0.0175	-10.3	0.1171	0.0528	31.1
24	Acetone	0.1857	0.1671	0.0186	10.0	0.3810	-0.1953	-105.2	0.3830	-0.1973	-106.2	0.2111	-0.0254	-13.7
25	Dioxane	0.2853	0.2063	0.0790	27.7	0.0554	0.2299	80.6	0.2738	0.0115	4.0	0.3122	-0.0269	-9.4
27	Nitrobenzene	0.0897	—[a]	—	—	0.2630	-0.1733	-193.2	0.1643	-0.0746	-83.2	0.1332	-0.0435	-48.5
28	Acetophenone	0.1878	0.1232	0.0646	34.4	0.3282	-0.1404	-74.8	0.2704	-0.0826	-44.0	0.1475	0.0403	21.5
29	Benzyl alcohol	0.1441	0.1666	-0.0225	-15.6	0.2782	-0.1341	-93.1	0.3061	-0.1620	-112.4	0.2429	-0.0988	-68.6
31	Methyl alcohol	0.1632	0.1489	0.0143	8.8	0.1988	-0.0356	-21.8	0.1325	0.0307	18.8	0.0777	0.0855	52.4
32	Ethyl alcohol	0.1789	0.1231	0.0558	31.2	0.2292	-0.0503	-28.1	0.2030	-0.0241	-13.5	0.1413	0.0376	21.0
33	Propyl alcohol	0.1791	0.1099	0.0692	38.6	0.2156	-0.0365	-20.4	0.2208	-0.0417	-23.3	0.1690	0.0101	5.6
34	Isopropyl alcohol	0.1937	0.1102	0.0835	43.1	0.1918	0.0019	1.0	0.2041	-0.0104	-5.4	0.1694	0.0243	12.5
35	Butyl alcohol	0.2016	0.1013	0.1003	49.8	0.1983	0.0033	1.6	0.2318	-0.0302	-15.0	0.1787	0.0229	11.4
36	Isobutyl alcohol	0.1524	0.0956	0.0568	37.3	0.1127	0.0397	26.0	0.1325	0.0199	13.1	0.1375	0.0149	9.8
39	1-Pentanol	0.1839	0.0958	0.0881	47.9	0.1582	0.0257	14.0	0.2176	-0.0337	-18.3	0.1772	0.0067	3.6
40	1-Hexanol	0.1905	0.0920	0.0985	51.7	0.1886	0.0019	1.0	0.2463	-0.0558	-29.3	0.1932	-0.0027	-1.4
42	1-Octanol	0.1987	0.0873	0.1114	56.1	0.1561	0.0426	21.4	0.2294	-0.0307	-15.5	0.1895	0.0092	4.6
43	Ethylene glycol	0.0884	0.0476	0.0408	46.2	0.1838	-0.0954	-107.9	0.0556	0.0328	37.1	0.0977	-0.0093	-10.5
46	Glycerol	0.0164	0.0441	-0.0277	-168.9	0.0794	-0.0630	-384.1	0.0073	0.0091	55.5	0.0198	-0.0034	-20.7
48	Acetic acid	0.1675	0.1560	0.0115	6.9	0.1825	-0.0150	-9.0	0.1517	0.0158	9.4	0.1708	-0.0033	-2.0
49	Propionic acid	0.1887	0.1446	0.0441	23.4	0.2145	-0.0258	-13.7	0.1972	-0.0085	-4.5	0.1752	0.0135	7.2
51	Dimethyl sulfoxide	0.5102	—	—	—	0.4207	0.0895	17.5	0.4575	0.0527	10.3	0.4938	0.0164	3.2
52	Pyridine	0.5348	0.4255	0.1093	20.4	0.3602	0.1746	32.6	0.3847	0.1501	28.1	0.4890	0.0458	8.6
53	Formamide	0.1525	—	—	—	0.2059	-0.0534	-35.0	0.1942	-0.0417	-27.3	0.0674	0.0851	55.8
54	N-Methylformamide	0.3428	—	—	—	0.3835	-0.0407	-11.9	0.3781	-0.0353	-10.3	0.4269	-0.0841	-24.5
55	N,N-Dimethylformamide	0.4909	—	—	—	0.4364	0.0545	11.1	0.4576	0.0333	6.8	0.4959	-0.0050	-1.0
57	N,N-Dimethylacetamide	0.5245	—	—	—	0.4462	0.0783	14.9	0.4786	0.0459	8.8	0.5253	-0.0008	-0.2
59	Water (pH 2.0)	0.0005	0.0005	0.0	0.0	0.0002	0.0003	60.0	0.0007	-0.0002	-40.0	0.0007	-0.0002	-40.0

[a] Dashed lines indicate that X_2 (calc.) could not be obtained with UNIFAC because of lack of UNIFAC parameters for these solvents.
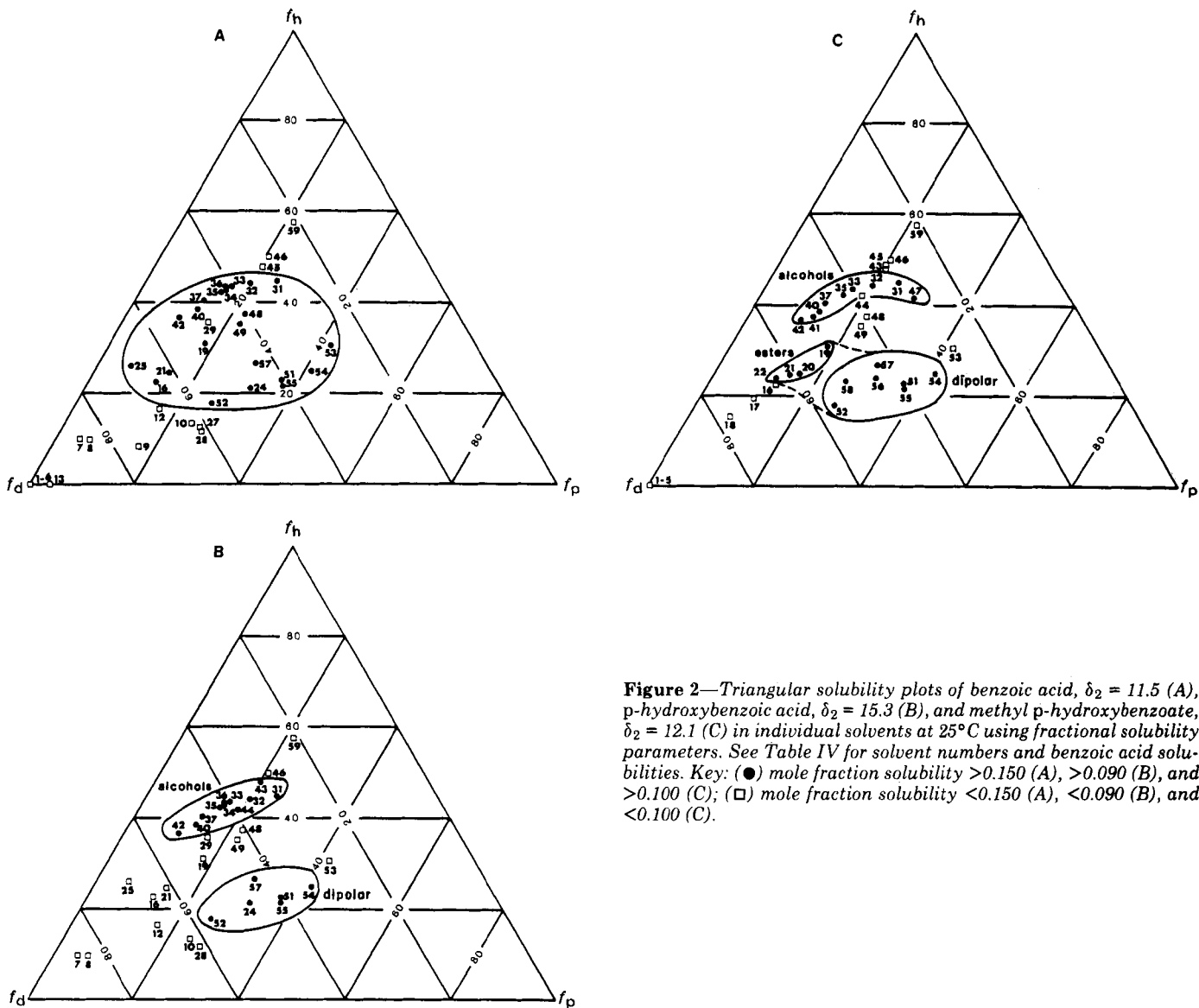
Figure 2—Triangular solubility plots of benzoic acid, $\delta_2 = 11.5$ (A), p-hydroxybenzoic acid, $\delta_2 = 15.3$ (B), and methyl p-hydroxybenzoate, $\delta_2 = 12.1$ (C) in individual solvents at 25°C using fractional solubility parameters. See Table IV for solvent numbers and benzoic acid solubilities. Key: (●) mole fraction solubility >0.150 (A), >0.090 (B), and >0.100 (C); (□) mole fraction solubility <0.150 (A), <0.090 (B), and <0.100 (C).

benzoate are shown in Fig. 2B and C, respectively. The data for these compounds are given in the following paper (25).

As observed in Fig. 2A high solubility of benzoic acid occurs in solvents having f_d = 0.25–0.70, f_p = 0.05–0.45, and f_h = 0.17–0.45, which fall in the center region of the diagram. Solvents with high f_d values, such as numbers 1–9, result in low solubility of benzoic acid. Glycols and water with high f_h values (numbers 43, 46, and 59) also yield poor solubility of benzoic acid. Benzyl alcohol (number 29) produces intermediate solubility, X_2 = 0.144, and because of its δ_d-, δ_p-, and δ_h-values, falls within the boundary of good solvents in Fig. 2A.

The partial parameters of benzoic acid can be estimated from Fig. 2A, noting that the center of the high solubility region is at $f_d \simeq 0.47, f_p \simeq$ 0.23, and $f_h \simeq 0.30$. Assuming that $\delta_2 = 11.45$ as the average of the data above, we may calculate that $\delta_{2d} = 8.9$, $\delta_{2p} = 4.4$, and $\delta_{2h} = 5.7$. These were much more definite than could be obtained by Hansen's (5) plotting method and quite possibly better than either Eq. 25 or the calculations done during 1974.

In Fig. 2B, it is observed that two distinct classes of solvents provide reasonable solubility for p-hydroxybenzoic acid, $\delta_2 = 15$; the alcohols and glycols (excluding glycerol, number 46) on the one hand and the strongly dipolar solvents such as N,N-dimethylformamide (number 55) and dimethyl sulfoxide (number 51). The fact that the moderately dipolar pyridine (number 52) is a good solvent, but the strongly dipolar form-amide (number 53) is not, shows the difficulty of classifying solvents in a general sense. It is the detailed matching of the partial parameters of solvent and solute that controls the specific solubilities. The two peak regions probably correspond to the two functional groups on the solute, as is found in elastomer swelling (5). Hydrocarbons, esters, and acids are

not good solvents for p-hydroxybenzoic acid, presumably because one or more partial parameters do not match.

Methyl p-hydroxybenzoate, $[\delta_2 = 12.1$ (26)] like benzoic acid $[\delta_2 = 11.5$ (15)] is semipolar and is best dissolved by solvents located in the central region of Fig. 2C. The good solvents could be considered to constitute one large central region of the diagram, but they are better separated into three distinct regions representing esters, alcohols, and strongly dipolar

Table V—Demonstration of Trial and Error Process for Calculating Benzoic Acid Solubility in Ethyl Acetate at 25°C Using Eqs. 20 and 21

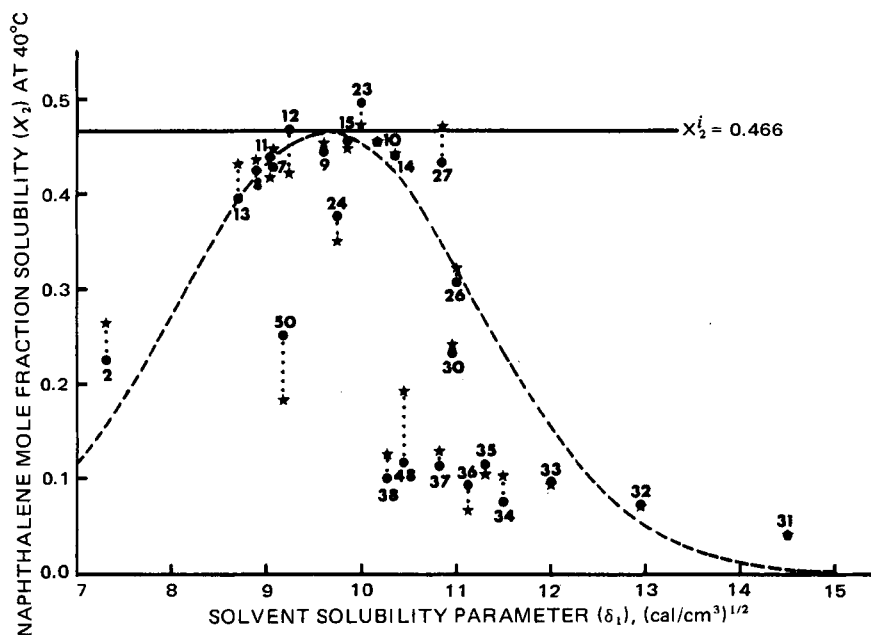| Step	X_2	$f(X_2)$
1	0.3	−2591063
2	0.1	3262236
3	0.2	−455342
4	0.15	1075195
5	0.19	−183640
6	0.185	−42185
7	0.183	15509
8	0.184	−13419
9	0.1835	1024
10	0.1836	−1868
11	0.18354	−133
12	0.18353	157
13	0.183535	12
14	0.1835352	6
15	0.1835354	0

Figure 3—*Solubility profile of naphthalene in individual solvents at 40°C. See Table I for solvent numbers. Key: (−−) regular solution curve; (——) ideal solubility line, $X_2^i = 0.466$; (●) experimental solubilities; (★) solubilities calculated using Eq. 29.*

solvents, respectively. The two acidic solvents, acetic acid (number 48) and propionic acid (number 49) lie in the center of this general solubility region yet were poor solvents for methyl p-hydroxybenzoate. If the two lower peaks are combined with dashed lines as shown in Fig. 2C, they can be explained as an interaction of the solvent with the hydroxyl group of the solute, whereas the upper peak may be a response of the solvent hydroxyl group to the ester group of methyl p-hydroxybenzoate.

The triangular diagram of Teas (24) appears to characterize these three solutes and the solvents which dissolve them in an illuminating manner. It is observed that all nonpolar solvents are congregated in the lower left corner.

Universal Function Group Activity Coefficient (UNIFAC) Method for Benzoic Acid Solubility—The UNIFAC (2) program was used to calculate the solubilities of benzoic acid in most of the solvents at 25°C. For 34 predictions, 16 calculated solubilities are within 30% error. Six solvent results could not be calculated due to unavailability of the interaction energies needed for functional groups in the UNIFAC tables. The results are listed in Table IV.

A Four-Parameter Solubility System—(Log α_2)/A of benzoic acid was regressed with the four new partial solubility parameters listed in Table I, as suggested by Eq. 16. The regression equation obtained was:

$$\frac{\log \alpha_2}{A} = 7.186\delta_{1d}^2 - 121.0\delta_{1d} + 0.4734\delta_{1p}^2 - 6.969\delta_{1p}$$

$$+ 0.6503\delta_{1a}\delta_{1b} - 1.033\delta_{1a} - 2.874\delta_{1b} + 522.79$$

$$n = 40, s = 5.89, r^2 = 0.83, F = 21.9, F(7,32,0.01) = 3.25 \quad \text{(Eq. 27)}$$

The estimated mole fraction solubilities of benzoic acid from Eq. 27 are shown in Table IV using the root-finding method (Eq. 21, Table V). Of the 40 estimates, 25 predicted solubilities are within 30% error of the experimental values.

To account for facile electron donation by the strongly dipolar solvents (numbers 51, 52, and 54–57), an indicator variable, I, was incorporated in the regression yielding:

$$\frac{\log \alpha_2}{A} = 2.125\delta_{1d}^2 - 36.90\delta_{1d} + 0.2188\delta_{1p}^2 - 2.603\delta_{1p}$$

$$+ 0.6139\delta_{1a}\delta_{1b} - 1.966\delta_{1a} - 2.955\delta_{1b} + 174.25 - 20.27I$$

$$n = 40, s = 3.38, r^2 = 0.94, F = 66.5, F(8,31,0.01) = 3.15 \quad \text{(Eq. 28)}$$

In calculating the solubilities, I was assigned a value of one for strongly dipolar solvents and zero for all other solvents in the series. The improvement of Eq. 28 over Eq. 27 by the use of the indicator variable, I, suggests that the highly polar solvents (numbers 51, 52, and 54–57, which in most cases strongly accept a proton from the solute and do not self-associate through intermolecular hydrogen bonding) be treated as solvents uniquely superior in solubilizing effect on benzoic acid. Investi-

gations should be made concentrating specifically on this class of unusual solvents for the dissolution of drugs, particularly of the proton-donor type.

As is evident to those familiar with the application of I, Eq. 28 in fact represents two equations. For solvents, exclusive of the dipolar ones, the equation contains terms in d-, p-, a-, and b-parameters plus the constant, 174.25. Here I equals zero. For solutions containing the dipolar solvents, I becomes unity and Eq. 28, in addition to identical terms in d, p, a, and b, now includes a constant, $174.25 - 20.27 = 153.98$. This smaller value for the constant decreases (log α_2)/A and accordingly increases X_2 for the solute in these solvents, as may be observed in Fig. 1. The inclusion of I therefore raises the parabolic-like curve of Eq. 28 sufficiently to pass through the experimental points for benzoic acid solubility in the strongly dipolar solvents. For methyl p-hydroxybenzoate and p-hydroxybenzoic acid, the very polar solvents form a separate subclass of solvents in Fig. 2B and C, and a simple addition of an indicator variable cannot provide a good fit of calculated values to experimental points (see Ref. 25).

The solubilities calculated from Eq. 28 using the root-finding method are listed in Table IV; 29 of 40 or almost three-quarters of the predictions are within 30% error. The mole fraction solubility of benzoic acid in the 40 solvents is plotted in Fig. 1. Calculated solubilities, using the four-parameter solubility system, are shown as stars on the figure and are connected by dotted lines to the experimental points, indicated by filled circles.

For naphthalene in single solvents at 40°C, the regression equation using the four-parameter solubility approach is:

$$\frac{\log \alpha_2}{A} = 0.5713\delta_{1d}^2 - 12.01\delta_{1d} - 0.09517\delta_{1p}^2 + 0.3381\delta_{1p}$$

$$+ 0.1673\delta_{1a}\delta_{1b} - 0.09187\delta_{1a} + 0.4824\delta_{1b} + 62.31$$

$$n = 26, s = 1.20, r^2 = 0.990, F = 257, F(7,18,0.01) = 3.85 \quad \text{(Eq. 29)}$$

The calculated solubilities are listed in Table III and plotted in Fig. 3. Of the 26 predictions, isopropyl alcohol (34%), isobutyl alcohol (31%), and acetic acid (68%) show >30% error. The four-parameter approach (Eq. 29) offers no significant advantage over three parameters (Eq. 19) for naphthalene, as observed in Table III.

Estimating Solubility Parameters of the Solute Using a Four-Parameter System—The regression equation obtained from the four-parameter system, as suggested by Eq. 16, can be transformed into an expression similar to Eq. 14 to predict the partial solubility parameters of the solute. For benzoic acid, Eq. 27 was rearranged to:

$$\frac{\log \alpha_2}{A} = 7.186(\delta_{1d} - 8.42)^2 + 0.4734(\delta_{1p} - 7.36)$$

$$+ 0.6503(\delta_{1a} - 4.42)(\delta_{1b} - 1.59) - 16.76 \quad \text{(Eq. 30)}$$

Comparing Eqs. 30 and 14, the solubility parameters of benzoic acid can be taken as $\delta_{2d} = 8.42$, $\delta_{2p} = 7.36$, $\delta_{2a} = 4.42$, and $\delta_{2b} = 1.59$. The total solubility parameter is:

$$\delta_T = (\delta_d^2 + \delta_p^2 + 2\delta_a\delta_b)^{1/2} = [(8.42)^2 + (7.36)^2 + 2(4.42)(1.59)]^{1/2}$$

$$\delta_T = 11.79 \qquad \text{(Eq. 31)}$$

The regression equation containing an indicator, i.e., Eq. 28, can be transformed to:

$$\frac{\log \alpha_2}{A} = 2.125(\delta_{1d} - 8.68)^2 + 0.2188(\delta_{1p} - 5.95)^2$$

$$+ 0.6139(\delta_{1a} - 4.81)(\delta_{1b} - 3.20) - 3.13 - 20.27I \quad \text{(Eq. 32)}$$

Equation 32 suggests that $\delta_{2d} = 8.68$, $\delta_{2p} = 5.95$, $\delta_{2a} = 4.81$, $\delta_{2b} = 3.20$, and $\delta_T = 11.90$ for benzoic acid. The total solubility parameter, δ_T, for benzoic acid obtained from Eqs. 30 and 32 compares satisfactorily with the value (11.5) given in the literature (15).

For naphthalene, Eq. 29 can also be changed to:

$$\frac{\log \alpha_2}{A} = 0.5713(\delta_{1d} - 10.51)^2 - 0.09517(\delta_{1p} - 1.78)^2$$

$$+ 0.1673(\delta_{1a} + 2.88)(\delta_{1b} - 0.55) - 0.24 \quad \text{(Eq. 33)}$$

Although Eq. 29 yields satisfactory solubilities for naphthalene, it is observed that δ_{2a} has been given the wrong sign in Eq. 33. If the sign is disregarded, $\delta_{2d} = 10.51$, $\delta_{2p} = 1.78$, $\delta_{2a} = 2.88$, and $\delta_{2b} = 0.55$, and the total solubility parameter is equal to 10.81. This value may be compared with $\delta_2 = 9.64$ for naphthalene as found in the literature (1). Since δ_{2a} has the wrong sign, however, the values must be rejected. Additional study is needed to determine why on occassion the regression procedure assigns the wrong sign to a parameter. The fault is not necessarily in the procedure, since Hansen's original plotting method has also been known to assign a negative value to a solute parameter—presumably because the center of maximum interaction lies closer to an axis than the radius of the circle of uncertainty (10–12).

Partial Solubility Parameters and Molecular Interactions—The magnitude of the solubility parameters of Table I should be noted as they relate to each class of solvents. The alcohols (numbers 29–42) like the carboxylic acids (numbers 48–50) show strong proton-donor, or acid, and moderately strong proton-acceptor, or basic, character. The glycols (numbers 43–47) have very high proton-donor qualities (δ_a). Dimethyl sulfoxide and pyridine (numbers 51 and 52, respectively) and the dialkylamides (numbers 55–58) are predominantly proton acceptors as reflected in their δ_b-values. Dimethyl sulfoxide has a large δ_p-value, as do formamide and methylformamide. Dioxane and aniline (numbers 25 and 26, respectively) are moderately strong Lewis bases (δ_b); aniline is also dipolar (δ_p). Ethylene dichloride and ethylidene chloride (numbers 10 and 11, respectively) show significant dipolarity by way of their δ_p-values, almost equal to that of acetone (number 24) and acetophenone (number 28). Methyl alcohol, (number 31), often considered to have solvent properties unlike the other alcohols, exhibits a relatively large δ_p-value. The ethers (numbers 16–18) are not dipolar, are weak Lewis acids (low δ_a-values), and show good proton-acceptor or basic (δ_b) character. The esters (numbers 19–22) show moderate dipolarity (δ_p). The moderate Lewis acid character of the esters, as reflected in their δ_a-values, is somewhat surprising. It is interesting to note the large Lewis acid (δ_a)-characteristics of ethylene bromide and ethylidene bromide (numbers 14 and 15).

A comparison of the partial solubility parameters of solvents and solutes provides an estimate of the molecular interactions between these species, particularly where high solubility results are found in Fig. 2. The partial solubility parameters for benzoic acid (Eq. 32) are $\delta_d = 8.68$, $\delta_p = 5.95$, $\delta_a = 4.81$, and $\delta_b = 3.20$. The solvents that dissolve benzoic acid to the greatest extent are dimethyl sulfoxide, pyridine, N,N-dimethylformamide, and N,N-dimethylacetamide. They have relatively large basic parameters, δ_b, favoring interaction with benzoic acid, which has an acidic parameter, $\delta_a = 4.8$. Formamide has a large basic parameter, $\delta_b = 7.6$, and should interact strongly with benzoic acid to produce significant solubility. The solubility is low (Table IV, Fig. 1) because formamide also has a large acidic parameter, $\delta_a = 5.7$ and tends to self-associate.

The partial solubility parameters of the solvents in Table I must be taken as tentative at this time; some will no doubt change as the work on solubility theory progresses. For now, these parameters lend a rough quantitative measure and a quasi-theoretical basis to the molecular forces involved in solvent–solvent and solvent–solute interactions.

CONCLUSIONS

This paper represents the second test of the extended Hansen solubility approach and the UNIFAC method. In an earlier study (1) the solubility of naphthalene in 24 solvents at 40°C was predicted satisfactorily by these two methods, UNIFAC being favored because it required no initial solubility data for regression as needed for the extended Hansen approach. It was recognized, however, that naphthalene was a poor model of a drug molecule.

In the present work, benzoic acid as well as naphthalene solubilities were studied in a wide range of solvents using UNIFAC and the extended Hansen solubility parameter approach. UNIFAC was less satisfactory for benzoic acid than the extended Hansen procedure, only 47% of the solubility results showing <30% error. (From solubility studies conducted in these laboratories, 30% was taken as a criterion of maximum allowable deviation from observed solubility.) Sixty percent of the solubilities were predicted by the Hansen approach (within 30% error of observed results). Apparently UNIFAC cannot satisfactorily reproduce the solubility results for more polar solutes like benzoic acid and its analogues; however, the interaction energy parameters for groups such as NH_2 and COOR are not currently found in the UNIFAC tables, and the application of UNIFAC to polar systems must await development of new parameters. The Hansen approach is also deficient, probably because its third solubility parameter, δ_h, cannot be expected to reflect both the electron-donor and electron-acceptor characteristics of complex organic drug molecules. An expanded four-parameter system was developed in this study, involving δ_d, δ_p, and both an electron-donor (δ_b) and electron-acceptor (δ_a) parameter. These new parameters were obtained as described and are listed in Table I for 59 solvents commonly used in pharmaceutical and industrial technology. Representative solvents were included from a number of classes: aliphatic and aromatic hydrocarbons, halogenated derivatives, ethers, esters, ketones, alcohols, glycols, acids, amides, and water. The four partial parameters of Table I are seen to describe the nonpolar, dipolar, and proton- or electron-transfer characteristics of each solvent.

Solubilities of naphthalene and benzoic acid were estimated using an expanded version of the Hansen equation with four, rather than three, solubility parameters. The success of the benzoic acid solubility correlations was increased by use of the new four-parameter system, 63% of the solubilities being predicted using four parameters as contrasted to 60% with three parameters. The strongly dipolar solvents (numbers 51, 52, and 54–58) were still not well represented with the four-parameter system. They were satisfactorily handled, however, when an indicator variable, I, was added to account for their irregular behavior.

The final equation involved separate parameters for weak dispersion forces, dipolar character, electron-donor and -acceptor effects, and a fifth "dummy" parameter or indicator variable for the strongly solvating amides and dimethyl sulfoxide. This expression, Eq. 28, successfully predicted benzoic acid solubilities for nearly three-fourths of the solvent systems. Cyclohexane (−87.3% error), ethylene chloride (−141.2% error), diethyl ether (−41.6% error), butyl acetate (31.1% error), nitrobenzene (−48.5% error), benzyl alcohol (−68.6% error), methyl alcohol (52.4% error), formamide (55.8% error), and N,N-dimethylacetamide (−40.0% error) produced errors larger than the accepted 30%. Only three were far above the 50% error range, and this is quite encouraging. For naphthalene, use of the four-parameter equation did not improve the accuracy over the three-parameter system. Only 3 of 26 solvents showed errors of >30% of the observed solubility whether the three- or the four-parameter approach was used.

Using the three-parameter system and triangular plots, the action of solvents on benzoic acid ($\delta_2 = 11.5$), p-hydroxybenzoic acid ($\delta_2 = 15$), and methyl p-hydroxybenzoate ($\delta_2 = 12$) was graphically demonstrated. Solvents of intermediate polarity (as measured by the three partial solubility parameters δ_d, δ_p, and δ_b), and belonging to various classes, successfully dissolved benzoic acid (Fig. 2A). p-Hydroxybenzoic acid was predominantly soluble in the alcohols and the dipolar amides (Fig. 2B); methyl p-hydroxybenzoate (Fig. 2C) was soluble in alcohols, esters, and the dipolar amide solvents. These triangular figures provide a particularly illuminating picture of the solubility of a drug in various groups of solvents, based on a three-parameter solubility classification. They also provide a means to calculate partial solubility parameters of drugs and other solid solutes. In a similar scheme, Snyder (27) has classified solvents into nine types on a triangular grid. The solubilities of p-hydroxybenzoic acid and methyl p-hydroxybenzoate are studied in some detail in the following report (25).

Benzoic acid, p-hydroxybenzoic acid, and methyl p-hydroxybenzoate appear to serve well as drug prototypes. The current study indicates the measure of success that can be expected with semiempirical approaches

to solubility theory at this stage of development. The four partial solubility parameters for solvents, particularly the new acid (δ_a) and base (δ_b) terms, should find use in the pharmaceutical sciences as well as in industrial technology. The multiple regression and triangular plot methods of estimating partial solubility parameters for solutes are promising steps toward characterizing the polar and nonpolar properties of drugs and related biochemicals. The partial solubility parameters of Table I are tentative and no doubt will be changed somewhat as dictated by additional findings.

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Expanded Solubility Parameter Approach II: p-Hydroxybenzoic Acid and Methyl p-Hydroxybenzoate in Individual Solvents

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Abstract □ The recently introduced four-parameter extended Hansen approach was used to study the solubility of p-hydroxybenzoic acid and methyl p-hydroxybenzoate in 32 and 35 individual solvents, respectively. The results are compared with those for benzoic acid in 40 solvents. Seventeen of the thirty-two or 53% of the calculated solubilities of p-hydroxybenzoic acid were within the established solubility criterion (i.e., <30% error from the experimental value). Twenty-two of thirty-six or 61% of the calculated solubility values for methyl p-hydroxybenzoate met the solubility criterion. Experimental excess free energies of solution for p-hydroxybenzoic acid and methyl p-hydroxybenzoate were plotted against theoretical values using the expanded four-parameter solubility regression equations. From such results, adjustments may be made in the partial solubility parameters to bring the calculated solubilities in line with experimental results. Multiple regression analyses were used to estimate the total solubility parameter and the four partial solubility parameters of the two benzoic acid derivatives. Satisfactory results were obtained for methyl p-hydroxybenzoate, but poor agreement was found for p-hydroxybenzoic acid for the total parameter when compared with the Fedors group contribution method. Both the multiple regression and group contribution methods may yield inaccurate solubility parameters for relatively polar solid solutes. Factor analysis was used to test the adequacy of three- and four-parameter approaches in the evaluation of drug solubility. A principal factor method without iteration and orthogonal factor rotation were used to compare the two expanded solubility parameter approaches. Factor analysis showed that four solubility parameters were significantly more independent and presumably more satisfactory than three parameters.

Keyphrases □ Solubility parameters, expanded—individual solvents, four-parameter extended Hansen approach, p-hydroxybenzoic acid, methyl p-hydroxybenzoate □ Extended Hansen approach—solubility of p-hydroxybenzoic acid and methyl p-hydroxybenzoate in individual solvents, four-parameter system □ Benzoic acid derivatives—p-hydroxybenzoic acid, methyl p-hydroxybenzoate, use as model drugs, solubility in individual solvents, four-parameter extended Hansen approach

The solubility of a number of drugs in mixtures of two solvents has been analyzed with the extended Hildebrand solubility approach (1, 2). Subsequently, the solubility of naphthalene and benzoic acid in individual solvents was studied using the Hansen three-parameter solubility approach (3, 4) and a new four-parameter solubility system