

interact with the internal surface of montmorillonite clay since the distance between the interlayers is wide enough for holding the molecule. This interaction might produce some heat, leading to the exothermic thermogram in Fig. 8.

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Extended Hansen Solubility Approach: Naphthalene in Individual Solvents

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Abstract □ A multiple regression method using Hansen partial solubility parameters, δ_D , δ_P , and δ_H , was used to reproduce the solubilities of naphthalene in pure polar and nonpolar solvents and to predict its solubility in untested solvents. The method, called the extended Hansen approach, was compared with the extended Hildebrand solubility approach and the universal-functional-group-activity-coefficient (UNIFAC) method. The Hildebrand regular solution theory was also used to calculate naphthalene solubility. Naphthalene, an aromatic molecule having no side chains or functional groups, is "well-behaved"; i.e., its solubility in active solvents known to interact with drug molecules is fairly regular. Because of its simplicity, naphthalene is a suitable solute with which to initiate the difficult study of solubility phenomena. The three methods tested (Hildebrand regular solution theory was introduced only for comparison of solubilities in regular solution) yielded similar results, reproducing naphthalene solubilities within ~30% of literature values. In some cases, however, the error was considerably greater. The UNIFAC calculation is superior in that it requires only the solute's heat of fusion, the melting point, and a knowledge of chemical structures of solute and solvent. The extended Hansen and extended Hildebrand methods need experimental solubility data on which to carry out regression analysis. The extended Hansen approach was the method of second choice because of its adaptability to solutes and solvents from various classes. Sample calculations are included to illustrate methods of predicting solubilities in untested solvents at various temperatures. The UNIFAC method was successful in this regard.

Keyphrases □ Naphthalene—solubility study, extended Hansen, extended Hildebrand, and UNIFAC approaches compared □ Solubility—of naphthalene in various solvents, extended Hansen, extended Hildebrand, and UNIFAC approaches compared □ Extended Hansen solubility approach—compared with extended Hildebrand and UNIFAC approaches, naphthalene solubility in various solvents

The solubility parameter concept (1) was originally designed to describe nonpolar solvent-solute systems, although it recently has been extended to the realm of commercial paints, inks, plastics, insecticides, and pharmaceuticals, which may include highly polar solvents and solutes.

The problem of estimating the solubility of crystalline solids in various solvents has been particularly intractable. This report uses partial solubility parameters together with

multiple regression analysis to obtain equations that predict solubilities within an error of <30% relative to experiment. Results using a partial parameter-multiple regression method, referred to here as the extended Hansen solubility approach, were compared with those obtained by the extended Hildebrand solubility approach (2) and the universal-functional-group-activity-coefficient (UNIFAC) method (3, 4).

The interaction of a solute and solvent follows either from weak van der Waals forces or from strong forces of a "chemical" nature, such as hydrogen bonding and Lewis acid-base interactions (5). For solutions of interest in the pharmaceutical and biological sciences, both physical and chemical forces are likely to be important.

THEORY

Partial Solubility Parameters—Burrell (6, 7) extended the original solubility parameter concept to estimate the solubility of coating materials (mainly polymers) in polar solvents of low, medium, and high hydrogen-bonding capacity. Hansen (8, 9) partitioned the cohesive energy density, $\Delta E/V$, for a species into contributions from dispersion forces, dipolar interactions, and hydrogen bonding:

$$\frac{\Delta E}{V} = \frac{\Delta E_D}{V} + \frac{\Delta E_P}{V} + \frac{\Delta E_H}{V} \quad (\text{Eq. 1})$$

or:

$$\delta^2 = \delta_D^2 + \delta_P^2 + \delta_H^2 \quad (\text{Eq. 2})$$

where:

$$\delta = (\Delta E^v/V)^{1/2} \cong \left(\frac{\Delta H^v - RT}{V} \right)^{1/2} \quad (\text{Eq. 3})$$

ΔE^v is the energy of vaporization of a liquid, ΔH^v is its enthalpy of vaporization, R is the gas constant, T is the absolute temperature, and V is the liquid molar volume. The quantity δ is the total solubility parameter, and δ^2 is the cohesive density for a solvent or solute. The term δ_D stands for the dispersion component of the total solvent or solute solubility parameter, δ_P is the polar component, and δ_H is the hydrogen-bonding component. These terms are the partial solubility parameters.

Table I—Naphthalene Parameters ($\delta_D = 9.4$, $\delta_P = 1.0$, $\delta_H = 1.9$) and Solubility at 40° in Various Solvents, $V = 123 \text{ cm}^3/\text{mole}$, $X_2^i(40^\circ) = 0.46594$

Solvent	Molar Volume ^a , V_1	Total Solubility Parameter ^a , δ_1	Dispersion Solubility Parameter, δ_D	Polar Solubility Parameter, δ_P	Hydrogen Bonding Solubility Parameter, δ_H	Mole Fraction Solubility, X_2	Reference for Solubility Data
Hexane	131.6	7.3	7.3	0.0	0.0	0.222	16
Carbon tetrachloride	97.1	8.7	8.7	0.0	0.3	0.395	16
Toluene	106.8	8.9	8.8	0.7	1.0	0.422	16
Ethylidene chloride	84.8	9.0	8.1	4.0	0.2	0.437	18
Benzene	89.4	9.1	9.0	0.0	1.0	0.428	16
Chloroform	80.7	9.3	8.7	1.5	2.8	0.467	19
Chlorobenzene	102.1	9.6	9.3	2.1	1.0	0.444	16
Acetone	74.0	9.8	7.6	5.1	3.4	0.378	16
Carbon disulfide	60.0	10.0	10.0	0.0	0.3	0.494	19
1,1-Dibromoethane	92.9	10.1 ^b	8.4	3.7	4.1	0.456	18
Ethylene dichloride	79.4	10.2	9.3	3.6	2.0	0.452	18
sec-Butanol	92.5	10.8	7.7	2.8	7.1	0.1122	17
Nitrobenzene	102.7	10.8	9.8	4.2	2.0	0.432	16
tert-Butanol	94.3	10.9 ^b	7.8	2.8	7.1	0.1009	17
Cyclohexanol	106.0	10.9	8.5	2.0	6.6	0.232	19
Aniline	91.5	11.0	9.5	2.5	5.0	0.306	16
Isobutanol	92.8	11.1	7.4	2.8	7.8	0.0925	17
Butanol	91.5	11.3	7.8	2.8	7.7	0.116	16
Isopropanol	76.8	11.5	7.7	3.0	8.0	0.0764	17
Ethylene dibromide	87.0	11.7	9.6	3.3	5.9	0.439	18
Propanol	75.2	12.0	7.8	3.3	8.5	0.0944	17
Acetic acid	57.6	13.0	6.8	6.0	9.3	0.117	16
Ethanol	58.5	13.0	7.7	4.3	9.5	0.0726	17
Methanol	40.7	14.5	7.4	6.0	10.9	0.0437	16

^a Molar volumes (cc/mole) and solubility parameters (cal/cm³)^{1/2} are obtained at 25°. ^b The solubility parameters for *tert*-butanol and 1,1-dibromoethane are not found in the literature. The former was calculated by the group contribution method (9), and the latter was obtained by reference to the values for ethylene dichloride, ethylidene chloride, and ethylene dibromide.

As used here, hydrogen bonding is not restricted to hydrogen bonds in the classical sense but also refers to any type of highly polar, oriented interaction. Partial solubility parameters were originally calculated and adjusted to provide estimates of solubility and elastomer swelling (8, 9).

The dispersion parameter, δ_D , was obtained from data for the compound's homomorph, defined as a saturated hydrocarbon having essentially the same chemical structure, size, and shape as those of the polar compound (8, 9). The polar parameter, δ_P , was calculated using a modified equation from Böttcher (10, 11):

$$\delta_P^2 = \frac{12,108}{V^2} \frac{\epsilon - 1}{2\epsilon + n_D^2} (n_D^2 + 2)\mu^2 \quad (\text{Eq. 4})$$

where V is the liquid molar volume, 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 Debye units. The hydrogen bond parameter for a hydroxyl compound is obtained from an expression:

$$\delta_H = \left(\frac{\Delta H}{V}\right)^{1/2} \quad (\text{Eq. 5})$$

where ΔH is an average enthalpy of formation for hydrogen bonding, 4650 cal/mole, for each hydroxy group. Barton (5) reviewed various methods of calculating partial parameters.

The partial solubility parameters of Hansen are available for a large number of liquid solvents (9). Partial solubility parameters for only a few solids (represented as supercooled liquids), such as naphthalene and succinic anhydride, can be found in the literature. Hansen and Beerbower (9) presented a table of group contributions for calculating partial solubility parameters; from these data, δ_D , δ_P , and δ_H may be calculated for a liquid or solid (supercooled liquid).

The values can be adjusted to obtain suitable numbers that correspond well with experimental solubility results. Hoy *et al.* (12) developed an extensive compilation of partial and total solubility parameters.

One possible approach to reproducing experimental solubilities for a drug in pure solvents would be to write the solubility equation (1, 2) in terms of partial solubility parameters, followed by multiple regression analysis toward an expression for the desired solubilities. This extended Hansen solubility approach is discussed later. Since the partial solubility parameters of Hoy *et al.* (12) differ somewhat from those of Hansen and Beerbower (9), it is important to use either one system or the other rather than a combination of the two. Regression techniques employing the Hoy parameters result in different equations from those obtained with the Hansen parameters.

Extended Hildebrand Approach—A technique called the extended Hildebrand approach (2) was developed to reproduce the solubilities of drugs such as xanthine derivatives in mixed solvents, including dioxane and water, water and polyethylene glycol 400, glycerin and propylene glycol, and dioxane and formamide. The interaction energy, W , is regressed against the solvent solubility parameter, δ_1 , to obtain W_{calc} which is then substituted into the extended solubility equation to reproduce the drug's solubility on the mole fraction scale. The derivation begins with a relation between the drug's mole fraction solubility, X_2 , the ideal solubility, X_2^i , and the activity coefficient, α_2 :

$$-\log X_2 = -\log X_2^i + \log \alpha_2 \quad (\text{Eq. 6})$$

where $\log \alpha_2$ is expressed in terms of solute and solvent cohesive energy densities, δ^2 and δ_1^2 , the solute-solvent interaction energy, W , and an "A factor" from regular solution theory (1):

$$-\log X_2 = -\log X_2^i + A(\delta_1^2 + \delta_2^2 - 2W_{\text{calc}}) \quad (\text{Eq. 7})$$

$$A = V_2\phi_1^2/2.303RT \quad (\text{Eq. 8})$$

where V_2 is the molar liquid volume of the solute, ϕ_1 is the volume fraction of the solvent, R is the molar gas constant, and T is the absolute temperature. A term, $[\ln(V_1/V_2) + 1 - (V_1/V_2)]$, from Flory-Huggins theory is sometimes added to solubility expressions such as Eq. 7 to account for the entropy of mixing of substances with considerably different molar volumes. The regression analyses discussed later showed that this term was statistically insignificant for the naphthalene solutions studied.

The extended solubility approach was tested with methylxanthines in binary solvent systems (2, 13, 14) and with naphthalene in some single solvents (15), but has not been explored in detail for individual solvent systems.

UNIFAC—A group contribution (UNIFAC) procedure was developed (3, 4) to investigate the solubilities of solids in pure and mixed liquid solvents. According to this method, the activity coefficient is separated into two parts: a combinatorial contribution, $\log \alpha^C$, which accounts for the molecular size and shape of the solute and solvent, and a residual contribution, $\log \alpha^R$, which accounts for intermolecular energies of attraction:

$$\log \alpha_2 = \log \alpha_2^C + \log \alpha_2^R \quad (\text{Eq. 9})$$

Details were given previously (4), and the method is briefly described in the Appendix.

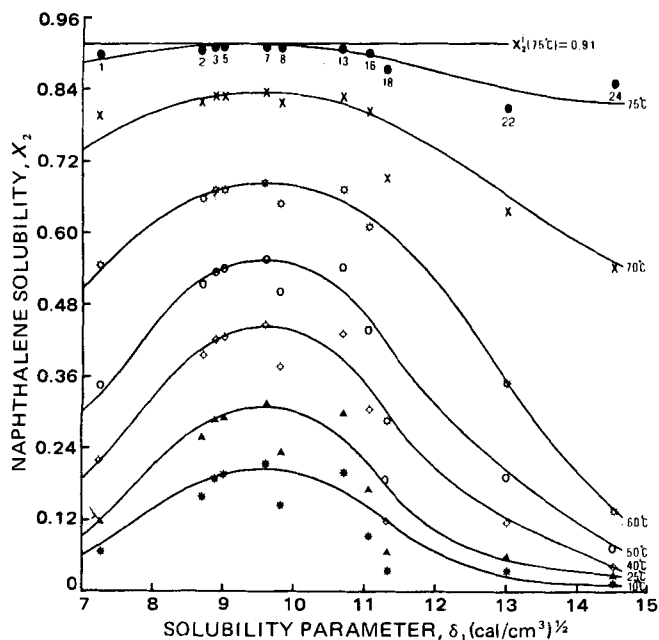


Figure 1—Solubility of naphthalene in solvents from results of Ward (16) determined at 10–75°. Key: ●, 10°; ▲, 25°; ○, 40°; □, 50°; ◇, 60°; ×, 70°; ●, 75°.

RESULTS AND DISCUSSION

The present study attempted to reproduce the solubility of naphthalene at 40° in solvents using three methods: (a) a partial solubility parameter method together with multiple regression, (b) the extended Hildebrand solubility approach (2, 13–15), and (c) the UNIFAC procedure (3, 4). Table I shows experimental solubilities reported previously (16–19), together with solvent solubility parameters (9) and molar volumes (9). Although the solubilities were obtained at 40°, δ_1 and V_1 are customarily calculated at 25°.

Mole fraction solubilities of naphthalene, as determined (16) at 10–75°, are plotted in Fig. 1 against δ_1 , the solubility parameter of the pure solvent. The curves drawn through the points are more symmetrical than would be expected for an organic solid dissolved in polar and nonpolar solvents representing different solvent classes. Some polar solvents, such as acetone and butanol, yield points that are displaced from their proper temperature lines, but most points appear in an orderly arrangement on the bell-shaped curves. Figure 1 shows that the mole fraction solubilities of naphthalene, in a range of $\delta_1 = 7.3$ –14.5, exhibit peaks in the curves; the peaks do not appear to shift with temperature. With increasing temperature, the naphthalene solubility curves become less peaked; at 75°, the curve is nearly horizontal, but $\delta_1 = \delta_2$ at the peak remains constant at ~ 9.6 over the 10–75° range. At 75°, naphthalene is only $\sim 5^\circ$ below its melting point ($mp = 80.2^\circ$), and its ideal solubility $X_2^i(75^\circ)$ is 0.9105. At this temperature, naphthalene forms nearly ideal solutions in the majority of solvents studied.

Multiple Regression and Extended Hansen Approach—Partial solubility parameters for naphthalene, $\delta_D = 9.4$, $\delta_P = 1.0$, and $\delta_H = 1.9$ (total parameter = 9.64), were estimated from a table of group contributions currently under preparation¹. An early version of the table is given in the literature (9). The regression subprogram² (20) allows a stepwise addition of independent variables, analysis of variance, and examination of the residuals by means of scatter plots. The multiple regression yielded Eq. 10 for naphthalene in 24 solvents at 40°:

$$\log \alpha_2 = 1.0488(\pm 0.1762)A(\delta_{1D} - \delta_{2D})^2 - 0.3148(\pm 0.0490)A(\delta_{1P} - \delta_{2P})^2 + 0.2252(\pm 0.0163)A(\delta_{1H} - \delta_{2H})^2 + 0.0451(\pm 0.0155) \quad (\text{Eq. 10})$$

$$n = 24 \quad s = 0.0559 \quad R^2 = 0.9765 \quad F = 277 \quad F(3,20,0.01) = 4.94$$

Results obtained with Eq. 10 may be substituted into Eq. 6 for $\log \alpha_2$ to calculate mole fraction solubility, X_2 , as shown in Table II. When solubilities (Table II) are calculated with Eqs. 10 and 6, the procedure is re-

ferred to as the extended Hansen approach. The results compare favorably with observed solubilities: only one residual is $>30\%$ (*tert*-butanol, 53% error), and about half the results exhibit errors of $<5\%$.

The extended Hansen approach may be used to estimate the solubility in solvents not included in the series under investigation. For example, the solubility of naphthalene in butyric acid at 40° is not found in Table II, but it may be calculated as follows. The partial parameters (9) for butyric acid are $\delta_D = 7.3$, $\delta_P = 2.0$, and $\delta_H = 5.2$. Combining these terms with the values for naphthalene, one obtains $(7.3 - 9.4)^2 = 4.41$, $(2.0 - 1.0)^2 = 1.00$, and $(5.2 - 1.9)^2 = 10.89$. These values are introduced into Eq. 10: $\log \alpha^2 = 1.0488A(4.41) - 0.3148A(1.00) + 0.2252A(10.89) + 0.0451$. Value A must be calculated first, using Eq. 8 with $V_2 = 123.0$, $V_1 = 92.48$, $R = 1.9872$, and $T = 40^\circ$ (313.15 °K). The volume fraction of the solvent, ϕ_1 , is unknown since it depends on the X_2 value, which is sought:

$$\phi_1 = V_1(1 - X_2)/[V_1(1 - X_2) + V_2X_2] \quad (\text{Eq. 11})$$

Value A is found by an iteration procedure (21), beginning with a value of 1.0 for ϕ_1 and iterating until X_2 or ϕ_1 no longer changes by more than some desired small value. The iteration yields $X_{2,\text{calc}} = 0.1959$. This result compares satisfactorily with $X_{2,\text{obs}} = 0.2487$, giving a calculated value within 21% of the observed mole fraction solubility.

Although calculation of the original regression equations requires an electronic computer, back-calculations (involving iteration) for estimating solubilities in various solvents can be done on a programmable hand calculator.

Polynomial Regression and Extended Hildebrand Approach—The term $(\log \alpha_2)/A$ was regressed versus δ_1 for naphthalene in the 24 solvents in a second- (quadratic) and third- (cubic) degree expression. To account for self-association of the alcohols, it was necessary to add an indicator variable, I , to the regression equations. In back-calculating solubilities, I is given the value of 1 for alcohols and zero for all other solvents in the series. The quadratic expression did not reproduce the solubility data adequately and was omitted from further considerations.

The cubic equation, together with an indicator variable, resulted in a squared correlation, R^2 , of 0.86:

$$\frac{\log \alpha_2}{A} = 6.1130(\pm 1.0859)I - 53.2569(\pm 19.6920)\delta_1 + 4.6506(\pm 1.8400)\delta_1^2 - 0.1290(\pm 0.0562)\delta_1^3 + 197.8011(\pm 69.0673) \quad (\text{Eq. 12})$$

$$n = 24 \quad s = 2.0223 \quad R^2 = 0.8648 \quad F = 32 \quad F(4,19,0.01) = 4.50$$

Residuals expressed in percentages were reasonable for the solubilities of naphthalene in most solvents at 40°. However, some large errors re-

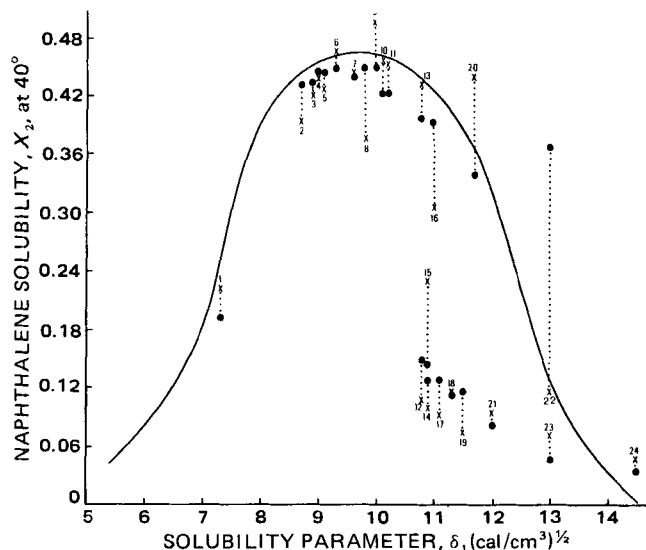


Figure 2—Solubility of naphthalene in 24 individual solvents at 40°. The data is from Refs. 16–19. The curve, calculated using the Hildebrand expression, Eq. 13, rises to a maximum at $\delta_1 = \delta_2 = 9.6$, equal to naphthalene's ideal solubility, $X_2^i(40^\circ) = 0.46594$. The experimental point (●) for each solvent is attached by a dotted line to the calculated solubility (×) for each solvent.

¹ By A. Beerbower.

² Programmed on The University of Texas Cyber computer system.

Table II—Four Methods of Solubility Analysis for Naphthalene in Pure Solvents at 40°

Solvent	Observed	Extended Hansen		Extended Hildebrand		UNIFAC		Regular Solution	
	X_2 (40°)	X_2	Residual	X_2	Residual	X_2	Residual	X_2	Residual
Hexane	0.222	0.2247	-0.0027	0.1934	0.0286	0.2629	-0.0409	0.2472	-0.0252
Carbon tetrachloride	0.395	0.3956	-0.0006	0.4311	-0.0361	0.4071	-0.0121	0.4464	-0.0514
Toluene	0.422	0.4072	0.0156	0.4345	-0.0125	0.4425	-0.0205	0.4529	-0.0309
Ethylidene chloride	0.437	0.4279	0.0091	0.4447	-0.0077	— ^a	— ^a	0.4584	-0.0214
Benzene	0.428	0.4192	0.0088	0.4437	-0.0157	0.4499	-0.0219	0.4603	-0.0323
Chloroform	0.467	0.4080	0.0590	0.4483	0.0187	0.4695	-0.0025	0.4640	0.0030
Chlorobenzene	0.444	0.4244	0.0196	0.4429	0.0011	0.3979	0.0461	0.4659	-0.0219
Acetone	0.378	0.4421	-0.0641	0.4484	-0.0704	0.3628	0.0152	0.4655	-0.0875
Carbon disulfide	0.494	0.4111	0.0829	0.4498	0.0442	0.4197	0.0743	0.4644	0.0296
1,1-Dibromoethane	0.456	0.4234	0.0326	0.4370	0.0190	0.3837	0.0723	0.4617	-0.0057
Ethylene dichloride	0.452	0.4547	-0.0027	0.4390	0.0130	— ^a	— ^a	0.4606	-0.0086
sec-Butanol	0.112	0.1446	-0.0324	0.1498	-0.0376	0.1132	-0.0010	0.4369	-0.3247
Nitrobenzene	0.432	0.4809	-0.0489	0.3952	0.0368	— ^a	— ^a	0.4334	-0.0014
tert-Butanol	0.1009	0.1549	-0.0540	0.1416	-0.0407	0.0819	0.0190	0.4303	-0.3294
Cyclohexanol	0.232	0.2307	0.0013	0.1275	0.1045	0.2080	0.0240	0.4255	-0.1935
Aniline	0.306	0.3856	-0.0796	0.3926	-0.0866	0.2689	0.0371	0.4250	-0.1190
Isobutanol	0.0925	0.0693	0.0232	0.1276	-0.0351	0.1474	-0.0549	0.4170	-0.3245
Butanol	0.116	0.1096	0.0064	0.1134	0.0026	0.1124	0.0036	0.4006	-0.2846
Isopropanol	0.076	0.0981	-0.0217	0.1165	-0.0401	0.0948	-0.0184	0.3959	-0.3195
Ethylene dibromide	0.439	0.3744	0.0646	0.3390	0.1000	0.3832	0.0558	0.3587	0.0812
Propanol	0.094	0.0828	0.0116	0.0813	0.0131	0.0939	0.0005	0.3344	-0.2400
Acetic acid	0.117	0.0871	0.0299	0.3090	-0.1920	0.1267	-0.0097	0.1273	-0.0103
Ethanol	0.0726	0.0611	0.0115	0.0491	0.0235	0.0552	0.0174	0.1233	-0.0507
Methanol	0.0437	0.0483	-0.0046	0.0347	0.0090	0.0489	-0.0052	0.0050	-0.0387

^a UNIFAC parameters not available for solvent functional groups.

sulted from this equation: cyclohexanol, 45%; *tert*-butanol, 40%; isobutanol, 38%; isopropanol, 53%; and acetic acid, 164%. The experimental points are shown in Fig. 2 attached by dotted lines to the solubilities predicted by use of the extended Hildebrand approach. The large error for acetic acid is unaccounted for but apparently results from the particular regression program and iteration procedure used. Alternative methods involving orthogonalization, root finding, and weighting functions are under investigation. The X_2 values and residuals are given in Table II, columns 5 and 6.

UNIFAC Method—Gmehling *et al.* (4) employed UNIFAC to estimate the solubilities of naphthalene, anthracene, and phenanthrene in several solvents. Their results were calculated, and new solvents were added in the current study; results shown in Table II, column 7, may be compared with the back-calculated mole fraction solubilities of the extended Hildebrand solubility method, column 5, and those obtained by the extended Hansen solubility approach, column 3. The extended Hansen and UNIFAC methods give remarkably similar results. As already indicated, a quantitative method for calculating solubilities in polar solvents is taken to be satisfactory if errors are no greater than ~30%. These two methods generally meet this standard. By contrast, the extended Hildebrand method gives errors of >30% for nine solvents. However, only one of these, acetic acid, produces a large error.

Regular Solution Theory—Column 9 of Table II shows solubilities of naphthalene in the 24 solvents at 40° calculated using the regular solution equation of Hildebrand and Scatchard for solids dissolved in liquid solvents (1). The expression is:

$$-\log X_2 = -\log X_2^i + A(\delta_1 - \delta_2)^2 \quad (\text{Eq. 13})$$

Equation 13 reproduces solubilities satisfactorily in nonpolar solvents (regular solutions) but fails for irregular systems with polar solvents showing self-association and solvation. The curve of Fig. 2 was plotted using the mole fractions calculated from the Hildebrand-Scatchard equation. Although the observed values are not well represented by Eq. 13 for polar solvents, the mole fraction solubility of naphthalene ($\delta_2 = 9.64$) in a range of solvents from hexane ($\delta_1 = 7.3$) to methanol ($\delta_1 = 14.5$) is at least in qualitative agreement with regular solution theory. For drug molecules having side chains and functional groups attached to the aromatic ring, the regular behavior of naphthalene solubilities is not expected to be found with single or binary solvents.

Temperature Effects—Several investigators (16–18, 22) plotted the mole fraction of naphthalene *versus* the reciprocal of absolute temperature; straight lines result for ideal and nearly ideal solutions. The slope of the ideal solution line provides a measure of the molar heat of fusion. For irregular solutions plotted in this manner, the lines ordinarily are curved. Chertkoff and Martin (23) evaluated solubility data employing a different plot, that of the solute mole fraction against the solubility parameter δ_1 of pure or mixed solvents. In this approach, an approximately bell-shaped curve is obtained that reaches a maximum at $\delta_1 = \delta_2$

in regular systems; the mole fraction at this point corresponds to the ideal solubility. Figures 1 and 2 represent graphs plotted in this manner. They provide some information not readily evident from plots of log mole fraction *versus* $1/T$.

It would be useful to employ the solubility data of Fig. 2 at 40° to obtain solubilities at other temperatures, as shown in Fig. 1. Temperature appears in the ideal solubility term, which may be written³ $\log X_2^i = (\Delta S^i/R) \log (T/T_m)$, and in $A = V_2\phi_1^2/2.303RT$. It might be reasoned that by use of the extended Hansen or extended Hildebrand regression equation (Eq. 10 or 12) and replacement of the temperature of 313°K by a value of 333°K, one could convert the solubility at 40° to an X_2 value at 60°.

The observed mole fraction solubility of naphthalene in hexane at 60° (333.15°K) is 0.547. The proper ideal solubility is used, and the temperature found in A is changed from 40° (313.15°K) to 333.15°K; an iteration is then conducted (21) using the extended Hansen approach to arrive at a new ϕ_1 value yielding $X_{2,\text{calc}} = 0.489$. This result represents a 10.6% error from the observed X_2 at 60°. The same procedure may be used to calculate the solubility of naphthalene in hexane at 20°. The error is 34%. Naphthalene forms an essentially regular solution in hexane, and the plot of log mole fraction *versus* $1/T$ for this solvent is straight, although it does not coincide with the ideal solubility line. For alcohols, plots of log X_2 *versus* $1/T$ are ordinarily curved, and extrapolation of naphthalene solubility in methanol at 40° to obtain X_2 at 60° by iteration results in an error of 31.3%. An attempt to extrapolate X_2 to 70 and 75°, however, produced errors of only 33 and 29.6%, respectively. At 20°, the result is 14.8% in error. The extended Hildebrand method yields similar results. Thus, the regression equations obtained at 40° give erratic solubility results for polar solvents at elevated temperatures. The errors are apparently due to the iteration procedure required in the extended Hansen and extended Hildebrand methods.

Hildebrand and Scott (1) discussed the influence of temperature on solubility parameters and provided δ values at various temperatures. Hansen and Beerbower (9) made estimates of the temperature coefficients of δ_D , δ_P , and δ_H . However, as they pointed out, these estimates are needed only for the most polar or hydrogen bonded systems, since the function $V_2\phi_1^2(\delta_1 - \delta_2)^2$ is independent of temperature for near-regular solutions. The previous example of nonlinear behavior of methanol solutions could presumably be improved by using the type of temperature coefficients they suggested.

Another approach is to regress the solubility data of naphthalene from 10 through 60° (Fig. 1) using a single equation. This procedure provides a more reasonable prediction of solubilities at various temperatures and will be reported later.

³ Ideal solubility is also calculated using the expression:

$$\log X^i = \frac{\Delta H_m}{2.303R} \left(\frac{T_m - T}{T_m T} \right)$$

Both forms are approximations, and it is not clear at this time which is more correct.

The UNIFAC method does not appear to suffer from the problems encountered with the regression approaches for calculating solubilities in polar solvents at elevated temperatures; it does not require an iteration procedure. In methanol at 40°, UNIFAC gives $X_{2,calc} = 0.0489$, a difference of 12% from $X_{2,obs}$; at 60°, $X_{2,calc}$ is 0.110, a difference of 17% from $X_{2,obs}$.

SUMMARY

The work of Hildebrand and Scott (1), Scatchard (24), Hansen (8), and several other investigators has led to increased understanding of solubility phenomena. Yet, the formulation of a satisfactory approach to describe the solubility of crystalline solids in pure and mixed polar solvents has proved to be particularly difficult.

The present report applied three methods. The UNIFAC method requires only the solute's heat of fusion, the melting point, and a knowledge of the chemical structure of the solute and solvent. This method, yielding essentially the same accuracy as obtained by the extended Hansen regression method (one exception is the solubility in isobutanol) is judged far superior for predicting solubilities of naphthalene in untested solvents.

The extended Hansen method must be accepted as the second best method studied. Although it required solubility data in the initial regression step, the use of partial solubility parameters accounts for polar and hydrogen-bonding forces in the various solvents. For this reason, an indicator variable is not required in the regression equation of the extended Hansen approach. Furthermore, if new solvents are to be tested in the system under study, use of their partial solubility parameters should allow estimation of naphthalene solubility within reasonable accuracy. This expectation was found for butyric acid, where the solubility of naphthalene was predicted within 21%.

In earlier studies (2, 13, 14), the extended Hildebrand approach was successful in reproducing the solubility of solid drugs in binary solvents, both polar and nonpolar. Although it is satisfactory in the current work for most solvents studied, this method cannot be expected to apply where strong interactions exist. The predictive power of the extended Hildebrand approach is, therefore, less than that of the other two procedures.

By knowing $X_{2,obs}$ at a specified temperature for naphthalene in nonpolar solvents, it is possible to calculate the solubility at other temperatures using the extended Hansen or Hildebrand approach. However, for polar solvents such as methanol, this simple procedure is not successful. UNIFAC appears to be more suitable for calculating the solubility of naphthalene in polar and nonpolar solvents at various temperatures.

Naphthalene, a relatively simple molecule, is a good solute to begin a study of solubility in pure solvents; however, it is a poor model for drug solubility. Although this molecule provides π electrons for solute-solvent interactions, its lack of functional groups and side chains renders it considerably less nonideal than those typically encountered in the pharmaceutical sciences.

Knowledge gained from these relatively simple and well-behaved systems must now be applied to real drug solutions in individual polar solvents before conclusions can be reached regarding the applicability of the extended Hansen, extended Hildebrand, and UNIFAC methods.

APPENDIX

The UNIFAC method is based on the well-known group contribution method and was developed to estimate activity coefficients in mixtures of nonelectrolytes. As stated by Eq. 9, the logarithmic activity coefficient is divided into two parts, combinatorial ($\log \alpha_2^C$) and residual ($\log \alpha_2^R$). The combinatorial part results essentially from differences in sizes and shapes of the molecules in the mixture; the residual part is due mainly to interaction energies of species in solution.

The method involves extensive use of equations and definition of terms,

but the user simply provides heats of fusion, melting points of solid solutes, and group numbers for the various atoms and chemical groups that make up the molecules. From the group numbers supplied, the computer program calculates volume, R , and area, Q , parameters as required for the combinatorial activity coefficient. Energies of interaction, a_{mn} and a_{nm} , are calculated for the residual activity coefficient, where m and n are interacting groups and $a_{mn} \neq a_{nm}$. Tables of volume, area, and interaction energy parameters for some 300 groups are found in the literature (25).

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