temperatures studied leads to a low apparent value. It may be speculated that the reaction involves a low-energy bond rotation. However, it is not the intent of this report to provide a detailed mechanistic evaluation of the process. Such studies are to be conducted.

The technique of differential pulse polarography has been applied to the detection of anhydrotetracycline in the presence of epianhydrotetracycline and used to study the rate of conversion of anhydrotetracycline to its epimer. The authors feel this is a unique application of this technique. It is also felt that this work proves that this method, which is somewhat simpler to utilize than most commonly employed analytical procedures, might be useful in studying the reactions of other tetracycline derivatives.

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Extended Hansen Approach: Calculating Partial Solubility Parameters of Solid Solutes

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Abstract □ A multiple linear regression method, known as the extended Hansen solubility approach, was used to estimate the partial solubility parameters, δ_d, δ_p, and δ_h for crystalline solutes. The method is useful, since organic compounds may decompose near their melting points, and it is not possible to determine solubility parameters for these solid compounds by the methods used for liquid solvents. The method gives good partial and total solubility parameters for naphthalene; with related compounds, less satisfactory results were obtained. At least three conditions, pertaining to the regression equation and the solvent systems, must be met in order to obtain reasonable solute solubility parameters. In addition to providing partial solubility parameters, the regression equations afford a calculation of solute solubility in both polar and nonpolar solvents.

Keyphrases □ Solubility, partial—extended Hansen approach, parameters of solid solutes, naphthalene, decomposition □ Naphthalene—extended Hansen approach, partial solubility parameters of solid solutes, decomposition □ Decomposition—extended Hansen approach, partial solubility parameters of solid solutes, naphthalene

A multiple regression method using Hansen partial solubility parameters, δ_d, δ_p, and δ_h, was reported (1) for calculating the solubility of naphthalene in pure polar and nonpolar solvents.

THEORETICAL

The method, called the extended Hansen solubility approach, uses a regression equation of three terms involving solvent and solute solubility parameters:

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

where X_2 and $X_2{}^i$ are the mole fraction solubility and mole fraction ideal solubility, and A is a term from regular solution theory:

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

where V_2 is the molar volume of the solute in the supercooled liquid state, ϕ_1 is the volume fraction of solvent, R is the gas constant, and T is the absolute temperature.

The partial solubility parameters for dispersion, δ_d, dipolar interaction forces, δ_p, and hydrogen bonding and other Lewis acid–base interactions, δ_h, are found in Eq. 1 for solvent (subscript 1) and solute (subscript 2). The coefficients C_0, C_1, C_2, and C_3 are provided in the computer output resulting from the least-squares analysis.

The equation obtained for naphthalene in 24 solvents by the extended Hansen solubility approach was (1):

$$\log \alpha_2 = \log \frac{X_2{}^i}{X_2} = 1.0488A(\delta_{1d} - \delta_{2d})^2 - 0.3148A(\delta_{1p} - \delta_{2p})^2 + 0.2252A(\delta_{1h} - \delta_{2h})^2 + 0.0451 \quad \text{(Eq. 3)}$$

This equation provided solubilities of naphthalene in polar and nonpolar solvents at 40° with <30% error (except for *tert*-butanol, 53% error); for ~50% of the cases results were obtained within <5% error. The method allowed the calculation of the solubility of naphthalene in solvents not included in the series under investigation. The extended Hansen solubility approach was tested against the UNIFAC method (2) and the extended Hildebrand solubility approach (3), two alternate methods undergoing recent development.

RESULTS AND DISCUSSION

The partial solubility parameters of Hansen and Beerbower (4) are available for a large number of liquids, but the values for only a few solids (represented as supercooled liquids) are found in the literature. A table was prepared of group contributions for calculating partial solubility

Table I—Solubility of Naphthalene in Individual Solvents at 40° [a]

Solvent	Molar Volume, V_1	Dispersion Solubility Parameter, δ_{1d}	Polar Solubility Parameter, δ_{1p}	Hydrogen Bonding Solubility Parameter, δ_{1h}	Mole Fraction Solubility, X_2	Eq. 7 $X_{2(calc)}$	Eq. 7 Error, %	Eq. 10 $X_{2(calc)}$	Eq. 10 Error, %	Eq. 12 $X_{2(calc)}$	Eq. 12 Error, %
Hexane	131.6	7.3	0.0	0.0	0.222	0.264	−18.9	0.305	−37.3	0.283	−27.5
Carbon tetrachloride	97.1	8.7	0.0	0.3	0.395	0.438	−10.9	0.420	−6.4	0.448	−3.4
Toluene	106.8	8.8	0.7	1.0	0.422	0.435	−3.1	0.419	0.7	0.442	−4.7
Ethylidene chloride	84.8	8.1	4.0	0.2	0.437	0.413	5.5	0.414	5.3	0.424	3.0
Benzene	89.4	9.0	0.5[b]	1.0	0.428	0.449	−4.9	0.431	−0.7	0.453	−5.8
Chloroform	80.7	8.7	1.5	2.8	0.467	0.425	9.0	0.421	9.8	0.431	7.7
Chlorobenzene	102.1	9.3	2.1	1.0	0.444	0.448	−0.9	0.416	6.3	0.445	−0.2
Acetone	74.0	7.6	5.1	3.4	0.378	0.388	−2.6	0.413	−9.3	0.394	−4.2
Carbon disulfide	60.0	10.0	0.0	0.3	0.494	0.467	5.5	0.437	11.5	0.458	7.3
1,1-Dibromoethane	92.9	8.4	3.7	4.1	0.456	0.387	15.1	0.390	14.5	0.394	13.6
Ethylene dichloride	79.4	9.3	3.6	2.0	0.452	0.456	−0.9	0.437	3.3	0.453	−0.2
sec-Butanol	92.5	7.7	2.8	7.1	0.1122	0.135	−20.3	0.139	−23.9	0.142	−26.6
Nitrobenzene	102.7	9.8	4.2	2.0	0.432	0.469	−8.6	0.427	1.2	0.453	−4.9
tert-Butanol	94.3	7.3[b]	2.5[b]	6.8[b]	0.1009	0.103	−2.1	0.1224	−21.3	0.1049	−4.0
Cyclohexanol	106.0	8.5	2.0	6.6	0.232	0.237	−2.2	0.209	9.9	0.246	−6.0
Aniline	91.5	9.5	2.5	5.0	0.306	0.400	−30.7	0.355	−16.0	0.387	−26.5
Isobutanol	92.8	7.4	2.8	7.8	0.0925	0.0745	19.5	0.0761	17.7	0.0760	17.8
Butanol	91.5	7.8	2.8	7.7	0.116	0.113	2.6	0.104	10.3	0.118	−1.7
Isopropanol	76.8	7.7	3.0	8.0	0.0764	0.104	−36.1	0.0943	−23.4	0.1094	−43.2
Ethylene dibromide	87.0	10.3[b]	1.7[b]	4.2[b]	0.439	0.428	2.5	0.360	17.9	0.392	0.7
Propanol	75.2	7.8	3.3	8.5	0.0944	0.0903	4.3	0.0729	22.8	0.0946	−0.2
Acetic acid	57.6	7.1[c]	3.9[c]	6.6[c]	0.117	0.200	−70.9	0.254	−117.	0.196	−67.5
Ethanol	58.5	7.7	4.3	9.5	0.0726	0.0637	12.3	0.0431	40.6	0.0659	9.2
Methanol	40.7	7.4	6.0	10.9	0.0412	0.0356	13.6	0.0190	53.9	0.0353	14.3
Butyric acid[d]	91.9	7.3	2.0	5.2	0.251	0.148	26.7	0.238	5.5	0.189	24.7
Water	18.0	7.6	7.8	20.7	1.76×10^{-5}	1.76×10^{-5}	0.0	7.57×10^{-7}	95.7	1.7×10^{-5}	1.7

[a] V_2 = 123 cm³/mole, X_2^i (40°) = 0.46594. [b] Values recalculated from Reference 1. [c] Changed from values used in Reference 1 to those found in Reference 4. [d] From Reference 7.

parameters for both liquids and solids (4). This method provides only rough estimates of δ_d, δ_p, and δ_h for crystalline solids, and it would be advantageous to have another method to obtain these values.

The approach suggested here involves regressing $(\log \alpha_2)/A$ against δ_{1d}, δ_{1p}, δ_{1h}, δ_{1d}^2, δ_{1p}^2, and δ_{1h}^2 using a number of solvents. The result of this procedure using an SPSS regression program (5) is the expression:

$$(\log \alpha_2)/A = -13.5114\delta_{1d} + 0.6702\delta_{1d}^2 + 0.5570\delta_{1p} - 0.1418\delta_{1p}^2 - 0.2448\delta_{1h} + 0.1326\delta_{1h}^2 + 68.0377 \quad \text{(Eq. 4)}$$

$n = 26$, $s = 1.45$, $R^2 = 0.986$, $F = 276$, $F(6, 20, 0.01) = 3.87$.

The terms for δ_{1d}, δ_{1d}^2, δ_{1p}, δ_{1p}^2, δ_{1h}, and δ_{1h}^2 are paired together with the coefficient of the squared term taken outside the parenthesis in each instance:

$$(\log \alpha_2)/A = 0.6702(\delta_{1d}^2 - 20.1603\delta_{1d}) - 0.1418(\delta_{1p}^2 - 3.9281\delta_{1p}) + 0.1326(\delta_{1h}^2 - 1.8462\delta_{1h}) + 68.0377 \quad \text{(Eq. 5)}$$

The terms in parentheses can be cast into the form of perfect squares if 20.1603 is taken as $2\delta_{2d}$, 3.9281 as $2\delta_{2p}$, and 1.8462 as $2\delta_{2h}$ in Eq. 5. This leads to the result:

$$(\log \alpha_2)/A = 0.6702(\delta_{1d}^2 - 20.1603\delta_{1d} + 101.6094) - 0.1418(\delta_{1p}^2 - 3.9281\delta_{1p} + 3.8575) + 0.1326(\delta_{1h}^2 - 1.8462\delta_{1h} + 0.8521) - (0.6702)(101.6094) + (0.1418)(3.8575) - (0.1326)(0.8521) + 68.0377 \quad \text{(Eq. 6)}$$

Therefore, 101.6094 is δ_{2d}^2 and $(101.6094)^{1/2} = 10.08 = \delta_{2d}$; and likewise for δ_{2p} and δ_{2h}:

$$(\log \alpha_2)/A = 0.6702(\delta_{1d} - 10.08)^2 - 0.1418(\delta_{1p} - 1.964)^2 + 0.1326(\delta_{1h} - 0.923)^2 + 0.3731 \quad \text{(Eq. 7)}$$

It is observed that the partial solubility parameters, $\delta_{2d} = 10.08$, $\delta_{2p} = 1.964$, and $\delta_{2h} = 0.923$, have been obtained by a regression method involving only solvent partial solubility parameters, together with experimental solubility data from which $(\log \alpha_2)/A$ is calculated. The total solubility parameter δ_T for naphthalene by this method is:

$$\delta_T^2 = \delta_{2d}^2 + \delta_{2p}^2 + \delta_{2h}^2 = (10.08)^2 + (1.964)^2 + (0.923)^2 = 106.32$$
$$\delta_T = (106.32)^{1/2} = 10.31 \quad \text{(Eq. 8)}$$

The partial solubility parameters from the literature (4) are $\delta_d = 9.4$, $\delta_p = 1.0$, and $\delta_h = 1.9$[1], leading to a $\delta_T = 9.64$. The total solubility parameter of naphthalene from its maximum solubility in 24 solvents has been estimated to be $\delta_T = 9.6$ (1); the value $\delta_T = 10.31$ was obtained in the present study (Eq. 8). When a different number of solvents or different kinds of solvents are employed in the regression, the δ values may vary, since the coefficients of the equation change with various solvents. The δ_T value obtained by multiple regression was 10.43 when 23 solvents were used.

Nonlinear regression (6) led to the following results:

$$(\log \alpha_2)/A = 0.7429\delta_{1d}^2 - 13.5559\delta_{1d} - 0.1440\delta_{1p}^2 + 0.5781\delta_{1p} + 0.1883\delta_{1h}^2 - 0.5987\delta_{1h} + 63.6363 \quad \text{(Eq. 9)}$$

$$(\log \alpha_2)/A = 0.7429(\delta_{1d} - 9.124)^2 - 0.1440(\delta_{1p} - 2.007)^2 + 0.1883(\delta_{1h} - 1.590)^2 + 1.902 \quad \text{(Eq. 10)}$$

$n = 26$, s(based on X_2) = 0.052, R^2(based on X_2) = 0.927

The total solubility parameter is obtained:

$$\delta_T^2 = \delta_{2d}^2 + \delta_{2p}^2 + \delta_{2h}^2 = (9.12)^2 + (2.01)^2 + (1.59)^2$$
$$\delta_T = (89.74)^{1/2} = 9.47 \quad \text{(Eq. 11)}$$

It is too early to claim validity for the use of multiple regression as a means of establishing total and partial solubility parameters for solid solutes. However, if multiple regression can be shown to yield consistent results in the future, the method may be useful for drugs, biochemicals, and similar organic solutes, the solubility parameters of which cannot be obtained by the methods used for solvents. The regression procedure would also provide a check on the group contribution method of Hansen and Beerbower (4) for obtaining partial solubility parameters.

In preliminary work with similar systems, it appears that certain conditions must apply for the method to be successful: (*a*) The constant term C_0 of Eq. 1 should be <1.0 or 2.0, as observed in Eqs. 7 and 10. (*b*) The regression equation must be one that successfully predicts solubilities of the solute in the solvent systems employed. (*c*) The regression equation must be obtained by using a sufficient number of solvents (20 is good, 40 is much better) with solubility parameters both below and above that of the solute. The larger the number of known solubilities used in the regression analysis, the better the chance of obtaining reasonable solute solubility parameters.

[1] The δ_h for naphthalene is given in Reference 4 as 2.9 but this is in error; the value was intended to be 1.9.

The first right hand term of Eqs. 7 and 10 express London interaction (dispersion forces) between solute and solvent. These omnidirectional forces do not operate only on 67% of the nearest neighbor molecules, as suggested by the coefficient of Eq. 7, nor on 74%, as shown in Eq. 10. Instead, the coefficient of the $(\delta_{1d} - \delta_{2d})^2$ term should be unity. This can be ensured in the regression method by moving this term to the left hand side of the expression for the calculation of coefficients, then returning it to the right side to display the final equation. The δ_{2d} was taken as 9.40 and the equation obtained was:

$$(\log\alpha_2)/A = (\delta_{1d} - 9.40)^2 - 0.1463(\delta_{1p} - 2.059)^2 + 0.1319(\delta_{1h} - 0.778)^2 + 0.8640 \quad \text{(Eq. 12)}$$

This method reduces the variables of regression by one, but it does not seriously reduce the correlation coefficient: R^2 of Eq. 7 is 0.986 and of Eq. 12 is 0.980. Also from Eq. 13, $\delta_T{}^2 = 9.42 + 2.059^2 + 0.7782$; $\delta_T = (93.205)^{1/2} = 9.65$.

Although this report is devoted to the calculation of solubility parameters for crystalline solids, Eqs. 7, 10, and 12 provide the calculation of the solubility of naphthalene in both polar and nonpolar solvents, as was demonstrated in an earlier report (1). The results, $X_{2(calc)}$, are found in Table I together with the percentage error for naphthalene solubility in each of the 26 solvents studied. Most of the solubilities were very satisfactory, ~50% exhibiting errors of <10%. Most values have an error of < ~30%. Isopropanol and acetic acid exhibited errors of >30% when Eqs. 7 and 12 were used. The predicted solubilities for naphthalene in hexane, acetic acid, ethanol, methanol, and water were >30% error using Eq. 10. The reason that solubilities in these five solvents are >30% cannot be stated definitively at this time. Ethanol, methanol, isopropanol, acetic acid, and water are highly hydrogen bonded and exhibit self-association. However, other polar solvents such as propanol, butanol, and cyclohexanol have reasonable values in this work. The error of 37% for hexane is surprising, as this solvent tends to form regular solutions with nonpolar solutes such as naphthalene.

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GLC Determination of Phenacemide in Tablets

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Abstract □ A GLC procedure was developed for phenacemide and was shown to be less time consuming than the official assay without sacrificing accuracy. The procedure involves extraction from powdered tablets and addition of pentylenetetrazol as the internal standard. The amount of phenacemide is determined by comparison of the ratio of the area under the curves to that of a standard.

Keyphrases □ Phenacemide—analysis in tablets, GLC determination, pentylenetetrazol □ Pentylenetetrazol—analysis of phenacemide in tablets, GLC determination □ GLC—phenacemide, analysis in tablets, pentylenetetrazol.

Phenacemide, an open chain analog of 5-phenylhydantoin, is used in temporal lobe epilepsy (psychomotor) which is refractory to other agents (1, 2). It is a white, odorless, and tasteless crystalline solid (3). While performing routine analyses in another experiment, a rapid method of analysis for phenacemide was needed. The official assay involves acid hydrolysis, extraction of the acidic products into chloroform, and back titration (4). The procedure is time consuming and requires much handling and transfer. Other methods for phenacemide determination have been developed but offer no distinct advantages (5–7).

This report outlines a rapid GLC method that has proven to be less time consuming. In addition to requiring less handling and transfer, it does not appear to sacrifice accuracy.

EXPERIMENTAL

Materials—Phenacemide powder[1] and phenacemide tablets[1] were utilized in the assay as received. Pentylenetetrazol[2] was used as the internal standard. Methanol[3] and isopropyl alcohol[3], ACS reagent grade, were used as solvents.

Apparatus—A basic gas chromatograph[4] with a flame ionization detector (FID) was used. A 3.17-mm, 1.83-m silicone column[5] was used. The temperature of the column and detector was maintained at 200 ± 20°. The flow rate of the carrier gas (helium) was ~20 ml/min. The detector was connected to an integrating recorder[6] for easy and accurate determination of area under the curve.

Standard Curve—Seven samples of varying ratios of phenacemide to pentylenetetrazol in methanol (Table I) were used to obtain a standard curve. Exact amounts of phenacemide and pentylenetetrazol were weighed directly into 10-ml volumetric flasks. A small volume of methanol was added to dissolve the sample and then made to volume with methanol.

Three microliters of each of the seven solutions was chromatographed and the results recorded. A standard curve was obtained by plotting the

[1] Abbott Laboratories, North Chicago, IL 60064.
[2] Knoll Pharmaceutical, Whippany, NJ 07981.
[3] Fisher Scientific, Norcross, GA 30091.
[4] Model 9500, Carle Instruments, Fullerton, CA 92631.
[5] 8% G.E. SF96 Carle Instruments, Fullerton, CA 92631.
[6] Model 1005, Beckman Instruments, Fullerton, CA 92631.

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