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Determination of three-component partial solubility parameters for temazepam and the effects of change in partial molal volume on the thermodynamics of drug solubility

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Summary

Three-component partial solubility parameters for temazepam were determined by the extended Hansen regression model. A high level of correlation was observed when the Flory-Huggins entropy correction was incorporated into the model. The partial molal volume of temazepam was determined in the saturated solutions and these experimental values further improved the correlation. The changes in molal volume are shown to affect both the entropy change and the enthalpy change, attributable to dispersion forces, occurring in the solution process. The dispersion forces operating between solute and solvent are corrected for changes in molal volume by the use of a derived equation. The final model for temazepam solubility showed a high degree of correlation, giving as values for the partial (Hansen) solubility parameters of temazepam: $\delta_D = 10.71$, $\delta_P = 4.79$, $\delta_H = 4.02$ $cal^{1/2}$ $cm^{-3/2}$. The experimental partial solubility parameters predicted the solubility of temazepam in 29 solvents with an average error of 33.4%.

Introduction

The extended Hansen model has been applied to the determination of partial solubility parameters for naphthalene (Martin et al., 1981; Wu et al., 1982), benzoic acid (Beerbower et al., 1984), *p*-hydroxybenzoic acid and methyl-*p*-hydroxybenzoate (Martin et al., 1984). Good correlation was found for naphthalene using this model, however, for the more polar compounds a less satisfactory correlation was observed, giving unreliable values for the solubility parameters. The correlation of the extended Hansen model was shown to be significantly improved by inclusion of the Flory-Huggins entropy correction, using sulphamethoxypyridazine as the solute (Bustamante et al., 1989).

The determination of partial solubility parameters for a solute by a regression model is dependent on having accurate values for the partial solubility parameters of the solvents used in the regression model. Hansen and Beerbower's (1971) three-component system of solubility parameters is possibly the best suited for use in solubility prediction, although there may be some doubt

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concerning these values for the partial solubility parameters (Bagley et al., 1970). These parameters account for the three main types of intermolecular interaction resulting from dispersion, polar (dipole-dipole) and hydrogen bonding forces. The three partial parameters are related to the total cohesive energy density, δ_T^2, by Eqn 1:

$$\delta_T^2 = \delta_D^2 + \delta_P^2 + \delta_H^2 \quad (1)$$

When all four terms in Eqn 1 could be evaluated independently, the correlation was good, giving confidence in the proposed values for the solubility parameters (Hansen and Beerbower, 1971). The contribution to the cohesive energy resulting from dispersion forces was determined on the basis of an appropriate homomorph in Hansen's system, however, the Lorentz-Lorenz expression relating electron polarisability to refractive index may give more accurate values for the dispersion partial solubility parameter (Karger et al., 1976). Bagley et al. (1971) have suggested that it may be possible to determine partial solubility parameters more accurately from measurements of the internal pressures in liquids than from the usual method involving heats of vaporisation.

The Hildebrand solubility parameter for non-polar compounds is defined by Eqn 2:

$$\delta = \left(E^v/V^0\right)^{1/2} \quad (2)$$

where E^v is the energy of vaporisation and V^0 is the molal volume of the pure liquid compound.

The solubility parameter is thus dependent on the molal volume of the compound. In the extended Hansen regression model a value is required for the molal volume of the solute being studied. In a number of previous reports on the application of solubility parameters to solid drug compounds, the group contribution method of Fedors (1974) has been used to estimate a value for the molal volume of the pure compound, represented as the hypothetical supercooled liquid. The pure liquid represents the most suitable standard state for solubility studies as it enables direct comparison of the activity coefficient of a solute in a range of solvents (Hildebrand and Scott, 1950). If Fedors' method is used to estimate the molal volume of the solute, then it is given this standard value throughout the range of solvents in which the solubility of the solute is tested. It is known, however, that molal volume changes can occur when a drug is dissolved in different solvents (Liron and Cohen, 1983) and an extreme example of a volume change occurring in a mixture is the 70% expansion in molal volume of iodine dissolved in perfluoroheptane (Hildebrand et al., 1970).

The purpose of the work reported in this paper is therefore to test the ability of the extended Hansen model to determine the partial solubility parameters of temazepam and to examine the effect of changes in the partial molal volume of the drug in solution on the thermodynamics of drug solubility.

Theoretical Considerations

The activity coefficient of a solid solute, γ_2, which accounts for deviations from ideal solubility behaviour is related to the mole fraction solubility of the drug, x_2, and the ideal solubility, x_2^i, by the equation:

$$\ln\frac{x_2^i}{x_2} = \ln\,\gamma_2 \quad (3)$$

After Beerbower et al. (1984), the extended Hansen equation is written as:

$$\ln\,\gamma_2 = \frac{V_2\phi_1^2}{RT}\left[C_1(\delta_{D1}-\delta_{D2})^2 + C_2(\delta_{P1}-\delta_{P2})^2 + C_3(\delta_{H1}-\delta_{H2})^2 + C_0\right] \quad (4)$$

where V_2 is the molal volume of the solute, Φ_1 denotes the volume fraction of the solvent, R is the gas constant, T represents the thermodynamic temperature and C_{0-3} are constants.

Eqn 4 accounts for deviations from ideality resulting from the presence of intermolecular forces and is derived from regular solution theory (Hildebrand and Scott, 1962). The quantity RT ln γ_2, obtained by multiplying through Eqn 4 by RT,

is called the excess free energy of the solute (Hildebrand and Scott, 1962). Throughout this paper, subscript 1 refers to the solvent and subscript 2 to the solute unless stated otherwise (this does not apply to the regression coefficients). Eqn 4 can be expanded to give the following regression model, where the partial solubility parameters of the solute are constant and are taken into the new regression coefficients:

$$\frac{RT}{V_2\Phi_1^2}\ln\gamma_2 = D_1\delta_{D1} + D_2\delta_{D1}^2 + D_3\delta_{P1} + D_4\delta_{P1}^2 + D_5\delta_{H1} + D_6\delta_{H1}^2 + D_0 \quad (5)$$

The Flory-Huggins size correction accounts for non-ideal entropy of mixing due to differences in the molal volumes of the solute and solvent and can be incorporated into the regression model as follows (Bustamante et al., 1989):

$$B = D_1\delta_{D1} + D_2\delta_{D1}^2 + D_3\delta_{P1} + D_4\delta_{P1}^2 + D_5\delta_{H1} + D_6\delta_{H1}^2 + D_0 \quad (6)$$

where

$$B = \frac{RT}{V_2\Phi_1^2}\left[\ln\gamma_2 - \ln\frac{V_2}{V_1} - 1 + \frac{V_2}{V_1}\right] \quad (7)$$

TABLE 1

Temazepam solubility and partial molal volume in 29 solvents, with Hansen partial solubility parameters and pure solvent molal volumes at 25 °C

No.	Solvent	Solvent molal volume (cm^3/mol)	Solvent partial solubility parameters			Temazepam solubility (mg/cm^3)	$\bar{V}_2^a$ (cm^3/mol)
			δ_D	δ_P	δ_H		
1	Benzene	89.4	9	0	1	58.519	286.3
2	Toluene	106.8	8.8	0.7	1	26.550	293.1
3	Hexane	131.6	7.3	0	0	1.337	–
4	Heptane	147.4	7.5	0	0	1.257	–
5	Cyclohexane	108.7	8.2	0	0.1	4.264	–
6	Acetone	74.0	7.6	5.1	3.4	81.075	189.6
7	Acetophenone	117.4	9.6	4.2	1.8	155.75	233.5
8	Cyclohexanone	104.0	8.7	3.1	2.5	180.65	242.6
9	Formamide	39.8	8.4	12.8	9.3	36.915	214.8
10	Dimethylformamide	77.0	8.5	6.7	5.5	358.91	240.0
11	Dichloromethane	63.9	8.9	3.1	3.0	466.61	224.5
12	Aniline	91.5	9.5	2.5	5.0	492.45	229.9
13	Terahydrofuran	81.7	8.2	2.8	3.9	257.94	216.1
14	Anisole	119.1	8.7	2.0	3.3	109.91	218.1
15	Diethyl phthalate	198.0	8.6	4.7	2.2	57.811	219.5
16	Methyl acetate	79.7	7.6	3.5	3.7	71.598	280.7
17	Ethyl acetate	98.5	7.7	2.6	3.5	42.997	206.5
18	Acetic anhydride	94.5	7.8	5.7	5.0	45.651	223.7
19	Methanol	40.7	7.4	6.0	10.9	39.461	221.0
20	Ethanol	58.5	7.7	4.3	9.5	15.147	244.5
21	Propanol	75.2	7.8	3.3	8.5	15.863	246.6
22	Butanol	91.5	7.8	2.8	7.7	15.936	252.8
23	Hexanol [b]	125.2	8.0	2.1	6.3	14.857	261.3
24	Propan-2-ol	76.8	7.7	3.0	8.0	6.457	285.1
25	Benzyl alcohol	103.6	9.0	3.1	6.7	279.44	249.9
26	Ethylene glycol	55.8	8.3	5.4	12.7	12.955	256.3
27	Propylene glycol	73.6	8.2	4.6	11.4	20.498	235.8
28	Acetonitrile	52.6	7.5	8.8	3.0	60.221	243.9
29	Water	18.0	7.6	7.8	20.7	0.101	–

[a] $\bar{V}_2$ is the partial molal volume of temazepam in solution.
[b] Taken from Beerbower et al. (1984).

The dependent variable, B, can also be written to incorporate the partial molal volume of the solute and solvent in the saturated solution:

$$B = \frac{RT}{\bar{V}_2 \Phi_1^2}\left[\ln \gamma_2 - \ln\frac{\bar{V}_2}{\bar{V}_1} - 1 + \frac{\bar{V}_2}{\bar{V}_1}\right] \quad (8)$$

The partial solubility parameters of the solute are then calculated from the regression coefficients as follows:

$$\delta_{D2} = -0.5D_1/D_2, \qquad \delta_{P2} = -0.5D_3/D_4,$$

$$\delta_{H2} = -0.5D_5/D_6$$

Materials and Methods

Temazepam (Farmitalia Carlo Erba, St. Albans, U.K.) solubilities were measured in triplicate using a normal-phase HPLC assay in each of the 29 solvents listed in Table 1. Solutions were agitated for a period of 48 h (sufficient time to ensure equilibrium) in a shaking water bath, maintained at 25 ± 0.1 °C. Solutions were filtered through Gelman, Acrodisk™ LC13, 0.45 μm filters prior to dilution and solubility measurement. The mobile phase consisted of ethanol (due to its miscibility with organic solvents) and methanol in the ratios 90:10% v/v, respectively. A single wavelength Waters 440 absorbance detector at 245 nm was used for solubility measurement, with a Waters M45 solvent delivery system and a 15 cm × 4.6 mm (i.d.) silica, 5 μm Ultrasphere™ (Beckman Ltd) normal-phase column. Injections were made via a Rheodyne 7010 injection valve, fitted with a 20 μl loop. Temazepam was used as external standard with calibration curves rectilinear in the concentration range 0–100 μg/ml, with correlation coefficients greater than 0.998.

The partial molal volume of temazepam in the saturated solution was determined by measurement of solution density in the saturated solution and four other solutions representing 0, 25, 50 and 75% of the saturation solubility of temazepam. Density measurements were made using 50 ml density bottles, calibrated with water at 25 °C. From the measured densities the number of moles of both solute and solvent per ml of solution could be determined, from which the volume of one mole of solution was calculated. The partial molal volume of temazepam was then determined by extrapolation of a graph of solution molal volume vs mole fraction of solute to unit fraction of the solute. The partial molal volume of temazepam is then given by the intercept on the y-axis at unit mole fraction of temazepam (Lewis and Randall, 1961). Values for the partial molal volume of temazepam in hexane, heptane, cyclohexane and water could not be determined due to the low solubility of temazepam.

The ideal solubility of temazepam was calculated from Eqn 9, having knowledge of the heat of fusion, ΔH^F and melting point, T_m of temazepam. These were determined by triplicate measurements using differential scanning calorimetry (Perkin Elmer DSC4) and found to be: $\Delta H^F = 6114.04$ cal/mol and $T_m = 432.46$ K.

$$\ln x_2^i = \frac{\Delta H^F}{RT_m}\ln\left(\frac{T}{T_m}\right) \quad (9)$$

The ideal solubility of temazepam at 25 °C is $x_2^i = 0.07095$. Partial solubility parameters at 25 °C were taken from Hansen and Beerbower (1971) and are listed in Table 1.

Results and Discussion

The extended Hansen regression model (Eqn 5) was applied to the experimental solubilities of temazepam in 29 solvents at 25 °C, giving the following values for the regression coefficients:

$D_1 = -10.878$ $D_3 = -2.321$ $D_5 = -0.609$ $D_0 = 77.895$
$D_2 = 0.317$ $D_4 = 0.168$ $D_6 = 0.086$

$n = 29$, $s = 2.481$, $r^2 = 0.899$, $F = 32.608$, $F(6,22,0.01) = 3.76$

This regression model shows that the heat of solution calculated from the partial solubility parameters accounts for a large proportion of the

excess free energy, with approx. 90% of the variance being explained.

When the Flory-Huggins entropy correction is added to the regression model (Eqn 6), with the dependent variable defined by Eqn 7, it is necessary to have a value for the molal volume of the drug in solution. A value for the molal volume can be approximated by the group contribution method of Fedors (1974), giving a value of 192.6 cm^3/mol for the molal volume of temazepam. With this value for the molal volume of temazepam in each of the 29 solvents and using the molal volumes of the pure solvents (Table 1), the model gave the following values for the regression coefficients:

$D_1 = -18.258$ $D_3 = -1.865$ $D_5 = -1.297$ $D_0 = 109.708$
$D_2 = 0.758$ $D_4 = 0.174$ $D_6 = 0.158$

$n = 29$, $s = 1.862$, $r^2 = 0.972$, $F = 129.069$, $F(6,22,0.01) = 3.76$

The Flory-Huggins entropy correction results in a significant improvement in the correlation of the solubility data. With the Fedors' estimate for the molal volume of temazepam, the entropy correction accounts for over 7% of the variance, showing that the differences in molal volume of the solute and solvent have a substantial effect on the solubility of temazepam.

Although Fedors' estimate of molal volume has been used as an approximation for the molal volume of the solute in solution, it has not been demonstrated in previous reports how good an approximation this may be to the actual volume or partial molal volume of the solute. The partial molal volume of temazepam in 25 of the solvents was determined (Table 1). It can be seen that the volume of the drug varies substantially in the range 189.6–293.1 cm^3/mol, with a relative standard deviation of 10.9% about the mean value of 240.6 cm^3/mol. These values show that Fedors' value for the molal volume is indeed a poor estimate for the volume of temazepam in solution.

To test the effect of these values for the partial molal volume of temazepam in solution on the regression model (Eqn 6), the dependent variable was defined according to Eqn 8. The partial molal volume of the solvent in each solution was calculated from a knowledge of the number of moles of both solute and solvent, together with the volumetric data determined experimentally. With the average value of 240.6 cm^3/mol assigned to the partial molal volume of temazepam in the four solvents for which volumetric data could not be determined, the following regression coefficients resulted:

$D_1 = -21.925$ $D_3 = -1.327$ $D_5 = -1.155$ $D_0 = 117.711$
$D_2 = 1.058$ $D_4 = 0.141$ $D_6 = 0.141$

$n = 29$, $s = 1.38$, $r^2 = 0.982$, $F = 204.302$, $F(6,22,0.01) = 3.76$

The results show that incorporation of the experimentally determined partial molal volumes gives further improvement to the correlation of the solubility data. This level of correlation is sufficiently high to give good values for the partial solubility parameters of the drug. However, analysis of the regression parameters shows that

TABLE 2

Multiple regression parameters for temazepam solubility in 29 solvents, with dependent variable defined by Eqn 8

Independent variable	Regression coefficient	Standard error	Partial F	t value	Probability
δ_D	$D_1 = -21.925$	10.795	4.125	2.031	0.0545
δ_D^2	$D_2 = 1.058$	0.645	2.688	1.640	0.1153
δ_P	$D_3 = -1.327$	0.282	22.121	4.703	0.0001
δ_P^2	$D_4 = 0.141$	0.022	41.809	6.466	0.0001
δ_H	$D_5 = -1.155$	0.177	42.631	6.529	0.0001
δ_H^2	$D_6 = 0.141$	0.009	273.732	16.545	0.0001

there is still some lack of correlation concerning the dispersion partial solubility parameter. These values are listed in Table 2.

The error involved in the δ_D terms in the regression analysis incorporating the partial molal volumes may well originate from the volume changes seen in these solutions of temazepam. If the system has expanded, the forces of attraction between the molecules are reduced and hence the solubility parameter should be adjusted to account for this. The regression analysis above suggests that the polar solubility parameter may be less affected by the volume changes as they are well correlated in the regression model. This is in agreement with a proposal of Hansen (Bagley et al., 1971) that the strong orientational factor associated with polar forces may affect the volume dependence of this type of intermolecular interaction. Hydrogen bonding forces are known to be of long range and are unaffected by relatively small volume changes (Bagley et al., 1971). Since dispersion forces are of short range, the value of δ_D for each of the solvents should be adjusted in order to account for the concomitant change in the solubility parameter with molal volume.

The development of the theory of dispersion forces by London and other workers has resulted in a number of equations relating the energy of interaction between two identical, nonpolar molecules. The basis of these equations is that the attractive force between two such molecules is proportional to the reciprocal of the sixth power of the intermolecular separation (Hildebrand et al., 1970).

The volume of a liquid is composed of two parts, the excluded volume or van der Waals volume of the individual molecules and the free volume in which the molecules move. The combination of the van der Waals volume and free volume gives the molecular volume of each molecule, with radius R, assuming spherical molecules. The intermolecular separation, d is then equal to $2R$. The value of R may vary with expansion or contraction of the liquid, resulting for example from changes in the partial molal volume, while the van der Waals radius, r, remains unchanged.

For a given pair of solvent molecules, the intermolecular potential, u, is given by (Hildebrand et al., 1970):

$$u = \frac{A}{d^6} \tag{10}$$

where A is a constant and d is the intermolecular separation.

From Eqn 10 it follows that the cohesive energy due to dispersion forces is given by:

$$E = \frac{C}{d^6} \tag{11}$$

where C is a constant.

The molecular volume, V^m, is equal to the molal volume of the pure solvent, V^0, divided by Avogadro's number, N_A. With R and d as defined previously, the molecular volume is given by:

$$V^m = \frac{V^0}{N_A} = \tfrac{4}{3}\pi R_1^3 = \tfrac{1}{6}\pi d_1^3 \tag{12}$$

The intermolecular separation can be cast in terms of the molal volume by rearrangement of Eqn 12:

$$d_1 = \left[\frac{6V^0}{\pi N_A}\right]^{1/3} \tag{13}$$

Since the solubility parameter is the square root of all of the cohesive energy divided by the molal volume for nonpolar compounds, the dispersion partial solubility parameter may be written as:

$$\delta_{D1} = \left[\frac{\dfrac{C}{d_1^6}}{\tfrac{4}{3}\pi R_1^3 N_A}\right]^{1/2} \tag{14}$$

From Eqn 14, a value can be obtained from the constant term in Eqn 11 in terms of the

dispersion partial solubility parameter of the solvent. Since $d_1 = 2R_1$:

$$C = \frac{\delta_{D1}^2 \pi d_1^9 N_A}{6} \tag{15}$$

If, as the result of the addition of a solute to the pure solvent, the partial molal volume of the solvent is different in the solution compared to the pure solvent, then the new radius for the solvent molecule is R_S, where the subscript (S) denotes the solvent in the two component solution. The value of R_S can be greater or less than the value of R_1, depending on whether the solvent has expanded or contracted due to the presence of the solute.

The constant term given by C in Eqn 15 can be assumed to be the same in both the pure solvent and the solute as an initial approximation. This can be substituted into an equation similar to Eqn 14, to give the dispersion partial solubility parameter for the solvent, having undergone a volume change, represented by a change in radius from R_1 to R_S, caused by the presence of the dissolved solute. The dispersion partial solubility parameter for the solvent in the solution can then be represented by $\delta_{D,S}$ in Eqn 16:

$$\delta_{D,S} = \left[\frac{\frac{1}{6}\left[\delta_{D1}^2 \pi d_1^9 N_A\right]}{\frac{d_S^6}{\frac{4}{3}\pi R_S^3 N_A}} \right]^{1/2} \tag{16}$$

By similar reasoning to the case for the pure solvent in Eqn 12, the partial molal volume of the solvent in the solution can be written as:

$$\bar{V}_S = \tfrac{4}{3}\pi R_S^3 N_A = \tfrac{1}{6}\pi d_S^3 N_A \tag{17}$$

By rearrangement of Eqn 17, values can be derived for R_S and d_S in terms of the partial molal volume of the solvent. By substitution of these values and the value for d_1 (Eqn 13) into Eqn 16 and simplifying, the following relationship results between the dispersion partial solubility parameter of the solvent in the solution compared to the pure solvent:

$$\delta_{D,S} = \left[\delta_{D1}^2 \left(\frac{V^0}{\bar{V}_S} \right)^3 \right]^{1/2} \tag{18}$$

The value of δ_D for each of the pure solvents was corrected by Eqn 18 using the experimentally determined values for the partial molal volume of the solvent in the solution. These new values for $\delta_{D,S}$ and $(\delta_{D,S})^2$ were then used as independent variables in the regression model (Eqn 6), incorporating the partial molal volumes of solute and solvent in the dependent variable defined by Eqn 8. This analysis resulted in the following values for the regression coefficients:

$D_1 = -17.714$ $D_3 = -1.333$ $D_5 = -1.126$ $D_0 = 98.68$
$D_2 = 0.827$ $D_4 = 0.139$ $D_6 = 0.140$

$n = 29$, $s = 1.199$, $r^2 = 0.985$, $F = 243.749$, $F(6,22,0.01) = 3.76$

TABLE 3

Multiple regression parameters for temazepam solubility in 29 solvents using adjusted dispersion partial solubility parameter

Independent variable	Regression coefficient	Standard error	Partial F	t value	Probability
$\delta_{D,S}$	$D_1 = -17.714$	4.236	17.485	4.182	0.0004
$\delta_{D,S}^2$	$D_2 = 0.827$	0.242	11.715	3.423	0.0024
δ_P	$D_3 = -1.333$	0.255	27.407	5.235	0.0001
δ_P^2	$D_4 = 0.139$	0.020	50.237	7.088	0.0001
δ_H	$D_5 = -1.126$	0.156	52.346	7.235	0.0001
δ_H^2	$D_6 = 0.140$	0.140	341.634	18.483	0.0001

This adjustment of the dispersion solubility parameters results in a further improvement in the correlation of the solubility data. Analysis of the partial regression parameters shows that there is a significant improvement in the dispersion partial solubility parameter, shown in Table 3.

This regression model gives the following relationship between the dependent variable, B and the partial solubility parameters of the solvent and temazepam:

$$B = 0.827(\delta_{D1} - 10.71)^2 + 0.139(\delta_{P1} - 4.79)^2 + 0.14(\delta_{H1} - 4.02)^2 - 1.63 \quad (19)$$

The high degree of correlation in this regression analysis suggests that this model may be suitable for the determination of the partial solubility parameters of drug molecules. It should be noted, however, that there may be some degree of error in the final regression analysis listed above. This results from the fact that the coefficient of $(\delta_{D1} - \delta_{D2})^2$, i.e., D_2, should be unity (Wu et al., 1982). It is likely that the main source of error in this regression model results from the measurement of solution density, since the adjusted values for the dispersion partial solubility parameter are very sensitive to errors in the density.

The success of this model in correlating the solubility of temazepam in solvents of such wide ranging polarity is encouraging and gives confidence in the values for the partial solubility parameters given by Hansen and Beerbower (1971). Further, this model uses the assumption that the interchange energy between unlike molecules is the geometric mean of the cohesive energy between like pairs. This assumption is generally held as being valid for systems in which dispersion forces only are operating, however, this assumption has often been blamed for the failure of solubility parameter theory in cases where polar forces are present (Martin et al., 1985). Srebrenik and Cohen (1976) argued that the failure of this approach may result from the neglect of the volume changes that can occur on mixing rather than the geometric mean assumption. The results of the regression analysis for temazepam support this view, with the geometric mean assumption being used to give the interchange energy of each of the three intermolecular forces used in the model.

The failure of the extended Hansen model for the polar solutes reported previously is likely to have resulted from a neglect of the volume changes that can occur in mixing. In the application of this model to the solubility of sulphamethoxypyridazine in 30 solvents (Bustamante et al., 1989) the polar and hydrogen bonding parameters showed a high degree of correlation, while the dispersion parameter was very poorly correlated. This is consistent with the observed behaviour of temazepam and also supports the fact that the interchange energy due to polar forces is largely unaffected by the volume changes that can occur on mixing.

The predicted solubilities in Table 4 show that the extended Hansen model can be used to predict the solubility of temazepam with a reasonable degree of accuracy. If the partial molal volume of temazepam in a particular solvent is unknown, the loss of accuracy in using an average value for the molal volume of temazepam without adjustment of the dispersion solubility parameter (column 6) is not generally too great. The calculated errors show that the poorest solubility predictions for temazepam occur in the alcohols, with the predicted solubility in propan-2-ol showing marked deviation from the experimental value. This lack of correlation with the alcohols may be the result of the polymerisation that can occur due to the strong hydrogen bonding power of these solvents. However, it may also be the case that the proposed values for the polar or hydrogen bonding solubility parameters of these solvents are inaccurate. Bagley et al. (1970) have drawn attention to possible errors in the polar and hydrogen bonding partial solubility parameters of these compounds. It is of interest to note that a reduction of the polar partial solubility parameters of ethanol, propanol and propan-2-ol by 1 unit results in an increase in the significance of the polar solubility parameter and a further increase in the significance of both the dispersion and hydrogen bonding partial solubility parame-

ters. This, however, conflicts with the proposal of Bagley et al. (1970) that the Hansen partial solubility parameters underestimated the magnitude of the polar interaction. Karger et al. (1976) have reported that the standard deviation in the Hansen dispersion solubility parameter may be as high as 0.7 $cal^{1/2}$ $cm^{-3/2}$. This error would then be transferred to the other partial solubility parameters also, as they are calculated by difference from the total solubility parameter determined from the heat of vaporisation. Further work is necessary to establish the possible errors that may be present in the partial parameters of Hansen and Beerbower. The fact that the polar forces appear to be independent of the volume changes that occur on mixing suggests that the

TABLE 4

Mole fraction solubility for temazepam and predicted mole fraction solubilities in 29 solvents

No.	Solvent	Temazepam mole fraction	Predicted solubilities (Eqn 19)			
			(Footnote 1)		(Footnote 2)	
			X_2 calc.	% error [a]	X_2 calc.	% error [a]
1	Benzene	0.0181321	0.01991	−9.81	0.02060	−13.61
2	Toluene	0.0096185	0.01323	−37.55	0.01584	−64.68
3	Hexane	0.0005855	0.00038	35.10	0.00038	35.10
4	Heptane	0.0006161	0.00055	10.73	0.00055	10.73
5	Cyclohexane	0.0015765	0.00185	−17.35	0.00296	−87.76
6	Acetone	0.0206991	0.01872	9.56	0.02110	−1.94
7	Acetophenone	0.0651702	0.08571	−31.52	0.09509	−45.91
8	Cyclohexanone	0.0679788	0.05789	14.84	0.05540	18.50
9	Formamide	0.0050084	0.00468	6.56	0.00467	6.76
10	Dimethylformamide	0.1137762	0.10082	11.39	0.09777	14.07
11	Dichloromethane	0.1322996	0.18836	−42.37	0.23114	−74.71
12	Aniline	0.1801868	0.16592	7.92	0.12886	28.49
13	Tetrahydrofuran	0.0785574	0.05782	26.40	0.05857	25.44
14	Anisole	0.0430890	0.06765	−57.00	0.03702	14.08
15	Diethyl phthalate	0.0384696	0.02730	29.03	0.02860	25.66
16	Methyl acetate	0.0199276	0.01639	17.75	0.01627	18.35
17	Ethyl acetate	0.0144756	0.00918	36.58	0.01023	29.33
18	Acetic anhydride	0.0148120	0.01243	16.08	0.01572	−6.13
19	Methanol	0.0054740	0.00713	−30.25	0.00714	−30.43
20	Ethanol	0.0029997	0.00558	−86.02	0.00709	−136.37
21	Propanol	0.0040287	0.00575	−42.73	0.00694	−72.26
22	Butanol	0.0049087	0.00529	−7.77	0.00624	−27.12
23	Hexanol	0.0063267	0.00472	25.40	0.00792	−25.18
24	Propan-2-ol	0.0016571	0.00493	−197.51	0.00622	−275.35
25	Benzyl alcohol	0.1107518	0.07522	32.08	0.06708	39.43
26	Ethylene glycol	0.0024212	0.00172	28.96	0.00189	21.94
27	Propylene glycol	0.0050604	0.00282	44.27	0.00190	62.45
28	Acetonitrile	0.0110091	0.01605	−45.79	0.00080	92.73
29	Water	0.0000061	6.8×10^{-6}	−11.84	2.0×10^{-7}	96.72
		Average percentage error:		33.4		48.3

[1] Predicted solubilities calculated using Eqn 19, with adjusted values for solvent dispersion partial solubility parameter, $\delta_{D,S}$. Experimentally determined values for the partial molal volumes were then used to give the activity coefficient (see Eqn 8) and mole fraction solubility by Eqn 3.

[2] Predicted solubilities calculated as in 1, with unadjusted values for dispersion partial solubility parameter, δ_D, with average value for temazepam molal volume = 240.6 cm^3/mol throughout and pure solvent molal volumes used in the calculation of the activity coefficient by Eqn 7.

[a] Percentage error = $100(X_2 \text{ exp.} - X_2 \text{ calc.})/X_2$ exp.

measurement of internal pressures in liquids may be used to give the dispersion solubility parameter, along similar lines to the proposal of Bagley et al. (1971). This would then give a more accurate picture of the magnitude of the polar and hydrogen bonding partial solubility parameters.

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