Descriptors for solutes from the solubility of solids: *trans*-stilbene as an example

PERKIN 2

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Received (in Cambridge) 23rd July 1998, Accepted 25th September 1998

Solubilities of *trans*-stilbene in 17 nonaqueous solvents are reported. These may be combined with literature values for the solubility in water and for the vapour pressure of stilbene to give 17 values of water–solvent partitions, P, and 17 values of gas–solvent partitions, L. Coefficients in the general solvation equations (i) and (ii) are known for all 34 of these systems, together with two additional equations for gas–water partitions. In equations (i) and (ii), the independent variables are solute descriptors as follows: R_2 is an excess molar refraction, π_2^H is the dipolarity/polarizability, $\Sigma\alpha_2^H$ and $\Sigma\beta_2^H$ are the overall hydrogen-bond acidity and basicity, Vx is the McGowan characteristic volume, and $\log L^{16}$ is a descriptor where L^{16} is the solute L-coefficient on hexadecane at 298 K.

$$\log \mathrm{SP} = c + rR_2 + s\pi_2^H + a\Sigma\alpha_2^H + b\Sigma\beta_2^H + vVx \quad \text{(i)}$$

$$\log \mathrm{SP} = c + rR_2 + s\pi_2^H + a\Sigma\alpha_2^H + b\Sigma\beta_2^H + l\log L^{16} \quad \text{(ii)}$$

We estimate R_2 as 1.45 and calculate Vx as 1.563, and then solve the total set of 36 equations to yield $\pi_2^H = 1.04$, $\Sigma\alpha_2^H = 0.00$, $\Sigma\beta_2^H = 0.34$ and $\log L^{16} = 7.525$ units. These descriptors reproduce the 36 observed log P and log L values with a standard deviation of only 0.086 log units. This represents an entirely new method for determining solvation descriptors and is also a quite novel method for the correlation and estimation of solubilities.

One of the most useful general methods for the analysis of solute effects in chemical and biochemical systems is the solvation parameter method of Abraham.[1] In essence, this takes the form of the linear free energy relationships (LFERs) eqn. (1) and eqn. (2), where SP is a property of a series of

$$\log \mathrm{SP} = c + rR_2 + s\pi_2^H + a\Sigma\alpha_2^H + b\Sigma\beta_2^H + vVx \quad (1)$$

$$\log \mathrm{SP} = c + rR_2 + s\pi_2^H + a\Sigma\alpha_2^H + b\Sigma\beta_2^H + l\log L^{16} \quad (2)$$

solutes in a given system, and the independent variables are solute descriptors as follows:[1] R_2 is an excess molar refraction, π_2^H is the dipolarity/polarizability, $\Sigma\alpha_2^H$ and $\Sigma\beta_2^H$ are the overall hydrogen-bond acidity and basicity, Vx is the McGowan characteristic volume,[2] and $\log L^{16}$ is a descriptor where L^{16} is the solute L-coefficient on hexadecane at 298 K.[3]

Eqn. (1) is usually employed for processes that take place in condensed phases, such as water–solvent partitions,[4] water–micelle partitions,[5] high performance liquid chromatography (HPLC),[6] microemulsion[7] and micellar[8] electro-kinetic chromatography, thin-layer chromatography,[9] solid phase extraction,[10] blood–brain distribution,[11] brain perfusion,[12] water–skin permeation[13] and tadpole narcosis.[14] The alternative eqn. (2) is used for gas-to-condensed phase processes, including gas–liquid[15] and gas–solid chromatography,[16] the solubility of gases and vapours in water,[17] organic solvents[18] and biological systems,[19] nasal pungency thresholds in man,[20] upper respiratory tract irritation in mice[21] and eye irritation in mice[22] and man.[23] One particular gas-to-condensed phase process to which eqn. (1) [as well as eqn. (2)] has been applied is the solubility of gases and vapours in water,[17] and Carr *et al.*[24] have recently used eqn. (2) in the analysis of supercritical HPLC.

A limiting factor on the general use of eqn. (1) and eqn. (2) is the availability of descriptors for solutes. There is no problem over Vx because this parameter can be calculated for any molecule simply from structure,[1,2] especially if the algorithm of Abraham[1] for the number of bonds in any molecule is used. For solutes that are liquid at 293 K, R_2 can be obtained from the liquid refractive index.[25] In the case of solid solutes, the hypothetical liquid refractive index can be calculated, but we prefer to obtain R_2 through addition of fragments or substructures. In any event, four descriptors in eqn. (1) and eqn. (2), *viz.* π_2^H, $\Sigma\alpha_2^H$, $\Sigma\beta_2^H$ and $\log L^{16}$, need to be determined for any given solute.

Our usual method is to set up calibration or reference equations, based on eqn. (1) and eqn. (2) for as many processes as possible. Values of log SP are determined or obtained from literature data, and the four unknown descriptors are taken as those that give the 'best-fit' of observed and calculated log SP values. We have recently explained this method in detail for the determination of descriptors for terpenes.[26] Since the solvation parameter model of Abraham is now widely used by various groups of workers,[24,27–33] we sought to explore further physicochemical processes that could be used to obtain solute descriptors. One such process is the solubility of solids. There is considerable literature data on solid solubilities; for example, Acree *et al.* have reported the solubilities of solids in a very large number of nonaqueous solvents.[34–38] In the present work we set out an entirely new method for the determination of descriptors that uses the solubility of a solute in solvents as the prime experimental observation.

Methodology

There are a number of possible approaches, depending on the availability of (i) the aqueous solubility of the solid at 298 K,

Table 1 Values of log C_S, log P and log L_S for *trans*-stilbene at 298 K

Solvent	Log C_S[a]	Log P[b]	Log P[c] Calc. from eqn. (1)	Dev.	Log L_S[d]	Log L_S[e] Calc. from eqn. (2)	Dev.
Hexane	−1.14	4.66	4.58	0.08	7.45	7.41	0.04
Heptane	−1.13	4.67	4.65	0.02	7.45	7.43	0.02
Octane	−1.12	4.68	4.79	−0.11	7.46	7.42	0.04
Nonane	−1.11	4.69	4.69	0.00	7.47	7.39	0.08
Decane	−1.11	4.69	4.64	0.05	7.47	7.36	0.11
Hexadecane	−1.13	4.67	4.65	0.02	7.46	7.52	−0.06
2,2,4-Trimethylpentane	−1.32	4.48	4.54	−0.06	7.27	7.23	0.04
Cyclohexane	−0.90	4.90	5.10	−0.20	7.68	7.69	−0.01
Tetrachloromethane	−0.40	5.40	5.38	0.02	8.18	8.22	−0.44
Acetonitrile	−0.74	5.06	5.09	−0.03	7.85	7.76	0.09
Benzene	−0.18	5.62	5.65	−0.03	8.40	8.48	−0.08
Toluene	−0.26	5.54	5.62	−0.08	8.32	8.42	−0.10
Chlorobenzene	−0.16	5.64	5.58	0.06	8.42	8.39	0.03
Methanol dry	−1.32	4.48	4.40	0.08	7.26	7.17	0.09
Ethanol dry	−1.27	4.53	4.70	−0.17	7.32	7.39	−0.07
Octan-1-ol dry	−1.10	4.70	4.76	−0.06	7.48	7.43	0.05
2,2,2-Trifluoroethanol dry	−2.04	3.76	3.70	0.06	6.54	6.77	−0.23
Gas to water (eqn. (2))	−5.80[f]				2.78	2.80	0.02
Gas to water (eqn. (1))		2.78	2.78	0.00			

[a] From ref. 34 after conversion to solubilities in mol dm^{-1}, and this work. [b] Calculated as log C_S − log C_W. [c] Calculated from eqn. (1) and estimated descriptors. [d] Calculated as log C_S − log C_G (−8.59 from ref. 40). [e] Calculated from eqn. (2) and estimated descriptors. [f] Ref. 39 where log C_S is the solubility of solid *trans*-stilbene in water.

and (ii) the saturated vapour pressure of the solid at 298 K. If both are available, we proceed as follows.

Let the solubility of a solid in mol dm^{-1} at 298 K be C_S and C_W respectively in a solvent and in water. Then the partition coefficient, P, between water and the solvent will be given by eqn. (3) provided that three specific conditions are met. Note that P refers to partition between water and any solvent.

$$P = C_S/C_W \text{ or } \log P = \log C_S - \log C_W \qquad (3)$$

These conditions are as follows. (i) The same solid phase must be in equilibrium with the saturated solutions in the solvent and in water; in practice this means that there should be no solvate or hydrate formation. (ii) The secondary medium activity coefficient of the solid in the saturated solutions must be unity (or near unity); this condition normally restricts the method to those solids that are sparingly soluble in water and nonaqueous solvents. (iii) For solids that are ionised in aqueous solution, C_W must refer to the solubility of the neutral form.

If these conditions are met, eqn. (3) allows the calculation of log P values between water and as many solvents as there are C_S values. Of course, these log P values will refer to partition between water and the dry organic solvent. For solvents that are partially miscible with water, such as butan-1-ol or ethyl acetate, such partitions will not be the same as those obtained from direct partition between water (saturated with the solvent) and the solvent (saturated with water) and care must be taken not to confuse the two sets of partitions. For solvents that are fully miscible with water, such as methanol, no confusion is possible, because log P must refer to the hypothetical partition between the two pure solvents. And for solvents that are almost completely immiscible with water, such as alkanes, cyclohexane, dichloromethane, trichloromethane, tetrachloromethane, and most aromatic solvents, there should be no confusion because indirect partition through eqn. (3) will be the same as direct partition.

Hence if C_W is known, values of C_S will lead to log P values through eqn. (3). An additional set of partitions can be calculated if the solid saturated vapour pressure at 298 K, VP°, is also available. VP° can be transformed into the gas phase concentration, C_G, and the gas–water and gas–solvent partitions, L or K, can then be obtained through eqn. (4) and eqn. (5).

$$L^W = C_W/C_G \text{ or } \log L^W = \log C_W - \log C_G \qquad (4)$$

$$L_S = C_S/C_G \text{ or } \log L_S = \log C_S - \log C_G \qquad (5)$$

Once again, eqn. (4) and eqn. (5) will only be valid if conditions (i)–(iii), above, are met. If log L^W, together with values of log P and log L_S are known, then, as we shall see, it is possible to obtain all the four unknown descriptors. If no VP° value is available, then from the various log P values, three descriptors can be calculated (π_2^H, $\Sigma\alpha_2^H$ and $\Sigma\beta_2^H$ but not log L^{16}). Finally, if VP° is known, but not C_W, various log L_S values can be obtained *via* eqn. (5). In principle, all four unknown descriptors can still be obtained, but in practice only if log L_S values are known for a very wide range of different solvents.

Experimental

trans-Stilbene (Aldrich, 96%) was recrystallized several times from methanol. *n*-Nonane (TCI, 99+%), *n*-decane (TCI, 99+%), *n*-hexadecane (Aldrich, 99+%), ethylene glycol (Aldrich, 99+%), benzene (HPLC, Aldrich, 99.9+%), toluene (anhydrous, Aldrich, 99.8%), 2,2,2-trifluoroethanol (Aldrich, 99+%), carbon tetrachloride (HPLC, Aldrich, 99.9+%) and chlorobenzene (HPLC, Aldrich, 99.9+%) were stored over activated molecular sieves before use. Gas chromatographic analysis showed solvent purities to be 99.7 mole percent or better.

Excess solute and solvent were placed in sealed amber glass bottles and allowed to equilibrate in a constant temperature bath at 25.0 ± 0.1 °C for five days with periodic agitation. Attainment of equilibrium was verified by repetitive measurements after three additional days of equilibration, and by approaching equilibrium from supersaturation by pre-equilibrating the solutions at a slightly higher temperature. Known aliquots of saturated *trans*-stilbene solutions were transferred into tared volumetric flasks and diluted quantitatively with methanol. Molar concentrations were determined spectrophotometrically at 294 nm. Experimental methodology is described in greater detail in an earlier paper.[34] Solubilities of *trans*-stilbene, as log C_S, are given in Table 1 as the average of 4–8 independent experimental determinations, and were reproducible to ±2%, in C_S.

Results and discussion

We illustrate the most useful situation, that where both C_W and VP° (C_G) are known, with the solute *trans*-stilbene. We have

Table 2 Coefficients in eqn. (1) and eqn. (2) for various processes

Process	*c*	*r*	*s*	*a*	*b*	*v*/*l*
A Water to solvent, eqn. (1)						
Hexane	0.361	0.579	−1.723	−3.599	−4.764	4.344
Heptane	0.325	0.670	−2.061	−3.317	−4.733	4.543
Octane	0.223	0.642	−1.647	−3.480	−5.067	4.526
Nonane	0.240	0.619	−1.713	−3.532	−4.921	4.482
Decane	0.160	0.585	−1.734	−3.435	−5.078	4.582
Hexadecane	0.087	0.667	−1.617	−3.587	−4.869	4.433
2,2,4-Trimethylpentane	0.288	0.382	−1.668	−3.639	−5.000	4.561
Cyclohexane	0.109	0.817	−1.700	−3.803	−4.907	4.645
Tetrachloromethane	0.260	0.573	−1.254	−3.558	−4.588	4.589
Acetonitrile	0.262	0.471	0.107	−1.377	−4.358	3.526
Benzene	0.142	0.464	−0.588	−3.099	−4.625	4.491
Toluene	0.143	0.527	−0.720	−3.010	−4.824	4.545
Chlorobenzene	0.040	0.246	−0.462	−3.038	−4.769	4.640
Methanol dry	0.329	0.299	−0.671	0.080	−3.389	3.512
Ethanol dry	0.208	0.409	−0.959	0.186	−3.645	3.928
Octan-1-ol dry	0.013	0.550	−1.205	−0.020	−4.262	4.253
2,2,2-Trifluoroethanol	0.368	−0.505	−0.677	−1.756	−0.325	3.123
(Gas to water)	−0.994	0.577	2.549	3.813	4.841	−0.869
B Gas to solvent, eqn. (2)						
Hexane	0.292	−0.169	0.000	0.000	0.000	0.979
Heptane	0.275	−0.162	0.000	0.000	0.000	0.983
Octane	0.215	−0.049	0.000	0.000	0.000	0.967
Nonane	0.200	−0.145	0.000	0.000	0.000	0.980
Decane	0.156	−0.143	0.000	0.000	0.000	0.989
Hexadecane	0.000	0.000	0.000	0.000	0.000	1.000
2,2,4-Trimethylpentane	0.275	−0.244	0.000	0.000	0.000	0.972
Cyclohexane	0.216	0.000	−0.179	0.000	0.000	1.019
Tetrachloromethane	0.282	−0.303	0.460	0.000	0.000	1.047
Acetonitrile	−0.042	−0.122	2.138	2.383	0.452	0.745
Benzene	0.107	−0.313	1.053	0.457	0.169	1.020
Toluene	0.121	−0.222	0.938	0.467	0.099	1.012
Chlorobenzene	0.053	−0.553	1.254	0.364	0.000	1.041
Methanol dry	−0.004	−0.215	1.173	3.701	1.432	0.769
Ethanol dry	0.012	−0.206	0.789	3.635	1.311	0.853
Octan-1-ol dry	0.071	−0.119	0.443	3.689	0.589	0.933
2,2,2-Trifluoroethanol	−0.133	−0.611	1.457	1.899	4.461	0.633
(Gas to water)	−1.271	0.822	2.743	3.904	4.814	−0.213

already reported solubilities in a large number of solvents,[34] and in Table 1 we collect solubility data that we use in the present work, as log C_S values. The solubility in water is known,[39] log $C_W = -5.80$, so that for partition between water and any solvent log $P = (\log C_S + 5.80)$. From the vapour pressure[40] at 298 K we have that log $C_G = -8.58$ so that the partition between the gas phase and any solvent, as log L_S, is given by log $L_S = (\log C_S + 8.58)$. There are 17 water–solvent systems for which we have both solubility data and the coefficients in eqn. (1). These coefficients are given in Table 2 with the dependent variable as log *P*. We also have one additional LFER based on eqn. (1) where the dependent variable is log L^W, making a total of 18 equations based on eqn. (1). The corresponding coefficients for LFERs based on eqn. (2) are also given, with the dependent variable as log L_S, and in one case as log L^W. We have 18 equations based on eqn. (2) which with the 18 equations based on eqn. (1) yield a total of 36 equations for which both solubility data and coefficients are available. Statistics for all these equations are given in Table 3. The characteristic volume of *trans*-stilbene is 1.5630 in units of 10^{-2} cm^3 mol^{-1}, and we estimate R_2 as 1.45 (in units of 10^{-1} cm^3 mol^{-1}) from known values[17] for benzene and styrene. We can therefore solve the set of 36 equations to yield the values of the unknown descriptors π_2^H, $\Sigma\alpha_2^H$, $\Sigma\beta_2^H$ and log L^{16} that best reproduce the dependent variables. A preliminary analysis showed that $\Sigma\alpha_2^H$ was effectively zero, as required for a solute that has no hydrogen-bond acidity, and so we set this descriptor as exactly zero and solved the 36 equations for π_2^H, $\Sigma\beta_2^H$ and log L^{16}. We found that with $\pi_2^H = 1.04$, $\Sigma\beta_2^H = 0.34$ and log $L^{16} = 7.525$, we could reproduce the 36 dependent variables with a standard deviation of 0.086 log units. The calculated values of log *P* and log *L* are given in Table 1, together with the residuals. The standard deviation is 0.088 for the 18 calculated and observed log *P* values, 0.085 for the 18 calculated and observed log *L* values, and 0.086 for the total 36 values.

The internal self-consistency of the calculations can be assessed by cross-validation[41] using the method known as 'leave-one-out'.[42] The first equation in the set of 36 is left out, and the remaining 35 equations solved to give the best-fit values of π_2^H, $\Sigma\beta_2^H$ and log L^{16}. The calculation is repeated, leaving out each equation in turn, so that 36 sets of best-fit values are obtained. An analysis of the 36 values of π_2^H, $\Sigma\beta_2^H$ and log L^{16} obtained in this way is given in Table 4. The s.d. values for each descriptor are very small indeed: 0.004 for π_2^H, 0.001 for $\Sigma\beta_2^H$ and 0.003 for log L^{16}. However, we do not feel that the present method of obtaining descriptors for solubility data will yield such small s.d. values in general. More likely possible errors are around 0.03 for π_2^H, $\Sigma\alpha_2^H$ and $\Sigma\beta_2^H$ and 0.02 for log L^{16} as found before[26] using a different source of experimental data, but essentially the same equations as listed in Table 2, together with equations for gas chromatographic retention data. If we simply sum the π_2^H and $\Sigma\beta_2^H$ values for benzene and styrene we can obtain a rough estimate of 1.17 and 0.30 for stilbene, so that our obtained values of 1.04 and 0.34 are in the expected range of values. We cannot sum styrene plus benzene to obtain log L^{16} for stilbene, because the number of atoms will not be correct. However, we have analysed three sets of gas-liquid chromatographic retention data,[43,44] and find a value of 7.574 ± 0.267, in agreement with the present value of 7.525 log units. An observed value for log *P* between water and wet octanol is 4.81,

Table 3 Statistics for the correlation equations in Table 2

Process	n	r	sd	F
A Water to solvent, eqn. (1)				
Hexane	173	0.9939	0.207	2721
Heptane	183	0.9923	0.254	2281
Octane	149	0.9922	0.205	1802
Nonane	64	0.9906	0.123	6418
Decane	62	0.9980	0.144	2790
Hexadecane	370	0.9982	0.124	20 236
2,2,4-Trimethylpentane	86	0.9986	0.090	5813
Cyclohexane	180	0.9968	0.131	5512
Tetrachloromethane	173	0.9982	0.119	15 658
Acetonitrile	59	0.9885	0.256	453
Benzene	213	0.9961	0.143	5317
Toluene	151	0.9968	0.130	4566
Chlorobenzene	94	0.9975	0.113	3457
Methanol dry	93	0.9940	0.156	1440
Ethanol dry	64	0.9952	0.173	1205
Octan-1-ol dry	99	0.9990	0.103	9536
2,2,2-Trifluoroethanol	26	0.9960	0.125	493
(Gas to water)	408	0.9976	0.151	16 810
B Gas to solvent, eqn. (2)				
Hexane	119	0.9982	0.102	15 683.3
Heptane	109	0.9986	0.088	19 486.7
Octane	105	0.9985	0.098	17 429.6
Nonane	55	0.9917	0.184	6310.5
Decane	60	0.9995	0.065	26 396.0
Hexadecane[a]	—	—	—	—
2,2,4-Trimethylpentane	84	0.9991	0.071	21 915
Cyclohexane	114	0.9978	0.115	12 839
Tetrachloromethane	173	0.9982	0.119	15 658
Acetonitrile	62	0.9952	0.199	1148
Benzene	175	0.9987	0.119	12 570
Toluene	121	0.9988	0.111	9968
Chlorobenzene	89	0.9988	0.103	9070
Methanol dry	93	0.9976	0.134	3680
Ethanol dry	74	0.9983	0.145	3534
Octan-1-ol dry	98	0.9975	0.135	3720
2,2,2-Trifluoroethanol	26	0.9981	0.116	1058
Water	392	0.9962	0.185	10 229

[a] The coefficients in Table 2 are defined as such.

Table 4 Statistical analysis of the determination of descriptors from *trans*-stilbene, using the 'leave-one-out' method

	Leave-one-out					
			95% CI		All data used	
Descriptor	Mean	sd	Lower	Upper	Mean[a]	Mean[b]
π_2^{H}	1.037	0.004	1.036	1.038	1.037	1.04
$\Sigma\beta_2^{H}$	0.343	0.001	0.342	0.344	0.343	0.34
Log L^{16}	7.523	0.003	7.524	7.523	7.526	7.525[c]

[a] Using all the 36 data points in Table 1, with no rounding-off; note that in all calculations R_2 was fixed at 1.45, Vx fixed at 1.5630, and $\Sigma\alpha_2^{H}$ was taken as zero. [b] Using all the 36 data points in Table 1, with values of π_2^{H} and $\Sigma\beta_2^{H}$ rounded-off to two decimal places. [c] This differs from 7.526 because when π_2^{H} and $\Sigma\beta_2^{H}$ are fixed at their rounded-off values, 7.525 leads to the minimum overall sd.

Table 5 Predicted values for some properties of *trans*-stilbene

Property	Prediction	Comment
Water–octanol partition	$\log P = 4.59$	Very lipophilic[a]
Water–chloroform partition	$\log P = 5.53$	Very lipophilic[b]
Aqueous narcosis	$\log (1/C) = 5.29$	Potent narcotic[c]
Blood–brain distribution	$\log \mathrm{BB} = 0.05$	Moderate distribution[d]
Gas–chloroform partition	$\log L = 8.54$	Vapour very soluble[e]
Gas–methanol partition	$\log L = 7.17$	Vapour very soluble[f]
Nasal pungency in humans	$\log \mathrm{NPT} = -0.66$	Very low NPT[g]
Eye irritation in humans	$\log \mathrm{EIT} = 0.31$	Very low EIT[h]

[a] Eqn. (1) from ref. 4. [b] Eqn. (1) from ref. 46. [c] Eqn. (1) from ref. 14 where C is the narcotic concentration in mol dm^{-3}; the minimum and maximum values of log(1/C) reported were 0.2 and 5.3 respectively. [d] Eqn. (1) from ref. 11 where BB = [conc in brain]/[conc in blood]; the minimum and maximum values reported were −1.5 and 1.1 respectively. [e] Eqn. (2) from ref. 46. [f] Eqn. (2) from ref. 47. [g] Eqn. (2) from ref. 20 where NPT is the nasal pungency threshold in ppm; the minimum and maximum values reported were 0.3 and 5.12 respectively but note that the smaller the value the more potent is the irritant. [h] Eqn. (2) from ref. 23 where EIT is the eye irritation threshold in ppm; the minimum and maximum values reported were 1.2 and 5.8 respectively but note that the smaller the value the more potent the irritant.

and a calculated value by the CLOGP programme of 4.43 is available.[45] Our descriptors lead to a value of 4.59, in very good agreement.

Our determined descriptors for *trans*-stilbene, $R_2 = 1.45$, $\pi_2^{H} = 1.04$, $\Sigma\alpha_2^{H} = 0$, $\Sigma\beta_2^{H} = 0.34$, $Vx = 1.5630$ and $\log L^{16} = 7.525$, show that this solute is very lipophilic. The large size will considerably aid partition from water into organic solvents, and the moderate dipolarity/polarisability and small hydrogen-bond propensity will counteract the size effect only to a small extent. Our solvation descriptors thus reveal quantitative chemical properties of *trans*-stilbene. They can also be used, through eqn. (1) and eqn. (2), to predict log P and log L values for many other water–solvent and gas–solvent partitions (*cf.* our estimation of log P for the water–wet octanol system, above) as well as to predict biological properties.

In Table 5 we give predicted values for *trans*-stilbene in a number of systems for which we have already published solvation equations, eqn. (1) and eqn. (2).[4,14,20,23,46,47] Values of log P for partition between water and organic solvents will always be very large because *trans*-stilbene is a very lipophilic compound, and hence our predicted log P value for the water–chloroform system is no less than 5.53 units. The high lipophilicity of *trans*-stilbene also leads to a very high narcotic activity in aqueous narcosis.[14] The size effect on blood–brain distribution is considerably less than in water–solvent partitions,[11] and *trans*-stilbene is predicted to be distributed into brain only moderately.

For partition from the gas phase to organic solvents, dipolarity/polarisability and hydrogen-bonding reinforce the size effect (the latter now expressed as log L^{16}). Not surprisingly, *trans*-stilbene vapour is predicted to be very soluble in chloroform[46] and methanol[47] solvents. Equations based on eqn. (2) have been published for the effects of vapours on nasal pungency thresholds (NPT)[20] and eye irritation thresholds (EIT)[23] in humans. In both cases the thresholds are predicted to be very low; that is *trans*-stilbene is potentially a strong irritant. However, the vapour pressure of solid *trans*-stilbene is so low, log P (ppm) = −1.20 at 298 K, that the predicted thresholds will not be reached at room temperature.

As well as comparing observed and calculated values of log P and log L, we can compare the observed and calculated solubilities directly because log C_S = (log P − 5.80). For the worst case of cyclohexane solvent, $\log P_{(\mathrm{obs})} = 4.90$ and $\log P_{(\mathrm{calc})} = 5.10$ which corresponds to observed and calculated values of log C_S of −0.90 and −0.70 respectively. In the best case of benzene solvent, the observed and calculated values of log C_S are −0.18 and −0.15, and for all 18 solvents the standard deviation in observed and calculated values is only 0.088 log units. Considering that no observed values of log C_S were omitted from analysis at all, such agreement suggests that we have to hand a completely new method for the correlation and prediction of the solubility of solids in nonaqueous solvents. We hope to report fully on this aspect later.

We have therefore been able to use an entirely new set of experimental observations, the solubility of a solid together with the saturated vapour pressure of the solid, to calculate descriptors in our LFER solvation equations, eqn. (1) and eqn. (2). These descriptors could then be used in solvation equations for completely different processes such as gas- and liquid-chromatography, or water–solvent partition in order to predict the behaviour of *trans*-stilbene or to analyse the interactions that take place between *trans*-stilbene and the phases involved. The present analysis of solubility data thus confirms and extends the generality of the solvation parameter model.

Acknowledgements

We are grateful to the European Commission for a studentship (to C. G.) Contract number: SMT4-CT96-2114 (DG12-RSMT).

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Paper 8/05769I