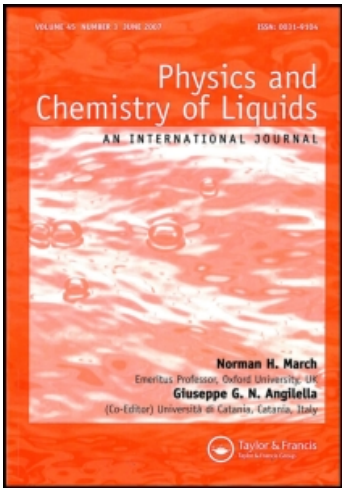

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Solubility of crystalline nonelectrolyte solutes in organic solvents: Mathematical correlation of ibuprofen solubilities with the Abraham solvation parameter model

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Solubility of crystalline nonelectrolyte solutes in organic solvents: Mathematical correlation of ibuprofen solubilities with the Abraham solvation parameter model

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The Abraham solvation parameter model is used to calculate the numerical values of the solute descriptors for ibuprofen from experimental solubilities in organic solvents. The mathematical correlations take the form of

$$\log(C_S/C_W) = c + e \cdot \mathbf{E} + s \cdot \mathbf{S} + a \cdot \mathbf{A} + b \cdot \mathbf{B} + v \cdot \mathbf{V}$$

$$\log(C_S/C_G) = c + e \cdot \mathbf{E} + s \cdot \mathbf{S} + a \cdot \mathbf{A} + b \cdot \mathbf{B} + l \cdot \mathbf{L}$$

where C_S and C_W refer to the solute solubility in the organic solvent and water, respectively, C_G is a gas phase concentration, **E** is the solute excess molar refraction, **V** is McGowan volume of the solute, **A** and **B** are measures of the solute hydrogen-bond acidity and hydrogen-bond basicity, **S** denotes the solute dipolarity/polarizability descriptor and **L** is the logarithm of the solute gas phase dimensionless Ostwald partition coefficient into hexadecane at 298 K. The remaining symbols in the above expressions are known solvent coefficients, which have been determined previously for a large number of gas/solvent and water/solvent systems. The Abraham solvation parameter model was found to describe the experimental solubility data of ibuprofen to within an overall standard deviation of 0.109 log units.

Keywords: Ibuprofen solubilities; Alcohol solvents; Partition coefficients; Molecular solute descriptors; Solubility predictions

1. Introduction

This work continues a systematic application of the Abraham solvation parameter model for describing the solubility behavior of both inert and self-associating solutes dissolved in neat organic solvents of varying hydrogen-bonding characteristics.

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Expressed in terms of molar solute solubilities, C_S, the basic model takes the following mathematical forms [1–13]:

$$\log(C_S/C_W) = c + e \cdot \mathbf{E} + s \cdot \mathbf{S} + a \cdot \mathbf{A} + b \cdot \mathbf{B} + v \cdot \mathbf{V} \quad (1)$$

$$\log(C_S/C_G) = c + e \cdot \mathbf{E} + s \cdot \mathbf{S} + a \cdot \mathbf{A} + b \cdot \mathbf{B} + l \cdot \mathbf{L} \quad (2)$$

depending upon whether one is describing transfer of the solute to the organic solvent from an aqueous solution, equation (1), or whether the process involves transfer from the gas phase, equation (2). In either case the mathematical description is a linear free energy relationship containing solute descriptors and process coefficients. The dependent variables in equations (1) and (2) are the experimental molar solubilities of the solute in the organic solvent, C_S, and in water, C_W, and the solute concentration in the gas phase, C_G, which is calculable from the saturated vapor pressure of the solid solute at 298.15 K.

The independent variables, or descriptors, are solute properties as follows: **E** and **S** refer to the excess molar refraction and dipolarity/polarizability of the solute, respectively, **A** and **B** denote the overall solute hydrogen-bond acidity and basicity, **V** is the McGowan volume of the solute and **L** is the logarithm of the solute gas hexadecane Ostwald partition coefficient at 298.15 K. The first four descriptors can be regarded as measures of the tendency of a solute to undergo various solute–solvent interactions, all of which are energetically favorable. The **L** and **V** descriptors are both measures of the size of the solute as well as measures of the cavity term that accommodates the solute, and of general solute–solvent dispersion interactions. The equation coefficients (c, e, s, a, b, v and l) depend upon the process or solvent system under consideration. In the case of solubility ratios and partition coefficients, where two solvent phases are involved, the equation coefficients represent differences in the solvent phase properties. A more detailed discussion of the basic model is published in a recent review article [14].

To date we have shown that the Abraham solvation parameter model provided a very good mathematical description of the solubility behavior of three pharmaceutically important non-steroidal anti-inflammatory drug (NSAID) molecules in organic solvents. The calculated solute descriptors of acetylsalicylic acid [8], naproxen [12] and ketoprofen [13] were found to describe the observed solute molar solubilities in organic solvents to within about 0.15 log units or less for most solute–solvent systems studied. In the present study we apply equations (1) and (2) to the NSAID molecule ibuprofen. Perlovich *et al.* [15] recently reported the solubility of ibuprofen in eight primary alcohols (methanol through 1-octanol), which can be used to calculate the molecular descriptors of this important drug molecule. While the published solubility is perhaps sufficient for this computation, we decided that a better value would be obtained by including additional experimental data for a few secondary and branched alcohols. For this reason, we measured the solubility of ibuprofen in 2-propanol, 2-butanol, 2-methyl-1-propanol, 1-decanol, methanol, ethanol, 1-propanol, 1-pentanol and 1-octanol. The latter five experimental measurements were performed to verify independently the published data of Perlovich *et al.* [15].

2. Materials and methods

Ibuprofen (Sigma-Adrich) was purchased from a commercial source and was dried for several hours at 60°C before use. The purity of the commercial sample was 99.7% (±0.3%), as determined by nonaqueous titration with freshly standardized sodium methoxide solution to the thymol blue endpoint according to the method of Fritz and Lisicki [16], except that toluene was substituted for benzene. Methanol (Aldrich, 99.8%, anhydrous), ethanol (Aaper Alcohol and Chemical Company, absolute), 1-propanol (Aldrich, 99 + %, anhydrous), 1-pentanol (Aldrich, 99 + %), 1-octanol (Aldrich, 99 + %, anhydrous), 2-propanol (Aldrich, 99 + %, anhydrous), 2-butanol (Aldrich, 99 + %, anhydrous), 2-methyl-1-propanol (Aldrich, 99 + %, anhydrous) and 1-decanol (Alfa Aesar, 99 + %) were stored over molecular sieves and distilled shortly before use. Gas chromatographic analysis showed solvent purities to be 99.7 mole percent or better.

Excess solute and solvent were placed in amber glass bottles and allowed to equilibrate in a constant temperature water bath at 25.0 ± 0.1°C for at least 24 h (often longer) with periodic agitation. After equilibration, the samples stood unagitated for several hours in the constant temperature bath to allow any finely dispersed solid particles to settle. Attainment of equilibrium was verified both by repetitive measurements the following day (or sometimes after two days) and by approaching equilibrium from supersaturation by pre-equilibrating the solutions at a slightly higher temperature. Aliquots of saturated ibuprofen solutions were transferred through a coarse filter into a tared volumetric flask to determine the amount of sample and diluted quantitatively with methanol for spectrophotometric analysis at 264 nm on a Bausch and Lomb Spectronic 2000. Concentrations of the dilute solutions were determined from a Beer–Lambert law absorbance *versus* concentration working curve.

Experimental molar concentrations were converted to (mass/mass) solubility fractions by multiplying by the molar mass of ibuprofen, volume(s) of volumetric flask(s) used and any dilutions required to place the measured absorbances on the Beer–Lambert law absorbance *versus* concentration working curve, and then dividing by the mass of the saturated solution analysed. Mole fraction solubilities were computed from solubility mass fractions using the molar masses of the solute and solvent. Experimental ibuprofen solubilities, X_S, in the organic solvents studied are listed in table 1. Numerical values represent the average of between four and eight independent determinations, and were reproducible to within ±2%. Published solubility data of Perlovich *et al.* [15] are reported in the last column of table 1. Examination of the numerical entries reveals that in four of five cases our observed mole fraction solubilities are within 2% of the literature values. The one noticeable exception is for 1-pentanol. Our experimental value of $X_S = 0.1833$ is considerably larger than the published literature value of $X_S = 0.148$. Differences in chemical purities and experimental methodologies can lead to differences of a few percent between values determined by two different research groups. In deciding which experimental value to use for the solubility of ibuprofen in 1-pentanol, we note that in the case of the smaller 1-alkanol solvents (methanol through 1-heptanol) the observed trend is for the measured mole fraction solubility to increase with increasing alkyl chain length. Our experimental value of $X_S = 0.1833$ fits the trend very nicely, whereas the much smaller value of Perlovich *et al.* [15] does not.

Table 1. Experimental ibuprofen mole fraction solubilities, X_S, in select organic solvents at 25°C.

Organic solvent	X_S (this work)	X_S (literature)
Methanol	0.06053	0.0601 [15]
Ethanol	0.08392	0.0833 [15]
1-Propanol	0.1417	0.142 [15]
1-Butanol	Not measured	0.162 [15]
1-Pentanol	0.1833	0.148 [15]
1-Octanol	0.1993	0.198 [15]
1-Decanol	0.2166	
2-Propanol	0.2334	
2-Butanol	0.2040	
2-Methyl-1-propanol	0.2011	

3. Results and discussion

The applicability of the Abraham solvation parameter model is relatively straightforward. The experimental mole fraction solubilities of ibuprofen are first converted into molar solubilities by dividing X_S, by the ideal molar volume of the saturated solution (i.e., $C_S \approx X_S/[X_S\ V_{Solute} + (1 - X_S)\ V_{Solvent}]$). A value of $V_{Solute} = 208.0\,cm^3\,mol^{-1}$ was used for the molar volume of hypothetical subcooled liquid ibuprofen. The logarithm of the solubility ratio, log (C_S/C_W), is calculated for each organic solvent for which we have process coefficients and experimental solubility data. For select solvents both "dry" and "wet" process coefficients have been reported. For solvents that are partially miscible with water, such as 1-butanol and ethyl acetate, the "wet" equation coefficients pertain to practical, direct partitioning studies where the solute is distributed between water (saturated with organic solvent) and organic solvent (saturated with water). In the case of solvents that are fully miscible with water, such as ethanol, only the "dry" equation coefficients have been reported. For solvents that are "almost completely immiscible" with water, such as alkanes, cyclohexane, dichloromethane and most aromatic solvents, the calculated solubility ratio, C_S/C_W, will be nearly identical to the observed partition coefficient determined from distribution studies. Table 2 gives the process coefficients for all of the solubility ratios, direct partition coefficients and chromatographic data that will be considered for both equations (1) and (2). The actual numerical values may differ slightly from values reported in earlier publications. Coefficients are periodically revised when additional experimental data become available. The molar solubility of ibuprofen in water, log $C_W = -3.76$ [17,18] (corrected for ionization) is used to calculate the solubility ratios, log (C_S/C_W), that are used in the solute molecular descriptor computation. Correction for ionization is necessary in solvents where appreciable ionization occurs. The quantity, C_W, refers to the solubility of the neutral form in water. Ionization is not a concern in the organic solvents that have dielectric constants much smaller than water.

For processes that involve solute transfer from the gas phase, the solid saturated vapor pressure at 298.15 K is needed to calculate the gas phase concentration, C_G. If one cannot find an experimental value for the solid solute at 298.15 K in the published literature, one can assume an estimated value in the preliminary calculations. The value can be adjusted if necessary in order to reduce the equation (2) deviations, and to make the equation (1) and equation (2) predictions internally consistent.

Table 2. Coefficients in equation (1) and equation (2) for various processes[a].

Process/solvent	*c*	*e*	*s*	*a*	*b*	v/*l*
A. Water to solvent: Equation (1)						
1-Octanol (wet)	0.088	0.562	−1.054	0.034	−3.460	3.814
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
1-Propanol (dry)	0.148	0.436	−1.098	0.389	−3.893	4.036
2-Propanol (dry)	0.063	0.320	−1.024	0.445	−3.824	4.067
1-Butanol (dry)	0.152	0.437	−1.175	0.098	−3.914	4.119
1-Pentanol (dry)	0.080	0.521	−1.294	0.208	−3.908	4.208
1-Hexanol (dry)	0.044	0.470	−1.153	0.083	−4.057	4.249
1-Heptanol (dry)	−0.026	0.491	−1.258	0.035	−4.155	4.415
1-Octanol (dry)	−0.034	0.490	−1.048	−0.028	−4.229	4.219
1-Decanol (dry)	−0.062	0.754	−1.461	0.063	−4.053	4.293
2-Butanol (dry)	0.106	0.272	−0.988	0.196	−3.805	4.110
2-Methyl-1-propanol (dry)	0.177	0.335	−1.099	0.069	−3.570	3.990
Chloroform	0.327	0.157	−0.391	−3.191	−3.437	4.191
1,2-Dichloroethane	0.227	0.278	−0.167	−2.816	−4.324	4.205
Cyclohexane	0.159	0.784	−1.678	−3.740	−4.929	4.577
Toluene	0.143	0.527	−0.720	−3.010	−4.824	4.545
HPLC-1	2.140	0.375	−1.028	−1.172	−2.932	3.305
HPLC-2	2.281	0.114	−0.573	−0.333	−2.223	2.593
HPLC-3	2.551	0.300	−0.911	−0.945	−1.096	2.042
HPLC-4	2.271	−0.118	−0.282	−1.003	−0.891	1.478
HPLC-5	2.666	0.681	−0.785	−1.635	−2.588	2.340
HPLC-6	−0.167	0.281	−0.486	0.173	−2.175	2.665
HPLC-7	0.113	0.328	−0.532	−0.062	−2.253	2.499
HPLC-C_{18}/TFE (gt_R)	1.430	0.430	−0.620	−0.750	−1.110	1.560
HPLC-Xter/TFE (gt_R)	1.260	0.470	−0.650	−0.810	−1.170	1.660
HPLC-C_{18}/MeOH (gt_R)	1.630	0.070	−0.260	−0.240	−1.260	1.450
HPLC-Xter/MeOH (gt_R)	1.470	0.110	−0.280	−0.280	−1.230	1.460
HPLC-C_{18}/ACN (gt_R)	1.700	0.080	−0.280	−0.420	−1.150	1.190
HPLC-Xter/ACN (gt_R)	1.490	0.180	−0.290	−0.440	−1.180	1.220
(Gas to water)	−0.994	0.577	2.549	3.813	4.841	−0.869
B. Gas to solvent: Equation (2)						
1-Octanol (wet)	−0.198	0.002	0.709	3.519	1.429	0.858
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
1-Propanol (dry)	−0.028	−0.185	0.648	4.022	1.043	0.869
2-Propanol (dry)	−0.060	−0.335	0.702	4.017	1.040	0.893
1-Butanol (dry)	−0.039	−0.276	0.539	3.781	0.995	0.934
1-Pentanol (dry)	−0.042	−0.277	0.526	3.779	0.983	0.932
1-Hexanol (dry)	−0.035	−0.298	0.626	3.726	0.729	0.936
1-Heptanol (dry)	−0.062	−0.168	0.429	3.541	1.181	0.927
1-Octanol (dry)	−0.119	−0.203	0.560	3.576	0.702	0.940
1-Decanol (dry)	−0.136	−0.038	0.325	3.674	0.767	0.947
2-Butanol (dry)	−0.013	−0.456	0.780	3.753	1.064	0.906
2-Methyl-1-propanol (dry)	0.012	−0.407	0.670	3.645	1.283	0.895
Cyclohexane	0.163	−0.110	0.000	0.000	0.000	1.013
1,2-Dichloroethane	0.011	−0.150	1.436	0.649	0.736	0.936
Chloroform	0.116	−0.467	1.203	0.138	1.432	0.994
Toluene	0.121	−0.222	0.938	0.467	0.099	1.012
(Gas to water)	−1.271	0.822	2.743	3.904	4.814	−0.213

[a]The solvents denoted as "dry" are those for which partitions refer to transfer to the pure dry solvent. The other partitions are from water (more correctly water saturated with solvent) to the solvent saturated with water (see text).

Available practical partition coefficient data for ibuprofen were retrieved from the published literature [19–23], along with 13 sets of chromatographic retention data [24,25]. The experimental aqueous solubility measurement is included in the solute descriptor computation. The updated version of the correlation of Abraham and Le [18]

$$(\log C_W)/5 = 0.079 - 0.191\,\mathbf{E} + 0.064\,\mathbf{S} + 0.231\,\mathbf{A} + 0.651\,\mathbf{B} - 0.157\,\mathbf{A}\cdot\mathbf{B} - 0.666\,\mathbf{V} \quad (3)$$

was used for the aqueous solubility. The cross $\mathbf{A}\cdot\mathbf{B}$ term was added to the model to account for hydrogen-bond interactions between the acidic and basic sites in the pure liquid or solid solute. Such interactions are not normally included in solubility ratio and partition coefficient correlations. In practical partitioning studies, the solute is generally at very low concentration and is surrounded by solvent molecules. In the case of solubility ratios the same equilibrium solid phase must be present for both C_S and C_W measurements. This allows contributions from breaking of crystal forces to cancel in the calculation of the solubility ratio. There is some disagreement in the published literature [26–31] concerning whether or not ibuprofen exhibits crystalline polymorphism, which would violate one of the requirements of using solubility ratios for the measured solute property. To address this concern we isolated and dried the equilibrium solid phase present in each saturated solution after performing the solubility measurements. A saturated solution of the solute in water was also prepared. Melting point temperatures of all isolated solid phases were identical to within ±1°C.

Combining all of the available experimental data we are able to construct a total of 50 equations based on the Abraham solvation parameter model. The characteristic McGowan volume of ibuprofen ($\mathbf{V} = 1.7771$) is calculated from the individual atomic sizes and number of bonds in each molecule [32]. The excess molar refraction of the solute is estimated as $\mathbf{E} = 0.730$. The set of 50 equations was then solved, using Microsoft "Solver", to yield the numerical values of the remaining solute descriptors that best described the combined equation (1) and equation (2) experimental data. The log C_G value was also calculated to give an internally consistent set of equation (1) and equation (2) values. The final set of molecular descriptors were $\mathbf{S} = 0.695$, $\mathbf{A} = 0.565$, $\mathbf{B} = 0.790$ and $\mathbf{L} = 7.184$; and the vapor phase concentration was log $C_G = -9.460$. Molecular descriptors reproduce the experimental equation (1) and equation (2) values for ibuprofen to within an overall standard deviation of 0.109 log units and 0.114 log units, respectively, as shown in table 3. Statistical information for equation (3) is included in the equation (1) statistical results. Statistically there is no difference between the set of 32 equation (1) values and the total set of 50 equation (1) and equation (2) values, thus suggesting that the value of log $C_G = -9.460$ is a feasible value for ibuprofen. Whether or not the assumed value is in accord with future vapor pressures, we can regard our value of log C_G simply as a constant that leads to calculations and predictions via equation (2). The Abraham solvation parameter provides a quantitative connection between solubility in nonaqueous solvents and chromatographic retention data (both gas–liquid chromatographic, glc, and high-performance liquid chromatographic, hplc, data). There is no model, to our knowledge, that includes such diverse systems. In the present study a single set of molecular descriptors was used to describe 50 measured values.

Table 3. Comparison between observed and back-calculated partitions and molar solubilities of ibuprofen based upon equations (1) and (2) and calculated molecular solute descriptors.[a]

		Equation (1)			Equation (2)		
Solvent	$\log C_S^{exp}$	$\log P^{exp,b}$	$\log P^{calc,b}$	$\log C_S^{calc}$	$\log L^{exp,c}$	$\log L^{calc,c}$	$\log C_S^{calc}$
1-Octanol (wet)		3.970[d]	3.829		9.670[d]	9.576	
Chloroform		3.025	3.100		8.725	8.961	
1,2-Dichloroethane		2.870	2.779		8.570	8.571	
Cyclohexane		1.877	1.692		7.577	7.360	
Toluene		2.484	2.592		8.184	8.222	
Methanol (dry)	0.070	3.830	3.689	−0.071	9.530	9.400	−0.060
Ethanol (dry)	0.070	3.830	4.045	0.285	9.530	9.626	0.166
1-Propanol (dry)	0.180	3.940	4.019	0.259	9.640	9.625	0.165
2-Propanol (dry)	0.330	4.090	4.018	0.258	9.790	9.675	0.215
1-Butanol (dry)	0.160	3.920	3.936	0.176	9.620	9.769	0.309
1-Pentanol (dry)	0.160	3.920	4.068	0.308	9.620	9.727	0.267
1-Hexanol (dry)	0.190	3.950	3.978	0.218	9.650	9.587	0.127
1-Heptanol (dry)	0.160	3.920	4.040	0.280	9.620	9.706	0.246
1-Octanol (dry)	0.070	3.830	3.735	−0.025	9.530	9.441	−0.019
1-Decanol (dry)	0.045	3.805	3.935	0.175	9.505	9.546	0.086
2-Butanol (dry)	0.246	4.006	3.840	0.080	9.706	9.565	0.105
2-Methyl-1-propanol (dry)	0.239	3.999	3.966	0.206	9.699	9.682	0.222
HPLC-1 (CHI)		4.578	4.594				
HPLC-2 (CHI)		4.543	4.629				
HPLC-3 (CHI)		4.357	4.366				
HPLC-4 (CHI)		3.352	3.345				
HPLC-5 (CHI)		3.675	3.808				
HPLC-6 (CHI)		2.756	2.815				
HPLC-7 (CHI)		2.585	2.608				
HPLC-C_{18}/TFE (gt_R)		2.940	2.785				
HPLC-Xter/TFE (gt_R)		2.850	2.719				
HPLC- C_{18}/MeOH (gt_R)		3.020	2.946				
HPLC-Xter/MeOH (gt_R)		2.920	2.820				
HPLC- C_{18}/ACN (gt_R)		2.590	2.533				
HPLC-Xter/ACN (gt_R)		2.480	2.407				
Gas-to-Water		5.700	5.633		5.700	5.714	

[a]Numerical values of the descriptors used in these calculations are: $\mathbf{E} = 0.730$, $\mathbf{S} = 0.695$, $\mathbf{A} = 0.565$, $\mathbf{B} = 0.790$, $\mathbf{V} = 1.7771$ and $\mathbf{L} = 7.184$.
[b]P is defined as the solubility ratio in the case of the "dry", i.e., $P = C_S/C_W$, or the practical partition coefficient, or the chromatographic retention data.
[c]L is defined as the solubility in the organic solvent divided by the gas phase concentration, i.e., $L = C_S/C_G$.
[d]Bouchard *et al.* [22] reported a slightly smaller 1-octanol/water partition coefficient of $P = 3.87$. Replacement of $P = 3.97$ and $L = 9.67$ by the experimental values of Bouchard *et al.* ($P = 3.87$ and $L = 9.57$) has an insignificant effect on the numerical values of the calculated solute molecular descriptors.

Readers will note that while the Abraham solvation parameter model has been employed to describe mathematically the solubility of ibuprofen in organic solvents, the computational methodology can be applied to other molecules of interest. The computational methodology requires experimental solubility data of the solute molecule in water and in a dozen other solvents for which equation coefficients are known. The solute descriptors, after they have been calculated, can be used to predict the solute solubility in any of the organic solvents for which equation coefficients are known. To date we have derived equation coefficients for 40 or so dry organic solvents and have calculated molecular descriptors for over 3000 common organic and pharmaceutical compounds. In addition, the solvation descriptors can be estimated from the structure of a compound [33], thus increasing the number of compounds whose solubility ratios can be predicted.

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