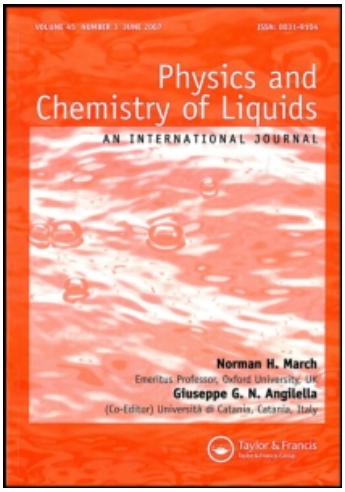

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MATHEMATICAL CORRELATION OF NAPROXEN SOLUBILITIES IN ORGANIC SOLVENTS WITH THE ABRAHAM SOLVATION PARAMETER MODEL

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The Abraham solvation parameter model is used to calculate the numerical values of the solute descriptors for naproxen from experimental solubilities in organic solvents. The solute descriptors are denoted as follows: **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, respectively, **S** is the solute dipolarity/polarizability descriptor and **L** is the logarithm of solute gas phase dimensionless Ostwald partition coefficient into hexadecane at 298 K. We estimate **E** as 1.510 and calculate **V** as 1.7821, and then solve a total of 40 equations to yield **S** = 2.022, **A** = 0.600, **B** = 0.673 and **L** = 9.207. These descriptors reproduce the observed log solubility ratios to within a standard deviation of only 0.073 log units.

Keywords: Naproxen solubilities; Alcohol solvents; Partition coefficients; Molecular solute descriptors

INTRODUCTION

Free energy of partition is an important thermodynamic variable that quantifies the Gibbs energy difference between a molecule in a given phase and the molecule dissolved in a second phase. Free energies of partition provide valuable information regarding molecular interactions between dissolved solute and surrounding solvent molecules, and can be used to calculate numerical values of partition coefficients that describe the equilibrium of a solute between two immiscible liquid phases. The partitioning process plays an important role in determining whether or not a given chemical is able to cross biological membranes. Mathematical correlations have been derived to

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describe the partitioning behavior of various chemicals between specific animal tissues and air (i.e., liver–air, kidney–air partition coefficients, etc.) based upon the substance's known organic solvent–air partition coefficients. Expressions can also be found in the environmental literature relating the partitioning behavior of known organic pollutants between the gas phase and a variety of natural substrates in soil, atmosphere and foliage to the pollutant's measured organic solvent–air partition coefficient. Experimental studies have further shown that the mass transfer coefficient of a solute across the interface of two immiscible liquid phases depends both upon the solute concentration in each phase and the partition coefficient.

The general solvation parameter model of Abraham [1–16] is one of the most useful approaches for the analysis and prediction of the free energies of partition. The basic model has been applied to numerous chemical and biological systems. For example, predictive equations exist for estimating the nonspecific aquatic toxicity of organic compounds to the fathead minnow (*Pimephales promelas*) [17]

$$-\log \mathrm{LC}_{50} = 0.99 + 0.24\,\mathbf{E} + 0.40\,\mathbf{A} - 3.65\,\mathbf{B} + 3.39\,\mathbf{V} \tag{1}$$

to the golden orfe (*Leuciscus idus melanotus*) [17]

$$-\log \mathrm{LC}_{50} = 0.15 + 1.40\,\mathbf{E} + 1.02\,\mathbf{A} - 2.17\,\mathbf{B} + 2.80\,\mathbf{V} \tag{2}$$

and to the guppy (*Poecilia reticulata*) [17]

$$-\log \mathrm{LC}_{50} = 0.71 + 0.60\,\mathbf{E} + 0.36\,\mathbf{A} - 3.15\,\mathbf{B} + 3.33\,\mathbf{V}, \tag{3}$$

where the subscript 2 denotes the solute. The dependent variable in Eqs. (1)–(3), $-\log \mathrm{LC}_{50}$, is the negative logarithm of the lethal molar concentration for killing one-half of that aquatic species after a 96-h exposure to that organic chemical. The independent variables, or descriptors, are solute properties as follows: **E** and **V** refer to the excess molar refraction and McGowan volume of the solute, respectively, and **A** and **B** are measures of the solute hydrogen-bond acidity and hydrogen-bond basicity, respectively. The solute descriptors are denoted using the simplified notation. The Abraham solute dipolarity/polarizability descriptor (denoted as **S**) and logarithm of the gas phase dimensionless Ostwald partition coefficient into hexadecane at 298 K (denoted as **L**) are not used in the above correlations. Similar equations have been developed for the immobilization of the water flea (*Daphnia magna*) [17] and for the inhibition of the bioluminescence in prokaryote (*Vibrio fischeri*; the acute Microtox test) [17]. The Abraham solvation parameter model has also been used to estimate the solubilities [11–16,18–20] and partition coefficients [4,7–10] of nonelectrolyte solutes dissolved in organic solvents, chromatographic retention times [1,21], rat blood–brain distribution, [22–24], permeation from water through human skin [24–26], nasal pungency threshold [27–29], eye irritation threshold [30,31], plant cuticle uptake [32] and human intestinal absorption [33,34]. Each estimate requires as input parameters the numerical values of the solute descriptors for the molecule under consideration.

Presently, we are in the process of developing/updating correlation equations for additional/existing solvent systems [7–10], and in developing new computational methodologies for calculating the solute descriptors from the available experimental data

and/or structural information [11–15]. Of particular interest are the carboxylic acid solutes that possess large numerical values of their hydrogen-bonding acidity descriptor. The existing values that we have for the molecular descriptors of many of the carboxylic acids were derived almost entirely from "practical" partitioning data. For some solutes, there was only very limited experimental data of marginal quality, and one or two incorrect data points could lead to the calculation of incorrect values for the molecular descriptors, as was the case in a recently completed solubility study involving acetylsalicylic acid [16]. For other carboxylic acid solutes there is insufficient experimental data to even calculate the solute descriptor values. For this reason solubilities of naproxen were measured in numerous organic solvents of varying polarity and hydrogen-bonding characteristics. Naproxen is expected to exist almost exclusively in monomeric form in each of the solvent studied. Results of these measurements, combined with published solubility and partition coefficient data, are used to calculate the solute descriptors for the Abraham solvation parameter model. Naproxen is a pharmaceutically important nonsteriodal antiinflammatory drug (NSAID) molecule. Once the solute descriptors are calculated, they can be used in the existing correlation equations to predict skin permeability and partition [24–26], rat blood–brain distribution [22–24] and human intestinal absorption [33,34].

MATERIALS AND METHODS

Naproxen was purchased from commercial source (TCI America, 99%) and was used as received. 1-Propanol (Aldrich, 99+%, anhydrous), 1-butanol (Aldrich, HPLC, 99.8+%), 1-pentanol (Aldrich, 99+%), 1-hexanol (Alfa Aesar, 99+%), 1-heptanol (Alfa Aesar, 99+%), 1-octanol (Aldrich, 99+%, anhydrous), 2-propanol (Aldrich, 99+%, anhydrous), 2-butanol (Aldrich, 99+%, anhydrous), 2-methyl-1-propanol (Aldrich, 99+%, anhydrous), 3-methyl-1-butanol (Aldrich, 99%, anhydrous), 1-decanol (Alfa Aesar, 99+%), 2-pentanol (Acros, 99+%), tetrahydrofuran (Aldrich, 99.9%, anhydrous), methyl acetate (Aldrich, 99.5%, anhydrous), butyl acetate (Aldrich, HPLC, 99.7%), diethyl ether (Aldrich, 99+%, anhydrous), diisopropyl ether (Aldrich, 99%, anhydrous), dibutyl ether (Aldrich, 99.3%, anhydrous) and 1,4-dioxane (Aldrich, 99.8%, anhydrous) 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 $25.0 \pm 0.1^{\circ}C$ 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 preequilibrating the solutions at a slightly higher temperature. Aliquots of saturated naproxen 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 320 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 for nine standard solutions. The standard solutions ranged in concentration from 2.18×10^{-4} to

TABLE I Experimental naproxen mole fraction solubilities, X_S, in selected organic solvents at 25°C

Organic solvent	X_S (*this work*)	X_S (*literature*)
1-Propanol	0.01302	0.0122 [35]
1-Butanol	0.01416	0.0139 [35]
1-Pentanol	0.01561	0.0147 [35]
1-Hexanol	0.01663	0.0166 [35]
1-Heptanol	0.01909	0.0201 [35]
1-Octanol	0.01604	0.0146 [35], 0.0166 [36]
1-Decanol	0.01630	
2-Propanol	0.01334	
2-Butanol	0.01418	
2-Methyl-1-propanol	0.00864	
3-Methyl-1-butanol	0.01204	
2-Pentanol	0.01504	
Diethyl ether	0.01984	
Diisopropyl ether	0.00585	
Dibutyl ether	0.00493	
1,4-Dioxane	0.10400	
Tetrahydrofuran	0.14180	
Methyl acetate	0.02746	
Butyl acetate	0.02342	

1.09×10^{-3} M. Identical absorbances were obtained for selected naproxen standard solutions that also contained up to 2 vol.% of the neat alcohol, ether and acetate solvents.

Experimental molar concentrations were converted to (mass/mass) solubility fractions by multiplying by the molar mass of naproxen, 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 analyzed. Mole fraction solubilities were computed from solubility mass fractions using the molar masses of the solute and solvent. Experimental naproxen solubilities, X_S, in the 19 organic solvents studied are listed in Table I. Numerical values represent the average between four and eight independent determinations, and were reproducible within ±1.5%. Published literature values [35,36] are reported in the last column of Table I. Examination of the numerical entries reveals that our observed mole fraction solubilities are within a few percent of the literature values. Slight differences in chemical purities and experimental methodologies can lead to differences of a few percent between values determined by two different research groups.

RESULTS AND DISCUSSION

The Abraham solvation parameter method relies on two linear free energy relationships, one for processes within condensed phases

$$SP = c + e \cdot \mathbf{E} + s \cdot \mathbf{S} + a \cdot \mathbf{A} + b \cdot \mathbf{B} + v \cdot \mathbf{V} \tag{4}$$

and the other for processes involving gas to condensed phase transfer

$$SP = c + e \cdot \mathbf{E} + s \cdot \mathbf{S} + a \cdot \mathbf{A} + b \cdot \mathbf{B} + 1 \cdot \mathbf{L}, \tag{5}$$

where *SP* denotes some property of a series of solutes in a fixed phase. The regression coefficients and constants (*c*, *e*, *s*, *a*, *b*, *v* and *l*) are obtained by the regression analysis of the experimental data for a specific process (i.e., a given partitioning process, a given stationary phase and mobile phase combination, etc.). In the case of partition coefficients, where two solvent phases are involved, the *c*, *e*, *s*, *a*, *b*, *v* and *l* coefficients represent differences in the solvent phase properties.

Equation (4) can predict partition coefficients, and for select solvents both ''dry'' and ''wet'' equation coefficients have been reported. For solvents that are partially miscible with water, such as 1-butanol and ethyl acetate, partition coefficients calculated as the ratio of the molar solute solubilities in the organic solvent and water are not the same as those obtained from direct partition between water (saturated with the organic solvent) and organic solvent (saturated with water). Care must be taken not to confuse the two sets of partitions. In the case of solvents that are fully miscible with water, such as methanol, no confusion is possible. Only one set of equation coefficients have been reported, and the calculated $\log P$ value 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 (see Eq. (6)) will be nearly identical to direct partition.

The predictive applicability of the Abraham solvation parameter model is relatively straightforward. We start with the set of equations that we have constructed for the partition of solutes between water and a given solvent. Table II gives the coefficients in Eq. (4) for the water–solvent partitions that is considered. The actual numerical values may differ slightly from the values reported in earlier publications. Coefficients are periodically revised when additional experimental data becomes available. Note that many of these are ''hypothetical partitions'' between pure water and the pure dry solvent; these are shown as ''dry'' in Table II. Although ''hypothetical,'' these partitions are very useful; as we show later, they can be used to predict solubilities (and activity coefficients) in the pure dry solvent. The partition coefficient of a solid between water and a solvent phase, *P*, is related to

$$SP = \log P = \log C_S - \log C_W \tag{6}$$

the molar solubility of the solid in water, C_W, and in the solvent, C_S. Hence, if C_W is known, predicted $\log P$ values based upon Eq. (4) will lead to predicted molar solubilities through Eq. (6). Three specific conditions must be met in order to use the Abraham solvation parameter model to predict the saturation solubilities. First, the same solid phase must be in equilibrium with the saturation solutions in the organic solvent and in water (i.e., there should be no solvate or hydrate formation). Second, the secondary medium activity coefficient of the solid in the saturated solutions must be unity (or near unity). This condition generally restricts the method to those solutes that are sparingly soluble in water and nonaqueous solvents. Finally, for solutes that are ionized in aqueous solution, C_W, refers to the solubility of the neutral form. For many carboxylic acids the correction should be fairly small, provided that the solute is not highly insoluble nor has a large acid dissociation constant. We use the solubility of naproxen in water, $\log C_W = -4.16$ [37] (corrected for ionization; other

TABLE II Coefficients in Eqs. (4) and (5) for various processes[a]

Process/solvent	*c*	*e*	*s*	*a*	*b*	*v/l*
(*A*) *Water-to-solvent: Eq.* (*4*)						
1-Octanol (wet)	0.088	0.562	−1.054	0.034	−3.460	3.814
Diethyl ether (dry)	0.330	0.401	−0.814	−0.457	−4.949	4.320
1,4-Dioxane (dry)	0.098	0.350	−0.083	−0.556	−4.826	4.172
Tetrahydrofuran (dry)	0.207	0.372	−0.392	−0.236	−4.934	4.447
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
Acetone (dry)	0.335	0.349	−0.231	−0.411	−4.793	3.963
Ethyl acetate (dry)	0.358	0.362	−0.449	−0.668	−5.016	4.155
HPLC-BK-20/10 (t'_R/10)	1.184	0.027	−0.148	−0.556	−0.839	1.098
HPLC-BK-40/10 (t'_R/10)	1.284	0.023	−0.381	−1.030	−1.734	2.417
(Gas-to-water)	−0.994	0.577	2.549	3.813	4.841	−0.869
(*B*) *Gas-to-solvent: Eq.* (*5*)						
1-Octanol (wet)	−0.198	0.002	0.709	3.519	1.429	0.858
Diethyl ether (dry)	0.288	−0.347	0.775	2.985	0.000	0.973
Tetrahydrofuran (dry)	0.189	−0.347	1.238	3.289	0.000	0.982
1,4-Dioxane (dry)	−0.034	−0.354	1.674	3.021	0.000	0.919
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
Acetone (dry)	0.154	−0.277	1.522	3.258	0.078	0.863
Ethyl acetate (dry)	0.203	−0.335	1.251	2.949	0.000	0.917
(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).

literature values include $\log C_W = -4.216$ [38], −4.20 [39,40]), to convert the predicted partition coefficients to saturation solubilities, which can then be compared to the experimentally determined values.

The second restriction may not be as important as initially believed. The Abraham solvation parameter model has shown remarkable success in correlating the solubility of several highly soluble crystalline solutes. For example, Eqs. (4) and (5) described the molar solubility of benzil in 24 organic solvents to within overall standard deviations of 0.124 and 0.109 log units, respectively. Standard deviations for acetylsalicylic acid dissolved in 13 alcohols, 4 ethers and ethyl acetate were 0.123 and 0.138 log units. Benzil [15] and acetylsalicylic acid [16] exhibited solubilities exceeding 1 M in several

of the organic solvents studied. In the case of acetylsalicylic acid it could be argued that the model's success relates back to when the equation coefficients were originally calculated for the dry solvents. The databases used in the regression analyses contained very few carboxylic acid solutes (benzoic acid, 2-hydroxybenzoic acid and 4-hydroxybenzoic acid). Most of the experimental data for carboxylic acids and other very acidic solutes was in the form of saturation solubilities, which were also in the 1–3 M range. Such arguments do not explain why Eqs. (4) and (5) described the measured benzil solubility data. The benzil solubilities were measured after most of the equation coefficients were determined.

For partition of solutes between the gas phase and solvents, Eq. (5) is used. (Equation coefficients are given elsewhere [18–20].) Predicted $\log L$ values can also be converted to saturation molar solubilities, provided that the solid saturated vapor pressure at 298.15 K, VP°, is available. VP° can be transformed into the gas phase concentration, C_G, and the gas–water and gas–solvent partitions, L_W and L_S, can be obtained through

$$SP = \log L_W = \log C_W - \log C_G \tag{7}$$

$$SP = \log L_S = \log C_S - \log C_G \tag{8}$$

Eqs. (7) and (8), respectively. As before, the computational method will be valid if conditions discussed above are met. If one cannot find an experimental vapor pressure for the 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 $\log L$ deviations, and to make the $\log P$ and $\log L$ predictions internally consistent.

To determine the solute descriptors for naproxen, we first convert the experimental mole fraction solubilities of naproxen into molar solubilities by dividing X_S, by the ideal molar volume of the saturated solution (i.e., $C_S \approx X_S/[X_S V_{solute} + (1 - X_S) \times V_{solvent}]$). A value of $V_{solute} = 198.70\,cm^3\,mol^{-1}$ was used for the molar volume of the hypothetical subcooled liquid naproxen. Dibutyl ether was excluded from the solubility analysis because we felt that dimerization of naproxen was inevitable in this larger ether solvent. Carboxylic acids are known to dimerize in saturated hydrocarbon and aromatic hydrocarbon solvents. It was noted, when the equation coefficients for dibutyl ether were calculated, that the derived equations did not describe the solubility behavior of several carboxylic acids (benzoic acid, 2-hydroxybenzoic acid, 4-hydroxybenzoic acid and 3-nitrobenzoic acid) [10]. The calculated $\log P$ values were always less than the observed $\log P$ values by the solubility method, as would be expected if dimerization did occur in dibutyl ether. Solubility measurements determine the total carboxylic acid concentration in the organic solvent, and unlike in the case of "practical" partition measurements, there is no convenient experimental means to correct the measured value for dimerization effects. Correlation equations for diethyl ether, tetrahydrofuran and 1,4-dioxane did describe the solubility behavior of benzoic acid, 2-hydroxybenzoic acid and 4-hydroxybenzoic acid [9]. The latter three ether solvents are included in the solubility analysis.

Available practical partition coefficient data for naproxen is then retrieved from the published literature [34,41], along with two sets of chromatographic retention data [42], experimental solubility data [35,36] for naproxen dissolved in methanol, ethanol,

ethyl acetate and acetone, and the experimental aqueous solubility measurement. The published extended correlation of Abraham and Le [40].

$$\left(\frac{\log C_W}{5}\right) = 0.104 - 0.201\,\mathbf{E} + 0.154\,\mathbf{S} + 0.434\,\mathbf{A} + 0.848\,\mathbf{B} - 0.672\,\mathbf{A}\cdot\mathbf{B} - 0.797\,\mathbf{V} \tag{9}$$

and its updated version (unpublished)

$$\left(\frac{\log C_W}{5}\right) = 0.079 - 0.191\,\mathbf{E} + 0.064\,\mathbf{S} + 0.231\,\mathbf{A} + 0.651\,\mathbf{B} - 0.157\,\mathbf{A}\cdot\mathbf{B} - 0.666\,\mathbf{V} \tag{10}$$

are used for the aqueous solubilities. 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 the partition coefficient correlations as the dissolved solute is surrounded by solvent molecules. In solubility determinations the equilibrium phase may be the pure crystalline solute, in which case, solute–solute interactions become significantly more important. Crystal lattice forces would have to be overcome in dissolving a crystalline material.

Combining the two sets of linear free energy relationships, we have a total of 40 equations for which partition data and equation coefficients are available. Not all of the solubility data can be used at the present time because we are missing equation coefficients for several of the organic solvents. The unused solubility data will be used in subsequent studies when we derive correlation equations for additional organic solvents. The characteristic McGowan volume of naproxen ($\mathbf{V} = 1.7821$) is calculated from the individual atomic sizes and number of bonds in the molecule [43] and $\mathbf{E}$ is estimated as 1.510. The set of 40 equations were then solved using Microsoft "Solver" to yield the values of the three unknown solute descriptors that best described the combined $\log P$ experimental partitioning data. The final set of molecular descriptors were: $\mathbf{S} = 2.022$, $\mathbf{A} = 0.600$, $\mathbf{B} = 0.673$ and $\mathbf{L} = 9.207$; and the vapor phase concentration was $\log C_G = -12.96$. The vapor phase concentration corresponds to a gas-to-water partition of $\log L_W = 8.80$, which is good agreement with the calculated values based upon Eqs. (4) and (5) (the last numerical entry in Table III). Equations (9) and (10) gave aqueous molar solubilities of $(\log C_W)/5 = -0.750$ and $(\log C_W)/5 = -0.754$, which are in good agreement with published experimental value of $(\log C_W)/5 = -0.832$ [37].

The final set of molecular descriptors reproduce the 40 experimental $\log P$ to within an overall standard deviation of 0.073 log units as shown in Table III. Individual standard deviations are 0.075 and 0.071 for the 22 calculated and observed $\log P$ values and 18 calculated and observed $\log L$ values, respectively. The aqueous solubility predictions are included in the $\log P$ statistical information. Statistically there is no difference between the set of 22 $\log P$ values and the total set of 40 $\log P$ and $\log L$ values, thus suggesting that the value of $\log C_G = -12.96$ is a feasible value for naproxen. Whether or not the assumed value is in accord with present or future experimental vapor pressures, we can regard our value of $\log C_G$ simply as a constant

TABLE III Comparison between observed and back-calculated partitions and molar solubilities of naproxen based upon Eqs. (4) and (5) and calculated molecular solute descriptors[a]

Solvent			*Eq. (4)*			*Eq. (5)*	
	$Log\ C_S$	$Log\ P^{exp}$	$Log\ P^{calc}$	$Log\ C_S^{calc}$	$Log\ L^{exp}$	$Log\ L^{calc}$	$Log\ C_S^{calc}$
1-Octanol (wet)		3.340	3.293		12.140	12.212	
Diethyl ether (dry)	−0.730	3.430	3.382	−0.778	12.230	12.080	−0.880
Tetrahydrofuran (dry)	0.200	4.360	4.437	0.277	13.160	13.183	0.223
1,4-Dioxane (dry)	0.030	4.190	4.311	0.151	12.990	13.090	0.130
Methanol (dry)	−0.691	3.469	3.448	−0.712	12.269	12.308	−0.652
Ethanol (dry)	−0.780	3.410	3.544	−0.616	12.210	12.213	−0.747
1-Propanol (dry)	−0.770	3.390	3.391	−0.769	12.190	12.119	−0.841
2-Propanol (dry)	−0.770	3.390	3.416	−0.744	12.190	12.186	−0.774
1-Butanol (dry)	−0.820	3.340	3.198	−0.962	12.140	12.176	−0.784
1-Pentanol (dry)	−0.848	3.312	3.243	−0.917	12.112	12.113	−0.847
1-Hexanol (dry)	−0.881	3.279	3.312	−0.848	12.079	12.125	−0.835
1-Heptanol (dry)	−0.875	3.285	3.263	−0.897	12.085	12.006	−0.954
1-Octanol (dry)	−0.996	3.164	3.241	−0.919	11.964	11.969	−0.991
1-Decanol (dry)	−1.070	3.090	3.082	−1.078	11.890	11.903	−1.057
2-Butanol (dry)	−0.820	3.340	3.399	−0.761	12.140	12.185	−0.775
2-Methyl-1-propanol (dry)	−1.030	3.130	3.209	−0.951	11.930	12.043	−0.919
Ethyl acetate (dry)	−0.460	3.700	3.623	−0.537	12.500	12.439	−0.521
Acetone (dry)	−0.077	4.083	3.984	−0.176	12.883	12.766	−0.194
HPLC-BK-20/10 ($t'_R/10$)		1.947	1.984				
HPLC-BK-40/10 ($t'_R/10$)		3.010	3.070				
Gas-to-water		8.800	9.031		8.800	9.140	

[a]Numerical values of the descriptors used in these calculations are: $\mathbf{E} = 1.510$, $\mathbf{S} = 2.022$, $\mathbf{A} = 0.600$, $\mathbf{B} = 0.673$, $\mathbf{V} = 1.7821$ and $\mathbf{L} = 9.207$.

that leads to calculations and predictions via Eq. (5). Our past experience in using different solution models has been that the better solution models will generally give back-calculated values that fall within 0.200 log units of the observed solute solubilities. The Abraham general solvation model meets this criterion.

Although our descriptors account very well for the experimental data on solubilities and partition coefficients, we have to address the question as to whether the descriptors are simply "fitting parameters" or whether they do indeed reflect the chemical properties of the solute concerned, that in the present case is naproxen. One way to do this evaluation is to estimate the descriptors of naproxen from the fragment groups that make up the molecule. For example, naproxen can be fragmented into the 2-methoxynaphthalene moiety (minus one of the aromatic ring hydrogen atoms) and the isobutanoic moiety (minus one of the CH3 hydrogen atoms). The known solute descriptors of 2-methoxynaphthalene and isobutanoic acid are tabulated in Table IV, along with the algebraic sum. We do not expect **S** and **B** to exactly equal the sum of the **S** and **B** descriptors of 2-methoxynaphthalene and isobutanoic acid, and so the found descriptors for naproxen are chemically reasonable. Once the descriptors are known, the values can be used to predict naproxen solubilities and partition coefficients in other solvent systems. The predicted partition coefficient for naproxen between 2-nitrophenyl octyl ether and water (unpublished correlation equation)

$$\log P = 0.117 + 0.595\,\mathbf{E} - 0.427\,\mathbf{S} - 2.207\,\mathbf{A} - 3.894\,\mathbf{B} + 3.552\,\mathbf{V} \qquad (11)$$

TABLE IV Solute descriptors for 2-methoxynaphthalene and isobutanoic acid

Solute	***E***	***S***	***A***	***B***
2-Methoxynaphthalene	1.39	1.13	0.00	0.35
Isobutanoic acid	0.20	0.60	0.61	0.45
Sum	1.59	1.73	0.61	0.80
Found for naproxen	1.51	2.02	0.60	0.67

is $\log P = 2.54$, which is in excellent agreement with the experimental value of $\log P = 2.51$ [44].

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