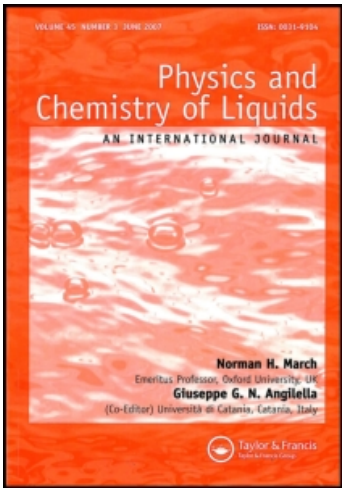

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Thermochemical behavior of dissolved Carboxylic Acid solutes: Part 2 - Mathematical Correlation of Ketoprofen Solubilities with the Abraham General Solvation Model

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THERMOCHEMICAL BEHAVIOR OF DISSOLVED CARBOXYLIC ACID SOLUTES: PART 2 – MATHEMATICAL CORRELATION OF KETOPROFEN SOLUBILITIES WITH THE ABRAHAM GENERAL SOLVATION MODEL

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

$$\log(C_S/C_W) = c + r \cdot R_2 + s \cdot \pi_2^H + \mathrm{a} \cdot \Sigma\alpha_2^H + \mathrm{b} \cdot \Sigma\beta_2^H + v \cdot V_x$$

$$\log(C_S/C_G) = c + r \cdot R_2 + s \cdot \pi_2^H + \mathrm{a} \cdot \Sigma\alpha_2^H + \mathrm{b} \cdot \Sigma\beta_2^H + l \cdot \log L^{(16)}$$

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, R_2 is the solute excess molar refraction, V_x is McGowan volume of the solute, $\Sigma\alpha_2^H$ and $\Sigma\beta_2^H$ are measures of the solute hydrogen-bond acidity and hydrogen-bond basicity, π_2^H denotes the solute dipolarity/polarizability descriptor and $L^{(16)}$ is 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. We estimate R_2 as 1.6500 and calculate V_x as 1.9779, and then solve a total of 19 equations to yield $\pi_2^H = 2.260$, $\Sigma\alpha_2^H = 0.550$ and $\Sigma\beta_2^H = 0.890$. These descriptors reproduce the 19 observed $\log(C_S/C_W)$ values with a standard deviation of only 0.123 log units. The $\log(C_S/C_G)$ correlation could not be used in the present study because of both lack of experimental vapor pressure data for ketoprofen at 298.15 K, and lack of the Ostwald partition coefficient for ketoprofen into hexadecane.

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

INTRODUCTION

Many diverse biological, toxicological and pharmacological processes are related to the differential solubility of solutes in aqueous and organic environments. A quantitative

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understanding of solute–solvent interactions is paramount to determining the biological profile of chemical compounds. Historically, many of the very early studies focused exclusively on developing correlational equations for predicting tissue/blood and organism toxicities based upon measured octanol/water partition coefficients. As additional experimental data became available, researchers expanded their studies to include more organic solvents, as well as aqueous micellar solvent media. In this regards, Abraham and coworkers [1–8] developed expressions for describing the partition of solutes between water and an organic solvent, and between the gas phase and a given solvent. The Abraham general solvation model is based upon two particular linear free energy relationships for describing the partition of solutes between water and a given solvent [1–8]

$$\log P = c + r \cdot R_2 + s \cdot \pi_2^H + a \cdot \Sigma\alpha_2^H + b \cdot \Sigma\beta_2^H + v \cdot V_x \tag{1}$$

and between the gas phase and a given solvent

$$\log L = c + r \cdot R_2 + s \cdot \pi_2^H + a \cdot \Sigma\alpha_2^H + b \cdot \Sigma\beta_2^H + l \cdot \log L^{(16)} \tag{2}$$

The dependent variables in Eqs. (1) and (2) are the log P (the partition coefficient of solute(s) between water and a given solvent) and log L (Ostwald solubility coefficient). The independent variables are the solute descriptors as follows: R_2 and V_x refer to the excess molar refraction and McGowan volume of the solute, respectively, $\Sigma\alpha_2^H$ and $\Sigma\beta_2^H$ are measures of the solute hydrogen-bond acidity and hydrogen-bond basicity, π_2^H denotes the solute dipolarity/polarizability descriptor and $L^{(16)}$ is the solute gas phase dimensionless Ostwald partition coefficient into hexadecane at 298 K. The Ostwald partition coefficient, L, is the inverse of the dimensionless Henry's law constant. For solutes that are reasonably volatile, $L^{(16)}$ can be determined experimentally by gas chromatography using a hexadecane stationary phase. The various process/solvent coefficients in Eqs. (1) and (2) (c, r, s, a, b, v and l) are calculated by multiple regression analysis. To date mathematical expressions have been deduced for approximately 40 or so dry solvents.

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 solute descriptors from available experimental solubility data and/or structural information [11–16]. Solubility measurements provide a very convenient means for including nonvolatile solutes in the regression analysis. Here, the partition coefficient is calculated as the ratio of the solute molar solubility in the organic solvent under consideration and water (or saturated vapor concentration in the case of the gas/liquid partition). Several of our preliminary unpublished correlation equations were derived from very limited experimental databases. As new experimental data becomes available existing correlation equations have been periodically updated, and existing values of the molecular solute descriptors have been refined by combining "practical" partitioning and saturation solubility data. Such analysis allows us to assess the internal consistency of large experimental databases and to identify possible outlier data points in need of re-measurement.

Of particular interest are the carboxylic acid solutes that possess large numerical values of their hydrogen-bonding acidity descriptors. The existing values that we have

for the molecular descriptors of many of the simple carboxylic acid solutes were derived almost entirely from "practical" partitioning data, with a few exceptions. Gas–liquid chromatographic data and water/solvent partition coefficients were used in a recent paper [16] to obtain descriptors of *n*-alkyl carboxylic acids from formic acid to *n*-tetracosanoic acid, and of seven branched chain alkyl carboxylic acids. For several carboxylic solutes, there was only very limited experimental partitioning data, 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 [17]. For the more structurally complex carboxylic acid solutes, there simply was not sufficient experimental partitioning data for even calculating a preliminary set of solute descriptors. Perlovich *et al.* [18] reported recently the solubility of ketoprofen in eight primary alcohol solvents (methanol through 1-octanol), which can be used to calculate the molecular solute descriptor values of this important nonsteriodal anti-inflammatory drug. While the published data is perhaps sufficient for this computation, we decided that a better value would perhaps be obtained by including an experimental data for other types of solvent molecules in the regression analysis. For this reason we have measured the solubility of ketoprofen in ethyl acetate, diethyl ether, 2-propanol, 2-methyl-1-propanol, 2-butanol, 1-decanol, methanol, ethanol, 1-propanol and 1-pentanol. The latter four experimental measurements were performed to verify independently the published data of Perlovich *et al.* [18]. Results of these measurements are interpreted using the Abraham general solvation equations.

MATERIALS AND METHODS

Ketoprofen was purchased from two commercial suppliers and was used as received. The purity of both commercial samples (Sigma and TCI America) was 99.7% ($\pm$0.4%), as determined by nonaqueous titration with freshly standardized sodium methoxide solution to the thymol blue endpoint according to the method of Fritz and Lisicki [19], except 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+ %), 2-propanol (Aldrich, 99+ %, anhydrous), 2-butanol (Aldrich, 99+ %, anhydrous), 2-methyl-1-propanol (Aldrich, 99+ %, anhydrous), 1-decanol (Alfa Aesar, 99+ %), ethyl acetate (Aldrich, HPLC, 99.9%) and diethyl ether (Aldrich, 99+ %, 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°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 ketoprofen 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 280 nm on a Bausch and Lomb Spectronic 2000. Concentrations of the dilute solutions were

TABLE I Experimental ketoprofen mole fraction solubilities, X_S, in select organic solvents at 25°C

Organic solvent	X_S (*this work*)	X_S (*literature*)
Methanol	0.0428	0.0396 [18]
Ethanol	0.0701	0.0640 [18]
1-Propanol	0.0848	0.0845 [18]
1-Pentanol	0.0776	0.0778 [18]
1-Decanol	0.0831	
2-Propanol	0.1269	
2-Butanol	0.1480	
2-Methyl-1-propanol	0.1009	
Ethyl acetate	0.1530	
Diethyl ether	0.1112	

determined from a Beer–Lambert law absorbance *versus* concentration working curve. The apparent molar absorptivities of the nine standard solutions varied systematically with molar concentration, and ranged from approximately $\varepsilon \approx 160$ to $155\,\mathrm{L\,mol^{-1}\,cm^{-1}}$ for ketoprofen concentrations from 1.57×10^{-3} to $7.87 \times 10^{-3}\,\mathrm{M}$. Identical molar absorptivities were obtained for select ketoprofen solutions that contained up to 2 vol% of the neat alcohol and ethyl acetate solvents.

Experimental molar concentrations were converted to (mass/mass) solubility fractions by multiplying by the molar mass of ketoprofen, 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 ketoprofen solubilities, X_S, in the 10 organic solvents studied are listed in Table I. Numerical values represent the average of between four and eight independent determinations, with the experimental reproducibility being ±1.5%. To within the stated experimental uncertainties, the mole fraction solubilities and calculated molar absorptivities were the same for both commercial samples of ketoprofen.

RESULTS AND DISCUSSION

Equation (1) actually predicts 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 has 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. (3)) will be nearly identical to direct partition.

TABLE II Coefficients in Eq. (1) for various processes[a]

Process/solvent	*c*	*r*	*s*	*a*	*b*	*v/l*
Water to solvent: Eq. (1)						
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	−4.959	4.320
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)	0.147	0.494	−1.195	0.495	−3.907	4.048
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	0.355	−1.099	0.069	−3.570	3.990
Ethyl acetate (dry)	0.358	0.362	−0.449	−0.668	−5.016	4.155
Chloroform	0.327	0.157	−0.391	−3.191	−3.437	4.191
2,2,4-Trimethylpentane	0.288	0.382	−1.668	−3.639	−5.000	4.561
Hexadecane	0.087	0.667	−1.617	−3.587	−4.869	4.433
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

[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).

The predictive applicability of the Abraham general solvation 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. (1) for the water–solvent partitions we shall consider. The actual numerical values may differ slightly from 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 is related to

$$P = C_S/C_W \quad \text{or} \quad \log P = \log C_S - \log C_W \tag{3}$$

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. (1) will lead to predicted molar solubilities through Eq. (3). Three specific conditions must be met in order to use the Abraham solvation model to predict 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 ketoprofen in water, $\log C_W = -3.16$ [20–22] (other literature values: $\log C = -3.29$ [23] and -3.25 [24], -3.33 [25], -3.43 [26]), to convert the predicted partition coefficients to saturation solubilities, which can then be compared to the experimentally determined values. Ionization is not a concern in the organic solvents that have dielectric constants much smaller than water.

The second restriction may not be as important as initially believed. The Abraham general solvation model has shown remarkable success in correlating the solubility of several very soluble crystalline solutes. For example, Eqs. (1) and (2) 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 [17] 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. (1) and (2) 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. (2) is used. (Equation coefficients for Eq. (2) are published in the chemical literature [11–15].) Predicted $\log L$ values can also be converted to saturation molar solubilities, provided that the solid saturated vapor pressure at 298.15 K, VP^{o}, is available. VP^{o} 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

$$L_W = C_W/C_G \quad \text{or} \quad \log L_W = \log C_W - \log C_G \tag{4}$$

$$L_S = C_S/C_G \quad \text{or} \quad \log L_S = \log C_S - \log C_G \tag{5}$$

Eqs. (4) and (5), respectively. As before, the computational method will be valid if conditions discussed above are met. We were unable to find experimental vapor pressure for ketoprofen at 298.15 K or a gas–liquid partition coefficient for ketoprofen in a hexadecane stationary phase in the published literature. The latter experimental value is needed to calculate the numerical value of $\log L^{(16)}$ needed in the Eq. (2) calculations. For the afore-mentioned reasons our determination of the numerical values of the solute descriptors of ketoprofen will be based entirely upon Eq. (1) and available solubility and "practical" partition coefficient data.

To determine the solute descriptors for ketoprofen, we first convert the experimental mole fraction solubilities of ketoprofen in chloroform [27], ethyl acetate, diethyl ether and the 12 alcohol solvents into molar solubilities by dividing X_S, by the ideal molar volume of the saturated solution (i.e., $C_S \approx X_S/[X_S V_{\text{Solute}} + (1 - X_S) V_{\text{Solvent}}]$). The

molar volume of the hypothetical subcooled liquid ketoprofen, $V = 185.75\,cm^3\,mol^{-1}$, was estimated as the molar volume of benzoic acid ($V_{Solute} = 104.4\,cm^3\,mol^{-1}$) + molar volume of benzil ($V_{Solute} = 183.0\,cm^3\,mol^{-1}$) – molar volume of benzaldehyde ($V_{Solute} = 101.65\,cm^3\,mol^{-1}$). Available practical partition coefficient data for ketoprofen is then retrieved from the published literature [28–30] for 1-octanol/water and 2,2,2-trimethylpentane/water systems, along with two sets of high-performance liquid chromatographic retention data [31]. This gives a total of 19 equations for ketoprofen for which partition data and equation coefficients are available. The characteristic McGowan volume of ketoprofen ($V_x = 1.9779$) is calculated from the individual atomic sizes and number of bonds in the molecule [32], and R_2 is estimated as 1.650. The set of 19 equations were then solved using Microsoft "Solver" to yield the values of the three unknown solute descriptors; $\pi_2^H = 2.260$, $\Sigma\alpha_2^H = 0.550$, $\Sigma\beta_2^H = 0.890$; that best described the experimental $\log P$ partitioning data. The molecular descriptors reproduce the 19 experimental $\log P$ values to within an overall standard deviation of 0.123 log units as shown in Table III. The molecular descriptors predict a hexadecane/water partition coefficient of $\log P = -0.005$, which is in excellent agreement with the value of $\log P = 0.000$ derived by Wohnsland and Faller [33] based upon membrane permeability measurements. The hexadecane/water partition was not included in the regression analysis because it is an indirect value. 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.

TABLE III Comparison between observed and back-calculated partitions and molar solubilities of ketoprofen based upon Eq. (1)

Solvent	$log\ C_S$	$log\ P^{exp}$	*Eq.* (1)	
			$log\ P^{calc}$,a	$log\ C_S^{calc}$,a
1-Octanol (wet)		3.120	3.116	
Trichloromethane		3.331	3.178	
2,2,4-Trimethylpentane		−0.310	−0.282	
HPLC BK-20/10 (t'_R/10)		1.898	2.013	
HPLC BK-40/10 (t'_R/10)		3.058	3.132	
Diethyl ether (dry)	−0.010	3.150	3.036	−0.124
Methanol (dry)	−0.040	3.120	3.280	0.120
Ethanol (dry)	0.016	3.176	3.343	0.183
1-Propanol (dry)	0.000	3.160	3.118	−0.042
2-Propanol (dry)	0.146	3.306	3.162	0.002
1-Butanol (dry)	−0.062	3.098	2.932	−0.228
1-Pentanol (dry)	−0.168	2.992	2.974	−0.186
1-Hexanol (dry)	−0.203	2.957	3.053	−0.107
1-Heptanol (dry)	−0.333	2.827	2.995	−0.165
1-Octanol (dry)	−0.366	2.794	2.972	−0.188
1-Decanol (dry)	−0.362	2.798	2.799	−0.361
2-Butanol (dry)	0.144	3.304	3.172	0.012
2-Methyl-1-propanol (dry)	−0.004	3.156	2.998	−0.162
Ethyl acetate (dry)	0.136	3.296	3.327	0.167
Hexadecane		0.000	−0.005[b]	

[a]Numerical values of the descriptors used in these calculations are: $R_2 = 1.650$, $\pi_2^H = 2.260$, $\Sigma\alpha_2^H = 0.550$, $\Sigma\beta_2^H = 0.890$ and $V_x = 1.9779$; [b]Value was derived from membrane permeability measurements, and was not included in the regression analysis for the molecular descriptor determination.

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