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Mathematical correlation of 1,2,4,5-tetramethylbenzene solubilities in organic solvents with the Abraham solvation parameter model

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The Abraham solvation parameter model is used to predict the experimental solubilities of 1,2,4,5-tetramethylbenzene in organic solvents, from the correlation equations, below, and already determined descriptors for 1,2,4,5-tetramethylbenzene. The mathematical correlations take the form of

$$\log(C_s/C_w) = c + e \cdot E + s \cdot S + a \cdot A + b \cdot B + v \cdot V$$

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

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 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 predict the experimental solubility data of 1,2,4,5-tetramethylbenzene to within an overall standard deviation of 0.15 log units.

Keywords: 1,2,4,5-Tetramethylbenzene solubilities; Alcohol solvents; Molecular solute descriptors; Solubility predictions

1. 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

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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 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 [1–8] is one of the most useful approaches for the analysis and prediction of free energies of partition in chemical and biochemical systems. The method relies on two linear free energy relationships, one for processes within condensed phases

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

and one for processes involving gas to condensed phase transfer

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

The dependent variable, $\log SP$, is some property of a series of solutes in a fixed phase. The independent variables, or descriptors, are solute properties as follows: \mathbf{E} and \mathbf{S} refer to the excess molar refraction and dipolarity/polarity descriptors of the solute, respectively, \mathbf{A} and \mathbf{B} are measures of the solute hydrogen-bond acidity and hydrogen-bond basicity, \mathbf{V} is the McGowan volume of the solute and \mathbf{L} is the solute gas phase dimensionless Ostwald partition coefficient into hexadecane at 298 K. The first four descriptors can be regarded as measures of the tendency of the given solute to undergo various solute–solvent interactions. The latter two descriptors, \mathbf{V} and \mathbf{L} , are both measures of solute size, and so will be measures of the solvent cavity term that will accommodate the dissolved solute. General dispersion interactions are also related to solute size, hence, both \mathbf{V} and \mathbf{L} will also describe the general solute–solvent interactions. The regression coefficients and constants (c , e , s , a , b , v and l) are obtained by regression analysis of 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.

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 data and/or structural information [11–15]. The existing values that we have for the

molecular descriptors of several crystalline organic compounds 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 crystalline solutes there is not sufficient experimental to even calculate the solute descriptor values. Of particular interest is verifying that the numerical values of the solute descriptors that we have for several organic compounds do indeed accurately predict/describe the compound's solubility and partitioning behavior.

For this reason solubilities of 1,2,4,5-tetramethylbenzene were measured in several alkane, alcohol, ether and alkanenitrile solvents of varying polarity and hydrogen-bonding characteristics. Results of these measurements are used to test the applications and limitations of equations (1) and (2) using the numerical values that we currently have for the solute descriptors of 1,2,4,5-tetramethylbenzene.

2. Materials and methods

1,2,4,5-Tetramethylbenzene (Aldrich, 99+%) was recrystallized twice from methanol. Hexane (Aldrich, 99%), heptane (Aldrich, 99%, anhydrous), octane (Aldrich, 99+%, anhydrous), decane (TCI, 99+%), hexadecane (Aldrich, 99%), cyclohexane (Aldrich, HPLC, 99.9+%), methylcyclohexane (Aldrich, 99+%, anhydrous), *tert*-butylcyclohexane (Aldrich, 99+%), isooctane (Aldrich, HPLC, 99.7%), ethanol (Aaper Alcohol and Chemical Company, absolute), methanol (Aldrich, 99.8%, anhydrous), 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), 2-methyl-2-propanol (Arco Chemical Company, 99+%), 3-methyl-1-butanol (Aldrich, 99%, anhydrous), 1-decanol (Alfa Aesar, 99+%), 4-methyl-2-pentanol (Acros, 99+%), 2-pentanol (Acros, 99+%), 2-ethyl-1-hexanol (Aldrich, 99%), diethyl ether (Aldrich, 99+%, anhydrous), dibutyl ether (Aldrich, 99.3%, anhydrous), ethylene glycol (Aldrich, 99.8%, anhydrous), acetonitrile (Aldrich, 99.8%, anhydrous), propionitrile (Aldrich, 99%) and butyronitrile (Aldrich, 99.7%, 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 $25.0 \pm 0.1^\circ\text{C}$ 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 1,2,4,5-tetramethylbenzene 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 275 nm on a Bausch and Lomb Spectronic 2000.

Table 1. Experimental 1,2,4,5-tetramethylbenzene mole fraction solubilities, X_s , in select organic solvents at 25°C.

| Organic solvent | X_s |
|-------------------------------|----------|
| Hexane | 0.2134 |
| Heptane | 0.2119 |
| Octane | 0.2131 |
| Decane | 0.2231 |
| Hexadecane | 0.2617 |
| Cyclohexane | 0.2046 |
| Methylcyclohexane | 0.2202 |
| Isooctane | 0.2032 |
| <i>tert</i> -Butylcyclohexane | 0.2296 |
| Methanol | 0.0108 |
| Ethanol | 0.0245 |
| 1-Propanol | 0.0374 |
| 1-Butanol | 0.0537 |
| 1-Pentanol | 0.0716 |
| 1-Hexanol | 0.0874 |
| 1-Heptanol | 0.1023 |
| 1-Octanol | 0.1197 |
| 1-Decanol | 0.1482 |
| 2-Propanol | 0.0349 |
| 2-Butanol | 0.0525 |
| 2-Methyl-1-propanol | 0.0437 |
| 2-Methyl-2-propanol | 0.0536 |
| 3-Methyl-1-butanol | 0.0620 |
| 2-Pentanol | 0.0698 |
| 4-Methyl-2-pentanol | 0.0802 |
| 2-Ethyl-1-hexanol | 0.1090 |
| Diethyl ether | 0.2138 |
| Dibutyl ether | 0.2393 |
| Ethylene glycol | 0.000754 |
| Acetonitrile | 0.0268 |
| Propionitrile | 0.0807 |
| Butyronitrile | 0.1324 |

Concentrations of the dilute solutions were determined from a Beer–Lambert law absorbance versus concentration working curve for nine standard solutions. The calculated molar absorptivity varied systematically with concentration, and ranged from approximately $\epsilon \approx 595 \text{ L mol}^{-1} \text{ cm}^{-1}$ to $\epsilon \approx 535 \text{ L mol}^{-1} \text{ cm}^{-1}$ for 1,2,4,5-tetramethylbenzene concentrations from 7.28×10^{-4} Molar to 3.28×10^{-3} Molar. Identical molar absorptivities were obtained for select 1,2,4,5-tetramethylbenzene solutions that contained up to 4 vol% of the neat alkane, alcohol, ether and alkanenitrile solvents.

Experimental molar concentrations were converted to (mass/mass) solubility fractions by multiplying by the molar mass of 1,2,4,5-tetramethylbenzene, 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 1,2,4,5-tetramethylbenzene solubilities, X_s , in the 32 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 $\pm 1.5\%$.

3. Results and discussion

Equation (1) 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 equation (3)) 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 2 gives the coefficients in equation (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 1. 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

$$SP = P = C_s/C_w \quad \text{or} \quad \log SP = \log P = \log C_s - \log C_w \quad (3)$$

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 equation (1) will lead to predicted molar solubilities through equation (3). The molar solubility of 1,2,4,5-tetramethylbenzene in water, $\log C_w = -4.59$ [17] is used to calculate the experimental solubility ratios, $\log(C_s/C_w)$, and to convert the predicted solubility ratios back to predicted molar solubilities.

Three specific conditions must be met in order to use the Abraham solvation parameter 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. 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 very soluble crystalline solutes. For example, equations (1) and (2) described

Table 2. Coefficients in equations (1) and (2) for various processes.^a

| Process/Solvent | c | r | s | a | b | v/l |
|--|--------|--------|--------|--------|--------|--------|
| <i>A. Water to solvent: Equation (1)</i> | | | | | | |
| 1-Octanol (wet) | 0.088 | 0.562 | -1.054 | 0.034 | -3.460 | 3.814 |
| 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 |
| 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 |
| Cyclohexane | 0.159 | 0.784 | -1.678 | -3.740 | -4.929 | 4.577 |
| Methylcyclohexane | 0.246 | 0.782 | -1.982 | -3.517 | -4.293 | 4.528 |
| Isooctane | 0.288 | 0.382 | -1.668 | -3.639 | -5.000 | 4.461 |
| Diethyl ether (dry) | 0.330 | 0.401 | -0.814 | -0.457 | -4.959 | 4.320 |
| Dibutyl ether (dry) | 0.203 | 0.369 | -0.954 | -1.488 | -5.426 | 4.508 |
| 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 |
| 2-Methyl-2-propanol (dry) | 0.197 | 0.136 | -0.916 | 0.318 | -4.031 | 4.113 |
| Ethylene glycol (dry) | -0.243 | 0.695 | -0.670 | 0.726 | -2.399 | 2.670 |
| Acetonitrile (dry) | 0.413 | 0.077 | 0.326 | -1.566 | -4.391 | 3.364 |
| (Gas to water) | -0.994 | 0.577 | 2.549 | 3.813 | 4.841 | -0.869 |
| <i>B. Gas to solvent: Equation (2)</i> | | | | | | |
| 1-Octanol (wet) | -0.198 | 0.002 | 0.709 | 3.519 | 1.429 | 0.858 |
| 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 |
| 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 |
| Cyclohexane | 0.163 | -0.110 | 0.000 | 0.000 | 0.000 | 1.013 |
| Methylcyclohexane | 0.318 | -0.215 | 0.000 | 0.000 | 0.000 | 1.012 |
| Isooctane | 0.275 | -0.244 | 0.000 | 0.000 | 0.000 | 0.972 |
| Diethyl ether (dry) | 0.288 | -0.347 | 0.775 | 2.985 | 0.000 | 0.973 |
| Dibutyl ether (dry) | 0.165 | -0.421 | 0.760 | 2.102 | -0.664 | 1.002 |
| 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 |
| 2-Methyl-2-propanol (dry) | 0.071 | -0.538 | 0.818 | 3.951 | 0.823 | 0.905 |
| Ethylene glycol (dry) | -0.876 | 0.278 | 1.431 | 4.584 | 2.525 | 0.558 |
| Acetonitrile (dry) | -0.007 | -0.595 | 2.461 | 2.085 | 0.418 | 0.738 |
| (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).

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 Molar 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 to 3 Molar range. Such arguments do not explain why equations (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, equation (2) is used. (Equation coefficients are given in table 2 for several organic solvents.) 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

$$SP = L_w = C_w/C_G \quad \text{or} \quad \log SP = \log L_w = \log C_w - \log C_G \quad (4)$$

$$SP = L_s = C_s/C_G \quad \text{or} \quad \log SP = \log L_s = \log C_s - \log C_G \quad (5)$$

equations (4) and (5), 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.

Descriptors for 1,2,4,5-tetramethylbenzene are already known, viz. $E=0.739$, $S=0.600$, $A=0.000$, $B=0.190$, $V=1.2800$ and $L=5.029$, so that combination of these descriptors with the coefficients in equations (1) and (2) allows the prediction of $\log(C_s/C_w)$ and $\log(C_s/C_G)$. The model predicts $\log(C_s/C_w)$ and $\log(C_s/C_G)$ values, which were then converted to molar solubilities using $\log C_w = -4.59$ and $\log C_G = -5.116$. Table 3 compares the observed 1,2,4,5-tetramethylbenzene molar solubilities, C_s^{exp} , to values predicted using the Abraham solvation parameter model. Thus the "predicted" values in the fifth and eighth columns of table 3 represent outright solubility predictions. None of the experimental data was used in the determination of the molecular solute descriptor values. For comparison purposes, all measured mole fraction solubilities of 1,2,4,5-tetramethylbenzene, X_s^{exp} , were converted into molar solubilities by dividing X_s^{exp} , by the ideal molar volume of the saturated solution (i.e., $C_s^{\text{exp}} \approx X_s^{\text{exp}}/[X_s^{\text{exp}}V_{\text{Solute}} + (1 - X_s^{\text{exp}})V_{\text{Solvent}}]$). The molar volume of the hypothetical subcooled liquid tetramethylbenzene, $V_{\text{Solute}} = 157.3 \text{ cm}^3 \text{ mol}^{-1}$, was estimated as $V_{\text{Solute}} = 2V_{\text{o-xylene}} - V_{\text{benzene}}$. Any errors resulting from our estimation of the tetramethylbenzene's hypothetical subcooled liquid molar volume, V_{Solute} , or the ideal molar volume approximation should have negligible effect of the calculated C_s^{exp} values. 1,2,4,5-Tetramethylbenzene is not too soluble in many of the solvents

Table 3. Comparison between observed and back-calculated partitions and molar solubilities of 1,2,4,5-tetramethylbenzene based upon equations (1) and (2) and existing values for molecular solute descriptors.^a

| Solvent | Equation (1) | | | | Equation (2) | | |
|---------------------------|--------------|-----------------------|------------------------|--------------------------|-----------------------|------------------------|--------------------------|
| | $\log C_s$ | $\log P^{\text{exp}}$ | $\log P^{\text{calc}}$ | $\log C_s^{\text{calc}}$ | $\log L^{\text{exp}}$ | $\log L^{\text{calc}}$ | $\log C_s^{\text{calc}}$ |
| 1-Octanol (wet) | – | 4.100 ^b | 4.095 | – | 4.626 | 4.815 | – |
| Hexane | 0.193 | 4.783 | 4.410 | –0.180 | 5.309 | 5.091 | –0.025 |
| Heptane | 0.151 | 4.741 | 4.499 | –0.091 | 5.267 | 5.099 | –0.017 |
| Octane | 0.119 | 4.709 | 4.540 | –0.050 | 5.235 | 5.042 | –0.074 |
| Decane | 0.076 | 4.666 | 4.452 | –0.138 | 5.192 | 5.024 | –0.092 |
| Hexadecane | 0.006 | 4.596 | 4.359 | –0.231 | 5.122 | 5.029 | –0.087 |
| Cyclohexane | 0.237 | 4.827 | 4.654 | 0.064 | 5.353 | 5.176 | 0.060 |
| Methylcyclohexane | 0.214 | 4.804 | 4.615 | 0.025 | 5.330 | 5.248 | 0.132 |
| Isooctane | 0.092 | 4.682 | 4.458 | –0.132 | 5.208 | 4.983 | –0.133 |
| Diethyl ether (dry) | 0.266 | 4.856 | 4.752 | 0.162 | 5.382 | 5.390 | 0.274 |
| Dibutyl ether (dry) | 0.156 | 4.746 | 4.643 | 0.053 | 5.272 | 5.223 | 0.107 |
| Methanol (dry) | –0.589 | 4.001 | 3.999 | –0.591 | 4.527 | 4.680 | –0.436 |
| Ethanol (dry) | –0.397 | 4.193 | 4.270 | –0.320 | 4.719 | 4.872 | –0.244 |
| 1-Propanol (dry) | –0.320 | 4.270 | 4.238 | –0.352 | 4.796 | 4.792 | –0.324 |
| 2-Propanol (dry) | –0.359 | 4.231 | 4.164 | –0.426 | 4.757 | 4.802 | –0.314 |
| 1-Butanol (dry) | –0.250 | 4.340 | 4.301 | –0.289 | 4.866 | 4.969 | –0.147 |
| 1-Pentanol (dry) | –0.195 | 4.395 | 4.332 | –0.258 | 4.921 | 4.943 | –0.173 |
| 1-Hexanol (dry) | –0.166 | 4.424 | 4.367 | –0.223 | 4.950 | 4.966 | –0.150 |
| 1-Heptanol (dry) | –0.147 | 4.443 | 4.444 | –0.146 | 4.969 | 4.958 | –0.158 |
| 1-Octanol (dry) | –0.121 | 4.469 | 4.296 | –0.294 | 4.995 | 4.922 | –0.194 |
| 1-Decanol (dry) | –0.100 | 4.490 | 4.344 | –0.246 | 5.016 | 4.939 | –0.177 |
| 2-Butanol (dry) | –0.261 | 4.329 | 4.252 | –0.338 | 4.855 | 4.876 | –0.240 |
| 2-Methyl-1-propanol (dry) | –0.340 | 4.250 | 4.194 | –0.396 | 4.776 | 4.858 | –0.258 |
| 2-Methyl-2-propanol (dry) | –0.261 | 4.329 | 4.245 | –0.345 | 4.855 | 4.872 | –0.244 |
| Ethylene glycol (dry) | –1.871 | 2.719 | 2.830 | –1.760 | 3.245 | 3.474 | –1.642 |
| Acetonitrile (dry) | –0.318 | 4.272 | 4.137 | –0.453 | 4.798 | 4.821 | –0.295 |
| Gas-to-water | – | 0.526 | 0.769 | – | 0.526 | 0.826 | – |

^a Numerical values of the descriptors used in these calculations are: $E=0.739$, $S=0.600$, $A=0.000$, $B=0.190$, $V=1.2800$ and $L=5.029$.

^b Experimental value is from Reference [18].

considered, and the $X_s^{\text{exp}}V_{\text{Solute}}$ term contributes very little to the molar volume of the saturated solution. The aqueous solubility prediction is included in the solubility computations. The published correlation of Abraham and Le [17]

$$(\log C_w)/5 = 0.104 - 0.2011E + 0.154S + 0.434A + 0.848B - 0.672A \cdot B - 0.797V \quad (6)$$

and its updated version (unpublished)

$$(\log C_w)/5 = 0.079 - 0.191E + 0.064S + 0.231A + 0.651B - 0.157A \cdot B - 0.666V \quad (7)$$

was used for the aqueous predictions. The cross $A \cdot B$ 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.

Examination of the numerical entries in table 3 reveals that equations (1) and (2) provided a very reasonable estimation of the solubility behavior of 1,2,4,5-tetramethylbenzene in acetonitrile, in two ether, in eight alkane and fourteen alcohol solvents. Overall standard deviations between predicted and observed values were 45 and 38% for equations (1) and (2), respectively. A predictive error of $\pm 50\%$ is acceptable for many design calculations encountered in the chemical and pharmaceutical industries. Expressed on a logarithmic molar scale basis, the Abraham solvation parameter model estimated the solubilities to within ± 0.16 and ± 0.14 log units, which is less than the standard deviation associated with the c, e, s, a, b, v and l coefficients for the individual organic solvent systems. Standard deviations for most of the individual solvent correlations fell in the range of ± 0.12 to ± 0.20 log units. Equations (6) and (7) gave aqueous molar solubility predictions of $(\log C_w)/5 = -0.812$ and $(\log C_w)/5 = -0.753$, which are in good agreement with the published experimental value of $(\log C_w)/5 = -0.918$ [17]. It was not possible to predict 1,2,4,5-tetramethylbenzene solubilities in all of the organic solvents studied because at present we have equation coefficients for only 50 or so different "dry" organic solvents. 1,2,4,5-Tetramethylbenzene solubilities were measured in solvents like propionitrile, butyronitrile, 2-pentanol, *tert*-butylcyclohexane and 3-methyl-1-butanol so that we would have more experimental data to use in subsequent studies to generate correlation equations for additional organic solvents. Based on our past experience using various solution models we have found that the better predictive equations estimate solubilities and infinite dilution activity coefficients to within ± 0.2 log units. The Abraham solvation parameter model meets this criterion.

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References

- [1] M.H. Abraham. *Chem. Soc. Rev.*, **23**, 73 (1993).
- [2] M.H. Abraham, G.S. Whiting, W.J. Shuely, R.M. Doherty. *Can. J. Chem.*, **76**, 703 (1998).
- [3] M.H. Abraham, G.S. Whiting, P.W. Carr, H. Ouyang. *J. Chem. Soc., Perkin Trans. 2*, 1385 (1998).
- [4] M.H. Abraham, J.A. Platts, A. Hersey, A.J. Leo, R.W. Taft. *J. Pharm. Sci.*, **88**, 670 (1999).
- [5] M.H. Abraham, J. Andonian-Haftvan, J.P. Osei-Owusu, P. Sakellariou, J.S. Urieta, M.C. Lopez, R. Fuchs. *J. Chem. Soc., Perkin Trans., 2*, 299 (1993).
- [6] M.H. Abraham, F. Martins, R.C. Mitchell, C.J. Salter. *J. Pharm. Sci.*, **88**, 241 (1999).
- [7] M.H. Abraham, J. Le, W.E. Acree Jr. *Collect. Czech. Chem. Commun.*, **64**, 1748 (1999).
- [8] M.H. Abraham, J. Le, W.E. Acree Jr, P.W. Carr. *J. Phys. Org. Chem.*, **12**, 675 (1999).
- [9] M.H. Abraham, A.M. Zissimos, W.E. Acree Jr. *New J. Chem.*, **27**, 1041 (2003).
- [10] M.H. Abraham, A.M. Zissimos, W.E. Acree Jr. *Phys. Chem. Phys. Chem.*, **3**, 3732 (2001).
- [11] M.H. Abraham, C.E. Green, W.E. Acree Jr. *J. Chem. Soc., Perkin Trans. 2*, 281 (2000).
- [12] M.H. Abraham, C.E. Green, W.E. Acree Jr, C.E. Hernandez, L.E. Roy. *J. Chem. Soc., Perkin Trans. 2*, 2677 (1998).

- [13] C.E. Green, M.H. Abraham, W.E. Acree Jr, K.M. De Fina, T.L. Sharp. *Pest Manag. Sci.*, **56**, 1043 (2000).
- [14] M.H. Abraham, N. Benjelloun-Dakhama, J.M.R. Gola, W.E. Acree Jr, W.S. Cain, J.E. Cometto-Muniz. *New J. Chem.*, **24**, 825 (2000).
- [15] W.E. Acree Jr, M.H. Abraham. *J. Solution Chem.*, **31**, 293 (2002).
- [16] A.K. Charlton, C.R. Daniels, W.E. Acree Jr, M.H. Abraham. *J. Solution Chem.*, **32**, 1087 (2003).
- [17] M.H. Abraham, J. Le. *J. Pharm. Sci.*, **88**, 868 (1999).
- [18] A.J. Leo. *The Medicinal Chemistry Project*, Pomona College, Claremont, CA 91711, USA (2002).