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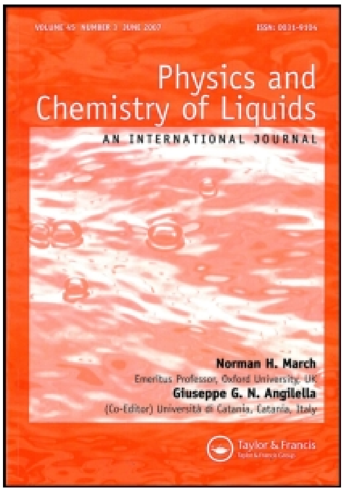

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Solubility of crystalline nonelectrolyte solutes in organic solvents: mathematical correlation of 4-chloro-3-nitrobenzoic acid and 2-chloro-5-nitrobenzoic acid solubilities with the Abraham solvation parameter model

Dawn M. Stovall[a]; Chelsea Givens[a]; Stephanie Keown[a]; Kaci R. Hoover[a]; Robin Barnes[a]; Cheridan Harris[a]; Jose Lozano[a]; Minh Nguyen[a]; Erick Rodriguez[a]; Jr William E. Acree[a]; Michael H. Abraham[b]
[a] Department of Chemistry, P. O. Box 305070, University of North Texas, Denton, TX 76203-5070, USA
[b] Department of Chemistry, University College London, London, WC1H 0AJ, UK

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Solubility of crystalline nonelectrolyte solutes in organic solvents: mathematical correlation of 4-chloro-3-nitrobenzoic acid and 2-chloro-5-nitrobenzoic acid solubilities with the Abraham solvation parameter model

DAWN M. STOVALL†, CHELSEA GIVENS†, STEPHANIE KEOWN†,
KACI R. HOOVER†, ROBIN BARNES†, CHERIDAN HARRIS†,
JOSE LOZANO†, MINH NGUYEN†, ERICK RODRIGUEZ†,
WILLIAM E. ACREE JR*† and MICHAEL H. ABRAHAM‡

†Department of Chemistry, P. O. Box 305070, University of North Texas,
Denton, TX 76203-5070, USA
‡Department of Chemistry, University College London,
20 Gordon Street, London, WC1H 0AJ, UK

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The Abraham solvation parameter model is used to calculate the numerical values of the solute descriptors for both 4-chloro-3-nitrobenzoic acid and 2-chloro-5-nitrobenzoic acid 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 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 4-chloro-3-nitrobenzoic acid and 2-chloro-5-nitrobenzoic to within overall standard deviations of 0.067 and 0.113 log units, respectively.

Keywords: 4-Chloro-3-nitrobenzoic acid solubilities; 2-Chloro-5-nitrobenzoic acid solubilities; Molecular solute descriptors; Solubility predictions

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*Corresponding author. Email: acree@unt.edu

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1. Introduction

Organic solvents are widely employed in many industrial applications, ranging from extraction, crystallization and cleaning/degreasing solvents, to solubilizing media for paint and pharmaceutical formulations. Due to increasing health and environmental awareness considerable effort has been directed in recent years to reducing (and preferably eliminating) harmful solvents from industrial processes. In some instances companies have found alternative technologies that do not utilize solvents. Unfortunately, solvent-free technologies generally require considerable redesign of manufacturing processes and major capital expenditures associated with new equipment purchases. Solvent substitution is more viable from an economical standpoint in that companies often are able to retain the existing process with very minor or even no modification. The key to the solvent substitution approach is finding a safe, suitable solvent having the desired physical, chemical and solubilizing properties.

The Abraham solvation parameter model provides a convenient method for estimating the solubilizing properties of a wide variety of organic solvents. The basic model relies on two linear free energy relationships, one for processes within condensed phases [1–10]

$$\mathrm{SP} = c + e \cdot \mathbf{E} + s \cdot \mathbf{S} + a \cdot \mathbf{A} + b \cdot \mathbf{B} + v \cdot \mathbf{V} \tag{1}$$

and one for processes involving gas to condensed phase transfer

$$\mathrm{SP} = c + e \cdot \mathbf{E} + s \cdot \mathbf{S} + a \cdot \mathbf{A} + b \cdot \mathbf{B} + l \cdot \mathbf{L} \tag{2}$$

The dependent variable in equations (1) and (2), SP, is some property of a series of solutes in a fixed phase. The independent variables, or descriptors, are solute properties described 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 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, and will be measures of the cavity term that will accommodate 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 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 [11].

To date we have shown that equations (1) and (2) satisfactorily correlate the observed solubility behavior of polycyclic aromatic hydrocarbons such as anthracene [12], pyrene [13], and fluoranthene [13], as well as the solubility behavior of benzil [14], ferrocene [15], buckminsterfullerene [16], diuron [17], monuron [17] and *trans*-stilbene [18] in a large number of organic solvents. Equations (1) and (2) have also been applied to the carboxylic acid solutes acetylsalicylic acid [19], 4-chlorobenzoic acid [20], 3-methylbenzoic acid [20], 4-nitrobenzoic acid [21] and 2-methylbenzoic acid [22]. Differences between the experimental and back-calculated SP values (SP calculated as the logarithm of the solute molar solubility in the organic solvent divided either by the solute molar solubility in water or by the solute gas phase concentration) were on the order of 0.12 log units or less for most of the fore-mentioned solutes. In the case of the five carboxylic acid solutes, the studies were limited to organic solvents in which the solute was believed to exist almost entirely in the undissociated monomeric form. Alkane and aromatic hydrocarbon solvents were excluded from the consideration, except in the case of a few published practical partition coefficients where the reported values had been corrected to account for dimerization effects. Carboxylic acids are known to dimerize in saturated hydrocarbons and in nonpolar aromatic hydrocarbons. Solute descriptors do depend upon the molecular structure, and the values for a carboxylic acid associated dimer would be different than those of the monomeric form.

Presently we are in the process of updating the numerical values of previously calculated molecular descriptors of phenols and carboxylic acid solutes so that the solutes can be used to develop correlation equations for additional partitioning processes. The calculated values that we have in our database for carboxylic acid solutes were derived almost entirely from "practical" partitioning data. For some of the carboxylic acid 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 [18]. In the present study we report the solubility of 4-chloro-3-nitrobenzoic acid and 2-chloro-5-nitrobenzoic acid in several alcohol, ether and alkylacetate solvents. Results of these measurements are interpreted using the Abraham solvation parameter model.

2. Materials and methods

4-Chloro-3-nitrobenzoic acid (Acros, 99.5%) and 2-chloro-5-nitrobenzoic acid (Acros, 99+%) were purchased from a commercial source and were used as received. The purity of the commercial samples was 99.8% (±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, [23] except that toluene was substituted for benzene. Ethanol (Aaper Alcohol and Chemical Company, absolute), 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+%), 2-pentanol (Acros, 99+%), 4-methyl-2-pentanol (Acros, 99+%), 2-methyl-1-pentanol (Aldrich, 99%), 2-ethyl-1-hexanol (Aldrich, 99%), 1,4-dioxane (Aldrich, 99.8%, anhydrous), tetrahydrofuran (Aldrich, 99.9%, anhydrous), methyl acetate (Aldrich, 99.5%, anhydrous), ethyl acetate (Aldrich, HPLC, 99.9%), propyl acetate (Aldrich, 99.5%), methyl butyrate (Aldrich, 99%), pentyl acetate (Aldrich, 99%), butyl acetate (Aldrich, HPLC, 99.7%), propylene carbonate (Aldrich, 99.7%, anhydrous), diethyl ether (Aldrich, 99+%, anhydrous), diisopropyl ether (Aldrich, 99%, anhydrous) and dibutyl ether (Aldrich, 99.3%, 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 ± 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 4-chloro-3-nitrobenzoic acid and 2-chloro-5-nitrobenzoic acid 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 on a Bausch and Lomb Spectronic 2000. Concentrations of the dilute solutions were determined from a Beer–Lambert law absorbance versus concentration working curve at either 292 nm (4-chloro-3-nitrobenzoic acid) or 280 nm (2-chloro-5-nitrobenzoic acid).

Experimental molar concentrations were converted to (mass/mass) solubility fractions by multiplying by the molar mass of carboxylic acid solute, 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 4-chloro-3-nitrobenzoic acid and 2-chloro-5-nitrobenzoic acid solubilities, X_S, in the organic solvents studied are listed in tables 1 and 2, respectively. Numerical values represent the average of between four and eight independent determinations, and were reproducible to within ±1.5%.

3. Results and discussion

Correlation of the measured solubility data using equations (1) and (2) is relatively straightforward. We start with the set of equations that have been constructed for the partition of solutes between water and a given solvent. Table 3 gives the coefficients in equation (1) for the condensed phase processes we shall consider. A more complete listing of equation coefficients is given elsewhere [11–17]. Note that in the case of the organic solvents, the process may pertain to either the "wet" practical partition of the solute between water (saturated with the organic solvent) and organic solvent (saturated with water) or to the hypothetical "dry" partition, which for a solid solute, is calculated as

$$\mathrm{SP} = \log P = \log C_S - \log C_W \tag{3}$$

the ratio of the molar solute solubility in the organic solvent, C_S, divided by the molar solute solubility in water, C_W . Hence if C_W is known, predicted SP values based upon equation (1) will lead to predicted molar solubilities through equation (3). For solutes that are ionized in aqueous solution, C_W refers to the solubility of the neutral form. The correction for ionization should be fairly small, provided that the carboxylic acid solute is not highly insoluble or has a large acid dissociation constant. We use the solubility of 4-chloro-3-nitrobenzoic acid in water, $\log C_W = -3.00$ [24] (corrected for ionization), and 2-chloro-5-nitrobenzoic acid, $\log C_W = -2.588$ (corrected for ionization, measured as part of the present study) to convert the predicted partition coefficients to saturation

Table 1. Experimental 4-chloro-3-nitrobenzoic acid mole fraction solubilities, X_S, in select organic solvents at 25°C.

Organic solvent	X_S
Ethanol	0.03348
1-Propanol	0.02812
1-Butanol	0.02874
1-Pentanol	0.03001
1-Hexanol	0.03320
1-Heptanol	0.03481
1-Octanol	0.03589
1-Decanol	0.03507
2-Propanol	0.03036
2-Butanol	0.02962
2-Methyl-1-propanol	0.01747
2-Methyl-2-propanol	0.03509
3-Methyl-1-butanol	0.02606
2-Pentanol	0.03290
2-Methyl-1-pentanol	0.02356
4-Methyl-2-pentanol	0.02890
2-Ethyl-1-hexanol	0.02399
Diethyl ether	0.02459
Diisopropyl ether	0.01289
Dibutyl ether	0.008711
Tetrahydrofuran	0.1710
1,4-Dioxane	0.1339
Methyl acetate	0.03520
Ethyl acetate	0.03534
Propyl acetate	0.02966
Butyl acetate	0.03029
Pentyl acetate	0.02420
Methyl butyrate	0.02410
Propylene carbonate	0.01343

Table 2. Experimental 2-chloro-5-nitrobenzoic acid mole fraction solubilities, X_S, in select organic solvents at 25°C.

Organic solvent	X_S
Ethanol	0.09140
1-Propanol	0.07550
1-Butanol	0.07350
1-Pentanol	0.08109
1-Hexanol	0.07980
1-Heptanol	0.07584
1-Octanol	0.07409
1-Decanol	0.07261
2-Propanol	0.09075
2-Butanol	0.08685
2-Methyl-1-propanol	0.05947
2-Methyl-2-propanol	0.1158
3-Methyl-1-butanol	0.07483
2-Pentanol	0.08349
Diethyl ether	0.05852
Diisopropyl ether	0.02621
Dibutyl ether	0.01630
Tetrahydrofuran	0.2744
Methyl acetate	0.07096
Ethyl acetate	0.07561
Propyl acetate	0.05988
Butyl acetate	0.06260

Table 3. Coefficients in equations (1) and (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
Diethyl ether (dry)	0.330	0.401	−0.814	−0.457	−4.949	4.320
Tetrahydrofuran (dry)	0.207	0.372	−0.392	−0.236	−4.934	4.447
1,4-Dioxane (dry)	0.098	0.350	−0.083	−0.556	−4.826	4.172
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
2-Methyl-2-propanol (dry)	0.197	0.136	−0.916	0.318	−4.031	4.113
Ethyl acetate (dry)	0.358	0.362	−0.449	−0.668	−5.016	4.155
(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
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
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
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).

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.

Equation (2) is used for processes involving gas phase transfers. Equation coefficients are given in table 3 for several organic solvents. Predicted SP 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 equations (4) and (5), respectively.

$$\mathrm{SP} = \log L_{\mathrm{W}} = \log C_{\mathrm{W}} - \log C_{\mathrm{G}} \tag{4}$$

$$\mathrm{SP} = \log L_{\mathrm{S}} = \log C_{\mathrm{S}} - \log C_{\mathrm{G}} \tag{5}$$

If one is unable to find an experimental vapor pressure for the given solute molecule, an estimated value can be used in the preliminary computations. The value can be adjusted then, if necessary, to reduce the $\log L$ deviations and to make the $\log P$ and $\log L$ predictions internally consistent.

To determine the solute descriptors for 4-chloro-3-nitrobenzoic acid and 2-chloro-5-nitrobenzoic acid, we first convert the experimental mole fractions in tables 1 and 2 into molar solubilities by dividing X_S by the ideal molar volume of the saturated solution (i.e., $C_S \approx X_S / [X_S \ V_{\mathrm{Solute}} + (1 - X_S) \ V_{\mathrm{Solvent}}]$). A value of $V_{\mathrm{Solute}} = 130.38\,\mathrm{cm^3\,mol^{-1}}$ was used for the molar volume of both hypothetical subcooled liquid solutes. Any errors resulting from the estimation of the hypothetical liquid molar volumes of the carboxylic acids, V_{Solute}, or from the ideal molar volume approximation should have only a very small effect on the calculated C_S values. 4-Chloro-3-nitrobenzoic acid and 2-chloro-5-nitrobenzoic are not overly soluble in many of the solvents considered, and the $X_S \, V_{\mathrm{Solute}}$ term contributes very little to the molar volume of the saturated solutions. Dibutyl ether was excluded from the solubility analysis because we felt that dimerization of carboxylic acids 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) [6]. 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, 1,4-dioxane and tetrahydrofuran did describe the solubility behavior of benzoic acid, 2-hydroxybenzoic acid and 4-hydroxybenzoic acid [4]. The latter three ether solvents are included in the solubility analysis.

Available practical partition coefficient data [25,26] and the aqueous solubility are retrieved from the chemical literature. The published correlation of Abraham and Le [27]

$$(\log C_{\mathrm{W}})/5 = 0.104 - 0.201\,\mathbf{E} + 0.154\,\mathbf{S} + 0.434\,\mathbf{A} + 0.848\,\mathbf{B} - 0.672\,\mathbf{A}\cdot\mathbf{B} - 0.797\,\mathbf{V} \tag{6}$$

and its updated version (unpublished)

$$(\log C_{\mathrm{W}})/5 = 0.079 - 0.191\,\mathbf{E} + 0.064\,\mathbf{S} + 0.231\,\mathbf{A} + 0.651\,\mathbf{B} - 0.157\,\mathbf{A}\cdot\mathbf{B} - 0.666\,\mathbf{V} \tag{7}$$

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 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 37 equations for 4-chloro-3-nitrobenzoic acid and a total of 35 equations for 2-chloro-5-nitrobenzoic acid for which partition data and equation coefficients are available. The McGowan volume of 4-chloro-3-nitrobenzoic acid ($\mathbf{V} = 1.2283$) and 2-chloro-5-nitrobenzoic acid ($\mathbf{V} = 1.2283$) is calculated from the individual atomic sizes and number of bonds in each molecule [28]. The excess molar refraction of both solutes is estimated as $\mathbf{E} = 1.250$. The sets of 37 and 35 equations were then solved, using Microsoft "Solver", to yield the numerical values of the remaining solute descriptors that best described the experimental $\log P$ and $\log L$ values. The two $\log C_G$ values were also calculated to give an internally consistent set of $\log P$ and $\log L$ values. The vapor concentration corresponds to a gas-to-liquid partition of $\log L_W = 7.21$ (4-chloro-3-nitrobenzoic acid) and $\log L_W = 6.95$ (2-chloro-5-nitrobenzoic acid), which are in good agreement with the calculated values based upon equations (1) and (2) (last numerical entries in tables 4 and 5). Equation (7) gave aqueous molar solubilities of $(\log C_W)/5 = -0.484$ (4-chloro-3-nitrobenzoic acid) and $(\log C_W)/5 = -0.482$ (2-chloro-5-nitrobenzoic acid), which are in good agreement with the measured values of $(\log C_W)/5 = -0.600$ (4-chloro-3-nitrobenzoic acid) and $(\log C_W)/5 = -0.518$ (2-chloro-5-nitrobenzoic acid). Numerical values of the solute descriptors are given in table 6. Molecular descriptors reproduce the experimental $\log P$ and $\log L$ values for 4-chloro-3-nitrobenzoic acid and 2-chloro-5-nitrobenzoic acid to within an overall standard deviation of 0.067 and 0.113 log units, respectively, as shown in tables 4–6. The aqueous solubility predictions are included in the $\log P$ statistical information. Based on our past experience with the Abraham solvation parameter model, we expect that one could use the molecular descriptors in table 6 to predict solubility and "practical" organic solvent/water partition coefficients

Table 4. Comparison between observed and back-calculated partitions and molar solubilities of 4-chloro-3-nitrobenzoic acid based upon equations (1) and (2) and calculated molecular solute descriptors.[a]

			Equation (1)			Equation (2)	
Solvent	$\log C_S$	$\log P^{exp}$	$\log P^{calc}$	$\log C_S^{calc}$	$\log L^{exp}$	$\log L^{calc}$	$\log C_S^{calc}$
1-Octanol (wet)		2.385	2.427		9.595	9.674	
Diethyl ether (dry)	−0.632	2.368	2.430	−0.570	9.578	9.587	−0.623
Tetrahydrofuran (dry)	0.280	3.280	3.222	0.220	10.490	10.442	0.232
1,4-Dioxane (dry)	0.165	3.165	3.025	0.025	10.375	10.242	0.032
Ethanol (dry)	−0.290	2.710	2.661	−0.339	9.920	9.738	−0.472
1-Propanol (dry)	−0.433	2.567	2.596	−0.404	9.777	9.777	−0.433
2-Propanol (dry)	−0.413	2.587	2.610	−0.390	9.797	9.780	−0.430
1-Butanol (dry)	−0.510	2.490	2.375	−0.625	9.700	9.740	−0.470
1-Pentanol (dry)	−0.561	2.439	2.424	−0.576	9.649	9.693	−0.517
1-Hexanol (dry)	−0.577	2.423	2.429	−0.571	9.633	9.699	−0.511
1-Heptanol (dry)	−0.609	2.391	2.358	−0.642	9.601	9.554	−0.656
1-Octanol (dry)	−0.642	2.358	2.340	−0.660	9.568	9.539	−0.671
1-Decanol (dry)	−0.733	2.267	2.267	−0.733	9.477	9.534	−0.676
2-Butanol (dry)	−0.499	2.501	2.478	−0.522	9.711	9.701	−0.510
2-Methyl-1-propanol (dry)	−0.728	2.272	2.359	−0.641	9.482	9.587	−0.623
2-Methyl-2-propanol (dry)	−0.435	2.565	2.520	−0.480	9.775	9.779	−0.431
Ethyl acetate (dry)	−0.450	2.550	2.579	−0.421	9.760	9.818	−0.392
Gas-to-water		7.210	7.206		7.210	7.216	

[a] Numerical values of the descriptors used in these calculations are: $\mathbf{E} = 1.250$, $\mathbf{S} = 1.470$, $\mathbf{A} = 0.700$, $\mathbf{B} = 0.440$, $\mathbf{V} = 1.2283$ and $\mathbf{L} = 6.685$.

Table 5. Comparison between observed and back-calculated partitions and molar solubilities of 2-chloro-5-nitrobenzoic acid based upon equations (1) and (2) and calculated molecular solute descriptors.[a]

			Equation (1)			Equation (2)	
Solvent	$\log C_S$	$\log P^{\mathrm{exp}}$	$\log P^{\mathrm{calc}}$	$\log C_S^{\mathrm{calc}}$	$\log L^{\mathrm{exp}}$	$\log L^{\mathrm{calc}}$	$\log C_S^{\mathrm{calc}}$
1-Octanol (wet)		2.130	2.431		9.080	9.400	
Diethyl ether (dry)	−0.171	2.417	2.401	−0.187	9.367	9.276	−0.262
Tetrahydrofuran (dry)	0.461	3.049	3.158	0.570	9.999	10.088	0.550
Ethanol (dry)	0.146	2.734	2.649	0.061	9.680	9.453	−0.085
1-Propanol (dry)	−0.022	2.566	2.583	−0.005	9.516	9.482	−0.056
2-Propanol (dry)	0.045	2.633	2.588	0.000	9.583	9.479	−0.059
1-Butanol (dry)	−0.111	2.477	2.376	−0.212	9.427	9.448	−0.090
1-Pentanol (dry)	−0.134	2.454	2.430	−0.158	9.404	9.402	−0.136
1-Hexanol (dry)	−0.198	2.390	2.426	−0.162	9.340	9.397	−0.141
1-Heptanol (dry)	−0.269	2.319	2.362	−0.226	9.269	9.282	−0.256
1-Octanol (dry)	−0.324	2.264	2.329	−0.259	9.214	9.245	−0.293
1-Decanol (dry)	−0.411	2.177	2.286	−0.302	9.127	9.254	−0.284
2-Butanol (dry)	−0.042	2.546	2.469	−0.119	9.496	9.404	−0.134
2-Methyl-1-propanol (dry)	−0.204	2.384	2.362	−0.226	9.334	9.303	−0.235
2-Methyl-2-propanol (dry)	0.070	2.658	2.494	−0.094	9.608	9.464	−0.074
Ethyl acetate (dry)	−0.126	2.462	2.531	−0.057	9.412	9.484	−0.054
Gas-to-water		6.950	7.010		6.950	7.040	

[a] Numerical values of the descriptors used in these calculations are: **E** = 1.250, **S** = 1.400, **A** = 0.670, **B** = 0.460, **V** = 1.2283 and **L** = 6.5131.

Table 6. Molecular descriptors and input properties for 4-chloro-3-nitrobenzoic acid and 2-chloro-5-nitrobenzoic acid.

Descriptor	4-Chloro-3-nitrobenzoic acid	2-Chloro-5-nitrobenzoic acid
Molecular descriptors		
E	1.250	1.250
S	1.470	1.400
A	0.700	0.670
B	0.440	0.460
V	1.2283	1.2283
L	6.6848	6.5131
Input properties		
$\log C_W$	−3.000	−2.588
$\log C_G$	−10.210	−9.538
Statistical information		
$\log P$ standard deviation	0.063	0.104
$\log L$ standard deviation	0.072	0.124

of the two carboxylic acids to within 0.20 log units for organic solvents in which carboxylic acid dimerization does not occur.

It should be noted that while the Abraham solvation parameter model has been employed to describe mathematically the solubility of 4-chloro-3-nitrobenzoic acid and 2-chloro-5-nitrobenzoic acid 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 (Pharma Algorithms, 2004 [29]), thus increasing the number of compounds whose log *P* and log *L* values can be predicted.

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