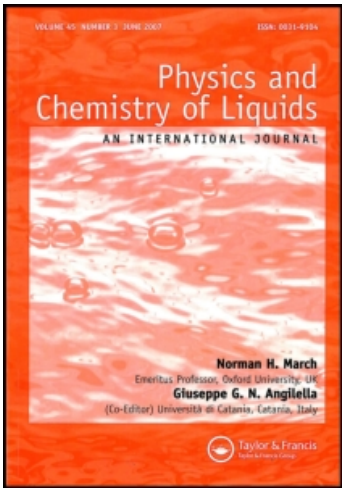

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Mathematical correlation of salicylamide solubilities in organic solvents with the Abraham solvation parameter model

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

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

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

where C_S and C_W refer to the solute solubility in the organic solvent and water, respectively, C_G is a gas phase concentration, **E** is the solute excess molar refraction, **V** is McGowan volume of the solute, **A** and **B** are measures of the solute hydrogen-bond acidity and hydrogen-bond basicity, **S** denotes the solute dipolarity/polarizability descriptor, and **L** is the logarithm of the solute gas phase dimensionless Ostwald partition coefficient into hexadecane at 298 K. The remaining symbols in the above expressions are known solvent coefficients, which have been determined previously for a large number of gas–solvent and water–solvent systems. The Abraham solvation parameter model was found to describe the available experimental solubility, partition coefficient, chromatographic retention and toxicity data of salicylamide within an overall SD of 0.091 log units.

Keywords: Salicylamide solubilities; Organic solvents; Partition coefficients; Molecular solute descriptors; Solubility predictions

1. Introduction

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

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biochemical systems. The method relies on two linear free energy relationships, one for processes within condensed phases

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

and one for processes involving gas to condensed phase transfer

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

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: **E** and **S** refer to the excess molar refraction and dipolarity/polarity descriptors of the solute, respectively, **A** and **B** are measures of the solute hydrogen-bond acidity and hydrogen-bond basicity, **V** is the McGowan volume of the solute and **L** is the logarithm of 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, **V** and **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 **V** and **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 [7–9] and for several biological processes [10,11], and in developing new computational methodologies for calculating solute descriptors from available experimental data and/or structural information [13–16]. 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 is 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. For other crystalline solutes, there is not sufficient experimental data to even calculate the solute descriptor values. Of particular interest are those solutes for which published biological and environmental data exist, but not calculated descriptors. For such solutes, we need to calculate the solute descriptors so that we can use the biological data in developing predictive correlations.

In the present study, solubilities of salicylamide were measured in several alcohol, ether and ester solvents of varying polarity and hydrogen-bonding characteristics. Solute descriptors are available for salicylamide; however, the numerical values were determined from practical partition coefficient data for only seven water-to-organic solvent systems. The additional solubility data provides the opportunity to test the predictive ability of the Abraham model by comparing the observed solubilities to calculated values based on our existing solute descriptors ($\mathbf{E} = 1.16$, $\mathbf{S} = 1.58$, $\mathbf{A} = 0.61$, $\mathbf{B} = 0.51$, $\mathbf{V} = 1.0315$, and $\mathbf{L} = 5.8176$). The calculated values represent outright predictions since none of the experimental solubility data was used in determining the solute descriptors. Once the predictive ability of the model was assessed, the

numerical values of the solute descriptors of salicylamide were updated based on the much larger dataset of practical partition coefficient data plus measured solubility data.

2. Materials and methods

Salicylamide (Aldrich, >99%) was used as received. 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%), 2-pentanol (Acros, >99%), 2-ethyl-1-hexanol (Aldrich, 99%), dibutyl ether (Aldrich, 99.3%, anhydrous), 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%) and butyl acetate (Aldrich, HPLC, 99.7%) were stored over molecular sieves and distilled shortly before use. Gas chromatographic analysis showed solvent purities to be 99.7 mol% 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 2 days) and by approaching equilibrium from supersaturation by pre-equilibrating the solutions at a slightly higher temperature. Aliquots of saturated salicylamide 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 300 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 calculated molar absorptivity varied systematically with concentration, and ranged from approximately $\varepsilon \approx 4100\,L\,mol^{-1}\,cm^{-1}$ to $\varepsilon \approx 3900\,L\,mol^{-1}\,cm^{-1}$ for salicylamide concentrations from $1.09 \times 10^{-4}\,M$ to $3.63 \times 10^{-4}\,M$. Identical molar absorptivities were obtained for select salicylamide solutions that contained up to 4 vol% of the neat alcohol, ester and ether solvents.

Experimental molar concentrations were converted to (mass/mass) solubility fractions by multiplying by the molar mass of salicylamide, 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 salicylamide solubilities, X_S, in the 23 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 ±1.5%. Published literature values are available for salicylamide dissolved in both methanol and ethyl acetate. Our measured values of $X_S = 0.04083$ (methanol) and $X_S = 0.07448$

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

Organic solvent	X_S
Methanol	0.04083
Ethanol	0.03847
1-Propanol	0.03307
1-Butanol	0.03037
1-Pentanol	0.03175
1-Hexanol	0.03270
1-Heptanol	0.03026
1-Octanol	0.02524
1-Decanol	0.02082
2-Propanol	0.03309
2-Butanol	0.03533
2-Methyl-1-propanol	0.02295
2-Methyl-2-propanol	0.02939
3-Methyl-1-butanol	0.02561
2-Pentanol	0.03336
2-Ethyl-1-hexanol	0.02409
Dibutyl ether	0.003961
1,4-Dioxane	0.1373
Tetrahydrofuran	0.1764
Methyl acetate	0.08377
Ethyl acetate	0.07448
Propyl acetate	0.06546
Butyl acetate	0.06075

(ethyl acetate) are in good agreement with the values reported by Nordström and Rasmuson [17], $X_S = 0.04060$ (methanol) and $X_S = 0.07549$ (ethyl acetate).

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

Table 2. 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
Oleyl alcohol (wet)	−0.359	−0.270	−0.528	−0.035	−4.042	4.204
Heptane	0.325	0.670	−2.061	−3.317	−4.733	4.543
Benzene	0.142	0.464	−0.588	−3.099	−4.625	4.491
Chloroform	0.327	0.157	−0.391	−3.191	−3.437	4.191
Diethyl ether (wet)	0.248	0.561	−1.016	−0.226	−4.553	4.075
Olive oil	−0.011	0.577	−0.800	1.470	−4.921	4.173
Dibutyl ether (dry)	0.203	0.369	−0.954	−1.488	−5.426	4.508
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
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
3-Methyl-1-butanol (dry)	0.123	0.370	−1.243	0.074	−3.781	4.208
2-Pentanol (dry)	0.115	0.455	−1.331	0.206	−3.745	4.201
Ethyl acetate (dry)	0.358	0.362	−0.449	−0.668	−5.016	4.155
Acetone (dry)	0.335	0.349	−0.231	−0.411	−4.793	3.963
Acetonitrile (dry)	0.413	0.077	0.326	−1.566	−4.391	3.364
Thin layer (RMw)	0.259	0.239	−0.662	−0.667	−3.006	3.603
Fathead minnow ($-\log LC_{50}$)	0.996	0.418	−0.182	0.417	−3.574	3.377
Tetrahymena pyriformis ($-\log IGC_{50}$)	0.616	0.413	−0.048	0.348	−2.707	2.944
RP-HPLC, MeCN (polarity value)	2.290	0.580	−1.240	−1.330	−3.090	3.320
RP-HPLC, MeOH (polarity value)	2.090	0.690	−1.530	−1.120	−3.010	3.750
(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
Heptane	0.275	−0.162	0.000	0.000	0.000	0.983
Benzene	0.107	−0.313	1.053	0.457	0.169	1.020
Chloroform	0.116	−0.467	1.203	0.138	1.432	0.994
Diethyl ether (wet)	0.206	−0.169	0.873	3.402	0.000	0.882
Dibutyl ether (dry)	0.165	−0.421	0.760	2.102	−0.664	1.002
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
2-Methyl-2-propanol (dry)	0.071	−0.538	0.818	3.951	0.823	0.905

(*Continued*)

Table 2. Continued.

Process/solvent	*c*	*e*	*s*	*a*	*b*	*v/l*
3-Methyl-1-butanol (dry)	−0.014	−0.341	0.525	3.666	1.096	0.925
2-Pentanol (dry)	−0.031	−0.325	0.496	3.792	1.024	0.934
Ethyl acetate (dry)	0.203	−0.335	1.251	2.949	0.000	0.917
Acetone (dry)	0.154	−0.277	1.522	3.258	0.078	0.863
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.

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 2. 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

$$\mathrm{SP} = P = \frac{C_S}{C_W} \quad \text{or} \quad \log \mathrm{SP} = \log P = \log C_S - \log C_W \tag{3}$$

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 equation (1) will lead to predicted molar solubilities through equation (3). The molar solubility of salicylamide in water, $\log C_W = -1.754$ [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.

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^0, is available. VP^0 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

$$\mathrm{SP} = L_W = \frac{C_W}{C_G} \quad \text{or} \quad \log \mathrm{SP} = \log L_W = \log C_W - \log C_G \tag{4}$$

$$\mathrm{SP} = L_S = \frac{C_S}{C_G} \quad \text{or} \quad \log \mathrm{SP} = \log L_S = \log C_S - \log C_G. \tag{5}$$

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

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

			Equation (1)			Equation (2)	
Solvent	$\log C_s^{exp}$	$\log P^{exp}$	$\log P^{calc}$	$\log C_s^{calc}$	$\log L^{exp}$	$\log L^{calc}$	$\log C_s^{calc}$
Dibutyl ether (dry)	−1.633	0.121	0.099	−1.655	7.725	7.650	−1.708
Tetrahydrofuran (dry)	0.288	2.042	1.946	0.192	9.646	9.462	0.104
1,4-Dioxane (dry)	0.171	1.925	1.876	0.122	9.529	9.389	0.031
Methanol (dry)	−0.035	1.719	1.559	−0.195	9.323	9.062	−0.296
Ethanol (dry)	−0.205	1.549	1.473	−0.281	9.153	8.868	−0.490
1-Propanol (dry)	−0.368	1.386	1.334	−0.420	8.990	8.822	−0.536
2-Propanol (dry)	−0.377	1.377	1.333	−0.421	8.981	8.836	−0.522
1-Butanol (dry)	−0.487	1.267	1.112	−0.642	8.871	8.743	−0.615
1-Pentanol (dry)	−0.537	1.217	1.114	−0.640	8.821	8.696	−0.662
1-Hexanol (dry)	−0.584	1.170	1.132	−0.622	8.774	8.698	−0.660
1-Heptanol (dry)	−0.670	1.084	1.012	−0.742	8.688	8.576	−0.782
1-Octanol (dry)	−0.796	0.958	1.057	−0.697	8.562	8.531	−0.827
1-Decanol (dry)	−0.961	0.793	0.904	−0.840	8.397	8.475	−0.883
2-Butanol (dry)	−0.425	1.329	1.279	−0.475	8.933	8.793	−0.565
2-Methyl-1-propanol (dry)	−0.611	1.143	1.166	−0.588	8.747	8.683	−0.675
2-Methyl-2-propanol (dry)	−0.512	1.242	1.287	−0.467	8.846	8.834	−0.524
3-Methyl-1-butanol (dry)	−0.635	1.119	1.046	−0.708	8.723	8.594	−0.764
2-Pentanol (dry)	−0.520	1.234	1.089	−0.665	8.838	8.643	−0.715
Ethyl acetate (dry)	−0.128	1.626	1.389	−0.365	9.230	8.925	−0.433
Acetone (dry)	0.199	1.953	1.768	0.014	9.557	9.285	−0.073
Acetonitrile (dry)	−0.223	1.531	1.293	−0.461	9.135	8.970	−0.388
Gas-to-water		7.604	7.601		7.604	7.614	

[a]Numerical values of the descriptors used in these calculations are: $\mathbf{E} = 1.160$, $\mathbf{S} = 1.580$, $\mathbf{A} = 0.610$, $\mathbf{B} = 0.510$, $\mathbf{V} = 1.0315$ and $\mathbf{L} = 5.8176$.

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 salicylamide are already known, namely, $\mathbf{E} = 1.16$, $\mathbf{S} = 1.58$, $\mathbf{A} = 0.61$, $\mathbf{B} = 0.51$, $\mathbf{V} = 1.0314$ and $\mathbf{L} = 5.8176$. The numerical values were calculated from measured octanol–water ($P = 1.28$ [18]), chloroform–water ($P = 0.54$ [19]), heptane–water ($P = -1.87$ [19]), benzene–water ($P = 0.050$ [19]), olive oil–water ($P = 0.40$ [19]) and oleyl alcohol–water ($P = 0.77$ [19]). Also available in our database is a numerical value of $\log L_W = 7.604$ that is needed to convert $\log P$ values to $\log L$ values. Combination of the solute 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 $\log C_W = -1.754$ and $\log L_W = 7.604$. The latter value corresponds to a molar gas phase concentration of $\log C_G = -9.358$. Table 3 compares the observed salicylamide molar solubilities, C_s^{exp}, to values predicted using the Abraham solvation parameter model. The "predicted" values in the fifth and eighth columns of table 3 represent outright solubility predictions. None of the experimental solubility data was used in the determination of the molecular solute descriptor values. For comparison purposes, all measured mole fraction solubilities of salicylamide, X_s^{exp}, were converted into molar solubilities by dividing X_s^{exp}, by the ideal molar volume of the saturated solution $\left(\text{i.e.,} C_s^{exp} \approx X_s^{exp}/[X_s^{exp} V_{Solute} + (1 - X_s^{exp}) V_{Solutet}]\right)$ A value of $V_{Solute} = 135\ cm^3\,mol^{-1}$

was used for the molar volume of the hypothetical subcooled liquid salicylamide. Any errors resulting from our estimation of the salicylamide's hyphothetical subcooled liquid molar volume, V_{Solute}, or the ideal molar volume approximation should have negligible effect on the calculated C_s^{exp} values. Salicylamide is not too soluble in many of the solvents considered, and the $X_s^{\text{exp}} V_{\text{Solute}}$ term contributes very little to the molar volumes of the saturated solutions. Also included in the comparison are solubility data reported by Nordström and Rasmuson [17] for salicylamide dissolved in acetone and acetonitrile. Examination of the numerical entries in table 3 reveals that equations (1) and (2) do provide a very reasonable estimation of the solubility behavior of salicylamide in the 21 solvents studied. Expressed on a logarithmic molar scale basis, the Abraham solvation parameter model estimated the solubilities to within ±0.12 (equation 1) and ±0.17 (equation 2) log units, which is less than the SD associated with the individual organic solvent system correlations.

It is possible to improve the descriptive ability of the model by recalculating the solute descriptors of salicylamide using all available experimental data. As noted previously, our existing values are based on practical partition coefficient data for eight water-to-organic solvent systems. Towards this goal, we have gathered together available partition coefficient [18,19] and chromatographic retention data [20,21], plus toxicity data in the form of the 96-hour median lethal molar concentration of salicylic towards the fathead minnow, $-\log \text{LC}_{50} = 3.13$ [22], and the 40-hour median inhibition grown molar concentration of salicylamide towards *T. pyriformis*, $-\log \text{IGC}_{50} = 2.76$ [23]. Included in the regression analysis is the aqueous molar solubility. The published correlation of Abraham and Le [24]

$$\log \frac{C_W}{5} = 0.104 - 0.2011\mathbf{E} + 0.154\mathbf{S} + 0.434\mathbf{A} + 0.848\mathbf{B} - 0.672\mathbf{A}\cdot\mathbf{B} - 0.797\,\text{V} \quad (6)$$

and its updated version (unpublished)

$$\log \frac{C_W}{5} = 0.079 - 0.191\mathbf{E} + 0.064\mathbf{S} + 0.231\mathbf{A} + 0.651\mathbf{B} - 0.157\mathbf{A}\cdot\mathbf{B} - 0.666\,\text{V} \quad (7)$$

was used for the aqueous predictions. The cross $\mathbf{A}\cdot\mathbf{B}$ term was added to the model to account for hydrogen-bond interactions between the acidic and basic sites in the pure liquid or solid solute. Such interactions are not normally included in solubility ratio and partition coefficient correlations. In practical partitioning studies, the solute is generally at very low concentration and is surrounded by solvent molecules. In the case of solubility ratios, the same equilibrium solid phase must be present for both C_S and C_W measurements. This allows contributions from breaking of crystal forces to cancel in the calculation of the solubility ratio.

Combining all retrieved experimental data, we have a total of 63 equations for which partition/toxicity data and equation coefficients are available. The characteristic McGowan volume of salicylamide is set equal to $\mathbf{V} = 1.0315$ and $\mathbf{E}$ is estimated as 1.160. The McGowan volume was calculated from the individual atomic sizes and number of bonds in the molecule [25] and the $\mathbf{E}$ descriptor is based on the PharmaAlgorithm fragment-based computation [26]. The set of 63 equations were then solved using Minitab to yield the values of the four unknown solute descriptors that best described

the equations (1) and (2) experimental partitioning and toxicity data. The final set of molecular descriptors were: $\mathbf{S} = 1.650$, $\mathbf{A} = 0.630$, $\mathbf{B} = 0.480$ and $\mathbf{L} = 5.91$; and the vapor phase concentration was $\log C_G = -9.439$. The vapor phase concentration corresponds to a gas-to-liquid partition coefficient of $\log L_W = 7.685$, which is in good agreement with the calculated values based upon equations (1) and (2) (the last numerical entry in table 4).

Examination of the numerical entries in table 4 reveals that the final set of molecular descriptors reproduce the 63 experimental $\log P$ and $\log L$ values to within an overall SD of 0.091 log units. Individual SDs were 0.091 and 0.093 log units for the 36 calculated and observed $\log P$ values and 27 calculated and observed

Table 4. Comparison between observed and back-calculated molar solubilities of salicylamide based upon equations (1) and (2) and updated values for molecular solute descriptors.[a]

			Equation (1)			Equation (2)	
Solvent	$\log C_s^{exp}$	$\log P^{exp}$	$\log P^{calc}$	$\log C_s^{calc}$	$\log L^{exp}$	$\log L^{calc}$	$\log C_s^{calc}$
1-Octanol (wet)		1.280	1.296		8.965	8.948	
Chloroform		0.540	0.527		8.225	8.210	
Heptane		−1.870	−1.974		5.815	5.897	
Benzene		0.050	0.170		7.735	7.879	
Diethyl ether (wet)		0.960	1.098		8.645	8.806	
Olive oil		0.400	0.355				
Oleyl alcohol (wet)		0.770	0.831				
Dibutyl ether (dry)	−1.633	0.121	0.165	−1.589	7.806	7.858	−1.581
Tetrahydrofuran (dry)	0.288	2.042	2.062	0.308	9.727	9.705	0.266
1,4-Dioxane (dry)	0.171	1.925	2.004	0.250	9.610	9.652	0.213
Methanol (dry)	−0.035	1.719	1.615	−0.139	9.404	9.246	−0.193
Ethanol (dry)	−0.205	1.549	1.519	−0.235	9.234	9.035	−0.404
1-Propanol (dry)	−0.368	1.386	1.382	−0.372	9.071	8.997	−0.442
2-Propanol (dry)	−0.377	1.377	1.385	−0.361	9.062	9.017	−0.422
1-Butanol (dry)	−0.487	1.267	1.149	−0.605	8.952	8.913	−0.526
1-Pentanol (dry)	−0.537	1.217	1.145	−0.609	8.902	8.865	−0.574
1-Hexanol (dry)	−0.584	1.170	1.175	−0.579	8.855	8.881	−0.558
1−Heptanol (dry)	−0.670	1.084	1.050	−0.704	8.769	8.727	−0.712
1-Octanol (dry)	−0.796	0.958	1.110	−0.644	8.643	8.708	−0.731
1-Decanol (dry)	−0.961	0.793	0.924	−0.830	8.478	8.636	−0.803
2-Butanol (dry)	−0.425	1.329	1.328	−0.426	9.014	8.975	−0.462
2-Methyl-1-propanol (dry)	−0.611	1.143	1.198	−0.556	8.828	8.847	−0.592
2-Methyl-2-propanol (dry)	−0.512	1.242	1.350	−0.404	8.927	9.029	−0.410
3-Methyl-1-butanol (dry)	−0.635	1.119	1.074	−0.680	8.804	8.757	−0.682
2-Pentanol (dry)	−0.520	1.234	1.112	−0.642	8.919	8.809	−0.630
Ethyl acetate (dry)	−0.128	1.626	1.494	−0.260	9.311	9.156	−0.283
Acetone (dry)	0.199	1.953	1.887	0.133	9.638	9.534	0.095
Acetonitrile (dry)	−0.223	1.531	1.416	−0.338	9.216	9.239	−0.200
Thin layer (RMw)		1.380	1.298				
Fathead minnow ($-\log LC_{50}$)		3.130	3.211				
T. pyriformis. ($-\log IGC_{50}$)		2.760	2.972				
RP-HPLC, MeCN (polarity)		2.010[b]	2.020				
RP-HPLC, MeOH (polarity)		2.060[c]	2.084				
Gas-to-water		7.685	7.711		7.685	7.720	

[a]Numerical values of the descriptors used in these calculations are: $\mathbf{E} = 1.160$, $\mathbf{S} = 1.650$, $\mathbf{A} = 0.630$, $\mathbf{B} = 0.480$, $\mathbf{V} = 1.0315$ and $\mathbf{L} = 5.91$.

[b]Relative solute polarity parameter determined from RP-HPLC retention data using an acetonitrile mobile phase; see Torres-Lapasio *et al*. [21].

[c]Relative solute polarity parameter determined from RP-HPLC retention data using a methanol mobile phase; see Torres-Lapasio *et al*. [21].

log L values, respectively. The aqueous solubility and toxicity calculations were included in the log P statistics. Statistically there is no difference between the set of 36 log P values and the total set of 63 log P and log L values, suggesting that the value of $\log C_G = -9.439$ is a feasible value for salicylamide. Whether or not the assumed value is in accord with future experimental vapor pressures, we can regard our value of $\log C_G$ simply as a constant that leads to calculations and predictions via equation (2). Based on our past experience using various solution models we have found that the better predictive equations estimate solubilities to within ± 0.2 log units. The Abraham solvation parameter model meets this criterion.

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