

Abraham Solvation Parameter Model: Determination of Experiment-Based Solute Descriptor Values for 3,5-Dimethoxybenzoic Acid Based on Measured Solubility Data

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Abstract

A spectroscopic method of chemical analysis is used to determine the mole fraction solubilities of 3,5-dimethoxybenzoic acid dissolved in propanenitrile, in eleven additional alkanol solvents (1-pentanol, 1-hexanol, 1-heptanol, 1-octanol, 2-methyl-1-propanol, 2-pentanol, 2-methyl-1-butanol, 3-methyl-1-butanol, 4-methyl-2-pentanol, 2-ethyl-1-hexanol, cyclopentanol), and in three additional alkyl alkanoate solvents (isopropyl acetate, *tert*-butyl acetate, methyl butyrate) at 298.15 K. Results from our experimental measurements, combined with published partition coefficient and solubility data, are used to calculate the Abraham model solute descriptors of the monomeric form of 3,5-dimethoxybenzoic acid. In total 62 experimental data points were used in the computation. The calculated solute descriptors describe the experimental solubility and partition coefficient data to within an overall standard deviation of 0.064 log units.

Key Words and Phrases

3,5-dimethoxybenzoic acid; Abraham model solute descriptors; molar solubility ratios; organic solvents

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1. Introduction

Quantitative structure-property relationships (QSPRs) and poly-parameter linear free energy relationships (ppLFERs) are widely used in the chemical manufacturing sector as a means to estimate the physical and chemical properties needed in the design of industrial processes. For example, mathematical expressions have been reported for estimating infinite dilution activity coefficients required in designing fractional distillation columns, for estimating water-to-organic solvent partition coefficients required to select an appropriate biphasic extraction system to remove chemical impurities from synthesized drug products, and for estimating chromatographic retention times needed to develop an analytical method to both identify and quantify the constituents present in unknown chemical samples. Each derived expression assumes that the physical and/or chemical property to be predicted is related to the molecule's inherent chemical structure. The challenge is to gain a good fundamental understanding of how the different structural features influence each property, and then to encode the structural information in a manner that can be used to generate numerical values of the desired property. Structural information can be encoded in the form of “descriptors” that can be as simple as the molecular formula, the molecular size, the polar surface area, topological indices, geometric parameters, and the various functional groups present in the molecule, or as complex as quantum chemical-based quantities such as the highest occupied molecular orbital (HOMO) and lowest occupied molecular orbital (LUMO) energies, multiple moments, maximum partial charges on individual atom types, Zefirov's empirical atomic partial charges, Mulliken atomic partial charges, and Gasteiger-Marsili empirical atomic partial charges.

The quantum chemical-based values can be easily calculated using commercial software packages such as DRAGON [1] and CODESSA [2]. Commercial software packages can generate more than a seven hundred different descriptors for a single chemical compound. Various filtering

and statistical methods are used to reduce calculated descriptors to a manageable number that yields a QSPR (or LFER) having good predictive applicability. Unfortunately, the “best” predictive expression obtained does not always offer a clear understanding of which structural features influence the given chemical (or physical) property. This can be very frustrating to both academicians and industrial design engineers, who are often left with strictly empirical predictive expressions with little (or no) firm theoretical basis. Moreover, a different set of descriptors is often required for each property to be predicted.

The poly-parameter linear free energy relationship developed and promoted by Abraham and coworkers [3-5] is widely used in the scientific community to describe a wide range of solute transfer processes of chemical and biological importance. Unlike other poly-parameter models the Abraham approach uses the same set of solute parameters (commonly referred to as solute descriptors) for each of the different solute transfer properties for which predictive mathematical correlations have been derived. For sample, in the case naphthalene one would use the same set of numerical descriptor values to predict the logarithm of the gas-to-organic solvent and water-to-organic solvent partition/transfer coefficients and molar solubilities of naphthalene in more than 130 different molecular organic solvents [6-8] and in more than 100 different ionic liquid solvents [9-11], as well as the blood-to-body tissue and gas-to-body tissue partition coefficients [12-15], and the adsorption coefficients for organic solutes on various polymeric adsorbents [16-19]. The latter partition coefficients are needed in performing pharmacokinetic modeling of a compound's adsorption, distribution, metabolism, excretion/elimination and toxicology properties in the body. Abraham model expressions have also been developed to predict the “baseline” lethal median molar concentration of compound to various aquatic organisms (fish, water fleas, tadpoles) [20-22], along with other important biological response properties such as nasal pungency [23], eye

irritation thresholds [24], decrease in respiratory frequency [25], minimum alveolar concentration [26] and convulsant activity of vapors and gases [27].

The basic Abraham model contains five solute-solvent product terms:

$$\text{Solute transfer property} = c_p + e_p \times \mathbf{E} + s_p \times \mathbf{S} + a_p \times \mathbf{A} + b_p \times \mathbf{B} + v_p \times \mathbf{V} \quad (1)$$

$$\text{Solute transfer property} = c_k + e_k \times \mathbf{E} + s_k \times \mathbf{S} + a_k \times \mathbf{A} + b_k \times \mathbf{B} + l_k \times \mathbf{L} \quad (2)$$

each of which describes a different type of molecular interaction believed to govern the given solute property under consideration. Hydrogen-bonding interactions are quantified by the $a \times \mathbf{A} + b \times \mathbf{B}$ terms on the right-hand side of Eqns. (1) and (2). In the first of the two respective terms, the solute molecule acts as the H-bond donor, while the solubilizing solvent medium acts as the H-bond acceptor. The roles of the solute and solubilizing medium are reversed in the case of the two $b \times \mathbf{B}$ terms. The remaining terms on the right-hand side of Eqns. (1) and (2) pertain to the excess polarizability portion of solute-solubilizing medium interactions resulting from the n - and π -electrons (the $e \times \mathbf{E}$ terms), the dipolarity/polarizability solute-solubilizing medium term (the $s \times \mathbf{S}$ terms) and the terms describing the ease of separating solvent molecules to create a solvent cavity of suitable size in which the dissolved solute molecule will reside (the $v_p \times \mathbf{V}$ and $l_k \times \mathbf{L}$ terms). The algebraic sign in front of the different product terms determines whether or not a given interaction increases or decreases the given solute property.

Equations 1 and 2 pertain to solute properties involving two condensed phases, and properties involving both a condensed phase and gas phase, respectively. The uppercase alphabetical characters used in the published Abraham model correlations represent solute descriptors ($\mathbf{E}$, $\mathbf{S}$, $\mathbf{A}$, $\mathbf{B}$, $\mathbf{V}$ and $\mathbf{L}$) which are defined as follows: $\mathbf{E}$ is the solute excess molar refractivity (units of $\text{dm}^3 \text{mol}^{-1}/10$), $\mathbf{S}$ refers to the solute dipolarity/polarizability, $\mathbf{A}$ and $\mathbf{B}$ denote the overall or summation hydrogen bond acidity and basicity, respectively, $\mathbf{L}$ is the logarithm of

the solute's dimensionless gas-to-hexadecane partition coefficient experimentally measured at 298.15 K, and V represents the McGowan volume (units of $\text{dm}^3 \text{ mol}^{-1}/100$) calculated from the number of chemical and the atomic volumes of the atoms contained in the solute molecule. Numerical values of the solute descriptors are either determined by regressing experimental data in accordance to the Eqns. (1) and (2) or are estimated using free and/or commercial software programs. The complementary solvent or process properties are denoted by the lowercase alphabetic characters. As mentioned above, the product of a solute descriptor times the complementary solvent/process property describes a specific type of molecular interaction believed to govern the particular solute property.

While the basic Abraham model can describe a wide range of solute properties, the properties that are generally used in the determination of experiment-based solute descriptors are the logarithms of chromatographic retention times or retention factors, logarithms of the solute's water-to-organic solvent partition coefficients, $\log P$, the logarithms of the solute's gas-to-organic solvent partition coefficients, $\log K$, and the logarithms of the solute's molar solubility ratios, $\log (C_{\text{S,organic}}/C_{\text{S,water}})$ and $\log (C_{\text{S,organic}}/C_{\text{S,gas}})$, where the subscripts "water", "organic" and "gas" denote the respective phase to which each solute concentration refers. These are the solute properties that would typically have the least experimental uncertainty. Pharmaceutical and biological response properties often have a much greater experimental uncertainty because of genetic, age and health condition differences between replicate test species and the difficulty that arises from developing an analytical method that would be specific for the desired solute molecule, as would be the case in blood-to-tissue partition coefficient determinations. Other chemical constituents present in the blood and tissue samples might interfere in the determination of the desired solute concentration.

Lately, we have been searching the published chemical and pharmaceutical literature for experimental solubility and partition coefficient that could be used to expand our private solute descriptor database. Recent additions to our database include hippuric acid [28], sancycline [29], *N*-hydroxyphthalimide [30], favipiravir [31], 4,5-dihydroxyanthraquinone-2-carboxylic acid [6], 2-naphthoxyacetic acid [32] and vitamin K4 [33]. Five of the seven solutes possess an unusual arrangement of atoms or exhibit intramolecular hydrogen-bond formation or exhibit keto-enol tautomerism. Compounds with special structural features can be used to further train the group contribution [34-36] and machine learning methods [35,36] that have been developed for estimating solute descriptors for compounds whose values had not been previously determined. Previous studies [6,29,37] have shown that internet-available machine learning methods, as well as select group contribution methods, often overestimate the **A** and **B** solute descriptor of compounds that exhibit intramolecular hydrogen-bond formation.

In the current communication we resume our determination of experiment-based solute descriptors using the published mole fraction solubility data of Feng et al. [38] for 3,5-dimethoxybenzoic acid dissolved in methanol, ethanol, 1-propanol, 1-butanol, 2-butanol, methyl acetate, ethyl acetate, propyl acetate, butyl acetate, acetone, butanone, tetrahydrofuran and acetonitrile. Solubilities were measured at 5 K temperature intervals from 283.15 K to 323.15 K using a gravimetric method of chemical analysis. Powder x-ray diffraction analysis revealed that the equilibrated samples did not undergo crystal transformation during the equilibration time. We augmented the experimental data obtained from the published paper of Feng et al. by measuring the mole fraction solubility of 3,5-dimethoxybenzoic acid dissolved in propanenitrile, in eleven additional alkanol solvents (1-pentanol, 1-hexanol, 1-heptanol, 1-octanol, 2-methyl-1-propanol, 2-pentanol, 2-methyl-1-butanol, 3-methyl-1-butanol, 4-methyl-2-pentanol, 2-ethyl-1-hexanol,

cyclopentanol), and in three additional alkyl alkanoate solvents (isopropyl acetate, *tert*-butyl acetate, methyl butyrate) at 298.15 K. 3,5-Dimethoxybenzoic acid lacks unusual structural features; however, determination of the molecule's solute descriptors is important in that the numerical values are needed in determining the descriptor values of the 3,5-dimethoxybenzoate anion. Abraham and Acree [39] proposed a method for determining solute descriptors of monocarboxylate anions based on the measured values of acid dissociation constant of carboxylic acid in both water and in a series of organic solvents or select binary aqueous-organic solvent mixtures. While estimated descriptor values obtained from group contribution and machine learning methods could be used for 3,5-dimethoxybenzoic acid, experiment-based values are preferred. As an informational note, 3,5-dimethoxybenzoic acid is effective in preventing skin wrinkles [38] and is an important chemical reagent in the synthesis of insect repellents, such as methyl 3,5-dimethoxybenzoate, which has been shown to be an effective antifeedant in deterring the feeding behavior pine weevil. Pine weevil infestation is a serious problem in Europe affecting conifer seedlings [40].

2. Organic Compounds and Experimental Methodology

3,5-Dimethoxybenzoic acid was purchased from commercial sources in the highest purity available (Acros Organics, Morris Plains, New Jersey, USA, 0.99 mass fraction) and was dried in an oven at 333 K for several days prior to use to remove trace amounts of moisture that may have been present in the commercial sample. The purity of the dried 3,5-dimethoxybenzoic acid sample was determined by titrimetric analysis with a freshly standardized aqueous sodium hydroxide solution to the phenolphthalein end point. Titrimetric analyses showed the purity of 3,5-dimethoxybenzoic acid to be 0.995 ± 0.005 mass fraction as determined by the average of seven independent titrations.

The fifteen organic solvents were purchased from commercial sources as follows: *tert*-butyl acetate (TCI America, Portland, Oregon, USA, 0.99 mass fraction), methyl butyrate (Aldrich Chemical Co., Milwaukee, WI, USA, 0.99 mass fraction), isopropyl acetate (Sigma-Aldrich Chemical Co., Milwaukee, WI, USA, 0.996 mass fraction), 1-pentanol (Aldrich Chemical Co., 0.99+ mass fraction), 1-hexanol (Alfa Aesar, Ward Hill, Massachusetts, USA, 0.99+ mass fraction), 1-heptanol (Alfa Aesar, 0.997 mass fraction), 1-octanol (Aldrich Chemical Co., 0.99+ mass fraction, anhydrous), 2-methyl-1-propanol (Sigma-Aldrich Chemical Co., 0.995 mass fraction, anhydrous), 2-methyl-1-butanol (Sigma-Aldrich Chemical Co., 0.99+ mass fraction), 3-methyl-1-butanol (Aldrich Chemical Co., 0.99 mass fraction, anhydrous), 2-pentanol (Thermo Scientific, Ward Hill, Massachusetts, USA, 0.99 mass fraction), 4-methyl-2-pentanol (Acros Organics, 0.99 mass fraction), 2-ethyl-1-hexanol (Acros Organics, 0.99 mass fraction), cyclopentanol (Aldrich Chemical Co., 0.99 mass fraction) and propanenitrile (Aldrich Chemical Co., 0.99 mass fraction). All fifteen solvents were stored over activated molecular sieves shortly before use to remove trace moisture. Gas chromatographic analysis (with thermal conductivity detection) indicated the organic solvent purities to be at least 0.997 mass fraction.

Solubilities were determined using a static method of equilibration with the concentrations of 3,5-dimethoxybenzoic acid in each of the saturated solutions obtained from spectrophotometric absorbance measurements. The experimental methodology employed in the current investigation has been described in earlier publications [41-43] and to conserve journal space only an abbreviated version will be presented here. Aliquots of the clear saturated solutions were transferred using a heated glass syringe into weighed volumetric flasks after the samples had equilibrated in a constant temperature water bath at 298.15 ± 0.05 K for at least three days with periodic agitation. The transferred aliquot was weighed on a Mettler Toledo ME104E electronic

analytical balance (Mettler Toledo, Columbus, OH, USA) and then diluted quantitatively with 2-propanol. Absorbances of the diluted solutions were recorded at 305 nm on a Milton Roy Spectronic 1000 Plus single-beam spectrophotometer (Milton Roy Company, Rochester, NY, USA). The concentration of each diluted solution was computed from a Beer-Lambert law absorbance versus concentration calibration curve generated from the measured absorbances of nine carefully prepared standard solutions of known 3,5-dimethoxybenzoic acid concentration. The calculated molar absorptivity, $\epsilon \approx 2850 \text{ L}/(\text{mol}^{-1} \text{ cm})$, was constant over the concentration range of 2.16×10^{-4} Molar to 7.20×10^{-4} Molar used to establish calibration curve.

To check for possible solid-solvate formation between 3,5-dimethoxybenzoic acid and the different organic mono-solvents, we determined the melting point temperature of the equilibrium solid residue that remained after the final set of solubility measurements were performed. The observed melting point temperature of the solid residue recovered from each of the equilibrated samples was within $\pm 1 \text{ K}$ of the melting point temperature of the commercial sample prior to contact with the organic solvents. The melting point temperature data showed no indication of either solid-solvate formation or polymorphism.

Molar concentrations obtained from the measured absorbances were converted to mass fraction solubilities by multiplying by the molar mass of 3,5-dimethoxybenzoic acid, by the volumes of the tared volumetric flask(s) used, and by 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 aliquot of the saturated sample taken for analysis. Mass fraction solubilities from both the spectrophotometric and volumetric determinations were converted to mole fraction solubilities using the molar masses of the carboxylic acid solute and respective organic mono-solvent.

3. Results and Discussion

The experimental mole fraction solubilities of 3,5-dimethoxybenzoic acid, x_S^{exp} , dissolved in propanenitrile, 1-pentanol, 1-hexanol, 1-heptanol, 1-octanol, 2-methyl-1-propanol, 2-pentanol, 2-methyl-1-butanol, 3-methyl-1-butanol, 4-methyl-2-pentanol, 2-ethyl-1-hexanol, cyclopentanol, isopropyl acetate, *tert*-butyl acetate and methyl butyrate at 298.15 K are tabulated in Table 1. The numerical values represent the average of between four and eight repetitive experimental measurements that were reproducible to within ± 2.5 relative percent. Our search of the published chemical and engineering literature did not find any solubility data for 3,5-dimethoxybenzoic acid in these fifteen organic solvents that we can use to compare our experimental data against. The only experimental solubility data that we found were the measured values of Feng et al. [38], along with the data of Wang and Zhang [44] for 3,5-dimethoxybenzoic acid in ethanol, and of Yao et al. [45] for 3,5-dimethoxybenzoic acid dissolved in ethanol, acetonitrile and acetone at 293.15 K. The latter experimental values were determined as part of study examining the effect that ultrasound-accelerated nucleation has on the crystallization process.

Table 1. Experimental mole fraction solubilities of 3,5-dimethoxybenzoic acid, x_S^{exp} , dissolved in organic solvents at 298.15 K

Organic Solvent	x_S^{exp}		Organic Solvent	x_S^{exp}
1-Pentanol	0.00488		4-Methyl-2-pentanol	0.00522
1-Hexanol	0.00562		2-Ethyl-1-hexanol	0.00414
1-Heptanol	0.00559		Cyclopentanol	0.00629
1-Octanol	0.00609		Isopropyl acetate	0.00482
2-Methyl-1-propanol	0.00308		<i>tert</i> -Butyl acetate	0.00360
2-Pentanol	0.00537		Methyl butyrate	0.00573
2-Methyl-1-butanol	0.00359		Propanenitrile	0.00223
3-Methyl-1-butanol	0.00413			

Most researchers, including us, report experimental solubility data in terms of mole fractions, x_S^{exp} , rather than molarities. The published Abraham model correlations that have been developed to describe solute transfer into organic solvents use molar solubility ratios. In Table 2 we have assembled the Abraham model equation coefficients for the solute transfer process that will be used to calculate the solute descriptor values for 3,5-dimethoxybenzoic acid. The tabulated coefficients for Eqn. (1) use $\log (C_{S,organic}/C_{S,water})$ for the dependent solute property, while the respective solute transfer property for Eqn. (2) is $\log (C_{S,organic}/C_{S,gas})$. For each molar solubility ratio, the numerical value of $C_{S,organic}$ is obtained by dividing the measured value of x_S^{exp} by the ideal molar volume of the saturated solution:

$$C_{S,organic} \approx x_S^{exp} / [x_S^{exp} V_{solute} + (1 - x_S^{exp}) V_{solvent}] \quad (3)$$

where V_{solute} and $V_{solvent}$ denote the molar volumes of the solute and organic solvent, respectively. A value of $V_{solute} = 0.1432 \text{ liters mol}^{-1}$ was used for the molar volume of the hypothetical subcooled liquid 3,5-dimethoxybenzoic acid. Any errors resulting from our estimation of 3,5-dimethoxybenzoic acid's hypothetical subcooled liquid molar volume, V_{Solute} , or the ideal molar volume approximation should have negligible effect of the calculated $C_{S,organic}$ values. The published mole fraction solubility data determined by Feng and coworkers [34] were converted to molar solubilities in similar fashion. We have tabulated in the second column of Table 3 the calculated values of $\log C_{S,organic}$ obtained from our measured mole fraction solubilities and the published data of Feng and coworkers. In total we have 28 experimental $\log C_{S,organic}$ to use in our solute descriptor calculations.

Table 2. Abraham Model Equation Coefficients in Eqn. (1) and Eqn. (2) for Various Processes

Solvent	<i>c</i>	<i>e</i>	<i>s</i>	<i>a</i>	<i>b</i>	<i>l</i>	<i>v</i>
Equation (1) Coefficients							
1-Octanol (wet)	0.088	0.562	-1.054	0.034	-3.460	0.000	3.814

Diethyl ether (wet)	0.248	0.561	-1.016	-0.226	-4.553	0.000	4.075
Methanol (dry)	0.276	0.334	-0.714	0.243	-3.320	0.000	3.549
Ethanol (dry)	0.222	0.471	-1.035	0.326	-3.596	0.000	3.857
1-Propanol (dry)	0.139	0.405	-1.029	0.247	-3.767	0.000	3.986
1-Butanol (dry)	0.165	0.401	-1.011	0.056	-3.958	0.000	4.044
1-Pentanol (dry)	0.150	0.536	-1.229	0.141	-3.864	0.000	4.077
1-Hexanol (dry)	0.115	0.492	-1.164	0.054	-3.978	0.000	4.131
1-Heptanol (dry)	0.035	0.398	-1.106	0.002	-4.342	0.000	4.317
1-Octanol (dry)	-0.034	0.489	-1.044	-0.024	-4.235	0.000	4.218
2-Butanol (dry)	0.127	0.253	-0.976	0.158	-3.882	0.000	4.114
2-Methyl-1-propanol (dry)	0.188	0.354	-1.127	0.016	-3.568	0.000	3.986
2-Methyl-1-butanol (dry)	0.143	0.388	-1.173	-0.024	-3.817	0.000	4.129
3-Methyl-1-butanol (dry)	0.111	0.337	-1.180	0.063	-3.880	0.000	4.218
2-Pentanol (dry)	0.117	0.443	-1.295	0.202	-3.676	0.000	4.160
4-Methyl-2-pentanol (dry)	0.096	0.301	-1.100	0.039	-4.081	0.000	4.242
2-Ethyl-1-hexanol (dry)	-0.033	0.566	-1.233	-0.068	-3.912	0.000	4.153
Cyclopentanol (dry)	0.332	0.522	-1.034	-0.106	-3.756	0.000	3.892
Tetrahydrofuran (dry)	0.207	0.372	-0.372	-0.236	-4.931	0.000	4.447
Methyl acetate (dry)	0.351	0.223	-0.150	-1.035	-4.527	0.000	3.972
Ethyl acetate (dry)	0.328	0.314	-0.348	-0.847	-4.899	0.000	4.142
Propyl acetate (dry)	0.362	0.280	-0.390	-0.975	-4.928	0.000	4.183
Isopropyl acetate (dry)	0.307	0.314	-0.481	-0.952	-4.779	0.000	4.159
Butyl acetate (dry)	0.289	0.336	-0.501	-0.913	-4.964	0.000	4.262
Methyl butyrate (dry)	0.238	0.368	-0.538	-1.031	-4.623	0.000	4.253
<i>tert</i> -Butyl acetate (dry)	0.456	0.324	-0.661	-1.068	-4.680	0.000	4.101
Acetone (dry)	0.313	0.312	-0.121	-0.608	-4.753	0.000	3.942
Butanone (dry)	0.276	0.296	-0.174	-0.714	-4.868	0.000	4.138
Acetonitrile (dry)	0.413	0.077	0.326	-1.566	-4.391	0.000	3.364
Propanenitrile (dry)	0.357	0.188	0.061	-1.515	-4.539	0.000	3.760
Gas-to-water	-0.994	0.577	2.549	3.813	4.841	0.000	-0.869

Equation (2) Coefficients

1-Octanol (wet)	-0.198	0.002	0.709	3.519	1.429	0.858	0.000
Diethyl ether (wet)	0.206	-0.169	0.873	3.402	0.000	0.882	0.000
Methanol (dry)	-0.039	-0.338	1.317	3.826	1.396	0.773	0.000
Ethanol (dry)	0.017	-0.232	0.867	3.894	1.192	0.846	0.000
1-Propanol (dry)	-0.042	-0.246	0.749	3.888	1.076	0.874	0.000
1-Butanol (dry)	-0.004	-0.285	0.768	3.705	0.879	0.890	0.000
1-Pentanol (dry)	-0.002	-0.161	0.535	3.778	0.960	0.900	0.000
1-Hexanol (dry)	-0.014	-0.205	0.583	3.621	0.891	0.913	0.000
1-Heptanol (dry)	-0.056	-0.216	0.554	3.596	0.803	0.933	0.000
1-Octanol (dry)	-0.147	-0.214	0.561	3.507	0.749	0.943	0.000
2-Butanol (dry)	-0.034	-0.387	0.719	3.736	1.088	0.905	0.000
2-Methyl-1-propanol (dry)	-0.003	-0.357	0.699	3.595	1.247	0.881	0.000
2-Methyl-1-butanol (dry)	-0.055	-0.348	0.601	3.565	0.996	0.925	0.000
3-Methyl-1-butanol (dry)	-0.040	-0.408	0.648	3.599	0.905	0.932	0.000
2-Pentanol (dry)	-0.064	-0.354	0.541	3.772	1.055	0.936	0.000

4-Methyl-2-pentanol (dry)	-0.013	-0.606	0.687	3.622	0.436	0.985	0.000
2-Ethyl-1-hexanol (dry)	-0.127	-0.339	0.551	3.397	0.722	0.963	0.000
Cyclopentanol (dry)	-0.151	-0.314	0.693	3.549	0.914	0.956	0.000
Tetrahydrofuran (dry)	0.189	-0.347	1.238	3.289	0.000	0.982	0.000
Methyl acetate (dry)	0.134	-0.477	1.749	2.678	0.000	0.876	0.000
Ethyl acetate (dry)	0.171	-0.403	1.428	2.726	0.000	0.914	0.000
Propyl acetate (dry)	0.246	-0.346	1.318	2.537	0.000	0.916	0.000
Isopropyl acetate (dry)	0.233	-0.495	1.324	2.550	0.000	0.928	0.000
Butyl acetate (dry)	0.154	-0.439	1.223	2.586	0.000	0.953	0.000
Methyl butyrate (dry)	0.201	-0.502	1.290	2.469	0.000	0.958	0.000
<i>tert</i> -Butyl acetate (dry)	0.178	-0.444	1.045	2.522	0.000	0.964	0.000
Acetone (dry)	0.127	-0.387	1.733	3.060	0.000	0.866	0.000
Butanone (dry)	0.124	-0.429	1.601	2.843	0.000	0.916	0.000
Acetonitrile (dry)	-0.007	-0.595	2.461	2.085	0.418	0.738	0.000
Propanenitrile (dry)	0.101	-0.433	1.981	2.509	0.399	0.801	0.000
Gas-to-water	-1.271	0.822	2.743	3.904	4.814	-0.213	0.000

Table 3. Comparison Between Inputted Logarithms of the Experimental Molar Solubility of the 3,5-Dimethoxybenzoic acid in the 28 Different Organic Mono-solvents, $\log C_{S,organic}$, and Back-Calculated Values Based on Eqns. 1 and 2

Solvent	$\log C_{S,organic}^{exp}$	$\log C_{S,organic}^{calc}$ (Eqn. 1) ^a	$\log C_{S,organic}^{calc}$ (Eqn. 2) ^a
Methanol	-1.032	-0.958	-0.932
Ethanol	-1.087	-1.063	-1.043
1-Propanol	-1.218	-1.178	-1.178
1-Butanol	-1.037	-1.289	-1.277
1-Pentanol	-1.349	-1.355	-1.351
1-Hexanol	-1.348	-1.384	-1.391
1-Heptanol	-1.405	-1.392	-1.421
1-Octanol	-1.415	-1.435	-1.523
2-Butanol	-1.210	-1.209	-1.240
2-Methyl-1-propanol	-1.470	-1.373	-1.378
2-Pentanol	-1.310	-1.319	-1.297
2-Methyl-1-butanol	-1.480	-1.434	-1.456
3-Methyl-1-butanol	-1.426	-1.382	-1.390
4-Methyl-2-pentanol	-1.387	-1.407	-1.385
2-Ethyl-1-hexanol	-1.579	-1.584	-1.594
Cyclopentanol	-1.136	-1.242	-1.211
Tetrahydrofuran	-0.350	-0.518	-0.559

Acetone	-0.848	-0.902	-0.864
Butanone	-0.965	-0.915	-0.922
Methyl acetate	-1.091	-1.118	-1.112
Ethyl acetate	-1.202	-1.212	-1.209
Propyl acetate	-1.308	-1.324	-1.364
Isopropyl acetate	-1.389	-1.418	-1.420
Butyl acetate	-1.496	-1.387	-1.408
<i>tert</i> -Butyl acetate	-1.576	-1.636	-1.632
Methyl butyrate	-1.301	-1.364	-1.365
Acetonitrile	-1.536	-1.561	-1.370
Propanenitrile	-1.503	-1.439	-1.449

^aCalculated using numerical values of the solute descriptors: of **E** = 0.950; **S** = 1.531; **A** = 0.684; **B** = 0.564; **V** = 1.3309; **L** = 6.699; and $\log C_{S,\text{water}} = -3.476$ and $\log C_{S,\text{gas}} = -11.170$.

We supplement the molar solubility data with two experimental partition coefficients, $\log P = 2.19$ [46] for water-to-1-octanol and $\log P = 1.84$ [46] for water-to-diethyl ether, retrieved from the published literature. The Abraham model equation coefficients needed for the partition coefficient correlations are denoted in Table 2 with the word “wet” following the organic solvent name. In the case of 1-octanol for which both the “wet” and “dry” solute transfer processes are given, one notes that equation coefficients are different. The presence of water in the organic solvent is sufficient to alter its solubilizing properties. For example, the water-saturated 1-octanol solvent medium exhibits greater hydrogen-bonding donor character as evidenced by its much larger b_k equation coefficient, $b_k = 1.429$ (wet) versus $b_k = 0.749$ (dry).

We also have two additional $\log (C_{S,\text{water}}/C_{S,\text{gas}})$ equations:

$$\log (C_{S,\text{water}}/C_{S,\text{gas}}) = -0.994 + 0.577 \mathbf{E} + 2.549 \mathbf{S} + 3.813 \mathbf{A} + 4.841 \mathbf{B} - 0.869 \mathbf{V} \quad (4)$$

$$\log (C_{S,\text{water}}/C_{S,\text{gas}}) = -1.271 + 0.822 \mathbf{E} + 2.743 \mathbf{S} + 3.904 \mathbf{A} + 4.814 \mathbf{B} - 0.213 \mathbf{L} \quad (5)$$

that describe the gas-to-water solute transfer process. Values of $\log (C_{S,\text{water}}/C_{S,\text{gas}})$ are used in converting experimental $\log P$ data for wet 1-octanol and for wet diethyl ether to the corresponding $\log K$ values through Eqn. (6) below:

$$\log K = \log P - \log (C_{S,\text{water}}/C_{S,\text{gas}}) \quad (6)$$

In total there are 62 mathematical equations that can be used in the regression analysis for determining 3,5-dimethoxybenzoic acid's six solute descriptors (**E**, **S**, **A**, **B**, **V** and **L**). The number of equations is more than sufficient to obtain a set of numerical values having predictive capabilities. Two of the six solute descriptors can be calculated solely from molecular structure considerations. The McGowan characteristic volume, **V** = 1.5003, is calculated from the volumes of the individual carbon, hydrogen and oxygen atoms, and number of chemical bonds in the molecule as described in a published paper by Abraham and McGowan [47]. The **E** solute descriptor, **E** = 0.950, is an estimated value obtained from the Absolv ADME suite 5.0 [48]. We note that the estimated value is roughly half-way between that of a previously studied trimethoxy-substituted benzoic acid (**E** = 1.001 for 3,4,5-trimethoxybenzoic acid [49]) and that of 4-methoxybenzoic acid (**E** = 0.899 [50]).

This leaves only four solute descriptors left to calculate, along with the aqueous molar solubility, $C_{S,\text{water}}$, and the gas phase concentration, $C_{S,\text{gas}}$, needed to obtain the logarithms of the molar solubilities ratios, $\log (C_{S,\text{organic}}/C_{S,\text{water}})$ and $\log (C_{S,\text{organic}}/C_{S,\text{gas}})$. These latter two values will be calculated as part of the regression analysis. The 62 Abraham model expressions were then solved simultaneously using the built-in Microsoft Excel Solver add-in to give: **E** = 0.950; **S** = 1.531; **A** = 0.684; **B** = 0.564; **V** = 1.3309; **L** = 6.699; $\log C_{S,\text{water}}$ = -3.476 and $\log C_{S,\text{gas}}$ = -11.170. Our experiment-based solute descriptors differ from the estimated values of **E** = 0.890; **S** = 1.250; **A** = 0.460; **B** = 0.730; **V** = 1.3309; and **L** = 6.610 obtained from the UFZ-LSER website [34] by

inputting the molecule's canonical Smiles code, COc1cc(cc(c1)OC)C(=O)O, into the internet software program. The experiment-based solute descriptors indicate that 3,5-dimethoxybenzoic acid is a better H-bond donor and possess more dipolar/polarizability character than what is suggested by the lower estimated **A** and **S** descriptor values. Readers are reminded that the calculated solute descriptors pertain to the monomeric form of 3,5-dimethoxybenzoic acid.

Table 3 provides a summarized comparison of the experimental molar solubility data to the back-calculated values using the solute descriptors determined from the regression analysis. Examination of the numerical entries reveals that the calculated molar solubilities differ only slightly from the observed values. This is not unexpected as the overall standard deviation associated with the regression analysis was $SD = 0.064$ log units. Individual standard deviations were $SD = 0.058$ log units and $SD = 0.070$ log units for the 31 calculated and observed log $(C_{S,organic}/C_{S,water})$ values and the 31 calculated and observed log $(C_{S,organic}/C_{S,gas})$ values, respectively. We further note that the back-calculated logarithm of the water-to-wet 1-octanol partition coefficient, $\log P = 2.156$, and of the water-to-wet diethyl ether partition coefficient, $\log P = 1.927$, are in good agreement with the experimental values of $\log P = 2.19$ [46] and $\log P = 1.84$ [46] used in the regression analysis. Differences between the experimental and back-calculated log P values are included in the standard deviation for the log $(C_{S,organic}/C_{S,water})$ values. Similarly, the differences for the gas-to-wet 1-octanol and gas-to-wet diethyl partition coefficients are included in the standard deviation calculation for the log $(C_{S,organic}/C_{S,gas})$ values.

There are several important chemical and biological processes that involve the transfer of both neutral molecules and ionic species. Abraham model correlations have been developed for the transfer of ionic species from water to slightly more than 30 different organic solvents [39], for the human skin permeability of ionic species [51], for the water-lipid membrane partitioning

of ionic species [52], for the brain permeation of ionic species [53], and for the percentage of human intestinal absorption of ionic species [54]. Each reported predictive expression requires the input of the solute descriptor values for the ionic species. Abraham and Acree [39,55] developed mathematical expressions for estimating the solute descriptors of monocarboxylate anions:

$$E_{\text{carboxylate anion}} = 0.15 + 1.00 E \quad (7)$$

$$S_{\text{carboxylate anion}} = 1.224 + 0.908 E + 0.827 S + 0.453 V \quad (8)$$

$$A_{\text{carboxylate anion}} = -0.208 - 0.058 S + 0.354 A + 0.076 V \quad (9)$$

$$B_{\text{carboxylate anion}} = 2.150 - 0.204 S + 1.217 B + 0.314 V \quad (10)$$

$$V_{\text{carboxylate anion}} = -0.0215 + 1.00 V \quad (11)$$

$$J^-_{\text{carboxylate anion}} = 1.793 + 0.267 E - 0.195 S + 0.350 V \quad (12)$$

from the known descriptor values of the parent carboxylic acid. Inserting the experiment-based solute descriptor values for 3,5-dimethoxybenzoic acid into Eqns. (7) – (12), we estimate the solute descriptors of the 3,5-dimethoxybenzoate anion to be: $E = 1.100$; $S = 3.956$; $A = 0.000$; $B = 2.942$; $V = 1.3094$ and $J^- = 2.309$. The estimated solute descriptors are similar in magnitude to reported experiment-based values for 2,6-dimethoxybenzoate ($E = 1.030$; $S = 4.27$; $A = 0.00$; $B = 3.51$; $V = 1.3094$ and $J^- = 2.527$ [39]) determined using the acid-base dissociation constant of the respective carboxylic acid in eight different organic mono-solvents. Placement of substituent functional groups at different aromatic ring positions can affect the solute descriptor values of benzoic acid derivatives and substituted benzoate anions.

4. Summary

The Abraham solvation parameter model has been shown to provide a reasonably accurate mathematical description of the experimental solubilities for 3,5-dimethoxybenzoic acid dissolved

in 16 different alcohols (methanol, ethanol, 1-propanol, 1-butanol, 1-pentanol, 1-hexanol, 1-heptanol, 1-octanol, 2-butanol, 2-methyl-1-propanol, 2-pentanol, 2-methyl-1-butanol, 3-methyl-1-butanol, 4-methyl-2-pentanol, 2-ethyl-1-hexanol, cyclopentanol), in 7 different alkyl alkanoates (methyl acetate, ethyl acetate, propyl acetate, butyl acetate, isopropyl acetate, *tert*-butyl acetate, methyl butyrate), in 2 alkanones (acetone, butanone), in 2 alkanenitriles (acetonitrile, propanenitrile), and in tetrahydrofuran at 298.15 K using the experiment-based solute descriptors determined in the current communication. The average differences between the experimental and back-calculated solubilities were less than 0.07 log units. The relatively small difference between the experimental and back-calculated values suggests that the calculated descriptor values will permit researchers to predict the solubility of 3,5-dimethoxybenzoic acid in additional organic mono-solvents, and in binary aqueous-methanol, aqueous-ethanol and aqueous-2-propanol solvent mixtures, where dimerisation does not occur. Carboxylic acids are known to exist largely in dimeric form in nonpolar solvents such as saturated alkane solvents [56-58]. At the present time there is not sufficient solubility data for 3,5-dimethoxybenzoic acid dissolved in saturated alkane solvents and in alkylbenzene solvents for us to calculate descriptor values for the carboxylic acid dimer.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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