



EXPERIMENTAL AND PREDICTED SOLUBILITIES OF 3,4-DIMETHOXYBENZOIC ACID IN SELECT ORGANIC SOLVENTS OF VARYING POLARITY AND HYDROGEN-BONDING CHARACTER

Kaci R. Bowen^[a], Timothy W. Stephens^[a], Helen Lu^[a], Kalpana Satish^[a], Danyang Shan^[a], William E. Acree, Jr.^{[a]*} and Michael H. Abraham^[b]

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Experimental solubilities are reported for 3,4-dimethoxybenzoic acid dissolved in 16 alcohol, 5 alkyl alkanoate, 5 alkoxyalcohol and 6 ether solvents. The measured solubility data were correlated with the Abraham solvation parameter model. Mathematical expressions based on the Abraham model predicted the observed molar solubilities to within 0.083 log units.

* Corresponding Author

Fax: 940-565-4318.

E-Mail: acree@unt.edu.

[a] Department of Chemistry, 1155 Union Circle Drive #305070, University of North Texas, Denton, TX 76203-5017 (USA).

[b] Department of Chemistry, University College London, 20 Gordon Street, London, WC1H 0AJ (UK).

Introduction

Solubility is one of the more important physicochemical properties of crystalline organic compounds as it plays such an important role in many manufacturing processes, including solvent selection for organic syntheses, for chemical separations by two-phase extractions involving either an aqueous-organic or a biphasic organic solvent system, and for purifications by recrystallizations. For organic syntheses one must select a suitable reaction solvent that can not only dissolve the starting reagent materials, but also can be removed easily after the chemical reaction is complete. Product isolation and purification can be accomplished by evaporation in the case of a volatile solvent media, or by filtration if the reaction product is crystalline. Recrystallization and extraction can be performed to remove undesired reaction by-products and excess reactants. Considerable attention has been afforded in recent years to measuring the solubility of crystalline organic compounds in organic solvents, and to developing mathematical expressions to predict the solubility behavior of various classes of organic compounds.

This study continues our systematic examination of the solubility behavior of substituted benzoic acids in organic solvents of varying polarity and hydrogen-bonding character. Substituted benzoic acids are of particular interest to us because several of the derivatives exhibit therapeutic properties. For example, acetylsalicylic acid (aspirin) is an "over-the-counter" non-steroidal anti-inflammatory drug (NSAID) taken orally to reduce fever and to relieve minor muscle pains and aches. 2-Hydroxybenzoic acid, the main

metabolite of acetylsalicylic acid, is an ingredient in skin care products for the treatment of acne, psoriasis and warts. Previous studies of reported solubility data for benzoic acid¹, 2-acetylsalicylic acid², 4-aminobenzoic acid³, 2-chloro-5-nitrobenzoic acid⁴, 3-chlorobenzoic acid⁵, 4-chlorobenzoic acid⁶, 4-chloro-3-nitrobenzoic acid⁴, 3,4-dichlorobenzoic acid⁷, 3,5-dinitrobenzoic acid⁸, 3,5-dinitro-2-methylbenzoic acid⁹, 2-hydroxybenzoic acid¹⁰, 2-methoxybenzoic acid¹¹, 4-methoxybenzoic acid¹¹, 2-methylbenzoic acid¹², 3-methylbenzoic acid⁶, 3-nitrobenzoic acid¹³, and 4-nitrobenzoic acid¹⁴ in various organic solvents. In the current study solubilities of 3,4-dimethoxybenzoic acid (also called veratric acid) were measured at 25 °C in several alcohol, alkyl alkanoate, alkoxyalcohol, 2-alkanone and ether solvents of varying polarity and hydrogen-bonding characteristics. The measured solubility data is correlated using the Abraham solvation parameter model.

Experimental

Chemicals: 3,4-Dimethoxybenzoic acid (Acros Organics, 99+ %) and water (Aldrich, HPLC Grade) were used as received. The purity of 3,4-dimethoxybenzoic acid was 99.8 % (±0.2 %) as determined by nonaqueous titration with a freshly standardized sodium methoxide solution to the thymol blue endpoint according to the method of Fritz and Lisicki¹⁵, except that benzene was replaced with toluene. Methyl acetate (Aldrich, 99.5 %, anhydrous), ethyl acetate (Aldrich, 99.8 %, anhydrous), propyl acetate (Aldrich, 99.5 %), butyl acetate (Aldrich, 99.7 %), pentyl acetate (Aldrich, 99 %), methyl butyrate (Aldrich, 99 %), propylene carbonate (Aldrich, 99+ %, anhydrous), diethyl ether (Aldrich, 99+ %, anhydrous), diisopropyl ether (Aldrich, 99 %, anhydrous), dibutyl ether (Acros Organics, 99+ %), 1,4-dioxane (Aldrich, 99.8 %, anhydrous), tetrahydrofuran (Aldrich, 99.9 %, anhydrous), methanol (Aldrich, 99.8 %, anhydrous), 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), 1-decanol (Alfa Aesar, 99+ %), 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), 2-pentanol (Acros Organics, 99+ %), 2-methyl-1-butanol (Aldrich, 99 %), 4-methyl-2-pentanol (Acros Organics, 99+ %), 2-methyl-1-pentanol (Aldrich, 99 %), 2-propanone (Aldrich, HPLC, 99.9 %), 2-butanone (Aldrich, HPLC, 99.7 %), 2-ethoxyethanol (Aldrich, 99 %), 2-isopropoxyethanol (Aldrich, 99 %), 2-butoxyethanol (Acros Organics, 99 %), and 3-methoxy-1-butanol (Aldrich, 99 %) were stored over molecular sieves and distilled shortly before use. Gas chromatographic analysis showed the organic solvent purities to be at least 99.7 mole percent.

Method: Excess solute and solvent were placed in sealed amber glass bottles and allowed to equilibrate in a constant temperature water bath at 25.0 ± 0.1 °C for at least 72 hours (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 to the bottom of the container. 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. Undissolved material from several containers were removed and analyzed to ensure that the equilibrium solid phase was indeed pure crystalline 3,4-dimethoxybenzoic acid. Melting point temperatures of the undissolved residues were identical that of recrystallized 3,4-dimethoxybenzoic acid.

Aliquots of saturated 3,4-dimethoxybenzoic acid solutions were transferred through a coarse filter into a tared volumetric flask to determine the mass of sample analyzed and diluted quantitatively with 2-propanol for spectrophotometric analysis at 286 nm on a Milton Roy Spectronic 1001 Plus. 2-Propanone and 2-butanone exhibited significant absorbances at the analysis wavelength, and it was necessary to remove the both solvents by evaporation at 60 °C prior to dilution with 2-propanol. 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 of the standard solutions varied slightly with concentration, $\epsilon \approx 4,700 \text{ L mol}^{-1} \text{ cm}^{-1}$ to $\epsilon \approx 4,900 \text{ L mol}^{-1} \text{ cm}^{-1}$, over the concentration range from $9.76 \times 10^{-5} \text{ M}$ to $3.25 \times 10^{-4} \text{ M}$.

Experimental molar concentrations were converted to (mass/mass) solubility fractions by multiplying by the molar mass of 3,4-dimethoxybenzoic acid, 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 3,4-dimethoxybenzoic acid mole fraction solubilities, X_S^{exp} , are listed in Table 1 for the 36 organic solvents studied. Numerical values represent the average of between four and eight independent determinations, and were reproducible to within ± 2 %. Published literature values of Li and coworkers¹⁶ are reported in the last column of Table 1. Literature values were measured using a dynamic method with laser monitoring to determine the temperature at which the suspended solid particles completely dissolved. The experimental uncertainty in the published solubility data is $\pm 4\%$. Examination of the numerical entries in Table 1 reveals that for the eight solvents for which independent literature values are available, our observed mole fraction solubilities are in good agreement with the published solubility data. Differences in experimental methodologies and chemical purities can lead to differences of a few percent between values determined by two different research groups.

Table 1. Experimental 3,4-dimethoxybenzoic acid mole fraction solubilities, X_S^{exp} , in selected organic solvents at 25 °C.

| Organic Solvent | X_S^{exp} | X_S^{exp} |
|---------------------|--------------------|-----------------------|
| Methanol | 0.00764 | |
| Ethanol | 0.00720 | 0.00753 ¹⁶ |
| 1-Propanol | 0.00643 | 0.00635 ¹⁶ |
| 1-Butanol | 0.00625 | 0.00570 ¹⁶ |
| 1-Pentanol | 0.00615 | |
| 1-Hexanol | 0.00615 | |
| 1-Heptanol | 0.00617 | |
| 1-Octanol | 0.00616 | |
| 1-Decanol | 0.00577 | |
| 2-Propanol | 0.00618 | 0.00606 ¹⁶ |
| 2-Butanol | 0.00651 | |
| 2-Methyl-1-propanol | 0.00450 | 0.00413 ¹⁶ |
| 2-Methyl-2-propanol | 0.00945 | |
| 3-Methyl-1-butanol | 0.00560 | |
| 2-Methyl-1-butanol | 0.00541 | |
| 2-Pentanol | 0.00593 | |
| 4-Methyl-2-pentanol | 0.00646 | |
| 2-Methyl-1-pentanol | 0.00573 | |
| Methyl acetate | 0.00854 | 0.00802 ¹⁶ |
| Ethyl acetate | 0.00813 | 0.00723 ¹⁶ |
| Propyl acetate | 0.00682 | |
| Butyl acetate | 0.00660 | |
| Pentyl acetate | 0.00654 | |
| Methyl butyrate | 0.00678 | |
| Propylene carbonate | 0.00799 | |
| Diethyl ether | 0.00313 | |
| Diisopropyl ether | 0.00143 | |
| Dibutyl ether | 0.00112 | |
| 1,4-Dioxane | 0.02897 | |
| Tetrahydrofuran | 0.03937 | |
| Propanone | 0.01177 | |
| Butanone | 0.01206 | 0.01200 ¹⁶ |
| 2-Ethoxyethanol | 0.03037 | |
| 2-Isopropoxyethanol | 0.02335 | |
| 2-Butoxyethanol | 0.01485 | |
| 3-Methoxy-1-butanol | 0.02547 | |

As part of the experimental measurements we did determine the solubility of 3,4-dimethoxybenzoic acid in water at 25 °C which is needed for the Abraham model correlations. The molar solubility of 3,4-dimethoxybenzoic acid in water is $C_W^{\text{sat}} = 0.00320$ M. One drop of hydrochloric acid was added to prevent ionization.

Results and Discussion

Abraham Model: During the past 20 years there have been numerous methods developed for predicting the solubility of crystalline nonelectrolyte compounds in organic solvents based on empirical and semi-empirical quantitative structure – property relationships (QSPR) for which the basic underlying solute-solvent molecular interactions are not always clearly defined. While such QSPR treatments may show some descriptive/predictive ability, they often require large experimental data sets for training purposes, and both the inputted solute parameters/properties and calculated equation coefficients encode no useful chemical information. The approach that we have taken in recent years in describing the solubility is based on the Abraham solvation parameter model¹⁷⁻¹⁹ which contains a realistic description of how solute and solvent molecules are believed to interact in solution. The basic Abraham model is based on two linear free energy relationships (LFERs) that quantify solute transfer between two phases. The first LFER quantifies solute transfer between two condensed phases.¹⁷⁻¹⁹

$$\log (SR \text{ or } P) = c_p + e_p E + s_p S + a_p A + b_p B + v_p V \quad (1)$$

and the second LFER describes solute transfer from the gas phase:¹⁷⁻¹⁹

$$\log (GSR \text{ or } K) = c_k + e_k E + s_k S + a_k A + b_k B + l_k L \quad (2)$$

where

P is the water-to-organic solvent partition coefficient or alkane-to-polar organic solvent partition coefficient, and

K is the gas-to-organic solvent partition.

For solubility predictions, the Abraham model uses the solubility ratio which is given by the ratio of the molar solubilities of the solute in the organic solvent, C_S^{sat} , and in water, C_W^{sat} (*i.e.*, $SR = C_S^{\text{sat}}/C_W^{\text{sat}}$). The gas phase solubility ratio is similarly calculated as the molar solubility in the organic solvent divided by the solute gas phase concentration (*i.e.*, $GSR = C_S^{\text{sat}}/C_G$), the latter value calculable from the solute vapor pressure above the solid at the solution temperature.

The independent variables in Eqns. 1 and 2 are the Abraham solute descriptors defined as follows: E represents

the solute excess molar refraction (in units of $\text{cm}^3 \text{mol}^{-1}/10$), S denotes to the solute dipolarity/polarizability, A and B quantify the overall solute hydrogen bond acidity and basicity, V is the solute's McGowan characteristic molecular volume (in units of $\text{cm}^3 \text{mol}^{-1}/100$) and L corresponds the logarithm of the gas-to-hexadecane partition coefficient measured at 298 K. The lower case regression coefficients and constants (c_p , e_p , s_p , a_p , b_p , v_p , c_k , e_k , s_k , a_k , b_k and l_k) in Eqns. 1 and 2 represent the complimentary condensed phase property and serve to characterize the specific condensed phase system under consideration. Solute descriptors when combined with the respective equation coefficients describe the contributions that each type of solute-solvent interaction makes to the overall solute transfer process. For example, the $a_p \cdot A$ and $a_l \cdot A$ terms in Eqns. 1 and 2 describe the hydrogen-bonding interactions between the H-bond donor sites on the solute and the H-bond acceptor sites on the solvent, while the $b_p \cdot B$ and $b_l \cdot B$ terms involve interactions between the solute H-bond acceptor sites and solvent H-bond donor sites.

The equation coefficients for all of the transfer processes considered in the present study are tabulated in Table 2. A more complete list of equation coefficients can be found elsewhere.¹⁹ The actual numerical values of the equation coefficients may differ slightly from values used in our much earlier publications. The coefficients are periodically revised when additional experimental data become available. Except for the practical “wet” water-to-1-octanol and water-to-diethyl ether partition coefficients (first two entries in Table 2), all of the listed transfer processes pertain to the “dry” anhydrous organic solvent. The “dry” equation coefficients are more applicable for solubility predictions as the condensed phase is not saturated with water as would be the case with the two “wet” partitioning processes.

Abraham Model Predictions: The predictive application of the Abraham model is relatively straightforward given that we have an existing set of preliminary solute descriptors for 3,4-dimethoxybenzoic acid ($E = 0.890$, $S = 1.570$, $A = 0.580$, $B = 0.760$, $V = 1.3309$, and $L = 6.670$) based on measured water-to-diethyl ether, water-to-octanol, gas-to-diethyl ether and gas-to-octanol practical partition coefficient data and calculated fragment group values.^{20,21} The numerical values of the existing solute descriptors are inserted into the sets of $\log SR$ correlations and $\log GSR$ correlations constructed from the equation coefficients given in Table 1. The predicted $\log SR$ values are then converted into 3,4-dimethoxybenzoic acid molar solubilities in the different organic solvents, C_S^{sat} , (more specifically into the logarithms of the molar solubilities, $\log C_S^{\text{sat}}$) using a value of $\log C_W^{\text{sat}} = -2.495$, which is based on our measured molar solubility of unionized 3,4-dimethoxybenzoic acid of $C_W^{\text{sat}} = 0.00320$. Similarly, the predicted $\log GSR$ values are converted into $\log C_S^{\text{sat}}$ values using a value of $\log C_S = -10.765$.

For comparison purposes, the measured molar fraction solubilities, X_S^{exp} , in Table 1 were converted to molar solubilities by dividing X_S^{exp} by the ideal molar volume of the saturated solution (*i.e.*, $C_S^{\text{exp}} \approx X_S^{\text{exp}} / [X_S^{\text{exp}} \cdot V_{\text{Solute}} + (1 - X_S^{\text{exp}}) \cdot V_{\text{Solvent}}]$).

Table 2. Coefficients in Eqn. (1) and Eqn. (2) for various Processes^a

| Process/solvent | <i>c</i> | <i>e</i> | <i>s</i> | <i>a</i> | <i>b</i> | <i>v/l</i> |
|--------------------------------------|----------|----------|----------|----------|----------|------------|
| A. Water to solvent: Eqn. (1) | | | | | | |
| 1-Octanol (wet) | 0.088 | 0.562 | -1.054 | 0.034 | -3.460 | 3.814 |
| Diethyl ether (wet) | 0.248 | 0.561 | -1.016 | -0.226 | -4.553 | 4.075 |
| Methanol (dry) | 0.276 | 0.334 | -0.714 | 0.243 | -3.320 | 3.549 |
| Ethanol (dry) | 0.222 | 0.471 | -1.035 | 0.326 | -3.596 | 3.857 |
| 1-Propanol (dry) | 0.139 | 0.405 | -1.029 | 0.247 | -3.767 | 3.986 |
| 2-Propanol (dry) | 0.099 | 0.344 | -1.049 | 0.406 | -3.827 | 4.033 |
| 1-Butanol (dry) | 0.165 | 0.401 | -1.011 | 0.056 | -3.958 | 4.044 |
| 1-Pentanol (dry) | 0.150 | 0.536 | -1.229 | 0.141 | -3.864 | 4.077 |
| 1-Hexanol (dry) | 0.115 | 0.492 | -1.164 | 0.054 | -3.978 | 4.131 |
| 1-Heptanol (dry) | 0.035 | 0.398 | -1.063 | 0.002 | -4.342 | 4.317 |
| 1-Octanol (dry) | -0.034 | 0.489 | -1.044 | -0.024 | -4.235 | 4.218 |
| 1-Decanol (dry) | -0.058 | 0.616 | -1.319 | 0.026 | -4.153 | 4.279 |
| 2-Butanol (dry) | 0.127 | 0.253 | -0.976 | 0.158 | -3.882 | 4.114 |
| 2-Methyl-1-propanol (dry) | 0.188 | 0.354 | -1.127 | 0.016 | -3.568 | 3.986 |
| 2-Methyl-2-propanol (dry) | 0.211 | 0.171 | -0.947 | 0.331 | -4.085 | 4.109 |
| 3-Methyl-1-butanol (dry) | 0.073 | 0.360 | -1.273 | 0.090 | -3.770 | 4.273 |
| 2-Pentanol (dry) | 0.115 | 0.455 | -1.331 | 0.206 | -3.745 | 4.201 |
| Diethyl ether (dry) | 0.350 | 0.358 | -0.820 | -0.588 | -4.956 | 4.350 |
| 1,4-Dioxane (dry) | 0.123 | 0.347 | -0.033 | -0.582 | -4.810 | 4.110 |
| Tetrahydrofuran (dry) | 0.223 | 0.363 | -0.384 | -0.238 | -4.932 | 4.450 |
| Propanone | 0.313 | 0.312 | -0.121 | -0.608 | -4.753 | 3.942 |
| Butanone | 0.246 | 0.256 | -0.080 | -0.767 | -4.855 | 4.148 |
| Methyl acetate (dry) | 0.351 | 0.223 | -0.150 | -1.035 | -4.527 | 3.972 |
| Ethyl acetate (dry) | 0.328 | 0.369 | -0.446 | -0.700 | -4.904 | 4.150 |
| Propyl acetate (dry) ^b | 0.288 | 0.363 | -0.474 | -0.784 | -4.939 | 4.216 |
| Butyl acetate (dry) | 0.248 | 0.356 | -0.501 | -0.867 | -4.973 | 4.281 |
| Propylene carbonate (dry) | 0.004 | 0.168 | 0.504 | -1.283 | -4.407 | 3.421 |
| (Gas to water) | -0.994 | 0.577 | 2.549 | 3.813 | 4.841 | -0.869 |
| B. Gas to solvent: Eqn. (2) | | | | | | |
| 1-Octanol (wet) | -0.198 | 0.002 | 0.709 | 3.519 | 1.429 | 0.858 |
| Diethyl ether (wet) | 0.206 | -0.169 | 0.873 | 3.402 | 0.000 | 0.882 |
| Methanol (dry) | -0.039 | -0.338 | 1.317 | 3.826 | 1.396 | 0.773 |
| Ethanol (dry) | 0.017 | -0.232 | 0.867 | 3.894 | 1.192 | 0.846 |
| 1-Propanol (dry) | -0.042 | -0.246 | 0.749 | 3.888 | 1.076 | 0.874 |
| 2-Propanol (dry) | -0.048 | -0.324 | 0.713 | 4.036 | 1.055 | 0.884 |
| 1-Butanol (dry) | -0.004 | -0.285 | 0.768 | 3.705 | 0.879 | 0.890 |
| 1-Pentanol (dry) | -0.002 | -0.161 | 0.535 | 3.778 | 0.960 | 0.900 |
| 1-Hexanol (dry) | -0.014 | -0.205 | 0.583 | 3.621 | 0.891 | 0.913 |
| 1-Heptanol (dry) | -0.056 | -0.216 | 0.554 | 3.596 | 0.803 | 0.933 |
| 1-Octanol (dry) | -0.147 | -0.214 | 0.561 | 3.507 | 0.749 | 0.943 |
| 1-Decanol (dry) | -0.139 | -0.090 | 0.356 | 3.547 | 0.727 | 0.958 |
| 2-Butanol (dry) | -0.034 | -0.387 | 0.719 | 3.736 | 1.088 | 0.905 |
| 2-Methyl-1-propanol (dry) | -0.003 | -0.357 | 0.699 | 3.595 | 1.247 | 0.881 |
| 2-Methyl-2-propanol (dry) | -0.053 | -0.443 | 0.699 | 4.026 | 0.882 | 0.907 |
| 3-Methyl-1-butanol (dry) | -0.052 | -0.430 | 0.628 | 3.661 | 0.932 | 0.937 |
| 2-Pentanol (dry) | -0.031 | -0.325 | 0.496 | 3.792 | 1.024 | 0.934 |
| Diethyl ether (dry) | 0.288 | -0.347 | 0.904 | 2.937 | 0.000 | 0.963 |
| 1,4-Dioxane (dry) | -0.034 | -0.389 | 1.724 | 2.989 | 0.000 | 0.922 |
| Tetrahydrofuran | 0.193 | -0.391 | 1.244 | 3.256 | 0.000 | 0.994 |
| Propanone | 0.127 | -0.387 | 1.733 | 3.060 | 0.000 | 0.866 |
| Butanone | 0.112 | -0.474 | 1.671 | 2.878 | 0.000 | 0.916 |
| Methyl acetate (dry) | 0.134 | -0.477 | 1.749 | 2.678 | 0.000 | 0.876 |
| Ethyl acetate (dry) | 0.182 | -0.352 | 1.316 | 2.891 | 0.000 | 0.916 |
| Propyl acetate (dry) ^b | 0.165 | -0.383 | 1.264 | 2.757 | 0.000 | 0.935 |
| Butyl acetate (dry) | 0.147 | -0.414 | 1.212 | 2.623 | 0.000 | 0.954 |
| Propylene carbonate (dry) | -0.356 | -0.413 | 2.587 | 2.207 | 0.455 | 0.719 |
| (Gas to water) | -1.271 | 0.822 | 2.743 | 3.904 | 4.814 | -0.213 |

^a The dependent variable is $\log SR$ and $\log GSR$ for all of the correlations, except for 1-octanol (wet) and diethyl ether (wet) where the practical water-to-1-octanol and water-to-diethyl ether partition coefficient was used. ^b The equation coefficients for propyl acetate are estimated as the average of the coefficients for ethyl acetate and butyl acetate.

The molar volume of the hypothetical subcooled liquid 3,4-dimethoxybenzoic acid, $V_{\text{solute}}=143.8 \text{ cm}^3 \text{ mol}^{-1}$, was estimated as the molar volume of benzoic acid ($V_{\text{benzoic acid}}=104.4 \text{ cm}^3 \text{ mol}^{-1}$) plus two times the molar volume of methoxybenzene ($V_{\text{methoxybenzene}} = 109.1 \text{ cm}^3 \text{ mol}^{-1}$) minus two times the molar volume of benzene ($V_{\text{benzene}} = 89.4 \text{ cm}^3 \text{ mol}^{-1}$). Any errors resulting from the

estimation of 3,4-dimethoxybenzoic acid's hypothetical subcooled liquid molar volume, V_{Solute} , or the ideal molar volume approximation will have negligible effect of the calculated C_S^{exp} values because 3,4-dimethoxybenzoic acid is not overly soluble in many of the solvents considered. From a mathematical standpoint, the $X_S^{\text{exp}} \cdot V_{\text{Solute}}$ term contributes very little to the molar volumes of the saturated solutions.

Table 3. Comparison Between Observed and Back-Calculated Molar Solubilities of 3,4-Dimethoxybenzoic Acid Based Upon Eqn. (1) and Eqn. (2), and Existing Molecular Solute Descriptors^a

| Solvent | Equation (1) | | | | Equation (2) | | |
|---------------------------|-------------------------|------------------------------|-------------------------------|--------------------------|------------------------------|-------------------------------|--------------------------|
| | $\log C_S^{\text{exp}}$ | $\log(C_S/C_W)^{\text{exp}}$ | $\log(C_S/C_W)^{\text{calc}}$ | $\log C_S^{\text{calc}}$ | $\log(C_S/C_G)^{\text{exp}}$ | $\log(C_S/C_G)^{\text{pred}}$ | $\log C_S^{\text{pred}}$ |
| 1-Octanol (wet) | | 1.480 ^b | 1.400 ^b | | 9.750 ^b | 9.767 ^b | |
| Diethyl ether (wet) | | 0.880 ^b | 0.984 ^b | | 9.150 ^b | 9.282 ^b | |
| Methanol (dry) | -0.735 | 1.760 | 1.793 | -0.702 | 10.030 | 10.164 | -0.601 |
| Ethanol (dry) | -0.916 | 1.579 | 1.606 | -0.889 | 9.849 | 9.979 | -0.786 |
| 1-Propanol (dry) | -1.070 | 1.425 | 1.469 | -1.026 | 9.695 | 9.817 | -0.948 |
| 2-Propanol (dry) | -1.097 | 1.398 | 1.453 | -1.042 | 9.668 | 9.822 | -0.943 |
| 1-Butanol (dry) | -1.169 | 1.326 | 1.341 | -1.154 | 9.596 | 9.701 | -1.064 |
| 1-Pentanol (dry) | -1.267 | 1.228 | 1.269 | -1.226 | 9.498 | 9.619 | -1.146 |
| 1-Hexanol (dry) | -1.309 | 1.186 | 1.231 | -1.264 | 9.456 | 9.586 | -1.179 |
| 1-Heptanol (dry) | -1.362 | 1.133 | 1.167 | -1.328 | 9.403 | 9.541 | -1.224 |
| 1-Octanol (dry) | -1.410 | 1.085 | 1.143 | -1.352 | 9.355 | 9.436 | -1.329 |
| 1-Decanol (dry) | -1.501 | 0.994 | 0.973 | -1.522 | 9.264 | 9.339 | -1.426 |
| 2-Butanol (dry) | -1.154 | 1.341 | 1.436 | -1.059 | 9.611 | 9.781 | -0.984 |
| 2-Methyl-1-propanol (dry) | -1.315 | 1.180 | 1.336 | -1.159 | 9.450 | 9.686 | -1.079 |
| 2-Methyl-2-propanol (dry) | -1.001 | 1.494 | 1.432 | -1.063 | 9.764 | 9.811 | -0.954 |
| 3-Methyl-1-butanol (dry) | -1.293 | 1.202 | 1.269 | -1.226 | 9.472 | 9.633 | -1.132 |
| 2-Pentanol (dry) | -1.267 | 1.228 | 1.295 | -1.200 | 9.498 | 9.666 | -1.099 |
| Diethyl ether (dry) | -1.525 | 0.970 | 1.124 | -1.371 | 9.240 | 9.417 | -1.348 |
| 1,4-Dioxane (dry) | -0.480 | 2.015 | 1.841 | -0.654 | 10.285 | 10.161 | -0.604 |
| Tetrahydrofuran (dry) | -0.328 | 2.167 | 1.954 | -0.541 | 10.437 | 10.281 | -0.484 |
| Propanone (dry) | -0.803 | 1.692 | 1.682 | -0.813 | 9.962 | 10.054 | -0.711 |
| Butanone (dry) | -0.879 | 1.616 | 1.734 | -0.761 | 9.886 | 10.093 | -0.672 |
| Methyl acetate (dry) | -0.973 | 1.522 | 1.559 | -0.936 | 9.792 | 9.852 | -0.913 |
| Ethyl acetate (dry) | -1.085 | 1.410 | 1.346 | -1.149 | 9.680 | 9.721 | -1.044 |
| Propyl acetate (dry) | -1.229 | 1.266 | 1.271 | -1.224 | 9.536 | 9.644 | -1.121 |
| Butyl acetate (dry) | -1.303 | 1.192 | 1.194 | -1.301 | 9.462 | 9.566 | -1.199 |
| Propylene carbonate (dry) | -1.029 | 1.466 | 1.404 | -1.091 | 9.736 | 9.644 | -1.121 |
| Gas-to-Water | | 8.270 | 8.256 | | | 8.270 | 8.269 |

^a Numerical values of the descriptors used in these calculations are: $E=0.890$, $S=1.570$, $A=0.580$, $B=0.760$, $V=1.3309$ and $L=6.670$.

^b Practical partition coefficient.

Examination of the numerical entries in Table 3 reveals that our existing solute descriptors provide a very reasonable estimation of the solubility behavior of 3,4-dimethoxybenzoic acid in diethyl ether, tetrahydrofuran, 1,4-dioxane, and in 15 alcohol and four alkyl acetate solvents. Standard deviations between predicted and observed values were 0.091 and 0.134 log units for Eqns. 1 and 2, respectively. The prediction of the practical water-to-diethyl ether partition coefficient ($\log P_{\text{exp}} = 0.8822$) and water-to-1-octanol partition coefficient ($\log P_{\text{exp}} = 1.4822$) is included in the standard deviation for Eqn. 1. A predictive error of ± 0.13 log units corresponds to approximately a

35 % error in estimating the molar solubility. Standard deviations of 0.091 and 0.134 log units are comparable to the standard deviations associated with the transfer coefficients for the individual solvents, which for most solvents fell in the range of ± 0.12 to ± 0.20 log units.

Equation coefficients are available for only 25 of the 36 organic solvents studied. 3,4-Dimethoxybenzoic acid solubilities were measured in solvents like 2-ethoxyethanol, 2-isopropoxyethanol, 2-butoxyethanol, 3-methoxy-1-butanol, 2-methyl-1-butanol, 2-methyl-1-pentanol, 4-methyl-2-pentanol, pentyl acetate and diisopropyl ether so that we

would have more experimental data to use in subsequent studies to generate solute transfer correlation equations for additional organic solvents. Predictions were not made for dibutyl ether because past studies suggest that carboxylic acids exhibit significant dimerization in this particular

solvent, in which case the measured solubility would represent the sum of the molar concentration of monomeric solute plus twice the molar concentration of the carboxylic acid dimer. Our existing solute descriptors pertain to the monomeric form of 3,4-dimethoxybenzoic acid.

Table 4. Comparison between observed and back-calculated molar solubilities of 3,4-dimethoxybenzoic acid based upon Eqn. (1) and Eqn. (2), and revised molecular solute descriptors^a

| Solvent | $\log C_S^{exp}$ | $\log (C_S/C_W)^{exp}$ | Equation (1) | | $\log (C_S/C_G)^{exp}$ | Equation (2) | |
|---------------------------|------------------|------------------------|-------------------------|-------------------|------------------------|-------------------------|-------------------|
| | | | $\log (C_S/C_W)^{calc}$ | $\log C_S^{calc}$ | | $\log (C_S/C_G)^{calc}$ | $\log C_S^{calc}$ |
| 1-Octanol (wet) | | 1.480 ^b | 1.371 | | 9.927 | 9.843 | |
| Diethyl ether (wet) | | 0.880 ^b | 0.967 | | 9.327 | 9.371 | |
| Methanol (dry) | -0.735 | 1.760 | 1.774 | -0.721 | 10.207 | 10.257 | -0.685 |
| Ethanol (dry) | -0.916 | 1.579 | 1.571 | -0.924 | 10.026 | 10.050 | -0.892 |
| 1-Propanol (dry) | -1.070 | 1.425 | 1.433 | -1.062 | 9.872 | 9.881 | -1.061 |
| 2-Propanol (dry) | -1.097 | 1.398 | 1.410 | -1.085 | 9.845 | 9.878 | -1.064 |
| 1-Butanol (dry) | -1.169 | 1.326 | 1.309 | -1.186 | 9.772 | 9.769 | -1.173 |
| 1-Pentanol (dry) | -1.267 | 1.228 | 1.226 | -1.269 | 9.675 | 9.675 | -1.267 |
| 1-Hexanol (dry) | -1.309 | 1.186 | 1.193 | -1.302 | 9.633 | 9.646 | -1.296 |
| 1-Heptanol (dry) | -1.362 | 1.133 | 1.133 | -1.362 | 9.580 | 9.601 | -1.341 |
| 1-Octanol (dry) | -1.410 | 1.085 | 1.116 | -1.379 | 9.532 | 9.499 | -1.443 |
| 1-Decanol (dry) | -1.501 | 0.994 | 0.932 | -1.563 | 9.441 | 9.395 | -1.547 |
| 2-Butanol (dry) | -1.154 | 1.341 | 1.396 | -1.099 | 9.788 | 9.838 | -1.104 |
| 2-Methyl-1-propanol (dry) | -1.315 | 1.180 | 1.291 | -1.204 | 9.627 | 9.742 | -1.200 |
| 2-Methyl-2-propanol (dry) | -1.001 | 1.494 | 1.389 | -1.106 | 9.941 | 9.862 | -1.080 |
| 3-Methyl-1-butanol (dry) | -1.293 | 1.202 | 1.313 | -1.182 | 9.649 | 9.684 | -1.258 |
| 2-Pentanol (dry) | -1.267 | 1.228 | 1.239 | -1.256 | 9.675 | 9.712 | -1.230 |
| Diethyl ether (dry) | -1.525 | 0.970 | 1.117 | -1.378 | 9.417 | 9.499 | -1.443 |
| 1,4-Dioxane (dry) | -0.480 | 2.015 | 1.887 | -0.608 | 10.462 | 10.307 | -0.635 |
| Tetrahydrofuran (dry) | -0.328 | 2.167 | 1.975 | -0.520 | 10.613 | 10.396 | -0.546 |
| Propanone (dry) | -0.803 | 1.692 | 1.723 | -0.772 | 10.139 | 10.198 | -0.744 |
| Butanone (dry) | -0.879 | 1.616 | 1.777 | -0.718 | 10.063 | 10.232 | -0.710 |
| Methyl acetate (dry) | -0.973 | 1.522 | 1.596 | -0.899 | 9.968 | 9.996 | -0.946 |
| Ethyl acetate (dry) | -1.085 | 1.410 | 1.367 | -1.128 | 9.857 | 9.841 | -1.101 |
| Propyl acetate (dry) | -1.229 | 1.266 | 1.290 | -1.205 | 9.713 | 9.760 | -1.182 |
| Butyl acetate (dry) | -1.303 | 1.192 | 1.212 | -1.283 | 9.639 | 9.679 | -1.263 |
| Propylene carbonate (dry) | -1.029 | 1.466 | 1.489 | -1.006 | 9.913 | 9.961 | -0.981 |
| Gas-to-Water | | 8.447 | 8.420 | | 8.447 | 8.446 | |

^a Numerical values of the descriptors used in these calculations are: $E = 0.950$, $S = 1.646$, $A = 0.570$, $B = 0.755$, $V = 1.3309$ and $L = 6.746$.

^b Practical partition coefficient.

Revision of Solute Descriptor Values: The existing values that we have for 3,4-dimethoxybenzoic acid do provide very good predictions for the observed solubility behaviour of the compound in alcohol, alkyl acetate and ether solvents. The values were based on only two experimental practical partition coefficients; however, and it is desirable to have values based on a database having greater chemical diversity. One of the criticisms that models of this type often encounter is that one must not make predictions outside of the chemical space used in determining the solute descriptors and/or equation coefficients. We can address this concern now since experimental data are available for updating the solute descriptors, and there is no reason for us not to perform the few additional calculations to update the numerical values. Combining the two sets of LFERs, $\log (SR \text{ or } P)$ and \log

($GSR \text{ or } K$) correlations, we have a total of 54 mathematical equations. The characteristic McGowan volume of 3,4-dimethoxybenzoic acid is known, $V = 1.3309$, from the summation of the individual atomic sizes less a contribution for each bond in the molecule.²³ The E solute descriptor is $E = 0.950$, which is slightly larger than the estimate used several years ago when our preliminary solute descriptors were initially calculated. The set of 54 equations were then solved using Microsoft “Solver” to yield the numerical values of the four remaining solute descriptors that best described the $\log (SR \text{ or } P)$ and $\log (GSR \text{ or } K)$ values. The updated set of molecular solute descriptors are $E = 0.950$, $S = 1.646$, $A = 0.570$, $B = 0.755$, $V = 1.3309$, and $L = 6.746$; and the vapor phase concentration was $\log C_G = -10.942$. The updated solute descriptors differ very slightly from our previous values. This is to be expected as our existing

solute descriptors did provide a very good mathematical description of the observed solubility behavior of 3,4-dimethoxybenzoic acid in the alcohol, alkyl acetate, and ether solvents. The updated solute descriptors reproduce the experimental log (*SR* or *P*) and log (*GSR* or *K*) values to within an overall standard deviation of 0.084 log units and 0.082 log units, respectively, as shown in Table 4. Statistically, there is no difference between the set of 27 log (*SR* and *P*) values and the total set of 54 log (*SR* or *P*) and log (*GSR* or *K*) values, thus suggesting that $\log C_G = -10.942$ is a feasible value for the 3,4-dimethoxybenzoic acid correlations.

The calculated solute descriptors of 3,4-dimethoxybenzoic acid do account very well for the observed solubilities and partition coefficients; however, the values must reflect chemical properties of the solute, otherwise, the descriptors would be simply “curve-fitting parameters”. Our solute descriptor database does contain benzoic acid (**E** = 0.730, **S** = 900, **A** = 0.590, **B** = 0.400, **V** = 0.9317 and **L** = 4.657) and other methoxy-substituted benzoic acids. Hoover et al.¹¹ previously determined solute descriptors for 2-methoxybenzoic acid (**E** = 0.899, **S** = 1.410, **A** = 0.450, **B** = 0.620, **V** = 1.3133 and **L** = 5.636) and 4-methoxybenzoic acid (**E** = 0.899, **S** = 1.250, **A** = 0.620, **B** = 0.520, **V** = 1.3133 and **L** = 5.741) based largely on experimental solubility data in neat alcohol and ether solvents. For benzoic acid, 4-methoxybenzoic acid and 3,4-dimethoxybenzoic acid, there is a progressive increase in the descriptors **E**, **S**, **B**, **V** and **L** with each added methoxy-functional group. The two lone electron pairs on the oxygen atom of each methoxy-substituent provide additional H-bond donor sites, and increase the electron density of the aromatic ring through resonance and/or inductive effects. The solute descriptors of 2-methoxybenzoic acid do not follow this trend. The lower than expected H-bond acidity for 2-methoxybenzoic acid is likely due to intramolecular hydrogen-bond formation, which has been suggested by both solution IR and proton, ¹³C and ¹⁷O NMR studies.²⁴⁻²⁸ Intramolecular H-bond formation would both reduce the H-bond basicity of the methoxy oxygen atom and increase the basicity of the oxygen atom in the carboxylic –OH group.

Conclusion

The Abraham solvation parameter model has been used to describe mathematically the observed solubility data for 3,4-dimethoxybenzoic acid dissolved in alcohol, alkyl acetate and ether solvents. The computation methodology used to calculate the solute descriptors requires experimental solubility data for the solute in water and in a dozen or so other solvents for Abraham equation coefficients are known. The solute descriptors, once calculated, can be used both to back-calculate the measured solubility data employed in the solute descriptor determination as well as to predict the solute's solubility in additional solvents for which equation coefficients are known.

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