Updated Abraham Model Correlations for Describing Solute Transfer into Both 2-Pentanol and 3-Methyl-1-butanol Based on Much Larger Data Sets

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Abstract

Mole fraction solubilities of 4-*tert*-butylbenzoic acid, 3-chlorobenzoic acid, 2-methyl-3-nitrobenzoic acid, 3-methyl-4-nitrobenzoic acid, 3,4,5-trimethoxybenzoic acid, isophthalic acid, 3-hydroxybenzoic acid, *o*-acetoacetaniside, 2,4-dihydroxybenzophenone, benzoin, paracetamol, 1,4-dichloro-2-nitrobenzene in 2-pentanol at 298.15 K. Results of the experimental measurements, combined with published literature data, were used to calculated revised equation coefficients for the Abraham model correlations for the 2-pentanol solvent. Revised equation coefficients are also reported for the 3-methyl-1-butanol Abraham model correlations based on much larger data sets containing 95 experimental data points.

Key Words and Phrases

Abraham model correlations; molar solubility ratios; partition coefficients; 2-pentanol solvent; 3-methyl-1-butanol solvent

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1. Introduction

The critical role that organic solvents play in chemical manufacturing processes is perhaps best illustrated by the effort that the different industries have devoted to developing a set of solvent selection guidelines [1-11]. Guidelines have been developed for virtually every stage in the manufacturing process, starting with the selection of a solvent suitable for use as a reaction medium in chemical synthesis to finding an organic solvent capable of cleaning the industrial machinery and glassware after the process is complete. Each manufacturing step may require a different organic solvent as no one solvent will likely be suitable for the entire process which may involve crystallization of the crude chemical product having a specific size and crystal morphology to facilitate downstream processing, as well as purification of the final product using either preparative liquid chromatography and/or biphasic liquid-liquid extraction to remove unreacted starting materials and any by products that have been formed during the course of synthetic method. In the case of pharmaceutical compounds intended for human consumption the purification process can be quite extensive as governmental regulations place limits on the amount of residual solvents and other impurities that the compound can contain [12]. The limits are solvent-specific and depend on the health risk posed by the solvent. Depending upon the chemical compound and its intended application, the industrial process may require that the commercial product be sold as a formulation, in which case one may need to find a dispersing or solubilizing agent in order to achieve a specified solubility. The solubility of crystalline compounds can also be altered through polymorphism and solvate formation, and suggestions have been published to aid in finding the most stable polymorph of a pharmaceutical compound [13-15].

The selection of a suitable organic solvent is by no means an easy task, and involves not only a careful consideration of the technical aspects (solvent boiling point temperature, viscosity,

solubilizing ability, heat capacity) required by the manufacturing processes, but also economical (purchase price, disposal cost, storage cost) and safety/health factors, and a careful assessment of both the short-term and long-term environmental impact. The assessment of the environment impact may also include what is referred to as a cradle-to-grave evaluation that considers everything from the raw materials and energy needed to prepare the organic solvent to the final cost associated with solvent disposal. Physical property and toxicity databases have been created for the more commonly used industrial organic solvents to aid in the design of new manufacturing processes. Properties for new organic solvents are continually being added to assist design engineers in identifying safer and more environmentally compatible solvent alternatives to replace the more toxic organic solvents currently being used in industrial manufacturing processes. Governmental regulations and policies have restricted the use of several organic solvents in certain industries, and to "keep ahead of the curve" design engineers hope to phase-out several of the more problematic solvents sooner rather than later. Chemicals that are candidates for possible future restrictions/bans according to the European Union's chemical regulation REACH include solvents like nitrobenzene, *o*-toluidine, formamide, *N*-methylpyrrolidone, trichloroethylene and 1,2,3-trichloropropane [16].

Predictive tools [16-23] have been developed to aid the manufacturing sector in the solvent selection process. The tools enable one to estimate the physical and thermodynamic properties of a wide range of organic solvents based solely on group contribution models deduced from molecular structure considerations, or based on more theoretical solution models which take into account our basic understanding of how molecules interact with their solubilizing media. Our contribution in the area of solvent selection has been two-fold: first to provide experimental solubility data for crystalline organic compounds dissolved in a wide range of organic solvents of

varying polarity and hydrogen-bonding ability, and (b) then to use our measured values in obtaining mathematical expressions that enable one to estimate the solubility of additional organic solutes based on the Abraham solvation parameter model [24-29]. Abraham model equations have been reported for predicting solubilities in more than 130 different organic mono-solvents [24-30], in 3 binary aqueous-alcoholic solvent mixtures [31-34], and in more than 100 different ionic liquid solvents [35-38]. We are continually determining predictive expressions for additional solvents, and updating the existing expressions as more experimental data becomes available. Recent additions to the list of organic solvents include transcutol [28], *tert*-butyl acetate [26], and dimethyl adipate [29].

In the present communication we have updated the existing Abraham model expressions for predicting the molar solubility of solid organic compounds and inorganic gases in both 3-methyl-1-butanol and 2-pentanol using data sets that contained 95 and 76 experimental values, respectively. Sprunger et al. [39] previously reported predictive expressions for 3-methyl-1-butanol based on much smaller data sets that contained only 62 data points:

$$\log (P \text{ or } C_{S,organic}/C_{S,water}) = 0.073(0.043) + 0.360(0.049)\,\mathbf{E} - 1.273(0.071)\,\mathbf{S} + 0.090(0.059)\,\mathbf{A} - 3.770(0.108)\,\mathbf{B} + 4.273(0.063)\,\mathbf{V} \quad (1)$$

(with N = 62, SD = 0.099, R^2 = 0.992, F = 2524)

$$\log (K \text{ or } C_{S,organic}/C_{S,gas}) = -0.052(0.038) - 0.430(0.069)\,\mathbf{E} + 0.628(0.092)\,\mathbf{S} + 3.661(0.073)\,\mathbf{A} + 0.932(0.132)\,\mathbf{B} + 0.937(0.019)\,\mathbf{L} \quad (2)$$

(with N = 62, SD = 0.121, R^2 = 0.998, F = 7861)

where the standard error in each calculated equation coefficients is given in parenthesis following the respective coefficient. The solute transfer properties, given on the left-hand side of Eqns. (1) and (2), represent the logarithm of the solute's water-to-organic solvent partition coefficient, log

P, the logarithm of the solute's gas-to-organic solvent partition coefficient, log *K*, or logarithms of molar solubility ratios, log ($C_{S,organic}/C_{S,water}$) and log ($C_{S,organic}/C_{S,gas}$). Molar solubility ratios are used for organic solvents that are completely miscible with water as "direct practical" partition coefficients can only be measured for biphasic partitioning systems, such as those systems used in solute extractions. For two completely miscible solvents, the molar solubility ratio is often referred to as a "hypothetical" partition coefficient or more formally as a solute transfer coefficient. The subscript "water", "organic" and "gas" denotes the phase to which the solute concentration refers.

The earlier equations exhibited good predictive applicability as evidenced by the small standard deviations of the residuals, SD = 0.099 log units and SD = 0.121 log units, near unity squared correlation coefficients, $R^2 = 0.992$ and $R^2 = 0.998$, and large Fisher F-statistics, F = 2524 and F = 7861. Both expressions should provide good predictions for additional compounds that fall within the predictive areas of chemical space covered by Eqns. (1) and (2). The predictive area of chemical space is defined by the solute descriptor values that were used in calculating the equation coefficients, which in the case of Eqns. (1) and (2) were: from **E** = -0.250 to **E** = 2.808; from **S** = 0.000 to **S** = 2.100; from **A** = 0.000 to **A** = 0.940; from **B** = 0.000 to **B** = 0.780; from **V** = 0.1086 to **V** = 1.7821; to **L** = -1.200 to **L** = 9.207. Best practices require that one not use Eqns. (1) and (2) to make predictions for new solutes having solute descriptors that fall far outside of the range of values given above, nor should one use Eqns. (1) and (2) to calculate solute descriptors of additional solutes that are expected to fall far outside of this range. Many of the larger active pharmaceutical molecules will fall outside of this range, and several research groups [40-45] are now determining the solubility of drug molecules in 3-methyl-1-butanol. Expanding the predictive area of chemical space covered by the Abraham model correlations for 3-methyl-1-butanol will facilitate our ongoing efforts in determining experiment-based solute descriptors for additional

organic compounds. At present experiment-based solute descriptors are known for more than 8,500 compounds; however, this represents only a minute fraction of the known chemical compounds [46-48].

Solute descriptors are described as follows: **E** denotes the molar refraction of the given solute in excess of that of a linear alkane having a comparable molecular size; **S** is a combination of the electrostatic polarity and polarizability of the solute; **A** and **B** refer to the respective hydrogen-bond donating and accepting capacities of the dissolved solute; **V** corresponds to the McGowan molecular volume of the solute calculated from atomic sizes and chemical bond numbers; and **L** is the logarithm of the solute's gas-to-hexadecane partition coefficient measured at 298.15 K. The numerical values that precede the solute descriptors represent the complementary solvent properties for 3-methyl-1-butanol which were determined by regressing experimental partition coefficient and molar solubility data in accordance with the basic Abraham model. The Abraham model will be described in greater detail in the Results and Discussion section when the computational methodology for calculating the updated equation coefficients is described.

Abraham model expressions for 2-pentanol were reported only in tabular format in several earlier papers [49-53] that illustrated the calculation of solute descriptors from measured solubility ratios, $C_{S,organic}/C_{S,water}$ and $C_{S,organic}/C_{S,gas}$. The data sets and associated statistics for the two existing Abraham model correlations for 2-pentanol were never reported *per se*. A search of the published chemical literature reveals that there has been sufficient experimental solubility reported for organic compounds dissolved in this alcohol mono-solvent during the last 10 years to merit updating our existing log (P or $C_{S,organic}/C_{S,water}$) and log ($K$ or $C_{S,organic}/C_{S,gas}$) Abraham model correlations for 2-pentanol. To increase the size of the data sets that will be used in calculating the revised equation coefficients, and to provide the scientific community with additional solubility

data to use in the design of manufacturing processes, we have measured the mole fraction solubilities of 4-*tert*-butylbenzoic acid, 3-chlorobenzoic acid, 2-methyl-3-nitrobenzoic acid, 3-methyl-4-nitrobenzoic acid, 3,4,5-trimethoxybenzoic acid, isophthalic acid, 3-hydroxybenzoic acid, *o*-acetoacetaniside, 2,4-dihydroxybenzophenone, benzoin, paracetamol, 1,4-dichloro-2-nitrobenzene in 2-pentanol at 298.15 K. Results of experimental measurements, combined with published literature data [54-63], provides us with 76 data points to use in updating the Abraham model correlations for 2-pentanol.

2. Chemical Materials and Experimental Methodology

2-Pentanol (CAS Registry Number: 6032-29-7; Thermo Fisher Scientific, Ward Hill, Massachusetts, USA, 99 %) was purchased from a commercial source, stored over activated molecular sieves and distilled shortly before use. Gas chromatographic analysis of the distilled 2-pentanol sample showed the purity to be 99.7 mass percent. Samples of *o*-acetoacetanisidide (Acros Organics, Morris Plains, New Jersey, USA, 99+ %), benzoin (Aldrich Chemical Company, 98 %), 4-*tert*-butylbenzoic acid (TCI America Chemical Company, Portland, Oregon, USA, 99+ %), 3-chlorobenzoic acid (Aldrich Chemical Company, 99 %), 1,4-dichloro-2-nitrobenzene (TCI America Chemical Company, 99+ %), 2,4-dihydroxybenzophenone (Acros Organics, 99 %), 3-hydroxybenzoic acid (Acros Organics, 99 %), isophthalic acid (Aldrich Chemical Company, 99 %), 2-methyl-3-nitrobenzoic acid (Aldrich Chemical Company, 99 %), 3-methyl-4-nitrobenzoic acid (Aldrich Chemical Company, 99 %), 4-methyl-3-nitrobenzoic acid (Aldrich Chemical Company, 99 %), paracetamol (Thermo Fisher Scientific, 98 %), and 3,4,5-trimethoxybenzoic acid (Aldrich Chemical Company, 99 %), were purchased from commercial sources in the highest mass percent available. Benzoin, 2,4-dihydroxybenzophenone and paracetamol were recrystallized three times from anhydrous methanol prior to use. All organic solutes were dried at 333 K for at

least 24 hours prior to use in order to remove trace moisture. The purities of the dried carboxylic acid samples were determined by titrimetric analysis with a freshly standardized aqueous sodium hydroxide solution to the phenolphthalein end point. Titrimetric analyses showed the purity of the seven benzoic acid derivatives to be 99.7 mass percent (or higher). ACS Reagent grade 2-propanol (Thermo Fisher Scientific) was used to dilute the samples prior to spectrophotometric analysis.

The mole fraction solubilities of the twelve crystalline organic compounds were measured using static equilibration method, followed by a spectrophotometric determination of the dissolved solute concentration in the equilibrated saturated solutions. Aliquots of the clear saturated solutions were transferred into tared 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 to facilitate dissolution and mixing. The flasks with the transferred aliquot of the saturated solution were then weighed on an electronic analytical balance and diluted quantitatively with 2-propanol. Absorbances of the diluted solutions and of the eight standard solutions of known solute concentrations were recorded on a Milton Roy Spectronic 1000 Plus spectrophotometer (Milton Roy, Rochester, NY, USA). The concentration of the individual diluted solutions was calculated using a Beer-Lambert law analysis based on absorbance versus concentration curve obtained from the measured absorbances of eight standard solutions. The analysis wavelengths and concentration ranges used for each solute have been reported in our earlier publications [51,56,62,64-70]. Molar concentrations were converted into mole fraction solubilities using the molar masses of 2-pentanol and the respective solutes, mass of the sample analyzed, volume of the volumetric flasks, and any dilutions that were needed in order to place the measured absorbances on the Beer-Lambert law curve. Repetitive measurements were performed on select samples to ensure that equilibrium saturation conditions had been achieved. Melting point temperatures on the equilibrated solid

phases recovered from the saturated solutions after the solubility measurements were performed in order to check for possible solid-to-solid phase transition and solvate formation. For each of the 12 crystalline solute–2-pentanol combinations studied, the melting point temperature of the equilibrated solid phase was within ±0.5 K of the melting point temperature of the commercial sample or recrystallized solute prior to contact with 2-pentanol.

3. Results and Discussion

The experimental mole fraction solubilities, $X_{S,organic}^{exp}$, of the 12 crystalline organic solutes in 2-pentanol at 298.15 K are tabulated in the second column of Table 1. The numerical values represent the average of 4 to 8 independent experimental determinations, which were reproducible to within ± 2.5 % (relative error). Also listed in the penultimate column of Table 1 are the mole fraction solubilities of isophthalic acid [51], 3-methyl-4-nitrobenzoic acid [62], and 3,4,5-trimethoxybenzoic acid [56] dissolved in 2-pentanol that were found in our search of the published chemical literature. Our measured experimental mole fraction solubilities differ from the three published literature values by an average absolute relative deviation of 3.5%, which is less than the combined uncertainty associated with the given experimental mole fraction solubilities.

Table 1. Measured Mole Fraction Solubilities, $X_{S,organic}^{exp}$, of 12 Crystalline Nonelectrolyte Solutes Dissolved in 2-Pentanol at 298.15 K

Solute	$X_{S,organic}^{exp}$	$X_{S,organic}^{lit}$	[Ref]
Noncarboxylic acid solutes			
o-Acetoacetanisidide	0.01050		

Benzoin	0.002479		
1,4-Dichloro-2-nitrobenzene	0.04011		
2,4-Dihydroxybenzophenone	0.01347		
Paracetamol	0.03637		
Carboxylic acid solutes			
4-*tert*-Butylbenzoic acid	0.08460		
3-Chlorobenzoic acid	0.1013		
3-Hydroxybenzoic acid	0.1099		
Isophthalic acid	0.00341	0.00324	[52]
2-Methyl-3-nitrobenzoic acid	0.02323		
3-Methyl-4-nitrobenzoic acid	0.01246	0.01264	[63]
3,4,5-Trimethoxybenzoic acid	0.01432	0.0137	[57]

The basic Abraham model, upon which Eqns. (1) and (2) are based, describe solute transfer between two condensed phases [72,73]:

$$\log (P \text{ or } SRW) = c_p + e_p \cdot \mathbf{E} + s_p \cdot \mathbf{S} + a_p \cdot \mathbf{A} + b_p \cdot \mathbf{B} + v_p \cdot \mathbf{V} + j_{p+} \cdot \mathbf{J}^+ + j_{p-} \cdot \mathbf{J}^- \quad (3)$$

and solute transfer from the gas phase into a condensed phase:

$$\log (K \text{ or } SRG) = c_k + e_k \cdot \mathbf{E} + s_k \cdot \mathbf{S} + a_k \cdot \mathbf{A} + b_k \cdot \mathbf{B} + l_k \cdot \mathbf{L}, \quad (4)$$

where the lowercase sets of alphabetical characters on the right-hand side of both expressions, (c_p, e_p, s_p, a_p, b_p and v_p) and (c_k, e_k, s_k, a_k, b_k and l_k), pertain to the solvent properties. The numerical values of each solvent property will differ from one solvent to another as each solvent has its own, unique solubility ability. Redetermination of the numerical values of (c_p, e_p, s_p, a_p, b_p and v_p) and

(c_k, e_k, s_k, a_k, b_k and l_k) for 2-pentanol and 3-methyl-1-butanol using much larger datasets is the objective of the current study. For notational simplicity we have substituted *SRW* and *SRG* into Eqns. (1) and (2) to denote the molar solubility ratios $C_{S,organic}/C_{S,water}$ and $C_{S,organic}/C_{S,gas}$, respectively.

We call attention to the two additional terms, $j_{p+}\mathbf{J}^+$ and $j_{p-}\mathbf{J}^-$, on the right-hand side of Eqn. (3). The additional terms pertain to ion-solvent interactions involving positively charged cationic solutes and negatively charged anionic solutes with surrounding solvent molecules. In other words, the Abraham model can describe solute transfer properties involving not only nonionic molecules, but ionic species as well. On of the motivations for updating our existing Abraham model correlations for 2-pentanol and 3-methyl-1-butanol at this point in time is future plans to extend the log (*P* or *SRW*) correlations to include solute transfer of ionic species into both organic mono-solvents from water. Updating the (c_p, e_p, s_p, a_p, b_p and v_p) becomes more tedious once the j_{p+} and j_{p-} numerical values have been determined. Experimental solubility data for α-amino acids provides a convenient means to calculate the j_{p+} and j_{p-} coefficients for a given organic mono-solvent or binary aqueous-organic solvent mixture. α-Amino acids exist in zwitterionic form, and will contain both a positively charged cationic and negatively charged anionic moiety. Abraham and Acree [74] have reported solute descriptors for several α-amino acids that can serve as the basis for calculating the j_{p+} and j_{p-} solvent coefficients. The other method [72,73] for calculating the j_{p+} and j_{p-} coefficients requires knowledge of the pK_a dissociation constants for carboxylic acids in the organic mono-solvent or binary aqueous-organic solvent whose j_{p+} and j_{p-} coefficients are to be calculated. Experimental acid dissociation constants for carboxylic acid solutes in organic solvents are not readily available in the chemical literature.

The Abraham model combines experimental molar solubility ratios and partition coefficients into a single mathematical expression that enables one to predict log (*P* or *SRW*) and/or log (*K* or *SRG*) values for additional organic solutes dissolved in the specified organic solvent. The first step in updating the existing correlations for 2-pentanol and 3-methyl-1-butanol begins with converting the mole fraction solubility data given in Table 1, along with the mole fraction solubility data that we retrieved from the published chemical literature, into molar solubilities. As noted earlier additional solubility data has been reported for crystalline organic solutes dissolved both in 2-pentanol [50,52,55-64] and in 3-methyl-1-butanol [41-45,50,52-54,56-58,62,64-69,75-82] after the existing correlations were first derived. The conversion from mole fraction to molar solubility is accomplished by dividing the numerical values of $X_{S,organic}^{exp}$ by the ideal molar volume of the saturated solution (*i.e.*, $C_{S,organic}^{exp} \approx X_{S,organic}^{exp}/[X_{S,organic}^{exp} V_{Solute} + (1 - X_{S,organic}^{exp}) V_{Solvent}]$). Numerical values of $V_{solvent} = 0.1095$ Liter mol^{-1} and $V_{solvent} = 0.1098$ Liter mol^{-1} were used for the molar volumes of 2-pentanol and 3-methyl-1-butanol, respectively. The calculated $C_{S,organic}$ values were then converted into molar solubility ratios, *SRW* and *SRG*, by dividing by $C_{S,water}$ and $C_{S,gas}$, respectively. The experimental log *SRG* and log *SRW* values at 298.15 K for organic solutes dissolved in 2-pentanol and 3-methyl-1-butanol are listed in the eighth and ninth columns of Tables 2 and 3. Also given in the tables are the numerical values contained in two earlier publications by Abraham, Acree and coworkers [39,55].

Regression analysis of the tabulated log (*P* or *SRW*) and log (*K* or *SRG*) values in accordance to Eqns. 3 and 4 yielded the following Abraham model correlations for solute transfer into 2-pentanol:

Table 2. Experimental Logarithms of Molar Solubility Ratios, Log *SRG* and Log *SRW*, and Experimental Logarithms of Partition Coefficients, Log *K* and log *P*, for Solutes Dissolved in 2-Pentanol at 298.2 K

Solute	**E**	**S**	**A**	**B**	**L**	**V**	Log (*K* or *SRG*)	Log (*P* or *SRW*)	Reference
Propane	0.000	0.000	0.000	0.000	1.050	0.5313	0.980	2.420	[55]
Butane	0.000	0.000	0.000	0.000	1.615	0.6722	1.490	3.010	[55]
Isobutane	0.000	0.000	0.000	0.000	1.409	0.6722	1.320	3.020	[55]
Propene	0.100	0.080	0.000	0.070	0.946	0.4883	0.960	1.930	[55]
1-Butene	0.100	0.080	0.000	0.070	1.529	0.6292	1.470	2.480	[55]
cis-2-Butene	0.142	0.080	0.000	0.050	1.737	0.6292	1.630	2.620	[55]
trans-2-Butene	0.126	0.080	0.000	0.050	1.664	0.6292	1.580	2.560	[55]
Isobutene	0.120	0.080	0.000	0.080	1.579	0.6292	1.470	2.330	[55]
1,3-Butadiene	0.320	0.230	0.000	0.100	1.543	0.5862	1.520	1.970	[55]
1,1-Difluoroethane	-0.250	0.490	0.040	0.050	0.517	0.4258	0.890	0.810	[55]
Chloroethane	0.227	0.400	0.000	0.100	1.678	0.5128	1.730	1.270	[55]
Dimethyl ether	0.000	0.270	0.000	0.410	1.285	0.4491	1.500	0.100	[55]
Heptane	0.000	0.000	0.000	0.000	3.173	1.0949	2.925	4.885	[55]
Methanol	0.278	0.440	0.430	0.470	0.970	0.3082	3.170	-0.570	[55]
Propan-1-ol	0.236	0.420	0.370	0.480	2.031	0.5900	3.916	0.356	[55]
Propan-2-ol	0.212	0.360	0.330	0.560	1.764	0.5900	3.556	0.076	[55]
Pentan-2-ol	0.195	0.360	0.330	0.560	2.840	0.8718	4.671	1.451	Unity
1,2,4,5-Tetramethylbenzene	0.739	0.600	0.000	0.190	5.029	1.2800	4.907	4.381	[55]
trans-Stilbene	1.350	1.210	0.000	0.230	7.456	1.5630	7.270	4.750	[53]
Biphenyl	1.360	0.990	0.000	0.260	6.014	1.3242	6.045	4.095	[55]
Acenaphthene	1.604	1.050	0.000	0.220	6.469	1.2586	6.246	3.886	[55]
Fluorene	1.588	1.060	0.000	0.250	6.922	1.3565	6.621	4.171	[55]
Anthracene	2.290	1.340	0.000	0.280	7.568	1.4544	7.324	4.294	[55]
Phenanthrene	2.055	1.290	0.000	0.290	7.632	1.4544	7.174	4.374	[55]

Fluoranthene	2.377	1.550	0.000	0.240	8.827	1.5850	8.338	4.887	[55]
Pyrene	2.808	1.710	0.000	0.280	8.833	1.5850	8.416	4.916	[55]
Hexachlorobenzene	1.490	0.990	0.000	0.000	7.390	1.4508	6.925	5.421	[55]
1,4-Dibromobenzene	1.150	0.860	0.000	0.040	5.324	1.0660	5.120	3.680	[55]
Benzil	1.445	1.590	0.000	0.620	7.611	1.6374	7.982	3.112	[55]
1-Nitronaphthalene	1.600	1.590	0.000	0.290	7.056	1.2600	7.204	3.008	[55]
Benzoic acid	0.730	0.900	0.590	0.400	4.657	0.9317	6.975	1.875	[55]
4-*tert*-Butylbenzoic acid	0.730	1.111	0.551	0.443	6.547	1.4953	8.990	3.766	This work
2-Methylbenzoic acid	0.730	0.840	0.420	0.440	4.677	1.0726	6.580	2.280	[55]
3-Methylbenzoic acid	0.730	0.890	0.600	0.400	4.819	1.0726	7.363	2.383	[55]
2-Methyl-3-nitrobenzoic acid	1.040	1.396	0.541	0.532	6.332	1.2468	8.772	2.035	This work
3-Methyl-4-nitrobenzoic acid	1.040	1.336	0.525	0.500	6.266	1.2468	8.649	2.285	[63], This work
3-Chlorobenzoic acid	0.840	0.950	0.630	0.320	5.197	1.0541	7.763	2.613	This work
4-Chlorobenzoic acid	0.840	1.020	0.630	0.270	4.947	1.0541	7.539	2.739	[55]
3,4-Dichlorobenzoic acid	0.950	0.920	0.670	0.260	5.623	1.1766	8.073	3.333	[65]
2-Methoxybenzoic acid	0.899	1.410	0.450	0.620	5.636	1.1313	7.941	1.141	[55]
4-Methoxybenzoic acid	0.899	1.250	0.620	0.520	5.741	1.1313	8.523	1.823	[55]
3,4-Dimethoxybenzoic acid	0.950	1.646	0.570	0.755	6.746	1.3309	9.982	1.535	[54]
3,4,5-Trimethoxybenzoic acid	1.001	1.760	0.603	0.850	7.711	1.5309	10.918	1.663	[57]
3-Nitrobenzoic acid	0.990	1.180	0.730	0.520	5.601	1.1059	8.960	1.880	[55]
4-Nitrobenzoic acid	0.990	1.520	0.680	0.400	5.770	1.1059	8.793	1.893	[55]
4-Aminobenzoic acid	1.075	1.650	0.940	0.600	5.916	1.0315	10.157	0.727	[55]
3,5-Dinitrobenzoic acid	1.250	1.630	0.700	0.590	6.984	1.2801	10.194	1.894	[55]
3,5-Dinitro-2-methylbenzoic acid	1.310	2.120	0.750	0.650	8.040	1.4210	11.692	1.736	[56]
2-Chloro-5-nitrobenzoic acid	1.250	1.400	0.670	0.460	6.513	1.2283	9.413	2.467	[55]
4-Chloro-3-nitrobenzoic acid	1.250	1.470	0.700	0.440	6.685	1.2283	9.685	2.475	[55]
Acetylsalicylic acid	0.781	1.690	0.710	0.670	6.279	1.2879	9.773	1.273	[55]
Isophthalic acid	1.100	1.360	1.055	0.585	6.144	1.1470	10.676	1.603	[52], This work
Naproxen	1.510	2.022	0.600	0.673	9.207	1.7821	12.093	3.293	[55]
2-Hydroxybenzoic acid	0.900	0.850	0.730	0.370	4.732	0.9904	7.527	2.167	[55]

3-Hydroxybenzoic acid	0.910	0.880	0.860	0.580	4.860	0.9904	8.269	1.269	This work
Diphenyl sulfone	1.570	2.100	0.000	0.720	8.577	1.6051	9.634	2.244	[55]
Xanthene	1.502	1.070	0.000	0.230	7.153	1.4152	6.915	4.415	[55]
Monuron	1.140	1.500	0.470	0.780	7.180	1.4768	9.552	1.921	[55]
Diuron	1.280	1.600	0.570	0.700	8.060	1.5992	10.653	2.653	[55]
1-Chloroanthraquinone	1.900	1.790	0.000	0.570	9.171	1.6512	9.359	3.325	[55]
Salicylamide	1.160	1.580	0.610	0.510	5.818	1.0315	8.838	1.234	[55]
Phenothiazine	1.890	1.560	0.310	0.300	8.389	1.4789	9.404	4.001	[55]
Benzocaine	1.030	1.310	0.310	0.690	6.406	1.3133	8.187	1.887	[55]
4-Nitrobenzyl chloride	1.270	1.420	0.000	0.360	6.290	1.2065	6.042	2.273	[55]
2-Ethylanthraquinone	1.41	1.545	0.000	0.557	8.781	1.8106	9.047	4.233	[58]
Thioxanthen-9-one	1.940	1.441	0.000	0.557	8.436	1.5357	8.722	3.654	[61]
2-Naphthoxyacetic acid	1.610	1.940	0.690	0.764	8.553	1.5003	11.766	1.847	[51]
N-Hydroxyphthalimide	1.280	1.986	0.806	0.624	6.662	1.0795	10.510	0.527	[62]
o-Acetoacetanisidide	1.190	2.333	0.264	1.025	8.563	1.6108	10.754	0.520	This work
Sorbic acid	0.480	0.904	0.528	0.432	4.047	0.9424	6.467	1.556	[59]
9-Fluorenone	1.600	1.490	0.000	0.350	7.474	1.3722	7.716	3.516	[60]
2,4-Dihydroxybenzophenone	1.730	2.030	0.490	0.700	9.060	1.5982	11.517	2.457	This work
Benzoin	1.585	2.115	0.196	0.847	9.159	1.6804	10.755	2.024	This work
Paracetamol	1.060	1.630	1.040	0.860	6.430	1.1724	11.451	0.551	This work
1,4-Dichloro-2-nitrobenzene	1.120	1.289	0.000	0.199	5.783	1.1354	5.762	2.861	This work
Ferrocene	1.394	0.900	0.000	0.230	6.003	1.2043	5.800	3.680	[50]

Table 3. Experimental Logarithms of Molar Solubility Ratios, Log *SRG* and Log *SRW*, and Experimental Logarithms of Partition Coefficients, Log *K* and log *P*, for Solutes Dissolved in 3-Methyl-1-butanol at 298.2 K

Solute	**E**	**S**	**A**	**B**	**L**	**V**	Log (*K* or *SRG*)	log (*P* or *SRW*)	Reference
Radon	0.000	0.000	0.000	0.000	0.877	0.3840	0.881	1.530	[39]
Hydrogen	0.000	0.000	0.000	0.000	-1.200	0.1086	-1.290	0.430	[39]
Propane	0.000	0.000	0.000	0.000	1.050	0.5313	0.973	2.410	[39]
Butane	0.000	0.000	0.000	0.000	1.615	0.6722	1.480	3.000	[39]
Isobutane	0.000	0.000	0.000	0.000	1.409	0.6722	1.320	3.020	[39]
Hexane	0.000	0.000	0.000	0.000	2.668	0.9540	2.388	4.210	[39]
Heptane	0.000	0.000	0.000	0.000	3.173	1.0949	2.891	4.850	[39]
Octane	0.000	0.000	0.000	0.000	3.677	1.2358	3.400	5.510	[39]
Propene	0.100	0.080	0.000	0.070	0.946	0.4883	0.963	1.930	[39]
1-Butene	0.100	0.080	0.000	0.070	1.529	0.6292	1.462	2.470	[39]
cis-2-Butene	0.142	0.080	0.000	0.050	1.737	0.6292	1.623	2.630	[39]
trans-2-Butene	0.126	0.080	0.000	0.050	1.664	0.6292	1.572	2.590	[39]
Isobutene	0.120	0.080	0.000	0.080	1.579	0.6292	1.462	2.390	[39]
1,3-Butadiene	0.320	0.230	0.000	0.100	1.543	0.5862	1.529	1.980	[39]
1,1-Difluoroethane	-0.250	0.490	0.040	0.050	0.517	0.4258	0.956	0.870	[39]
Chloroethane	0.227	0.400	0.000	0.100	1.678	0.5128	1.782	1.320	[39]
Dimethyl ether	0.000	0.270	0.000	0.410	1.285	0.4491	1.457	0.060	[39]
1,4-Dioxane	0.329	0.750	0.000	0.640	2.892	0.6810	3.340	-0.370	[39]
2-Butanone	0.166	0.700	0.000	0.510	2.287	0.6879	3.010	0.290	[39]
Nitromethane	0.313	0.950	0.060	0.310	1.892	0.4237	2.730	-0.220	[39]
Methanol	0.278	0.440	0.430	0.470	0.970	0.3082	3.068	-0.670	[39]
Ethanol	0.246	0.420	0.370	0.480	1.485	0.4491	3.510	-0.160	[39]
3-Methyl-1-butanol	0.192	0.390	0.370	0.480	3.011	0.8718	4.771	1.530	[39]
Ferrocene	1.394	0.900	0.000	0.230	6.003	1.2043	5.785	3.665	[50]
Toluene	0.601	0.520	0.000	0.140	3.325	0.8573	3.300	2.650	[39]

1,2,4,5-Tetramethylbenzene	0.739	0.600	0.000	0.190	5.029	1.2800	4.860	4.330	[39]
trans-Stilbene	1.350	1.210	0.000	0.230	7.456	1.5630	7.250	4.730	[53]
Biphenyl	1.360	0.990	0.000	0.260	6.014	1.3242	5.980	4.034	[39]
Acenaphthene	1.604	1.050	0.000	0.220	6.469	1.2586	6.180	3.867	[39]
Fluorene	1.588	1.060	0.000	0.250	6.922	1.3565	6.560	4.112	[39]
Anthracene	2.290	1.340	0.000	0.280	7.568	1.4544	7.280	4.251	[39]
Phenanthrene	2.055	1.290	0.000	0.290	7.632	1.4544	7.130	4.332	[39]
Fluoranthene	2.377	1.550	0.000	0.240	8.827	1.5850	8.250	4.813	[39]
Pyrene	2.808	1.710	0.000	0.280	8.833	1.5850	8.340	4.845	[39]
Chlorobenzene	0.718	0.650	0.000	0.070	3.657	0.8388	3.756	2.940	[39]
Hexachlorobenzene	1.490	0.990	0.000	0.000	7.390	1.4508	7.030	5.526	[39]
1,4-Dibromobenzene	1.150	0.860	0.000	0.040	5.324	1.0660	5.140	3.696	[39]
Benzil	1.445	1.590	0.000	0.620	7.611	1.6374	7.930	3.060	[39]
Benzocaine	1.030	1.310	0.310	0.690	6.406	1.3133	8.100	1.800	[39]
4-Nitrobenzyl chloride	1.080	1.350	0.000	0.350	5.806	1.1539	6.110	2.341	[39]
1-Nitronaphthalene	1.600	1.590	0.000	0.290	7.056	1.2600	7.090	3.001	[39]
Benzoic acid	0.730	0.900	0.590	0.400	4.657	0.9317	6.900	1.801	[39]
4-*tert*-Butylbenzoic acid	0.730	1.111	0.551	0.443	6.547	1.4953	8.831	3.606	[67]
2-Methylbenzoic acid	0.730	0.840	0.420	0.440	4.677	1.0726	6.560	2.181	[39]
3-Methylbenzoic acid	0.730	0.890	0.600	0.400	4.819	1.0726	7.280	2.304	[39]
2-Methyl-3-nitrobenzoic acid	1.040	1.396	0.541	0.532	6.332	1.2468	8.764	2.027	[68]
3-Methyl-4-nitrobenzoic acid	1.040	1.336	0.525	0.500	6.266	1.2468	8.530	2.166	[63]
4-Methyl-3-nitrobenzoic acid	1.040	1.461	0.659	0.521	6.434	1.2468	9.297	1.983	[76]
3-Chlorobenzoic acid	0.840	0.950	0.630	0.320	5.197	1.0541	7.700	2.552	[39]
4-Chlorobenzoic acid	0.840	1.020	0.630	0.270	4.947	1.0541	7.190	2.391	[39]
3,4-Dichlorobenzoic acid	0.950	0.920	0.670	0.260	5.623	1.1766	8.012	3.272	[64]
2-Methoxybenzoic acid	0.899	1.410	0.450	0.620	5.636	1.1313	7.910	1.107	[39]
4-Methoxybenzoic acid	0.899	1.250	0.620	0.520	5.741	1.1313	8.420	1.721	[39]
3,4-Dimethoxybenzoic acid	0.950	1.646	0.570	0.755	6.746	1.3309	9.472	1.202	[54]
3,4,5-Trimethoxybenzoic acid	1.001	1.760	0.603	0.850	7.711	1.5309	10.788	1.533	[57]

3-Nitrobenzoic acid	0.990	1.130	0.730	0.530	5.535	1.1059	8.640	1.795	[39]
4-Nitrobenzoic acid	0.990	1.520	0.680	0.400	5.770	1.1059	8.701	1.802	[39]
4-Aminobenzoic acid	1.075	1.650	0.940	0.600	5.916	1.0315	10.060	0.628	[39]
3,5-Dinitrobenzoic acid	1.250	1.630	0.700	0.590	6.984	1.2801	10.150	1.847	[39]
3,5-Dinitro-2-methylbenzoic acid	1.310	2.120	0.750	0.650	8.040	1.4210	11.595	1.638	[56]
2-Chloro-5-nitrobenzoic acid	1.250	1.400	0.670	0.460	6.513	1.2283	9.370	2.415	[39]
4-Chloro-3-nitrobenzoic acid	1.250	1.470	0.700	0.440	6.685	1.2283	9.580	2.373	[39]
Acetylsalicylic acid	0.781	1.690	0.710	0.670	6.279	1.2879	9.790	1.216	[39]
Naproxen	1.510	2.022	0.600	0.673	9.207	1.7821	12.000	3.196	[39]
2-Hydroxybenzoic acid	0.900	0.850	0.730	0.370	4.732	0.9904	7.430	2.042	[39]
Diphenyl sulfone	1.570	2.100	0.000	0.720	8.577	1.6051	9.630	2.254	[39]
Xanthene	1.502	1.070	0.000	0.230	7.153	1.4152	6.880	4.380	[39]
Monuron	1.140	1.500	0.470	0.780	7.180	1.4768	9.620	1.994	[39]
Diuron	1.280	1.600	0.570	0.700	8.060	1.5992	10.730	2.758	[39]
p-Anisidine	1.050	1.240	0.160	0.670	5.207	1.0160	6.540	0.800	[39]
1-Chloroanthraquinone	1.900	1.790	0.000	0.570	9.171	1.6512	9.319	3.279	[39]
Salicylamide	1.160	1.580	0.610	0.510	5.818	1.0315	8.723	1.119	[39]
Phenothiazine	1.890	1.560	0.310	0.300	8.389	1.4789	9.415	4.012	[39]
9-Fluorenone	1.600	1.490	0.000	0.350	7.474	1.3722	7.665	3.465	[39]
Thianthrene	2.240	1.390	0.000	0.360	8.541	1.5426	8.295	4.295	[39]
o-Acetoacetanisidide	1.190	2.333	0.264	1.025	8.563	1.6108	10.831	0.597	[66]
Xanthone	1.640	1.173	0.000	0.563	7.466	1.4309	7.559	3.149	[75]
Vanillyl alcohol	1.053	1.861	0.802	0.865	6.522	1.1743	10.310	-0.112	[77]
Benzoin	1.585	2.115	0.196	0.847	9.159	1.6804	10.683	1.952	[65]
2-Ethylanthraquinone	1.410	1.545	0.000	0.557	8.781	1.8106	8.927	4.113	[58]
Isophthalic acid	1.100	1.360	1.055	0.585	6.144	1.1470	10.509	1.536	[52]
Benzenesulfonamide	1.130	2.137	0.651	0.647	6.524	1.0971	9.812	0.042	[42]
o-Toluenesulfonamide	1.130	2.157	0.692	0.595	7.076	1.2380	10.459	0.844	[40]
p-Toluenesulfonamide	1.130	2.203	0.680	0.679	7.108	1.2380	10.577	0.488	[41]
Methyl 2-sulfamoylbenzoate	1.170	2.813	0.664	0.928	8.476	1.4533	12.428	-0.248	[43]

1,4-Dichloro-2-nitrobenzene	1.120	1.289	0.000	0.199	5.783	1.1354	5.960	3.058	[69]
1-Hydroxybenzotriazole	1.630	1.029	0.385	0.828	5.590	0.9229	7.079	-0.099	[78]
Pyrazanimide	1.030	1.458	0.331	0.856	4.976	0.8906	7.234	-0.683	[82]
Terephthalaldehyde	1.030	1.235	0.000	0.566	5.235	1.030	5.820	1.229	[80]
Chlorpropamide	1.224	2.234	0.734	0.988	9.712	1.8986	13.463	2.080	[79]
2-Mercapto-1,3,4-thiadiazole	1.116	1.066	0.365	0.457	4.285	0.7224	6.005	0.658	[81]
Bezafibrate	1.893	2.490	0.770	1.770	13.672	2.682	17.992	2.292	[44]
N-Hydroxyphthalimide	1.280	1.986	0.806	0.624	6.662	1.0795	10.437	0.454	[62]
2,4-Dihydroxybenzophenone	1.730	2.030	0.490	0.700	9.060	1.5982	11.558	2.498	This work[a]
2-Naphthoxyacetic acid	1.610	1.940	0.690	0.764	8.553	1.5003	11.724	1.805	[51]

[a] Mole fraction solubility is $X_{S,organic}^{exp} = 0.01485$.

log (*P* or *SRW*) = 0.117(0.056) + 0.443(0.049) **E** – 1.295(0.066) **S** + 0.202(0.056) **A**

– 3.676(0.107) **B** + 4.160(0.081) **V** (5)

(with N = 76, SD = 0.113, SEE = 0.117, R^2 = 0.992, F = 1,851)

log (*K* or *CSRG*) = –0.064(0.040) – 0.354(0.060) **E** + 0.541(0.075) **S** + 3.772(0.055) **A**

+ 1.055(0.107) **B** + 0.936(0.021) **L** (6)

(with N = 76, SD = 0.114, SEE = 0.118, R^2 = 0.999, F = 10,995)

Included in the statistical analysis is the standard error of the estimate (SSE). The Abraham model correlations given by Eqns. 5 and 6 are statistically very good with standard deviations of the residuals of 0.113 log units and 0.114 log units, respectively. Figure 1 compares the observed log (*K* or *SRG*) values against the back-calculated values based on Eqn. 6. The experimental data covers a range of approximately 11.2 log units, from log *K* = 0.890 for 1,1-difluoroethane to log ($C_{S,organic}/C_{S,gas}$) = 12.093 for naproxen. The comparison between the experimental log (*P* or *SRW*) data and back-calculated values based on Eqn. 5 is graphically depicted in Figure 2. The predictive area of chemical space covered by the updated Abraham model correlations for 2-pentanol is: **E** = -0.250 to **E** = 2.808; from **S** = 0.000 to **S** = 2.333; from **A** = 0.000 to **A** = 1.055; from **B** = 0.000 to **B** = 1.025; from **V** = 0.3082 to **V** = 1.8106; to **L** = 0.517 to **L** = 9.207. Both expressions are expected to provide reasonably accurate predictions for additional solutes whose descriptor values fall within this range.

There are 33 more experimental values in the two 3-methyl-1-butanol data sets than when our initial correlations were published. This represents a 53 % increase in the number of experimental data points. Regression analysis of the 95 log (*P* or *SRW*) and log (*K* or *SRG*) values in the ninth and eighth columns of Table 3 gave the following two Abraham model correlations:

log (*P* or *SRW*) = 0.111(0.030) + 0.337(0.030) **E** – 1.180(0.036) **S** + 0.063(0.041) **A**

– 3.880(0.059) **B** + 4.218(0.042) **V** (7)

(with N = 95, SD = 0.091, SEE = 0.094, R^2 = 0.996, F = 4667)

log (*K* or *SRG*) = –0.040(0.026) – 0.408(0.041) **E** + 0.648(0.044) **S** + 3.599(0.046) **A**

+ 0.905(0.066) **B** + 0.932(0.012) **L** (8)

(with N = 95, SD = 0.102, SEE = 0.105, R^2 = 0.999, F = 21151)

for describing the partitioning behavior and molar solubility of solutes dissolved in 3-methyl-1-butanol. As expected both correlations provide a very good mathematical description of the measured experimental data as evidenced by the small standard deviations of the residuals, SD = 0.091 and SD = 0.103, and near unity values for the squared correlation coefficients, R^2 = 0.996 and R^2 = 0.999. Figures 3 and 4 depict a graphical comparison of the experimental log (*K* or *SRG*) and log (*P* or *SRW*) data versus back-calculated values from Eqns. 8 and 7, respectively.

Careful examination of Eqns. (1), (2), (7) and (8) reveals that there is very little difference between the equation coefficients from our correlations and the updated values based on the much larger data sets. What is important though is that the predictive area of chemical space for our updated correlations has increased, most notably the range for the **L** solute descriptor increased from an upper value of **L** = 9.207 to an upper value of **L** = 13.672. Significant increases were also noted in the upper values of the **S** solute descriptor (from **S** = 2.100 to **S** = 2.813), **B** solute descriptor (from **B** = 0.80 to **B** = 1.770) and **V** solute descriptor (from **V** = 1.7821 to **V** = 2.6815). As noted earlier several research groups [40-46] are now determining the solubility of drug molecules in 3-methyl-1-butanol. The expanded predictive area of chemical space covered by the Abraham model correlations for 3-methyl-1-butanol will facilitate our ongoing efforts in determining experiment-based solute descriptors for additional pharmaceutical compounds.

Summary

Previously published Abraham model expressions describing solute transfer into both 2-pentanol and 3-methyl-1-butanol have been updated using data sets that contain 76 and 95 experimental values, respectively. The larger data sets contain organic solutes and inorganic gases exhibiting greater chemical diversity as evidenced by a wide range of molecular polarity and hydrogen-bonding character. Compared to earlier correlations, the newly derived expressions obtained from the larger data sets cover a much larger predictive area of chemical space. Best practices require that one not use Abraham model expressions to make predictions for new solutes having solute descriptors that fall far outside of the range of values used in determining the equation coefficients, nor should one use such expressions to calculate solute descriptors of additional solutes that are expected to fall far outside of this range. Many of the larger active pharmaceutical molecules fell outside of the range covered by the earlier 3-methyl-1-butanol and 2-pentanol correlations.

Acknowledgement

The authors acknowledge the National Science Foundation's Research Experiences for Undergraduates (REU) program (CHE-1757946) for supporting Catherine Webber's participation in this research study. Trisha Kandi, Ramya Motati, Saikiran Motati, Nikita Shanmugam, Amy Zhou, Emily Yao thank the University of North Texas's Texas Academy of Mathematics and Science (TAMS) program for providing a summer research scholarship award.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by the National Science Foundation Research Experience for Undergraduates (REU) program Division of Chemistry [CHE-1757946].

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Figure 1

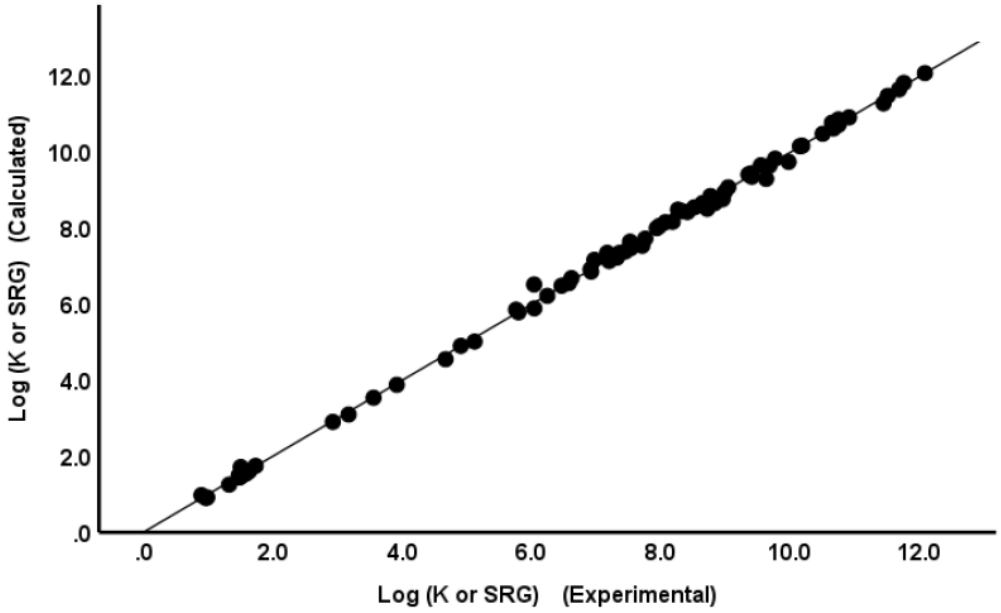

Figure 1. Graphical comparison of experimental log (*K* or *SRG*) data for 76 nonelectrolyte organic solutes dissolved in 2-pentanol and back-calculated values based on Eqn. (6).

Figure 2

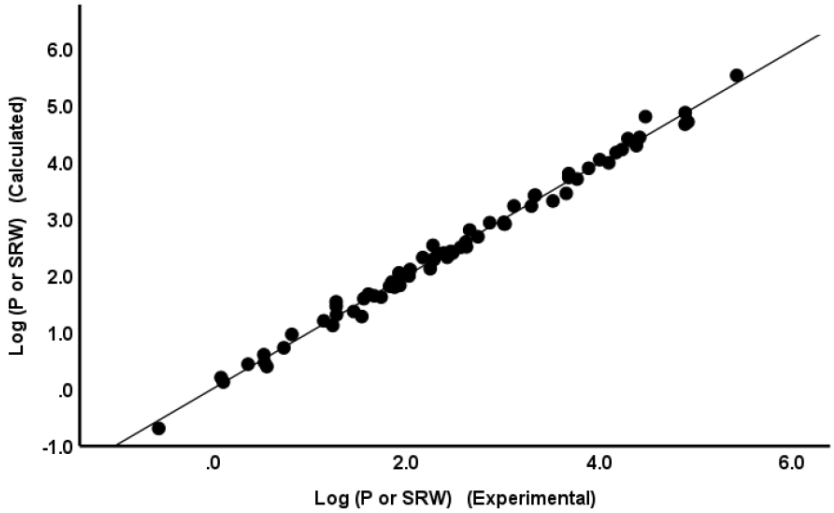

Figure 2. Graphical comparison of experimental log (*P* or *SRW*) data for 76 nonelectrolyte organic solutes dissolved in 2-pentanol and back-calculated values based on Eqn. (5).

Figure 3

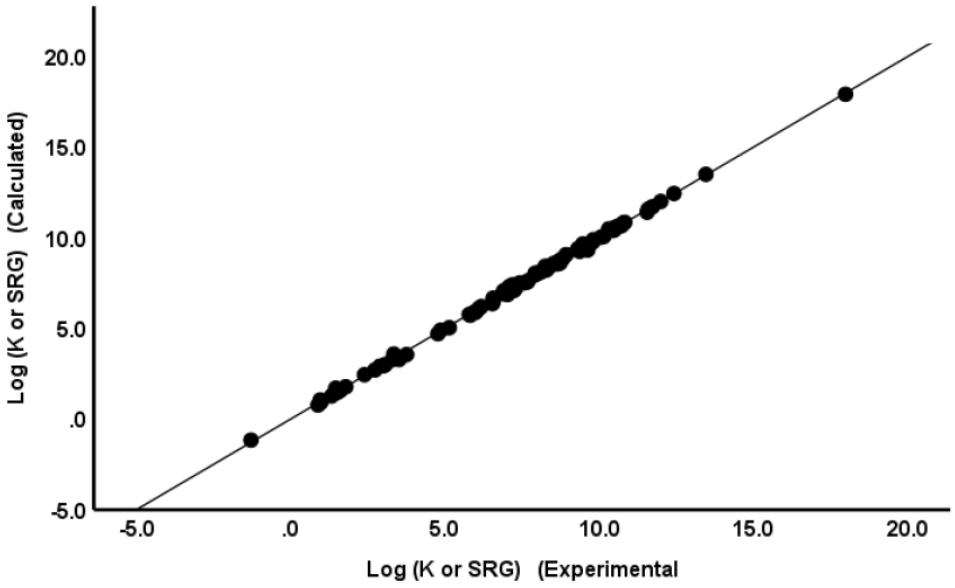

Figure 3. Graphical comparison of experimental log (*K* or *SRG*) data for 95 nonelectrolyte organic solutes and inorganic gases dissolved in 3-methyl-1-butanol and back-calculated values based on Eqn. (8).

Figure 4

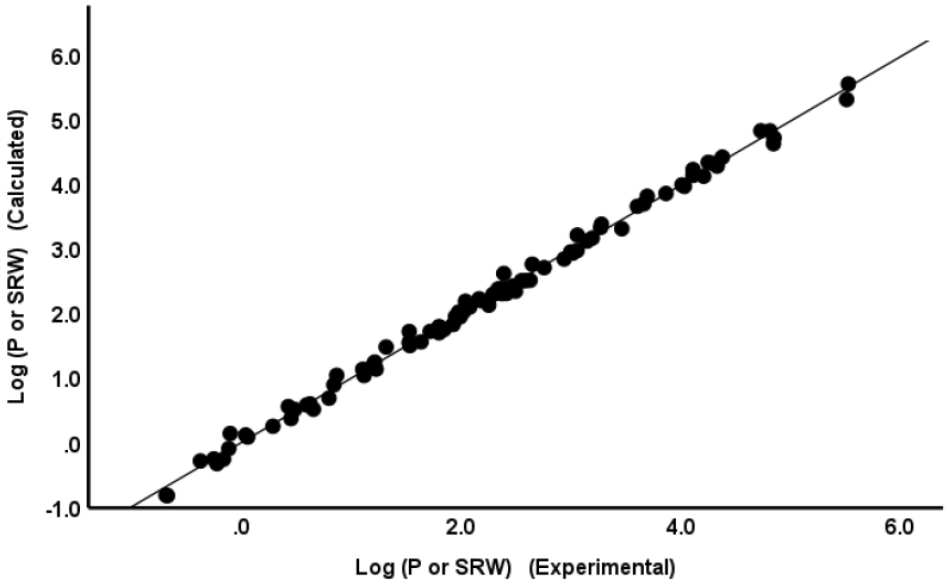

Figure 4. Graphical comparison of experimental log (*P* or *SRW*) data for 95 nonelectrolyte organic solutes and inorganic gases dissolved in 3-methyl-1-butanol and back-calculated values based on Eqn. (7).