Equations for the Correlation and Prediction of Partition Coefficients of Neutral Molecules and Ionic Species in the Water-isopropanol Solvent System.

Michael H. Abraham [1] ● William E. Acree Jr. [2] ● Clara Rafols [3] ● Marti Roses [4]

Abstract

We use literature data on solubilities of 46 compounds in the water-isopropanol (IPA) system to obtain the corresponding partition coefficients, P, for transfer from water to water-IPA mixtures. We have then used our previously constructed linear free energy equation to obtain equations that correlate $\log_{10} P$ at water-IPA intervals across the entire water-IPA system. These equations can then be used to predict partition coefficients and solubilities of further compounds in the water-IPA systems at 298 K. The coefficients in our linear free energy equation encode information on the physicochemical properties of the water-IPA mixtures. We show that the hydrogen bond basicity of the water-IPA mixtures only increases slightly from water to IPA, but that the hydrogen bond acidity of the mixtures decreases markedly from water to IPA in a smooth continuous manner.

We have also used data on ions and on ionic species to set out equations for the estimation of their partition coefficients from water to water-IPA mixtures. We find that for partition from water to IPA itself, $\log_{10} P = -1.81$ for H^+

Key words Water-isopropanol ● Solubilities ● Partition coefficients ● Hydrogen bond acidity ● Hydrogen bond basicity ● Linear free energy relationship ● Ionic species

□   Michael H. Abraham

m.h.abraham@ucl.ac.uk

1   Department of Chemistry, University College London, 20 Gordon St, London,

WC1H 0AJ, UK. E-mail: m.h.abraham@ucl.ac.uk

33   2   Department of Chemistry, University of North Texas, 1155 Union Circle Drive

34   #305070, TX 76203-5017, Denton, TX 76203-5017, USA. E-mail: bill.acree@unt.edu

35   3   Departament de Química Analítica and Institut de Biomedicina (IBUB). Universitat

36   de Barcelona. Martí i Franquès 1-11, 08028, Barcelona, Spain. E-mail: marti.roses@ub.edu

37   4   Departament de Química Analítica and Institut de Biomedicina (IBUB). Universitat

38   de Barcelona. Martí i Franquès 1-11, 08028, Barcelona, Spain. E-mail: crafols@ub.edu

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41   **1 Introduction**

42   There is now considerable interest in the solubility of solid compounds in organic solvents,

43   both in mono solvents and in water-solvent mixtures. Of the latter, water-alcohol mixtures

44   have been well studied, particularly water-methanol, water-ethanol and water-isopropanol

45   (IPA) mixtures. The main methods used to analyze the solubility of a given compound in

46   a particular water-solvent system are the Joubain-Acree method [1, 2], and the Kamlet-Taft

47   sovatochromic equation [3-4]. These methods can be used to interpolate solubilities of the

48   given compound at various water-solvent compositions but cannot predict solubilities of

49   other compounds in the given water-solvent system. We have set out linear free energy

50   relationships, LFERs, for the partition of neutral and ionic compounds in the water-ethanol

51   [5, 6] and water-methanol [7] systems that can be used to predict partition coefficients, and

52   then solubilities, of further compounds in these systems. These LFERs appear to be the

53   only ones available for such predictions, and in view of the importance of the water-IPA

54   system, we have now extended our method to the latter system.

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57   **2 Methodology**

58   We start with our well-known LFER, Eq. 1, [8-12] for the partition of neutral molecules

59   (non-electrolytes) from water to another solvent or solvent system,

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61    $$\text{Log}_{10} P = c + e\boldsymbol{E} + \mathbf{s}\boldsymbol{S} + a\boldsymbol{A} + b\boldsymbol{B} + v\boldsymbol{V} \tag{1}$$

62

In Eq. 1, the dependent variable is $\log_{10} P$, where P is the water to solvent partition coefficient for a series of non-electrolytes in a given water to solvent system. The independent variables are descriptors as follows. [8-11]. E is the non-electrolyte (or solute) excess molar refractivity in units of $(cm^3\,mol^{-1})/10$, S is the solute dipolarity/ polarizability, A and B are the overall or summation solute hydrogen bond acidity and basicity, and V is the solute McGowan characteristic volume in units of $(cm^3\,mol^{-1})/100$ [13]. The use of Eq. 1 has been reviewed several times [14-16]; the review of Clarke and Mallon [16] is particularly detailed. In brief, values of $\log_{10} P$ in a specific water to solvent system are obtained for a set of compounds with known values of the descriptors E, S, A, B and V. Then a set of simultaneous equations on the lines of Eq. 1 is set up with the values of $\log_{10} P$ as the dependent variable, and the five descriptors as the independent variables. The set of simultaneous equations is then solved to obtain the (unknown) coefficients e, s, a, b and v.

The method we use makes use of the solubilities of neutral molecules in water and water-IPA mixtures. Provided that no hydrate or solvate formation takes place, the partition coefficient, P, for transfer from water to a given water-IPA solvent can be obtained from the solubility of a neutral solute in the two systems, Eq. 2, where S_s and S_w are the molar solubilities, $mol\,dm^{-3}$, at 298 K in a water-IPA system and in water, respectively.

$P = S_s / S_w$ (2)

Solubilities are known for a number of neutral molecules in the water-IPA system. We used only data for compounds that had been studied across the entire composition range, and in Table 1 we list the compounds that we used together with their descriptors,

Table 1. Descriptors for the compounds used in the analysis

Solute	E	S	A	B	V
2-Hydroxybenzoic acid	0.900	0.85	0.73	0.37	0.9900
Benzene	0.610	0.52	0.00	0.14	0.7160

Toluene	0.601	0.52	0.00	0.14	0.8570
Ethylbenzene	0.613	0.51	0.00	0.15	0.9980
Propylbenzene	0.604	0.50	0.00	0.15	1.1390
Butylbenzene	0.600	0.51	0.00	0.15	1.2800
Isopropylbenzene	0.602	0.49	0.00	0.16	1.1390
tert-Butylbenzene	0.619	0.49	0.00	0.18	1.2800
Piperonal	0.990	1.35	0.00	0.49	1.0230
Helium	0.000	0.00	0.00	0.00	0.0680
Naproxen	1.510	2.02	0.60	0.67	1.7820
Gallic Acid	1.290	1.42	1.53	0.90	1.1080
Decanedioic acid	0.350	1.36	1.12	0.87	1.6660
Nitrous oxide	0.068	0.35	0.00	0.10	0.2810
Oxiracetam	1.035	1.75	0.70	1.48	1.1350
Benzoic acid	0.730	0.90	0.59	0.40	0.9320
2-Bromobenzoic acid	1.000	1.00	0.64	0.53	1.1070
3-Bromobenzoic acid	1.000	1.10	0.64	0.27	1.1070
2-Iodobenzoic acid	1.310	1.27	0.74	0.46	1.1900
3-Iodobenzoic acid	1.310	1.27	0.64	0.26	1.1900
5,7-Dibromo-8-hydroxyquinoline	2.100	2.16	0.09	0.78	1.4530
2,6-Dichloro-4-nitroaniline	1.566	1.83	0.14	0.52	1.2350
2-Methoxy-4-nitroaniline	1.220	1.68	0.17	0.46	1.1900
Risperidone	2.830	2.30	0.00	1.93	3.0400
Microflavin	1.794	2.28	0.65	2.29	3.2760
Rebamipide	2.450	2.40	0.87	2.09	2.5870
Monobenzone	1.420	1.63	0.53	0.62	1.5830
5-Nitrosalicylaldehyde	1.240	2.15	0.69	0.56	1.1060
Buprofezin	1.719	2.17	0.00	1.71	2.4520
4-Amino-2,6-dimethoxypyrimidine	1.050	1.37	0.25	0.73	1.1330
6-Chloroguanine	2.144	1.64	0.53	0.79	1.0450
4-Formylbenzoic acid	1.010	1.38	0.65	0.52	1.0880
Allopurinol	1.590	2.08	0.30	0.78	0.8820
Ketoconazole	3.140	3.31	0.00	2.56	3.7210
Lamotrigine	2.267	2.03	0.35	0.96	1.6450
Celecoxib	2.040	2.44	0.60	1.26	2.4680
a-Trichloromethylbenzyl acetate	1.101	1.43	0.00	0.48	1.7220
Benzafibrate	1.893	2.49	0.77	1.77	2.6820
Apixaban	3.690	4.10	0.35	2.78	3.3490
Milrinone	1.627	1.67	0.13	1.21	1.5940
Edaravone	1.354	1.24	0.18	0.87	1.3440
Nisoldipine	1.560	2.59	0.25	1.45	2.9170
Bifonazole	2.620	2.20	0.00	1.21	2.5010

		1.626	2.27	0.30	0.88	1.4620
Dinitolmide						
Isoniazid		1.190	1.77	0.71	1.14	1.0315
Clotrimazole		2.400	1.65	0.00	1.24	2.6230

There are various scales used to express solubilities. Since partition coefficients are normally expressed on the molar concentration scale, we converted, where necessary, solubilities recorded on other scales to molar solubilities. Several different solvent compositions are used: mol fraction, weight % or volume %, and we converted experimental solubilities on the mol fraction or weight % scale to solubilities on the volume % solvent scale. Then from the molar solubilities we used Eq. 2 to obtain values of $\log_{10} P$ for transfer of the neutral solutes from water to various vol% IPA systems. These are given in Table 2, together with references for the data on solubilities [17-54].

Table 2. Values of compound partition coefficients, as $\log_{10} P$, from water to various water-IPA systems with % volume IPA at 298 K.

		% Volume IPA				
Compound	Ref	100	95	90	80	70
2-Hydroxybenzoic acid	17	2.390	2.202	2.105	1.920	1.701
Benzene	18	2.110	2.065	2.003	1.866	1.698
Toluene	18	2.605	2.521	2.456	2.305	2.117
Ethylbenzene	18	3.222	3.092	3.017	2.839	2.633
Propylbenzene	18	3.661	3.479	3.386	3.167	2.953
Butylbenzene	18	4.325	3.932	3.829	3.599	3.357
Isopropylbenzene	18	3.727	3.588	3.475	3.287	3.073
tert-Butylbenzene	18	4.138	3.910	3.813	3.592	3.363
Piperonal	19	1.574	1.750	1.897	1.962	1.844
Helium	20	0.496	0.448	0.400	0.307	0.222
Naproxen	21	3.288	3.342	3.365	3.325	3.178
Gallic acid	22	0.716	0.735	0.764	0.760	0.689
Decanedioic acid	23	2.320	2.345	2.513	2.627	2.454
Nitrous oxide	24	0.681	0.664	0.604	0.466	0.349
Oxiracetam	25	-2.183	-2.329	-2.393	-2.396	-2.256
Benzoic acid	26	1.872	2.028	2.129	1.767	1.352
2-Bromobenzoic acid	27	2.088	2.125	2.116	1.795	1.239

Compound						
3-Bromobenzoic acid	27	2.944	2.816	2.700	2.481	2.220
2-Iodobenzoic acid	27	2.555	2.469	2.296	1.772	1.326
3-Iodobenzoic acid	27	3.240	3.112	2.980	2.733	2.420
5,7-Dibromo-8-hydroxyquinoline	28	1.499	1.491	1.478	1.437	1.380
2,6-Dichloro-4-nitroaniline	29	1.770	1.615	1.373	0.929	0.615
2-Methoxy-4-nitroaniline	30	1.863	1.664	1.549	1.340	1.120
Risperidone	31	3.384	3.033	2.731	2.198	1.743
Microflavin	32	3.073	2.474	1.989	1.314	0.893
Rebamipide	33	1.205	0.975	0.776	0.493	0.317
Monobenzone	34	3.049	2.898	2.708	2.270	1.836
2-Hydroxy-5-nitrobenzaldehyde	35	0.883	0.702	0.546	0.327	0.196
Buprofezin	36	1.791	1.340	1.035	0.659	0.441
4-Amino-2,6-dimethoxypyrimidine	37	0.821	0.650	0.573	0.484	0.407
6-Chloroguanine	38	0.414	0.421	0.413	0.416	0.398
4-Formylbenzoic acid	39	1.636	1.428	1.226	0.892	0.650
Allopurinol	40	-0.840	-0.146	0.039	0.031	-0.043
Ketoconazole	41	2.819	3.335	3.363	2.905	2.331
Lamotrigine	42	1.795	2.311	2.403	2.178	1.808
Celecoxib	43	3.613	3.530	3.330	2.733	2.114
a-Trichloromethylbenzyl acetate	44, 45	4.041	3.923	3.927	3.750	3.324
Bezafibrate	46	2.436	2.209	1.963	1.515	1.154
Apixaban	47	0.226	0.760	0.846	0.676	0.481
Milrinone	48	1.017	0.934	0.829	0.648	0.502
Edaravone	49	1.433	1.507	1.624	1.712	1.610
Nisoldipine	50	4.258	4.260	4.224	4.168	4.010
Bifonazole	51	4.100	3.992	3.926	3.684	3.221
Dinitolmide	52	0.948	0.801	0.652	0.409	0.250
Isoniazid	53	-1.307	-0.814	-0.517	-0.207	-0.072
Clotrimazole	54	5.161	4.909	4.578	3.807	3.056

105

106 **Table 2** (continued)

Compound	60	50	40	30	20	10	0
2-Hydroxybenzoic acid	1.503	1.202	0.905	0.602	0.411	0.191	0
Benzene	1.501	1.265	0.972	0.571	0.395	0.167	0
Toluene	1.896	1.625	1.275	0.777	0.560	0.250	0
Ethylbenzene	2.390	2.090	1.702	1.087	0.812	0.391	0
Propylbenzene	2.698	2.355	1.895	1.199	0.908	0.437	0
Butylbenzene	3.081	2.714	2.210	1.417	1.011	0.474	0
Isopropylbenzene	2.817	2.484	2.040	1.354	0.752	0.256	0
tert-Butylbenzene	3.091	2.743	2.272	1.511	0.945	0.397	0
Piperonal	1.621	1.342	1.045	0.755	0.482	0.227	0
Helium	0.146	0.082	0.033	-0.001	-0.017	-0.017	0

Naproxen	2.933	2.601	2.192	1.717	1.185	0.607	0
Gallic acid	0.588	0.479	0.373	0.273	0.181	0.096	0
Decanedioic acid	2.131	1.749	1.359	0.984	0.633	0.310	0
Nitrous oxide	0.258	0.187	0.133	0.089	0.054	0.024	0
Oxiracetam	-2.006	-1.678	-1.305	-0.918	-0.551	-0.234	0
Benzoic acid	1.012	0.743	0.529	0.356	0.215	0.097	0
2-Bromobenzoic acid	0.759	0.415	0.194	0.064	0.001	-0.015	0
3-Bromobenzoic acid	1.965	1.599	1.272	0.905	0.550	0.252	0
2-Iodobenzoic acid	0.979	0.708	0.494	0.322	0.181	0.062	0
3-Iodobenzoic acid	2.134	1.718	1.356	0.944	0.580	0.258	0
5,7-Dibromo-8-hydroxyquinoline	1.302	1.199	1.061	0.882	0.653	0.365	0
2,6-Dichoro-4-nitroaniline	0.404	0.260	0.161	0.090	0.039	0.001	0
2-Methoxy-4-nitroaniline	0.907	0.711	0.534	0.376	0.236	0.110	0
Risperidone	1.359	1.035	0.762	0.528	0.327	0.151	0
Microflavin	0.615	0.424	0.288	0.186	0.109	0.048	0
Rebamipide	0.206	0.133	0.085	0.052	0.028	0.012	0
Monobenzone	1.447	1.110	0.820	0.570	0.352	0.161	0
2-Hydroxy-5-nitrobenzaldehyde	0.117	0.069	0.039	0.021	0.010	0.003	0
Buprofezin	0.303	0.209	0.142	0.093	0.055	0.025	0
4-Amino-2,6-dimethoxypyrimidine	0.333	0.263	0.200	0.143	0.091	0.045	0
6-Chloroguanine	0.336	0.272	0.226	0.156	0.105	0.065	0
4-Formylbenzoic acid	0.473	0.341	0.239	0.159	0.095	0.041	0
Allopurinol	-0.089	-0.104	-0.098	-0.080	-0.054	-0.025	0
Ketoconazole	1.813	1.375	1.008	0.699	0.437	0.212	0
Lamotrigine	1.440	1.111	0.826	0.579	0.365	0.178	0
Celecoxib	1.605	1.191	0.853	0.574	0.340	0.139	0
a-Trichloromethylbenzyl acetate	2.795	2.249	1.728	1.244	0.803	0.399	0
Bezfibrate	0.869	0.643	0.459	0.308	0.182	0.074	0
Apixaban	0.338	0.241	0.178	0.137	0.111	0.070	0
Milrinone	0.383	0.288	0.209	0.143	0.088	0.040	0
Edaravone	1.412	1.176	0.933	0.699	0.478	0.273	0
Nisoldipine	3.724	3.386	3.040	2.592	1.979	1.110	0
Bifonazole	2.681	2.140	1.630	1.162	0.738	0.351	0
Dinitolmide	0.149	0.084	0.042	0.014	-0.004	-0.016	0
Isoniazid	-0.011	0.017	0.028	0.030	0.028	0.023	0
Clotrimazole	2.392	1.821	1.331	0.911	0.547	0.227	0

Once the coefficients in Eq. 1 have been obtained for a given solvent system, it is then possible to extend the scope of the equation to include partitions of permanent ions, such as K^+ or Br^-, cationic species derived from the deprotonation of carboxylic acids and

112   phenols, and anionic species derived from the protonation of bases [6, 7, 55-61]. Data on

113   these partitions can be used to obtain the ionic descriptors J^+ and J^- in Eq. 3.

114

115   $$Log_{10} P = c + eE + sS + aA + bB + vV + j^+ J^+ + j^- J^- \qquad (3)$$

116

117   The $j^+ J^+$ term refers to cations and the $j^- J^-$ term refers to anions. Cations have $\mathbf{J}^- = 0$,

118   anions have $J^+ = 0$ and neutral compounds have $\mathbf{J}^- = J^+ = 0$, so that the solvent coefficients

119   c, e, s, a, b and v are the same for neutral molecules, ions and ionic species [55-61]. Thus

120   for transfer from water to methanol, Eq. 4 applies to neutral compounds only, and Eq. 5

121   applies to neutral compounds, ions and ionic species [7].

122

123   $$Log_{10} P = 0.276 + 0.334\,E - 0.714\,S + 0.243A - 3.320\,B + 3.549\,V \qquad (4)$$

124   $$Log_{10} P = 0.276 + 0.334\,E - 0.714\,S + 0.243A - 3.320\,B + 3.549\,V - 2.609\,J^+ + 3.027\,J^-$$

125   $$(5)$$

126

127   The most straightforward method of obtaining general method of obtaining data for the

128   determination of the ionic descriptors is from Gibbs energies of transfer of ions from water

129   to a given solvent, $\Delta G^o{}_t$ (or the equivalent $log_{10} P$). In order to obtain 'single-ion' values,

130   some particular convention needs to be established. A common such convention, and one

131   that we have used throughout our work, is the TATB convention that $\Delta G^o{}_t$ (or $log_{10} P$) for

132   Ph_4As^+ or $Ph_4P^+ = \Delta G^o{}_t$ (or $log_{10} P$) for Ph_4B^-. Kalidas, Marcus and Hefter [62-64] have

133   published compilations of Gibbs energies of transfer of ions using the TATB convention.

134   For ionic species, the most useful procedure is by an electrochemical method, based on

135   the determination of pKa values in water and the given solvent. For anions derived from

136   carboxylic acids or phenols, Eq. 6 is used. Here $P(A^-)$ is the required partition coefficient

137   from water to a solvent of an anion, $P(HA)$ is the partition coefficient of the neutral

138 compound, $P(H^+)$ is the partition coefficient of the hydrogen ion, and $pK_a(aq)$ and $pK_a(s)$

139 are the pKa values of the compound in water and the given solvent.

140

141 $\text{Log}_{10} P(A^-) = \log_{10} P(HA) - \log_{10} P(H^+) + pK_a(aq) - pK_a(s)$ (6)

142 A similar equation can be used for the determination of partition coefficients of protonated

143 amine cations,

144

145 $\text{Log}_{10} P(BH^+) = \log_{10} P(B) + \log_{10} P(H^+) - pK_a(aq) + pK_a(s)$ (7)

146

147 In Eq. 7, BH^+ refers to the protonated amine and B to the neutral amine. To be consistent

148 with our previous work, all values for single ions, including $\log_{10} P(H^+)$ in Eq. 5 and Eq.

149 7, must be based on the TATB convention. $pK_a(s)$ values for carboxylic acids and phenols

150 in water-IPA are available [65-70], but we have been unable to find any data on the pK_a of

151 bases in the IPA systems.

152

153

154 **3 Results and Discussion**

155 Application of Eq. 1 to the data in Table 2 is straightforward and yields 11 equations, one

156 for each of the water-IPA systems. The obtained regression coefficients are given in Table

157 3, together with the number of compounds, N, and the regression standard deviation, SD.

158 For solution of a set of simultaneous equations, these are the only statistical parameters

159 calculated. We also checked on the effect of using a smaller selection of parameters but

160 found decidedly poorer statistics. Thus for the set of 46 compounds partitioned from water

161 to 100% IPA, $SD = 0.096$ (Table 3) using five descriptors. If E is omitted $SD = 0.155$, if S

162 is omitted SD is 0.352, if A is omitted $SD = 0.242$, if B is omitted $SD = 1.028$ and if V is

163 omitted $SD = 1.498$ so that all five descriptors are needed. Also given in Table 3 are details

164 of our 100 % isopropanol regression [71] that we have obtained previously with a much

165 larger data set. ($N = 148$)

166

167

Table 3. Regression coefficients in the LFER, Eq. 1, for the partition of neutral compounds

from water to water-isopropanol mixtures, as $\log_{10} P$ at 298 K.

% IPA	*SD*	*N*	*c*	*e*	*s*	*a*	*b*	*v*
100 [a]	0.159	148	0.099	0.343	-1.049	0.406	-3.827	4.033
100	0.096	46	0.167	0.346	-1.024	0.299	-3.725	3.926
95	0.234	46	0.109	0.426	-0.815	0.218	-3.639	3.620
90	0.349	46	0.128	0.416	-0.730	0.222	-3.598	3.465
80	0.458	46	0.138	0.269	-0.540	0.132	-3.431	3.184
70	0.502	46	0.160	0.120	-0.395	0.048	-3.150	2.866
60	0.510	46	0.174	0.006	-0.280	-0.015	-2.803	2.517
50	0.488	46	0.167	-0.091	-0.169	-0.080	-2.382	2.132
40	0.441	46	0.115	-0.156	-0.054	-0.102	-1.937	1.725
30	0.355	46	-0.028	-0.189	0.098	-0.068	-1.433	1.252
20	0.287	46	-0.001	-0.217	0.126	-0.151	-0.860	0.802
10	0.154	46	-0.030	-0.117	0.098	-0.044	-0.457	0.400
0			0	0	0	0	0	0

171 [a] Ref. 55.

172

The regression coefficients for partition into 100 % IPA using the 148 [71] or 46 data
sets are very similar, suggesting that the 46 data set is a representative sample set. The *SD*
values for many of the regressions are larger than we would like. However, plots of the
coefficients against % IPA are quite smooth curves, see Fig. 1 and Fig. 2, suggesting that
the coefficients themselves are reasonable and could be used to predict further values of
$\log_{10} P$ for compounds for which we have descriptors. These are available for some 8500
neutral compounds [72, 73]. Once $\log_{10} P$ values are predicted, they can then be used to
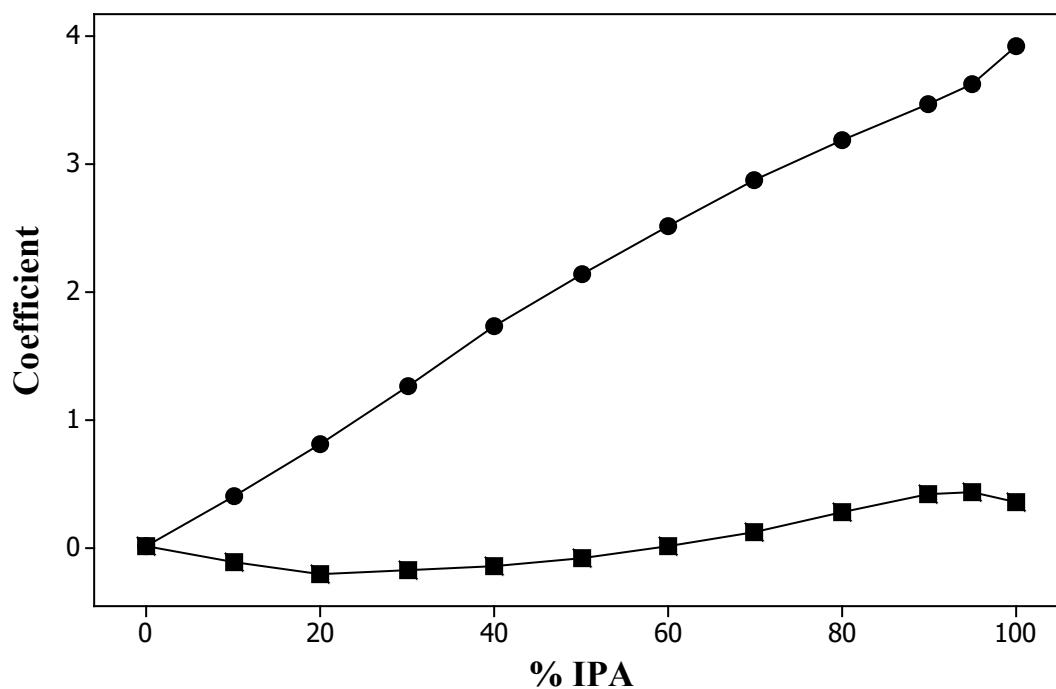predict solubilities through Eq. 2.
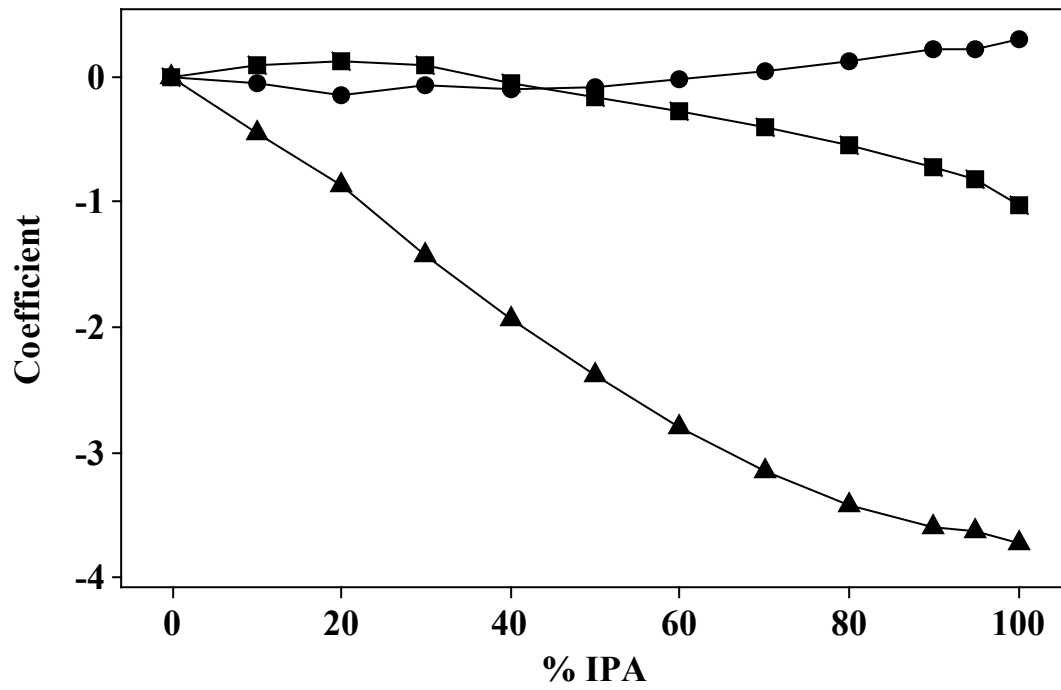
187   Fig. 1. Plots of the *a*-coefficient,● the *b*-coefficient, ▲ and the *s*-coefficient, ■ against

188   % IPA

189

190

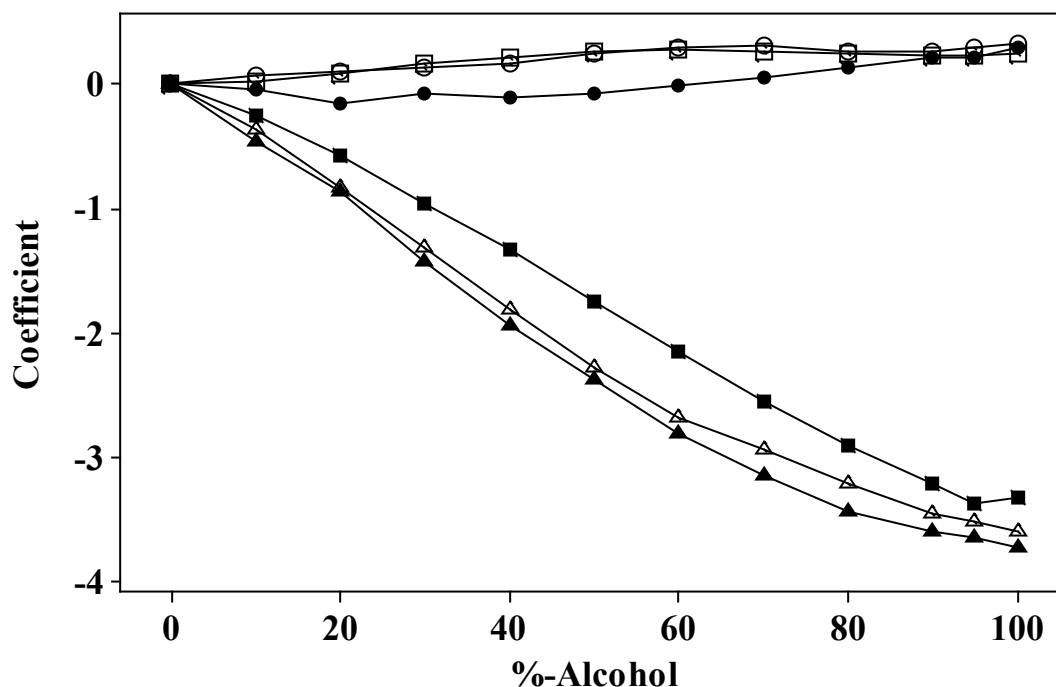Fig. 2. Plots of the e-coefficient, ■ and the v-coefficient, ● against % IPA

The coefficients in Eq. 1 are not just fitting coefficients, but they encode the physicochemical properties of the corresponding solvent. With regard to water-alcohol systems, the *a*-coefficient and the *b*-coefficient are particularly important. The *a*-coefficient is a measure of the hydrogen bond basicity of the solvent compared to that of water (because solutes that are hydrogen bond acids will interact with hydrogen bond solvents) and the *b*-coefficient is a measure of the hydrogen bond acidity of the solvent compared to that of water (because solutes that are hydrogen bond bases will interact with solvents that are hydrogen bond acids).

In Fig. 3, we show plots of the *a*-coefficient and the *b*-coefficient against % alcohol for the water-methanol, the water-ethanol and the water-IPA systems. In all three cases, the *a*-coefficient hardly alters with % alcohol, so that the hydrogen bond basicity of the three water-alcohol systems remains almost the same as that of water itself. In contrast, the *b*-coefficients become progressively smaller with increase in the % alcohol, so that the solvent hydrogen bond acidity becomes much less than that of water with increase in the % alcohol

209

210

Fig. 3. Plots of the *a*-coefficient against the % alcohol for the water-methanol, □ the water-ethanol,○ and the water-IPA ● systems, and plots of the *b*-coefficient against the % alcohol for the water-methanol, ■ the water-ethanol, Δ and the water-IPA ▲ systems.

Calculation of the ionic descriptors is not so straightforward, because of a lack of data on the partition of ions. However, some data on the transfer of ions from water to IPA and water-IPA mixtures are available [62-64]. All our studies on the transfer of ions use the TATB convention, so that key data on ions are the partition coefficients for the tetraphenylarsonium cation and the tetraphenylborate anion. A value for the transfer of the latter from water to 100% IPA is given as $\log_{10} P = 2.59$ on the i-PeBu$_3$N$^+$/ BPh$_4^-$ convention [65], as compared to values for transfer to methanol (3.98), ethanol (3.73) and propan-1-ol (4.37), all on the TATB convention [62-64]. By comparison to all these values we have taken $\log_{10}$ Ph$_4$B $^-$ as 3.75. The value for transfer of Ph$_4$As$^+$ from water to various solvents is always a little larger than that for Ph$_4$B $^-$ and we take $\log_{10}$ Ph$_4$As$^+$ as 3.85 for

226   transfer from water to IPA. Once these values for the TATB ions have been assigned, it is

227   possible to use data on the alkali metal cations and the halide anions [62-64] to derive $\log_{10}$

228   P values on the TATB convention.

229   To obtain $\log_{10} P(A^-)$ from Eq. 5 requires a knowledge of pKa in water and in IPA and

230   water-IPA mixtures. These are available for a number of carboxylic acids and phenols [65-

231   70]. We also need $\log_{10} P(H^+)$. We find that with $\log_{10} P(H^+)$ =-1.81 for transfer from

232   water to 100 % IPA we could include anions derived from carboxylic acids and phenols.

233   Chantooni and Kolthoff [65] give values of $\log_{10} P(H^+)$ from water to methanol and from

234   methanol to IPA, leading to -1.60 or -1.90 for transfer from water to IPA, so that our value

235   of -1.81 is in excellent agreement.

236   Finally, we have descriptors (that include J^+ and J) for a number of α-amino-acids [74]

237   that we can use.

238   We finished up with data for transfer from water to IPA of 40 ions and anionic species,

239   see Table 4, that yielded J^+ = -2.983 and J = 3.190 in Eq. 3. Although we have had to

240   make a number of approximations, the resulting values of J^+, J and also of $\log_{10} P(H^+)$

241   seem quite reasonable by comparison to those for other alcohols [6, 7, 65], see Table 5. We

242   caution, however, that we have no data on the partition of protonated bases from water to

243   IPA. A knowledge of these values would considerably help to strengthen our analysis.

244   The SD between calculated and observed values of $\log_{10} P$ in Table 4 is 0.12, in line

245   with the overall SD of 0.096 (Table 3).

246

247   **Table 4.** Values of $\log_{10} P$ for the transfer of ions and ionic species from water to

248   isopropanol

Solute	$\log_{10} P$ calc	$\log_{10} P$ obs	Ref
K+	-2.80	-2.81	62, 63
Rb+	-3.04	-3.07	62,63
Cs+	-2.71	-2.74	62,63
Ph4As+	3.66	3.85	See text
Cl-	-3.98	-3.93	62,63
Br-	-3.45	-3.41	62,63
I-	-2.98	-2.96	62,63

BPh4-	3.88	3.75	See text
Benzoic acid, anion	-2.82	-2.85	70
3,4-Dimethylbenzoic acid, anion	-2.35	-2.41	69
3-Nitrophenol, anion	-1.77	-1.44	70
4-Nitrophenol, anion	-1.81	-1.79	70
4-Chlorophenol, anion	-1.76	-1.71	69
3-Bromophenol, anion	-1.52	-1.23	69
4-Bromophenol, anion	-1.48	-1.61	69
Carprofen, anion	-1.37	-1.59	68
Ibuprofen, anion	-1.11	-1.09	68
Butibufen, anion	-0.90	-1.22	68
Fenbufen, anion	-2.43	-2.36	68
Ketoprofen, anion	-2.20	-2.44	68
Flurbiprofen, anion	-1.54	-1.52	68
Naproxen, anion	-1.71	-1.69	68
Diclofenac, anion	-1.16	-0.92	68
Betaine	-1.35	-1.36	74
Glycine	-3.29	-3.32	74
α-Alanine	-3.19	-3.12	74
α-Aminobutanoic acid	-2.88	-2.92	74
b-Alanine	-2.75	-2.76	74
Norvaline	-2.34	-2.40	74
Norleucine	-1.75	-1.80	74
Valine	-2.58	-2.63	74
Leucine	-2.07	-2.00	74
Phenylalanine	-1.88	-1.90	74
Biapenem	-4.76	-4.68	74
L-Tyrosine	-2.46	-2.49	74
D-Tryptophan	-1.99	-2.01	74
D-Histidine	-1.75	-1.76	74
Aspartic acid	-1.08	-1.08	74
L-Cysteine	-1.54	-1.57	74
2,4-Dinitrophenylalanine	-1.51	-1.52	74

249

250

251 **Table 5.** Values of J^+, J^- and of $\log_{10} P(\text{H}^+)$ for some alcohols

Alcohol	$j+$	$j-$	$\log_{10} P(\text{H}^+)$
Methanol	-2.609	3.027	-1.53 [7]
Ethanol	-3.172	3.146	-1.95 [6]
Propan-1-ol	-3.077	2.834	-0.80 [65]

Butan-1-ol	-3.605	2.685	-0.90 [65]
Propan-2-ol	-2.983	3.190	-1.81 This work
t-Butyl alcohol			-2.00 [65]

252

253   Once we have values for the partition of anions and cations from water to 100 % IPA,

254   we can use these, together with the available data for transfer from water to the more

255   aqueous systems, to estimate values for partition from water to water-IPA mixtures. We

256   have also data on pKa for carboxylic acids and phenols in water-IPA mixtures [65-70], and

257   we can calculate $\log_{10} P$ values for the α-amino-acids [74]. These yield values of j^{+} and j^{-}

258   for water-IPA mixtures. However, we regard our values as only provisional, especially

259   because we are unable to include any values for the partition of protonated bases. We give

260   in Table 6 a summary of our provisional findings

261

262   **Table 6**. Results on calculations on water-isopropanol mixtures.

Vol %	$j+$	$j-$	$\log_{10} P(Ph_4As^{+})$	$\log_{10} P(BPh_4^{+})$	$\log_{10} P(H^{+})$
10	-0.705	0.183	0.45	0.40	0.050
20	-1.077	0.404	0.95	0.90	0.050
30	-1.053	0.921	1.65	1.55	-0.080
40	-0.621	1.526	2.10	2.00	-0.100
50	-0.776	2.027	2.55	2.45	-0.050
60	-1.021	2.532	2.95	2.85	-0.147
70	-1.356	2.873	3.30	3.20	-0.125
80	-1.847	3.117	3.60	3.50	-0.063
90	-1.999	3.145	3.80	3.70	-0.300
95	-2.433	3.005	3.85	3.75	-0.821
100	-2.983	3.190	3.85	3.75	-1.806

263

264

265   As shown in Fig. 3, there is a large variation in the solvent *b*-coefficient across the

266   water-methanol, water-ethanol and water-isopropanol systems. Since the complementary

267   solute property to solvent hydrogen bond basicity is the solute hydrogen bond acidity we

268   might expect that there would be a large effect on solvation of the potassium ion, for

269   example, leading to large effects on $\log_{10} P$. Indeed, $\log_{10} P$ for K^{+} varies from -1.47 (to

270   methanol) [63] to -2.87 (to ethanol) [63] and to - 2.81 (to isopropanol). In a similar vein, the

271   very small variation in solvent hydrogen bond acidity, Fig. 3, would be expected to lead to

272   a small variation in $\log_{10} P$ for the (basic) chloride ion. But values for Cl^- are -2.31 (to

273   methanol), [64] -3.56 (to ethanol) [64] and -3.93 (to isopropanol), much larger differences than

274   expected, so other factors must be involved.

275

276

277   **4 Conclusions**

278   We have shown that the general LFER, Eq. 1, used to correlate solubilities and water-

279   solvent partition coefficients of neutral compounds in a wide range of mono solvents and

280   in water-methanol and water-ethanol systems can be applied to solubilities and partition

281   coefficients in the water-IPA system at various % volume IPA from water to IPA itself.

282   The obtained equations can then be used to predict solubilities and partition coefficients at

283   298 K for a wide variety of neutral compounds over the entire range of water-IPA mixtures.

284   The equations we have constructed encode the physicochemical properties of the water-

285   IPA mixtures, and we show that the hydrogen bond acidity of the mixtures slightly

286   increases from water to IPA, and the hydrogen bond basicity of the mixtures greatly

287   diminishes from water to IPA in a smooth manner.

288   Using the somewhat limited data on the transfer of ions and ionic species, we have

289   obtained the coefficients in the ionic Eq. (3) that can now be used to estimate the transfers

290   of other ions and ionic species for which we have the necessary descriptors [55, 56].

291   Important findings are values of log P for the partition of the hydrogen ion from water to

292   water-IPIA mixtures, including the value of -1.80 for transfer from water to IPA itself.

293

294   **Acknowledgements**

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