



On the solubility of nicotinic acid and isonicotinic acid in water and organic solvents

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ABSTRACT

We have determined the solubility of nicotinic acid in four solvents and the solubility of isonicotinic acid in another four solvents. These results, together with literature data on the solubility of nicotinic acid in five other organic solvents and isonicotinic acid in four other organic solvents, have been analyzed through two linear Gibbs energy relationships in order to extract compound properties, or descriptors, that encode various solute–solvent interactions. The descriptors for nicotinic acid and isonicotinic acid can then be used in known equations for partition of solutes between water and organic solvents to predict partition coefficients and then further solubility in a host of organic solvents, as well as to predict a number of other physicochemical properties.

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1. Introduction

The pyridine carboxylic acids picolinic acid (2-pyridine carboxylic acid CAS 98-98-6), nicotinic acid (3-pyridine carboxylic acid CAS 59-67-6) and isonicotinic acid (4-pyridine carboxylic acid CAS 55-22-1) are important chemicals used as food additives and in the drug industry. They exist in solution potentially as four species; a protonated cationic species, a deprotonated anionic species, a zwitterion and the neutral species [1–5]. García *et al.* [3] have shown that in water near pH values from about 2.8 to 3.6 the dominant species in the case of picolinic acid is the zwitterion (98%) with the remainder being the cationic species. The concentration of the neutral form was very low. Similar results were found for nicotinic acid and isonicotinic acid. In a very detailed investigation on nicotinic acid, Nagy and Takács-Novák [4] found that the ratio of zwitterion to neutral form lies between 23.4 and 31.7, so that the neutral form in water exists to about 4%. They show also that in the pure organic solvents methanol and tetrahydrofuran the zwitterion exists to only about 3%, the major species being the neutral form (97%). Other workers have also found that the zwitterion is the predominant form in water near the isoelectric point [5] but that in a solvent such as 50 w/w% ethanol, the zwitterion to neutral ratio is near to zero [1,2]. It is thus reasonably clear that for the pyridine carboxylic acids near the isoelectric point in water, the

zwitterion is the dominant form and that in pure organic solvents the acids exist almost entirely as the neutral form.

This has considerable implications for experiments in which partition coefficients for a pyridine carboxylic acid between water and organic solvents are measured. Depending on the pH of the aqueous solution, partition will be between some mixture of cationic, anionic, zwitterionic and neutral forms in water and the neutral form in the organic solvent. Only by applying some correction for the (low) percentage of the neutral form in water can a partition coefficient for the neutral form be obtained [4]. This not the case for the solubility in organic solvents because the acids exist in these solvents as the neutral form. Thus solubility in various solvents can be compared, because they are solubility of the same form, providing, of course, that no solvate formation occurs.

In a very detailed study, Gonçalves and da Piedade [6] determined the solubility of nicotinic acid in water, ethanol, propanone, diethyl ether, acetonitrile and dimethyl sulfoxide, and checked for any possible solvate formation. They found no evidence of solvate formation, either in water or in the organic solvents. Gonçalves and da Piedade [6] correlated their solubility data against a number of solvent parameters. Not surprisingly, they found much better correlations when water was excluded from the correlation equations. Song *et al.* [7] determined the solubility of isonicotinic acid in methanol, ethanol, propan-1-ol, propan-2-ol and propan-1,2-diol, and Wang *et al.* [8] have measured the solubility of isonicotinic acid in water.

Although solubility of a given compound in a series of solvents is intrinsically valuable, we wish to show that such solubility data encodes a large amount of extra information that can be extracted

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and then used to obtain data on various physicochemical processes. Our method is not restricted to nicotinic acid and isonicotinic acid, but applies quite generally to solubility of a given compound in a series of solvents. While there is sufficient experimental solubility data for nicotinic acid in the earlier paper by Gonçalves and Piedade to illustrate our approach; solubility data for isonicotinic is rather limited. As part of this study, we have measured the solubility of nicotinic acid in four additional alcohol solvents (namely, butan-1-ol, pentan-1-ol, hexan-1-ol and butan-2-ol) and the solubility of isonicotinic acid in propanone, tetrahydrofuran, pentan-1-ol and butan-2-ol at $T = 298.2$ K.

2. Experimental

Nicotinic acid (0.99 mass fraction, TCI America) and isonicotinic acid (0.99 mass fraction, Aldrich Chemical Co.) were purchased from commercial sources and further purified by sublimation under reduced pressure. Chemical analyses by high-performance liquid chromatography showed only a single peak in the chromatogram for each compound.

The organic solvents butan-1-ol (0.998 mass fraction, anhydrous, Aldrich), butan-2-ol (0.995 mass fraction, anhydrous, Aldrich), pentan-1-ol (0.99 + mass fraction, ACS Reagent Grade, Aldrich), hexan-1-ol (0.99 + mass fraction, anhydrous, Aldrich), propanone (0.998 mass fraction, CHROMASOLV for HPLC, Aldrich) and tetrahydrofuran (0.999 mass fraction, anhydrous, Aldrich) were stored over molecular sieves to remove trace water and distilled shortly before use. Gas chromatographic analyses showed purities to be 0.998 mass fraction or higher. The provenance and purity values of our materials are listed in table 1a.

Excess solute and solvent were sealed in amber glass bottles and allowed to equilibrate in a constant temperature water bath at (298.2 ± 0.1) K for at 2 days with periodic agitation. After equilibration, the samples stood without agitation for several hours in the constant temperature bath to allow any finely dispersed solid particles to settle. Attainment of equilibrium was verified both by repetitive measurements the following day (or sometimes after 2 days) and by approaching equilibrium from saturation by pre-equilibrating the solutions at $T = 313.2$ K. Aliquots of the saturated nicotinic acid and isonicotinic acid solutions were transferred through a coarse filter into a tarred volumetric flask, weighed and diluted quantitatively with anhydrous methanol for spectroscopic analysis at 265 nm. For the solubility determination in propanone the solvent was removed by evaporation at $T = 323$ K prior to dilution with methanol. Propanone absorbs at the analysis wavelength. Concentrations of the dilute solutions were determined from a Beer–Lambert law absorbance versus concentration working curve based on absorbance measurements for standard solutions of known concentrations covering the range of $(2.04 \cdot 10^{-4}$ to $5.44 \cdot 10^{-4})$ mol·dm⁻³ and of $(4.45 \cdot 10^{-4}$ to $8.90 \cdot 10^{-4})$ mol·dm⁻³ for nicotinic acid and isonicotinic acid, respectively.

Experimental molar concentrations were converted to mass fraction solubility by multiplying by the molar mass of the

pyridinecarboxylic acid solute, volume(s) of the volumetric flask(s) used, and any dilutions required to place the measured absorbance on the Beer–Lambert law absorbance versus concentration working curve, and then dividing by the mass of the saturated solution analyzed. The values of the mole fraction solubility were computed from solubility mass fractions using the molar masses of the solute and solvent. Experimental mole fraction nicotinic acid and isonicotinic acid solubilities, x_1 , in the organic solvents studied are listed in table 1b along with the respective standard deviations, σ . Numerical values represent the average of between six and eight independent determinations.

3. Computation methods

Our method is based on two linear free energy relationships, equations (1) and (2).

$$\lg P = c + eE + sS + aA + bB + vV, \quad (1)$$

$$\lg K = c + eE + sS + aA + bB + lL. \quad (2)$$

Equation (1) is used when the dependent variable is a water-phase partition coefficient, as $\lg P$, for a series of solutes in a given system. Equation (2) is used when the dependent variable is a gas to phase partition coefficient, as $\lg K$ [9–11].

The independent variables in equations (1) and (2) are solute descriptors as follows [9–11]: E is the solute excess molar refractivity in units of $(\text{cm}^3 \cdot \text{mol}^{-1})/10$, S is the solute dipolarity/polarizability, A and B are the overall or summation hydrogen bond acidity and basicity, and V is the McGowan characteristic volume in units of $(\text{cm}^3 \cdot \text{mol}^{-1})/100$. The symbol L is the logarithm of the gas-hexadecane partition coefficient at $T = 298$ K. The solute descriptors are obtained from a variety of experimental data, including water-solvent partition coefficients, solubility in organic solvents, and chromatographic data, as detailed previously [9–11]. The descriptors, in effect, summarize the propensity of a given solute to interact with surrounding solvent molecules, and the various terms in equations (1) and (2) show how the various resultant interactions contribute to an overall effect. The coefficients in equations (1) and (2) are obtained by multiple linear regression analysis, and serve to characterize the system under consideration. These coefficients are listed in table 2 for a number of systems considered in this work.

Equations (1) and (2) can be applied to solubility through the relationships shown in equations (3) and (4).

$$P = C/C_w, \quad (3)$$

$$K = C/C_g, \quad K_w = C_w/C_g, \quad K = PK_w. \quad (4)$$

In these equations C and C_w are the values of the solubility of a solute, in mol·dm⁻³, in a solvent and in water respectively, and C_g is

TABLE 1a
Provenance, purities, and CAS numbers of chemicals used in this study.

Component	Supplier	Mass fraction purity ^a	CAS number
Nicotinic acid	TCI America	0.99	59-67-6
Isonicotinic acid	Aldrich	0.99	55-22-1
Butan-1-ol	Aldrich	0.998	71-36-3
Butan-2-ol	Aldrich	0.995	78-92-2
Pentan-1-ol	Aldrich	>0.99	71-41-0
Hexan-1-ol	Aldrich	>0.99	111-27-3
Propanone	Aldrich	0.998	67-64-1
Tetrahydrofuran	Aldrich	0.999	109-99-9

^a Supplier stated purity checked using gas chromatography.

TABLE 1b
Mole fraction solubility, x_1 of nicotinic acid and isonicotinic acid in some organic solvents.

Solvent	x_1	σ^a
<i>Nicotinic acid</i>		
Butan-1-ol	0.00306 (6)	0.000045
Pentan-1-ol	0.00332 (8)	0.000043
Hexan-1-ol	0.00362 (7)	0.000063
Butan-2-ol	0.00360 (6)	0.000058
<i>Isonicotinic acid</i>		
Pentan-1-ol	0.000529 (7)	0.0000093
Butan-2-ol	0.000569 (7)	0.0000080
Propanone	0.000602 (8)	0.000011
Tetrahydrofuran	0.00117 (6)	0.000023

^a Standard deviation in the experimental mole fraction solubility.

TABLE 2
Coefficients in equations (1) and (2) for water-solvent and gas-solvent partitions.

Solvent	<i>c</i>	<i>e</i>	<i>s</i>	<i>a</i>	<i>b</i>	<i>l</i>	<i>v</i>
<i>Water-solvent</i>							
Methanol	0.276	0.334	−0.714	0.243	−3.320	0.000	3.549
Ethanol	0.222	0.471	−1.035	0.326	−3.596	0.000	3.857
Propan-1-ol	0.139	0.405	−1.029	0.247	−3.767	0.000	3.986
Butan-1-ol	0.165	0.401	−1.011	0.056	−3.958	0.000	4.044
Pentan-1-ol	0.150	0.536	−1.229	0.141	−3.864	0.000	4.077
Hexan-1-ol	0.115	0.492	−1.164	0.054	−3.978	0.000	4.131
Propan-2-ol	0.063	0.320	−1.024	0.445	−3.824	0.000	4.067
Butan-2-ol	0.127	0.253	−0.976	0.158	−3.882	0.000	4.114
Diethyl ether	0.248	0.561	−1.016	−0.226	−4.553	0.000	4.075
Tetrahydrofuran	0.207	0.307	−0.392	−0.236	−4.934	0.000	4.447
Ethyl acetate	0.328	0.369	−0.446	−0.700	−4.904	0.000	4.150
Propanone	0.313	0.312	−0.121	−0.608	−4.753	0.000	3.942
Acetonitrile	0.413	0.077	0.326	−1.566	−4.391	0.000	3.364
Dimethylformamide	−0.305	−0.058	0.343	0.358	−4.865	0.000	4.486
DMSO	−0.194	0.327	0.791	1.260	−4.540	0.000	3.361
Octan-1-ol, wet	0.088	0.562	−1.054	0.034	−3.460	0.000	3.814
Toluene	0.125	0.431	−0.644	−3.002	−4.748	0.000	4.524
Octane	0.241	0.690	−1.769	−3.545	−5.011	0.000	4.511
Gas–water, lg <i>K_w</i>	−0.994	0.577	2.549	3.813	4.841	0.000	−0.869
<i>Gas-solvent</i>							
Methanol	−0.039	−0.338	1.317	3.826	1.396	0.773	0.000
Ethanol	0.017	−0.232	0.867	3.894	1.192	0.846	0.000
Propan-1-ol	−0.042	−0.246	0.749	3.888	1.076	0.874	0.000
Butan-1-ol	−0.004	−0.285	0.768	3.705	0.879	0.890	0.000
Pentan-1-ol	−0.002	−0.161	0.535	3.778	0.960	0.900	0.000
Hexan-1-ol	−0.014	−0.205	0.583	3.621	0.891	0.913	0.000
Propan-2-ol	−0.060	−0.335	0.702	4.017	1.040	0.893	0.000
Butan-2-ol	−0.034	−0.387	0.719	3.736	1.088	0.905	0.000
Diethyl ether	0.288	−0.347	0.775	2.985	0.000	0.973	0.000
Tetrahydrofuran	0.189	−0.347	1.238	3.289	0.000	0.982	0.000
Propanone	0.127	−0.387	1.733	3.060	0.000	0.866	0.000
Acetonitrile	−0.007	−0.595	2.461	2.085	0.418	0.738	0.000
DMSO	−0.556	−0.223	2.903	5.037	0.000	0.719	0.000
Octan-1-ol, wet	−0.198	0.002	0.709	3.519	1.429	0.858	0.000
Toluene	0.085	−0.400	1.063	0.501	0.154	1.011	0.000
Octane	0.215	−0.049	0.000	0.000	0.000	0.967	0.000
Gas–water, lg <i>K_w</i>	−1.271	0.822	2.743	3.904	4.814	−0.213	0.000

the saturated vapour concentration of the solute, again in mol·dm^{−3}. Note that *P*, *K* and *K_w* are dimensionless. Equations (3) and (4) require that in the saturated solutions in water and the solvent the same species is in equilibrium with the solid phase, and that no solvates are present. The solubility in water and in a series of solvents of a given solute can then be converted into a series of lg *P* values between water and the solvents. These lg *P* values are ‘hypothetical’ values between water and the dry organic solvent, and are not the same as ‘real’ partition coefficients between water saturated with an organic solvent and an organic solvent saturated with water. The only real partition coefficients we shall deal with are for partition between water and octanol, and we refer to these as partitions into wet octanol.

Once lg *P* values are available for partition into a series of solvents for which the coefficients in equations (1) and (2) are known, see table 2, it is possible to set up a series of simultaneous equations that can be solved by trial-and-error to yield the unknown solute descriptors. The number of equations can be considerably increased through equation (4), by taking *K_w* as another unknown and converting all the values of lg *P* into the corresponding values of lg *K*. Some simplification is possible because *E* can be obtained from known structural fragments of the solute and *V* can simply be calculated from structure. The unknown descriptors are then *S*, *A*, *B*, *L* and lg *K_w*. In principle, these can be obtained from five simultaneous equations, but in practice there may be considerably more equations that can be solved for the five unknowns by trial-and-error.

4. Results and discussion

4.1. Solubility measurements

The mole fraction solubility of nicotinic acid at *T* = 298.2 K measured by us and by Gonçalves and Piedade [6] were converted to molar solubility (mol·dm^{−3}) and are listed in table 3. The solubility of isonicotinic acid in two aprotic solvents and in two alcohols determined by us are also given in table 3, together with values of solubility given by Song *et al.* [7] and Wang *et al.* [8].

4.2. Analysis of the data

Values of the solubility in table 3 for nicotinic acid were combined with the observed solubility in water (lg *C_w* = −0.86) to yield corresponding lg *P* values through equation (3). We also had an additional lg *P* value because this has been determined for partition of the neutral species from water to wet octanol [12]. Taking all equations together, no sensible result could be obtained, obviously because *C_w* refers the solubility of the zwitterion, and *C* refers to the solubility of neutral nicotinic acid. We can circumvent this difficulty by taking lg *C_w* as an ‘unknown’ descriptor and allowing its value to float. We now have yet another descriptor to determine, but since we have 22 simultaneous equations, as shown in table 4, this is no problem. The value obtained for the floating lg *C_w* descriptor will be the solubility of the neutral species in water.

TABLE 3Solubility of nicotinic acid and isonicotinic acid in organic solvents and water, at $T = 298.2$ K.

Solvent	Solubility/mol·dm ⁻³	Ref.
<i>Nicotinic acid</i>		
Butan-1-ol	0.03325	This work
Pentan-1-ol	0.03028	This work
Hexan-1-ol	0.02895	This work
Butan-2-ol	0.03899	This work
Ethanol	0.0631	[6]
Diethyl ether	0.00764	[6]
Propanone	0.0194	[6]
Acetonitrile	0.00384	[6]
DMSO	0.9528	[6]
Water	0.138	[6]
<i>Isonicotinic acid</i>		
Pentan-1-ol	0.00483	This work
Butan-2-ol	0.00616	This work
Propanone	0.00483	This work
Tetrahydrofuran	0.0144	This work
Methanol	0.0152	[7]
Ethanol	0.00977	[7]
Propan-1-ol	0.0103	[7]
Propan-2-ol	0.00709	[7]
Water	0.0467	[8]

TABLE 4Calculated and observed lg P values for nicotinic acid, at $T = 298.2$ K.

Solvent	Lg P calc	Lg P obs
<i>Water-solvent</i>		
Butan-1-ol	0.554	0.600
Pentan-1-ol	0.596	0.594
Hexan-1-ol	0.489	0.540
Butan-2-ol	0.621	0.669
Ethanol	0.948	0.878
Diethyl ether	0.075	-0.039
Propanone	0.361	0.365
Acetonitrile	-0.388	-0.338
DMSO	2.034	2.057
Octan-1-ol, wet	0.674	0.660
Gas-water, lg K_w	7.791	7.790
<i>Gas-solvent</i>		
Butan-1-ol	8.369	8.390
Pentan-1-ol	8.401	8.384
Hexan-1-ol	8.280	8.330
Butan-2-ol	8.430	8.459
Ethanol	8.703	8.668
Diethyl ether	7.803	7.751
Propanone	8.168	8.155
Acetonitrile	7.448	7.452
DMSO	9.862	9.847
Octan-1-ol, wet	8.418	8.450
Gas-water, lg K_w	7.789	7.790

We took E for nicotinic acid as 0.88, the sum of E for pyridine (0.63) and the carboxylic acid fragment (0.25), and calculated V as 0.8906 (cm³·mol⁻¹)/100. The other descriptors, together with lg C_w were obtained by trial-and-error. The complete set of descriptors is shown in table 5. These yield the calculated values shown in table 4. Our calculated value of lg C_w for the neutral form was -2.078 , with C_w in mol·dm⁻³. This solubility compares with that of -0.86 lg units for the zwitterionic form in water [6], so the

TABLE 5

Descriptors for nicotinic acid and isonicotinic acid.

	E	S	A	B	V	L	Lg K_w
Nicotinic acid	0.88	1.03	0.86	0.65	0.8906	4.579	7.79
Isonicotinic acid	0.88	1.29	0.81	0.51	0.8906	4.796	7.59

neutral to zwitterion equilibrium coefficient is $(-0.86 - 2.08) = 1.22$ lg units. This corresponds to about 5% neutral form in water at the isoelectric point, in good agreement with the value of 4% obtained by Nagy and Takács-Novák [4].

Although we show in table 4 the calculated and observed lg P values for nicotinic acid, a more direct comparison with experiment is provided by the calculated and observed lg C values. These are derived from the given calculated lg P values and our calculated value of -2.078 for lg C_w , and are in table 6. For the nine solvents the average error between values of the calculated and observed solubility is 0.004, the average absolute error is 0.045 and the standard deviation is 0.059 lg units. Hence our method seems capable of predicting further solubility to within, say, 0.10 lg units.

We used exactly the same procedure in the case of isonicotinic acid, taking E and V as the same as for nicotinic acid. In addition to the solubility data, there is also a value of lg $P = 0.85$ for distribution of neutral isonicotinic acid in the water to (wet) octan-1-ol system [12]. As before, lg C_w was allowed to float and was found to be -3.120 lg units. The resulting set of descriptors is in table 5 and the calculated and observed lg P values are in table 7. The corresponding lg C values are in table 8. For the eight calculated and observed values, the average error is 0.003, the absolute average error is 0.034 and the standard deviation is 0.059 lg units, so that further predictions of lg C can be made to within about 0.10 lg units, just as for nicotinic acid. Wang *et al.* [8] give the solubility of isonicotinic acid in water at $T = 298$ K as -1.33 lg units. If this is for the zwitterion, then lg P for the neutral to zwitterion equilibrium is $(-1.33 + 3.12) = 1.79$ lg units, which corresponds to about 1.5% of the neutral species in aqueous solution at the isoelectric point.

The stratagem of allowing a calculated aqueous solubility of the neutral form to 'float' yields aqueous solubility for neutral nicotinic acid and isonicotinic acid (as lg C_w) of -2.078 and -3.120 respectively. When these values of solubility are used to calculate the percentage of neutral acid to zwitterionic acid in water, quite reasonable percentages are obtained, suggesting that the stratagem is a viable method of analysis. It can also be used to analyze the solubility of compounds in organic solvents when the solubility in water is either impossible or difficult to measure, for example if the compound is very hydrophobic. If an aqueous solubility of the neutral species is available, then values of lg P can be obtained straight away through equation (3). The descriptors for nicotinic acid and isonicotinic acid, see table 5, as calculated from the lg P values are chemically reasonable, again suggesting that our method of analysis is soundly based.

One very large advantage of the present method is that the various solute-solvent interactions, as encoded in the solute

TABLE 6Comparison of calculated and observed values of solubility for nicotinic acid, at $T = 298.2$ K.

Solvent	Lg P calc	Lg C calc	Lg C obs
Butan-1-ol	0.554	-1.524	-1.478
Pentan-1-ol	0.596	-1.482	-1.484
Hexan-1-ol	0.489	-1.589	-1.538
Butan-2-ol	0.621	-1.457	-1.409
Ethanol	0.948	-1.130	-1.200
Diethyl ether	0.075	-2.003	-2.117
Propanone	0.361	-1.717	-1.713
Acetonitrile	-0.388	-2.466	-2.416
DMSO	2.034	-0.044	-0.021
Octan-1-ol, wet	0.674	-1.404	
Dimethylformamide	1.138	-0.940	
Ethyl acetate	0.100	-1.978	
Dichloromethane	-1.221	-0.857	
Toluene	-1.798	-3.876	
Octane	-3.262	-5.340	

TABLE 7
Calculated and observed lg *P* values for isonicotinic acid, at *T* = 298.2 K.

Solvent	Lg <i>P</i> calc	Lg <i>P</i> obs
<i>Water-solvent</i>		
Pentan-1-ol	0.811	0.804
Butan-2-ol	0.903	0.910
Propanone	1.026	1.030
Tetrahydrofuran	1.282	1.278
Methanol	1.313	1.302
Ethanol	1.166	1.110
Propan-1-ol	0.997	1.134
Propan-2-ol	1.017	0.971
Octan-1-ol, wet	0.883	0.850
Gas–water, lg <i>K_w</i>	7.585	7.587
<i>Gas-solvent</i>		
Pentan-1-ol	8.413	8.391
Butan-2-ol	8.474	8.496
Propanone	8.654	8.617
Tetrahydrofuran	8.854	8.864
Methanol	8.881	8.889
Ethanol	8.751	8.697
Propan-1-ol	8.598	8.721
Propan-2-ol	8.634	8.558
Octan-1-ol, wet	8.413	8.437
Gas–water, lg <i>K_w</i>	7.587	7.587

TABLE 8
Comparison of calculated and observed values of solubility for isonicotinic acid, at *T* = 298.2 K.

Solvent	Lg <i>P</i> calc	Lg <i>C</i> calc	Lg <i>C</i> obs
Pentan-1-ol	0.811	−2.309	−2.316
Butan-2-ol	0.903	−2.217	−2.211
Propanone	1.026	−2.094	−2.090
Tetrahydrofuran	1.282	−1.838	−1.843
Methanol	1.313	−1.807	−1.818
Ethanol	1.166	−1.954	−2.010
Propan-1-ol	0.997	−2.123	−1.986
Propan-2-ol	1.017	−2.103	−2.149
Octan-1-ol, wet	0.883	−2.237	
Diethyl ether	0.581	−2.539	
Acetonitrile	0.399	−2.721	
DMSO	2.813	−0.307	
Toluene	−1.151	−4.271	
Octane	−2.843	−5.963	

descriptors, can be used to predict a large number of physicochemical properties. We have equations on the lines of equation (1) for partitions between water and nearly 100 solvents [11], as well as equations for partition into numerous ionic liquids [13], and so solubility of nicotinic acid and isonicotinic acid in all these solvents can be predicted by simple arithmetic. As examples, we give in tables 6 and 8 a number of predicted values of solubility of the neutral forms of the acids as calculated from the equation coefficients in table 1, the descriptors in table 5 and our calculated aqueous solubility values for the neutral forms. If a solvent is required that leads to a large solubility or one that leads to a small solubility, it is trivial to run through our list of equations for lg *P*, and to calculate values of lg *P* and then of lg *C*. As can be seen from tables 6 and 8, there is a very large range of solubility depending on the solvent. Of course, if solubility is known in a solvent for which the coefficients in equation (1) are unknown, all that can be done is

to calculate the corresponding water–solvent partition coefficient. The solubility of nicotinic acid in 3-methylpyridine is 0.424 mol·dm^{−3} at *T* = 298.2 K [16] which leads to a value of lg *P* = 1.70 for the neutral form.

As well as solubility, other physicochemical properties can also be predicted once the descriptors in equation (1) are available, for example enthalpies of solvation in various solvents [14]. Mutelet and Rogalski [15] have used the descriptors in equation (1) and (2) to construct equations for the correlation and prediction of normal boiling points, critical temperature and critical pressure.

5. Conclusions

The solubility of a given compound in a series of solvents encodes a large amount of data on interactions between the compound, as a solute, and the various solvents. These interactions can be expressed quantitatively by a series of descriptors that can be extracted from the solubility data through the linear free energy relationships, equation (1) and (2). Once descriptors are available for a compound, they can then be combined with equations that have already been constructed to yield predictions of solubility in a large number of additional solvents, as well as predictions of various other physicochemical properties. The method is completely transparent, and the calculations involve no more than simple arithmetic. If a solubility of a given species in water is available, as well as solubility in a series of solvents, then the derived lg *P* values can be used as the dependent variable in equation (1) straight away. If an aqueous solubility is not available, it can be calculated by a trial-and-error procedure from the experimental solubility in organic solvents. The examples of nicotinic acid and isonicotinic acid illustrate the procedure for cases where the solubility of a neutral species is known in organic solvents, but not in water, where the zwitterionic species predominates. For the two compounds here examined, solubility in a very large number of solvents can be predicted to about 0.10 lg units.

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