



# 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  $(298.2 \pm 0.1)$  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<sup>-3</sup> and of  $(4.45 \cdot 10^{-4}$  to  $8.90 \cdot 10^{-4})$  mol·dm<sup>-3</sup> 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,  $\sigma$ . 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<sup>-3</sup>, in a solvent and in water respectively, and  $C_g$  is

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

Solvent	$x_1$	$\sigma^a$
<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

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

Component	Supplier	Mass fraction purity <sup>a</sup>	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

<sup>a</sup> Supplier stated purity checked using gas chromatography.

<sup>a</sup> Standard deviation in the experimental mole fraction solubility.

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