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Potentiometric Titration Study of the Temperature and Ionic Strength Dependence of the Acidity Constants of Nicotinic Acid (Niacin)

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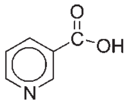
Supporting Information

ABSTRACT: The influence of temperature (T) and ionic strength (I_m) on the stoichiometric (molality scale) acidity constants of nicotinic acid in aqueous solution was investigated by potentiometry (H^+-glass electrode). The background salt used was potassium chloride, and the temperature and ionic strength ranges covered were $283.15 \text{ K} < T < 318.15 \text{ K}$ and $0.05 \text{ mol}\cdot\text{kg}^{-1} < I_m < 0.52 \text{ mol}\cdot\text{kg}^{-1}$, respectively. Acidity constants at zero ionic strength were derived by means of a Debye–Hückel type formalism, and their temperature dependence was obtained through a van't Hoff analysis. This led to $\text{p}K_{a1} = 2.19 \pm 0.06$ and $\text{p}K_{a2} = 4.86 \pm 0.03$ at 298.15 K and to the corresponding standard molar enthalpies and entropies of proton dissociation in the temperature range of the experiments, $\Delta_r H^\circ_{m,1} = (4.5 \pm 3.5) \text{ kJ}\cdot\text{mol}^{-1}$, $\Delta_r S^\circ_{m,1} = -(26.8 \pm 11.8) \text{ J}\cdot\text{K}^{-1}\cdot\text{mol}^{-1}$, $\Delta_r H^\circ_{m,2} = (12.5 \pm 2.1) \text{ kJ}\cdot\text{mol}^{-1}$, and $\Delta_r S^\circ_{m,2} = -(51.2 \pm 7.0) \text{ J}\cdot\text{K}^{-1}\cdot\text{mol}^{-1}$. These values were compared with previously reported data.

INTRODUCTION

Nicotinic acid (NA, CAS number [59-67-6]), pyridine-3-carboxylic acid, also known as niacin or vitamin B_3, is a water-soluble vitamin, and an indispensable dietary factor for humans and animals.[1,2] In humans nicotinic acid nutritional deficiency can lead to the development of pellagra, a systemic disorder that can progress to a severe photosensitive dermatitis and, ultimately, result in dementia and death.[3,4] Nicotinic acid has also found important pharmacological applications, particularly in the treatment of hypercholesterolemia and atherosclerosis.[5,6] Its current world demand has been estimated to be 35 000–40 000 t.[1,7,8]



Nicotinic acid (NA)

We recently started a systematic investigation of nicotinic acid and some of its derivatives that, up to now, has been mainly centered on the relationship between structure and thermodynamic stability of both the isolated molecules and the corresponding crystal forms.[9,10] This effort has been fostered by the significance of this family of compounds as active pharmaceutical ingredients (APIs) and the importance of evaluating how strongly changes in crystallinity, morphology, particle size distribution, etc. are reflected by the thermodynamic stability of a particular sample. Indeed, such changes are known to often have a significant impact on, for example, the solubility, dissolution rate, shelf life, and therapeutic time-window of an API and hence on its end-use applications.[11−13]

Equally important is the energetics of nicotinic acid in aqueous solution, which we also began to address through enthalpy of solution and dilution measurements by solution and flow calorimetry.[14] In this context, the acid–base properties of the compound (characterized by acidity constants that are normally given in terms of the corresponding pK_a values) play a central role, since they determine the extent of protonation/deprotonation and the concentrations of species that are present in a solution at equilibrium under specific conditions. Knowledge of this composition is often required for the correct assignment of thermodynamic results to a well-defined state,[14] and it may also be, for example, a key aspect in the study of drug permeation.[15]

Aqueous nicotinic acid is an amphiprotic system where four species may be present in equilibrium (Scheme 1): one positively charged (AH_2^+), two of isoelectric type ($AH^\pm$ and AH^o), and a fourth one negatively charged (A^-). Several studies have been devoted to the investigation of the relative importance of each isoelectric species in aqueous solutions. Some early views favored the predominance of the AH^o form.[16] However, a consensus seems now to exist that the $AH^o \leftrightarrow AH^\pm$ equilibrium is strongly shifted toward the zwitterionic species,[17−29] with the contribution of AH^o to the equilibrium mixture at approximately 293 to 298 K estimated in ~ 3 %,[27] ~ 6 %,[25] 7 % to 8 %,[17] 10 %,[18,24] and 22 %,[19] according to different authors. This conclusion was supported by a variety of information, namely: (i) the use of Hammett relationships to predict the equilibrium constant of the $AH^o \leftrightarrow AH^\pm$ process;[17,25] (ii) the comparison of the ultraviolet (UV) spectrum of isoelectric nicotinic acid with that of the corresponding methyl ester;[18] (iii) the dependence of the infrared spectrum (IR)[30] and the ^{1}H and ^{13}C nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectroscopy chemical shifts[22] of aqueous nicotinic acid on the pH of the solution and its content

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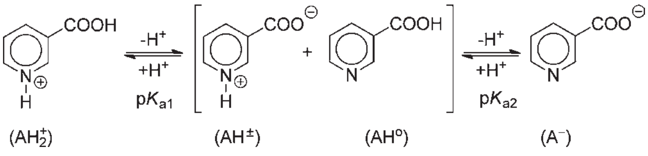
Scheme 1



in dimethyl sulfoxide; (iv) the failure to produce copper complexes containing nicotinic acid with an nonionized −COOH group in acidic media;[21] (v) entropic and enthalpic considerations based on equilibrium and solution calorimetry measurements;[20,31] and (vi) computational chemistry results.[27,28] Although for some applications, such as the interpretation of the pH dependence of partition coefficients of drugs, the equilibrium constants (normally dubbed microconstants) relating all four species in Scheme 1 may be required,[27,32] their determination is not aimed in this work.

There have been several determinations of the stoichiometric (molarity or molality scale, pK'_{a1} and pK'_{a2}) and thermodynamic (pK_{a1} and pK_{a2}) acidity constants of nicotinic acid in aqueous solution by using UV spectroscopy,[16,21,23,26,33−36] potentiometry,[18,19,21,23−26,29,37,38] conductivity,[39] and ^{13}C NMR[22] measurements, but in most cases, they were based on experiments carried out at a single temperature or ionic strength, none involving a systematic study of both the influence of temperature and ionic strength on the results. At temperatures close to ambient (293 to 298 K) the reported pK'_a or pK_a values (the last often calculated from stoichiometric counterparts by using Debye−Hückel type approaches) for the first and second proton dissociation equilibriums vary in the ranges 1.87 to 3.60 and 4.67 to 5.12, respectively.[16,18,19,21−26,29,33−39] To the best of our knowledge, the temperature dependence of pK_{a1} or pK_{a2} has only been investigated twice.[36,39] These studies further afforded the corresponding enthalpies and entropies of ionization through van't Hoff plots (second law method).[40] Direct measurements of the enthalpies of ionization of nicotinic acid have also been performed by calorimetry.[20,31,41−43]

This work describes the potentiometric determination of the stoichiometric (molality scale) acidity constants of nicotinic acid in the temperature and ionic strength ranges (283.15 to 318.15) K and (0.05 to 0.52) $mol \cdot kg^{-1}$, respectively, which cover physiological relevant conditions. The background electrolyte chosen (KCl) is also of biological significance. Thermodynamic acidity constants at zero ionic strength were further derived from their stoichiometric counterparts by means of extrapolations based on a Debye−Hückel type formalism. Despite some well-documented difficulties associated with, for example, electrode calibration, asymmetry and liquid junction potentials, or potential drifts, potentiometry using a combined glass pH electrode has been shown to be a fast and convenient method to obtain reliable pK_a values, provided that an adequate experimental procedure and analysis of the titration data is performed.[44−46] To the best of our knowledge, no previous potentiometric investigation of both the influence of temperature and ionic strength on the acidity constants of nicotinic acid has been reported. The systematic study here described thus allows test the application of this technique to an important pharmaceutical acid/base system, where both pK_a values belong to the acid zone of the titration curve and overlapping ionization exists ($pK_{a1} - pK_{a2} < 4$).[34] We also aim to provide data that are consistent with our previously thermodynamic studies of aqueous nicotinic acid.[14]

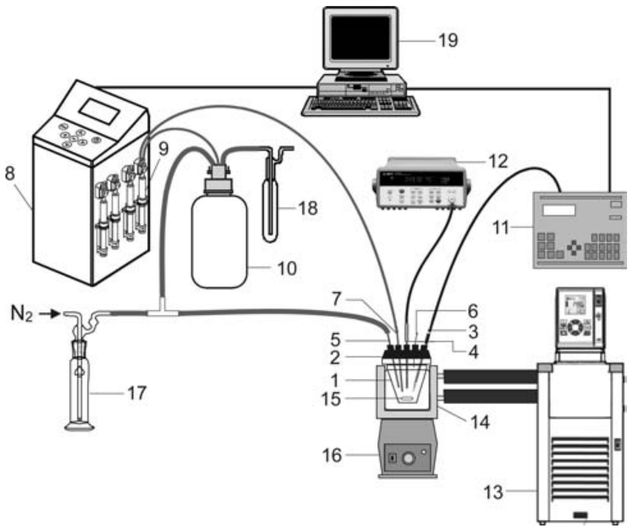


Figure 1. Scheme of the potentiometric titration apparatus: 1, Double walled Metrohm 6.1418.220 glass vessel; 2, Metrohm 6.1414.010 lid; 3, Radiometer Analytical Red Rod pHC2401 combined pH electrode; 4, Pt100 platinum resistance thermometer; 5, N_2 gas inlet; 6, N_2 gas outlet; 7, buret dispenser tip (steel needle); 8, four channel Crison Multi-Buret 45 automatic buret; 9, Hamilton 1 cm^3 syringe; 10, Methrom 6.1608.040 polyethylene storage flask closed by an Omnifit 00945Q-3 V GL45 cap; 11, PHM240 Radiometer Analytical pH meter; 12, Agilent 34970A 6 1/2 digits multimeter; 13, JULABO F33-ME thermostatic bath; 14, polyurethane layer for thermal isolation; 15, Teflon coated stirring bar; 16, Metrohm E649 stirring plate; 17, gas-washing glass bottle containing distilled and deionized water; 18, bubbler; 19, computer.

■ MATERIALS AND METHODS

Materials. The nicotinic acid sample (Acrös, 99.5%), purified by sublimation at 393 K and 1.33 Pa, was the same employed in a previous calorimetric study.[14] This material had been characterized in terms of chemical purity, phase purity, and morphology by elemental analysis, diffuse reflectance infrared Fourier-transform (DRIFT) spectroscopy, ^{1}H and ^{13}C NMR, GC-MS, X-ray powder diffraction, scanning electron microscopy (SEM), and differential scanning calorimetry (DSC).[14] None of these analyses showed evidence of impurities.

The stock solutions of HCl ($(0.1000 \pm 0.0020)\ mol \cdot dm^{-3}$), NaOH 1 $mol \cdot dm^{-3}$ (nominal concentration), and KCl ($(1.0000 \pm 0.0004)\ mol \cdot dm^{-3}$) used in the titrations were prepared from Panreac ampules containing (0.100 ± 0.002) mol of HCl or (1.000 ± 0.002) mol of NaOH or from solid KCl (Panreac, 99.5%), respectively. The dilutions or dissolutions were performed with distilled and deionized water from a Milli-Q Plus system (conductivity 0.1 $\mu S \cdot cm^{-1}$). To minimize carbonation, the NaOH solutions were stored and handled under nitrogen atmosphere. All weightings of chemicals for the preparation of solutions were done with a precision of ± 0.01 mg with a Mettler Toledo XS205 balance.

Potentiometric Titrations. The potentiometric titration apparatus is illustrated in Figure 1. It consists of a (20−90) cm^3 double walled Metrohm 6.1418.220 glass vessel (1), closed by a Metrohm 6.1414.010 lid (2). The lid supports a Radiometer Analytical Red Rod pHC2401 combined pH electrode (3), a

Table 1. Stoichiometric (Molality Scale) Acidity Constants (pK'_{a1} and pK'_{a2}) of Nicotinic Acid at Different Temperatures and Ionic Strengths, and Corresponding Thermodynamic Acidity Constants for $I_m = 0$ (in Bold), and $\Delta\varepsilon_2$ Parameters from eq 15

	T/K				
I_m/mol·kg^{-1}	283.15	293.15	303.15	310.15	318.15
			pK'_{a1}		
0.05	2.473 ± 0.013	2.395 ± 0.018	2.297 ± 0.010	2.193 ± 0.012	2.286 ± 0.012
0.10	2.122 ± 0.011	2.027 ± 0.015	1.916 ± 0.021	2.149 ± 0.010	1.929 ± 0.029
0.15	2.274 ± 0.012	2.137 ± 0.020	2.105 ± 0.015	2.075 ± 0.013	2.238 ± 0.007
0.21	2.190 ± 0.009	2.215 ± 0.013	2.055 ± 0.010	2.172 ± 0.008	2.421 ± 0.008
0.52	2.354 ± 0.017	2.121 ± 0.024	2.207 ± 0.011	2.218 ± 0.009	2.095 ± 0.017
pK_{a1}	**2.283 ± 0.062**	**2.179 ± 0.062**	**2.116 ± 0.065**	**2.161 ± 0.024**	**2.194 ± 0.084**
			pK'_{a2}		
0.05	4.853 ± 0.007	4.792 ± 0.009	4.668 ± 0.005	4.613 ± 0.005	4.619 ± 0.005
0.10	4.817 ± 0.005	4.738 ± 0.009	4.532 ± 0.003	4.550 ± 0.003	4.558 ± 0.007
0.15	4.754 ± 0.005	4.713 ± 0.004	4.617 ± 0.005	4.559 ± 0.003	4.539 ± 0.003
0.21	4.779 ± 0.005	4.716 ± 0.007	4.616 ± 0.004	4.572 ± 0.003	4.554 ± 0.003
0.52	4.838 ± 0.011	4.744 ± 0.010	4.592 ± 0.006	4.620 ± 0.006	4.594 ± 0.002
pK_{a2}	**4.977 ± 0.020**	**4.926 ± 0.010**	**4.796 ± 0.038**	**4.752 ± 0.011**	**4.754 ± 0.012**
$\Delta\varepsilon_2$	**0.358 ± 0.076**	**0.292 ± 0.037**	**0.285 ± 0.142**	**0.419 ± 0.043**	**0.954 ± 0.141**
$R^{2\ a}$	0.88	0.95	0.57	0.97	0.95

[a] Coefficients of determination for the least-squares fittings of eq 15.

Pt100 platinum resistance thermometer (4), for temperature measurement, a N_2 gas inlet (5), and the corresponding outlet consisting of PTFE tube (0.8 mm ID, 1.6 mm OD) from Omnifit (6), and a Metrohm MTR61541030 buret dispenser tip (7). Dispensing of solutions to the cell was by means of a four channel Crison Multi-Buret 45 automatic buret (8) and a Hamilton 1 cm^3 syringe (9). The syringe could be automatically filled from a Methrom 6.1608.040 polyethylene storage flask closed by an Omnifit 00945Q-3 V GL45 cap (10) that contained the reagent solution. The volume additions had a precision better than $\pm$ 0.001 cm^{-3}, as experimentally confirmed in a series of test runs were a selected volume of water was dispensed, weighed, and checked by using the known density of water[47] at the working temperature. The electrode 3 measurements were monitored by a PHM240 Radiometer Analytical pH meter (11). The Pt100 temperature sensor 4 was connected in a four wire configuration to an Agilent 34970A 6 1/2 digits multimeter (12) and had been previously calibrated against a standard platinum resistance thermometer, which had been standardized at an accredited facility in accordance to the International Temperature Scale ITS-90. This setup allowed temperature measurements with a resolution of $\pm$ 0.01 K. The temperature of the solution was maintained constant to within $\pm$ 0.02 K, by circulating a thermostatted water−ethanol mixture (3:1 v/v) through the jacket of glass vessel 1. Control of the temperature of the circulating fluid mixture was achieved by means of a JULABO F33-ME thermostatic bath (13). To ensure better temperature control and shorter thermal equilibration periods the vessel 1 was further isolated from the surroundings by a polyurethane layer of 20 mm thickness (14). During the titrations the solution was kept under magnetic stirring using a Teflon-coated bar (15) and a Metrohm E649 stirring plate (16). An inert atmosphere was maintained inside the cell 1 and the storage flask 10, by continuously bubbling water saturated nitrogen through the corresponding solutions at a flow rate of (1.5 ± 0.1) $cm^3 \cdot s^{-1}$. To ensure saturation the N_2 gas entering the cell and the storage flask was previously bubbled through distilled and deionized water contained in a gas-washing bottle (17). A bubbler (18) was placed at the nitrogen exit of flask 10. Finally, a computer (19) controlled the additions from the buret and the data acquisition, by means of a software package also developed in this work.

In a typical experiment the cell, 1, was loaded with 0.5 cm^3 of 0.1 $mol \cdot dm^{-3}$ nicotinic acid, 0.5 cm^3 of 0.1 $mol \cdot dm^{-3}$ HCl, (20 to 25) cm^3 of H_2O, and the volume of 1 $mol \cdot dm^{-3}$ KCl solution necessary to fix the ionic strength at a desired value. Stirring and N_2 purging was initiated and after an equilibration period of 10 to 15 min, the titration was started. The procedure was computer controlled and involved successive additions of 0.005 cm^{-3} of 1 $mol \cdot dm^{-3}$ NaOH. After each addition the system was first allowed to equilibrate for 120 s. Then ten electrode potential readings by the pH meter separated by 1.5 s were acquired. If the difference between the minimum and maximum values of those readings was smaller than 0.05 mV, their average value was computed and stored, and a new 0.005 cm^{-3} addition of NaOH solution was automatically performed. The total volume of base dispensed in a titration was 0.2 cm^3.

Each nicotinic acid titration was preceded by a calibration of the pH electrode in terms of hydrogen ion concentration. This involved a titration of NaOH (1 $mol \cdot dm^{-3}$) with HC1 (0.1 $mol \cdot dm^{-3}$) under temperature and ionic strength conditions mimicking, as much as possible, those of the main experiment. The exact concentration of the NaOH solution was determined from the end point of the titration, based on the second derivative of the experimental curve describing the variation of the cell potential, E, with the added volume of NaOH solution (V_{NaOH}). From this curve and the exact concentration of the NaOH a linear relationship between the cell potential E and $\log[H^+]$ could be obtained

$$E = k + s \log \frac{[H^+]}{c^o} \tag{1}$$

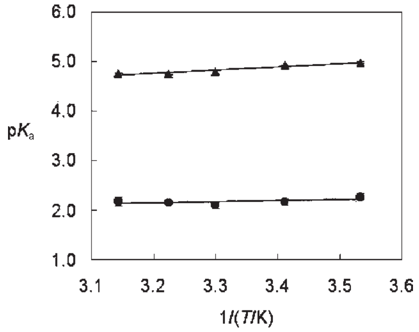


Figure 2. Acidity constants of nicotinic acid as a function of the temperature: (●) pK_{a1} and (▲) pK_{a2}.

where c^o = 1 mol·dm^{-3} is the standard state concentration. The values of the slope s and ordinate k were determined by using the program GLEE (version 3.0.21).[48] The percentage of carbonation of the NaOH solution was also determined by Gran's method[49,50] as implemented in the program GLEE (version 3.0.21), and the solution was rejected if % CO_3^{2-} > 1 %.

■ RESULTS AND DISCUSSION

The first and second thermodynamic acidity constants of nicotinic acid (K_{a1} and K_{a2}, respectively) correspond to the processes

$$AH_2^+(aq) + H_2O(aq) \rightleftharpoons AH(aq) + H_3O^+(aq) \qquad (2)$$

$$AH(aq) + H_2O(aq) \rightleftharpoons A^-(aq) + H_3O^+(aq) \qquad (3)$$

with AH = $AH^{\pm}$ + AH^o (see Scheme 1), and are given in molality scale by

$$K_{a1} = \frac{a_{AH}a_{H_3O^+}}{a_{AH_2^+}a_{H_2O}} = \frac{\gamma_{AH}\gamma_{H_3O^+}}{\gamma_{AH_2^+}a_{H_2O}}\frac{m_{AH}m_{H_3O^+}}{m_{AH_2^+}m^o} = \frac{\gamma_{AH}\gamma_{H_3O^+}}{\gamma_{AH_2^+}}K'_{a1} \qquad (4)$$

$$K_{a2} = \frac{a_{A^-}a_{H_3O^+}}{a_{AH}a_{H_2O}} = \frac{\gamma_{A^-}\gamma_{H_3O^+}}{\gamma_{AH}a_{H_2O}}\frac{m_{A^-}m_{H_3O^+}}{m_{AH}m^o} = \frac{\gamma_{A^-}\gamma_{H_3O^+}}{\gamma_{AH}}K'_{a2} \qquad (5)$$

Here $a_i = \gamma_i m_i/m^o$ represents the activity of a given species i of molal concentration m_i, γ_i is the corresponding activity coefficient, m^o = 1 mol·kg^{-1} is the standard state concentration that makes a_i dimensionless and, K'_{a1} and K'_{a2} are the first and second stoichiometric (molality scale) acidity constants. According to normal practice it was assumed that $a_{H_2O} \sim 1$ and that the small departures of the water activity from unity could be incorporated in the values of K'_{a1} and K'_{a2}. This approximation seems reasonable in the present work considering that osmotic coefficient (ϕ_m) measurements[51] on KCl aqueous solutions with molalities, m_{KCl}, in the range (0.1 to 0.5) mol·kg^{-1} and temperatures of (283 to 298) K lead to 0.984 < a_{H_2O} < 0.997, by using[52]

$$\ln a_{H_2O} = -\frac{2m_{KCl}\phi_m}{1000}M_{H_2O} \qquad (6)$$

where M_{H_2O} is the molar mass of water. The pK'_{a1} and pK'_{a2} values at different temperatures and ionic strengths, obtained in this work are shown in Table 1. They were derived from the corresponding acidity constants in molarity scale calculated from the analysis of the titration curves by using the HyperQuad2008 suite of programs (see the Supporting Information).[53] The conversion from molarity (K'_c) to molality (K'_m) scale was based on[40]

$$K'_m = K'_c c^o(\rho m^o)^{-1} \qquad (7)$$

where c^o = 1 mol·dm^{-3} and m^o = 1 mol·kg^{-1} are the standard state concentrations in molarity and molality scales, respectively, and ρ is the mass density of the aqueous KCl solutions in kg·dm^{-3}.[54–56]

The HyperQuad2008 analysis of each titration curve leads to a pair of pK'_{a1} and pK'_{a2} values and to their assigned standard deviations, σ. The results in Table 1 represent weighted means of 3 to 6 of such determinations (see the Supporting Information), and the uncertainties quoted are the corresponding standard errors.[57] The weights were taken as $1/\sigma^2$.

According to the specific ion interaction model, the activity coefficients of the species in eqs 4 and 5 may be described by[58,59]

$$\log \gamma_{H_3O^+} = -D + \varepsilon_{H_3O^+,K^+}\frac{m_{K^+}}{m^o} + \varepsilon_{H_3O^+,Cl^-}\frac{m_{Cl^-}}{m^o} \qquad (8)$$

$$\log \gamma_{AH} = \varepsilon_{AH,K^+}\frac{m_{K^+}}{m^o} + \varepsilon_{AH,Cl^-}\frac{m_{Cl^-}}{m^o} \qquad (9)$$

$$\log \gamma_{AH_2^+} = -D + \varepsilon_{AH_2^+,K^+}\frac{m_{K^+}}{m^o} + \varepsilon_{AH_2^+,Cl^-}\frac{m_{Cl^-}}{m^o} \qquad (10)$$

$$\log \gamma_{A^-} = -D + \varepsilon_{A^-,K^+}\frac{m_{K^+}}{m^o} + \varepsilon_{A^-,Cl^-}\frac{m_{Cl^-}}{m^o} \qquad (11)$$

In eqs 8 to 11, $\varepsilon_{i,j}$ are the coefficients representing the interaction between species i and j, m^o = 1 mol·kg^{-1} is the standard state concentration that makes the $\varepsilon_{i,j}$ parameters dimensionless, and D is the Debye–Hückel term, given by[59]

$$D = z_i^2\frac{A\sqrt{I_m}}{1 + 1.5\sqrt{I_m}} \qquad (12)$$

with

$$A/\text{kg}^{1/2}\cdot\text{mol}^{-1/2} = 4.70307 \times 10^{-6}(T/K)^2 - 1.94302 \times 10^{-3}(T/K) + 0.67064 \qquad (13)$$

where T represents the absolute temperature. Equation 13 was derived from a polynomial fit (coefficient of determination R^2 = 0.9991) to the data recommended by Grenthe, Wanner, and Östhols[59] in the temperature range (273.15 to 348.15) K. From eqs 4, 5, and 8 to 11 it is possible to conclude that

$$pK'_{a1} = pK_{a1} + \Delta\varepsilon_1 I_m \qquad (14)$$

$$pK'_{a2} + 2D = pK_{a2} + \Delta\varepsilon_2 I_m \qquad (15)$$

with:

$$\Delta\varepsilon_1 = (\varepsilon_{H_3O^+,Cl^-} + \varepsilon_{H_3O^+,K^+}) + (\varepsilon_{AH,Cl^-} + \varepsilon_{AH,K^+}) - (\varepsilon_{AH_2^+,K^+} + \varepsilon_{AH_2^+,Cl^-}) \qquad (16)$$

$$\Delta\varepsilon_2 = (\varepsilon_{H_3O^+,Cl^-} + \varepsilon_{H_3O^+,K^+}) - (\varepsilon_{AH,Cl^-} + \varepsilon_{AH,K^+}) + (\varepsilon_{A^-,Cl^-} + \varepsilon_{A^-,K^+}) \qquad (17)$$

Thus, according to eq 14, pK_{a1} and $\Delta\varepsilon_1$ can be determined from the ordinate and slope, respectively, of a pK'_{a1} vs I_m plot. Similarly

Table 2. Standard Molar Enthalpies and Entropies of Proton Ionization for Nicotinic Acid

T	$\Delta_r H^o_{m,1}$	$-\Delta_r S^o_{m,1}$	$\Delta_r H^o_{m,2}$	$-\Delta_r S^o_{m,2}$	
K	$kJ \cdot mol^{-1}$	$J \cdot K^{-1} \cdot mol^{-1}$	$kJ \cdot mol^{-1}$	$J \cdot K^{-1} \cdot mol^{-1}$	method[a]
283.15 to 318.15	4.5 ± 3.5[b]	-26.8 ± 11.8[b]	12.5 ± 2.1[b]	-51.2 ± 7.0[b]	potentiometry (vH)
298.15			10.75 ± 0.21[c]		calorimetry
298.15	3.14 ± 0.29[d]		11.34 ± 0.29[d]		calorimetry
288 to 408	-0.2 ± 1.1[e]	39.2 ± 3.2[e]	11.8 ± 0.7[e]	54.4 ± 2.1[e]	spectrophotometry (vH)
298.15	2.1[f]				calorimetry
298.15	3.0 ± 1.0[g]		8.0 ± 1.0[g]		calorimetry
288.15 to 323.15			11.9 ± 0.1[h]	54.5 ± 0.2[h]	conductivity (vH)
298.15	2.38 ± 0.50[i]		13.94 ± 0.70[i]		calorimetry

[a] vH = van't Hoff plot. [b] This work. [c] Reference 20. [d] Reference 41. [e] Reference 36. [f] Reference 42. [g] Reference 43. [h] Reference 39. [i] $I_m = 0.25$ ($NaClO_4$), reference 31.

Table 3. Thermodynamic Acidity Constants, pK_{a1} and pK_{a2}, of Nicotinic Acid at 298.15 K

pK_{a1}	pK_{a2}	method
2.19 ± 0.06[a]	4.86 ± 0.03[a]	potentiometry
2.03 ± 0.05[b]	4.83 ± 0.05[b]	
1.98 ± 0.04[c]	5.00 ± 0.31[c]	spectrophotometry
1.99[d]	4.88[d]	spectrophotometry
2.09 ± 0.02[e]	4.75 ± 0.02[e]	spectrophotometry
2.09 ± 0.04[f]	4.83 ± 0.02[f]	potentiometry; emf measurement, spectrophotometry
2.10 ± 0.01[g]	4.87 ± 0.01[g]	spectrophotometry
2.12 ± 0.03[h]	4.90 ± 0.03[h]	potentiometry
	4.67[i]	potentiometry
2.14 ± 0.02[j]	5.06 ± 0.05[j]	spectrophotometry
	4.92[k]	conductimetry
2.86 ± 0.11[l]	5.12 ± 0.06[l]	potentiometry

[a] This work. [b] Recommended in the database of reference 62. [c] Reference 26. [d] Reference 36. [e] Reference 33. [f] Reference 23. [g] Reference 34. [h] Mean of five values from reference 19. [i] Reference 38. [j] Reference 35. [k] Reference 39. [l] Reference 29.

it can be concluded from eq 15 that a plot of $pK'_{a2} + 2D$ vs I_m affords pK_{a2} and $\Delta\varepsilon_2$. The data in Table 1 do not evidence any significant dependence of pK'_{a1} on I_m. In fact, linear least-squares fittings of eq 14 to those results led to: $pK'_{a1} = 2.27 \pm 0.11$ and $\Delta\varepsilon_1 = 0.07 \pm 0.43$ for $T = 283.15$ K; $pK_{a1} = 2.23 \pm 0.11$ and $\Delta\varepsilon_1 = -0.24 \pm 0.41$ for $T = 293.15$ K; $pK_{a1} = 2.08 \pm 0.12$ and $\Delta\varepsilon_1 = 0.16 \pm 0.44$ for $T = 303.15$ K; $pK_{a1} = 2.13 \pm 0.04$ and $\Delta\varepsilon_1 = 0.14 \pm 0.15$ for $T = 310.15$ K; and $pK_{a1} = 2.22 \pm 0.15$ and $\Delta\varepsilon_1 = -0.14 \pm 0.60$ for $T = 318.15$ K. The uncertainties in the $\Delta\varepsilon_1$ terms are larger than the actual values and the mean of the results obtained for the five studied temperatures is $\Delta\varepsilon_1 = 0.0 \pm 0.1$. Therefore the pK_{a1} values assigned to each temperature in Table 1 (indicated in bold) correspond to averages of the related pK'_{a1} results for different ionic strengths. The values of pK_{a2} and $\Delta\varepsilon_2$ determined by linear least-squares fitting of eq 15 to plots of $pK'_{a2} + 2D$ vs I_m are also summarized in Table 1, which also includes the coefficients of determination of those fittings.

The pK_{a1} and pK_{a2} values obtained at different temperatures were fitted to eq 18 by linear least-squares regression (Figure 2)

$$pK_a = \frac{a}{T} + b \qquad (18)$$

where the slope a is related to the standard molar proton dissociation enthalpy ($\Delta_r H^o_{m,1}$ in the case of reaction 2 and $\Delta_r H^o_{m,2}$ in the case of reaction 3) of nicotinic acid at the average of the highest and lowest temperatures of the range covered in the experiments, $T_m = 301.6$ K, by[40] $\Delta_r H^o_m = aR \ln 10$ ($R = 8.314472\ J \cdot K^{-1} \cdot mol^{-1}$ is the gas constant).[60] The corresponding entropy change is associated with the ordinate b by $\Delta_r S^o_m = -bR \ln 10$. The obtained results were for reaction 2 $a = 236.9 \pm 185.1$, $b = 1.400 \pm 0.616$, $\Delta_r H^o_{m,1} = (4.5 \pm 3.5)\ kJ \cdot mol^{-1}$, and $\Delta_r S^o_{m1} = -(26.8 \pm 11.8)\ J \cdot K^{-1} \cdot mol^{-1}$ and for reaction 3 $a = 653.2 \pm 109.8$, $b = 2.672 \pm 0.365$, $\Delta_r H^o_{m,2} = (12.5 \pm 2.1)\ kJ \cdot mol^{-1}$, and $\Delta_r S^o_{m2} = -(51.2 \pm 7.0)\ J \cdot K^{-1} \cdot mol^{-1}$. The uncertainties assigned to a, b, $\Delta_r H^o_m$, and $\Delta_r S^o_{m2}$ correspond to standard errors. The above $\Delta_r H^o_m$ and $\Delta_r S^o_m$ results are compared in Table 2 with the analogous results taken from the literature or calculated from published data.[20,36,39,41−43] The poor precision of $\Delta_r H^o_{m,1} = (4.5 \pm 3.5)\ kJ \cdot mol^{-1}$ reflects the difficulty in extracting proton dissociation enthalpies from the slopes of van't Hoff plots when the variations of pK_a with temperature are very weak. This is also the case of $\Delta_r H^o_{m,1} = -(0.2 \pm 1.1)\ kJ \cdot mol^{-1}$, which was derived from a van't Hoff analysis of the single[36] previously reported pK_{a1} vs T data found in the literature. The $\Delta_r H^o_{m,1}$ here reported is, nevertheless, in good agreement within the experimental uncertainty with the corresponding values directly obtained by calorimetric measurements, carried out at 298.15 K (Table 2). The small difference between the reference temperature of (301.6 and 298.15) K is unlikely to change this conclusion, since the associated enthalpy corrections are expected to be clearly within the experimental uncertainty of the measurements. An analogous line of reasoning applies to the discussion of $\Delta_r S^o_{m1}$. The overall agreement between the $\Delta_r H^o_{m,2}$ and $\Delta_r S^o_{m,2}$ values obtained in this work and previously published is good.

Finally, eq 18 and the appropriate values of the a and b parameters for reactions 2 and 3 lead to $pK_{a1} = 2.19 \pm 0.06$ and $pK_{a2} = 4.86 \pm 0.03$, respectively, at 298.15 K. The indicated uncertainties represent standard deviations and were calculated from the differences between the pK_a values given by eq 18 and their experimental equivalents.[61] The pK_{a1} and pK_{a2} values determined in this work at 298.15 K are compared in Table 3 with corresponding published data.[19,23,26,29,33−36,38,39,62] When necessary the stoichiometric values taken from the literature were first corrected to $I_m = 0$, based on Davies equation,[63] and then converted to molality scale by using eq 7 and the mass density of water at 298.15 K, $\rho = 0.997048\ kg \cdot dm^{-3}$.[47] As shown in Table 3, the thermodynamic acidity constants of nicotinic acid here reported are in the range of previous determinations: 1.98 to 2.86 for pK_{a1} and 4.67 to 5.12 for pK_{a2}. The agreement with pK_{a2} = 4.83 ± 0.05[62] given in a reference database is also good, within the combined uncertainty intervals. Somewhat poorer agreement is observed when the recommended pK_{a1} = 2.03 ± 0.05,[62] and the result obtained in this work are compared.

■ ASSOCIATED CONTENT

Supporting Information. Table S1 with the values of pK'_{a1} and pK'_{a2} obtained from each individual titration experiment. Tables S2 and S3 with the densities of aqueous KCl solutions used to convert the ionic strength and pK'_{a} values from molarity to molality scale. This material is available free of charge via the Internet at http://pubs.acs.org.

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