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ZWITTERIONIC PYRIDINECARBOXYLIC ACIDS

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A study of the acid–base behaviour of the three isomeric pyridinecarboxylic acids (picolinic, nicotinic and isonicotinic acid) was carried out using spectrophotometric and potentiometric measurements. The cationic form of picolinic acid converts partially into the corresponding zwitterion (pK_1) within a borderline acidity range where neither the pH scale nor the acidity functions work satisfactorily. Protonation of the carboxyl groups (p$K_3$3) occurred at the highest acidity levels employed. The medium effects observed on the spectral curves were corrected by factor analysis. The potentiometric measurements gave values for pK_1 and pK_2 only, which were in good agreement with those determined spectrophotometrically.

INTRODUCTION

The three positional isomeric pyridinecarboxylic acids (NRCOOH), the *ortho* form picolinic acid (PA), the *meta* form nicotinic acid (NA) and the *para* form isonicotinic acid (INA), manifest dibasic acid properties owing to the ability of the nitrogen atom to undergo protonation. The capto-dative effect of these acids has provoked a great deal of interest in connection with the existence of barriers to internal rotation.[1] PA is an electrolyte of biological importance, and some of its derivatives exhibit remarkable physiological activity;[2] further, PA is an efficient catalyst in the oxidation of organic substrates by Cr(VI), one of the most potent inorganic carcinogens, by accelerating the Cr(VI) to Cr(IV) step and stabilizing the Cr(IV) state relative to Cr(VI).[3,4] As proton transfer steps are involved in this and many other electron transfer reactions,[5,6] a knowledge of the acid–base behaviour of the three isomers is important. However, the data on the acid–base equilibria so far reported are not entirely satisfactory. Jellinek and Urwin[7] gave only two pK values, the lowest being attributed to the deprotonation of the carboxyl group and the highest to the ionization of the protonated ring nitrogen.[8]

It has been suggested that the major part of these species are present in solution as neutral ions ($^{+}$HNRCOO^{-}), and the minor parts as uncharged species (NRCOOH), but Liang *et al.*,[9] based on NMR measurements, did not account for the zwitterionic form of these acids. The difference between zwitterionic and amphoteric species is often unclear; thus, *m*-aminophenol, an amphoteric species, exhibits two well separated acid–base equilibria,[10] whereas *m*-aminobenzoic acid, a zwitterion, undergoes two overlapping equilibria.[11]

In this work, the ionization constants pK_1, pK_2 and pK_3 for the three isomers were determined by potentiometric and spectrophotometric measurements and evidence for the existence of zwitterions ($^{+}$HNRCOO^{-}) is reported.

EXPERIMENTAL

Reactants of the highest purity commercially available, all from Aldrich, were used without further purification: PA (99%), INA (98%), NA (99%), methyl isonicotinate (98%) and methyl nicotinate (99%). The solutions were freshly prepared with doubly distilled, deionized water and stored in the dark; nitrogen was bubbled through before they were used. Volumetric manipulations were made with sulphuric acid solutions standardized by titration. Stock substrate acidic solutions of the three isomers were prepared with a sufficient substrate concentration so that they gave suitable acidity and convenient absorbance.

The spectral curves were recorded on a Milton Roy 3000 spectrophotometer with a diode-array detection system, equipped with a temperature cell-holder adapter electrically regulated and controlled by a computer. Absorbance measurements were performed at least in duplicate at three wavelengths, at the absorption maximum and at both sides. The extent of ionization of each isomer was determined spectrophotometrically by measuring the ratios of protonated to unprotonated base, C_{SH_+}/C_S, from the absorptivities of the acidic and basic

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forms as ionization ratios $I = (\varepsilon - \varepsilon_S)/(\varepsilon_{SH^+} - \varepsilon)$, where ε_{SH^+}, ε_S and ε are the absorptivities of the protonated form, the non-protonated form and the form at intermediate acidities, respectively. These absorptivities were replaced by the corresponding absorbances A_{SH^+}, A_S and A provided provided that the Beer–Lambert law is obeyed.

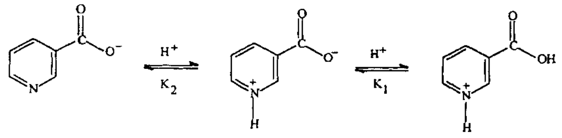
In the potentiometric experiments, the titrant was added with a microburette (±0·001 ml), pH readings were taken with a Radiometer M62 pH meter (±0·01 units) and the titration curves were plotted with a Radiometer ABU 12 autoburette. The temperature was maintained constant at 25±0·01 °C with an LTD 6 Grant circulator.

RESULTS AND DISCUSSION

The changes in the spectral curves of the three isomers with solution pH shows that the cationic form ($^+$HNRCOOH) is essentially the only species present in acidic medium and the anionic form (NRCOO$^-$) the only species in basic medium, whereas the two forms co-exist at intermediate acidities.

Spectrophotometric study

The pK_1 and pK_2values for the three isomers:



were calculated within the pH scale with the equation[12]

$$\log I = -n\,\mathrm{pH} + n\,\mathrm{pK}_{SH^+} \qquad (1)$$

with the exceptions of (a) the pK_1 of INA and (b) the pK_1 of PA (see below). Plots of absorbance vs pH gave sigmoid curves that allowed the I and pK values to be calculated.

(a) Figure 1 shows the spectrophotometric-titration curve of A vs pH corresponding to the pK_1 of INA; only an incomplete curve was obtained, which lacked the optical absorbances at the highest acidity values and, in particular, the important A_{SH^+} value. To determine a reliable A^{SH^+} value with the data points of Figure 1, we used the Sommer method:[13] when the additivity of absorbances of the substrate S and the conjugate acid SH$^+$ ($A = \varepsilon_{SH^+}C_{SH^+} + \varepsilon_S C_S$) and a mass balance ($C_T = C_S + C^{SH^+}$) are introduced into the definition equation of K_1, the following equation is obtained:

$$Y_1 = \frac{1}{\varepsilon_{SH^+}} + \frac{K_1}{\varepsilon_{SH^+}} X_1 \qquad (2)$$

where $Y_1 = 10^4 C_0/A$, $X_1 = (A - C_0\varepsilon_S)/[\mathrm{H}^+]A$ and C_0 ($1\cdot 63 \times 10^{-4}$ M) represents the total INA concentration.

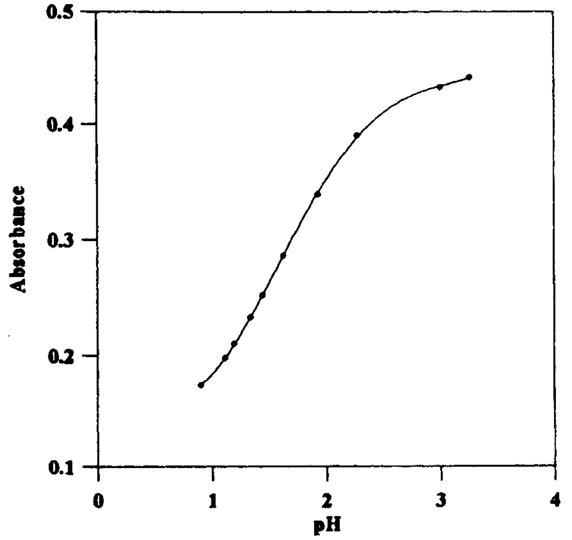


Figure 1 Spectrophotometric titration curve of absorbance vs pH corresponding to pK_1 of INA. $\lambda = 240$ nm

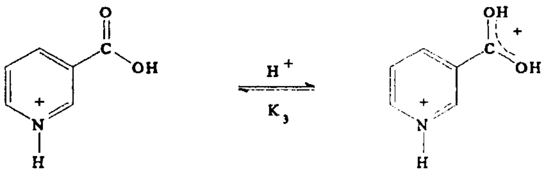
The slope and intercept of the straight-line plot of Y_1 vs X_1 give K_1 and ε_{SG^+}, respectively.

(b) The protonation of PA (pK_1) occurs within a borderline acidity range (around pH 1 and below) where neither the pH scale nor the acidity functions work satisfactorily.[14] Therefore, to determine the pK_1 of PA, we used the Hammett equation:

$$\log I = -mH_0 + \mathrm{p}K_1 \qquad (3)$$

with the Hammett acidity function H_0 taken in accordance with the investigated acidity range.[15] Given that this equation has been shown several times to be incorrect (if $m \neq 1$), we checked the reliability of this pK_1 value by a potentiometric technique, as described below.

The third acid–base equilibrium, the protonation on the carboxyl group (pK_3) for the three isomers:



occurs at high acidity levels, outside the pH scale; for this reason, the use of an appropriate acidity function was necessary. We used the excess acidity method according to the equation

$$\log I - \log C_{H^+} = m^*X \ (\text{or } -n_{ij}M_c) + \mathrm{p}K_{SH^+} \qquad (4)$$

where the acidity functions X and M_c represent the difference between the observed acidity and that of the system if it would behave ideally.[16,17] The slope, or solvation coefficient), m^* (or n_{ij}), characteristic of each base, is a measure of the influence of solvation by hydrogen bonding on the stability of the protonated base.[18] Thus the strength of a given base can be determined by its pK and m^* values in a reference solvent; water was chosen as the reference solvent, which implies $m^* = 0$ for the H_3O^+–H_2O acid–base pair. The relatively high values of $m^* = 1·39$ for PA, 1·58 for NA and 1·43 for INA reflect the weak solvation of the three isomers, this solvation being least in the *meta* isomer owing to a greater delocalization (compared with the *ortho* and *para* forms) of the positive charge of the protonated carboxyl group.

As the spectral curves corresponding to pK_1 and pK_3 of PA showed medium effects, in order to calculate reliable values of the ionization ratios, I, we used factor analysis;[13,19] this method decomposes the experimental absorbances into the minimum number of independent components capable of reproducing the absorbance curves. The absorbance is expressed as an average absorbance $\bar{A}$ corrected by the characteristic vectors v_1, $v_2, \ldots$:

$$A = \bar{A} + c_1 v_1 + c_2 v_2 + \cdots \tag{5}$$

It has been demonstrated that only two vectors are sufficient, the first vector accounting for the changes in hydrogen ion concentration and the second for the medium effects upon a protonation equilibrium.[20] From the absorbance values measured at several wavelengths, the characteristic vectors v_1 and v_2 and the weighing factors c_1 and c_2 were determined at each acid concentration. The ionization ratios, calculated as $I = [c_1 - c_{1(S)}]/[c_{1(SH^+)} - c_1]$, were replaced in equation (3) to determine the pK_1 of PA and in equation (4) to determine the pK_3 of PA.

Table 1 lists the pK_1, pK_2 and pK_3 constants calculated within the acidity ranges indicated. Neta and Patterson[21] reported p$K_3 = -0·17$ for the 4-carboxypyridinyl radical cation in propan-2-ol, whereas we report here p$K_3 = -1·58$ for the deprotonation of the cation, which reflects the higher electron density of the latter.

Potentiometric study

The titration curve of the three isomers displayed only two inflections, corresponding to pK_1 and pK_2. The titration curve of INA with 0·020 M NaOH displayed the complete S-shaped curve of pK_2 and only the upper part of the curve corresponding to pK_1 (Figure 2); the latter was completed with a second titration starting from the same initial conditions, this time using 0·020 M hydrochloric acid. The pK_1 and pK_2 values of the three isomers were calculated by a non-linear least-squares analysis of the curves, and corroborated with the Speakman method of linear extrapolation;[11] introducing a mass and a charge balance into the definition equations of the apparent equilibrium constants, K_1^M and K_2^M, gives

$$[H^+] = \frac{1}{K_1^M} \cdot \frac{[H^+]^2 R}{1 - R} - K_2^M \tag{6}$$

with $R = ([RCOO^-] + [^+NRCOO^-])/C$; $C = C_0 V/(V_T + V)$ is the sum of concentrations involved in the equilibria, where V and C_0 are the initial volume and the initial concentration of the isomer titrated and V_T the titrant volume.

The activity coefficients $a_i = 10^{-AZ_i F_J}$ of the ionic species were calculated from F_J, a function of the ionic strength J:[10]

$$F_J = \frac{J^{1/2}}{1 + 1·5 J^{1/2}} \tag{7}$$

Table 1. pK_1, pK_2 and pK_3 values for the three isomers calculated by spectrophotometric and potentiometric measurements within the acidity ranges given in parentheses

	Spectrophotometric			Potentiometric	
Acid	pK_1	pK_2[a]	pK_3[b]	pK_1	pK_2
Picolinic	0·90 ± 0·02[a] (0·05–0·20 M)	5·02 ± 0·12 (pH 3 69–7·42)	−0·84 ± 0·06 (0·48–2·29 M)	1·03	4·99
Nicotinic	1·98 ± 0·04 (pH 0·97–3·60)	5·00 ± 0·31 (pH 4·04–6·33)	−2·40 ± 0·35 (0·83–2·29 M)	1·96	4·98
Isonicotinic	1·59 ± 0·06 (pH 0·92–3·26)	4·94 ± 0·19 (Ph 3·60–7·00)	−1·58 ± 0·30 (1·33–4·16 M)	1·57	4·92

[a] Averaged values obtained using the H_0 acidity functions,[15] equation (3), $\bar{m} = 1·29$·

[b] Average values obtained using the X and M_C acidity functions,[16,17] equation (4)·

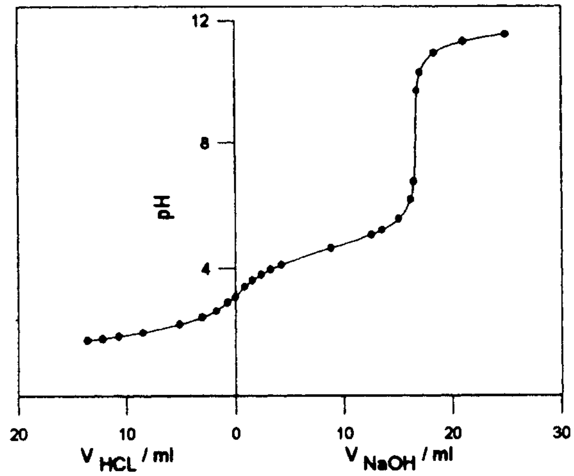


Figure 2. Titration curve of pH vs titrant volume (V, ml) corresponding to pK_1 and pK_2 of INA. [NaOH] = 0·020 M; [HCl] = 0·020 M

and the ionic and zwitterionic concentrations as

$$[^+\text{HNRCOOH}] = \frac{C[\text{H}^+]^2}{[\text{H}^+]^2 + K_1^{\text{M}}[\text{H}^+] + K_1^{\text{M}}K_2^{\text{M}}} \quad (8)$$

$$[\text{NRCOO}^-] = \frac{CK_1^{\text{M}}K_2^{\text{M}}}{[\text{H}^+]^2 + K_1^{\text{M}}[\text{H}^+] + K_1^{\text{M}}K_2^{\text{M}}} \quad (9)$$

$$[^+\text{HNRCOO}^-] = \frac{C[\text{H}^+]K_1^{\text{M}}}{[\text{H}^+]^2 + K_1^{\text{M}}[\text{H}^+] + K_1^{\text{M}}K_2^{\text{M}}} \quad (10)$$

Substitution of these concentrations into equation (6) gives

$$[\text{H}^+]f_i = \frac{1}{K_1}\cdot\frac{[\text{H}^+]^2F}{1-F} - K_2 \quad (11)$$

Kl_1 and K_2 being the corresponding thermodynamic constants. As an example, Table 2 lists the change in concentration of the $^+$HNRCOOH, $^+$HNRCOO$^-$ and NRCOO$^-$ species with solution pH, starting from 1 M PA. The chief species present in solution initially ($V_T = 0$) was the zwitterion; as the solution pH increased, the zwitterionic form decreased and the anionic form increased. The contribution of the non-zwitterionic neutral form was considered to be negligible given the high constant reported for the equilibrium NRCOOH $\rightleftharpoons$ $^+$HNRCOO$^-$. Similar variations arose with the NA and INA isomers. Equation (11) can be solved by successive approximations:[11] with initial approximate values for K_1^{M} and K_2^{M}, we obtain K_1 and K_2 for each J and F_J data pair; if the ionic strength J calculated does not agree (within the desired margin of error) with the experimental value introduced in equation (7), then the process is iterated until convergence is achieved. The pK_1 and pK_2 values calculated were in good agreement with those determined spectrophotometrically.

Spectral evidence for the existence of the zwitterion forms can be achieved by comparing the pK values of the three isomeric acids investigated with those of the respective methyl esters. The pK values of INA methyl ester (3·38 ± 0·10) and NA methyl ester (3·31 ± 0·06) are intermediate between pK_1 and pK_2; Figure 3 shows the close similarity of the spectral curves of protonated NA and protonated NA methyl ester (left), both recorded at the acidic edge of the respective acidity

Table 2. Variation of the PA ionic and zwitterionic concentrations, with C defined according to equation (6), and [NaOH] = 0·020 M and C_0 = 1·000 M

pH	V_T (cm^3)	$^+$HNRCOOH	$^+$HNRCOO$^-$	NRCOO$^-$	C
2·81	0·00	0·015	0·978	0·006	0·999
3·59	1·00	0·002	0·916	0·014	0·932
3·98	2·10	—	0·828	0·075	0·903
4·21	3·10	—	0·749	0·116	0·865
4·39	4·10	—	0·672	0·157	0·829
4·50	5·00	—	0·614	0·185	0·800
4·62	6·10	—	0·548	0·218	0·766
4·72	7·10	—	0·491	0·246	0·737
4·78	9·10	—	0·436	0·251	0·687
4·87	10·10	—	0·389	0·275	0·664
4·99	11·30	—	0·330	0·308	0·638
5·06	12·22	—	0·296	0·325	0·621
5·17	13·30	—	0·249	0·352	0·601
5·38	15·00	—	0·174	0·398	0·572
5·71	17·10	—	0·091	0·448	0·539

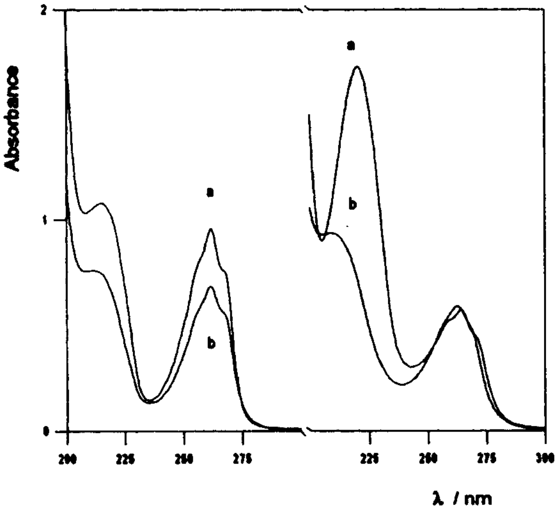


Figure 3. UV spectral curves for (a) $1{\cdot}2 \times 10^{-4}$ M NA and (b) $1{\cdot}0 \times 10^{-4}$ M NA methyl ester recorded at the acidic (left, pH = 1·22) and basic (right, pH = 4·71) edges of the respective equilibria ranges.

ranges, whereas the curves at the basic edge (right) differed considerably from each other. This feature shows that $^{+}HNRCOOCH_3$ is the spectrophotometric equivalent of $^{+}HNRCOOH$; as substitution of the carboxylic hydrogen by a methyl group has no influence on the acid–base behaviour of the pyridinecarboxylic acids, this observation points to a chemical species (the zwitterion) distinct from the anionic form and from the neutral form.

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