

Acid-base properties and isomerism of nicotinic acid

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The structure of nicotinic acid in solvents of different polarity is discussed on the basis of u.v. spectral data and acid-base properties.

На основании УФ спектров и кислотно-щелочных свойств никотиновой кислоты и ее производных обсуждается строение никотиновой кислоты в растворителях с разной полярностью.

According to the literature there is no doubt about the structure of nicotinic acid in mineral acid or alkali hydroxide solutions. However, rather controversial opinions on the structure of the substance can be found in the literature when the state at the isoelectric point is considered. Structure *I* [1], *II* [2—4] or an equilibrium mixture [5] have been assigned to nicotinic acid at the isoelectric point on the basis of its u.v. spectral data for aqueous solutions. The present work answers the question on the basis of the comparison of u.v. spectral data and acid-base properties of nicotinic acid and its esters in solvents of different polarity



Experimental

Benzoic and nicotinic acid were commercial products of reagent grade purity (Lachema, Brno). Picolinic acid [6], nicotinic acid ethyl [7] and phenyl ester [8] were prepared as described in the literature. Nicotinic acid *N*-butyl betaine was newly prepared following the directions given in [9]: a sample of potassium salt of nicotinic acid was dried and digested with *n*-butyl iodide (reagent grade, Lachema, Brno) for 5 h. The solvent was removed, the residue converted [9] to a hydrochloride and recrystallized from alcohol—petroleum ether. The obtained white crystals (~40%), melting at 151—153°C, were soluble in water and alcohol but insoluble in nonpolar solvents.

For $C_{10}H_{14}O_2ClN$ (215.68) calculated: 55.69% C, 6.54% H, 6.49% N; found: 55.51% C, 6.42% H, 6.50% N.

For the determination of pK ethanolic (Lachema, Brno) and aqueous solutions of substances under investigation were prepared (50, 30, and 10 w/w %; in the further text exclusively the solutions having weighing component ratio of the mixed solvent are given). The ionic strength ($\mu = 0.1$) was maintained with sodium perchlorate (reagent grade, Lachema, Brno). Titrations were performed with 0.1 M sodium hydroxide (reagent grade, Lachema, Brno) in the same solvent. pH was measured [10] using a glass electrode. The measurements in ethanol were run against a 0.1 M silver chloride electrode, those in water against a saturated calomel electrode. The u.v. spectra for 10^{-4} M solutions in water or 50% ethanol were obtained with a Pye Unicam SP 1800 spectrophotometer. For the spectrophotometric determination of pK , solutions of the substances were mixed with solutions of perchloric acid (reagent grade, Jenapharm) of various concentration (in 50% ethanol or water), or with mixtures of 0.1 M perchloric acid and 0.1 M- KH_2PO_4 (reagent grade, Lachema, Brno) in 50% ethanol or water. During these experiments pH was measured with a hydrogen electrode against references as above. The calculations of pK were done as described previously [10, 11].

Results and discussion

The pK corresponding to the protonation of the pyridine ring were measured spectrophotometrically. It was found for ethyl and phenyl esters of nicotinic acid in 50% ethanol that $pK = 1.84 \pm 0.06$ ($\lambda = 262$ nm) and 1.80 ± 0.02 ($\lambda = 240$ nm), respectively. The found values agree, within the experimental error, with those [11] found for nicotinic acid ($pK = 1.80$) in the same solvent. When water was used as the solvent pK found for nicotinic acid and its ethyl ester were equal to 2.07 ± 0.03 ($\lambda = 235$ nm) and 3.34 ± 0.02 ($\lambda = 261$ nm), respectively. During these calculations the activity coefficients were assumed to be equal to unity. It can be concluded that in 50% ethanol a substitution of the carboxyl group of nicotinic acid resulting in the formation of nicotinic acid ethyl or phenyl ester has no effect upon the basicity of the pyridine ring. This agrees with the general conception of organic chemistry according to which the inductive effects show themselves only at the positions closest to the substituents and their influence diminishes sharply with the distance. The identical pK values found in 50% ethanol for nicotinic acid and its ethyl and phenyl ester suggest that at the isoelectric point nicotinic acid possesses structure I. As the polarity of the solvent changes the basicity of the substances alters as well. When water was used as the solvent (cf. 50% ethanol in the previous experiments) the pK of the ethyl ester changed similarly as was observed with other basic substances [10]. For nicotinic acid the same values varied considerably less.

The pK_a values calculated for ionic effective radius $r = 0.8$ nm are given in Table 1; their dependence upon reversed permittivity of the solvent can be seen in Fig. 1. For relative permittivity values given in [12] were used. The accuracy of the

measurements, in terms of pK units, found for the separated reference electrodes was ± 0.02 [13], the reproducibility of the measurements was ± 0.01 , except that found with nicotinic acid *N*-butyl betaine in which case it was ± 0.03 . Only values found for aqueous solutions can be compared with those in the literature. The pK values found for benzoic acid agree well with the literature (4.19 [14]). Several data can be found for nicotinic (4.96 [5], 4.91—4.95 [1], 4.68—4.76 [14]) and picolinic acid (5.50 [5], 5.30—5.39 [15]). The values found during this work (Table 1) are within those found by previous authors. For *N*-butyl betaine a similar value was found as that given [5] for trigonelline (2.55).

Table 1
 pK_a Values found by titration at room temperature
 (ionic strength $\mu = 0.1$; $r = 0.8$ nm)

Substance	Weight % of ethanol			
	0	10	30	50
Benzoic acid	4.20	4.24	4.80	5.44
Nicotinic acid	4.81	4.51	4.41	4.59
Picolinic acid	5.39	5.17	5.11	5.18
Nicotinic acid <i>N</i> -Butyl betaine	2.80	2.66	2.81	2.84

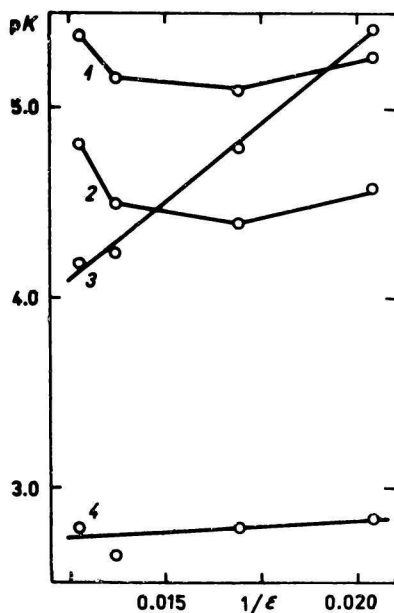


Fig. 1. Dependence of pK_a of nicotinic acid and related substances upon $1/\epsilon$.
 1. Picolinic acid; 2. nicotinic acid; 3. benzoic acid; 4. nicotinic acid *N*-butyl betaine.

A common method [16] using model compounds was used for studies of the structure of nicotinic acid by u.v. spectroscopy. The u.v. spectral data obtained for nicotinic acid and its ethyl ester in 50% ethanol (pH 3.3) and water (pH 3.24) are given in Table 2. In 50% ethanol similar spectra were obtained for both substances. The short-wave maximum of the ester was bathochromically and hyperchromically shifted, compared with that of the acid. The short-wave maximum in the spectrum

Table 2

Ultraviolet spectral data for nicotinic acid and its derivatives in 50% (w/w) ethanol and water

	Nicotinic acid	Ethyl ester	<i>N</i> -Butyl betaine
λ_{\max} , nm (log ϵ)	217 (3.82)	219 (3.89)	212 sh (3.88)
50% ethanol	256 sh (3.45)	256 sh (3.38)	258 sh (3.48)
pH 3.30	263 (3.49)	263 (3.45)	265 (3.57)
	270 sh (3.34)	270 sh (3.30)	271 (3.52)
λ_{\max} , nm (log ϵ)	—	220 (3.73)	—
Water	255 sh (3.38)	256 sh (3.54)	258 sh (3.59)
pH 3.24	261 (3.42)	262 (3.60)	265 (3.67)
	268 sh (3.37)	268 sh (3.51)	271 sh (3.62)

of *N*-butyl betaine lies below 210 nm. The spectra obtained for aqueous solutions of nicotinic acid and its *N*-butyl betaine were very similar. In the case of *N*-butyl betaine the long-wave absorption band observed for aqueous solution showed a slight hyperchromic effect, compared to that found in the spectrum of the same substance taken in 50% ethanol. The spectrum of the ethyl ester taken in the same solvent differed from the spectra of the former two substances by the presence of a short-wave maximum. The long-wave maximum of the ester showed a hyperchromic effect, when compared with that of the acid. It follows from the similarity of the spectra of the acid and its ethyl ester taken in 50% ethanol that in less polar solvents (such as 50% ethanol) the acid can be better formulated as *I*, which was confirmed also by dipole moment measurements [17]. In polar solvents (such as water) the spectrum of the acid resembles that of its *N*-butyl betaine. We agree therefore with others [3, 4] that in this case the acid can be formulated as *II*. This change in the structure as a result of the change of the solvent polarity explains the anomalous dependence of pK of the acid upon the relative permittivity of the solvent. A similar dependence was found for picolinic acid, whereas benzoic acid, owing to its stable structure, shows a linear dependence of pK vs. $1/\epsilon$ (Fig. 1). The pK values of *N*-butyl betaine of nicotinic acid are only slightly dependent upon $1/\epsilon$ of the solvent.

It follows from the results obtained (the found pK values and u.v. spectral data) that in less polar solvents (50% ethanol) nicotinic acid possesses structure *I*; in more polar aqueous solvents the results obtained by both methods prefer structure *II*.

Note added in proof.

The problem concerning isomerism of nicotinic acid in solutions of various polarity was studied using ¹H.n.m.r. spectroscopy and identical results were obtained. (Khan Tauquir, Halle, J. C., Simonnin, M. P., and Schaal, R., *J. Phys. Chem.* **81**, 587 (1977).) Thereby the reliability of both communications is increasing.

References

1. Hughes, E. B., Jellinek, H. H. G., and Ambrose, A. B., *J. Phys. Chem.* **52**, 414 (1948).
2. Jaffé, H. H., *J. Amer. Chem. Soc.* **77**, 4445 (1955).
3. Stephenson, H. P. and Sponer, H., *J. Amer. Chem. Soc.* **79**, 2050 (1957).
4. Green, R. F. and Tong, H. K., *J. Amer. Chem. Soc.* **78**, 4896 (1956).
5. Thunus, L., *J. Pharm. Belg.* **21**, 491 (1966).
6. Becker, H., *Organikum. Organická syntéza.* (Organicum. Organic Synthesis.) P. 362. Academia, Prague, 1971.
7. Gilman, H. and Broadbent Smith, H., *J. Amer. Chem. Soc.* **70**, 2755 (1948).
8. Meyer, H. and Graf, R., *Ber.* **61**, 2202 (1928).
9. Ternájkó, L., *Monatsh. Chem.* **21**, 446 (1900).
10. Mollin, J., Kašpárek, F., and Lasovský, J., *Chem. Zvesti* **29**, 39 (1975).
11. Mollin, J., *Collect. Czech. Chem. Commun.* **40**, 2266 (1975).
12. Akérlöf, G., *J. Amer. Chem. Soc.* **54**, 4151 (1932).
13. Bacarella, A. L., Grunwald, E., Marschall, H. P., and Purlee, L. E., *J. Phys. Chem.* **62**, 856 (1958).
14. Gelsema, W. J., De Ligny, C. L., and Visserman, G. F., *Rec. Trav. Chim. Pays-Bas* **84**, 1129 (1965).
15. Evans, R. F., Herington, E. F. C., and Kynaston, W., *Trans. Faraday Soc.* **49**, 1248 (1953).
16. Shriner, R. L., Fuson, R. C., and Curtin, D. Y., *Systematic Identification of Organic Compounds*, p. 206. Wiley, New York, 1964.
17. Kúthan, J., Musil, L., and Jehličká, V., *Collect. Czech. Chem. Commun.* **42**, 283 (1977).

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