^{1}H NMR Studies of Solvent and Substituent Effects on Strong Intramolecular Hydrogen Bonds

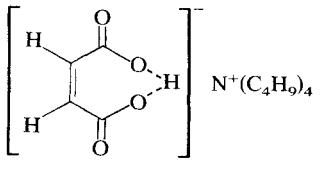
Bogumił Brzezinski and Miroslaw Szafran*
Institute of Chemistry, A. Mickiewicz University, 60780 Poznań, Poland

Chemical shifts of H-bonded protons in tetrabutylammonium hydrogen maleate and 14-substituted picolinic acid *N*-oxides have been measured in a number of dry solvents, of different activity, in order to distinguish between symmetrical single minimum and asymmetrical hydrogen bonds. In tetrabutylammonium hydrogen maleate the resonance was observed at 20.70 ppm and its was independent of the nature of the solvent used. The chemical shift value of picolinic acid *N*-oxide varies with the solvent. These observations suggest that the hydrogen bond is symmetrical in tetrabutylammonium hydrogen maleate but that it is asymmetrical in picolinic acid *N*-oxide. The chemical shifts of substituted picolinic acid *N*-oxides were correlated with σ_p, σ_m and ΔpK_a. The substituent and solvent effects are compared and the position of the intramolecular H-bonded protons in picolinic acid *N*-oxides are estimated and discussed.

INTRODUCTION

From dielectric[1] and ^{1}H NMR[2–5] investigations it has become evident that the effect of solvents on proton transfer from acid to bases depends on the nature of the complex. In complexes of phenols and carboxylic acids (AH) with amines and pyridines (B) the value of $\Delta pK_a = pK_{B^+H} - pK_{AH}$ for 50% proton transfer decreases strongly with increasing solvent polarity (ϵ).[1,2] On the other hand, in complexes of carboxylic acids with pyridine and quinoline *N*-oxides,[3,4] the ΔpK_a value for 50% proton transfer is independent of solvent polarity.

The above results were derived from complexes with intermolecular hydrogen bonds. The investigations of the solvent effects are limited to nonpolar solvents ($\epsilon \leq 15$) in such complexes. Usually, in aprotic solvents, an increase of dielectric constant leads to an increase in the solvation power and intermolecular hydrogen bonds can be broken. In this paper we extend the investigations of solvent and substituent effects to intramolecular hydrogen bonds since they are more stable and, therefore, more polar solvents can be used. Tetrabutylammonium hydrogen maleate (**1**) and picolinic acid *N*-oxides (**2**) have been selected for study.



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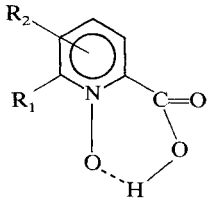

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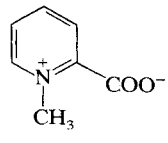
The hydrogen maleate ion is one of the many investigated systems with a short intramolecular hydrogen bond:[6–17] the O···H···O distance is 2.437(4) Å.[11] Neutron diffraction studies indicate that the mean square amplitude of the proton thermal motion along the O···H···O axis is equal to 0.017 Å^2. The intramolecular hydrogen bond is also very stable in selected organic[9,12,16] and aqueous[7] solutions. The experimental results indicate that the potential energy curve is symmetrical both in the solid state and in solution, with a single broad minimum or a double minimum with the potential barrier being comparable in height to zero point level. Theoretical calculations[17] have also confirmed these results.

The intramolecular hydrogen bond in picolinic acid *N*-oxide is also very short, the O···H···O distance being 2.39 Å.[18] Picolinic acid *N*-oxide is of interest because of its relationship to homarine (**3**), which appears to be of importance in the metabolism of invertebrates.[19] The O···H···O distance in 6-methylpicolinic acid *N*-oxide is 2.41 Å.[20]



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EXPERIMENTAL

Tetrabutylammonium hydrogen maleate was prepared by mixing a methanolic solution of the acid with an equivalent amount of an aqueous solution of tetrabutylammonium hydroxide. The solution was evaporated to dryness under reduced pressure and the residue recrystallized from diethyl ether–benzene solution, m.p. 67 °C.

The picolinic acid *N*-oxides were prepared by methods described in the literature: picolinic acid *N*-oxide,[21] m.p. 164 °C (dec); 4-nitropicolinic acid *N*-oxide,[21] m.p. 146 °C (dec); 4-methoxypicolinic acid

* Author to whom correspondence should be addressed.

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N-oxide,[21] m.p. 154 °C (dec); 4-ethoxypicolinic acid *N*-oxide,[21] m.p. 145–6 °C (dec); 4-methylpicolinic acid *N*-oxide,[22] m.p. 169 °C (dec); 5-methylpicolinic acid *N*-oxide,[22] m.p. 163 °C (dec); 6-methylpicolinic acid *N*-oxide,[23] m.p. 177 °C (dec); 4-bromo-6-methylpicolinic acid *N*-oxide,[23] m.p. 152 °C (dec); 4-nitro-6-methylpicolinic acid *N*-oxide,[23] m.p. 155 °C (dec); 4-methoxy-6-methylpicolinic acid *N*-oxide,[23] m.p. 172 °C (dec); 4-amino-6-methylpicolinic acid *N*-oxide,[23] m.p. 299 °C; 4-aminopicolinic acid *N*-oxide,[23] m.p. 217–8 °C (dec).

Synthesis of 4-*N*,*N*-dipropylaminopicolinic acid *N*-oxide

4-Chloropyridine *N*-oxide was converted to 4-chloro-2-cyanopyridine,[24] m.p. 85 °C (15%), and oxidized with glacial acetic acid and hydrogen peroxide (30%) to 4-chloro-2-cyanopyridine *N*-oxide, m.p. 130–2 °C (63%), 0.013 mol of which was refluxed with *n*-dipropylamine (10 cm^3) for 6 h. Dipropylamine. HCl was filtered off and excess dipropylamine removed from the filtrate under high vacuum. The residue was dissolved in ether and passed over Al_2O_3; the solvent was evaporated and the residue refluxed with 10% NaOH (10 cm^3) and ethanol (10 cm^3) for 100 h. The mixture was concentrated under vacuum and acidified with hydrochloric acid (to pH ~4) to give crude 4-*N*,*N*-dipropylaminopicolinic acid *N*-oxide (0.003 mol, 0.67 g, 22%). Recrystallization from ethanol gave the pure acid, m.p. 154 °C.

Anal. Calcd for $C_{12}H_{18}N_2O_3$:
C, 60.5; H, 7.6; N, 11.8.
Found: C, 60.4; H, 7.6; N, 11.7.

All solvents were purified by standard methods and stored over molecular sieves (4Å or 3Å) for one week before use. The preparation of the solutions and the transfer of non-aqueous solutes were carried out in a dry box.

The ^{1}H NMR spectra were measured at 60 MHz on a Varian EM 360 spectrometer at 24 ± 2 °C. All chemical shifts were reported downfield relative to a sharp solvent resonance and then converted to δ values. The line width of the resonance peak of the H-bonded protons was usually about 2–5 Hz at 0.3 mol dm^{-3} and tended to increase with dilution. In some cases, e.g. in pyridines and DMSO-d_6, the line width approaches 10–15 Hz and a trace of water caused an increase of band width. Picolinic acid *N*-oxide was reasonably soluble (up to 0.5 M) in only a few solvents (Nos. 1, 2, 3, 5, 6, 16 in Table 1), and in these cases the resonance was concentration independent. In 4-aminopicolinic acid *N*-oxide and 4-amino-6-methylpicolinic acid *N*-oxide the amino proton resonance peak was observed at 7.20 and 7.42 ppm, respectively. The band width of the NH_2 proton resonance was approximately 6 Hz.

RESULTS AND DISCUSSION

The chemical shifts of the protons involved in hydrogen bonding in the compounds investigated in a number of solvents of various properties are summarized in Tables 1 and 2. As expected, the observed chemical shift of the H-bonded protons for tetrabutylammonium hydrogen maleate (TBHM) is, within the experimental reproducibility, constant and independent of the solvent used. On the other hand,

Table 1. Chemical shift of H-bonded protons in tetrabutylammonium hydrogen maleate (TBHM) and picolinic acid *N*-oxide (PIANO) in various solvents

Number	Solvent	ε[a] (25 °C)	E_T[a]	pK_a[b]	δ (ppm) TBHM	δ (ppm) PIANO
1	Dimethyl sulphoxide	48.9	45.0	−1.80	20.70[d]	19.03
2	Nitromethane	38.57	46.3		—	18.96
3	Acetonitrile	37.50	46.0	−10.0	20.69	18.89
4	Benzyl cyanide		42.9			18.80
5	Benzonitrile	25.2	42.0			18.67
6	Acetone	20.5	42.2	−7.2	20.68	18.67
7	1,2-Dichloroethane	10.37	41.9		20.68	18.37
8	Dichloromethane	8.9	41.1		20.73	18.39
9	Chloroform	4.70	39.1		20.69	—
10	Tetrahydrofuran	7.39	37.4	−2.02	20.73	18.17
11	Ethyl acetate	6.03	38.1	−4.47	20.70	—
12	Benzene	2.27	34.5		20.68	—
13	1,4-Dioxane	2.21	36.0	−2.92	—	18.03
14	2-Chloropyridine		41.9	0.60	20.71	19.06
15	3-Bromopyridine			2.84		18.73
16	Pyridine	12.3	40.2	5.21	20.71	19.02
17	2-Methylpyridine	9.94	38.3	5.97	20.67	18.75
18	Quinoline	9.22	39.4	4.81	20.74	18.80
19	2,4,6-Trimethylpyridine	8.00[c]		7.51	—	18.67
20	2,6-Dimethylpyridine	7.23	36.7	6.65	20.73	18.53

[a] From Ref. 32. [b] From Ref. 33. [c] From Ref. 34.
[d] δ Values for sodium hydrogen maleate and potassium hydrogen maleate are 20.33 and 20.62 ppm, respectively.

Table 2. Substituent effect on the relative chemical shift of the hydrogen bonded proton of R_1,R_2-picolinic acid *N*-oxides in DMSO-d_6

	R_1	R_2	Δδ (ppm)	σ_p or σ_m N→O	σ_p or σ_m COOH	ΔpK_a[a]
1	6-Me	4-NO_2	−2.97	0.778	0.710	
2	6-Me	4-Br	−0.98	0.232	0.391	
3	6-Me	H	0[b]	0	0	
4	6-Me	4-Me	0.55	−0.170	−0.069	
5	6-Me	4-OMe	1.05	−0.268	0.115	
6	6-Me	4-NH_2	1.20	−0.660	−0.161	
7	H	4-NO_2	−2.70	0.778	0.710	−5.19
8	H	H	0[c]	0	0	−3.39
9	H	5-Me	0.14	−0.069	−0.170	−3.29
10	H	4-Me	0.50	−0.170	−0.069	−2.98
11	H	4-OEt	1.04	−0.250	0.150	
12	H	4-OMe	1.22	−0.268	0.115	−2.04
13	H	4-NH_2	1.27	−0.660	−0.161	−1.10
14	H	4-NPr_2	1.43	−0.600± 0.213	−0.211	−1.22
				−0.927	−0.261	

[a] From Refs 41 and 42.
[b] δ = 19.43 ppm.
[c] δ = 19.03 ppm.

as Forsén *et al.* have shown,[9,16,25] the chemical shift of the H-bonded protons in hydrogen maleate salts varies with the electronegativity and size of the cation. Our results support this inference, although there are differences of 0.2–0.4 ppm, which are probably caused by residual water in the solvents.[26] Hence, in our case the difference in the chemical shifts between potassium and sodium hydrogen maleate in DMSO-d_6 is only 0.29 ppm (Table 1).

Jones and Dyer[27] have shown that in ionic complexes the δ value of the H-bonded proton depends strongly on the contact distance between the anion and cation, the maximum downfield shifts being observed in 'free' anions. Association of the cation with the anion causes the downfield chemical shift of the H-bonded proton to be smaller.

On the basis of these considerations it can be concluded that the contact distance between Bu_4N^+ and the hydrogen maleate ion is constant in the solvents investigated. This is not surprising since the large Bu_4N^+ ion (ion radius is 4.94 Å[28]) has a very low specific short range solvation in all the non-aqueous solvents.

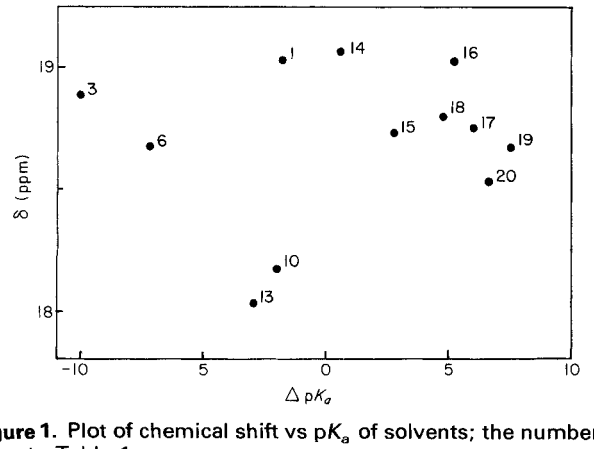


Figure 1. Plot of chemical shift vs pK_a of solvents; the numbers refer to Table 1.

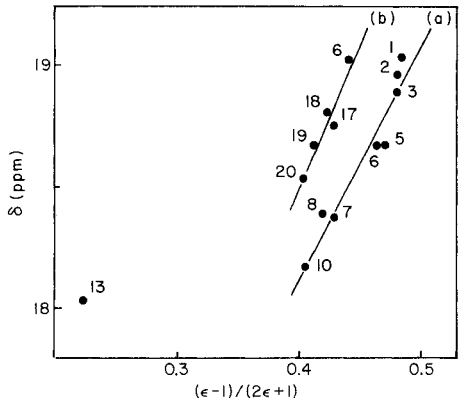


Figure 2. Plot of chemical shift vs the Kirkwood function; the numbers refer to Table 1. (a) $\delta = 14.3095 + 9.5364(\varepsilon-1)/(2\varepsilon+1)$; $R = 0.968$. (b) $\delta = 13.8227 + 11.6971(\varepsilon-1)/(2\varepsilon+1)$; $R = 0.960$.

In picolinic acid *N*-oxide the hydrogen bond is asymmetric and the observed chemical shifts vary with the nature of the solvent (Table 1). Figure 1 shows a plot of chemical shift against the aqueous pK_a values of the solvents; a similar diagram was obtained by plotting δ against the Kamlet-Taft β scale.[29] The lack of correlation suggests that the extent of breaking of the intramolecular bond by the solvents is small and can be neglected. This conclusion agrees with Kolthoff's[30] results for acid salts of *o*-phthalic and a homologous series of oxalic acids. We have also found recently that such very weak intramolecular hydrogen bonds, as in 2-(*N*-methylcarboxyamido)quinoline, are only partially broken by strongly basic solvents.[31]

Figure 2 shows the relationship between the chemical shift of the H-bonded protons of picolinic acid *N*-oxide and the Kirkwood function. The group of pyridine solvents is separated from the other solvents. The good linear correlations suggest that the interaction between the investigated acid and the solvents is mainly of the non-specific type. However,the positive deviation for 1,4-dioxane and the separate correlation for the pyridine solvents must be due to small, specific, solvent effects.

The non-specific and specific solute–solvent interaction is very often correctly described by empirical polarity parameters, e.g. E_T.[32] The chemical shift is plotted against the E_T parameter in Fig. 3. As can be

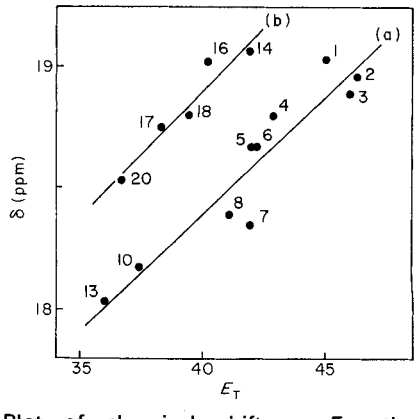


Figure 3. Plot of chemical shift vs E_T; the numbers refer to Table 1. (a) $\delta = 14.5637 + 0.0957\,E_T$; $R = 0.944$. (b) $\delta = 14.6663 + 0.1060\,E_T$; $R = 0.962$.

seen, 1,4-dioxane is on the line for the non-pyridine solvents. The straight lines drawn in Figs 2 and 3 indicate that the character of the solute–solvent interaction is more complex than that described solely by the dielectric constant or E_T functions.

It is well known that when a polar molecule is dissolved in an aromatic solvent (e.g. benzene or pyridine) the solute proton absorptions are usually shifted relative to their position in an inert solvent, such as neopentane, hexane or even chloroform, due to the ASIS effect.[35] As shown in Fig. 3, the chemical shifts for two aromatic solvents [benzyl cyanide (4) and benzonitrile (5)] lie on the line of the non-pyridine solvents; the observed separation is therefore not caused by the ASIS effect. It is possible that an interaction through the ring nitrogen is responsible for this effect.

In summary, it appears that the observed downfield shift of the H-bonded protons with increasing solvent activity (this term covers both non-specific and specific interactions with the dissolved molecule) reflects a continuous shift of the proton from the carboxylic group to the *N*-oxide group, making the structure more polar. Other evidence supporting this conclusion is found in the study of substituent effects on the chemical shift.

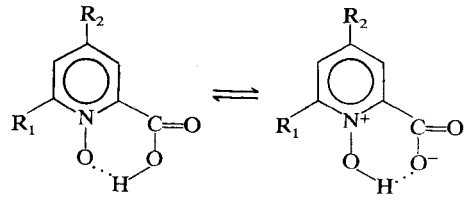
A substituent usually changes either the proton-acceptor or the proton-donor properties of the *N*-oxide and carboxylic groups, and the overall effect should be reflected in the difference of chemical shift between the substituted and unsubstituted picolinic acid *N*-oxides, $\Delta\delta$. The values of $\Delta\delta$ obtained in DMSO-d_6 (Table 2) correlate well with σ_p and σ_m parameters,[36] though deviations to high field are observed for the strongest donor substituents (NH_2, NPr_2). Omission of the deviant points gives Eqn (1), with an excellent correlation coefficient $R = 0.995$; $n = 11$.

$$\Delta\delta = -0.0613 - 4.0405\sigma_p + 0.4182\sigma_m \qquad (1)$$

The coefficients in Eqn (1) indicate that the influence of substituents on proton-acceptor properties of the *N*-oxide group are ten times stronger than on the proton-donor properties of the carboxylic group.

The observed downfield shift of H-bonded protons with increasing electron-donating properties of substituents reflects the increase of hydrogen bond strength and the displacement of the proton from the carboxylic to the *N*-oxide group. The downfield shift is, however, limited. The largest downfield shift is expected for a symmetrical hydrogen bridge. By analogy to the hydrogen phthalate ion,[16] a downfield shift of up to 21 ppm can be expected, which corresponds to $\Delta\delta$ equal to 1.97 and 1.57 ppm for substituted picolinic- and 6-methylpicolinic-acid *N*-oxide, respectively. The observed $\Delta\delta$ values (Table 2) are lower then those predicted, which is consistent with the postulation that the hydrogen bonds in picolinic acid *N*-oxides are asymmetric. On the other hand, the large negative deviation of points for acids with the strongest electron-donor substituents (NH_2 and NPr_2) from Eqn (1) suggests that the proton in these acids is transferred from the carboxylic to the *N*-oxide group.

The position of the proton in the investigated acids



(2)

can be formally described by a rapid tautomeric equilibrium, shown in Eqn (2). The proton transfer step in complexes with a strong hydrogen bond is so fast that it is not rate determining.[37]

If the equilibrium shown in Eqn (2) is operative, the chemical shift, δ, should also correlate with ΔpK_a—the difference between the dissociation constants of substituted 1-hydroxypyridinium ions and substituted benzoic acids.[3] Indeed, a plot of the observed chemical shift of the H-bonded proton for substituted picolinic acid *N*-oxides, against ΔpK_a consists of two intersecting straight lines (Fig. 4). A similar correlation between δ and ΔpK_a has been previously observed in complexes with an intermolecular hydrogen bond.[2–4,38,39] The point of intersection corresponds to a symmetrical hydrogen bond. The chemical shift for the intersection point, $\delta = 21.05$ ppm, is in excellent agreement with the experimental value for tetrabutylammonium hydrogen *o*-phthalate, $\delta = 21$ ppm. In acids 7–12 (Fig. 4) the proton appears to be closer to the oxygen of the carboxylic group, but in acids 13 and 14 the proton is closer to the oxygen of the *N*-oxide group.

The above interpretation agrees well with the chemical reactivity. Many years ago one of us showed that 4-R-6-methylpicolinic acid *N*-oxides give an ester ($R = NO_2$), betaine ($R = NH_2$) or a mixture of ester and betaine ($R = OMe$)[40] with diazomethane.

In summary it appears that, in complexes containing a symmetrical hydrogen bond with a single minimum energy curve, the chemical shift of an H-bonded proton is independent of the nature of the solvent. In the case of strong and asymmetric hydrogen bonds the chemical shift varies with the nature of the solvent. Correlations between the chemical shift, δ, and ΔpK_a

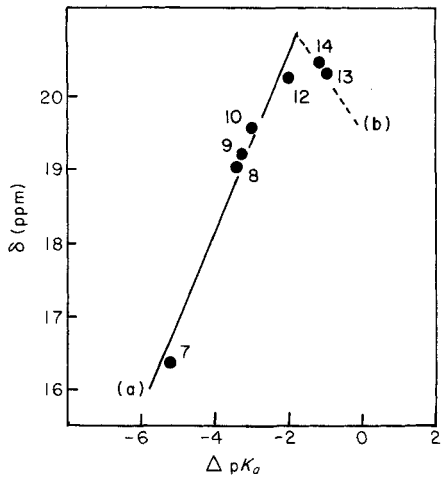


Figure 4. Plot of chemical shift vs the difference between the pK_a of the conjugate acids of substituted pyridine *N*-oxides[41] and the pK_a of substituted benzoic acids;[42] the numbers refer to Table 2. (a) $\delta = 23.2046 + 1.2855\,\Delta pK_a$; $R = 0.986$. (b) $\delta = 18.8333 - 1.3333\,\Delta pK_a$.

are very similar for inter- and intra-molecular hydrogen bonds. This suggests that the dynamics of proton transfer in anhydrous aprotic solvents are very similar for inter- and intra-molecular bonded series.

Acknowledgements

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