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NITROGEN-15 NMR STUDIES OF HYDROGEN BONDING AND PROTON TRANSFER IN COMPLEXES OF PYRIDINE *N*-OXIDES WITH DICHLOROACETIC ACID IN $CDCl_3$

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The ^{15}N NMR chemical shifts of eight substituted pyridine *N*-oxides (B) and their complexes (AHB) with methanol and dichloroacetic and trifluoromethanesulfonic acids were measured in chloroform-*d* at the natural abundance level. The measured chemical shifts are strongly affected by substituents, hydrogen bond strength and protonation. The plot of the relative chemical shifts, $\Delta\delta(^{15}N) = \delta(AHB) - \delta(B)$, against ΔpK_a gives a titration curve that reflects the variation of the hydrogen bond strength and the proton moves from the acid to the *N*-oxide. According to previous IR data, in the complexes from the inversion region ($\Delta pK_a = 1{\cdot}26$), the proton is either delocalized ($B\cdots H\cdots A$) or more likely the lifetime is so short ($\leq 10^{-13}$ s) that the method does not recognize the $B\cdots H{-}A$ and $B^{+}H\cdots A^{-}$ species. Protonation of pyridine *N*-oxides shifts the nitrogen signal *ca* 50 ppm to lower frequencies compared with the *ca* 123 ppm for pyridines.

1. INTRODUCTION

Both ^{15}N and ^{14}N chemical shifts are very sensitive to medium effects, e.g. solvent, hydrogen bonding, protonation, concentration and temperature.[1] Depending on the nature of the solvent and the substrates, these effects may be as high as several tens of ppm. The largest shielding variations occur when the nitrogen lone pair is sp^2 hybridized and is available for hydrogen bonding with protic solvents or protonation.

N-Oxidation of pyridines shifts the nitrogen (25 ± 8 ppm)[2] and carbon (*ca* 10 ppm at *ortho* and *para* positions)[3] signals upfield. When the lone pair in pyridine is protonated, the nitrogen chemical shift moves *ca* 123 ppm to higher field.[4] For pyridine *N*-oxide itself, the difference from pyridinium ion, *ca* 100 ppm, is more than twice the difference (39·3 ppm)[5] between C-1 of phenoxide ion and benzene, which serve as isoelectronic models.

In pyridines the nitrogen atom withdraws either σ or π electrons. When pyridines are converted into pyridine *N*-oxides, the oxygen atom withdraws σ electrons mostly from the nitrogen atom, whereas it donates π electrons to the ring via the nitrogen atom.[6] These interactions vary with solvents and substituents.

The solvent effects on the nitrogen[2,7,8] and carbon[9,10] shielding of pyridine and pyridine *N*-oxide are comparable. The solvent effect on the UV spectra of pyridines differs from that of pyridine *N*-oxides. The $^1L_b \leftarrow {}^1A$ transition in pyridine shows no wavelength shift or a minute batochromic shift; polar solvents produce a hyperchromic effect.[11] *N*-Oxidation of pyridines produces in non-polar solvents a considerably red shift and hyperchromic effect, presumably because of lengthening of the conjugated system. When hydrogen bonding of the oxygen atom occurs in hydroxylic solvents, the bands of the *N*-oxides are shifted back to the blue, and almost coincide with those of the parent heterocycles.[11] Protonation caused further hypsochromic shifts.[12]

Mesomeric dipole moments[13] and ^{13}C substituent chemical shifts[14] (^{13}C SCS) have been used to described interactions of substituents with benzene, pyridine and pyridine *N*-oxide rings. In this approach, monosubstituted pyridines and their *N*-oxides were treated as disubstituted benzenes and strong mutual interactions between a given substituent and the ring nitrogen atoms were shown.

Another difference between pyridines and their *N*-oxides is the number of lone pairs of electrons. In

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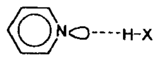
pyridine the lone pair on the nitrogen atom can interact directly with only one molecule of a protic solvent (**1**), whereas in pyridine *N*-oxide two molecules of protic solvents can interact with two lone pairs on the oxygen atom (**2**).[15]



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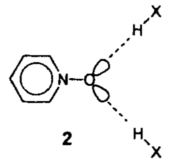

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Previously, we have used the ^{15}N probe to study the hydrogen bonding and proton transfer in complexes of substituted pyridines with trifluoroacetic acid.[4] In this paper, we report the effects of the hydrogen bonding and protonation on the nitrogen shielding in complexes of substituted pyridine *N*-oxides with dichloroacetic acid. These complexes have been studied using various techniques[14,16–18] but not ^{15}N NMR spectroscopy.

RESULTS AND DISCUSSION

The ^{15}N NMR chemical shifts of the substituted pyridine *N*-oxides and their complexes in $CDCl_3$ and CH_3OH are summarized in Table 1. The observed deviations in the chemical shifts can be explained by the effects of substituents, solvents, hydrogen bonding and protonation. *Para* substitution consistently induces much larger changes than *ortho* and the N SCS = δ(4-XPyNO) − δ(PyNO) values fit equation (1) with satisfactory precision (Figure 1).

$$\mathrm{N\ SCS} = a + b^{*}\sigma_p \qquad (1)$$

where $a = -9{\cdot}71$; $b = 33{\cdot}94$; SD = 4·17; $r^2 = 0{\cdot}958$; $n = 16$; $F_{stat} = 338{\cdot}79$; σ_p is the Hammett substituent constant taken from Ref. 20. Note that both ^{15}N and ^{14}N chemical shifts were used and the SD value is smaller than the experimental precision of the latter chemical shifts. The ^{14}N data were taken from Refs 2 and 8 and included electron-donating and withdrawing substituents. Data for 4-substituted pyridines from Refs 2 and 4 fit equation (1) less satisfactorily: $a = -6{\cdot}18$; $b = 38{\cdot}27$; $r^2 = 0{\cdot}795$; SD = 8·41; $F_{stat} = 50{\cdot}35$; $n = 15$. The dual substituent parameter equation (N SCS = $\rho_{I}\sigma_{I} + \rho_{R}\sigma_{R}$) does not improve the correlations. Additionally, the correlation of N SCS with mesomeric dipole moments is also poor.

The observed shielding of the nitrogen atom in pyridine *N*-oxides with proton donors is attributed in part to the effect of the substituent and to hydrogen bonding. The differences between the ^{15}N chemical shifts of the complex and the free base, $\Delta\delta(^{15}N) = \delta$(X-PyNO·HA) − δ(X-PyNO), can be treated as a hydrogen bond parameter. The shape of the plot of $\Delta\delta^{15}$N (ppm) against ΔpK_a (Figure 2) is similar to that of a titration (sigmoidal) curve; the degree of proton transfer is near 0 or 100% in the two plateau regions.

The relationship between $\Delta\delta(^{15}N)$ and ΔpK_a is given by equation (2) (for details see Ref. 21), where $\Delta\delta(^{15}N)_{HB}$ and $\Delta\delta(^{15}N)_{PT}$ are the differences of the chemical shifts for the B··· HA and $B^+H\cdots A^-$ species, respectively, and *C* and *D* are constants.

$$\Delta\delta(^{15}N) = \frac{\Delta\delta(^{15}N)_{HB} + \Delta\delta(^{15}N)_{PT}{*}10^{(C+Dx)}}{1 + 10^{(C+Dx)}} \qquad (2)$$

Equation (2) was solved by a least-squares program and the following values were derived: $\Delta\delta(^{15}N)_{HB} = -7{\cdot}44$ ppm; $\Delta\delta(^{15}N)_{PT} = -49{\cdot}48$ ppm; $C = -0{\cdot}3337$; $D = 0{\cdot}2656$; SD = 2·6 ppm; $n = 12$. The inversion point (where the degree of protonation is estimated to be 50%) was calculated from equation (3) and it is at $\Delta pK_a = 1{\cdot}26$ [$pK_a(B^+H) = 2{\cdot}61$].

$$\log \frac{\Delta\delta^{15}N_{HB} - \Delta\delta^{15}N}{\Delta\delta^{15}N - \Delta\delta^{15}N_{PT}} = C + Dx \qquad (3)$$

This value is very close to the value of 1·53 ± 0·16 derived from IR (centre of gravity and integrated intensity of the broad absorption) and proton chemical shifts.[16] The estimated value of $\Delta\delta(^{15}N)_{PT}$ is consistent with the observed data for complexes with CF_3SO_3H (Table 1). The $\Delta\delta(^{15}N)_{PT}$ value for pyridine *N*-oxide (−49·5 ppm) is much lower than that for pyridine (−123 ppm).[4] *O*-Methylation of pyridine *N*-oxide (−38·5 ppm) and *N*-methylation of pyridine (−115·9 ppm) cause slightly smaller shifts than protonation.

The observed variation of the nitrogen shielding in pyridines and pyridine *N*-oxides is controlled by an interaction of the electron lone pair on heteroatoms (nitrogen in pyridines or oxygen in *N*-oxides) with the electron sextet of the aromatic ring and protonation. The former interaction caused similar variations, whereas the latter effected different variations of the nitrogen shielding in pyridines and pyridine *N*-oxides. The medium polarity effect on the nitrogen shielding of pyridine and its *N*-oxide is of the same sign and order of magnitude and does not exceed 6 ppm. The hydrogen bonding effect depends mainly on the proton donor properties of the solvent and exceeds *ca* 10, 21 and 30 ppm for $CHCl_3$, MeOH and H_2O, respectively. Witanowski *et al.*[8] have shown that hydrogen bonding to the oxygen atom in pyridine *N*-oxide produces nitrogen shielding changes comparable to those found when nitrogen is directly involved in hydrogen bonding, such as in pyridine. Our results show that for

Table 1. ^{15}N NMR chemical shifts of substituted pyridine *N*-oxides and their complexes with methanol and dichloroacetic, trifluoromethanesulfonic and perchloric acid in chloroform-d_1, or methanol and ^1H NMR in dichloromethane

			Chemical shift (ppm)			pK_a		
Pyridine *N*-oxides	Solvent	Proton donor	*N*-Oxide	Complex	$\Delta\delta(^{15}N)$	of *N*-oxide	ΔpK_a^a	^1H NMR[b]
PyNO	$CHCl_3$		−85 ± 1[c] −86·78[d]			0·79		
	CH_3OH			−94 ± 1[c] −97·53[d]				
	$CDCl_3$	$CHCl_2COOH$			(−17·8)[e]		−0·56	16·33
4-Cl-PyNO	$CDCl_3$	–	−91·6			0·36		
	$CDCl_3$	$CHCl_2COOH$		−106·9	−15·3		−0·99	15·62
	$CDCl_3$	CH_3OH		−97·6	−6·0		−15·18	
	$CDCl_3$	CF_3SO_3H		−141·6	−50·0			
4-Me-PyNO	$CDCl_3$	–	−95·9			1·09		
	$CDCl_3$	$CHCl_2COOH$		−117·0	−21·1		−0·26	17·09
	$CDCl_3$	CH_3OH		−103·1	−7·2		−14·45	
	$CDCl_3$	CF_3SO_3H		−146·0	−50·1			
	CH_3OH			−104·6				
	CH_3OH			−105 ± 2[c]				
	CH_3OH	$HClO_4$		−143·7	−47·8		~9	
4-Me-PyN$^+$OMe·I$^-$	CH_3OH			−134·4				
3,4-Me_2-PyNO	$CDCl_3$	–	−98·5			1·48		
	$CDCl_3$	$CHCl_2COOH$		−119·2	−20·7		0·13	17·22
2,4,6-Me_3-PyNO	$CDCl_3$	–	−101·2			1·99		
	$CDCl_3$	$CHCl_2COOH$		−124·4	−23·2		0·64	16·98
4-MeO-PyNO	$CDCl_3$	–	−112·3			2·41		
	$CDCl_3$	$CHCl_2COOH$		−141·0	−28·7		1·06	17·88
4-MeO−2,6-Me_2PyNO	$CDCl_3$	–	−113·1			3·45		
	$CDCl_3$	$CHCl_2COOH$		−143·2	−30·1		2·10	17·95
4-NMe_2-PyNO	$CDCl_3$	–	−126·0			4·05		
	$CHCl_3$		−131 ± 5[c]					
	$CDCl_3$	$CHCl_2COOH$		−169·2	−43·2		2·70	17·85
4-NMe_2−2,6-Me_2PyNO	$CDCl_3$	–	−127·3			4·75		
	$CDCl_3$	$CHCl_2COOH$		−164·7	−37·4		3·40	16·98
	$CDCl_3$	CH_3OH		−136·5	−9·2		−10·79	
	$CDCl_3$	CF_3SO_3H		−175·5	−48·2		>6·6	

[a] $\Delta pK_a = pK_a(B^+H) - pK_a(AH)$; p$K_a$ values for $CHCl_2COOH$ (1·35), CH_3OH (15·54), CF_3SO_3H (<−1·86), $HClO_4$ (−8) and HCl (−7) were taken from Ref. 19.

[b] Data in CH_2Cl_2 from Ref. 16.

[c] Chemical shift for nitrogen−14 from Ref. 2.

[d] Chemical shift for nitrogen−14 from Ref. 8.

[e] Value estimated from equation. (2).

protonation this similarity is broken; protonation of pyridines and their *N*-oxides shifts the resonance signals to lower frequencies by *ca* 120 and 50 ppm, respectively.

To explain a zone of rapid variation on the sigmoidal curve in a narrow range of ΔpK_a, two extreme approaches can be distinguished. A more likely hypothesis considers the tautomeric equilibrium of H-bonded complex (neutral) and H-bonded ion pair (polar) [equation (4)].

$$B\cdots HA \rightleftharpoons B^+H\cdots A \qquad (4)$$

$$B\cdots H\cdots A \qquad (5)$$

In this model the proton is considered to be localized closer to acid or base and the complex can be described by various potential energy curves with two minima. In the other approach, the proton is considered to be delocalized [equation (5)]. The potential energy curve in this case can be asymmetric with a single minimum, which moves from the donor to the acceptor molecule with increase in ΔpK_a. It is usually very difficult to distinguish between these two possibilities.

The complexes that are close to the inversion point show the most intense broad absorption in the IR spectra; the centre of gravity of this absorption reaches the lowest wavenumber, while the proton chemical shift

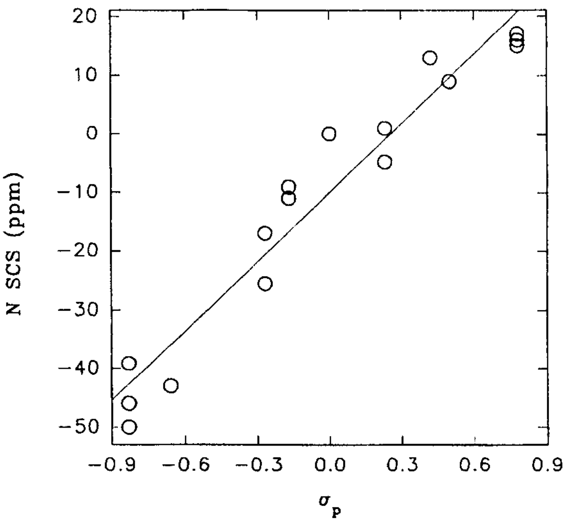

Figure 1. Plot of ^{15}N and ^{14}N SCS values of 4-substituted pyridine *N*-oxides against Hammett σ_p values. The N SCS values were calculated from data in Table 1 and Refs 2 and 8. The σ_p values were taken from Ref. 20

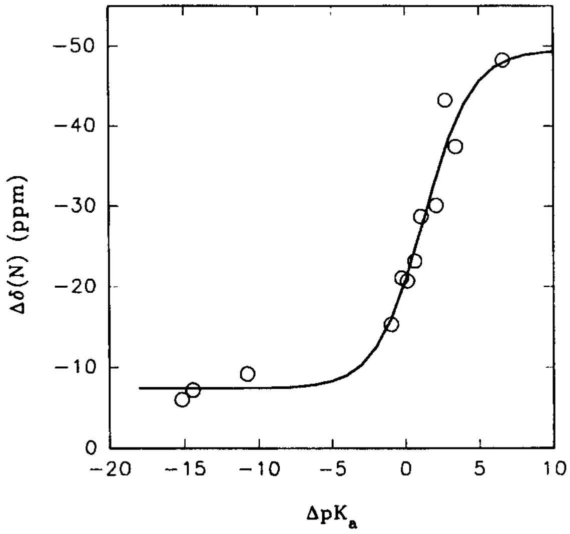

Figure 2. Plot of $\Delta\delta(^{15}N) = \delta(X\text{-}PyNO\cdot HA) - \delta(X\text{-}PyNO)$ versus $\Delta pK_a = pK_a(B^+H) - pK_a(AH)$. The line was derived with equation (2)

is *ca* 18 ppm.[16] This shows that the shortest hydrogen bond is in complexes that are close to the inversion point.

The simultaneous existence of tautomers can be confirmed experimentally when their lifetime is longer than the observation time. When the lifetime is shorter than the observation time, an average situation is observed, which cannot be distinguished from the situation described by the delocalization model [equation (5)]. Recently, we have shown that in UV spectrophotometry both B···HA and $B^+H\cdots A^-$ species in complexes of 2,6-dichloro-4-nitrophenol with pyridines and pyridine *N*-oxides were detected.[22] In pyridine complexes, however, the lifetime is longer than in pyridine *N*-oxide complexes. We believe that a similar situation arises in complexes with carboxylic acids. In the second-derivative FTIR spectra, we have observed two carbonyl bands for complexes of pyridines with carboxylic acids and only a single band for complexes of pyridine *N*-oxides.[17] As in FTIR spectroscopy of the latter complexes, only one species [equation (5)] was observed with a lifetime shorter than 10^{-13} s.

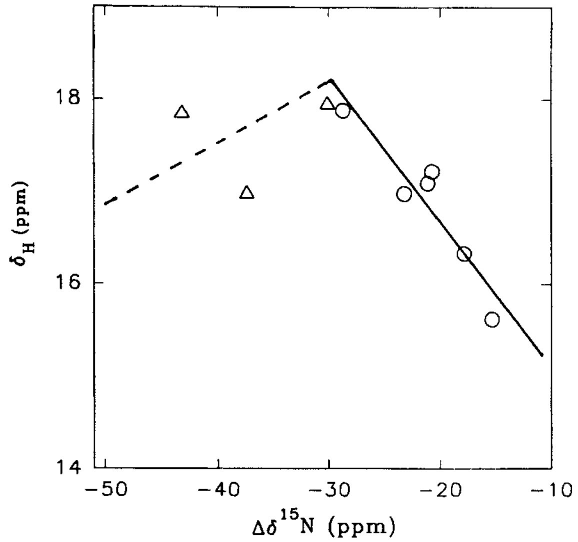

Figure 3. Plot of chemical shift (δ_H) against nitrogen relative chemical shift ($\Delta\delta^{15}$N). (○ Data for complexes below inversion point; (Δ) data for complexes above inversion point (see Fig. 2)

Generally, interactions between acids and bases in solutions depend strongly on their proton-donor and proton-acceptor properties, concentrations, acid–base ratio, solvent (its polarity, proton-donor and proton-acceptor properties), temperature (pK_a, of AH and B, electric permittivity and viscosity are temperature dependent) and impurities (e.g. traces of water and free ions) (see e.g., Ref. 23).

In this work the results were interpreted using a model of reversible proton transfer in H-bonded complexes. One of the referees suggested considering the contribution of the nonstoichiometric complexes. Indeed, such complexes (e.g. B·HA·HA, B·HA·HA·HA, or B·H·B·A) have been recognized by IR[17] and ^{15}N NMR[24] spectroscopy and conductivity,[25] measurements when an excess of acid or base was added to the equimolar complex (BHA), and they all participate in proton transfer. However, in equimolar complexes of pyridine *N*-oxides with trifluoroacetic and dichloroacetic acid, these non-stoichiometric complexes are not formed.[17]

Figure 3 shows the correlation of the chemical shifts of the H-bonded protons and $\Delta\delta(^{15}N)$. Although only three scattered data represent complexes above the inversion point, the plot is similar to that reported previously for complexes of pyridines with trifluoroacetic acid.[4] A similar type of correlation was derived between the chemical shifts of H-bonded protons or the centre of the broad infrared absorption and pK_a for complexes of pyridines and pyridine *N*-oxides with carboxylic acids.[16] This confirmed that $\Delta\delta(^{15}N)$ is a measure of hydrogen-bond strength and protonation.

EXPERIMENTAL

Complexes were prepared as described in Ref. 16 and 4-Me-$C_5H_4N^+OCH_3$ I^- as described in Ref. 26.

The ^{15}N NMR spectra were recorded on a Bruker AM 500 spectrometer operating at a frequency of 50·70 MHz using the INEPT pulse sequence optimized on a 10 Hz coupling constant with a relaxation delay of 2 s. Typically 400–800 scans were acquired. The signal of nitromethane was used as external reference (0 ppm). Sample concentrations were 0·2 M and the temperature was 300 K.

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