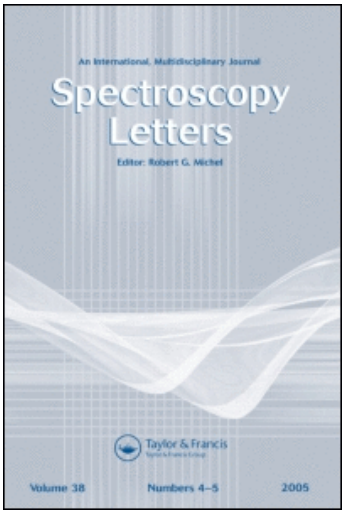

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^{1}H NMR Spectra of Substituted Aminopyridines

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^{1}H NMR SPECTRA OF SUBSTITUTED AMINOPYRIDINES

KEY WORDS: ^{1}H NMR, Substituent effect, Aminopyridines

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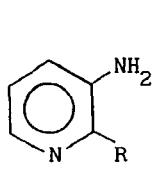
ABSTRACT

Substituent effects on the ^{1}H NMR spectra of forty four vicinally substituted 2-, 3- and 4-aminopyridines have been investigated. The results show that chemical shifts of the *ortho* and *para* protons with respect to the variable substituent follow well the dual substituent parameter treatment (DSP). It indicates their electronic origin.

INTRODUCTION

As part of a comprehensive study of the structure-reactivity relationships and physicochemical properties of vicinally substituted pyridines[1] multinuclear NMR investigations have been recently reported.[2] However, surprisingly very little work has been carried out on ^{1}H NMR data of the above compounds.[2a,b] It seems that in such a case it is important to search chemical shifts of aromatic protons by means of their correlations with the single and multiparameter substituent approach.

The present paper is devoted to the ^{1}H NMR study of the ring substituent effect in 2-substituted 3-aminopyridines (Series **1**), 4-substituted 3-aminopyridines (Series **2**), 3-substituted 2-aminopyridines (Series **3**) and 3-substituted 4-aminopyridines (Series **4**).



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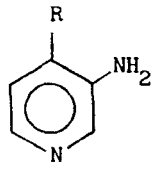

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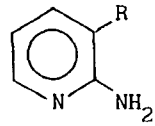

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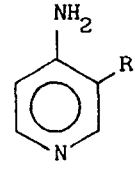

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EXPERIMENTAL

2-, 3- and 4-aminopyridines, 2,3- and 3,4-diaminopyridines as well as 3-amino-2-chloropyridine were purchased from Aldrich and recrystallized before use. Other pyridines were obtained as described previously.[1,3] The purity of all compounds was checked by thin-layer chromatography.

^{1}H NMR spectra were measured at 200 MHz in FT mode on a Varian XL-200 spectrometer for approximately 0.05 M solutions in $CDCl_3$--DMSO (5:1) with TMS as an internal standard. The typical conditions were as follows: spectral width 2.6 kHz, pulse width 11.3 μs, acquisition time 5.77 s, number of data points 32 K and temperature 20 ± 1°C.

The aryl protons constitute an ABX system.[2a,b] The assignments are based on the literature data and couplings typical of monosubstituted pyridines[4-6] as well as of some vicinally substituted nitropyridines.[2,7,8] Additionally, a comparison of experimental chemical shifts with those calculated on the basis of shielding parameters developed by Zanger and Simons[4] was made.

RESULTS AND DISCUSSION

The proton chemical shifts of forty four vicinally substituted aminopyridines are reported in Tables 1 and 2. It is observed that coupling constants J (H,H) for the investigated compounds do not show any reasonable dependence on the substituent effect, and they are not submitted here.

The chemical shifts, δ's, for the investigated Series were as follows:

Series 1 δ (H-6) < δ (H-4) < δ (H-5)

Series 2 δ (H-2) < δ (H-6) < δ (H-5)

Series 3 δ (H-6) < δ (H-4) < δ (H-5)

Series 4 δ (H-2) < δ (H-6) < δ (H-5)

As seen, protons in the position 6 (Series 1 and 3) and in the position 2 (Series 2 and 4) absorb at the lowest field. However, no clear tendency to the substituent effect appears throughout Series. Probably the proximity effect of both fixed NH_2 and R groups as well as the conformational change or substituent interaction with the ring nitrogen atom are strongly responsible for such a situation.[1,2]

The *ortho* and *para* protons with respect to R are largely sensitive to the substituent effect (see Δ in Tables 1 and 2). The *para* protons in Series 4 are the only exception. Perhaps here R is not a strongly cross-interacting group and the transmission of its electronic effect is decreased by the fixed 4-amino function.[1] The same was concluded in the case of ^{13}C NMR chemical shifts[2d] as well as pK_a values[1b] for 3-substituted 4-aminopyridines.

The variable substituent exerts only a little effect on the proton chemical shifts in the *meta* position. It is in agreement with our previous studies on ^{13}C NMR spectra of vicinally substituted benzenes[9] and pyridines.[2c,d]

The present data are also useful for discussing the hydrogen bonding effect. *Ortho*-nitroanilines are commonly assumed to be intramolecularly hydrogen bonded, although some controversy exists

TABLE 1

^{1}H NMR Chemical Shifts (δ, ppm) of 2-R-3-Aminopyridines (Series 1) and 3-R-2-Aminopyridines (Series 3)

	2-R-3-aminopyridines					3-R-2-aminopyridines				
R	H-4	H-5	H-6	NH_2 NH	Me CH_2	H-4	H-5	H-6	NH_2 NH	Me CH_2
H[a]	6.96	6.92	7.92	4.14		7.35	6.52	7.95	5.98	
Me	6.94	6.89	7.92	3.38	2.37	7.14	6.50	7.85	4.89	1.99
F	6.90	6.76	7.70	5.48		no compound				
Cl	7.02	6.99	7.74	4.36		7.51	6.56	7.95	5.35	
Br	7.16	7.03	7.75	4.29		7.61	6.88	7.97	5.30	
OMe	6.80	6.67	7.52	3.80	3.93	no compound				
OEt	no compound					6.83	6.57	7.65	4.89	1.38
										3.99
NH_2	6.72	6.50	7.60	6.20[b]		c				
NHMe	6.94	6.74	7.68	3.20	2.60	6.61	6.59	7.42	4.98	2.58
				4.98					2.80	
NHPh	7.58	6.82	7.77	3.35		no compound				
				4.56						
NMe_2	6.88	6.82	7.77	3.88	2.76	no compound				
COOEt	6.92	6.84	7.65	6.27	1.01	8.13	6.57	8.20	6.72	1.35
					4.11					4.33
$CONH_2$	7.77	7.16	7.93	7.26[d]		8.22	6.56	8.02	7.08[d]	
CN	7.32	7.17	7.76	5.84		no compound				
NO_2	7.56	7.41	7.78	7.70		8.38	6.72	8.35	7.71	
Δ[e]	0.86	0.91	0.41			1.77	0.38	0.93		

[a] δ (H-2) is 8.02 and δ (H-3) is 6.47 ppm for 3- and 2-aminopyridines, respectively; [b] δ of 2-NH_2 protons, protons of 3-NH_2 absorb at 4.80 ppm; [c] See chemical shifts for 2,3-diaminopyridine; [d] Signals at 6.80 and 6.50 ppm correspond to δ of protons in $CONH_2$ for Series 1 and 3, respectively; [e] Δ means range of SCSs.

TABLE 2

^{1}H NMR Chemical Shifts (δ, ppm) of 4-R-3-Aminopyridines (Series 2) and 3-R-4-Aminopyridines (Series 4)

	3-R-4-aminopyridines					4-R-3-aminopyridines				
R	H-2	H-5	H-6	NH_2 NH	Me CH_2	H-2	H-5	H-6	NH_2 NH	Me CH_2
H[a]	8.01	6.51	8.01	6.06		see Table 1				
Me	8.04	6.50	8.02	4.50	2.02	7.99	6.91	7.89	3.95	2.14
Et	8.08	6.48	8.05	4.78	1.20	no compound				
					2.46					
F	8.16	6.75	7.92	5.70		no compound				
Cl	8.21	6.69	8.00	5.26		no compound				
Br	8.36	6.60	8.06	5.06		no compound				
OMe	7.85	6.42	7.60	5.36	4.61	7.97	6.66	7.93	3.97	3.83
NH_2	7.60	6.35	7.44	5.36[b]		c				
NHMe	7.62	6.48	7.57	5.48	2.76	8.06	6.31	7.71	4.19	2.79
				4.72					5.53	
NHPh	8.12	6.63	7.95	6.66		7.94	6.98	7.67	3.95	
				4.20					4.94	
NMe_2	8.09	6.53	7.96	4.80	2.68	7.98	6.75	7.93	3.87	2.72
COOEt	8.30	6.59	7.92	6.90	1.20	8.20	7.59	7.91	6.85	1.39
					4.18					4.35
$CONH_2$	8.27	6.55	7.90	6.64[d]		8.24	7.54	7.86	6.70[d]	
NO_2	8.82	6.54	7.98	7.79		8.55	7.73	7.78	7.50	
Δ[e]	1.25	0.40	0.62			0.95	1.42	0.49		

[a] δ (H-3) is 6.51 ppm for 4-aminopyridine; [b] δ of 4-NH_2 protons, protons of 3-NH_2 absorb at 4.61 ppm; [c] See chemical shifts for 3,4-diaminopyridine; [d] Signals at 5.06 and 4.85 ppm correspond to δ of protons in $CONH_2$ for Series 2 and 4, respectively; [e] Δ See Table 1.

about the preferred conformation.[7] There is a hydrogen bonding between the amino and the nitro group in four aminonitropyridines. Moreover, there is no important through-space interaction between the ring aza atom and the amino-hydrogen of NH_2 and NHX groups for Series 1 and 3, respectively, though in substituted pyridines the "effective size" of the electron lone pair on the ring nitrogen atom has been shown as very important.[10] However, the downfield shift of protons in the fixed amino group, when R is CO_2Et and $CONH_2$, could be attributed to the hydrogen bonding between C=O and fixed NH_2 functions. Other NH signals are in the normal upfield position. It can be concluded that the relatively larger downfield effect observed for the protons of NH_2 and NHX groups in the positions 2 and 4 in comparison with those in the position 3, is attributed rather to the efficiency of the resonance interaction with the ring nitrogen atom than to tautomeric equilibria.[2b,11]

Reasonably good linear relationships for the proton chemical shifts of *para* hydrogens to R *vs* those of appropriate carbons[2d] in the same Series have been obtained. Thus, for Series 1, *i.e.* δ [H(5)] *vs* δ [C(5)], the regression parameters are: slope, A = 0.039, correlation coefficient, r = 0.969, standard deviation, s = 0.080, number of points, n = 12 (NHPh, CO_2Et were omitted). Similarly, for Series 3, *i.e.* δ [H(6)] *vs* δ [C(6)], the results are: A = 0.036, r = 0.964, s = 0.086 for n = 10. The point for R = $CONH_2$ is the most unfitted one. For Series 4, *i.e.* δ [H(6)] *vs* δ [C(6)], the correlation parameters are: A = 0.032, r = 0.957, s = 0.117 for n = 10 (NO_2 not included). One would suggest that chemical shifts of both protons and carbons are mainly controlled by polar substituent effects.[1,2,12]

Only for Series 3 the linear dependence was found for the chemical shifts of *para* hydrogens with respect to R *vs* σ_p^+ parameters.[13] Thus, the results are as follows: A = 0.32, r = 0.965, s = 0.071 for n = 10. For other Series the points were scattered and r values were lower than 0.75.

TABLE 3

DSP Correlations[a] of the Proton Chemical Shifts in Substituted Aminopyridines

Series	Proton	Correlation	r	s	F	n
1	H-5	$0.42\sigma_I + 0.53\sigma_R^o + 6.89$	0.840	0.131	30	14
2	H-2	$0.67\sigma_I + 0.54\sigma_R^o + 8.10$	0.971	0.102	96	7[b]
	H-5	$0.96\sigma_I + 0.98\sigma_R^- + 7.05$	0.948	0.137	72	10
	H-5	$0.96\sigma_I + 1.15\sigma_R^- + 7.01$	0.980	0.089	149	8[c]
3	H-4	$0.41\sigma_F + 1.44\sigma_R^- + 7.48$	0.972	0.101	134	10
	H-6	$0.41\sigma_I + 0.90\sigma_R^- + 7.91$	0.988	0.045	327	10
4	H-2	$0.79\sigma_I + 0.58\sigma_R^- + 8.07$	0.879	0.156	41	14
	H-2	$0.63\sigma_I + 0.54\sigma_R^- + 8.06$	0.967	0.114	80	11[d]
	H-6	σ_I, σ_R^-	<0.5			14

[a] σ_I, σ_F, σ_R^o and σ_R^- were taken from ref.[13,16]: r, correlation coefficient; s, standard deviation; F, test for the significance of correlation; n, number of points; [b] NMe_2, NHPh and NHMe are omitted, for n = 10, r = 0.810 (s = 0.152, F = 16); [c] NMe_2 and NHPh are excluded; [d] NH_2, NMe_2 and NO_2 are not included.

A reasonably good estimation of the sensitivity of the proton chemical shifts to both localized and delocalized electronic effects was found when the dual substituent parameter approach (DSP)[14] was used (Table 3). In general, the DSP treatment rationalizes proton chemical shifts much better than single substituent parameter equation (SSP). Moreover, some additional information due to the relative importance of inductive/field and resonance competitions[14] may be obtained. The magnitudes of ρ_R and ρ_I coefficients show that the most chemical shifts of *ortho* and *para*

protons to R are controlled by its resonance effect (Series **1**, **2** and **3**). Poor correlation results for Series **1** seem to indicate an influence of the inconvenient steric situation of R in the position 2. Worse fits for chemical shifts of the *ortho* proton 2 (Series **2** and **4**) seem to reflect the proximity effect of the ring nitrogen atom as well as R and NH_2 groups, simultaneously.[1a] One would assume that in this particular case a prevalence of the field/inductive contribution is evident (see Table 3). The main reasons for common outliers (see footnote, Table 3) have been discussed previously.[1,2] Unfortunately, the more complex model including steric parameters[15a] as well as Reynolds' short-range factors[15b] does not improve significantly the correlations of proton chemical shifts in the *ortho* position with respect to R.

Although in the present work the DSP treatment is quite effective, it produced much better results in the case of ^{13}C NMR data.[2d] Combinations of the substituent parameters used here are the same as those for ^{13}C NMR chemical shifts of the appropriate *para* carbon atoms.[2c,d] It means that both proton and carbon chemical shifts of the *para* positions may be controlled by similar effects. However, it seems that ^{1}H NMR chemical shifts are less complex than ^{13}C NMR chemical shifts.[12] The sensitivity of proton and carbon chemical shifts to the substituent, and the ring nitrogen atom influences are comparable but not equivalent, since the distance of proton and carbon at the same ring position from the reaction "probe" is different. It follows that contributions of the proximity as well as the relative inductive/field-resonance effect are not strictly identical.

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