Methylpyridylbenz-X-azoles. ^{1}H NMR Study

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The shielding parameters of benz-X-azolyl substituents in various positions of the pyridine nucleus were determined by means of a regression analysis procedure. Analogously the shielding contributions of pyridyl substituents on homocyclic protons of benz-X-azoles were derived. The results evidence some interactions between the two heterocyclic systems when the benz-X-azolyl substituents are linked at the pyridine α-position.

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In the field of homocyclic compounds, the correlation between proton chemical shifts and systematic structure variations has been extensively investigated [1]. The additivity of substituent effects on the proton chemical shifts in *meta* and *para* substituted benzenes is generally assessed [2], whereas significant deviations are frequently observed in the case of adjacent substituents [1,3,4].

In the field of heteroaromatics, the pyridine protons

Table I

Pyridine Protons Chemical Shifts, δ (ppm) (formula I)

Compound number	Structure X_1	X_2 [a]	X_3 [a]	Pyridine protons 2	3	4	5	6	$>$C-CH$_3$	$^+>$N-CH$_3$
1	N	2-BO	4-Me		8.18		7.44	8.64	2.48	
2	N	2-BN	4-Me		8.22		7.31	8.57	2.46	
3	N	2-BS	4-Me		8.18		7.39	8.57	2.48	
4	N-salt	2-BO	4-Me		8.79		8.21	9.22	2.78	4.75
5	N	2-BN-salt	4-Me		8.04		7.69	8.85	2.55	
6	N-salt	2-BN-salt	4-Me		8.63		8.47	9.42	2.79	4.25
7	N	2-BS-salt	4-Me		8.26		7.72	8.83	2.58	
8	N	2-BO	6-Me		8.15	7.93	7.48		2.63	
9	N	2-BN	6-Me		8.16	7.86	7.35		2.60	
10	N	2-BS	6-Me		8.14	7.91	7.44		2.60	
11	N-salt	2-BO	6-Me		8.67	8.70	8.32		3.02	4.60
12	N	2-BN-salt	6-Me		8.06	8.17	7.74		2.69	
13	N	4-BO	6-Me	8.69	7.85		7.94		2.63	
14	N	4-BN	6-Me	8.62	7.90		7.99		2.62	
15	N	4-BS	6-Me	8.64	7.80		7.88		2.62	
16	N-salt		6-Me	9.12	8.53		8.71		2.94	4.33
17	N-salt	4-BN	6-Me	9.08	8.44		8.62		2.90	4.27
18	N-salt	4-BS	6-Me	9.12	8.54		8.69		2.95	4.31
19	N	4-BS	H	8.80	8.02		8.02	8.80		
20	N-salt	4-BS	H	9.11 [b]	8.69 [b]		8.69 [b]	9.11 [b]		4.42
21 [c]	N	3-BO	4-Me	9.23			7.50	8.64	2.76	
22	N	3-BN	4-Me	8.97			7.46	8.56	2.67	
23	N	3-BS	4-Me	9.00			7.49	8.61	2.67	
24	N-salt	3-BO	4-Me	9.76			8.30	9.08	3.08	4.53
25	N-salt	3-BN	4-Me	9.32			8.17	8.91	2.93	4.42
26	N-salt	3-BS	4-Me	9.48			8.28	9.04	2.91	4.46
27	N	3-BO	6-Me	9.18		8.36	7.46		2.58	
28	N	3-BN	6-Me	9.24		8.38	7.42		2.57	
29	N	3-BS	6-Me	9.12		8.28	7.42		2.57	
30	N-salt	3-BO	6-Me	9.83		9.09	8.27		2.94	4.45
31	N-salt	3-BN	6-Me	9.68		8.97	8.22		2.88	4.38
32	N-salt	3-BS	6-Me	9.76		9.06	8.22		2.91	4.43
33	N	H	H	8.48	7.28	7.68	7.28	8.48		
34	N	H	4-Me	8.44	7.21		7.21	8.44	2.32	
35	N	H	6-Me	8.42	7.15	7.65	7.22		2.47	
36	N-salt	H	4-Me	8.86	7.97		7.97	8.86	2.62	4.32
37	N-salt	H	6-Me	9.00	7.94	8.50	8.06		2.82	4.27

[a] The number before the symbol indicates the position of the substituent in the pyridine ring. [b] Non iterative values. [c] The chemical shifts of the compounds **21-37** have been determined previously [12].

Table II

Benzazole Protons Chemical Shifts, δ (ppm) (formula II)

Compound number	Structure Y_1	Y_2	Y_3	Protons 4	5	6	7	$^+\!\!>$N-CH_3
1	O	4-Me-2-Py	BX	7.83	7.49	7.46	7.86	
2	NH	4-Me-2-Py	BX	[a]	7.23 [b]	7.23 [b]	[a]	
3	S	4-Me-2-Py	BX	8.09	7.57	7.49	8.15	
4	O	4-Me-2-Py-salt	BX	7.97	7.68	7.59	8.04	
5	NCH_3	4-Me-2-Py	BX-salt	8.15	7.79	7.79	8.15	4.06
6	NCH_3	4-Me-2-Py-salt	BX-salt	8.24	7.90	7.90	8.24	4.09
7	S	4-Me-2-Py	BX-salt	8.48	7.99	7.91	8.60	4.58
8	O	6-Me-2-Py	BX	7.86	7.50	7.46	7.91	
9	NH	6-Me-2-Py	BX	7.56 [b]	7.21 [b]	7.21 [b]	7.68 [b]	
10	S	6-Me-2-Py	BX	8.08	7.56	7.49	8.15	
11	O	6-Me-2-Py-salt	BX	7.98	7.68	7.60	8.05	
12	NCH_3	6-Me-2-Py	BX-salt	8.15	7.79	7.79	8.15	4.07
13	O	6-Me-4-Py	BX	7.81	7.50	7.46	7.85	
14	NH	6-Me-4-Py	BX	7.66	7.27	7.27	7.66	
15	S	6-Me-4-Py	BX	8.13	7.60	7.53	8.20	
16	O	6-Me-4-Py-salt	BX	7.91	7.64	7.57	7.98	
17	NH	6-Me-4-Py-salt	BX	7.74	7.38	7.38	7.74	
18	S	6-Me-4-Py-salt	BX	8.23	7.70	7.65	8.35	
19	S	4-Py	BX	8.15	7.61	7.55	8.21	
20	S	4-Py-salt	BX	8.20	7.66	7.62	8.31	
21 [c]	O	4-Me-3-Py	BX	7.84	7.51	7.48	7.89	
22	NH	4-Me-3-Py	BX	7.70	7.29	7.29	7.70	
23	S	4-Me-3-Py	BX	8.15	7.62	7.55	8.22	
24	O	4-Me-3-Py-salt	BX	7.92	7.62	7.56	7.98	
25	NH	4-Me-3-Py-salt	BX	7.73	7.32	7.32	7.77	
26	S	4-Me-3-Py-salt	BX	8.24	7.71	7.66	8.37	
27	O	6-Me-3-Py	BX	7.81	7.47	7.45	7.84	
28	NH	6-Me-3-Py	BX	7.68	7.27	7.27	7.68	
29	S	6-Me-3-Py	BX	8.11	7.60	7.52	8.18	
30	O	6-Me-3-Py-salt	BX	7.92	7.61	7.56	7.95	
31	NH	6-Me-3-Py-salt	BX	7.74	7.35	7.35	7.74	
32	S	6-Me-3-Py-salt	BX	8.19	7.69	7.63	8.34	
33 [d]	O	H	BX	7.77	7.41	7.41	7.67	
34 [e]	NH	H	BX	7.65	7.22	7.22	7.65	
35 [e]	NCH_3	H	BX	7.69	7.22	7.27	7.54	
36 [d]	S	H	BX	8.08	7.57	7.50	8.14	

[a] The signals are overlapped by the large NH band. [b] Non iterative values. [c] The chemical shifts of the compounds **21-32** have been determined previously [12]. [d] In acetone, reference [13]. [e] Reference [14].

have received particular attention, the overall effect of the substituents obviously being more complex than in benzene. Wu and Dailey [5] have interpreted the proton chemical shifts of 4-substituted pyridines as the sum of the contributions of the substituent and of the ring nitrogen. The additivity constants of several 2, 3, and 4-substituted pyridines were empirically determined by Zanger and Simons [6], who derived from these constants the proton chemical shifts of bisubstituted pyridines with errors comparable with those observed for the benzenoid counterparts. Proton nmr study on six series of substituted carboxymethylpyridines showed an additive effect due to the substituent, to the ester group and to the pyridine nitrogen [7]. Proton nmr spectra of 6-chlorobenz-X-azolylpyridines were also studied [8].

In previous papers a series of 2-(methylpyridyl)benz-X-azoles, including the corresponding quaternary salts and polymethine dyes, have been described [9-11]. These systems are useful models to evaluate the mutual influences between the azine and azole rings when these are linked in different potisiton. The nmr spectra of the series of methyl-3-pyridylbenz-X-azoles and of their methiodides have been previously investigated [12] and the model of the additivity of the substituent contributions calculated by linear multiple regression analysis gave satisfactory results.

In this paper the same approach is applied to the proton chemical shifts of methyl-2 and 4-pyridyl derivatives. The general formula I summarizes the structures and the symbols of the bases and of the methiodides investigated in the present paper.

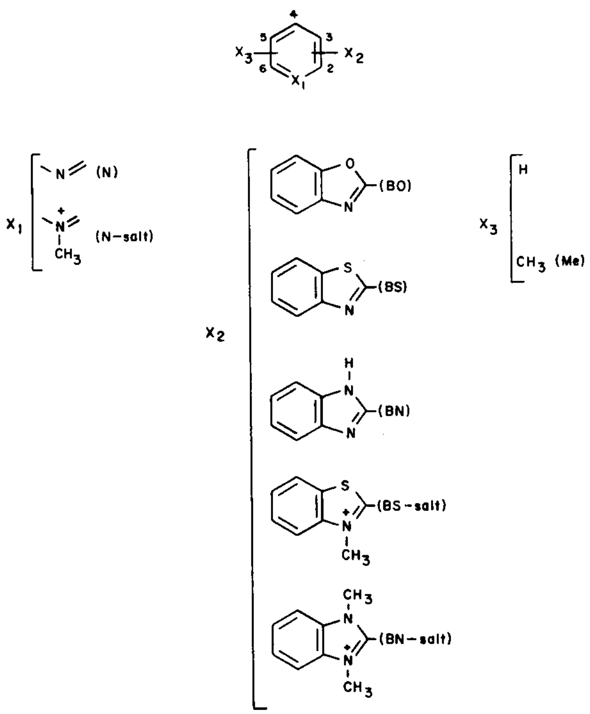
Table III

Coupling Constants (Hz)

Compound number [a]	Pyridine protons J_{23}	J_{25}	J_{34}	J_{35}	J_{36}	J_{45}	J_{56}	Benzazole protons J_{45}	J_{46}	J_{47}	J_{56}	J_{57}	J_{67}
1				1.27	0.75		5.08	8.43	1.06	0.72	7.52	1.30	8.03
2				1.72	0.75		5.03	8.1 [b]	1.0 [b]	— [c]	7.2 [b]	1.0 [b]	8.1 [b]
3				1.65	0.88		5.01	8.10	1.16	0.63	7.35	1.29	8.08
4				1.72	0.00		6.22	8.30	1.01	0.82	7.49	1.03	8.15
5				2.04	0.72		5.07	8.48	1.03	0.25	7.23	1.03	8.47
6				1.85	0.03		6.18	8.51	0.98	0.11	7.29	0.98	8.51
7				1.51	0.62		5.01	8.63	1.03	0.67	7.27	1.28	8.25
8			7.64	0.93		7.72		8.50	0.61	0.75	7.11	1.10	8.13
9			7.74	1.05		7.67		8.5 [b]	0.5 [b]	0.0 [b]	7.5 [b]	0.5 [b]	8.5 [b]
10			7.70	1.00		7.81		8.38	0.97	0.81	7.36	1.27	8.00
11			8.12	2.01		7.53		8.22	1.18	0.73	7.36	1.22	8.13
12			7.46	0.52		8.21		8.27	1.02	0.44	7.22	1.02	8.27
13	5.13	0.84		1.83				8.57	0.80	0.92	7.50	0.87	7.93
14	5.18	0.69		1.59				8.15	1.15	0.70	7.27	1.15	8.15
15	5.21	0.79		1.76				8.07	1.24	0.67	7.30	1.26	8.02
16	6.45	0.03		2.08				8.17	1.14	0.67	7.62	1.18	8.26
17	6.59	0.03		1.75				8.22	1.04	0.60	6.80	1.04	8.22
18	6.62	0.05		2.07				8.18	1.24	0.67	7.11	1.14	8.14
19	5.15	1.01		1.64	1.01		5.15	8.18	1.18	0.65	7.40	1.22	8.20
20	6.7 [b]	0.0 [b]		0.3 [b]	0.0 [b]		6.7 [b]	8.22	1.11	0.45	7.39	1.12	7.95

[a] See Table I for pyridine protons and Table II for benzazole protons. [b] Non iterative values. [c] See note [a] in Table II.

GENERAL FORMULA 1



Pyridine and benzazole proton chemical shifts are listed in Tables I and II and coupling constants in Table III.

Pyridine Protons.

Assuming the additivity of substituent effects, the chemical shifts δ of any pyridine ring proton can be expressed by the equation (1)

$$\delta = \Sigma\Delta\delta_x + \delta_o \qquad (1)$$

where $\Delta\delta_x$ is the contribution of the substituent X to the chemical shift of the considered proton and δ_o is the chemical shift of the corresponding proton in the base structure. Substituent contributions and δ_o for each proton are evaluated by the least squares solution of n linear equations of the form (1), n being the number of compounds in the series.

Regression analysis was performed on chemical shifts of 2 and 4-benzazolylpicolines (Nos. **1-20** in Table I) together with those, previously determined [12], of 3-benzazolylpicolines (Nos. **21-32**) and pyridines (Nos. **33-37**). This enables a comparison of the effect of the benzazolyls in the various positions of the pyridine ring to be made.

Tables IVA-B list the calculated contributions of the substituents and the relative statistical tests and Table V lists the calculated values of the chemical shifts and the residuals.

The results show that generally good correlations can be formulated; the lowest multiple correlation coefficients R are obtained for H_2 and H_6, which are the protons subjected to the strongest interaction with the ring nitrogen. The contribution of the quaternization for the β and γ

Table IV A

Calculated Substituent Contributions to the Chemical Shifts of Pyridine Protons (ppm) and Statistical Tests

	Pyridine protons				
Substituent [a]	H_2	H_3	H_4	H_5	H_6
Py-salt	0.485 (0.037) [b] (+) [c]	0.654 (0.029) (+)	0.744 (0.043) (+)	0.771 (0.015) (+)	0.443 (0.038) (+)
2-BO		0.894 (0.043) (+)	0.240 (0.068) (+)	0.250 (0.029) (+)	0.280 (0.072) (+)
2-BN		0.963 (0.055) (+)	0.157 (0.086)	0.104 (0.037) (+)	0.141 (0.090)
2-BS		0.933 (0.055) (+)	0.207 (0.086)	0.189 (0.037) (+)	0.141 (0.090)
2-BN-salt		0.791 (0.048) (+)	0.467 (0.086) (+)	0.486 (0.032) (+)	0.485 (0.072) (+)
2-BS-salt		1.011 (0.073) (+)		0.501 (0.049) (+)	0.401 (0.090) (+)
3-BO	0.831 (0.062) (+)		0.650 (0.068) (+)	0.270 (0.029) (+)	0.210 (0.072) (+)
3-BN	0.634 (0.062) (+)		0.600 (0.068) (+)	0.205 (0.029) (+)	0.085 (0.072)
3-BS	0.671 (0.062) (+)		0.595 (0.068) (+)	0.240 (0.029) (+)	0.175 (0.072)
4-BO	0.166 (0.079)	0.658 (0.055) (+)		0.706 (0.037) (+)	
4-BN	0.111 (0.079)	0.638 (0.055) (+)		0.686 (0.037) (+)	
4-BS	0.164 (0.066) (+)	0.666 (0.046) (+)		0.671 (0.031) (+)	0.254 (0.090) (+)
4-Me	−0.170 (0.076) (+)	−0.086 (0.054)		−0.073 (0.035) (+)	−0.051 (0.090)
6-Me	−0.029 (0.069)	−0.130 (0.048) (+)	0.023 (0.086)	−0.058 (0.032)	
δ_o	8.526	7.335	7.680	7.292	8.480
Statistical tests	n [d] = 25, k [e] = 9, R [f] = 0.985, S [g] = 0.090, p [h] < 0.001	n = 25, k = 11, R = 0.994, S = 0.063, p < 0.001	n = 14, k = 9, R = 0.997, S = 0.068, p < 0.001	n = 37, k = 14 R = 0.997, S = 0.043, p < 0.001	n = 18, k = 11, R = 0.988, S = 0.072, p < 0.001

[a] The number before the symbol indicates the position of the substituent in the pyridine ring (formula I). [b] Standard deviation of the contribution. [c] (+) Indicates a significance level $p < 0.005$. [d] Number of compounds used for the regression analysis. [e] Number of explanatory variables (substituents) entered in the regression equation; the explanatory variables are allowed to enter the regression equation if F value > 0.1. [f] Multiple correlation coefficient. [g] Standard deviation of the estimate. [h] Significance level of the estimate.

Table IV B

Calculated Substituent Contributions to the Chemical Shifts of Pyridine $\geqslant$C-CH_3 Protons (ppm) and Statistical Tests

Substituent [a]	Contribution
Py-salt	0.309 (0.010) (+)
o-BO	0.444 (0.025) (+)
o-BN	0.324 (0.025) (+)
o-BS	0.314 (0.025) (+)
m-BO	0.162 (0.018) (+)
m-BN	0.124 (0.020) (+)
m-BS	0.141 (0.020) (+)
m-BN-salt	0.198 (0.022) (+)
m-BS-salt	0.259 (0.033) (+)
p-BO	0.121 (0.025) (+)
p-BN	0.086 (0.025) (+)
p-BS	0.101 (0.025) (+)
o-N [b]	0.164 (0.013) (+)
δ_o	2.321
Statistical tests:	n = 34; k = 13; R = 0.993; S = 0.028; p < 0.001.

[a] The symbols *o*-, *m*-, *p*- are used, as in the benzene ring, to indicate the relative position of the hetaryl and the methyl groups. [b] This symbol indicates the effect of the pyridine nitrogen on the α-linked methyl protons.

protons is higher than for the α proton. The benzazolyls exert the greatest effect on the *ortho* protons (0.6-1 ppm) but the effect varies with the position of the substituent in the ring. The greatest effect is observed when the substituents are in the 2-position, while the effects in 3 and 4 positions are essentially the same. The effect of 3-BO on the *ortho* protons differs, being larger on H_2 than on H_4. The *ortho* contribution of the *N*-methylbenzazolylium cations could only be evaluated for *N*-methylbenzothiazolylium and *N,N*-dimethylbenzimidazolylium linked at the 2-position. Whereas the benzothiazolyl and its methyl cation give contributions of the same magnitude, the *N,N*-dimethylbenzimidazolylium contribution is smaller than that of the benzimidazolyl. This suggests some interaction, steric and/or anisotropic, between the pyridine ring and the dimethylbenzimidazolylium, which lowers the substituent deshielding effect.

The *meta* contributions of the benzazolyls vary in the range 0.1-0.3 ppm, the lowest values corresponding to the effects of the 4-substituents on the 2-proton. Both the *N,N*-dimethylbenzimidazolylium and *N*-methylbenzothiazolylium produce a greater *meta* effect (0.4-0.5 ppm) than the

Table V

Calculated Values of Pyridine Proton Chemical Shifts and Residuals (ppm)

Compound	H_2		H_3		H_4		H_5		H_6		$\gt$C-CH_3	
number [a]	Calcd.	Δ [b]	Calcd.	Δ	Calcd.	Δ	Calcd.	Δ	Calcd.	Δ	Calcd.	Δ
1			8.142	0.038			7.469	−0.029	8.709	−0.069	2.483	−0.003
2			8.212	0.008			7.323	−0.013	8.570	0.000	2.445	0.015
3			8.182	−0.002			7.408	−0.018	8.570	0.000	2.462	0.018
4			8.797	−0.007			8.241	−0.031	9.151	0.069	2.792	−0.012
5			8.040	0.000			7.705	−0.015	8.914	−0.064	2.519	0.031
6			8.694	−0.064			8.476	−0.006	9.356	0.064	2.828	−0.038
7			8.260	0.000			7.720	0.000	8.830	0.000	2.580	0.000
8			8.098	0.052	7.943	−0.013	7.484	−0.004			2.647	−0.017
9			8.168	−0.008	7.860	0.000	7.337	0.013			2.609	−0.009
10			8.138	0.002	7.910	0.000	7.422	0.018			2.626	−0.026
11			8.753	−0.083	8.687	0.013	8.256	0.064			2.956	0.064
12			7.996	0.064	8.170	0.000	7.719	0.021			2.683	0.007
13	8.663	0.027	7.863	−0.013			7.939	0.001			2.647	−0.017
14	8.608	0.012	7.843	0.057			7.919	0.071			2.609	0.011
15	8.660	−0.021	7.870	−0.070			7.905	−0.025			2.626	−0.006
16	9.147	−0.027	8.517	0.013			8.711	−0.001			2.956	−0.016
17	9.092	−0.012	8.497	−0.057			8.691	−0.071			2.918	−0.018
18	9.145	−0.025	8.525	0.015			8.677	0.013			2.935	0.015
19	8.690	0.110	8.000	0.020			7.963	0.057	8.734	0.066		
20	9.174	−0.064	8.655	0.035			8.735	−0.045	9.176	−0.066		
21	9.187	0.043					7.489	0.011	8.639	0.001	2.766	−0.006
22	8.990	−0.020					7.424	0.036	8.514	0.046	2.646	0.024
23	9.027	−0.027					7.459	0.031	8.604	0.006	2.636	0.034
24	9.672	0.088					8.261	0.039	9.081	−0.001	3.074	0.006
25	9.475	−0.155					8.196	−0.026	8.956	−0.046	2.954	−0.024
26	9.512	−0.032					8.231	0.049	9.046	−0.006	2.944	−0.034
27	9.328	−0.148			8.353	0.007	7.504	−0.044			2.606	−0.026
28	9.130	0.110			8.303	0.077	7.439	−0.019			2.571	−0.001
29	9.168	−0.048			8.298	−0.018	7.474	−0.054			2.586	−0.016
30	9.813	0.017			9.097	−0.007	8.276	−0.006			2.914	0.026
31	9.615	0.065			9.047	−0.077	8.211	0.009			2.879	0.001
32	9.653	0.107			9.042	0.018	8.246	−0.026			2.894	0.016
33	8.526	−0.046	7.335	−0.055	7.680	0.000	7.292	−0.012	8.480	0.000		
34	8.356	0.084	7.249	−0.039			7.219	−0.009	8.429	0.011	2.321	−0.001
35	8.497	−0.077	7.204	−0.054	7.703	−0.053	7.234	−0.014			2.485	−0.015
36	8.841	0.019	7.903	0.067			7.990	−0.020	8.871	−0.011	2.630	−0.010
37	8.981	0.019	7.859	0.081	8.447	0.053	8.005	0.055			2.794	0.026

[a] See Table I. [b] Δ = observed − calculated value. Observed values are listed in Table I.

corresponding benzazolyls.

The *para* contributions, related only to the benzazolyls in the 2 and 3 positions, are slightly smaller than the *meta* ones. The quaternized benzazolyls show greater effects than those of the corresponding benzazolyls.

The $\gt$C-CH_3 (X_3 = Me) chemical shifts give a good correlation with the structural parameters, including also the ring nitrogen. The deshielding effects, when the benzazolyl and the methyl are in *ortho* position, are important and vary in the order BO > BN ≅ BS, while the *meta* and *para* contributions are smaller and not significantly different from each other. The contributions of the benzazolylium cations to the *meta* *C*-methyl protons are larger than those of the corresponding benzazolyls.

Regression analysis could not be performed on the +$\gt$N-CH_3 protons of the quaternized pyridines due to insufficient data. Nevertheless, by comparing the values in Table I a trend can be observed, namely that the order of the deshielding contributions of benzazolyls is *ortho* > *meta* > *para* and benzoxazolyl > benzothiazolyl > benzimidazolyl. The chemical shift value of the dimethiodide (No. **6**) appears to be anomalous, showing an upfield shift relative to the corresponding picoline methiodide. This result is consistent with that obtained for the *ortho* contribution of the *N,N*-dimethylbenzimidazolylium group and strengthens the evidence of the above mentioned interaction between the rings.

Table VI

Calculated Substituent Contributions to the Chemical Shifts of Benzazole Protons (ppm) and Statistical Tests

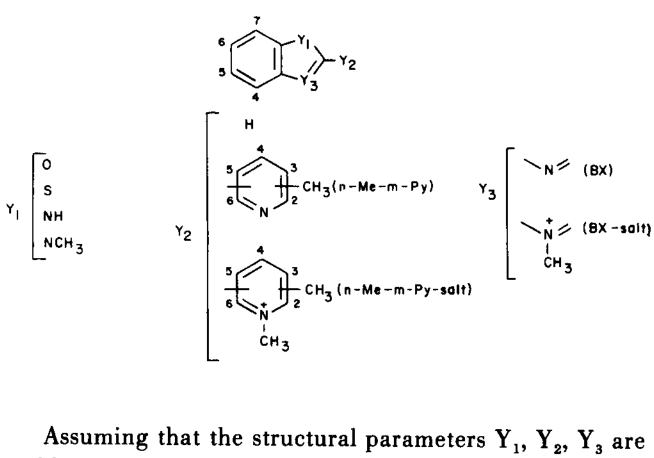
Position [a]	Substituent	Benzazole protons H_4	H_5	H_6	H_7
Y_1	S	0.465 (0.015) (+)	0.089 (0.013) (+)	0.063 (0.010) (+)	0.532 (0.020) (+)
	O	0.177 (0.015) (+)	–	–	0.187 (0.021) (+)
	NCH_3	0.097 (0.028) (+)	−0.183 (0.026) (+)	−0.112 (0.020) (+)	–
	NH	–	−0.249 (0.013) (+)	−0.209 (0.010) (+)	–
Y_2	4-Me-2-Py-salt	0.156 (0.030) (+)	0.213 (0.027) (+)	0.166 (0.021) (+)	0.251 (0.043) (+)
	6-Me-2-Py-salt	0.190 (0.036) (+)	0.240 (0.033) (+)	0.186 (0.025) (+)	0.293 (0.052) (+)
	4-Me-3-Py-salt	0.137 (0.025) (+)	0.163 (0.022) (+)	0.147 (0.017) (+)	0.230 (0.034) (+)
	6-Me-3-Py-salt	0.123 (0.025) (+)	0.163 (0.022) (+)	0.147 (0.017) (+)	0.200 (0.034) (+)
	6-Me-4-Py-salt	0.133 (0.025) (+)	0.186 (0.022) (+)	0.167 (0.017) (+)	0.213 (0.034) (+)
	4-Py-salt	0.123 (0.036) (+)	0.130 (0.033) (+)	0.142 (0.025) (+)	0.208 (0.052) (+)
	4-Me-2-Py	0.025 (0.027)	0.041 (0.022)	0.024 (0.017)	0.081 (0.037) (+)
	6-Me-2-Py	0.016 (0.023)	0.046 (0.021) (+)	0.027 (0.016)	0.110 (0.033) (+)
	4-Me-3-Py	0.070 (0.025) (+)	0.086 (0.022) (+)	0.074 (0.017) (+)	0.127 (0.034) (+)
	6-Me-3-Py	0.040 (0.025)	0.059 (0.022) (+)	0.047 (0.017) (+)	0.090 (0.034) (+)
	6-Me-4-Py	0.040 (0.025)	0.069 (0.022) (+)	0.054 (0.017) (+)	0.093 (0.034) (+)
	4-Py	0.073 (0.036)	0.080 (0.033) (+)	0.072 (0.025) (+)	0.108 (0.052)
Y_3	BX-salt	0.398 (0.030) (+)	0.456 (0.026) (+)	0.441 (0.020) (+)	0.451 (0.033) (+)
δ_o		7.613	7.440	7.414	7.570
Statistical tests		$n = 35$, $k = 16$, $R = 0.995$, $S = 0.031$, $p < 0.001$	$n = 36$, $k = 16$, $R = 0.994$, $S = 0.028$, $p < 0.001$	$n = 36$, $k = 16$, $R = 0.996$, $S = 0.022$, $p < 0.001$	$n = 35$, $k = 15$, $R = 0.991$, $S = 0.045$, $p < 0.001$

[a] General formula II.

Benzazole Protons.

Regression analysis was performed on the chemical shifts of the benzazole carbocyclic protons. The compounds under investigation are represented more conveniently by the general formula II.

GENERAL FORMULA II



Assuming that the structural parameters Y_1, Y_2, Y_3 are additive, good correlations have been obtained for each proton as shown in Table VI, where the calculated group contributions are listed together with the statistical tests. In Table VII the calculated chemical shifts and the residuals are reported. The results of the analysis indicate the preeminent effect of the heteroatom at Y_1 on the proton chemical shifts (57-68% of the total variance explained), followed by the quaternization of the azole nitrogen (21-31% of the total variance explained) (data not reported in Table VI). The substitution at Y_2 seems to be much less important. The heteroatom contributions vary in the orders S > O > NCH_3 ≅ NH, with the greatest differences for H_7 and H_4. The Y_2-substituent contributions are very small (generally < 0.1 ppm) when the substituents are pyridines and slightly greater (0.1-0.3 ppm) when they are *N*-methylpyridinium cations.

$+\!>\!N\text{-}CH_3$ Protons.

Comparing the chemical shifts in Table II with the available literature data for the quaternary salts of unsubstituted benzazoles [15] a downfield shift of *N*-methylproton chemical shift can be observed for the benzothiazolyl derivative (4.58 *vs* 4.48 ppm). In contrast, an anomalous upfield shift (4.06-4.09 *vs* 4.15 ppm) is observed by introducing a pyridine or a pyridinium substituent in the *N,N*-dimethylbenzimidazolylium cation, strengthening the hypothesis of a steric interaction between the two rings, previously advanced.

The additivity model of the substituent contributions, calculated by linear multiple regression analysis, leads to a satisfactory agreement between the experimental and the calculated chemical shifts. This might be useful to make

Table VII

Calculated Values of Benzazole Proton Chemical Shifts and Residuals (ppm)

Compound number	H_4 Calcd.	H_4 Δ [b]	H_5 Calcd.	H_5 Δ	H_6 Calcd.	H_6 Δ	H_7 Calcd.	H_7 Δ
1	7.815	0.015	7.482	0.008	7.439	0.021	7.839	0.021
2	—	—	7.233	−0.003	7.230	0.000	—	—
3	8.102	−0.012	7.571	−0.001	7.502	−0.012	8.184	−0.034
4	7.946	0.024	7.653	0.027	7.581	0.009	8.008	0.032
5	8.133	0.017	7.756	0.034	7.767	0.023	8.103	0.047
6	8.264	−0.024	7.927	−0.027	7.909	−0.009	8.272	−0.032
7	8.500	−0.020	8.028	−0.038	7.942	−0.032	8.635	−0.035
8	7.806	0.054	7.486	0.014	7.442	0.018	7.867	0.043
9	7.628	−0.068	7.238	−0.028	7.233	−0.023	7.680	0.000
10	8.093	−0.013	7.576	−0.016	7.505	−0.015	8.212	−0.062
11	7.980	0.000	7.680	0.000	7.600	0.000	8.050	0.000
12	8.123	0.027	7.760	0.030	7.771	0.019	8.131	0.019
13	7.830	−0.020	7.510	−0.010	7.469	−0.009	7.851	−0.001
14	7.653	0.007	7.261	0.009	7.260	0.010	7.664	−0.004
15	8.117	0.013	7.599	0.001	7.532	−0.002	8.196	0.004
16	7.923	−0.013	7.626	0.014	7.582	−0.012	7.971	0.009
17	7.746	−0.006	7.378	0.002	7.373	0.007	7.784	−0.044
18	8.211	0.019	7.716	−0.016	7.645	0.005	8.316	0.034
19	8.150	0.000	7.610	0.000	7.550	0.000	8.210	0.000
20	8.200	0.000	7.660	0.000	7.620	0.000	8.310	0.000
21	7.860	−0.020	7.526	−0.016	7.489	−0.009	7.884	−0.006
22	7.683	0.017	7.278	0.012	7.280	0.010	7.697	0.003
23	8.147	0.003	7.616	0.004	7.552	−0.002	8.229	−0.009
24	7.927	−0.007	7.603	0.017	7.562	−0.002	7.987	−0.007
25	7.749	−0.019	7.354	−0.034	7.353	−0.033	7.800	−0.030
26	8.214	0.026	7.693	0.017	7.625	0.035	8.332	0.038
27	7.830	−0.020	7.500	−0.030	7.462	−0.012	7.847	−0.007
28	7.653	0.027	7.251	0.019	7.253	0.017	7.660	0.020
29	8.117	−0.007	7.589	0.011	7.525	−0.005	8.192	−0.012
30	7.913	0.007	7.603	0.007	7.562	−0.002	7.957	−0.007
31	7.736	0.004	7.354	−0.004	7.353	−0.003	7.770	−0.030
32	8.201	−0.011	7.693	−0.003	7.625	0.005	8.302	0.038
33	7.790	−0.020	7.440	−0.030	7.414	−0.004	7.757	−0.087
34	7.613	0.037	7.192	0.028	7.206	0.014	7.570	0.080
35	7.710	−0.020	7.258	−0.038	7.302	−0.032	7.570	−0.030
36	8.077	0.003	7.530	0.040	7.478	0.022	8.102	0.038

[a] See Table II. [b] Δ = observed − calculated value. Observed values are listed in Table II.

tentative assignments of the nmr spectra of substituted pyridines which are usually difficult to assign due to the different influence of the ring nitrogen on the chemical shifts of the α, β and γ protons.

This study has shown that the benzazolyl contributions to the chemical shifts of the *ortho* pyridine protons are almost the same whether the substituent is in the β or γ positions, but different when in the α-position. The greater contributions of α-benzazolyls might suggest the existence of some interaction between the benzazole moiety and the pyridine nitrogen which increases the deshielding effect of the substituents. On the other hand a different interaction seems to predominate with the *N,N*-dimethylbenzimidazolylium cation producing a significant decrease of the deshielding effect on H_3 as well as a shielding effect on the $^{+}{>}N\text{-}CH_3$ protons of the azole-pyridine systems.

Finally, the low value of the benzazolyl *para* contributions suggests that the effect of these substituents is primarily inductive.

EXPERIMENTAL

The synthesis of the bases and of their methiodides has been described previously [9,11].

The ^1H nmr spectra were recorded at room temperature on a Varian-EM 390 spectrometer (90 MHz) in DMSO-d_6 solution (*ca.* 0.3 *M*). TMS was used as an internal standard. The nmr parameters of benzazole carbocyclic protons and of pyridine protons were iteratively computed using the LAOCOON3 program [16]. The RMS errors were ≤ 0.1 Hz. Spectra of benzoxazoles and of benzothiazoles were analysed as ABCD systems and those of benzimidazoles as AA'BB' systems. Pyridine protons were treated as ABX systems (AA'XX' for Nos. **19, 20**).

Regression analyses were carried out on a OH-5560 Olivetti Computer-Hitachi, using the stepwise procedure of the SPSS programs [17].

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