Carbon-13 NMR Spectra of Isomeric 2-Arylimidazopyridines

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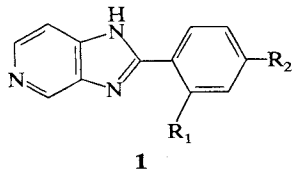
The ^{13}C NMR spectra of some 2-arylimidazo-[4,5-*c*]- and -[4,5-*b*]-pyridines and their protonated forms have been studied. The nitrogen atom of the pyridine ring has been shown to be the most basic nitrogen in these compounds.

INTRODUCTION

2-Arylimidazopyridines are the structural and isoelectronic analogues of 2-arylbenzimidazoles. The latter have found wide application as monomers for thermostable polymers, intermediate products in dye synthesis, UV stabilizers and in a number of other fields. Isomeric imidazopyridines have not been adequately studied from this point of view. We have carried out the syntheses of 2-arylimidazo-[4,5-*c*]- (**1**) and -[4,5-*b*]-pyridines (**2**) by condensation of 3,4- and 2,3-diaminopyridines with substituted benzoic acids.

^{13}C NMR chemical shift values are known often to be correlated with π-electron densities at the nuclei of aromatic systems. Therefore, it was of interest to determine the effect of the nitrogen position in the conjugated ring, and the substituted phenyl in position 2, on the distribution of electron density in systems **1** and **2**.



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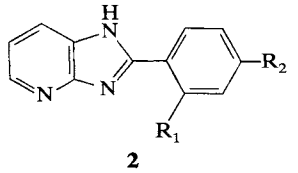

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(**a**) $R_1 = R_2 = H$
(**b**) $R_1 = OH$, $R_2 = H$
(**c**) $R_1 = H$, $R_2 = NH_2$
(**d**) $R_1 = OH$, $R_2 = NH_2$

The study of the ^{13}C NMR spectra of the protonated forms of 2-arylimidazopyridines is a problem of some interest, since the investigation of their acid–base properties[1] has shown that the analysis of numerical values of ionization constants does not allow the sequence of protonation centres to be readily determined. In such cases ^{13}C NMR spectroscopy is almost the only method for the determination of protonation centres. For example, the investigation of the protonation of imidazo[4,5-*c*]pyridine and 2-methylthioimidazo[4,5-*c*]pyridine has shown[2] that, depending on the nature and position of the substituents, the proton can add either to the nitrogen atom of the pyridine or to those of the imidazole ring.

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EXPERIMENTAL

The synthesis and purification of compounds **1a–d** have been described earlier.[1] Compounds **2a–d** were obtained by the condensation of 2,3-diaminopyridine with substituted benzoic acids according to Ref. 1, and purified by crystallization from water–ethanol mixtures. The structures of the compounds obtained were proved by the presence of characteristic absorption bands in the IR spectra, and their composition was confirmed by elemental analysis (Table 1).

^{13}C NMR spectra were measured on a JEOL FX-90 Q spectrometer at 22.49 MHz. The FT recording conditions were as follows: spectral width, 5000 Hz; data points, 8 K; pulse angle, 30°; pulse repetition time, 2.0–3.0 s. Chemical shifts were measured at 27 °C, TMS being used as internal reference, with an accuracy of ±0.05 ppm. The concentration was from 0.05 to 0.20 mol l^{-1} (see tables for solvents). The spectra of protonated imidazopyridines were recorded under the same conditions after the addition of 1 equivalent of trifluoroacetic acid to deuteriomethanol solutions of the compounds.

RESULTS AND DISCUSSION

The ^{13}C NMR spectra of 2-arylimidazo[4,5-*c*]pyridines recorded in methanol-d_4 are well resolved and the signals corresponding to all 12 carbon atoms can be observed. However, owing to the poor solubility of some 2-arylimidazo[4,5-*b*]pyridines in deuteriomethanol, their spectra were recorded in dimethyl sulphoxide-d_6. These are poorly resolved, the peaks are broadened and some signals are only within the noise level even after considerable accumulation (up to 2000 accumulations). Obviously, this is caused by the ability of dimethyl sulphoxide to effect specific solvation of the compounds examined.

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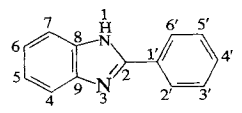
Table 1. Melting points, yields and elemental analysis data for compounds 2a–d

Compound	Yield (%)	M.p. (°C)	Found (%) C	H	N	Formula	Calc. (%) C	H	N
2a	62	285–286	73.90	4.81	21.27	$C_{12}H_9N_3$	73.83	4.65	21.52
2b	75	323–325	68.39	4.32	19.95	$C_{12}H_9N_3O$	68.40	4.29	19.82
2c	73	294–296	68.13	4.92	26.06	$C_{12}H_{10}N_4$	68.56	4.79	26.65
2d	79	307–309	63.10	4.15	24.68	$C_{12}H_{10}N_4O$	63.80	4.47	24.70

Table 2. ^{13}C NMR chemical shifts (ppm) of 2-phenylbenzimidazole, benzimidazole and imidazo[4,5-*c*]pyridine



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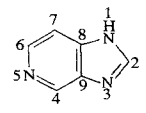

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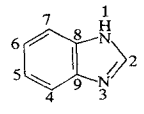

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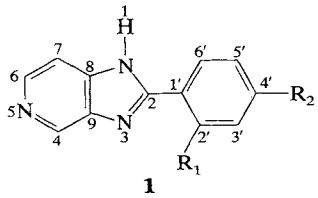
Compound	Solvent	C-2	C-4	C-5	C-6	C-7	C-8	C-9	Ref.
3	CD_3OD	152.84	115.23	123.19	123.19	115.23	139.70	139.70	3
3[a]	DMSO-d_6	152.12	116.07	123.48	123.48	116.07	139.85	139.85	3
4	D_2O	148.07	140.76	—	142.76	112.48	143.96	139.10	2
5	—	141.50	115.40	122.90	122.90	115.40	137.90	137.90	4

[a] Chemical shifts of the phenyl ring: C-1′ 130.67; C-2′,6′ 130.00; C-3′,5′ 127.71; C-4′ 131.10 ppm.

Table 3. ^{13}C NMR chemical shifts (ppm) of 2-arylimidazopyridines



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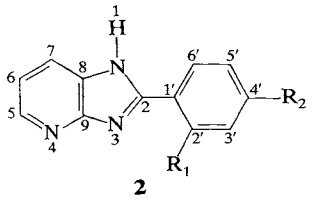

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Compound	Solvent	C-2	C-4	C-5	C-6	C-7	C-8	C-9	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′
1a	CD_3OD	157.16	139.16	—	141.77	110.68	145.03	139.87	131.10	130.29	128.45	132.29	128.45	130.29
1b	CD_3OD	159.87	137.98	—	141.07	110.68	144.59	138.69	114.15	157.59	118.59	133.76	120.65	128.29
1c	CD_3OD	158.35	137.39	—	141.29	110.35	145.51	139.39	117.78	129.96	115.61	153.21	115.61	129.96
1d	CD_3OD	157.92	137.06	—	141.40	110.03	144.38	138.14	103.20	161.60	102.12	154.45	108.40	129.21
2a	DMSO-d_6	152.66	—	143.72	117.99	[a]	[a]	[a]	129.53	126.66	128.94	130.45	128.94	126.66
2b	DMSO-d_6	153.15	—	144.32	118.53	123.25	[a]	[a]	112.14	158.19	117.23	132.35	119.24	126.66
2c	DMSO-d_6	154.07	—	142.37	117.18	122.16	[a]	[a]	116.42	128.07	113.50	151.15	113.50	128.07
2c	CD_3OD	156.89	—	144.05	119.02	123.19	132.89	153.86	118.26	129.64	115.15	152.83	115.15	129.64
2d	DMSO-d_6	154.67	—	142.91	117.72	[a]	132.94	[a]	100.28	160.14	99.95	153.04	106.40	127.58

[a] Weak signal.

Table 4. Difference in chemical shifts (ppm) between 2-phenylbenzimidazole (3) and 2-phenylimidazo-[4,5-*c*]- (1a) and -[4,5-*b*]-pyridines (2a)

Compound	C-2	C-4	C-5	C-6	C-7	C-8	C-9
3→1a	+4.32	+23.84	—	+18.58	−4.55	+5.33	+0.17
3→2a	+0.54	—	+20.24	−5.49	+8.00	−6.80	+14.10

The signals in the ^{13}C NMR spectra of the compounds were assigned by comparison of the data obtained and calculated according to an additivity scheme. Table 2 presents the literature data for the model compounds: unsubstituted imidazo[4,5-*c*]pyridine for the assignment of the signals in the hetero fragment of compounds **1a–d**, and 2-phenylbenzimidazole for compounds **2a–d**. The mutual influence of the azole hetero fragment and the aryl substituent was estimated according to the data for benzimidazole and 2-phenylbenzimidazole. Amino and oxy group contributions to the chemical shifts of the aryl fragment were taken from Ref. 4. Assigned in such a manner, the ^{13}C chemical shifts in the 2-arylimidazopyridines are presented in Table 3.

The change of chemical shifts in the transition from 2-phenylbenzimidazole (**3**) to the 2-arylimidazopyridines is consistent with the concept of the pyridine ring as a strong electron-withdrawing system. Thus, assuming a direct dependence between the ^{13}C chemical shift values and the electron density (i.e. displacement of the chemical shift downfield with decreasing electron density on the carbon atom), the change in the distribution of electron density in the compounds examined in comparison with benzimidazole could be estimated according to the data in Table 4.

Table 5. ^{13}C NMR chemical shifts (ppm) of cations of 2-arylimidazopyridines

Compound	C-2	C-4	C-5	C-6	C-7	C-8	C-9	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′
1a	161.38	133.59[a]	—	134.89	112.20	148.76	140.58	129.04[b]	130.51	129.04[b]	133.59[a]	129.04	130.51
1c	162.82	130.25	—	134.24	111.60	150.09	139.82	115.55	130.83	115.28	154.51	115.28	130.83
1d	[c]	130.72	—	134.30	111.44	149.30	138.04	101.36	161.87	101.09	156.24	108.84	129.91
2c	157.00	—	142.64	124.17	129.53	132.51	149.09	120.54	131.05	115.45	155.64	115.45	131.05

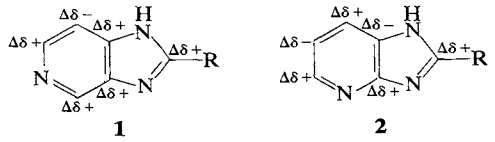
[a] Signals of C-4 and C-4′ are unresolved.
[b] Signals of C-1′ and C-3′ are unresolved.
[c] Weak signal.

Table 6. Changes of the chemical shifts (ppm) on protonation of imidazopyridines and benzimidazole

Compound	C-2	C-4	C-5	C-6	C-7	C-8	C-9	C-1′	C-2′	C-3′	C-4′	C-5′	C-6′
5[a]	−1.9	−1.0	+4.4	+4.4	−1.0	−8.1	−8.1						
4[b]	+4.24	−4.75	—	+5.73	+2.51	+2.78	−1.15						
1a	+4.22	−5.48	—	−6.88	+1.52	+3.73	+0.71	−2.06	+0.22	+0.59	+1.30	+0.59	+0.22
1c	+4.47	−7.14	—	−7.05	+1.25	+4.58	+0.43	−2.23	+0.87	−0.33	+1.30	−0.33	+0.87
1d		−6.34	—	−7.10	+1.41	+4.92	−0.10	−1.84	+0.27	−1.03	+1.79	+0.44	+0.70
2c	+0.11	—	−1.41	+5.15	+6.34	−0.38	−4.77	+2.28	+1.41	+0.30	+2.81	+0.30	+1.41

[a] Data from Ref. 2.
[b] Data from Ref. 4.

These changes, i.e. the polarization of the molecule on substitution of the phenylene ring by a pyridine ring, can be presented according to the following scheme:



1 **2**

It is particularly interesting that the transmission of the influence of the pyridine nitrogen to C-2 is clearly displayed in imidazo[4,5-*c*]pyridines, which is in good agreement with the data on the transmission of the substituent effect through position C-5(6) and C-2 in benzimidazoles.[3]

In order to determine the protonation centre, ^{13}C NMR spectra of the protonated forms of some 2-arylimidazo[4,5-*c*]- and 2-arylimidazo[4,5-*b*]-pyridines have been studied. The results of these measurements are given in Table 5. The criteria for the protonation centre determination were similarities in the chemical shift sign and value changes of the compounds examined and of their structural analogues. The changes of the chemical shifts in monoprotonated forms of 2-arylimidazopyridines relative to the neutral compound, and also those on protonation of benzimidazole (**5**) and unsubstituted imidazo[4,5-*c*]pyridine (**4**), are shown in Table 6.

During monoprotonation of **1a**, **c** and **d** the C-6 chemical shifts undergo the greatest changes. Considerable changes are also observed for other carbon atoms of the hetero fragment. They differ in sign and value from the $\Delta\delta$ values found on benzimidazole protonation, and are analogous to those for unsubstituted imidazo[4,5-*c*]pyridine, which was shown[2] to be protonated first on N-5. Thus, in 2-arylimidazo[4,5-*c*]pyridines, the nitrogen atom of the pyridine ring is the most basic.

The protonation of 2-(4-aminophenyl)imidazo[4,5-*b*]pyridine (**2c**) also differs from that of benzimidazole in the effect on the chemical shifts. A closer analogy in this case is the effect on the chemical shifts of pyridine (for the *o*-, *m*- and *p*-positions, the $\Delta\delta$ values in ppm are −8.0, +4.6 and +12.1,[4] respectively), which again testifies that the nitrogen atom of the pyridine ring (N-4) is the centre of protonation.

Judging by the data in Table 6, the nature of the changes in the electron properties of these molecules is different. Nevertheless, the cations of these compounds display the predominant transmission of substituent effects from position C-5(6) to C-2.[3]

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