PROTONATION OF PYRROLO[1,2-*a*]BENZIMIDAZOLE DERIVATIVES

L. M. Alekseeva, G. G. Dvoryantseva,
I. V. Persianova, Yu. N. Sheinker,
R. M. Palei, and P. M. Kochergin

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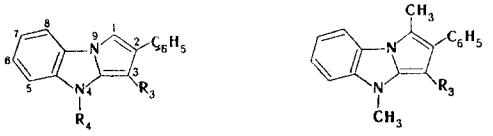
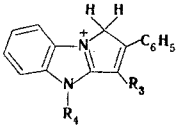
The protonation of a number of pyrrolo[1,2-*a*]benzimidazole derivatives in trifluoroacetic acid was studied by PMR spectroscopy. 1,3-Unsubstituted compounds are protonated exclusively at the C_1 atom. Under similar conditions, pyrrolobenzimidazoles that have a methyl group in the 1 position form a mixture of two protonated forms, which correspond to the addition of a proton to C_1 and C_3, respectively. The relative percentage of the C_3-protonated form decreases successively (from 81 to 18%) on passing from the 3-unsubstituted compound to the corresponding 3-phenyl and 3-methyl derivatives. The basicity constants of the pyrrolobenzimidazoles decrease symbatically with an increase in the relative percentage of this form. The relative proton-acceptor capacity of indolicine, pyrrolo[1,2-*a*]-imidazole, and pyrrolo[1,2-*a*]benzimidazole were examined on the basis of the protonation data and the reactivity indexes, calculated by the simple Hückel MO method.

In developing our investigation of the protonation of condensed heteroaromatic systems with a common nitrogen atom [1,2], it seemed of interest to study the structures of the cations of pyrrolo[1,2-*a*]-benzimidazole derivatives, data on which are extremely limited [3]. For this, we measured the PMR spectrum of neutral (in CCl_4) and protonated (in CF_3COOH) forms of pyrrolo[1,2-*a*]benzimidazole derivatives (I-VII) [4-6] and determined the basicity constants of 21 compounds of this series in nitromethane. The experimental results are presented in Tables 1 and 2.



I R_3=H, R_4=CH_3; II R_3=H, R_4=$CH_2C_6H_5$; III R_3=CH_3, R_4=CH_3; IV R_3=C_6H_5, R_4=$CH_2C_6H_5$;
V R_3=H; VI R_3=CH_3; VII R_3=C_6H_5

From an examination of the PMR spectra of 1-unsubstituted pyrrolobenzimidazole derivatives (I-IV) it follows that these compounds are protonated exclusively at C_1 in CF_3COOH to give monocations Ia-IVa:



Ia-IVa

The spectra of Ia-IVa (Fig. 1 and Table 1) contain a signal with an intensity of two proton units at 5.33-5.57 ppm, which should pertain to the protons of the CH_2 group in the 1 position. The signal of the methylidyne proton attached to C_3, which is observed in the spectra of bases I and II at 5.53-5.57 ppm (doublet, $J_{1,3}$ = 1.2 Hz) is shifted to weak field on protonation and appears in the spectra of cations Ia and

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TABLE 1. Chemical Shifts in the PMR Spectra of Pyrrolo[1,2-*a*]-benzimidazole Bases and Their Cations (δ, ppm)

Comp.	Bases ($CDCl_3$)			Cations (CF_3COOH)							
				α Form (Ia-VIIa)				β Form (Vb-VIIb)			
	1-H	3-H	4-R[a]	1-CH_2	3-CH	4-R[a]	%	1-CH	3-CH_2	4-R[a]	%
I	[b]	5,57	3,51	5,57	7,38	4,17	100	—	—	—	—
II	[b]	5,53	5,05	5,54	7,31	5,67	100	—	—	—	—
III	[b]	2,36[c]	3,69	5,33	2.66[c]	4,28	100	—	—	—	—
IV	[b]	[b]	5,04	5,38	[b]	5,69	100	—	—	—	—
V	2,69[c]	5,35	3,50	1,90[c] 5,93	7,31	4,15	19	2,87[c]	4,38	4,20	81
VI	2,57[c]	2,25[c]	3,70	1,72[c]	2,63[c]	4,25	82	2,84[c]	1,64[c] 4,68	4,25	18
VII	2,65[c]	[b]	3,46	1,89[c] 5,82	[b]	3,57	60	2,92[c]	5,68	3,90	40

[a]The chemical shifts of the CH_3 and CH_2 groups of the substituent attached to N_4 are presented. [b]The proton signals are situated at 6.5-7.0 ppm. [c]These are the chemical shifts of the CH_3 groups in the 1 and 3 positions.

TABLE 2. Basicity Constants in Nitromethane (ΔpK_a relative to diphenylguanidine) of Pyrrolo[1,2-*a*]benzimidazole Derivatives

Compound	R_1	R_2	R_3	R_4	ΔpK_a
I	H	C_6H_5	H	CH_3	1,80
II	H	C_6H_5	H	$CH_2C_6H_5$	1,88
III	H	C_6H_5	CH_3	CH_3	0,60
IV	H	C_6H_5	C_6H_5	$CH_2C_6H_5$	2,15
V	CH_3	C_6H_5	H	CH_3	4,50
VI	CH_3	C_6H_5	CH_3	CH_3	2,35
VII	CH_3	C_6H_5	C_6H_5	CH_3	3,45
VIII	H	*p*-$CH_3C_6H_4$	H	CH_3	1,30
IX	H	*p*-$CH_3OC_6H_4$	H	CH_3	1,33
X	H	*p*-BrC_6H_4	H	CH_3	2,60
XI	H	*m*-$NO_2C_6H_4$	H	CH_3	3,48
XII	H	*p*-$NO_2C_6H_4$	H	CH_3	3,80
XIII[a]	H	C_6H_5	H	CH_3	1,33
XIV[a]	H	*p*-BrC_6H_4	H	CH_3	1,85
XV	H	C_6H_5	H	C_2H_5	1,24
XVI	H	*p*-$NO_2C_6H_4$	H	C_2H_5	3,44
XVII	H	*p*-$CH_3OC_6H_4$	H	$CH_2C_6H_5$	1,50
XVIII	H	*p*-BrC_6H_4	CH_3	CH_3	2,30
XIX	H	C_6H_5	C_6H_5	CH_3	1,72
XX	H	*p*-BrC_6H_4	C_6H_5	CH_3	2,60
XXI	H	*p*-$NO_2C_6H_4$	C_6H_5	CH_3	3,75

[a]In XIII and XIV, $R_5 = R_6 = CH_3$, while $R_5 = R_6 = H$ in the other compounds.

IIa as a singlet* at 7.3-7.4 ppm. The signal of the protons of the CH_3 group attached to C_3 and of the protons of the substituent attached to N_4 (CH_3 and $CH_2C_6H_5$) are also shifted to weak field relative to the position of these signals in the spectra of the corresponding bases. The deshielding of the methyl and methylene protons attached to N_4 ($\Delta\delta$ = 0.6-0.7 ppm) is approximately double that of the CH_3 group attached to C_3 ($\Delta\delta$ = 0.30 ppm). This indicates considerable delocalization of the positive charge on the N_9 and N_4 atoms of cations Ia-IVa.

In CF_3COOH, 1-substituted pyrrolobenzimidazoles (V-VII) form a mixture of two forms of cations (Va-VIIa and Vb-VIIb), the structures of which correspond to the addition of a proton to the C_1 and C_3 atoms, respectively.

*The change in the spin–spin coupling constant ($J_{1,3}$) on passing from the bases to the cations is apparently associated with a change in the hybridization of the C_3 atom.

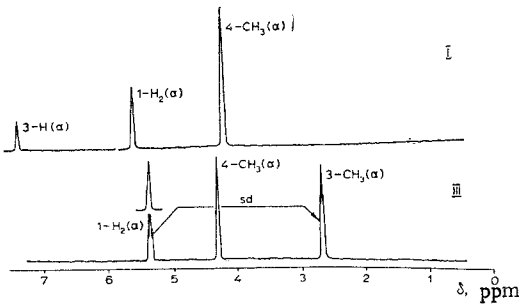


Fig. 1. PMR spectra of 2-phenyl-4-methylpyrrolo[1,2-*a*]benzimidazole (I) and 2-phenyl-3,4-dimethylpyrrolo[1,2-*a*]benzimidazole (III) in CF_3COOH.

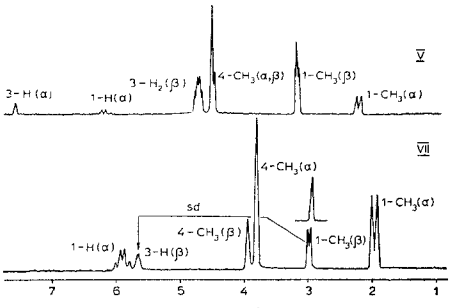
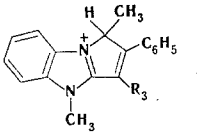
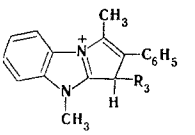


Fig. 2. PMR spectra of 1,4-dimethyl-2-phenylpyrrolo[1,2-*a*]benzimidazole (V) and 1,4-dimethyl-2,3-diphenylpyrrolo[1,2-*a*]-benzimidazole (VII) in CF_3COOH.



Va-VIIa



Vb-VIIb

The quartet of the proton (5.68-5.93 ppm) and the doublet of the methyl group (1.89-1.90 ppm) attached to C_1 (an A_3X system, J_{AX} = 7.5 Hz) correspond to structures Va-VIIa in the spectra of the cations of these compounds. The signal of the methylidyne proton (7.31 ppm) and of the CH_3 group (2.63 ppm) attached to C_3 appear in the spectra of Va and VIa, respectively.

Structure Vb is characterized by signals of the CH_2 group in the 3 position (4.38 ppm) and of the CH_3 group attached to C_1 (2.87 ppm). The signal of the methyl group attached to C_3 in the spectrum of cation VIb is a doublet with a spin–spin coupling constant of 7.5 Hz (1.64 ppm). Because of the low concentration of this form (18%), the quartet of the proton attached to C_3 cannot be observed. The signal at 5.68 ppm with an intensity of one proton unit was assigned to the proton attached to C_3 of the VIIb cation. The signal of the methyl group in the 1 position in the spectra of cations Vb-VIIb is shifted by 0.18-0.27 ppm to weak field relative to the spectra of the bases. The signals of the protons of the CH_3 group attached to N_4, which are affiliated with structures Va-VIIa and Vb-VIIb, are distinctly separated in the spectra of the cations of V-VII.

The presence of homoallyl spin–spin coupling constants is characteristic for the cations of pyrrolobenzimidazoles that contain a CH_3 group in the 3 (III) or 1 position (V-VII): $J_{1\text{-}H,3\text{-}CH_3}$ (IIIa) = $J_{1\text{-}CH_3,3\text{-}H}$ (Vb) = 1.5 Hz; $J_{1\text{-}CH_3,3\text{-}H}$ (VIb) = $J_{1\text{-}H,3\text{-}CH_3}$ (VIa) = $J_{1\text{-}CH_3,3\text{-}H}$ (VIIb) = 2.5 Hz. The spin–spin coupling of the indicated protons was proved by the double resonance method (Figs. 1 and 2).

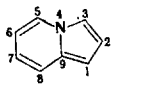
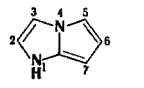
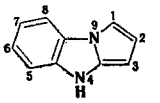
Thus, like the previously investigated pyrrolo[1,2-*a*]imidazole [2] and indolicine [7,8] derivatives, in acid media pyrrolo[1,2-*a*]benzimidazole derivatives display two proton centers capable of addition – the carbon atoms of the pyrrole portion of the molecule, which are in the α and β positions relative to the common nitrogen atom.* However, the basicity and relative proton-acceptor capacity of the α and β positions change substantially in the series of these systems. Thus in CF_3COOH, α,β-unsubstituted pyrroloimidazoles form a mixture of α- and β-protonated forms [2], while the corresponding derivatives of pyrrolobenzimidazole and indolicine under the same conditions are protonated only at the α-carbon atom of the pyrrole portion of the molecule.

The presence of a substituent in the α or β position of the molecule leads to a decrease in the proton-acceptor capacity of the carbon atom bonded to it. All of the investigated β-substituted compounds of the systems under consideration are protonated exclusively at the α-carbon atom. The introduction of a CH_3 group into the α position alters the direction of protonation of all three systems to favor predominantly the formation of the β-protonated form. In this case, the relative amount of this form present is 95, 81, and 52% in the α-methyl derivatives of pyrroloimidazole, pyrrolobenzimidazole, and indolicine,† respectively. Substantial differences are also observed in the protonation of α,β-disubstituted derivatives of these heterocycles. Thus α,β-dimethyl-substituted indolicines form exclusively the α form of the cation, while α,β-dimethyl-substituted pyrrolobenzimidazole (VI) forms a mixture of α and β forms, in which the

*For convenience, the 3 and 1 positions of indolicine, the 7 and 5 positions of pyrrolo[1,2-*a*]imidazole, and the 1 and 3 positions of pyrrolo[1,2-a]benzimidazole are designated as the α and β positions.

† We obtained the data presented above using 0.15 M solutions of 2-phenyl-3-methylindolicine in CF_3COOH.

TABLE 3. Reactivity Indexes (RI)* and Energy Indexes† of Indolicine, Pyrrolo[1,2-*a*]imidazole, and Pyrrolo[1,2-*a*]benzimidazole Bases and Cations

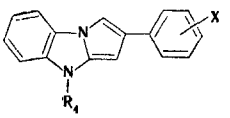
Compound	RI (base)					Energy indexes, β units						
						base			α cation		β cation	
	position	q_π	f_π	F_i	$L^+(\beta)$	E_{UOMO}	E_π	E_D	E_D	ΔE_D	E_D	ΔE_D
	3 (α) 1 (β)	1,170 1,192	0,267 0,253	0,515 0,477	1,82 1,88	0,333	13,298	3,130	2,760	−0,370	2,430	−0,700
	5 (α) 7 (β)	1,211 1,240	0,274 0,266	0,541 0,479	1,72 1,81	0,273	13,083	2,825	2,529	−0,296	2,321	−0,504
	1 (α) 3 (β)	1,180 1,224	0,268 0,226	0,526 0,469	1,77 1,85	0,298	18,950	4,700	4,420	−0,280	4,160	−0,540

*Symbols: q_π are the π-electron densities, f_π are the "boundary" electron densities, F_i are the free valence indexes, and L^+ are the electrophilic localization energies.

†Symbols: E_{UOMO} is the upper occupied MO energy, E_π is the π-electron energy, E_D is the delocalization energy, and $\Delta E_D = E_D^{base} - E_D^{cation}$.

amount of β cation present is 18%.* It is interesting to note that the proton-acceptor capacity of the β-carbon atom in α-methyl derivatives of pyrrolobenzimidazole (VI, VII) depends on the character of the substituent in the β position: the percentage of the β form doubles on passing from CH_3 to C_6H_5.

It follows from the data presented above that the proton-acceptor capacity of the β-carbon atom increases in the order indolicine < pyrrolobenzimidazole < pyrroloimidazole. The basicities of these systems increase in the same order. The pK_a values in nitromethane, measured relative to diphenylguanidine, are 1.2-3.8 for α,β-unsubstituted pyrrolobenzimidazoles (Table 2, I, II, VIII-XVII). The analogous values, found under the same conditions, in the series of α,β-unsubstituted pyrroloimidazoles [2] generally range from +1 to −1. The measured (in 80% ethanol) basicity constants of α,β-unsubstituted compounds – 2-phenyl-4-methylpyrrolo[1,2-*a*]benzimidazole (I) and 1-benzyl-6-(p-tolyl)pyrrolo[1,2-*a*]imidazole [2] – are 6.86 and 8.63, respectively. The basicity constants of α,β-unsubstituted indolicines [9] in 60% ethanol are 3.5-5.2. Consequently, the investigated heteroanalogs of indolicine are strong bases, and the basicities of α,β-unsubstituted pyrroloimidazoles are, on the average, two to three orders of magnitude greater than the basicities of the corresponding pyrrolobenzimidazoles and four to five orders of magnitude greater than the basicities of indolicine.



In the pyrrolobenzimidazoles I and VIII-XII, which differ only in the character of the substituent X in the phenyl ring attached to C_2, satisfactory correlation is observed between the pK_a values and the σ_{para} and σ_{meta} constants of McDaniel and Brown [10]. The dependence obtained is expressed by the equation

$$\Delta pK_a = 1.87 + 2.42\sigma$$

(correlation coefficient r = 0.99, mean-square deviation s = 0.09).

*The protonation of α,β-disubstituted pyrrolo[1,2-*a*]imidazoles was not investigated.

The basicity constants of 3-substituted pyrrolobenzimidazoles (III, IV, XVIII-XXI) lie approximately in the same interval of values (ΔpK_a = 0.60-3.75) as for the corresponding 1,3-unsubstituted compounds. The introduction of a substituent into the 1 position leads to a considerable decrease in basicity. The change in the ΔpK_a values in the series of 3-substituted compounds VI, VII, and V (2.35, 3.45, and 4.50) is symbatic with the increase in the relative percentage of the β-protonated form of the cation (18, 40, and 81%).

Several energy indexes and reactivity indexes (RI), which we calculated by the simple Hückel MO method for indolicine, pyrrolo[1,2-*a*]imidazole, and pyrrolo[1,2-*a*]benzimidazole, are presented in Table 3. The relative RI values correspond to the high reactivity of the α position of the pyrrole portion of these molecules. In addition, the differences in the RI for the α and β positions in all of the compounds proved to be relatively small. The maximum differences in these positons appear in the free valence indexes (F_i), and $F_\alpha > F_\beta$ for all of the compounds. It should be noted that the increase in the F_α values in the order indolicine < pyrrolobenzimidazole < pyrroloimidazole is symbatic with the increase in the basicities of these systems.

Calculation of the energy indexes demonstrated that the investigated systems are characterized by the presence of a relatively high-lying upper occupied level (E_{UOMO}), and this level increases in the same sequence as F_α. It follows from the calculation of the delocalization energies (E_D) that protonation at the carbon atom of the pyrrole ring adjacent to the common nitrogen atom is more favorable energetically in all of the compounds, but the difference in the ΔE_D values for the two protonated forms (α and β) decreases in the order indolicine > pyrrolobenzimidazole > pyrroloimidazole.

Thus the energy indexes and RI are in qualitative agreement with the change in the relative proton-acceptor capacity of the α- and β-carbon atoms of the pyrrole ring in the examined heteroaromatic systems.

EXPERIMENTAL

Compounds V-VII with mp 101-103, 114-115, and 137-138°, respectively, were obtained via a method similar to that used to prepare I-IV and VIII-XXI [4-6].

PMR Spectra. The PMR spectra of 0.15 M solutions of the investigated substances in CCl_4 (bases) and CF_3COOH (cations) were measured with a JNM-4H-100 spectrometer. The chemical shifts are presented on the δ scale with $(CH_3)_4Si$ as the internal standard.

Basicity Constants. The basicity constants in nitromethane were measured using ΔpK_a, which is equal to pK'_a of diphenylguanidine (DPG) minus pK'_a of the test substance as the relative measure of the basicity. The pK'_a values were determined graphically from the potentiometric titration curves of $2.5 \cdot 10^{-3}$ M solutions of the pyrrolobenzimidazoles with 0.125 N $HClO_4$ [11]. The instability of the pyrrolobenzimidazoles in nitromethane requires that the titration be carried out rapidly (3-5 min) and that the system be monitored for the absence of changes (the appearance of additional inflection points) on the titration curve.

All of the investigated compounds were synthesized immediately prior to measurement of the PMR spectra and basicity constants.

Calculation of the Structure and Energy Indexes. The structure and energy indexes of the indolicine, pyrroloimidazole, and pyrrolobenzimidazole bases and cations were calculated by the simple Hückel MO method with the parameters in [12]. The $\equiv C-X-Y$ hyperconjugation model ($h_C = -0.1$, $h_Y = -0.2$, $k_{CX} = 0.6$, and $k_{XY} = 2.0$) [13] was used for the methylene groups in the α- and β-protonated forms of the compounds. An auxiliary induction parameter ($h_C = 0.1h_X$ and $0.05h_X$) was introduced for all of the carbon atoms that form a bond with the heteroatom (C−X).

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