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

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

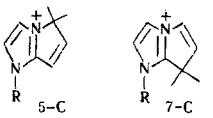
UDC 547.741'781:541.67

The protonation of a number of pyrrolo[1,2-*a*]imidazole derivatives in trifluoroacetic acid was studied by PMR spectroscopy. The 5,7-unsubstituted compounds form a mixture of two forms of cations, the structures of which correspond to the addition of a proton to the C_5 and C_7 atoms of the two-ring system with predominance (60-90%) of the 5-C cation. The introduction of a CH_3 group into the 5 position changes the direction of protonation to favor predominant (95%) formation of the 7-C cation. The 7-methyl derivatives of pyrroloimidazole are protonated exclusively at the C_5 atom. It is demonstrated that the basicity of the pyrroloimidazoles considerably surpasses the basicity of indolicine derivatives. The comparative proton-acceptor capacity of these systems is compared with the energy indexes and the reactivity indexes calculated by the simple MO LCAO method.

An investigation of electrophilic substitution reactions in the pyrrolo[1,2-*a*]imidazole series [1] has revealed a similarity in the reactivity of this two-ring system and the reactivity of the isoelectronic indolicine system. Electrophilic attack is directed primarily to the 5 position, and, if it is occupied, to the 7 position of the two-ring system. When the 5 and 7 positions are free, the formation of 5,7-disubstituted pyrroloimidazoles is observed.

In this connection, it seemed of interest to study the protonation of pyrroloimidazole derivatives as a typical electrophilic addition reaction. For this, we studied the PMR spectra of the bases (in CCl_4 and $CDCl_3$) and of the cations (in CF_3COOH) of a number of pyrroloimidazole derivatives [1-4] (I-XIV, Table 1). The experimental results obtained are presented in Table 2.

On the basis of data on the protonation of indolicine [5] and several of its heteroanalogs [6,7], it could be assumed that the structures of the cations of the investigated compounds should correspond to the addition of a proton to the C_5 or C_7 atoms of the pyrroloimidazole two-ring system to form 5-C or 7-C cations:*

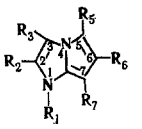


The centers of protonation of 5- and 7-methyl-substituted pyrroloimidazoles (XIII and XIV) are unambiguously determined from the character of the splitting of the signals of the protons of the pyrrole ring (Fig. 1). An examination of the spectrum of XIII in CF_3COOH indicates that this compound forms a mixture of two protonated forms corresponding to the structures of the 7-C (95%) and 5-C (5%) cations. The singlets at 4.24 ppm (2H) and 2.54 ppm (3H) observed in the spectrum of this compound were ascribed, respectively, to the methylene group attached to C_7 and to the methyl group attached to C_5 of the 7-C cation. The quartet of a proton (δ = 5.63 ppm) and a doublet of a CH_3 group (δ = 1.79 ppm) attached to the C_5 atom (A_3X system,

*The 5 and 7 positions of the pyrrolo[1,2-*a*]imidazole two-ring system correspond to the 3 and 1 positions of the indolicine molecule.

S. Ordzhonikidze All-Union Scientific-Research Institute of Pharmaceutical Chemistry, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 492-497, April, 1972. Original article submitted April 26, 1971.

TABLE 1*



Comp.	R_1	R_2	R_3	R_5	R_6	R_7
I	CH_3	H	H	H	p-ClC_6H_4	H
II	C_2H_5	H	H	H	p-$CH_3C_6H_4$	H
III	C_6H_5	H	H	H	C_6H_5	H
IV	C_6H_5	H	H	H	p-$CH_3C_6H_4$	H
V	$C_6H_5CH_2$	H	H	H	C_6H_5	H
VI	$C_6H_5CH_2$	H	H	H	p-$CH_3C_6H_4$	H
VII	$C_6H_5CH_2$	H	H	H	p-$CH_3OC_6H_4$	H
VIII	C_2H_5	Cl	H	H	p-$CH_3C_6H_4$	H
IX	C_2H_5	Cl	H	H	p-$CH_3OC_6H_4$	H
X	C_6H_5	C_6H_5	C_6H_5	H	CH_3	H
XI	C_6H_5	C_6H_5	C_6H_5	H	p-BrC_6H_4	H
XII	C_6H_5	C_6H_5	C_6H_5	H	p-$O_2NC_6H_4$	H
XIII	C_2H_5	Cl	H	CH_3	p-$C_6H_5C_6H_4$	H
XIV	C_3H_7	Cl	H	H	p-BrC_6H_4	CH_3

*Compounds IV, VI, VIII-X, and XII-XIV were previously described in [1-4]. Compounds I-III, V, VII, and XI (mp 158-160, 135-137, 120-122, 151-153, 91-92, and 103-104°, respectively) were synthesized for this investigation via the methods described in [1-4].

TABLE 2. Characteristics of the PMR Spectra and Basicities of the Investigated Compounds

Comp.	ΔpK_a	Chemical shifts, ppm												Percent of protonated forms	
		base[a]				5-C cation				7-C cation					
		5-H	7-H	R_1	R_6[b]	5-CH_2	7-CH	R_1	R_6[b]	7-CH_2	R_1	R_6[b]		5-C	7-C
I	−1,02	6,64	5,33	3,40	—	5,30	7,10	3,99		4,62	4,05			78	22
II	—	6,67	5,39	3,72 1,35	2,27	5,32	7,08	4,30 1,65	2,46	4,27	4,30 1,65	2,41		65	35
III	0,98	c	6,06	—	—	5,49	7,17	—	—	4,43	—	—		91	9
IV	0,86	c	6,09	—	2,30	5,46	7,09	—	2,46	4,43	—	2,43		87	13
V	—	6,79	5,41	4,86	—	5,30	6,66	5,39	—	3,89	5,46	—		90	10
VI	−0,99	6,77	5,39	4,86	2,30	5,27	6,61	5,38	2,43	3,82	5,44	2,39		68	32
VII	−1,28	6,90	5,28	4,96	3,80	5,27	6,55	5,37	3,99	3,82	5,44	3,99		85	15
VIII	0,22	c	5,52	3,91 1,39	2,34	5,35	6,98	4,32 1,64	2,47	4,35	4,32 1,64	2,42		d d	
IX	0,10	c	5,58	3,93 1,39	3,82	5,32	6,96	4,30 1,65	3,95	4,32	4,30 1,65	3,95			
X	−0,25	6,60	5,37	—	2,19	5,03	6,58	—	2,42	3,94	—	2,25		92	8
XI	—	c	5,91	—	—	5,59	c	—	—	4,47	—	—		78	22
XII	2,31	c	5,94	—	—	5,70	c	—	—	4,47	—	—		62	38
XIII	—	2,43[e]	5,38	3,94 1,40	—	5,63 1,79[e]	7,09	4,40 1,66	—	4,24	4,40 1,66	—		5	95
XIV	−0,12	6,52	2,26[e]	3,94 1,77 0,99	—	5,19	2,53[e]	4,43 2,05 1,17	—	—	—	—		100	0

[a]See [1,4] for the assignment of the signals of the protons attached to C_5 and C_7 of the pyrroloimidazole two-ring system.
[b]The chemical shifts of the protons of the methyl and methylene groups of the substituents in the 1 and 6 positions are presented.
[c]The signals of these protons are overlapped by the signals of the protons of the phenyl groups (7.0-7.5 ppm).
[d]The percentages of the forms were not determined because of overlapping of the proton signals.
[e]The chemical shifts of the protons of a CH_3 group attached to the C_5 and C_7 atoms.

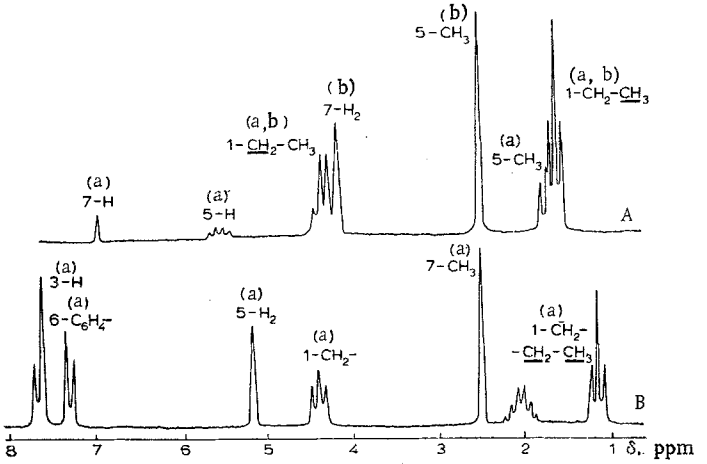


Fig. 1. PMR spectrum of XIII in CF_3COOH (A) and PMR spectrum of XIV in CF_3COOH (B): a) signals of the protons of the 5-C cation; b) signals of the protons of the 7-C cation.

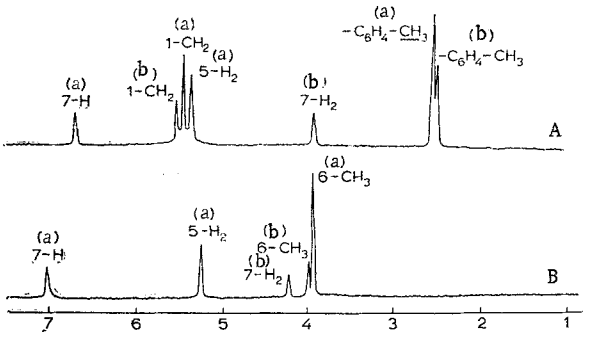


Fig. 2. PMR spectrum of VI in CF_3COOH (A) and PMR spectrum of X in CF_3COOH (B): a) signal of the protons of the 5-C cation; b) signals of the protons of the 7-C cation.

TABLE 3. Results of Quantum-Mechanical Calculations

Compound	Position	RI (bases) q_π	RI (bases) f_π	RI (bases) F	RI (bases) L+(β)	Energy indexes (in β units) E_{UOMO}	base E_π	base E_D	5-C (3-C) cation E_D	5-C (3-C) cation ΔE_D[a]	7-C (1-C) cation E_D	7-C (1-C) cation ΔE_D[a]
	1	1,192	0,253	0,477	1,88	0,338	13,298	3,130	2,760	−0,37	2,430	−0,70
	3	1,170	0,267	0,515	1,82							
	5	1,211	0,274	0,541	1,72	0,273	13,083	2,825	2,529	−0,29	2,321	−0,50
	7	1,240	0,266	0,480	1,81							
	5[b]	1,205	0,272	0,546		0,275	12,816	2,558	2,529	−0,03	2,321	−0,24
	7[b]	1,231	0,262	0,477								

[a] $\Delta E_D = E_D$ (cation) − E_D (base).
[b] $k_{N_4C} = 0.8$.

J_{AX} = 7.5 Hz), as well as the singlet of a methylidyne proton attached to C_7 (δ = 7.09 ppm), correspond to the 5-C cation. The presence of only two singlets of the protons of the methylene (5.19 ppm) and methyl (2.53 ppm) groups in the spectrum of the cation of XIV indicates that this compound is protonated exclusively at C_5.

It follows from a comparison of the spectra of XIII and XIV that the signals of the protons of the 7-CH_2 and 5-CH_2 groups in the corresponding cations (7-C and 5-C) have substantially different chemical shifts ($\Delta\delta_{5,7}$ = 1.0-1.4 ppm). A similar difference in the shielding of the methylene groups in the 1 and 3 positions was previously observed in indolicine cations [5]. We used this difference to establish the structures of the cations of 5,7-unsubstituted pyrroloimidazole derivatives (I-XII). A singlet (3.82-4.57 ppm), which is shifted to stronger field by 1.0-1.2 ppm, is observed along with the signal of the 5-CH_2 group (5.03-5.70 ppm) in the spectra of these compounds. This signal is assigned to the 7-CH_2 group in the 7-C cation. The signals of the CH_2 and CH_3 groups of the benzyl and tolyl substituents in the 1 and 6 positions of the two-ring system, in addition to the signals of the 5-CH_2 and 7-CH_2 groups, which are affiliated with the 5-C and 7-C cations, also differ distinctly in the spectra of III-VI (Fig. 2).

Thus, in contrast to 1,3-unsubstituted indolicines [5], which are protonated only at the C_3 atom, pyrroloimidazole derivatives under similar conditions form a mixture of two protonated forms – 5-C and 7-C. The ratio of these forms changes as a function of the donor-acceptor properties of the substituents in the imidazole portion of the molecule and in the 6 position of the two-ring system, but the percentage of the 5-C cation, as follows from the PMR spectra, is always predominant (60-90%). The presence of a CH_3 group in the 5 or 7 position of the pyrrole ring leads to a sharp decrease in the proton-acceptor capacity of the carbon atom bonded to it. As noted above, 7-methyl-substituted pyrroloimidazole (XIV) is protonated exclusively at C_5. In contrast, the introduction of a CH_3 group into the 5 position (XIII) changes the direction of protonation of the molecule to favor the predominant (95%) formation of the 7-C cation. It should be noted that the direction of protonation in 3-methyl derivatives of indolicine also changes, but the percentage of the 1-C cation does not exceed 70% [5]. It follows from these results that the difference in the proton-acceptor capacity of the C_5 and C_7 atoms of pyrroloimidazole decreases in comparison with the C_3 and C_1 atoms of indolicine.

The change in the pK_a values of the investigated compounds demonstrated that their basicities considerably (by two to five orders of magnitude) exceed the basicities of indolicine derivatives. Thus, in 80% ethanol the pK_a value of 1-benzyl-6-(p-tolyl)pyrroloimidazole (VI) is 8.63, while the pK_a of indolicine and the most basic 1,2-dimethylindolicine in 60% ethanol is 3.5 and 6.37, respectively [8]. In nitromethane, ΔpK_a for most of the investigated pyrroloimidazoles ranges from –1 to +1 (Table 2), which makes these compounds close in basicity to such strong bases as triethylamine [ΔpK_a = –1.15, pK_a (H_2O) = 11.01] and diphenylguanidine [ΔpK_a = 0, pK_a = 0, pK_a (H_2O) = 10.12].

The reactivity indexes (RI) and energy indexes of the isoelectronic indolicine and pyrroloimidazole systems, which we calculated by the simple MO LCAO method, are compared in Table 3. The relative values of the "boundary" π-electron densities (f_π) and the indexes of free valence (F) and energies of electrophilic localization (L^+) correspond to the greatest reactivity, with respect to electrophilic substitution reactions, in the 5 position of pyrroloimidazole and the 3 position of indolicine,* which is in agreement with the experimental data [1, 8]. The F values characterize the high activity of the investigated compounds in electrophilic additions to the C_5 and C_7 atoms of pyrroloimidazole and the C_3 and C_1 atoms of indolicine and are in agreement with the experimentally observed proton-acceptor capacity of these atoms in the indicated two-ring systems [$F_{5(3)} > F_{7(1)}$].

The reactivity indexes indicate a certain increase in the reactivity on passing from indolicine to pyrroloimidazole, but the differences in these indexes proved to be relatively small.

The considerably larger proton-acceptor capacity of pyrroloimidazole as compared with indolicine is apparently primarily due to energy factors. Calculation of the energy indexes demonstrated that both systems are characterized by the presence of a comparatively high-energy upper occupied level (E_{UOMO}), and the energy of the UOMO increases on passing from indolicine to pyrroloimidazole. It follows from a com-

*The results of our calculations, like the data in [5], indicate the absence of a correlation between the relative reactivity and the magnitudes of the π-electron densities (f_π) on the C_7 and C_5 atoms of pyrroloimidazole and the C_1 and C_3 atoms of indolicine.

parison of these values and the delocalization energies (E_D) that the aromatic π system of the pyrrolo-[1,2-*a*]imidazole base is less stable. At the same time, the difference in the E_D values of the corresponding protonated forms of these compounds decreases appreciably. It is essential to note that the transition from the aromatic structure of the base to the structures of the cations with sp^3-hybridized atoms in the 7 or 5 positions of pyrroloimidazole is associated with a lesser decrease in E_D than in the case of indolicine. Protonation at the carbon atom adjacent to the common nitrogen atom is energetically more favorable in both compounds, but the difference in E_D of the observed forms of cations decreases in pyrroloimidazole.

Our variation of the heteroparameters demonstrated that the energy indexes, primarily E_D, are especially sensitive to the values of the resonance integrals for the N_4C bond. Thus, from a comparison of the two computational variants (a and b) presented in Table 3, it is seen that a decrease in the k_{N_4C} bond integral of 0.1 has virtually no effect on the reactivity index but has a fully appreciable effect on the magnitude of E_D. The certain decrease in this integral in the pyrroloimidazole base as compared with indolicine (variant b) apparently is more in keeping with a difference in the geometry of these two-ring systems. The considerably smaller decrease in E_D on passing from the base to the pyrroloimidazole cations corresponds to this computational variant.

Thus the greater proton-acceptor capacity of pyrroloimidazole as compared with indolicine is apparently explained by the lower stability of the electron-superfluous π system of the base and the greater energetic favorability of transition of this system to the monocation form.

EXPERIMENTAL

The PMR spectra of 0.15 M solutions of the investigated compounds in CCl_4, $CDCl_3$, and CF_3COOH were recorded with a JNM-4H-100 spectrometer. The chemical shifts were measured on the δ scale with tetramethylsilane as the internal standard. The basicity constants of the investigated substances in nitromethane were measured. The relative measure of the basicity in nitromethane was the ΔpK_a value, which is equal to the pK_a' value of diphenylguanidine (DPG) minus the pK_a' value of the test substance [9]. The pK_a' values were determined by a graphical method as the pH at the point of semineutralization. The titration of $1 \cdot 10^{-3}$ M solutions of the substances was carried out automatically with a 0.125 N $HClO_4$ solution in nitromethane with glass and calomel electrodes with a Radiometer titrograph. The pK_a' value for DPG was determined daily at the beginning and end of each series of determinations. In contrast to the pK_a' value, the ΔpK_a value was constant within the limits of 0.05 pK_a units.

The structural and energy indexes of the bases and the indolicine and pyrroloimidazole cations were calculated by the simple MO LCAO method with the parameters in [10]. The $\equiv C-X-Y$ hyperconjugation model ($h_C = -0.1$, $h_Y = -0.2$, $k_{CX} = 0.6$, and $k_{XY} = 2.0$) [11] was used for the methylene groups in the 5-C (3-C) and 7-C (1-C) cations. An auxiliary induction parameter was introduced for all of the carbon atoms forming a carbon bond with the heteroatom (C–X): $h_C = 0.1h_X$ and $0.05h_X$.

LITERATURE CITED

1. A. A. Druzhinina, P. M. Kochergin, and L. M. Alekseeva, Khim. Geterotsikl. Soedin., 405 (1972).
2. A. A. Druzhinina and P. M. Kochergin, Khim. Geterotsikl. Soedin., 532 (1967).
3. A. A. Druzhinina, P. M. Kochergin, and N. P. Bychkova, Khim. Geterotsikl. Soedin., 856 (1969).
4. P. M. Kochergin, Yu. N. Sheinker, A. A. Druzhinina, R. M. Palei, and L. M. Alekseeva, Khim. Geterotsikl. Soedin., 826 (1971).
5. W. L. F. Armarego, J. Chem. Soc., B, 191 (1966).
6. M. Yu. Kornilov, G. G. Dyadyusha, and F. S. Babichev, Khim. Geterotsikl. Soedin., 905 (1968).
7. B. B. Molly, D. H. Reid, and S. McKenzie, J. Chem. Soc., 4368 (1965).
8. W. L. Mosby, Heterocyclic Systems with Bridgehead Nitrogen Atoms, New York–London (1961), pp. 1, 239.
9. C. A. Sreally, Analyt. Chem., 31, 1952 (1959).
10. B. Pullman and A. Pullman, Quantum Biochemistry, Wiley (1963).
11. G. Berthier and A. Pullman, Bull. Soc. Chim. France, Nos. 1-2, 88 (1950).