INVESTIGATION OF THE PROTONATION OF 5-AZAINDOLE DERIVATIVES BY PMR SPECTROSCOPY

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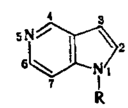
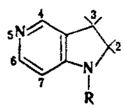
The protonation of some 5-azaindoles and 5-azaindolines by trifluoroacetic acid in media with different dielectric constants was studied by PMR spectroscopy. Protonation occurs at the nitrogen atom of the pyridine ring. The structures of the monocations of 5-azaindole, 5-azaindoline, and their 1-phenyl derivatives correspond to a considerable contribution of the quinoid structure with transfer of positive charge to the nitrogen atom of the pyrrole fragment of the molecule. On the basis of an investigation of the chemical shifts of the protons of 1-phenyl-5-azaindole and 1-phenyl-5-azaindoline on the trifluoroacetic acid concentration in methylene chloride, acetonitrile, and deuteroacetone, a protonation mechanism in which transfer of a proton from the donor to the acceptor in slightly polar media occurs through the formation of a hydrogen-bonded complex of the base with the acid is proposed.

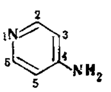
The peculiarities of the electrophilic substitution reactions of azaindoles and the effect of substituents in the α position relative to the nitrogen atom of the pyridine ring on the reactivity of the pyrrole portion of the molecule [1, 2] make it pssible to assume that protonation of the azaindole ring plays a considerable role in these processes. In addition to the position of the protonation center of the molecule, the distribution of positive charge in the ion has a substantial effect on the reactivity of the protonated form. In this connection, a study of the structure of the protonated forms of 5-azaindoles and their 2,3-dihydro derivatives, which are peculiar cyclic analogs of 4-aminopyridine, seemed of particular interest in the light of recent data on the quinoid structure of the monocation of 4-aminopyridine, which corresponds to transfer of positive charge from the cationoid center to the exocyclic amino group [3]. For this purpose, we investigated the PMR spectra of the neutral bases and monocations of 5-azaindole (I), 5-azaindoline (II), 1-phenyl-5-azaindole (III), 1-phenyl-5-azaindoline (IV), 1-acetyl-5-azaindoline (V), and 4-aminopyridine (VI).



I, III



II, IV, V



VI

I, II R=H; III, IV R=C_6H_5; V R=$COCH_3$

The experimental data are presented in Table 1.

An examination of the PMR spectra demonstrated that protonation of all of the investigated compounds (I-V) occurs at the nitrogen atom of the pyridine ring [$N_{(5)}$]. This follows unambiguously from the change in the multiplicity of the signals of the protons of the pyridine ring in the spectra of the ions relative to the spectra of the neutral molecules, a change caused by spin-spin coupling with the proton attached to $N_{(5)}$. Spin-spin coupling with $N_{(1)}-H$ is also observed in the spectrum of the monocation of 4-aminopyridine. A comparison of the spectra of I in CH_2Cl_2 and CF_3COOH shows that protonation of this molecule leads to a considerable (by 0.41-0.54 ppm) deshielding of the protons of the pyrrole ring. In addition to this, the changes

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TABLE 1. PMR Spectra

Compound	Medium	Chemical shifts, δ, ppm					J, Hz						
		2-H	3-H	4-H	6-H	7-H	23	37	45	47	56	57	67
I	CH_2Cl_2	7,39	6,67	8,97	8,28	7,42	3,3	1,0	—	0,9	—	—	5,8
	CF_3COOH	7,80	7,13	9,00	8,30	7,99	3,4	1,0	6,7	0,9	6,7	—	6,7
II	CH_2Cl_2	3,63	3,03	8,05	8,00	6,44	17,0*	—	—	0	—	—	5,2
	CF_3COOH	4,06	3,31	7,75	7,85	6,69	18,0	—	6,7	0	6,7	1,0	6,7
III	CH_2Cl_2	—	6,76	8,93	8,29	—	3,5	0,9	—	0,9	—	—	5,7
	CF_3COOH	—	7,29	9,10	8,35	—	3,5	0,9	6,6	0,9	6,6	—	6,6
IV	CH_2Cl_2	4,01	3,13	8,15	8,11	6,88	17,0	—	—	0	—	—	5,6
	CF_3COOH	4,44	3,44	7,86	7,92	6,82	18,0	—	6,7	0	6,7	1,0	6,7
V	CH_2Cl_2	4,07	3,20	8,34	8,31	7,93	17,5	—	—	0	—	—	5,4
	CF_3COOH	4,54	3,59	8,49	8,65	8,52	17,5	—	—	0	—	—	6,5
VI	CH_2Cl_2	—	—	—	8,18	6,46	—	—	—	—	—	—	4,5
	CF_3COOH	—	—	—	8,00	6,95	—	—	—	—	6,2	—	6,2

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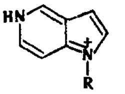
* $J_{23} = J_{cis} + J_{trans}$ (AA'XX' system).

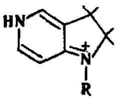
TABLE 2. Chemical Shifts of the Protons of the Pyridine Ring in 5-Azaindolines II and IV

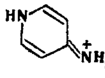
Position of the proton	Chemical shifts, Δσ, ppm			
	bases		cations	
	II	IV	II	IV
4	0,92	0,78	1,26	1,24
6	0,28	0,18	0,45	0,43
7	0,78		1,30	

in the chemical shifts of the protons in the α and β positions relative to the pyridine nitrogen atom (0.02-0.03 and 0.57 ppm, respectively) are considerably lower than those observed on protonation of pyridine under similar conditions (0.35 and 1.04 ppm) [4, 5]. The difference from pyridine is even more distinctly displayed in the case of 5-azaindolines II and IV, the protonation of which leads to a shift in the signals of the α protons (4-H and 6-H) to strong field by 0.15-0.30 ppm. Similar changes in the shielding of the ring protons are also observed on passing from neutral 4-aminopyridine to its monocation, to which quinoid structure VIa was previously [3] assigned on the basis of a detailed investigation of the IR and PMR spectra (of 1 N solutions in DCl and D_2O).

It is known that the appearance of a positive charge in the molecule leads to deshielding of the protons in, for example, the PMR spectra of anilinium salts [6]. Protonation of pyridine derivatives to form ions of the "pyridinium" type, regardless of the character of the substituent, always leads to a weak-field shift of the signals of the ring protons. The predominance of the quinoid structure in the ion induces a loss in the "aromaticity" and the associated decrease in the effect of the ring currents, which compensates for a large part of the deshielding. The similarity in the change in the spectra of 5-azaindolines (II, IV) and 4-aminopyridine attests to predominance of the quinoid structure in the cations of IIa and IVa. The contribution of this sort of structure in the cation decreases as the electron-acceptor properties of the substituent attached to the pyrrole ring nitrogen atom increase. Thus protonation of 1-acetyl-5-azaindoline (V) is accompanied by a weak-field shift in the signals of the protons of the pyridine ring, similar to that which was observed in the protonation of 4-nitraminopyridine [7].


Ia, IIIa


IIa, IVa


VIa

On the basis of data on the diamagnetic anisotropy in quinones [8], the decrease in the effect of the ring currents of the six-membered ring on passing to the quinoid structure of the cation can be estimated to be 0.3-0.4 ppm. The difference in the change in the chemical shifts of the protons of the six-membered ring on protonation of 5-azaindole (I) and its 1-phenyl derivative (III) as compared with pyridine is characterized by about the same value. These data provide a basis for assuming a considerable contribution of the quinoid structure also in the cations of 5-azaindoles (Ia, IIIa).

An estimate of the ring currents of the pyrrole fragment in the neutral and protonated forms of the molecules give useful information regarding the structure of the cations of 5-azaindoles. The chemical shifts of the protons of the pyridine ring in 5-azaindolines II and IV, which were found relative to the corresponding 5-azaindoles I and III, are presented in Table 2. The signals of the protons of the pyridine ring are shifted to strong field on passing from azaindoles to their 2,3-dihydro derivatives. From the data in Table 2, one should note the close (in magnitude) increase in the shielding of the protons in the 4 and 7 posi-

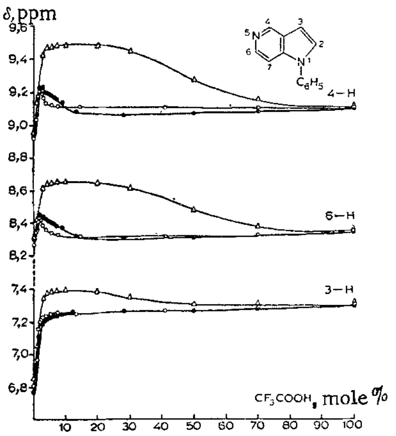


Fig. 1

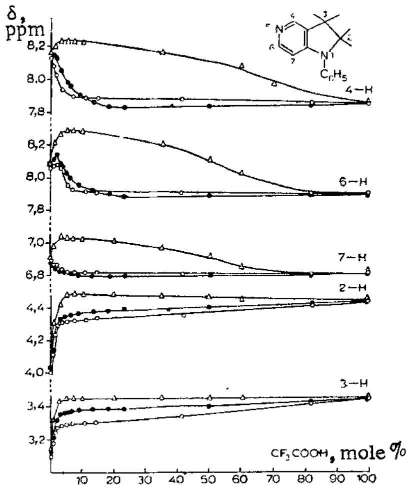


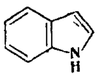
Fig. 2

Fig. 1. Dependence of the chemical shifts of the protons of 1-phenyl-5-azaindole (III) on the CF_3COOH concentration in CH_2Cl_2 (○), CH_3CN (●), and $(CD_3)_2CO$ (△).

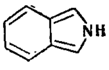
Fig. 2. Dependence of the chemical shifts of the protons of 1-phenyl-5-azaindoline (IV) on the CF_3COOH concentration in CH_2Cl_2 (○), CH_3CN (●), and $(CD_3)_2CO$ (△).

tions, which are about the same distance from the center of the pyrrole ring ($\Delta\sigma_4 \approx \Delta\sigma_7$), and the substantially smaller increase in the shielding of the further removed proton in the 6 position ($\Delta\sigma_{4(7)} \gg \Delta\sigma_6$). It follows from these results that the $\Delta\sigma$ values are due mainly to the change in the anisotropy of the five-membered ring in the azaindolines as compared with the azaindoles and characterize the effect of the ring currents of the pyrrole ring in the neutral and protonated forms of the 5-azaindoles. An approximate estimate shows that the overall contribution of the other effects [the change in the local shielding of the protons due to the transmitted (through the system of chemical bonds) electronic effects caused by hydrogenation of the double bond in the 2,3 position and the effect of the magnetic anisotropy of the pyrrolidine ring with allowance for deviation of the CH_2 group in the 2 position from the plane of the two-ring system in 5-azaindolines*] to the difference in the changes of the chemical shifts ($\Delta\sigma_{4(7)} - \Delta\sigma_6$) is ~ 0.1 ppm, i.e., substantially less than the experimentally observed differences ($\Delta\sigma_{4(7)} - \Delta\sigma_6 = 0.6{-}0.8$ ppm).

The following are observed on passing from neutral bases to the monocations of the investigated molecules: 1) an increase in the $\Delta\sigma$ values for all of the protons of the pyridine ring; 2) an increase in the difference in the change in the shielding for the protons in different positions relative to the center of the pyrrole ring ($\Delta\sigma_{4(7)} - \Delta\sigma_6$). These data attest to an increase in the ring currents in the pyrrole fragment on protonation of I and III molecules. It follows from a comparison of the effects of the ring currents in the



VII



VIII

aromatic indole system (VII) and the ortho quinoid system of isoindole (VIII), calculated within the same approximation [11], that the ring currents in the six-membered ring decrease, while those in the five-membered ring increase on passing from VII to VIII. In the light of these data, our experimental results are in more complete agreement with predominance of the quinoid structure in the cations of the investigated 5-azaindoles (Ia, IIIa).

In order to study the mechanism of protonation, we investigated the dependence of the chemical shifts of the protons of 1-phenyl-5-azaindole (III) and 1-phenyl-5-azaindoline (IV) on the trifluoroacetic acid concentration in three solvents — methylene chloride, acetonitrile, and deuteroacetone. The experimental curves are presented in Figs. 1 and 2. In the step involving protonation of the molecules (up to 10-15 mole %

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* For these estimates, we used data on the relative effect of vinyl and ethyl groups on the chemical shifts of the ring protons in substituted pyridines [9] and the magnetic anisotropies of the C—C and C—H bonds taken from [10].

CF_3COOH), the character of the curves depends relatively little on the medium for the protons of the pyrrole fragment but differs sharply for the protons of the pyridine ring. In methylene chloride and acetonitrile when the acid–base ratio is close to equimolar (2-3 mole % CF_3COOH), one observes the appearance of maxima or inflection points on the curves for the protons in the α position relative to the cationoid center (4-H, 6-H). When the acid concentration is increased from 10-15 to 100 mole %, the changes in the chemical shifts of all of the protons in these media are minimal and depend practically linearly on the trifluoroacetic acid concentration; this indicates complete conversion of the molecules to the monoprotonated form and the absence of considerable effects of solvation of the monocations by the solvent. Before the curves exit into the linear portions (at from 5-7 to 8-10 mole % CF_3COOH), the multiplicity of the signals of the protons of the pyridine ring changes due to spin–spin coupling with the proton attached to $N_{(5)}$. A further increase in the acid concentration does not affect the spin–spin coupling constant. The results make it possible to assume that protonation of the investigated compounds with trifluoroacetic acid in media with relatively low dielectric constants occurs through formation of a hydrogen-bonded complex, which can be observed near the equimolar ratio of acid and base in the absence of appreciable effects of solvation of the protonated form by the solvent.

$$B + HA \underset{A}{\rightleftarrows} B^{+}\ldots H\ldots A^{-} \underset{B}{\rightleftarrows} HB^{+} + A^{-}.$$

The formation of ion pairs during the interaction of bases with halogen-substituted carboxylic acids in slightly polar media was previously established from the IR spectra in the case of pyridine and aliphatic amines (for example, see [12-14]). The elucidation of the problem of whether the extremal points observed on the experimental curves (Figs. 1 and 2) correspond to the formation, in the investigated systems, of complexes of one type or to the presence of a molecular complex ⟷ ion pair equilibrium requires further study of the IR and PMR spectra of such systems.

The character of the dependences of the chemical shifts of the protons of the pyridine ring of II and IV on the trifluoroacetic acid concentration in deuteroacetone displays sharp differences. No maxima or inflection points are observed on the curves when the acid–base ratio is equimolar. An increase in the CF_3COOH concentration from zero to 5-7 mole % in this medium is accompanied by a smooth shift in all of the signals to weak field. The "plateau" on the curves corresponds to trifluoroacetic acid concentrations of 7-20 mole %. In this concentration interval, the signals of the protons in the 4 and 6 positions are shifted to weak field by 0.3-0.4 ppm relative to the position of the corresponding signals in the spectra of the monocations, measured in methylene chloride and acetonitrile at the same acid concentrations. A further increase in the acid concentration in deuteroacetone (above 30 mole %) leads to a shift in the signals of the protons of the pyridine ring to strong field. This sort of character of the curves attests to the pronounced effect of solvation of the monocations* in this solvent, which is apparently associated with the formation of complexes of the $B^{+}H\ldots O=C(CD_3)_2$ type, which is stable in the CF_3COOH concentration range that corresponds to the "plateau" on the curves. This process should lead to a rapid shift of equilibrium B to the right, and the intermediate acid–base complex cannot therefore be observed in this medium. The appearance of the spin–spin coupling constants of the protons of the pyridine ring with the proton attached to $N_{(5)}$ in the spectra of the monocations of the investigated compounds in deuteroacetone is observed only in the vicinity of an equimolecular ratio of acid and solvent (~ 50 mole % CF_3COOH); this is apparently due to the rapid dissociation of the $B^{+}H\ldots O=C(CD_3)_2$ complexes in excess trifluoroacetic acid.

EXPERIMENTAL

The investigated compounds were synthesized and characterized by previously described methods [15, 16]. The PMR spectra of 0.30 M solutions of the substances in methylene chloride, acetonitrile, deuteroacetone, trifluoroacetic acid, and mixtures of these solvents with trifluoroacetic acid were measured. The measurements were made with JNM 4H-100 and C-60HL spectrometers. The chemical shifts are presented on the δ scale relative to tetramethylsilane (internal standard). The complete reversibility of the dependences of the chemical shifts on the CF_3COOH concentration in the investigated media was verified by dilution (with the solvent) of solutions containing various CF_3COOH concentrations.

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* The close values of the chemical shifts of the protons of the bases in all three solvents indicate the absence of appreciable differences in the effects of solvation of the neutral form.

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