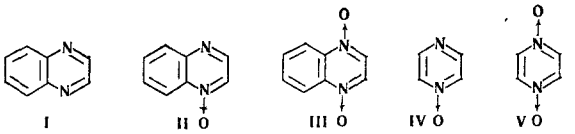
PMR SPECTRA OF PROTONATED PYRAZINE AND QUINOXALINE N-OXIDES

T. N. Ul'yanova, G. G. Dvoryantseva,
L. M. Alekseeva, Yu. N. Sheinker, and A. S. Elina

UDC 541.67+543.42+547.86

The dependence of the chemical shifts of the protons of quinoxaline and quinoxaline and pyrazine N-oxides and N,N-dioxides on the acid concentration was studied. The changes in the PMR spectra on passing from the neutral bases to the monocations were examined. The first protonation of pyrazine and quinoxaline N-oxides occurs at the N_4 nitrogen atom.

The investigation of the protonation of aromatic azines and their N-oxides, which contain several cationoid centers in their molecules, is of considerable interest. In this research we have studied the dependence of the chemical shifts on the acid concentration in the PMR spectra of quinoxaline (I), its N-oxide and N,N'-dioxide (II and III), pyrazine N-oxide (IV), and pyrazine N,N'-dioxide (V).

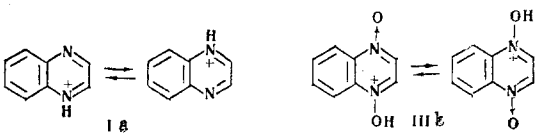


I II O III O IV O V O

An examination of the nature of the changes in the PMR spectra during primary protonation of I, III, and V was used to establish the structures of the monocations of II and IV.

The protonation of quinoxaline (I) was studied in solutions of trifluoroacetic acid in methylene chloride, while the protonation of pyrazine and quinoxaline N-oxides II-V was studied in aqueous (D_2O) solutions of deuterosulfuric acid.* The dependence of the chemical shifts of the protons of the investigated compounds on the acid concentration is presented in Figs. 1-3.

Retention of symmetry (singlet from the protons of the pyrazine ring and an AA'BB' system of protons of the benzene ring)† is characteristic for the PMR spectra of compounds with two equivalent cationoid centers (I, III, and V) over the entire range of acid concentrations. This attests to the presence of rapid proton exchange in the cations.



Ia OH IIIb

All of the signals are shifted to weak field with increasing acid concentration. The largest shifts of the signals in the spectrum of I (see Fig. 1) are observed when the trifluoroacetic acid concentration changes from 0 to 20%. Further increase in the percentage of acid in the mixture up to 100% trifluoroacetic acid leads to

* The use of one protonating medium (solvent and protonating agent) for all of the substances proved to be impossible because of their different solubilities, basicities, and stabilities in these media.
† The PMR spectra of bases I-V and monocation Ib are described in [1-3].

S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical Chemistry Institute, Moscow. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 846-852, June, 1971. Original article submitted December 13, 1970.

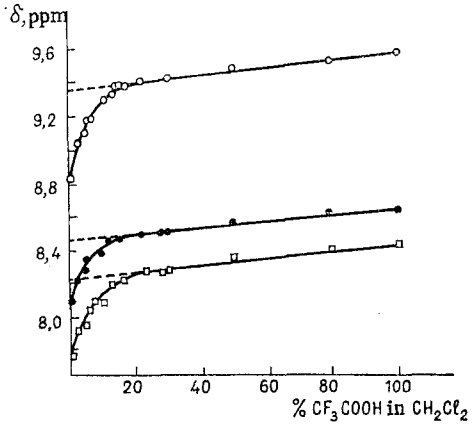


Fig. 1. Dependence of the chemical shifts of the protons of quinoxaline (I) on the trifluoroacetic acid: ○ indicates 2-H, 3-H; ● indicates 5-H, 8-H; □ indicates 6-H, 7-H.

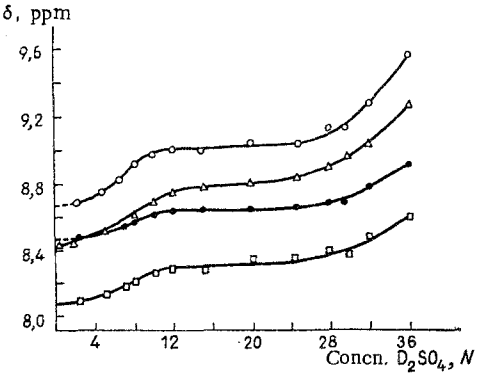


Fig. 2. Dependence of the chemical shifts of the protons of quinoxaline N,N-dioxide (III) and pyrazine N,N'-dioxide (V) on the deuterosulfuric acid concentration: ○ indicates 2-H, 3-H (III); ● indicates 5-H, 8-H (III); □ indicates 6-H, 7-H (III); Δ indicates 2-H, 3-H, 5-H, 6-H (V).

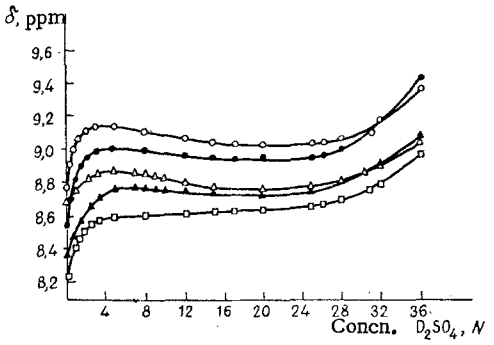


Fig. 3. Dependence of the chemical shifts of the protons of pyrazine N-oxide (IV) and quinoxaline N-oxide (II) on the deuterosulfuric acid concentration: ● indicates 2-H (II); ○ indicates 3-H (II); □ indicates 8-H (II); ▲ indicates 2-H, 6-H (IV); Δ indicates 3-H, 5-H (IV).

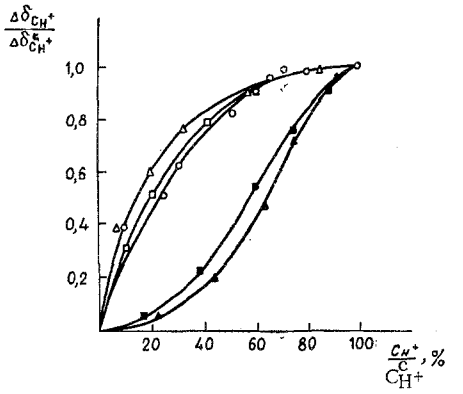


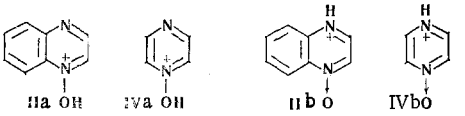
Fig. 4. Dependence of $\frac{\Delta\delta_{C_{H^+}}}{\Delta\delta^{C}_{H^+}}$ on $\frac{C_{H^+}}{C^{C}_{H^+}}$ for the 2-H proton in I-V (primary protonation curves): ○ indicates I; Δ indicates II; ▲ indicates III; □ indicates IV; ■ indicates V.

relatively small changes in the chemical shifts; in this range all of the dependences obtained are close to linear. These results indicate that quinoxaline forms a monocation in trifluoroacetic acid while, in a mixture containing 20% trifluoroacetic acid and 80% methylene chloride, the minimum concentration of acid (we will designate it by $C^{C}_{H^+}$) at which the compound is practically completely converted to the protonated form is reached.

There are two inflection points on the graphs of the dependence of the chemical shifts of the protons of quinoxaline N,N'-dioxide (III) and pyrazine N,N'-dioxide (V) (Fig. 2) on the acid concentration. The first points, which correspond to complete conversion of these compounds to monocations IIIa and Va, are observed at D_2SO_4 concentrations of 11.0 N ($C^{C}_{H^+}$ for III) and 13.6 N ($C^{C}_{H^+}$ for V). In the interval from 11-14 to 25-27 N D_2SO_4 both compounds exist as monocations, and relatively small changes are observed in the chemical shifts, which depend approximately linearly on the acid concentration. Above 25-27 N D_2SO_4, there is again a sharp increase in the chemical shifts that is associated with secondary protonation of the III and V molecules. The relative $C^{C}_{H^+}$ values are in agreement with the higher basicity of quinoxaline N,N-dioxide

as compared with pyrazine N,N'-dioxide. The similarity in the character of the dependence of the chemical shifts of the protons on the acid concentration during primary and secondary protonation is due to the presence of two equivalent cationoid centers in the III and V molecules.

Changes of different magnitude in the chemical shifts of the protons in different positions of the pyrazine ring are observed in the spectra of quinoxaline N-oxide (II) and pyrazine N-oxide (IV) as the acid concentration increases.* The protonation of these compounds leads to a greater shift to weak field of the 2-H signal as compared with the 3-H signal. The difference in the chemical shifts of these protons ($\Delta\delta_{2,3}$) decreases in the cations as compared with the neutral bases and changes sign on passing to the dications. Two inflections corresponding to complete conversion of the molecules to the monoprotonated form and the inception of secondary protonation are also distinctly isolated on the graphs of the dependence of the chemical shifts on the acid concentration for II and IV (Fig. 3). Primary protonation of quinoxaline and pyrazine N-oxides, in accordance with the high basicity of these compounds, is complete at considerably lower concentrations of acid (3-5 N D_2SO_4) than in the case of N,N-dioxides III and V. The character of the changes in the chemical shifts during the formation of mono- and dications of II and IV differs; this is apparently associated with the presence in them of two nonequivalent cationoid centers – the oxygen atom of the N → O group and the N_4 atom. Depending on which of these centers in quinoxaline and pyrazine N-oxides undergoes primary protonation, the IIa, IVa or IIb, IVb structures should be ascribed to the corresponding monocations:



In this connection, a comparison of the experimental curves obtained for I-V in the intervals of acid concentrations corresponding to the formation of monocations is of interest.

The changes in the chemical shifts during primary protonation are determined principally by a change in the position of the equilibrium between the neutral and monoprotonated forms of the molecule as a function of the acid concentration.† Consequently, the form of the $\Delta\delta_{C_{H^+}} = f(C_{H^+})$ function in the interval $0 \leq C_{H^+} \leq C^c_{H^+}$ should depend on the nature of the cationoid center. This is confirmed by a comparison of the experimental curves obtained for quinoxaline (I) and its N,N'-dioxide (III). For a comparison of this sort, it is convenient to express the changes in the acid concentration during primary protonation of the compounds studied in percent of the corresponding C_{H^+} values. If the change in the chemical shift of the proton under consideration which corresponds to complete conversion of the neutral base to the monocation is designated by $\Delta\delta_{C^c_{H^+}}$,‡ the ratio $\Delta\delta_{C_{H^+}}/\Delta\delta_{C^c_{H^+}}$ for each $0 \leq C_{H^+} \leq C^c_{H^+}$ value determines the mole fraction of protonated form, the value of which, in this case, is independent of the selection of the protonating agent. It follows from Fig. 4 that a rapid increase in the monocation concentration at low acid concentrations is characteristic for quinoxaline, which is protonated at the nitrogen atom. Thus, when $C_{H^+} = 0.5C^c_{H^+}$, the equilibrium is shifted to favor the formation of monocation Ib by ~80%. In III and V, the protonation of which occurs at the oxygen atom of the N → O group, the dependence of $\Delta\delta_{C_{H^+}}/\Delta\delta_{C^c_{H^+}}$ on $C_{H^+}/C^c_{H^+}$ corresponds, on the other hand, to a slow increase in the fraction of the monoprotonated form of the molecules in the same interval of acid concentrations ($0 \leq C_{H^+} \leq 0.5C^c_{H^+}$). When $C_{H^+} = 0.5C^c_{H^+}$, no more than 40% of these molecules are converted to the corresponding monocations IIIa and Va.

A similar dependence found for quinoxaline and pyrazine N-oxides proved to be similar to that observed for quinoxaline and corresponds to protonation of these compounds at the N_4 nitrogen atom with the formation of monocations IIb and IVb.

*The signals of the protons in the 2, 3, and 8 positions in the spectrum of II are easily isolated; in the spectrum of IV, this is true for the protons in the 2, 6, 3, and 5 positions.

† An examination of the linear portions of the graphs makes it possible to assume that the contributions of the effects of the medium at low acid concentrations that correspond to primary protonation are relatively small.

‡ The $\delta C^c_{H^+}$ value is determined at the inflection point (or maximum) of the investigated curve.

TABLE 1. Chemical Shifts of the Protons in the PMR Spectra of the Bases (B) and Cations (C) of Some Mono- and Diazines and Their N-Oxides

Compound	Form	Medium	Position	Chemical shifts, ppm	
				δ	Δδ*
Pyridine [4]	B	D_2O	2, 6	8,58	
			3, 5	7,47	
			4	7,88	
	C	18 *N* D_2SO_4	2, 6	8,84	0,26
			3, 5	8,19	0,72
			4	8,73	0,85
Pyridine N-oxide [4]	B	D_2O	2, 6	8,42	
			3, 4, 5	7,7	
	C	18 *N* D_2SO_4	2, 6	8,81	0,39
			3, 5	8,10	0,4
			4	8,49	0,8
Pyrazine [5]	B	D_2O	2, 3, 5, 6	8,58	
	C†	64,4% H_2SO_4	2, 3, 5, 6	9,01	0,43
Pyrazine N-oxide	B	D_2O	2, 6	8,38	
			3, 5	8,69	
	C	20 *N* D_2SO_4	2, 6	8,77	0,39
			3, 5	8,79	0,10
1,4-Pyrazine N,N'-dioxide	B	D_2O	2, 3, 5, 6	8,44	
		20 *N* D_2SO_4	2, 3, 5, 6	8,79	0,35
Quinoline [6,7]	B	CCl_4	2	8,81	
			3	7,27	
			4	8,00	
			5	7,69	
			6	7,44	
			7	7,62	
			8	8,06	
	C	CF_3COOH	2	9,11	0,30
			3	8,19	0,92
			4	9,29	1,29
			5, 6, 7	8,05—8,40	
Quinoxaline	B	CH_2Cl_2	2, 3	8,82	
			5, 8	8,10	
			6, 7	7,76	
	C‡	CH_2Cl_2/CF_3COOH	2, 3	9,36	0,54
			5, 8	8,46	0,36
			6, 7	8,23	0,47
Quinoxaline N-oxide	B	D_2O	2	8,55	
			3	8,74	
			5, 6, 7	7.7—7,9	
			8	8,23	
	C	20 *N* D_2SO_4	2	8,95	0,40
			3	9,02	0,28
			5, 6, 7	8,1—8,3	
			8	8,64	0,41
1,4-Quinoxaline-N,N'-dioxide	B‡	D_2O	2, 3	8,68	
			5, 8	8,45	
			6, 7	8,07	
	C	20 *N* D_2SO_4	2, 3	9,03	0,35
			5, 8	8,65	0,20
			6, 7	8,30	0,23

*The difference in the chemical shifts of the protons in the cation and base ($\Delta\delta_i = \delta_i^C - \delta_i^H$).

†Chemical shifts corrected for the effects of the medium.

‡Chemical shifts found by extrapolation to zero acid concentration.

The addition of a second proton to IIb and IVb, just like the addition to IIIa and Va, should proceed at the oxygen atom of the N → O group. In accordance with this, a similarity is observed in the character of the dependence of the chemical shifts on the acid concentration during secondary protonation of these compounds (from comparison of the graphs in Figs. 2 and 3 in the interval from 25 to 36 N D_2SO_4).

A further confirmation of the structures of monocations IIb and IVb follows from an examination of the changes in the chemical shifts of the protons ($\Delta\delta_i$) in the investigated compounds on passing from the neutral bases to the monocations. In Table 1 these values are compared with the chemical shifts of the protons of the bases and cations of pyridine [4], pyrazine [5], quinoline [6, 7], and pyridine N-oxide [4]. The chemical shifts of the protons of the quinoxaline monocation are determined by extrapolation of the linear portions of the graphs (Fig. 1) to zero acid concentration, which makes it possible to exclude the contributions of the effects of the medium (the effect of the volume magnetic susceptibility and polarization of the

solvent) to the $\Delta\delta_i$ values. Because of the more complex character of the dependences of the chemical shifts on the acid concentration for quinoxaline and pyrazine N-oxides, this sort of extrapolation cannot be carried out. The δ_i and $\Delta\delta_i$ values presented in Table 1 for II-V were measured in 0.20 M solutions of the compounds in D_2O and 20 N D_2SO_4 and include the effects of the medium. It can be assumed, however, that the effects of the medium can be disregarded when comparing the $\Delta\delta_i$ values for the investigated N-oxides with the analogous values for pyridine and pyridine N-oxide measured under similar conditions (0.17 M solutions of the compounds in D_2O and 18 N D_2SO_4) [4].

Protonation of pyridine and quinoline leads to deshielding of the protons of the pyridine ring in the order $\Delta\delta_2 < \Delta\delta_3 < \Delta\delta_4$. The relatively small changes in the chemical shifts of the protons in the α position relative to the cationoid center in the azines are usually explained by the magnetic anisotropy of the nitrogen atom [8, 9]. As a result of the proton exchange observed in the pyrazine and quinoxaline monocations, the α and β positions relative to the cationoid center in these compounds become indistinguishable. However, the changes in the chemical shifts of the 2-H and 3-H protons ($\Delta\delta_2 = \Delta\delta_3$) on protonation of these compounds (0.43 and 0.54 ppm) are close to the average values between the $\Delta\delta_2$ and $\Delta\delta_3$ values in pyridine (0.49 ppm) and quinoline (0.61 ppm), respectively. Consequently, the addition of a proton to the nitrogen atom of the "pyridine" type in azines leads to greater deshielding of the β protons of the heteroaromatic ring than is observed for the α protons.

The protonation of pyridine N-oxide, in contrast to pyridine, induces about the same changes in the chemical shifts of the protons in the α and β positions relative to the cationoid center ($\Delta\delta_2 \approx \Delta\delta_3 \approx 0.4$ ppm). In accordance with this, the chemical shifts of the protons of the pyrazine ring change by about the same amount (0.35 ppm) on passing from the neutral pyrazine and quinoxaline N,N'-dioxides to their monocations.

On the basis of these results it can be assumed that the protonation of pyrazine and quinoxaline N-oxides at the oxygen atom of the N → O group to form cations IIa and IVa should have been accompanied by about the same shift to weak field of the 2-H and 3-H signals, so that the difference in the chemical shifts of these protons should not have changed substantially. On the other hand, the addition of a proton to N_4 should lead to a considerably greater shift of the 2-H signal (the β position relative to the N_4 cationoid center) as compared with 3-H and to a decrease in the difference of the δ_2 and δ_3 values for cations IIb and IVb as compared with the neutral bases; this is actually observed. Furthermore, it should be noted that on passing from IIb to IIIa, just as on passing from IVb to Va, the position of the 3-H signal (the α proton relative to the N_4 cationoid center) is practically unchanged; this is in good agreement with the close values of the chemical shifts of the α protons (2-H) in pyridine and pyridine N-oxide cations.

The conclusions regarding the structure of the pyrazine N-oxide cation (IVb) that flow out of an examination of the PMR spectra are in complete agreement with the results of an investigation of the UV spectra of neutral and protonated pyrazine N-oxides [10].

EXPERIMENTAL

The PMR spectra of the compounds were measured with a JNM-4H-100 spectrometer. The measurements were made from 0.20 M solutions of the compounds in methylene chloride–trifluoroacetic acid mixtures (for quinoxaline) and D_2O–D_2SO_4 mixtures (for pyrazine and quinoxaline N-oxides and N,N'-dioxides). The CF_3COOH concentration in the solvent was expressed in volume percent, while the D_2SO_4 concentration was expressed in terms of normality.

The chemical shifts were measured in the δ scale. Tetramethylsilane was used as the internal standard for the solutions in CH_2Cl_2–CF_3COOH, while sodium 4,4-dimethyl-4-silapentane-1-sulfonate, the signals of which are taken as zero in the δ scale, was the internal standard for solutions in D_2O–D_2SO_4.

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