ELECTRONIC SPECTRA AND STRUCTURES OF PROTONATED PYRAZINE AND QUINOXALINE N-OXIDES

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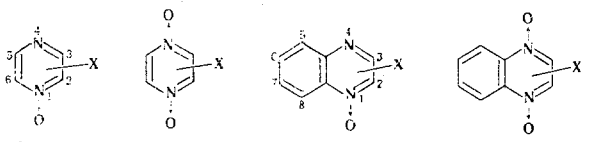
The electronic spectra of neutral molecules and monocations of N-oxides of 2- and 3-substituted pyrazines and quinoxalines were measured, and their ionization constants in water were determined. The position of the protonation center in the investigated compounds was established.

The protonation of pyrazine and quinoxaline N-oxides were previously investigated by PMR spectroscopy [1]. It was shown that the protonation of unsubstituted pyrazine and quinoxaline 1-N-oxides occurs initially at the unoxidized ring-nitrogen atom (N_4). However, when the spectra of protonated N-oxides in aqueous acid solutions are measured, the N–H signal and the constants for spin–spin coupling with this proton cannot, as a rule, be fixed because of rapid proton exchange. Most derivatives of diazine N-oxides are only slightly soluble in solvents suitable for PMR spectroscopy. In this connection, it seemed of interest to determine the ionization constants and examine the electronic spectra of protonated diazine N-oxides.

We measured the electronic spectra and ionization constants in water of a number of pyrazine (I-IX) and quinoxaline (X-XIX) monoxides and N,N'-dioxides.



I-VII VIII, IX X-XVII XVIII, XIX

I, VIII, X, XVIII X=H; II, IX, XI, XIX X=2-NH_2; III, XII X=2-OCH_3; IV X=2-$NHCOCH_3$; V, XIII X=2-Cl; VI, XV X=3-NH_2; VII X=3-$COOCH_3$; XIV X=2-$COOCH_3$; XVI X=3-OCH_3; XVII X=3-$COOC_2H_5$

It follows from an analysis of the spectra of the neutral molecules and cations of pyridine [2] and its N-oxide [3] that protonation of these systems has an opposite effect on the position and intensity of the transitions observed above 210 nm. The addition of a proton to the pyridine nitrogen atom leads to a decrease in the energies and an increase in the force of the oscillators of both long-wave transitions, whereas protonation at the oxygen atom of the N → O group causes an increase in the energies of the transitions and a decrease in the intensity of the $^1A_1 \rightarrow {}^1A_1$ transition. The changes in the spectra of N-oxides of monosubstituted pyridines on passing from neutral molecules to the monocations depend to a considerable degree on the type of substituent and its position relative to the N → O group [4]. However, the hypsochromic shift and the decrease in the intensity of the long-wave band in the spectra of a number of 2- and 4-substituted derivatives are sufficiently characteristic indications of protonation at the oxygen atom of the N → O groups. The spectra of the cations of pyridine derivatives are similar to the spectra of cations of the corresponding N-oxides. On the basis of these data and a preliminary study of the spectra of pyrazine and aminopyrazine N-oxides [5], one can isolate two principal experimental criteria that make it possible

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TABLE 1. UV Spectra of Neutral Molecules and Monocations and Ionization Constants in Water of Pyrazine N-Oxides

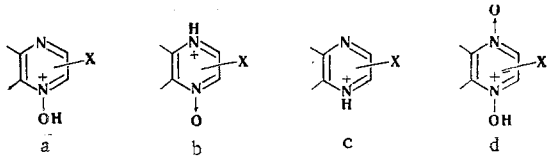
Compound	Medium	λ_{max}, nm (lg ε)	pK_a
I	0,001 *N* H_2SO_4	263 (4,09) 214 (4,11)	−0,15
	12,7 *N* H_2SO_4	286 (4,11) 229 (4,02)	
II	pH=4,0	334 (3,80) 248 (3,74) 229 (4,39)	0,79
	7,1 *N* H_2SO_4	364 (3,86) 285 (3,61) 248 (4,32)	
III	0,001 *N* H_2SO_4	308 (3,85) 260 (3,89) 220 (4,23)	−0,51
	11,4 *N* H_2SO_4	324 (3,98) 284 (3,86) 236 (4,11)	
IV	0,001 *N* H_2SO_4	314 (3,82) 268 (3,95) 238 (4,39)	
	8,58 *N* H_2SO_4	333 (3,94) 287 (3,85) 253 (4,36)	
V	0,1 *N* H_2SO_4	297 (3,44) 264 (4,00) 222 (4,22)	−1,31
	15,3 *N* H_2SO_4	303 (3,83) 286 (3,97) 239 (4,13)	
VI	pH=6,0	336 (3,67) 262 (3,92) 235 (4,29)	1,47
	2,36 *N* H_2SO_4	342 (3,73) 279 (3,95) 227 (4,32)	
VII	1,08 *N* H_2SO_4	300 (3,30) 270 (3,98) 228 (4,24)	−2,45
	15,3 *N* H_2SO_4	320 (3,51) 291 (3,92) 241 (4,03)	
VIII	0,01 *N* H_2SO_4	308 (4,35) 222 (4,24)	
	20,0 *N* H_2SO_4	294 (4,18) 225 (4,07)	
IX	0,001 *N* H_2SO_4	364 (3,89) 295 (4,15) 261 (4,03) 235 (4,29)	−0,18
	14,1 *N* H_2SO_4	343 (3,71) 282 (3,95) 230 (4,32)	

TABLE 2. ^1L_W Band in the Spectra of Neutral Molecules and Cations and Ionization Constants of Quinoxaline N-Oxides in Water

Compound	λ_{max}, nm (lg ε)		pK_a
	base	cation	
X	339 (3,88)	342 (4,06)	0,25
XI	368 (3,81)	349 (3,90)	1,09
XII	352 (3,80)	377 (3,85)	−0,60
XIII	343 (3,82)	348 (3,99)	−1,21
XIV	342 (3,76)	351 (3,88)	−0,63
XV	379 (3,73)	370 (3,76)	2,68
XVI	—*	—*	−1,54
XVII	343 (3,95)	352 (3,99)	−2,19
XVIII	372 (4,23)	346 (4,08)	
XIX	404 (3,79)	370 (3,72)	1,06

* The identification of the ^1L_W transition in the spectrum of XVI is difficult because of overlapping of the bands.

to establish the center of protonation of pyrazine and quinoxaline N-monoxides: 1) the change in the position and intensity of the long-wave (^1L_W) band when these compounds are converted from the neutral to the monoprotonated form; 2) comparison of the spectra of the monocations of the 1-N-oxides with the spectra of the monocations of the corresponding pyrazine and quinoxaline derivatices and their 1,4-N,N-dioxides. If the investigated compound is protonated at the oxygen atom of the N → O group (structure a), the spectrum of its monocation should be similar to the spectrum of the monocation of the corresponding diazine (c).



a b c d

The similarity in the spectra of the monocations of the 1-N-oxides and the corresponding 1,4-N,N-dioxides (d) should correspond to the addition of a proton to the nitrogen atom of the heteroring (b).

Protonation of pyrazine (VIII) and 2-aminopyrazine (IX) 1,4-N,N-dioxides (Table 1) is accompanied by a distinct hypsochromic shift ($\Delta\lambda$ = −14 and −21 nm) and a decrease in the intensity of the long-wave band. The number of transitions observed in the investigated region of the spectrum of monocation IX decreases as compared with the spectrum of the neutral molecule. Consequently, the addition of a proton to the oxygen atom of the N → O group has a similar effect on the spectra of the N-oxides of the corresponding pyridine and pyrazine derivatives. Opposite changes in the spectra occur on protonation of pyrazine 1-N-oxides I-VII. The number of absorption bands does not change on passing from neutral molecules to the

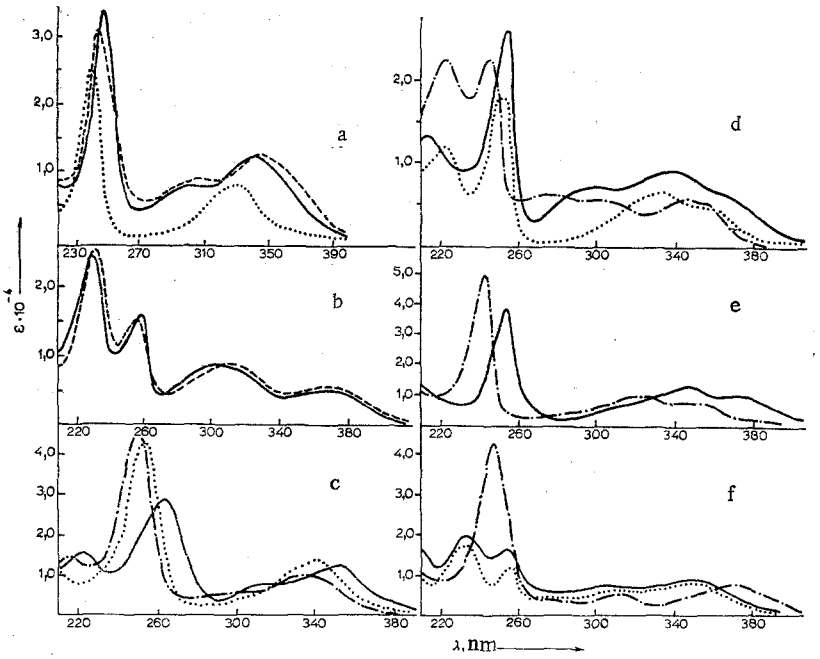


Fig. 1. UV spectra: a) monocations of quinoxaline and its 1-N-oxide and 1,4-N,N-dioxide; b) monocations of 3-aminoquinoxaline 1-N-oxide and 2-aminoquinoxaline 1,4-N,N-dioxide; c) neutral molecule and monocation of 3-carbethoxyquinoxaline 1-N-oxide and the monocation of 2-carbethoxyquinoxaline; d) neutral molecule and monocation of 3-methoxyquinoxaline 1-N-oxide and monocation of 2-methoxyquinoxaline; e) neutral molecule and monocation of 2-methoxyquinoxaline 1-N-oxide; f) neutral molecule and monocation of 2-aminoquinoxaline 1-N-oxide and monocation of 2-aminoquinoxaline. The neutral molecules are designated by (—— · ——), the monocations of the 1-N-oxides are designated by (———), the monocations of the 1,4-dioxides are designated by (-----), and the monocations of the unoxidized quinoxalines are designated by (.....).

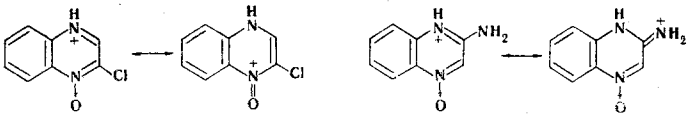
corresponding monocations. Both low-energy transitions are shifted to the long-wave region, and an increase in the intensity of the ^1L_W band is observed for all of the compounds. The spectra of monocations I-VII differ sharply from the spectra of the monocations of the corresponding pyrazine derivatives [6]. In addition, a complete analogy between the spectra of the monocations of pyrazine 1-N-oxides (I) and 3-aminopyrazine 1-N-oxide (VI) and the corresponding 1,4-N,N-dioxides VIII and IX is observed. These data make it possible to conclude that the protonation of the investigated pyrazine 1-N-oxides (I-VII) occurs at the unoxidized ring-nitrogen atom (N_4) (structure b). This is in complete agreement with the results of a study of the PMR spectra [1]. All of the bands in the spectrum of the cation of 3-aminopyrazine 1-N-oxide (VI) are located in the higher-energy region as compared with the spectrum of the cation of 2-aminopyrazine 1-N-oxide (II). The same differences are observed in the spectra of the cations of 2- and 3-aminopyrazines [6], and this corresponds to an ortho and meta orientation of the amino group relative to the N_4 cationoid center in VIb and IIb. The decrease in the magnitude of the bathochromic shift of the ^1L_W band on protonation of VI ($\Delta\lambda$ = 6 nm) as compared with II ($\Delta\lambda$ = 30 nm) is probably due to the partial contribution of the o-quinoid structure with transfer of positive charge to the amino group in the monocation of VIb. A similar effect is apparently the reason for the hypsochromic shift of the ^1L_W band ($\Delta\lambda$ = −9 nm) observed on passing from the neutral molecule to the monocation of 3-aminoquinoxaline 1-N-oxide (Table 2, XV). The protonation of this compound and of unsubstituted quinoxaline 1-N-oxide (X) occurs at the N_4 atom. This is confirmed by the complete analogy between the spectra of the monocations of X and XV and the spectra of the monocations of the corresponding 1,4-N,N-dioxides XVIII and XIX (Fig. 1). Consequently, all of these compounds add a proton to the N_4 atom. The identical structures of the monocations of 2- and 3-methoxyquinoxaline 1-N-oxides were established by PMR spectroscopy [1].

Thus the bathochromic shift of the ^1L_W band is a sufficiently characteristic indication of protonation of diazine 1-N-oxides at the unoxidized ring nitrogen atom. On the other hand, at least two effects – addition of a proton to the oxygen atom of the N → O group and redistribution of the positive charge in ions of the amidinium type – may be the reason for the hypsochromic shift of this band. In the latter case, more reliable information regarding the position of the protonation center of the molecule can be obtained on the basis of a comparison of the spectra of the monocations of the investigated and model compounds. Proceeding from these data, the considerable hypsochromic shift ($\Delta\lambda = -19$ nm) found in the spectrum of 2-aminoquinoxaline 1-N-oxide (XI) does not correspond to protonation of this molecule at N_4, inasmuch as the cation of XIb is not an amidinium ion. On the other hand, the spectrum of the cation of XI proved to be extremely similar to the spectrum of the cation of 2-aminoquinoxaline (Fig. 1). Consequently, the oxygen atom of the N → O group is the preferred center of protonation of 2-aminoquinoxaline 1-N-oxide. This result is in agreement with the data obtained by IR spectroscopy of salts of 2-aminoquinoxaline N-oxides [7].

The proposed structure of the protonated pyrazine and quinoxaline N-oxides is in agreement with the ionization constants of these compounds (Tables 1 and 2). Most of the investigated N-oxides are weak bases. As in a number of the corresponding unoxidized diazines [8], COOR, Cl, and OCH_3 groups reduce the basicities of pyrazine and quinoxaline N-monoxides. In this case, the inductive effect predominates in the influence of substituents such as Cl and OCH_3. The basicities of pyrazine and quinoxaline 1-N-oxides are reduced considerably more markedly when such substituents are introduced into the 3 rather than the 2 position. Inasmuch as the inductive effect falls as the distance to the cationoid center increases, this order of decrease in the basicities corresponds to protonation of these compounds at N_4.

An amino group reduces the basicities of pyrazine and quinoxaline N-oxides. The ΔpK_a values of 2- and 3-aminopyrazine 1-N-oxides (II and VI) (+0.94 and +1.62) and of 3-aminoquinoxaline (XV) (+2.43) proved to be close to the values for 3- and 2-aminopyridines (+0.75 and +1.63) and 2-aminoquinoline (+2.49) [9]. These data are in agreement with an ortho orientation of the NH_2 group relative to the N_4 basic center in VI and XV and a meta orientation in II. The considerable difference in the ionization constants of 2-aminopyrazine 1-N-oxide and 1,4-N,N-dioxide (0.79 and −0.18) confirms the conclusion that these compounds are protonated at different centers. However, the close pK_a values for 2-aminoquinoxaline 1-N-oxide and 1,4-N,N-dioxide (1.09 and 1.06) correspond to protonation of both compounds at the same center (N_1−O).

Inasmuch as quinoxaline 1-N-oxides XII-XV have the same relative orientation of the substituent and cationoid center as the corresponding unoxidized quinoxalines [8], it was of interest to examine the effect of N-oxidation on the basicity. This effect can be characterized by the Δ' pK_a values, which are the differences between the pK_a values of the 1-N-oxide and the pK_a values of the unoxidized quinoxalines [8]. 1-N-Oxidation of quinoxaline and its 2-methoxy and 3-amino derivatives leads to a decrease in the basicity that is greater, the greater the +C effect of the substituent (Δ' $pK_a = -0.31$, −0.68, and −1.28). The negative inductive effect of the N → O group predominates in these compounds. The ionization constants of 2-chloro- and 2-carbomethoxyquinoxaline 1-N-oxides, on the other hand, prove to be higher than the ionization constants of the corresponding quinoxalines (Δ' $pK_a = +0.11$ and +0.07). The inductive effect of the N → O group in this case is probably compensated by stabilization of the protonated form through resonance with the p-quinoid structure, which is impossible in the unoxidized system. In 3-aminoquinoxaline 1-N-oxide resonance of this type apparently does not play a substantial role, and, as in unoxidized α-aminoazines, resonance with the o-quinoid structure of the amidinium type, which corresponds to transfer of positive charge to the exocyclic amino group, makes the primary contribution to stabilization of the protonated form.



EXPERIMENTAL

The UV spectra of the investigated compounds were measured with an EPS-3-spectrophotometer. The ionization constants were determined spectrophotometrically at 25° in aqueous solutions of sulfuric acid with a known acidity function (H_0) [10]. The acid concentration was determined by potentiometric titration with an OP-205 pH-meter. The optical densities at the analytical wavelengths were measured with an SF-4 spectrophotometer.

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