EFFECT OF THE pH OF THE MEDIUM ON THE CHEMICAL SHIFTS IN THE PMR SPECTRA AND ON THE DISTRIBUTION OF THE π-ELECTRON DENSITY

I. 3-HYDROXYQUINOLINE DERIVATIVES

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The dependence of the chemical shift of the ring protons on the pH of the medium for a number of 3-hydroxyquinoline derivatives was studied by PMR spectroscopy. The regions of ionization of the molecules, which correspond to the ranges of acidic, neutral, and alkaline media, were found. In D_2O, 3-hydroxyquinoline is present only in the uncharged hydroxy form. The presence of intramolecular hydrogen bonding in 4-dimethylaminomethyl-3-hydroxyquinoline has a substantial effect on the character of the dependence of the chemical shift on the pH of the medium; the existence of separate protonation of the nitrogen atoms of the ring and the side chain of 4-dimethylaminomethyl-3-hydroxyquinoline was established. The distribution of the π-electron density in the 3-hydroxyquinoline molecule is in good agreement with its chemical behavior during electrophilic substitution.

A complex study of the peculiarities of electrophilic substitution reactions in a number of 3-hydroxypyridine derivatives by means of PMR spectroscopy and chemical methods has demonstrated that the α and α' positions of the pyridine ring are the most reactive ones [1-3]. The presence of a nitrogen atom in the aromatic ring leads to a number of peculiarities in the physicochemical properties of 3-hydroxypyridine as compared with phenol [4-6].

An investigation of the change in the chemical shifts of the protons in 3-hydroxypyridine derivatives on the pH of the medium made it possible to determine the regions of the existence of cationic, neutral, dipolar, and anionic forms, to determine the mechanism of the formation of ion pairs, and to investigate the effect of intramolecular hydrogen bonding in ortho-substituted 3-hydroxypyridines on the trend of the dependence of the chemical shifts on the pH [6]. The regularities found helped to explain the specific behavior of 3-hydroxypyridine derivatives in electrophilic substitution reactions and to build up a more complete concept of their reactivities and electronic structures.

In the light of the data presented, it was of interest to ascertain the principles of the change in the chemical shifts and π-electron densities on adjacent carbon atoms in acidic, neutral, and alkaline media in a number of 3-hydroxypyridine derivatives containing condensed benzene rings. For this, we investigated the PMR spectra of a number of 3-hydroxyquinoline derivatives as a function of the pH of the medium. The distribution of the π charges in the neutral, cationic, and anionic states of 3-hydroxyquinoline was also calculated by the LCAO MO method using the Hückel approximation. The anionic state is of interest from the point of view of aminomethylation reactions, which proceed in alkaline media. The distribution of the electron density in the cationic state is of significance for other electrophilic substitution reactions that proceed in acidic media (nitration and halogenation, for example). The chemical shifts of the protons of the pyridine ring for a number of 3-hydroxyquinoline derivatives are presented in Table 1. The dependences

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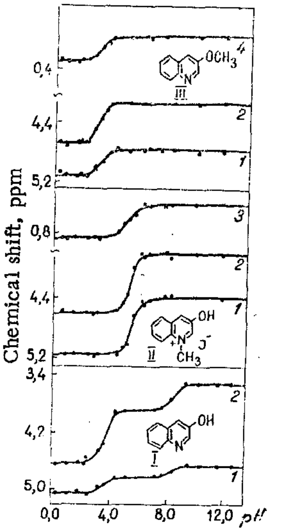

Fig. 1

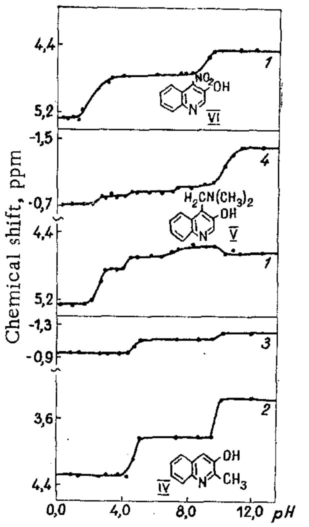

Fig. 2

Fig. 1. Dependence of the chemical shift of the ring protons on the pH of the medium for I-III: 1) 2-H; 2) 4-H; 3) $\overset{+}{N}CH_3$; 4) OCH_3.

Fig. 2. Dependence of the chemical shift of the ring protons on the pH of the medium for IV-VI: 1) 2-H; 2) 4-H; 3) CH_3; 4) $N(CH_3)_2$.

TABLE 1. Chemical Shifts (ppm) in the PMR Spectra of 3-Hydroxyquinoline Derivatives

Compound	Name	2-H			4-H			Other groups	Acidic media	Neutral media	Alkaline media
		acidic media	neutral media	alkaline media	acidic media	neutral media	alkaline media				
I	3-Hydroxyquinoline	5,03	4,80	4,66	4,63	3,90	3,53	—	—	—	—
II	1-Methyl-3-hydroxyquinolinium iodide	5,19	4,40	4,40	4,61	3,81	3,81	$\overset{+}{N}CH_3$	0,86	0,40	0,40
III	3-Methoxyquinoline	5,13	4,78	4,78	4,70	4,17	4,17	OCH_3	0,35	0,20	0,20
IV	2-Methyl-3-hydroxyquinoline	—	—	—	4,29	3,84	3,37	CH_3	−0,96	−1,13	−1,20
V	4-Dimethylaminomethyl-3-hydroxyquinoline	5,27 4,84	4,70 4,58	4,65	—	—	—	$N(CH_3)_2$	−0,70 −0,80	−0,85 −0,93	−1,37
VI	4-Nitro-3-hydroxyquinoline	5,27	4,78	4,48	—	—	—	—	—	—	—

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* The chemical shifts were measured relative to dioxane.

of the chemical shifts of the ring protons and the substituent groups on the pH of the medium are presented in Figs. 1 and 2.

An examination of the set of dependences of the PMR chemical shifts on the pH of the medium for various 3-hydroxyquinoline derivatives demonstrates, as in the case of 3-hydroxypyridine [6], that there are three horizontal sections that correspond to the ranges of acidic, neutral, and alkaline media (Figs. 1 and 2). The first protonation causes the most noticeable changes in the chemical shifts of the ring and substituent protons. These changes are considerably weaker on passing to alkaline media and depend on the structure of the compound under consideration. The dissociation of the OH group increases the electron-donor properties of oxygen, the shielding of the ring protons consequently increases, and all of the PMR signals are shifted to stronger field. Protonation, on the other hand, shifts the signals to weak field.

"Neutral" and Anionic States

In contrast to 3-hydroxypyridine [6], an analysis of the UV spectra of 3-hydroxyquinoline [7, 8], demonstrated that a dipolar structure is practically completely absent in aqueous solutions. This should undoubtedly be reflected in the character of the dependences of the chemical shifts also. The dependences of the chemical shifts on the pH for the protons of the pyridine ring and the substituents of 3-hydroxyquinoline

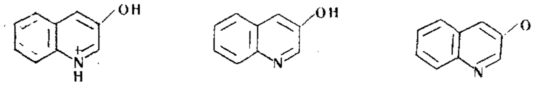
TABLE 2. π-Electron Densities (q_{π}) on the C-2 and C-4 Atoms of 3-Hydroxyquinoline

Medium	q_{π}	
	C-2	C-4
Acidic	0,2384	0,0374
Neutral	0,1024	−0,0110
Alkaline	0,0830	−0,1045

(I), its methiodide (II), and 3-methoxyquinoline (III) are presented in Fig. 1. Model compound II has a fixed dipolar structure in alkaline media. The absence of a change in the chemical shifts of the protons in aqueous media for pH > 5.5 indicates the correctness of the model that we selected for the dipolar structure and confirms the presence of the latter over the entire range of change in the pH (> 5.5), including solutions in D_2O. Compound III cannot dissociate at all. A comparison of the chemical shifts of the protons of the pyridine ring of I with the chemical shifts of II and III demonstrated that, in aqueous media, the chemical shifts for 3-hydroxyquinoline differ markedly from the shifts of its methiodide and are close to the shifts of the corresponding protons of 3-methoxyquinoline, in which the existence of a dipolar form is impossible. The opposite regularity was observed in the case of 3-hydroxypyridine [6].

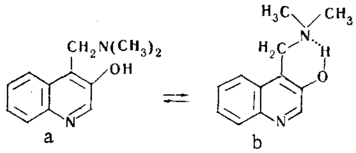
We also studied the behavior of the proton signals of the pyridine ring of 3-hydroxyquinoline at various dioxane concentrations in D_2O. Only a slight shift in the absorption band is observed in the UV spectra as the dioxane fraction in the water is increased. The picture is similar in the PMR spectra: for the proton in the 2 position (2-H), the difference in the chemical shift in dioxane and D_2O is ~ 0.03 ppm. These changes are more significant in the case of the 4-H proton.

Thus we have established the following forms of the state of the molecule as a function of the pH of the medium for 3-hydroxyquinoline derivatives:



A shift of the PMR signals to strong field is observed on passing from neutral to alkaline media. In all of the investigated compounds, the greatest changes in the chemical shift are experienced by the 4-H proton, while these changes are much weaker for the 2-H proton and to a great degree depend on the structure of the compound under investigation. A comparison of the dependences of the chemical shifts of 3-hydroxyquinoline and 4-dimethylaminomethyl-3-hydroxyquinoline distinctly illustrates the differences in the behavior of these compounds in neutral and alkaline media. In fact, in the case of 4-dimethylaminomethyl-3-hydroxyquinoline, the emergence of the curve onto the horizontal portion that corresponds to the neutral state occurs at much higher pH values (~ 4.3) than in 3-hydroxyquinoline itself (pH ~ 3.7).

The presence of strong intramolecular hydrogen bonding and the absence of a dipolar structure in aqueous solution also leave their stamp on the character of the dependence (see Fig. 2b). While transition to the anionic state was observed at pH ~ 11.0 in the case of aminomethyl-substituted 3-hydroxypyridines, the character of the dependence differs somewhat in the case of 4-dimethylaminomethyl-3-hydroxyquinoline. A successive shift of the PMR signals to stronger field occurs for pH > 4.5, and an examination of the dependences demonstrates the presence of two plateaus at pH values from 4.5 to 10.5. With a sufficient degree of probability, it can be assumed that an equilibrium of the following form exists in this range:



As the pH increases, the equilibrium is shifted to favor form *a*, and this in turn leads to an increase in the acidic properties of the hydroxy group, and, symbatically with this, a gradual shift of the proton signals to stronger field is observed. The presence of only one plateau for the "neutral" state of the molecule is characteristic for 3-hydroxypyridine [6] and 4-hydroxyisoquinoline [9], in which the dipolar form makes a substantial contribution to the equilibrium. Total ionization of the hydroxy group occurs for pH > 10, and this leads to a sharp shift in the signals of the methyl groups of the substituent to strong field. However, in this case, the shift in the 2-H signal, although only slight (~ 0.05 ppm), to weaker field is not entirely understood. It is possible that hydrogen bonding between the ring nitrogen atom and the solvent molecule affects the magnitude of the chemical shift in this case.

As in the case of 3-hydroxypyridines [6], it is much more difficult to estimate the role of intramolecular hydrogen bonding in the trend of the dependence for nitro derivatives of 3-hydroxyquinoline. The fact that the transition to the anionic form in VI occurs at lower pH values (~ 8.5) than in V, in which the contribution of hydrogen bonding plays the leading role, indicates the lesser significance of intramolecular association in these compounds.

It should be noted that, from a comparison of the chemical shifts of the protons of 3-hydroxyquinoline derivatives over the entire range of change in the pH values, the proton signals are shifted to weaker field than in the case of 3-hydroxypyridine. This is apparently associated with the effect of a condensed benzene ring.

Cationic State

The proton signals are shifted to weak field on passing to acidic media. The emergence of the dependence onto the horizontal section indicates total protonation of the investigated compound. The maximum changes in the chemical shift are observed for the protons in the 4 position. The insignificant shifts of the signals of the protons in the ortho position relative to the heteroatom are undoubtedly associated with the effect of the anisotropy of the unshared pair of p electrons of nitrogen. As seen from [10], the nitrogen atom has the greatest effect on the γ- and β-protons during the protonation of pyridine, while the chemical shift of the α-protons changes only slightly. This circumstance also leaves its stamp on the trend of the curve of the dependence for 3-hydroxyquinoline derivatives.

Protonation at two centers – the ring nitrogen and the substituent nitrogen – is possible in the case of 4-dimethylaminomethyl-3-hydroxyquinoline. The presence of two ranges of pH values 4.25-3.0 and < 2.0 is clearly seen in Fig. 2b. However, the explanation of the sequence of substitution proved to be extremely complicated in the case of the indicated compounds. On the one hand, the literature data from an investigation of the basicity of amines attest to high basicity of the side chain. On the other hand, the presence of a hydroxyl group in the pyridine ring leads to partial protonation of the side-chain nitrogen throughout the formation of a strong intramolecular hydrogen bond and, as a consequence of this, to a decrease in the basicity of the side-chain nitrogen. In view of the difficulty involved in estimating the indicated effects in determining the sequence of the protonation of the ring and side-chain nitrogens, it is necessary to formulate special experiments.

The reactivities of the 3-hydroxyquinolines in electrophilic substitution are determined by a number of factors, primarily by the distribution of the electron density in the ring. In this paper, we have made a comparison of the chemical shifts of the 2-H and 4-H protons with the π charges on adjacent carbon atoms in media with different pH values. The results of the calculation of the surplus electron density $q_{\pi}{}^{i}$ (a positive q_{π} denotes a reduction in charge as compared with unity) for 3-hydroxyquinoline are presented in Table 2. In neutral media, the electron density on the carbon atoms of the pyridine ring increases in the order $C_4 > C_2$. This sequence is preserved in alkaline and acidic media. The electron density on the carbon atoms decreases on passing from neutral to acidic media, and the magnitude of this change increases in the order $C_2 > C_4$. On passing from neutral to alkaline media, the electron density increases in the order $C_4 > C_2$.

The distribution of the π charge in the 3-hydroxyquinoline molecule that we found is in good agreement with its chemical behavior during electrophilic substitution. In addition, the sequence of the positioning of the PMR signals of the protons of the pyridine ring in the direction of decreasing magnetic field (Table 1) also coincides with the order of substitution of the various positions of 3-hydroxyquinoline in aminomethylation, halogenation, and nitration. Thus we have established that 3-hydroxyquinoline initially forms 4-substituted derivatives in electrophilic substitution reactions [11]. The aminomethylation reactions depend markedly on the pH of the medium, but the highest yields of Mannich bases were obtained in alkaline media.

Calculation of the anion of 3-hydroxyquinoline demonstrates an increase in the electron density, first in the 4 position and then in the 2 position, and the appearance of a negative charge in the 4 position, which also facilitates the electrophilic substitution of 3-hydroxyquinoline. The calculated distribution of the π charges of the anion of 3-hydroxyquinoline indicates that the 4 position should be the most reactive one, which is in agreement with the chemical shifts of the protons of the pyridiene ring (Table 1). A similar substitution sequence also follows from the calculation of the cation of 3-hydroxyquinoline and was observed in the nitration of the latter under acidic conditions.

EXPERIMENTAL

The chemical shifts were measured with an HA-100 spectrometer. Dioxane was used as the internal standard. The accuracy in the measurements of the chemical shifts was ± 0.02 ppm. The solvents were D_2SO_4, D_2O, and mixtures of D_2O with D_2SO_4 or NaOD. The solution volumes were ~7 ml. The pH values were measured with a pH meter of the LPU-01 type, while the pD values were calculated by adding 0.4 to the corresponding pH value [12]. The intermediate pH values were obtained by the addition of acid or alkali to D_2O.

The π-electron density was calculated by the Hückel LCAO MO method from the program presented by Tutkevich.

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