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

II.* 4-HYDROXYISOQUINOLINE DERIVATIVES

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The dependence of the chemical shifts of the ring protons on the pH of the medium for a number of 4-hydroxyquinoline derivatives was studied by means of PMR spectroscopy. The dipolar and uncharged hydroxy forms exist in equilibrium in aqueous solutions. The effect of intramolecular hydrogen bonding on the character of the dependence of the chemical shift on the pH of the medium in the case of 3-piperidinomethyl-4-hydroxyisoquinoline was investigated. The possibility of the separate protonation of the ring nitrogen and the side-chain nitrogen in 3-piperidinomethyl-4-hydroxyisoquinoline was established. The distribution of the π-electron density in 4-hydroxyisoquinoline is in good agreement with its chemical behavior.

In our previous paper [1], we studied the effect of the pH of the medium on the position of the PMR signals and on the distribution of the π-electron density on the carbon atoms adjacent to the nitrogen atom in 3-hydroxyquinoline derivatives. It was shown that, in contrast to 3-hydroxypyridines, in D_2O, 3-hydroxyquinoline exists practically completely in the form of a neutral molecule and that it behaves like β-naphthol in aminomethylation reactions.

At the same time, an investigation of electrophilic substitution reactions, particularly the aminomethylation of 4-hydroxyquinoline, has demonstrated that this compound behaves like 3-hydroxypyridine derivatives [2]. Hence, one should have expected the existence of general regularities in the behavior of these

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*See [1] for communication I.

TABLE 1. Chemical Shifts (ppm) in the PMR Spectra of 4-Hydroxyisoquinoline Derivatives*

Compound	Name	1-H			3-H			Other groups	Acidic media	Neutral media	Alkaline media
		acidic media	neutral media	alkaline media	acidic media	neutral media	alkaline media				
I	4-Hydroxyisoquinoline	5,25	4,33	4,21	4,45	3,90	3,80	—	—	—	—
II	2-Methyl-4-hydroxyisoquinolinium iodide	5,19	4,30	4,30	4,55	3,94	3,94	$\overset{+}{N}CH_3$ not measured			
III	4-Methoxyisoquinoline	5,27	5,04	5,04	4,20	4,03	4,03	OCH_3	0,33	0,26	0,26
IV	3-Piperidinomethyl-4-hydroxyisoquinoline	5,28 4,82	4,69	4,55	—	—	—	NC_5H_{10}	0,00 −0,50	−0,88	−1,08
V	3-Methyl-4-hydroxyisoquinoline	5,12	4,60	4,46	—	—	—	CH_3	−1,05	−1,20	−1,30

*The chemical shifts were measured relative to dioxane.

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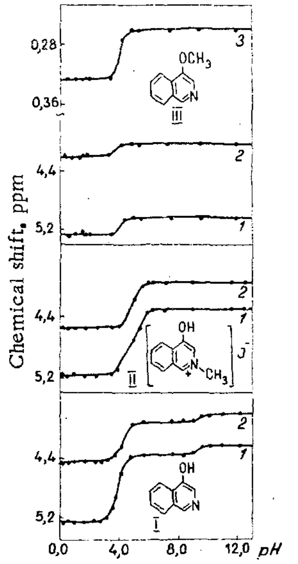


Fig. 1

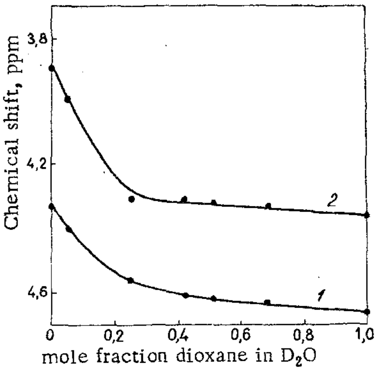


Fig. 2

Fig. 1. Dependence of the chemical shift of the protons on the pH of the medium for I-III: 1) 1-H; 2) 3-H; 3) OCH_3.

Fig. 2. Dependence of the chemical shift of the ring protons of 4-hydroxyisoquinoline on the dioxane concentration in D_2O: 1) 1-H; 2) 3-H.

TABLE 2. π-Electron Density (q_π) on the C-1 and C-3 Atoms of 4-Hydroxyisoquinoline

Structure	q_π	
	C-1	C-3
Cationic	0,2185	0,1374
Neutral	0,0760	0,0321
Dipolar	0,1411	0,0722
Anionic	0,0005	−0,0398

compounds in media with various pH values. We therefore investigated the dependence of the position of the PMR signals of 4-hydroxyisoquinoline derivatives on the pH (Table 1) and calculated the distribution of the π-electron density in the neutral, cationic, and anionic states of the molecule by means of the Hückel LCAO MO method (Table 2).

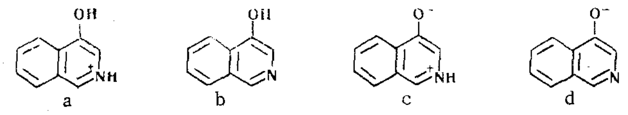
As in the case of 3-hydroxypyridines [3] and 3-hydroxyquinolines [1], three characteristic regions, which should be ascribed, respectively, (in the direction of increasing pH) the cationic, neutral, and anionic forms of 4-hydroxyisoquinoline, are readily isolated on the curve of the dependence of the chemical shifts on the pH.

On the basis of a comparison of the chemical shifts of the protons of 4-hydroxyisoquinoline (I) (Fig. 1 and Table 1) with the shifts of the corresponding protons of its methiodide (II), which has a fixed dipolar structure above pH 6, and of 4-methoxyisoquinoline (III), which is not at all capable of dissociation, we demonstrated the possibility of the presence of a dipolar form in aqueous media. The reliability of this conclusion is confirmed by an analysis of the UV spectra of 4-hydroxyisoquinoline [4].

A study of the behavior of the PMR signals of 4-hydroxyisoquinoline at various dioxane concentrations in water (Fig. 2) shows that the changes in the chemical shift amount to 0.33 and 0.46 ppm for the 1-H and 3-H protons, respectively. As in the case of 3-hydroxypyridine, a shift of the PMR signals to stronger field is observed as the dioxane concentration is reduced, and a sharp shift sets in at concentrations below 25 mole %.

A similar shift of the absorption bands of the UV spectra was also observed in [4], in which it was established that 70% of the 4-hydroxyisoquinoline is in the dipolar form in D_2O.

Thus the following four forms are possible for 4-hydroxyisoquinoline derivatives, depending on the pH of the medium: a) cationic, b) neutral, c) dipolar, and d) anionic:



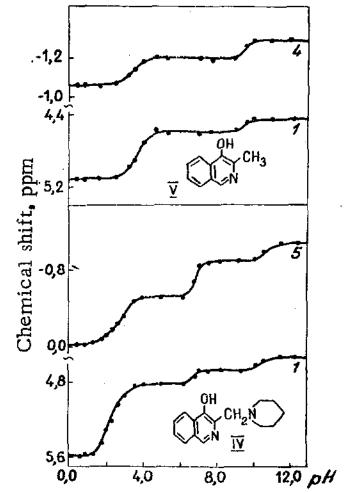


Fig. 3. Dependence of the chemical shift of the protons on the pH of the medium for IV and V: 1) 1-H; 2) CH_3; 3) NC_5H_{10}.

As one should have expected, the presence of intramolecular hydrogen bonding in the case of 4-hydroxyisoquinoline has a substantial effect on the nature of the dependence of the chemical shift on the pH. This is particularly apparent from a comparison of the dependences of 3-methyl-4-hydroxyisoquinoline (V) and 3-piperidinomethyl-4-hydroxyisoquinoline (IV) (Figs. 3a and 3b, respectively). Thus, in the case of IV, conversion to the neutral state occurs at much higher pH (6.5) than for V (3.5), in which intramolecular hydrogen bonding is absent. A decrease in the acidic properties of the hydroxy proton due to hydrogen bonding also results in the fact that the conversion to the anionic state in the case of IV occurs at higher pH (~10.5) than in the case of V (~9.5).

The small changes in the chemical shifts for all of the 4-hydroxyisoquinoline derivatives (~0.15 ppm) on conversion from the neutral states (b and c) to the anionic state (d) are possibly associated with a substantial contribution of form c to the equilibrium. The ring protons experience the greatest changes on passing to acidic media. Thus, for 4-hydroxyisoquinoline itself, the changes in the chemical shift amount to 0.92 and 0.55 ppm for 1-H and 3-H, respectively. The shift in 1-H for V is 0.52 ppm, while the shift in 1-H for IV is 0.88 ppm toward the weak field side.

Two plateaus at pH 6.5-3.0 and from 2.0 and below are observed on the curve for 3-piperidinomethyl-4-hydroxyisoquinoline (Fig. 3). As in the case of 4-dimethylaminomethyl-3-hydroxyquinoline [1], protonation at two centers – the ring nitrogen and the side-chain nitrogen – is possible for this compound. However, by virtue of the difficulties indicated in [1], the establishment of the site of primary protonation requires additional investigations.

We also made a comparison of the chemical shifts of the 1-H and 3-H protons of 4-hydroxyisoquinoline with the π charges on the carbon atoms adjacent to the nitrogen atom in media with various pH values (Table 2). The electron density on the carbon atoms of the pyridine ring increases in the order $C_3 > C_1$ for all of the investigated forms of the state of the molecule. Transition from acidic media to neutral and alkaline media is associated with an increase in the electron density on the carbon atoms. As in the case of 3-hydroxyquinoline, the charge distribution found in 4-hydroxyisoquinoline is in agreement with the chemical behavior of this compound in electrophilic substitution reactions. Aminomethylation proceeds most successfully in alkaline media. Calculation of the anion of 4-hydroxyisoquinoline demonstrates that the most reactive position is the 3 position of the pyridine ring of 4-hydroxyisoquinoline. This is in agreement also with the PMR chemical shifts of 4-hydroxyisoquinoline (Table 1).

EXPERIMENTAL

The chemical shifts were measured with an HA-100 spectrometer with dioxane as the internal standard. The method used to prepare the samples is presented in [1]. The π-electron densities were calculated by the Hückel LCAO MO method.

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