BASICITY OF 3-FORMYL-4,7-DIAMINOCOUMARINS AND THEIR AZOMETHINE DERIVATIVES

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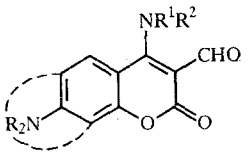
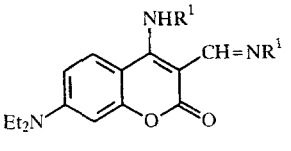
The basicity of a series of 3-formyl-4,7-diaminocoumarins and their azomethine derivatives was studied. By using PMR data, it was determined that primary protonation of most aldehydes affects the nitrogen atom in the 7 position and, in the case of azomethines, the nitrogen atom of the azomethine group.

Previously [1], we synthesized a series of novel 3-formyl-4,7-diaminocoumarins and Schiff bases based on them. It was determined that aldehydes and azomethines that are derivatives of primary amines exist in the form of molecules with intramolecular hydrogen bonds, with a chelate proton being bonded to a nitrogen atom in the 4 position.

For study of the mutual effect of substituents in the 3 and 4 positions, in the present paper the pK_a values of conjugated acids in water–ethanol solutions were also determined for compounds I-XI (Table 1).



I–IX



X, XI

I—VII, X, XI R = C_2H_5; VIII R—R = -$(CH_2)_2O(CH_2)_2$-; IX R = -$(CH_2)_3$—C ortho; I, X R^1 = cyclo C_6H_{11}; II, XI R^1 = $CH_2C_6H_5$; III R^1 = C_6H_5; I—III R^2 = H; IV R^1 = R^2 = C_2H_5; V R^1—R^2 = -$(CH_2)_5$-; VI, VIII, IX R^1—R^2 = -$(CH_2)_2O(CH_2)_2$-; VII NR^1R^2 = N-imidazolyl

Acidification of solutions of aldehydes I-VI, VIII, and IX resulted in the disappearance of the long-wave absorption maximum and an increase of a new maximum in the shorter-wave region (λ_{max} 320-340 nm). Quenching of fluorescence of the considered compounds occurred simultaneously. Such patterns mean that coumarins I-VI, VII, and IX undergo protonation at the nitrogen atom in the 7 position [2]. From the data of Table 1, it is evident that the pK_a values of comarins I and II are approximately 0.5 of an order lower than in the case of the corresponding 4-(dialkylamino) derivatives IV-VI. In itself, this fact does not seem unexpected, but it was shown previously [2] that in the series of 4,7-diaminocoumarins, dialkylamino groups in the 4 position exhibit weaker electron-donor properties than do monoalkylamino groups because of steric hindrances with the $C_{(5)}$–H fragment. In our opinion, reversal of this trend for aldehydes IV-VI is due to the conformational state of the formyl group, which is directly bonded to the nitrogen atom of the $C_{(7)}$–N fragment and experiences steric hindrances from the dialkylamino group in the 4 position. A result of these hindrances may be partial turning of the aldehyde group, accompanied by decrease of charge transfer from the $C_{(7)}$–N nitrogen atom and, as a result, increase of basicity. Independent confirmation of this follows from the ^{13}C NMR spectra of coumarins II and VI [1], where, in particular, the stronger-field chemical shift of the $C_{(3)}$ atom for coumarin VI in comparison with coumarin II ($\Delta\delta \sim 7$ ppm) indicates high electron-donor ability of the benzylamino group in the 4 position in comparison with the morpholine substituent.

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TABLE 1. Acid–Base Properties of Coumarins I-XI in 1:1 Water–Ethanol Solutions

Compound	Absorption λ_{max}, nm		pK_a	pK_a^*
	of neutral molecule	of monocation		
I	383	320	-0,03	-11,05
II	386	330	-0,12	-9,54
III	393	333	-0,21	-10,05
IV	407	343	0,49	-9,35
V	407	320	0,61	-13,51
VI*	415	320	0,46	-14,84
VII**	465	485 340	4,45 -0,35	6,38 -19,18
VIII	395	325	-1,13	-12,90
IX	435	333	-0,71	-15,69
X**	377	410 342	6,22 -0,07	10,93 -10,34
XI**	367	404 338	6,04 -0,32	11,88 -10,59

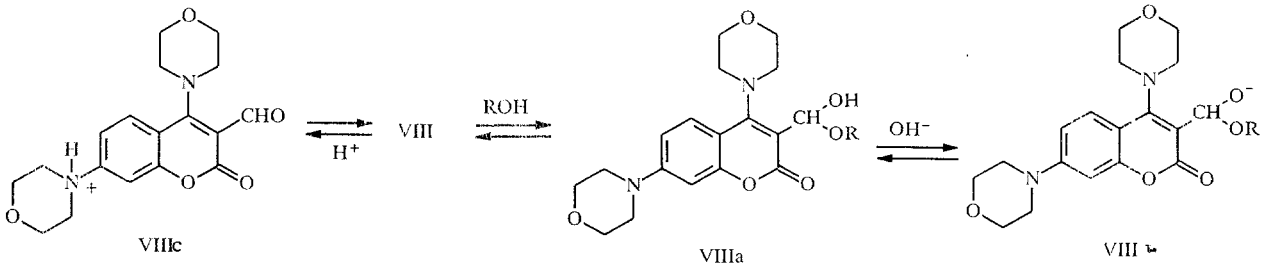
*According to data of [3].

**Data are presented for mono- and dications (see text).

The high pK_a^1 of aldehyde VII is related to a change of the site of first protonation, which, in this case, occurs at the $N_{(3)}$ nitrogen atom in the imidazole ring. A confirmation of this is the bathochromic shift of the absorption maximum in going to the monocation with retention of weak fluorescence in the long-wave region. Indeed, in weaker media, for coumarin VII it was also possible to observe second protonation occurring at the $C_{(7)}$–N atom (Table 1).

The site of first protonation in compounds X and XI is the nitrogen atom of the azomethine group. A proof of that is the long-wave shift of the absorption maximums, as well as characteristic changes in the PMR spectra observed during acidification of solutions of the coumarins [1]. Thus, for example, protonation of azomethine X by trifluoroacetic acid in a CD_3OD medium results in strong weak-field shift of the peak of the cyclohexyl methine proton of the substituent in the 3 position ($\Delta\delta \sim 0.53$ ppm) and strong-field shift of the peak of the analogous proton in the 4-(cyclohexylamino) group ($\Delta\delta$ −0.31 ppm). The azomethine proton also experiences a significant strong-field shift ($\Delta\delta$ −0.26 ppm). Changes in the chemical shift of the remaining protons in the monocation of compound X are small, but it is not possible to observe the chelate proton because of rapid deuterium exchange. The observed picture agrees with primary protonation of the nitrogen atom of the azomethine group. Additional confirmation of this is structuring of the peaks of the cyclohexyl protons in acid media, which are converted from broadened peaks to triplets as a result of disturbance of the dynamics of tautomeric equilibrium. The spin–spin coupling constant of these peaks ($^3J \sim 10$ Hz) indicates equatorial arrangement of both cyclohexyl substituents [1].

A rather unexpected pattern was observed in studying the acid–base properties of 4-morpholino derivative VIII. In weakly acid media at pH 1-6, we detected for this compound the existence of form VIIIa, having shorter-wave absorption and fluorescence than in the case of the starting aldehyde. It was also found that the conversion of coumarin VIII to form VIIIa is completely reversible and, therefore, not related to hydrolytic abstraction of a morpholino group. In our opinion, hydration of aldehyde VIII or formation of a hemiacetal occurs in the mentioned pH range:



VIIIc VIIIa VIII b

In more-alkaline media (pH 11-14), it is possible to observe deprotonation of form VIIIa with formation of anion VIIIb, having even stronger fluorescence. However, at low pH values, for coumarin VIII there is a region ($0.5 < pH < 2.0$) where only the aldehyde form exists, and, with further acidification, this form undergoes protonation at the $C_{(7)}-N$ nitrogen atom.

It should be noted that the formation of VIIIb-type anions in alkaline media was also observed for other aldehydes, but the presence of form VIIIa was observed only for the 4-morpholino derivative. The reason for this may be both the relative compactness of the morpholino group, which, inhibiting planar arrangement of the formyl substituent, nevertheless creates no serious steric hindrances for the tetrahedral dihydroxy- or hydroxyalkoxymethyl group, and the comparatively weak electron-donor properties of the morpholino group, retaining sufficient activity of the carbonyl fragment. An indirect confirmation of this is the fact that the basicity of morpholine is approximately three orders lower than that of piperidine or diethylamine.

Table 1 also gives pK_a^* values of conjugated acids calculated by Foerster's method. A sharp decrease of the basicity of the studied compounds during excitation is also characteristic of other 7-aminocoumarins because the S_1 state of these molecules is a charge-transfer state.

EXPERIMENTAL

The UV spectra and fluorescence spectra were recorded with a Hitachi EPS-3T spectrophotometer. The pK_a values were determined by a spectrometric method in 50% ethanol. The error in the determination of pK_a was ± 0.04. The proton donor was hydrochloric acid. The pH values were measured with universal pH meter ÉV-74 with glass and calomel electrodes.

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