ACID—BASE CHARACTERISTICS OF FUNCTIONALLY 4-SUBSTITUTED 4-ALKYL-7-AMINOCOUMARINS

M. A. Kirpichënok, L. A. Karandashova, and I. I. Grandberg

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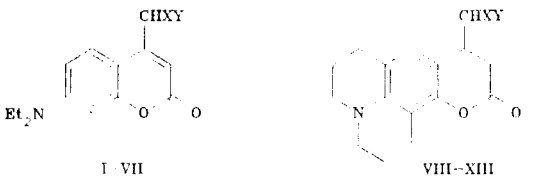
The acidity and basicity of derivatives of the 7-aminocoumarin series containing a CH-acid group (ethyl acetate, acetone, acetonitrile, acetylacetone, malonic, acetoacetic, or cyanoacetic esters) at position 4 and a diethylamino group or a julolidine fragment at position 7 were investigated. It was established that the CH acidity of the functionally 4-substituted derivatives depends on steric factors.

In [1] we reported on the synthesis of new luminophores of the 7-aminocoumarin series (I-XIII), containing the fragments of typical CH acids at position 4. Such compounds are promising as fluorescent labels [2], fluoroionophores [3], synthons in condensation reactions, etc.. Since the reactivity and chelating ability of the substances depends on the nature of the mutual electronic and steric effects of the functionally substituted alkyl- and aminocoumarin fragments, in the present work we studied the acid—base characteristics of compounds (I-XIII) (Table 1).



I—III, VIII—X X=H; IV, V, VII, VIII, XI, XIII X=CO_2Et; VI, XII X=$COCH_3$; I, IV, VIII Y=CO_2Et; II, V, VI, IX, XI, XII Y=$COCH_3$; III, VII, X, XIII Y=CN

As solvent we used the 1:1 ethanol—water system, which is universal with respect to its solvating capacity and is suitable for comparison with existing published data on the acid—base and luminescence-spectral characteristics of 7-aminocoumarins [4-6]. In addition, the properties of this system are not very sensitive to change in its composition [7]. Initially we determined the acidity of the coumarins (I-XIII). The addition of alkali (potassium hydroxide) to solutions of the investigated compounds is accompanied by disappearance of the long-wave absorption maximum (λ_{max}^{ab} 395-430 nm), by fluorescence quenching, and by an increase in the new absorption maximum in the region of 370-390 nm. Thus, the transition to the anionic forms of the coumarins (I-XIII) leads to a hypsochromic shift of the long-wave absorption by 6-41 nm. According to published data [8,9], such spectral changes during deprotonation are regular and are due to an increase in the electron-donating characteristics of the substituent at position 4. Special spectral behavior is exhibited by derivatives of cyanoacetic ester (VII) and (XIII), which in the neutral form absorb in the most long-wave region and in the anionic form absorb in the shortest region compared with other coumarins. This fact indicates more effective conjugation between the carbanion that forms and the coumarin fragment. The reason for this may be decrease of the steric hindrances in the presence of the compact CN group, which secures maximum coplanarity between the anionic and heterocyclic fragments (see below, conformation A). In the case of the coumarin (VIII) the deprotonation process in the pure form could not be detected in the employed solvent system as a result of the hydrolytic cleavage of the ethoxycarbonyl group (at pH $\geq$ 12.5).

The calculated pK_a values of the functionally monosubstituted coumarins (I-III, IX, X) lie in the range of 12.0-12.3. Consequently, the acidifying effect of the aminocoumarinyl fragment is comparable, for example, with the effect of such an electron-withdrawing group as the ester group. The comparatively narrow range of pK_a values

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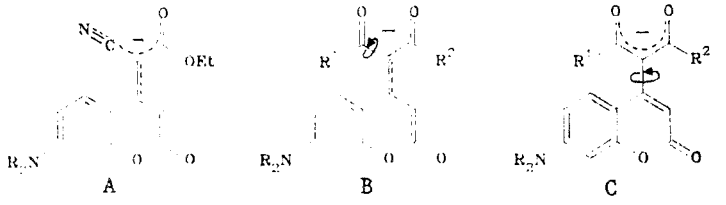
TABLE 1. Acid—Base and Spectral Characteristics of 7-Aminocoumarins (I-XIII) in the 1:1 Ethanol—Water System

Compound	Absorption λ_{max}, nm			pK_a	pK^*_a	pK_{BH}	pK^*_{BH}
	neutral molecule	mono-cation	mono-anion				
I	395	314	384	12,20	10,70	1,50	−13,41
II	393	312	387	12,00	11,14	1,75	−12,37
III	396	310	388	11,97	10,69	1,26	−13,72
IV	402	314	386	11,09	8,95	1,15	−13,62
V	401	310	384	8,67	6,32	1,50	−14,12
VI	404	320	384	8,74	6,17	1,16	−12,54
VII	407	310	373	4,62	−0,08	0,82	−15,44
VIII	410	326	—	—	—	−0,27	−13,75
IX	410	332	392	12,04	9,69	−0,20	−14,43
X	411	322	394	12,36	10,22	−0,66	−15,21
XI	416	325	403	8,74	7,03	−0,34	−14,89
XII	420	327	405	9,00	7,07	−0,43	−14,98
XIII	429	328	386	4,99	−0,57	−0,83	−16,23

of the investigated compounds means that the 4-coumarinyl substituent, which levels out the various electron-withdrawing powers of the functional groups, makes a significant contribution to delocalization of the negative charge in the anion. In such a case there is evidently no need to consider any steric effects.

A different situation arises for the functionally disubstituted coumarins (IV-VII, XI-XIII), where the acidity of the coumarins (VII) and (XIII) is approximately four orders of magnitude higher than for the other compounds. This effect cannot be explained solely in terms of the electronic effects of the CN, $COCH_3$, and $CO_2C_2H_5$ groups, since the difference in the acidity of the initial methylene compounds is not greater than two orders of magnitude [10]. The most likely explanation lies in the above-mentioned steric hindrances (see the scheme), which arise in the anion between one of the functional groups and the "peri position" [the $C_{(5)}$—H ($C_{(8)}$—H) bond*] of the carbocyclic part of the molecule [5]. In the mesomeric anions of the coumarins (VII) and (VIII) conformations of type A, in which such hindrances are absent and large delocalization of the negative charge is consequently achieved, can be realized.



For the coumarins (IV-VI, XI, XII), on the other hand, the structures of the anions can be described better by formulas B or C, in which the region where the negative charge is concentrated is localized so that one (in the case of B) or both (C) functional groups are withdrawn from the plane of the heterocycle.

For a more detailed discussion we studied the ^{13}C NMR spectra of the coumarins (VI) and (VII) in deuterochloroform and also in deuteroethanol under conditions where the neutral and anionic forms exist (Table 2). The greatest differences in the ^{13}C NMR chemical shifts of the coumarins (VI) and (VII) in deuterochloroform are observed for the $C_{(3)}$, $C_{(4)}$, and $C_{(5)}$ atoms ($\Delta\delta$ 1.1-7.5 ppm), which are situated directly in the zone of influence of the functionally disubstituted 4-alkyl group. A similar conclusion can be reached during comparison of the ^{13}C NMR spectra of compounds (VI) and (VII) with the spectrum of 4-methyl-7-diethylaminocoumarin (XIV) [11]. The small downfield shift of the signals for the $C_{(3)}$ and $C_{(7)}$ atoms ($\Delta\delta$ 2.4 and 1.3 ppm and 0.4 and 0.7 ppm respectively) for the coumarins (VI) and (VII) compared with the model 7-diethylaminocoumarin (XV) [11] demonstrates the weak electron-withdrawing characteristics of the functionally substituted alkyl substituent at position 4. Earlier [1] it was established by PMR spectroscopy that the coumarin (VI) exists in deuterochloroform in the chelate form. Additional evidence for this can be obtained from the signal of the C_α atom, attached to the $C_{(4)}$ atom, which appears in the spectrum of the coumarin (VII) as a normal methine signal, while in the coumarin (VI) it is shifted significantly downfield (Table 2). The different form in which the coumarins (VI) and (VII) exist in

*Here and subsequently the numbering of the analogous carbon atoms in the julolidine derivatives (VIII-XIII) is given in parentheses.

TABLE 2. ^{13}C NMR Spectra of the Coumarins (VI, VII)

Compound	Solvent	Chemical shifts, δ, ppm (SSCC, Hz)												
		$C_{(2)}$	$C_{(3)}$	$C_{(4)}$	$C_{(4a)}$, m	$C_{(5)}$, d	$C_{(6)}$, dd	$C_{(7)}$, m	$C_{(8)}$, dd	$C_{(8a)}$, dd	4-$C_{(\alpha)}$	NCH_2, t	NCH_2CH_3, q	other carbon atoms
VI	$CDCl_3$	161,4 (d J=4,4)	111,2 (d J=170,2)	151,4 (d J=4,1)	108,7	126,6 (J=159,6)	108,7 (J=160,3; J=5,7)	150,9	97,5 (J=160,1; J=5,3)	156,4 (J=9,5; J=5,4)	108,4 m	44,5 (J=135,5)	12,2 (J=126,5)	23,3 (q J=128,5; CH_3); 190,1 (m C=O)
	C_2D_5OD	163,3 (d J=4,4)	112,2 (d J=171,2)	153,2 (d J=4,1)	110,2	128,0 (J=159,8)	110,6 (J=160,7; J=5,6)	152,7	98,7 (J=160,1; J=5,4)	157,9 (J=9,5; J=5,3)	109,8 m	45,7 (J=131,5)	13,1 (J=126,6)	23,9 (q J=128,0, CH_3); 109,8 (m, C=O)
	C_2D_5OD*	164,0 s	112,3 (d J=171,2)	154,0 m	110,2	128,5 (J=159,8)	110,8 (J=160,7; J=5,6)	150,0	98,9 (J=160,1; J=5,4)	158,0 (J=9,5; J=5,3)	109,8 m	45,8 (J=131,5)	13,1 (J=126,6)	24,8 (m, CH_nD_{3-n}, where n=0, 1, 2, 3); 190,8 (m, C=O)
VII	$CDCl_3$	160,8 (t, J=2,6)	110,1 (dd J=171,9; J=5,5)	143,6 m	105,8	124,9 (J=158,8)	109,1 (J=160,9; J=5,5)	151,2	97,9 (J=160,8; J=5,1)	156,5 (J=10,0; J=5,7)	40,8 (dd J=137,0; J=6,0)	45,0 (J=136,0)	12,4 (J=126,8)	13,9 (q J=128,0, CH_3); 64,2 (t, J=149,4 OCH_2); 113,7 (t J=10,8 CN); 163,0 (m, C=O)
	C_2D_5OD	162,6 s	110,0 m	146,6 m	106,9	126,9 (J=159,9)	110,5 (J=161,3; J=5,6)	152,8	98,7 (J=160,7; J=5,3)	157,8 (J=10,0; J=5,5)	41,5 m	45,8 (J=136,2)	13,0 (J=126,8)	14,4 (q, J=128,0, CH_3); 64,8 (t, J=149,6, OCH_2); 115,5 (m CN); 165, (m C=O)
	C_2D_5OD*	166,5 s	95,9 m	156,2 m	109,2	128,8 (J=160,5)	108,5 (J=159,1; J=5,7)	150,8	98,4 (J=158,9; J=5,3)	157,1 (J=10,0; J=5,5)	59,5 s	45,3 (J=135,0)	13,1 (J=126,8)	15,4 (q, J=128,0, CH_3); 60,0 (t J=149,6, OCH_2); 128,6 (s, CN); 171,6 (m, C=O)

*In the presence of 2 eq of C_2D_5ONa.

deuterochloroform also shows up in the substantial difference between the chemical shifts of the $C_{(3)}$ atoms ($\Delta\delta$ 7.5 ppm) in these compounds.

The ^{13}C NMR spectra of the coumarins (VI, VII) in C_2D_5OD are similar on the whole to their spectra in deuterochloroform. In the case of the coumarin (VII), however, rapid isotope exchange between the protons at the C_α and $C_{(3)}$ atoms is observed even in the absence of bases and leads to a change in the form of the respective signals and to disappearance of the $^1J_{^{13}C-^1H}$ spin—spin coupling constant in the single-resonance spectrum. The difference in the spectra of the coumarins (VI) and (VII) becomes particularly strong with the addition of a base (C_2D_5ONa) to the deuteroethanol solutions of these compounds. In the case of the coumarin (VI) the transition to the anion is hardly accompanied by any changes at all in the ^{13}C NMR chemical shifts. Moreover, the fast recording of the spectrum indicates the absence of deuteroexchange at the $C_{(3)}$ atom and only records the slow deuteroexchange in the methyl groups of the acetylacetonyl residue. Such an effect indicates a chelated enolate structure, isolated from the effect of the coumarinyl substituent (conformation C). Consequently, the similar pK_a values of the coumarin (VI) and acetylacetone (pK_a 9.0) are explained by the structural proximity of the anionic fragments of these compounds. On the other hand, the transition to the monoanion of the coumarin (VII) is accompanied by marked changes in the chemical shifts of the $C_{(3)}$, $C_{(4)}$, and C_α atoms and the carbon atom of the CN and $CO_2C_2H_5$ groups and signifies substantial structural rearrangement, affecting the pyrone ring of the molecule. The nature of the observed changes agrees best with the mesomeric structure of the anion (formula A) with, possibly, preferred localization of the electron density at the oxygen atom of the carbonyl group.

Table 1 also gives the pK_a^* values of the investigated CH acids, calculated by Forster's method [12]. For most coumarins the acidity increases by 1-3 orders of magnitude during excitation. The exceptions are compounds (VII) and (XIII), where the increase in the acidity amounts to approximately five orders of magnitude.

In the second part of the work we investigated the basicity of the coumarins (I-XIII) and determined the pK_{BH} values of the conjugate acids of these compounds in the same solvent system (Table 1). The protonation of the coumarins (I-XIII) is accompanied by a significant hypsochromic shift of the long-wave absorption maximum ($\Delta\lambda_{max}$ 80-100 nm) and by fluorescence quenching. In spite of the fact that the spectral characteristics of the monocations in the series of diethylamino or julolidine derivatives practically coincide ($\Delta\lambda_{max}^{K^+}$ 5-10 nm), the pK_{BH} values of the coumarins within each series vary in the range of 0.5-1.0. Among the functionally monosubstituted coumarins the 4(9)-cyanomethyl derivatives (III) and (X) have reduced basicity (ΔpK_{BH} 0.3-0.5). In the series of functionally disubstituted coumarins (IV-VII, XI-XIII) an analogous conclusion holds for the derivatives of cyanoacetic ester (VII, XIII). This relationship is evidently due to the high electron-withdrawing power of the nitrile group [13]. The enhanced basicity of the derivatives of acetoacetic ester (V, XI) in the series of related compounds looks somewhat anomalous, and this may be due to the formation of the enolic forms during protonation [1]. Comparison of the pK_{BH} values of compounds (I-XIII) with the corresponding values of 4(9)-unsubstituted or 4(9)-methylated coumarins [4] indicates an appreciable reduction in the basicity under the influence of the functional groups (ΔpK_{BH} 0.2-1.0), which make the 4(9)-alkyl substituent as a whole a weak electron acceptor. As expected [4-6,8], the julolidine derivatives (VIII-XIII) are approximately 1.5-2.0 orders of magnitude less basic than their 7-diethylamino analogs (I-VII).

Calculation of the pK_{BH}^* values according to Forster (Table 1) indicates an abrupt decrease (12-16 orders of magnitude) in the basicity of compounds (I-XIII) during photoexcitation. Similar behavior is also typical of other 7-aminocoumarins [4-6,8,9,11], since the excited state of the molecules of these compounds is a state with charge transfer [8].

EXPERIMENTAL

The 7-aminocoumarins (I-XIII) were obtained by the method in [1]. The luminescence-spectral investigations were conducted on a Hitachi EPS-3T spectrophotometer fitted with a G-3 fluorescence attachment.

The pK_a and pK_{BH} values were determined according to [14] in 50% ethanol on a universal pH-meter with glass and calomel electrodes. The oxonium-ion donor was H_2SO_4, and a 30% solution of potassium hydroxide in 50% ethanol was used as base. The error in the determination of the pK_a and pK_{BH} values amounted to ± 0.04. Twice-distilled water was use to prepare the solutions.

The ^{13}C NMR spectra were obtained on a Bruker WM-250 instrument. For determination of the spectra of the anions in deuteroethanol we used 2 eq of the base (C_2D_5ONa).

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SYNTHESIS AND LUMINESCENCE-SPECTRAL AND ACID—BASE CHARACTERISTICS OF 3-AMINOMETHYL-7-DIALKYLAMINOCOUMARINS

A. V. Sokolov, M. A. Kirpichenok, N. S. Patalakha, and I. I. Grandberg

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A series of 3-aminomethyl-7-dialkylaminocoumarins were obtained as a result of the reactions of 7-diethylaminocoumarin, 4-methyl- and 4-chloro-7-diethylaminocoumarins, 4-methyl-7-pyrrolidinocoumarin, 4-methyl-7-piperidinocoumarin, 2,3,6,7-tetrahydro-1H,5H-quinolizino[9,9a,1-gh]coumarin, and 9-methyl-, 9-chloro-, and 9-morpholino-2,3,6,7-tetrahydro-1H,5H-quinolizino-[9,9a,1-gh]coumarins with formaldehyde and with a series of primary and secondary amines.

Known electrophilic substitution reactions in the 7-aminocoumarin series are mainly limited to examples of alkylation [1], halogenation [2], and formylation [3,4] and lead to the synthesis of 3-substituted derivatives. In the present work we examined the problem of introducing various aminomethyl groups at position 3 in order to obtain new luminophores, including water-soluble dyes, that could be found in the salts of such compounds. The particular interest in the luminescence-spectral characteristics of the 3-aminomethyl-7-aminocoumarins is due also to the fact that more rigid structures with an intramolecular hydrogen bond, can in principle be produced during the protonation of these substances, and this can in turn lead to an increase in the quantum yield of fluorescence [5].

As starting materials we used a series of 7-dialkylaminocoumarins (I-IX). Compounds (IV) and (V) were synthesized for the first time from 4-methyl-7-aminocoumarin by alkylation with 1,4-chlorobromobutane and 1,5-dibromopentane in DMFA solution in the presence of sodium bicarbonate (Tables 1-3). We used the Mannich reaction to introduce the aminomethyl group at position 3 [6]. tert-Butylamine, allylamine, benzylamine, piperidine, morpholine, N-methyloctadecylamine, and imidazole were brought into reaction with the coumarins (I-IX). The syntheses were conducted in acetic acid solution with the addition of 3 eq of formaldehyde in the form of formalin, and as a result the coumarins (X-XXVI) were obtained with yields of 60-95% (Table 1).

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