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

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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], synthsins 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).

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 ($\lambda_{\text{max}}$ 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

<table>
<thead>
<tr>
<th>Compound</th>
<th>Absorption λ&lt;sub&gt;max&lt;/sub&gt;, nm</th>
<th>pK&lt;sub&gt;a&lt;/sub&gt;</th>
<th>pK&lt;sub&gt;a&lt;/sub&gt;*</th>
<th>pK&lt;sub&gt;BII&lt;/sub&gt;</th>
<th>pK&lt;sub&gt;BB&lt;/sub&gt;*</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>395</td>
<td>314</td>
<td>384</td>
<td>12.20</td>
<td>10.70</td>
</tr>
<tr>
<td>II</td>
<td>393</td>
<td>312</td>
<td>387</td>
<td>12.09</td>
<td>11.14</td>
</tr>
<tr>
<td>III</td>
<td>396</td>
<td>310</td>
<td>388</td>
<td>11.97</td>
<td>10.69</td>
</tr>
<tr>
<td>IV</td>
<td>402</td>
<td>314</td>
<td>386</td>
<td>11.09</td>
<td>8.95</td>
</tr>
<tr>
<td>V</td>
<td>401</td>
<td>310</td>
<td>384</td>
<td>8.67</td>
<td>6.32</td>
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<tr>
<td>VI</td>
<td>404</td>
<td>320</td>
<td>384</td>
<td>8.74</td>
<td>6.17</td>
</tr>
<tr>
<td>VII</td>
<td>407</td>
<td>310</td>
<td>373</td>
<td>4.62</td>
<td>-0.08</td>
</tr>
<tr>
<td>VIII</td>
<td>410</td>
<td>326</td>
<td>392</td>
<td>12.04</td>
<td>9.69</td>
</tr>
<tr>
<td>IX</td>
<td>410</td>
<td>332</td>
<td>392</td>
<td>12.36</td>
<td>10.22</td>
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<tr>
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<td>394</td>
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<td>7.03</td>
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<tr>
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<td>416</td>
<td>325</td>
<td>403</td>
<td>9.00</td>
<td>7.07</td>
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<tr>
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<td>420</td>
<td>327</td>
<td>405</td>
<td>4.99</td>
<td>-0.57</td>
</tr>
<tr>
<td>XIII</td>
<td>429</td>
<td>328</td>
<td>386</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

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<sub>3</sub>, and CO<sub>2</sub>C<sub>2</sub>H<sub>5</sub> 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<sup>*</sup> 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 <sup>13</sup>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 <sup>13</sup>C NMR chemical shifts of the coumarins (VI) and (VII) in deuterochloroform are observed for the C(3), C(4), and C(5) atoms (Δδ 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 <sup>13</sup>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 (Δδ 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<sub>α</sub> 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

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