EVALUATION OF THE ACIDIC PROPERTIES OF HYDROXYCOUMARINS AND CHOICE OF SOLVENTS FOR PERFORMING POTENTIOMETRIC ANALYSIS

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The relative acidity constants (pK_a) for 17 hydroxycoumarins in water, methanol, acetone (Ac), dimethylformide (DMFA), and dimethyl sulfoxide (DMSO) have been determined by Henderson's method. The existence of a linear relationship between pK_a in water and pK_a in acetone, dimethylformamide, and dimethyl sulfoxide has been established. From the pK_a values the sequence of neutralization of the hydroxy groups has been determined: their acidic properties decrease in the sequence 4-OH > 7-OH > 6-OH > 8-OH. A quantitative evaluation of the conditions of titration in five solvents on the basis of the titration constants (pK_t) and of the values of the potential jumps and the shape of the potentiometric titration curves has permitted acetone to be proposed as the optimum solvent for the performance of potentiometric analysis.

The acidic properties of the hydroxycoumarins [3] are more pronounced than those of the anthraquinone derivatives [1] and flavonoid compounds [2] considered previously. As for the other two classes of compounds mentioned, there is no information in the literature on the acidic properties of the hydroxycoumarins in organic solvents nor the results of a comparison of these magnitudes with the analogous magnitudes in water. At the same time, a knowledge of the acidity constants is necessary for performing the analysis of these compounds and also for determining the conditions of chromatographic separation.

We have investigated the acidic properties of hydroxycoumarins in water, methanol, acetone (Ac), dimethylformamide (DMFA) and dimethyl sulfoxide (DMSO) with the aim of selecting conditions for potentiometric analysis.

Like the hydroxyanthraquinones [1] and flavonoids [2], under the conditions of the experiment hydroxycoumarins were acids of different strengths and basicities. Each of the overwhelming majority of hydroxycoumarins investigated had a single hydroxyl and titrated as a monobasic acid in all the solvents investigated. The titration curves showed that the sharpest jump was observed in acetone. On the titration of dihydroxycoumarins having hydroxyls in positions 4 and 7, two potential jumps were observed for each of these compounds in all the solvents investigated. In the case of the 6,7- and 7,8-dihydroxycoumarins in water and methanol there was only one potential jump, while in acetone and dimethylformamide each had two jumps. It is obvious that hydroxy groups in position 6 and 8 did not titrate under the experimental conditions, since monohydroxycoumarins with free hydroxyls in positions 6 and 8 do not titrate in an aqueous medium and the potential jumps in methanol are insignificant.

A calculation of pK_a values showed that the acidities fell in the sequence 4-OH- > 7-OH- > 6-OH- > 8-OH-coumarin (Table 1).

On passing from water to organic solvents, the pK_a values of the hydroxycoumarins increased, the linear relationship between $pK_a^{H_2O}$ and pK_a^M being characterized by the following equations:

$$pK_a^{Ac} = 1.73\ pK_a^{H_2O} - 0.59;$$

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TABLE 1. Values of the Relative Acidity Constants (pK_a) of Coumarin Derivatives

Compound	Solvent				
	water	methanol	acetone	DMFA	DMSO
1. 4-Hydroxycoumarin	4.10	8 70	7,60	8.15	9 53
2. 4-Hydroxy-5-methylcoumarin	4,20	8,11	8.34	9.40	10,77
3. 4-OH; 3-(CH(C$_6$H$_5$)–CH$_2$–C(=O)–CH$_3$) coumarin (zoocoumarin)	4,70	9.63	7 81	8.45	9,90
4. 3,3-Methoxycarbonylmethylenebis(4-hydrocoumarin) (neodicoumarin)	4,37	5,71	7,37	5.75	6,23
5. 6-Hydroxy-5,7-dimethoxycoumarin (fraxinol)	Does not titrate	8.63	11.26	9,29	12,62
6. 7-Glucosyloxy-6-hydroxycoumarin (cichoriin)	9,05	12,97	15 17	13,37	14,42
7. 7-Hydroxycoumarin (umbelliferone)	6 18	11,94	13,38	12.63	14.83
8. 7-Hydroxy-6-methoxycoumarin (scopoletin)	6.50	11,78	9 08	10,86	11,08
9. 6-Glucosyloxy-7-hydroxycoumarin (esculin)	7.45	10.89	9.79	11 54	11.81
10. 7-Hydroxy-6-(1,4,4-trimethylcyclohex-2-en-1-yl)coumarin (peucenol)	8,12	10,79	12,08	11,56	11,70
11. 8-Glucosyloxy-8-hydroxycoumarin (daphnin)	Does not titrate	12,42	14 40	12 19	13.47
12. 7,8-Dihydroxycoumarin (daphnetin)	6,44	11,35	14,08	11 77	13,18
13. 6,7-Dihydroxycoumarin (esculetin)	7,63	11,58	9,19	10,89	11.22
14. 8-Hydroxyfuro[3,2,6,7]coumarin (xanthotoxol)	8,02	10 87	13,02	13,16	14,80
15. 5-Hydroxyfuro[3,2,6,7]coumarin (bergaptol)	7,97	11.335	12 38	11,45	12,11
16. 4,7-Dihydroxycoumarin	4.60	10 83	14,83	13,80	15,71
	7.14	8,03	14.17	11,67	13.90
17. 4,7-Dihydroxy-5-methylcoumarin	4,23	10,15	13 37	11 12	12,96
	7,31	8,17	7,50	9,75	9.06
		10,39	10,04	11.04	12,54
			7,08	8,81	9,09
			9,90	11,44	12,67

$$pK_a^{DMFA} = 0.81\ pK_a^{H_2O} + 5.4;$$
$$pK_a^{DMSO} = 0.99\ pK_a^{H_2O} + 5.2.$$

The equations show the existence of a differentiation of the acidic properties of the coumarins in the series of solvent mentioned and, as in the case of the hydroanthraquinones and flavonoids, the greatest differentiating action is possessed by dimethyl sulfoxide, followed by acetone and dimethylformamide.

The values of pK_t show an improvement in the conditions of titration in the following sequence of organic solvents: dimethylformamide, acetone, dimethyl sulfoxide. The conditions of titration of the hydroxycoumarins with $pK_a^{H_2O} \geq 9$ improved to a greater degree, which permits the titration of the coumarins fraxinol and daphnin, which do not titrate in water, and clearer potential jumps to be obtained for bergaptol, xanthotoxol, and peucenol.

It has also been established that for the separate titration of the hydroxycoumarins according to their dissociation steps a pK_a difference of 2.54 in water, 2.12 in methanol, 2.82 in acetone, 2.27 in dimethylformamide and 3.48 in dimethyl sulfoxide is required. It follows from Table 1 that the optimum conditions for titration are created by dimethyl sulfoxide and acetone.

In view of the dissolving capacities of the solvents mentioned, the values of the potential jumps, and the forms of the titration curves, it is preferable to perform the analysis in acetone.

The order of neutralization in the titration of the dihydroxycoumarins has been determined from a calculation of the pK_a values of each of the hydroxy groups of the monohydroxycoumarins. It has been established that when 4- and 7-hydroxy groups are present the 4-hydroxy group, which has $pK_a^{H_2O}$ = 4.1-4.91, pK_a^{Ac} = 7.5-7.88; pK_a^{DMFA} = 8.15-8.81, pK_a^{DMSO} = 6.5-8.09 must undergo neutralization first and the 7-hydroxy group for which pK_a = 6.18-6.50; 9.08-9.79; 10.86-11.54 and 11.54-11.81 second.

When 6- and 7-hydroxy groups (esculetin) and 7- and 8-hydroxy groups (daphetin) are present simultaneously, the 7-hydroxy group titrates first, since the pK_a values of the

TABLE 2. Values of the Titration Constants (pK_t) of the Hydroxycoumarins

Compound	Solvent									
	water		methanol		acetone		dimethyl-formamide		dimethyl sulfoxide	
	pK_t	pK_t	pK_t	pK_t	pK_t	pK_t	pK_t	pK_t	pK_t	pK_t
1. 4-Hydroxycoumarin	9.90		8,00		15,60		9,85		23,70	
2. 4-Hydroxy-5-methyl coumarin	9.80		8,58		14,16		9,66		22,50	
3. 4-OH-3-C(C$_6$H$_5$)(—C(=O)—CH$_3$)—coumarin (zoocoumarin)	9,30		7,07		15 29		9,55		23,30	
4. 3,3-Ethoxycarbonyl-methylbis(4-hydroxy coumarin)	9 63		10 99	2,92	15,73	3,99	12,25	3,54	27,07	6,39
5. 6-Hydroxy-5,7-dimethoxycoumarin (fraxinol)	Does not titrate		3,73		7,93		4,63		18,47	
6. 7-Glucosyloxy-6-hydroxycoumarin (cichoriin)	4,95		4,76		9,80		5,37		18,88	
7. 7-Hydroxycoumarin (umbelliferone)	7,82		4,92		14,02		7,14		22,32	
8. 7-Hydroxy-6-methoxycoumarin (scopoletin)	7,50		5,81		13,31		6,46		21,49	
9. 6-Glucosyloxy-7-hydroxycoumarin (esculin)	6,55		5,97		11,02		6,44		21 60	
10. 7-Hydroxy-6-(1,4,4-trimethylcyclohex-2-en-1-yl)coumarin (peucenol)	5 88		4 28		8,70		5,80		19,83	
11. 7-Glucosyloxy-8-hydroxycoumarin (daphnin)	Does not titrate		5,35		9 02		6,23		20.12	
12. 7,8-Dihydroxycoumarin (daphnetin)	7,56		5.12		13,91	3,83	7.11	2.27	22,08	3,58
13. 6,7-Dihydroxycoumarin (esculetin)	6,47		5 83		10,12	2,45	6 55	2.35	21,19	3,60
14. 4,7-Dihydroxycoumarin	9 40	2,54	8,67	2,12	15,60	3,54	9,25	2 58	24 24	3 48
15. 4,7-Dihydroxy-5-methylcoumarin	9.77	3,08	8,53	2.22	16,02	7,82	9.19	2,63	23,40	3 58
16. 8-Hydroxyfuro[2',3',6,7]coumarin (xanthotoxol)	5 98		5,365		8.92		6 33		19,40	
17. 5-Hydroxyfuro[2',3',6,7]coumarin (bergaptol)	6 03		5 81		9.73		6 88		20,34	

6-hydroxy group are 15.17 in acetone, 13.37 in DMFA, and 14.42 in DMSO and the pK_a values of the 8-hydroxy group are 14.08, 11.77, and 13.18, respectively. Neither of these compounds titrates in water. The separate determination of the hydroxy groups can be performed only in acetone and dimethyl sulfoxide with the neutralization first of the 6- and then of the 8-hydroxy group.

EXPERIMENTAL

The investigation was performed on a Radiometer automatic potentiometer with a glass-calomel electrode system. The titrants were a standard 0.01 N benzene–methanol (4:1) solution of tetraethylammonium hydroxide and a 0.01 N methanolic solution of sodium hydroxide. Dilute solutions (0.02 N) were used at an experimental temperature of 20 ± 1°C. The purity of the substances investigated was checked chromatographically in the benzene–methanol (8:2) and benzene–acetic acid (5:2) systems with the sorbent KSK silica gel [4] and in the cyclohexane–ethyl acetate–methanol (12:4:1) system with alumina as the sorbent [5]. The spots were revealed in UV light before and after treatment of the chromatograms with a 5% ethanolic solution of caustic soda.

The pK_a values in the solvents investigated were calculated by means of a modified Henderson formula [1, 2, 6].

SUMMARY

1. The relative acidities (pK_a values) of 17 hydroxycoumarins in water, methanol, acetone, dimethylformamide, and dimethyl sulfoxide have been determined.

2. Linear equations have been derived for the relationship between $pK_a^{H_2O}$ and pK_a in acetone, dimethylformamide, and dimethyl sulfoxide.

3. On the basis of the titration constants (pK_t), the shapes of the curves, and sizes of the potential jumps, acetone has been proposed as the optimum solvent for performing potentiometric analysis.

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BASICITY CONSTANTS OF NATURAL ISOFLAVONOIDS

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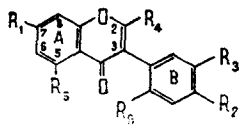
The basicities (pK_{BH+}) of 13 natural isoflavones have been determined spectrophotometrically in sulfuric acid solutions. It has been shown that the change of basicity in this series of compounds depends on the geometry of the molecules and on intramolecular effects.

Quantitative information on the basicities of natural flavonoids is not only of interest for judging their electronic structure but may also have practical use, for example, in pharmaceutical analysis. At the present time, the basicities of the flavonones and flavonols have been studied in fairly great detail [1-4], but there is almost no such information on isoflavonoid compounds.

We have determined the basicities of a number of natural isoflavonoids possessing valuable pharmacological properties – in particular, pronounced antiatherosclerotic activity [5] – by a spectrophotometric method.

Structures of the compounds studied:



I. $R_1=R_2=R_3=R_4=R_5=R_6=H$
II. $R_1=OH$; $R_2=R_3=R_4=R_5=R_6=H$
III. $R_1=R_2=OH$; $R_3=R_4=R_5=R_6=H$
IV. $R_1=OH$; $R_2=OCH_3$; $R_3=R_4=R_5=R_6=H$
V. $R_1=R_2=OCH_3$; $R_3=R_4=R_5=R_6=H$
VI. $R_1=OH$; $R_2=R_3=OCH_3$; $R_4=R_5=R_6=H$
VII. $R_1=R_2=R_3=OCH_3$; $R_4=R_5=R_6=H$
VIII. $R_1=OH$; $R_4=CH_3$; $R_2=R_3=R_5=R_6=H$
IX. $R_1=R_2=OCH_3$; $R_5=OH$; $R_3=R_4=R_6=H$
X. $R_1=R_2=R_5=OH$; $R_3=R_4=R_6=H$

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