Synthesis, Structure and Acid-Base Behaviour of Some 4-Hydroxycoumarin Derivatives

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The compound 3,3′-[(4-hydroxy-3-methoxy-5-nitrophenyl)methylene]-bis(4-hydroxy-2*H*-1-benzopyran-2-one) (**1**) crystallizes in the monoclinic system, space group $P2_1/n$, with cell constants a = 16.859(4), b = 6.1624(15), c = 25.164(4) Å, β = 98.019(19)°. The two 4-hydroxycoumarin fragments are intramolecularly hydrogen-bonded between hydroxyl and carbonyl groups. The pH-dependent color changes of 4-hydroxycoumarin derivatives were studied by means of potentiometric and spectrophotometric titration. On the basis of the results obtained, the use of 3,3′-[(4-hydroxy-3-methoxy-5-nitrophenyl)methylene]-bis(4-hydroxy-2*H*-1-benzopyran-2-one) as an indicator in alkalimetry and acidimetry is proposed.

Key words: 4-Hydroxycoumarin, X-Ray Diffraction Analysis, Acid-Base Titration, Spectrophotometry, Indicators

Introduction

The coumarin unit is a chromophore with an absorption maximum at 306 – 320 nm. The presence of auxochromic substituents may result in a bathochromic shift with the appearance of absorption in the visible spectral region. With substituents exhibiting acid-base properties, the wavelength at which an absorption maximum is observed depends on the degree of deprotonation. It is known that in an alkaline medium, 6-acetyl-5-hydroxy-4-methylcoumarin is bright yellow, while in an acid medium the solution is colourless [1]. 3-Carbethoxy-4-[2-[4-(dimethylamino)phenyl]ethenyl]coumarin reveals several colour transitions and its application in titrimetric analysis is quite promising [2, 3].

To the best of our knowledge, there are no data in the literature describing the acid-base indicator properties of bis-coumarins and/or other 4-hydroxycoumarin derivatives. In the present study the colour changes in solutions of 4-hydroxycoumarin derivatives depending on the pH of the medium are investigated. On the basis of the results obtained, the application of some of the investigated substances as acid-base indicators is proposed.

Results and Discussion

The 4-hydroxycoumarin derivatives are insoluble in water, but dissolve readily in alkaline hydroxides due to the acidic nature of the enolic hydroxyl group. Upon dissolution in alkaline hydroxides, the corresponding salts are formed, while with an excess of the hydroxide and/or upon heating, the coumarin lactone ring is cleaved.

It was established that the arylidene-bis(4-hydroxy-2*H*-1-benzopyran-2-ones) containing a hydroxyl group in *p*-position with respect to the aldehyde group of the aromatic aldehyde form alkaline solutions with persistent colour. Obviously, the enolic hydroxyl groups in the coumarin moieties are also important. In an alkaline medium, the solution containing 3,3′-[(4-hydroxy-3-methoxy-5-nitrophenyl)methylene]-bis(4-hydroxy-2*H*-1-benzopyran-2-one) (**1**) becomes red-orange, while the alkaline solution of the epoxy-compound 3,3′-[(4-hydroxy-3-methoxy-5-nitrophenyl)methylene]-4,4′-epoxydicoumarin (**2**) is almost colourless [4, 5].

On the basis of the colour changes of solutions of compound **1** at various pH values, its indicator range was determined. The experimentally established range

Table 1. Determination of the interval of conversion of compound **1**.

Substance	pH	Runs A	Runs B	Runs C	Average value	Interval of conversion
1	pH_1	8.5	8.3	8.4	8.4	6.6 – 8.4 yellow – red-orange
	pH_2	6.5	6.6	6.5	6.6	

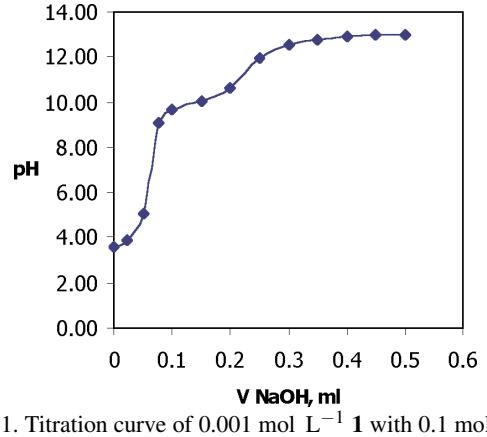


Fig. 1. Titration curve of 0.001 mol L^{-1} **1** with 0.1 mol L^{-1} NaOH in 96 % ethanol.

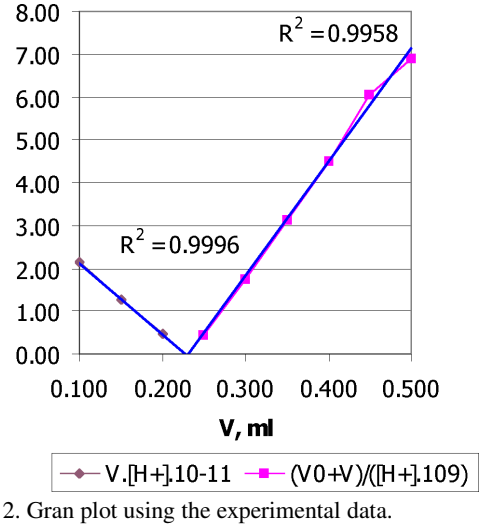


Fig. 2. Gran plot using the experimental data.

is close to that of *o*-nitrophenol, suggesting that the *o*-position of the nitro group with respect to the phenolic hydroxyl group in this compound is the reason for its acid-base indicator behaviour (Table 1).

The pK_a values of the compounds studied cannot be determined potentiometrically in water because these compounds are water-insoluble. The method of Gran was used and the value of pK_a = 9.8 was found for compound **1**. The titration curve is represented in

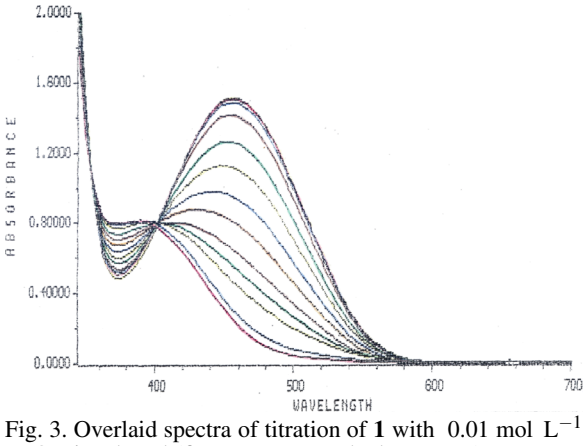


Fig. 3. Overlaid spectra of titration of **1** with 0.01 mol L^{-1} NaOH in ethanol (first spectrum at the lowest pH).

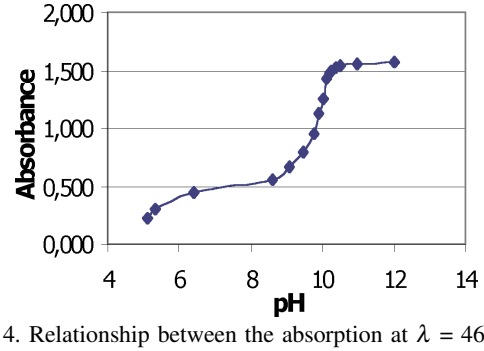


Fig. 4. Relationship between the absorption at λ = 460 nm and the pH of the solution of **1** in ethanol.

Fig. 1. A Gran-plot using the experimental data is shown in Fig. 2.

Absorption spectrophotometry was used in the investigation of the pH-dependence. Fig. 3 shows the absorption spectra of an ethanol solution of compound **1** upon titration with sodium hydroxide. The ethanol solution reveals an absorption maximum in the range of 365 – 420 nm. Alkalization of the solution results in a shift of the maximum to 460 nm. Well expressed isobestic points at 352 and 404 nm are observed, indicating the existence of a protonated and a deprotonated form in equilibrium. After the addition of each portion of sodium hydroxide to the solution studied, the pH value was measured and the experimental titration curve plotted in pH/absorption coordinates (Fig. 4).

Table 2 shows the results from the back titration of sodium hydroxide (0.01 mol L^{-1}) with hydrochloric acid (0.01 mol L^{-1}) using a solution (0.001 mol L^{-1}) of **1** in 96 % ethanol as an indicator. The colour transition (the indicator range) in aqueous medium of this compound is in the pH range of 6.6 – 8.4. The equiv-

Table 2. Results of the titration of 0.01 mol L^{-1} solutions of NaOH and HCl using **1** as an indicator.

Sample No.	Volume NaOH [mL]	Theoretical volume HCl [mL]	Experimental volume HCl [mL]	Deviation [%]
1.	20.00	20.00	20.00	0.00
2.	20.00	20.00	20.02	+0.10
3.	20.00	20.00	20.00	0.00
4.	20.00	20.00	19.98	−0.10
5.	20.00	20.00	20.02	+0.10
		average values:	20.00	+0.02

Standard deviation, s = 0.02; percent error $\varepsilon = 0.07\,\%$.

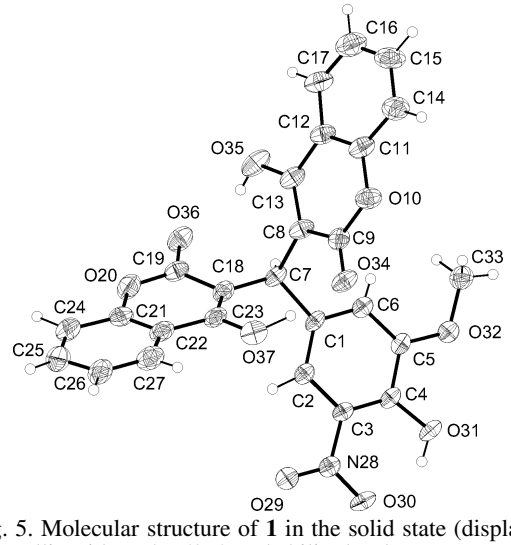


Fig. 5. Molecular structure of **1** in the solid state (displacement ellipsoids at the 50 % probability level).

alence point upon titration of strong protolytes with a concentration of 0.01 mol L^{-1} is in the pH range of 5 – 9 [6].

In conclusion, compound **1** is appropriate as an acid-base indicator. This compound can be dissolved in a readily available, cheap, safe, and water-miscible solvent, 96 % ethanol. It has the highest molar absorptivity in the visible spectral region, *i. e.*, it can be used at a sufficiently low concentration. Its presence does not affect the protolysis equilibrium during the acid-base titration. The acid-base equilibrium for a given pH value is rapidly established, so that the changes in the intensity with time are minimal.

Crystal structure

Yellow plates suitable for an X-ray diffraction analysis were grown by slow evaporation of an acetone solution of compound **1**. Crystallographic data are listed in Table 3, the molecular structure is shown in Fig. 5.

Table 3. Crystal data and structure refinement for **1**.

Empirical formula	$C_{26}H_{17}NO_{10}$
Formula weight	503.41
Temperature [K]	213(2)
Wavelength [Å]	1.54184
Crystal system, space group	monoclinic, $P2_1/n$
Unit cell dimensions	a = 16.859(4) Å b = 6.1624(15) Å, β = 98.019(19)° c = 25.164(4) Å
Volume [$Å^3$]	2588.8(10)
Z	4
Density (calculated), g cm^{-3}	1.292
Absorption coefficient, mm^{-1}	0.859
F(000)	1040
Crystal description	yellow plate
Crystal size [mm^3]	$0.25 \times 0.25 \times 0.1$
θ range for data collection [deg]	14.90 – 61.12
Index ranges	$-1 \le h \le 19$, $0 \le k \le 6$, $-28 \le l \le 28$
Reflections collected	4276
Independent reflections	3859
R(int)	0.0403
Reflections observed [$I \ge 2\sigma(I)$]	2175
Absorption correction	psi-scans
Max./min. transmission	0.9398/0.7441
Data/refined parameters	3859/370
Goodness-of-fit on F^2	0.953
Final R indices $R1/wR2$ [$I \ge 2\sigma(I)$]	0.0879/0.2223
Final R indices $R1/wR2$ (all data)	0.1493/0.2501

Table 4. Selected bond lengths (Å) for **1**.

C3 – N28	1.443(6)	C13 – O35	1.331(6)
C4 – O31	1.359(5)	C18 – C23	1.332(7)
C5 – O32	1.354(6)	C18 – C19	1.503(7)
C7 – C18	1.491(7)	C19 – O36	1.199(6)
C7 – C8	1.516(7)	C19 – O20	1.318(6)
C8 – C13	1.364(7)	O20 – C21	1.386(7)
C8 – C9	1.471(7)	C22 – C23	1.463(8)
C9 – O34	1.207(6)	C23 – O37	1.338(6)
C9 – O10	1.359(6)	N28 – O29	1.223(5)
O10 – C11	1.377(6)	N28 – O30	1.252(5)
C12 – C13	1.441(7)	O32 – C33	1.417(7)

Table 5. Selected bond angles (deg) for **1**.

O34 – C9 – O10	115.5(5)	O34 – C9 – C8	124.4(5)
O35 – C13 – C8	123.1(5)	O35 – C13 – C12	114.1(4)
O36 – C19 – O20	119.3(5)	O36 – C19 – C18	122.8(5)
O37 – C23 – C22	114.0(5)		

Two 4-hydroxycoumarin moieties are linked through a methylene bridge on which one hydrogen atom has been replaced by a 4-hydroxy-3-methoxy-5-nitrophenyl residue. Bond lengths and angles are given in Tables 4 and 5. Most of the distances are of expected length. The C1 – C7 distance of 1.539(6) Å is slightly longer than an unstrained C(sp^3) – C(Ar) bond [7, 8]. The exocyclic angles

about C8 (C13 – C8 – C7 124.0(5)°; C9 – C8 – C7 119.0(4)°) and for C18 (C19 – C18 – C7 113.9(4)°, C23 – C18 – C7 127.0(5)°) are analogous to those of the bromine derivative. These results show that two 4-hydroxycoumarin residues are arranged in a position which permits the formation of two intramolecular hydrogen bonds between the hydroxyl group of one coumarin fragment and the lactone carbonyl group of the other (O34···O37 2.650 Å, O35···O36 2.747 Å) [9, 10]. An analogous structure of a bis-coumarin with this type of location of two coumarin residues and two intramolecular hydrogen bonds between them was confirmed by the calculations of Trendafilova *et al.* [11, 12].

Experimental Section

Chemicals were reagent grade and were purchased from Fluka. Melting points were measured using a Boetius hot plate microscope (Germany) and are uncorrected. IR spectra (nujol) were recorded on an IR-spectrometer FTIR-8101M Shimadzu. ^{1}H NMR spectra were recorded at ambient temperature on a Bruker 250 WM (250 MHz) spectrometer in [D_6]acetone. Chemical shifts are given in ppm (δ) relative to TMS used as an internal standard. Mass spectra were recorded on a Jeol JMS D 300 double focusing mass spectrometer coupled to a JMA 2000 data system. The compounds were introduced *via* a direct inlet probe, heated from 50 to 400 °C at a rate of 100 °C/min. The ionization current was 300 mA, the accelerating voltage was 3 kV and the chamber temperature was 150 °C. TLC was performed on precoated plates Kieselgel 60 F_{254} Merck (Germany) with a layer thickness of 0.25 mm and UV detection (254 nm). Yields of TLC-homogeneous isolated products are given. The analyses indicated by the symbols of the elements were within ±0.3 % of the theoretical values. The HP 8452 A UV/vis spectrophotometer (Hewlett-Packard, USA, diode-array detector, quartz cell 1 cm thick, step width 2 nm, scanning rate 1 s), and a Metrohm 744 pH-meter (Metrohm, Switzerland) were used.

*Synthesis of 3,3′-[(4-hydroxy-3-methoxy-5-nitrophenyl)-methylene]-bis(4-hydroxy-2H-1-benzopyran-2-one) (**1**)*

4-Hydroxycoumarin (3.24 g, 20 mmol) and 4-hydroxy-3-methoxy-5-nitrobenzaldehyde (1.97 g, 10 mmol) in 50 mL of glacial acetic acid were mixed under stirring and heated at reflux until yellow crystals separated (5.5 h). After cooling the product was filtered and recrystallized from acetonitrile. Yield 4.36 g (87 %), m. p. 171 – 173 °C. TLC (hexane/chloroform/acetone 5 : 3 : 2): R_f = 0.13. Anal. $C_{26}H_{17}NO_{10}$ (503.41): calcd. C 62.03, H 3.38, N 2.78; found C 62.08, H 3.62, N 2.63. – IR (nujol) ν = 1651, 1607, 1456, 1377, 1098, 762 cm^{-1}. – ^{1}H NMR (DMSO): δ = 3.6 – 3.8 s (3H), 5.1 s (1H), 5.4 – 6.1 s (2H), 6.1 – 6.3 s (1H), 7.0 – 8.0 m (10H). – MS: *m/z* (%) = 503 (13), 468 (4), 341 (15), 310 (5), 264 (2), 149 (3), 120 (100), 92 (64), 63 (46).

*Synthesis of 3,3′-[(4-hydroxy-3-methoxy-5-nitrophenyl)-methylene]-4,4′-epoxydicoumarin (**2**)*

4-Hydroxycoumarin (3.24 g, 20 mmol) and 4-hydroxy-3-methoxy-5-nitrobenzaldehyde (1.97 g, 10 mmol) in 50 mL acetic acid anhydride were mixed under stirring and heated at reflux for 3 h. After cooling the product was filtered and was recrystallized from acetonitrile. Yield 2.06 g (43 %), m. p. 278 – 281 °C. TLC (hexane/acetone 2 : 1): R_f = 0.37. Anal. $C_{26}H_{15}NO_9$ (485.40): calcd. C 64.33, H 3.09, N 2.89; found C 63.98, H 3.46, N 3.12. – IR (nujol): ν = 1779, 1732, 1672, 1613, 1456, 1179, 762 cm^{-1}. – ^{1}H NMR ([D_6]DMSO): δ = 3.1 – 3.4 s (3H), 5.0 – 5.1 s (1H), 6.8 – 7.0 s (1H), 7.5 – 8.5 m (10H). – MS: *m/z* (%) = 503 (13), 468 (4), 341 (15), 310 (5.5), 264 (1.5), 149 (3), 120 (100), 92 (64), 63 (46).

Photometric titration

Sodium hydroxide solutions (0.1 mol L^{-1} and 0.01 mol L^{-1}); hydrochloric acid solutions (0.1 mol L^{-1} and 0.01 mol L^{-1}); phosphate buffers prepared from two solutions: I: 8 g anhydrous NaH_2PO_4 dissolved in water (1000 mL), and II: 9.47 g anhydrous Na_2HPO_4 dissolved in water (1000 mL).

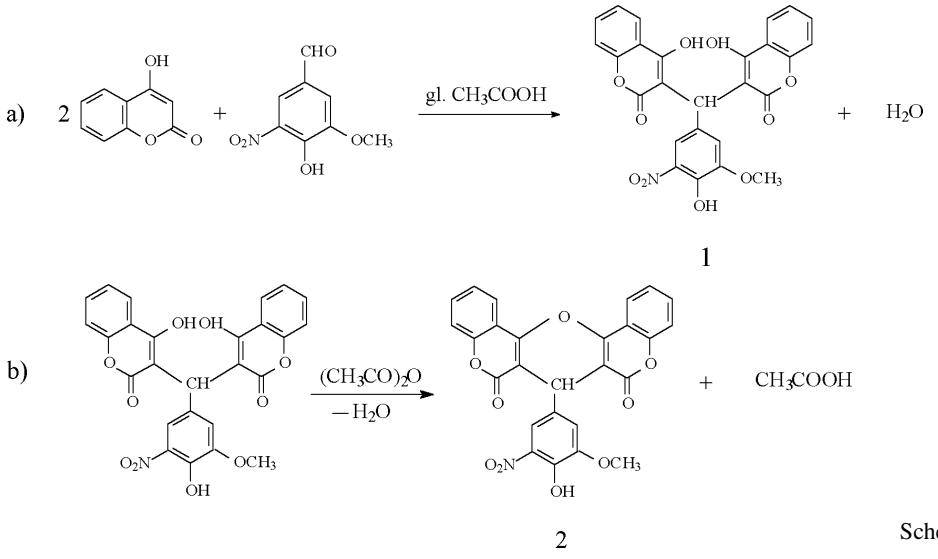
An aliquot (5 mL) of a solution of the investigated compound in 96 % ethanol (0.001 mol L^{-1}) was diluted three-fold with ethanol in order to obtain a solution with optimal absorption in the visible spectral region. This solution was titrated with sodium hydroxide (0.01 mol L^{-1}) in 96 % ethanol. After the addition of each portion of 0.001 mL, the pH value and the absorption of the solution were measured. From the overlaid spectra, the absorption at λ_{max} was determined at each pH value.

Potentiometric titration

After the addition of each portion of titrant, the pH value of the solution was measured at r. t.

X-Ray crystal structure analysis

Data collection was carried out at −60 °C using graphite-monochromated CuK_α radiation (λ = 1.5418 Å) on an Enraf Nonius four-circle diffractometer. The unit cell constants were determined and refined using the CAD4-EXPRESS program. A semiempirical absorption correction was performed using the PLATON/ABS PSI program [13]. The structure was solved with Direct Methods by SHELXS-97 [14] and refined with SHELXL-97 [15] by least-squares methods based on F^2. All non-hydrogen atoms were refined anisotropically and all



Scheme 1.

hydrogen atom positions were taken from the electron density map and refined isotropically. The plots of the molecular structure were made using the program DIAMOND [16].

Complete data collection parameters and details of the structure solution and refinement are given in Table 3. CCDC 628866 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

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