Experimental and theoretical investigation of the structure and nucleophilic properties of 4-aminocoumarin

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Abstract

4-Aminocoumarin **2** was prepared in high yield via solventless reaction. The structure of the **2** was determined with single crystal X-ray analysis. The detailed NMR and IR spectra were reported for the first time. DFT calculations [B3LYP/6-31+G**] showed good agreement between the theoretical and experimental values for the optimized and X-ray structures, as well as between the vibrational and NMR spectroscopy. The thermodynamic pK_{BH+} values were calculated using three different methods: Yates and McClelland (with H_A acidity functions), Excess Acidity Method and Bunnett and Olsen Method. The experimental and theoretical data presented are consistent with the weak nucleophilic properties of **2**.

Keywords: 4-Aminocoumarin, crystal structure, spectra, nucleophilic properties

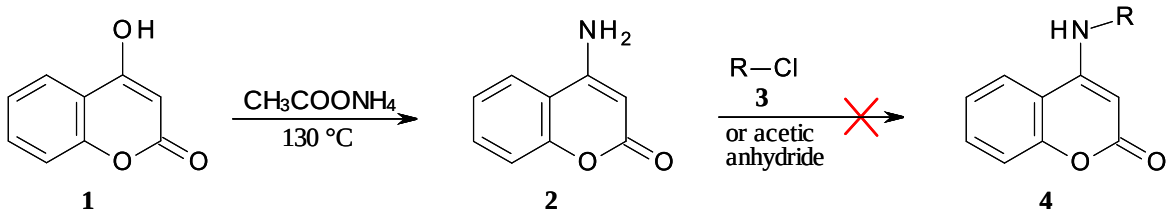
Introduction

Coumarin and its derivatives from natural products, either semi-synthetic or synthetic, represent one of the most active classes of compounds exhibiting a wide spectrum of biological activity. Additionally, coumarin derivatives are used as additives in food and cosmetic industry. Due to the significance of these compounds, the quest for efficient syntheses of coumarin ring compounds[1] as well as new bioactive derivatives from known coumarins[2] is topic.

From the group of aminocoumarins, 3-aminocoumarin and 7-aminocoumarin derivatives are well studied. The 3-aminocoumarin moiety can be recognized in the molecular structure of

several natural antibiotics, such as novobiocin, chlorobiocin, coumermycin, etc. These antibiotics and their derivatives are in the research focus.[3] In addition, some simple N-acylderivatives of 3-aminocoumarin exhibit an anti-inflammatory activity[4] and antimicrobial activity against the Gram-positive bacteria.[5] Most of the publications for 7-aminocoumarin derivatives present interesting photochemical behavior of these compounds[6] and many of them can be used as fluorescent markers.[7] Furthermore, some platinum complexes of 7-aminocoumarins have been synthesized and evaluated for their *in vitro* cytotoxicity against Caco-2T cells.[8] Derivatives of 4-aminocoumarin **2** were not studied that much, although some of them possess biological activity as well.[9]

The interesting chemical and physical properties and the pharmacological effects of aminocoumarin derivatives were the main motivation for starting this research. At first, the compound **2** was synthesized as a starting compound for the synthesis of large spectra of new coumarin derivatives. However, during the research we have noticed that the amino group in this compound was very weak nucleophile. In contrast to 3-aminocoumarin, aniline, naphthylamine or similar compounds, which are also weak bases, the amino group of **2** did not react with **3** (Scheme 1; alkyl halides, acyl halides, acetic anhydride, etc) to obtain **4** (N-substituted derivatives). Considering reactions of **2**, in few publications only it was presented that instead with nitrogen, electrophiles can form a bond with carbon in position 3 (position C8 in Figure 1).[10] To our knowledge, in only three references, reactions of nitrogen in **2** were presented,[11] however, the reported yields of the desired products were very poor. Generally, N-substituted derivatives of **2** have been obtained by the reactions of amino compounds with 4-chlorocoumarin[12,10a] or 4-hydroxycoumarin **1**.[13]



Scheme 1

Detailed knowledge of the structure and spectral behavior of **2** is a necessary prerequisite for understanding its chemical and biological properties. To our surprise, neither NMR nor IR spectra of the title compound have been studied in detail. The purpose of the present study is to elucidate the structure by single crystal X-ray diffraction, UV, NMR and IR spectroscopy. The experimental data will be accompanied by theoretical prediction at different level of approximation in order to draw out the conclusion on the structure-property relationship.

Results and Discussion

Synthesis and crystal growth

Synthesis of **2** was performed at 130 ºC via solid state reaction of **1** with excess of ammonium acetate (Scheme 1). Excellent pale yellow crystals for X-ray measurement were obtained by slow cooling of ethanol solution of **2**.

Crystal structure

Molecular structure of compound **2** is shown in Figure 1. The selected bond lengths and angles are given in Table 1.

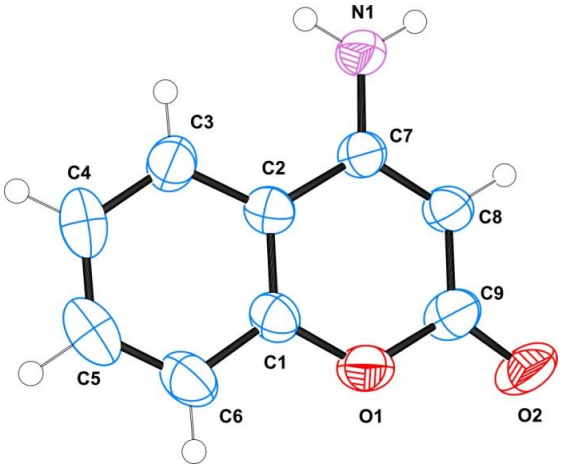


Figure 1. The molecular structure of the title molecule with the atom-numbering scheme; displacement ellipsoids are drawn at the 50 % probability level.

In the molecule of the title compound **2** (Figure 1), the bond lengths and angles are within normal ranges.[14] The 4-aminocoumarin is almost a planar molecule (rms of 0.0146 Å for the chromene ring). The deviation of planarity is possibly caused by the intermolecular hydrogen bonding, which builds pseudo-layers parallel to *bc* plane (Table 2, Figure 2). The pseudo-layers are stacked trough π-π interaction, as evidenced by the distance of ca. 3.48 Å between the chromene ring mean planes.

The C7-N1 bond distance (1,335 Å) is just somewhat longer then an average C=N double bond and little bit shorter then C≈N bond in pyridine (1,337 Å),[15] indicating a considerable degree of double bond character.

Table 1. Selected bond lengths and angles from crystallographic data and comparison with the theoretical data[a]

Parameter	X-ray	B3LYP/6-31+G**	HF/6-31+G**
C2—C1	1.386 (4)	1.408	1.389
C2—C3	1.403 (4)	1.403	1.399
C2—C7	1.450 (4)	1.460	1.466
O1—C1	1.374 (3)	1.360	1.360
N1—C7	1.335 (3)	1.374	1.370
C8—C7	1.372 (4)	1.370	1.347
C8—C9	1.399 (4)	1.437	1.440
O2—C9	1.239 (3)	1.213	1.395
C1—C6	1.372 (4)	1.399	1.390
C3—C4	1.368 (4)	1.389	1.377
C6—C5	1.376 (4)	1.389	1.378
C5—C4	1.379 (4)	1.403	1.399
C1—C2—C3	117.6 (3)	118.1	118.3
C1—C2—C7	118.1 (3)	117.2	117.0
C3—C2—C7	124.3 (3)	124.6	124.7
C1—O1—C9	120.5 (2)	122.1	123.2
C7—C8—C9	122.3 (3)	122.9	122.2
C6—C1—O1	115.9 (3)	116.5	116.6
C6—C1—C2	122.1 (3)	121.1	121.3
O1—C1—C2	122.0 (3)	122.4	122.1
O2—C9—O1	113.9 (3)	116.9	118.0
O2—C9—C8	127.2 (3)	126.8	125.5
O1—C9—C8	118.9 (3)	116.2	116.5
C4—C3—C2	120.8 (3)	121.1	120.9
N1—C7—C8	121.6 (3)	121.8	122.3
N1—C7—C2	120.3 (3)	119.2	118.8

[a] For atom numbering see Figure 1.

Table 2. Hydrogen bond geometry for 4-Aminocoumarin

	D—H [Å]	H...A [Å]	D...A [Å]	D—H...A [º]
NH0A...O1[i]	0.860	2.149	2.938	152.32
N-H0B...O1[i i]	0.860	2.103	2.925	159.75
Symmetry operation: (i) -*x*+1/2, *y*-1/2, -*z*+1/2 (ii) *x*, -*y*, *z*+1/2				

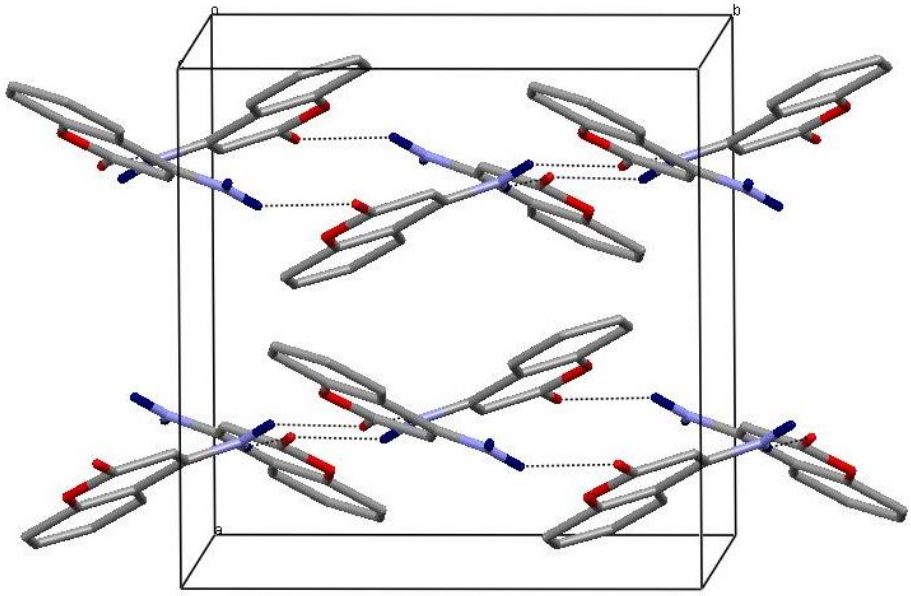


Figure 2. Crystal packing along the *c* axis showing the propagation of the pseudo-layers propagating parallel to *bc* plane.

Infrared spectra

Selected numeric values of measured frequencies together with calculated B3LYP/6-31+G** frequencies and intensities and PED matrix are presented in the Table 3. As one can see, the correlation between experimental and scaled theoretical frequencies is very high. In our study, to determine the types of molecular motion associated with each of the observed experimental bands, the computed vibrational data was used.

The greatest differences between theoretical and experimental IR data correspond to the NH_2 stretching vibrations. The calculations predict that the higher-frequency band (3588 cm^{-1}) corresponds to the asymmetric NH_2 mode, whereas the other one (3478 cm^{-1}) is assigned to the symmetric one. The measured amino frequencies of 3394 and 3219 cm^{-1} are significantly lower than theoretically predicted ones, due to the formation of strong hydrogen bonds in solid state. The theory predicted the low intensities of the *ν*(PhH) bands. In solid state IR spectra it is a problem to distinguish these fundamental bands.

With a qualitative agreement between theory and experiment, the (C=O) band is the strongest one in the spectrum. Experimentally, the very strong band detected at 1634 cm^{-1}, is considerably lower than the value of 1729 cm^{-1}, measured for unsubstituted coumarin.[16] The lower frequency value is an indication for the occurrence of strong conjugation between the C=O and NH_2 groups. The normal vibration, dominated by ν(C-N) coordinate was predicted near 1400 cm^{-1} and measured at 1438 cm^{-1}. For aromatic amines, the frequency of the ν(C-N) band appears at 1360-1250 cm^{-1} frequency region. The significantly higher frequency in our conjugated molecule is

another evidence for the occurrence of charge transfer towards the electron withdrawing CO group.

Table 3. Selected theoretical and experimental vibrational frequencies (ν in cm^{-1}) and IR integrated intensities (A in $km.mol^{-1}$) of 4-aminocoumarin

$\nu_{calc.}$ [a]	$A_{calc.}$	$\nu_{exp.}$	Approximate description[b]
3588	30.2	3394	$100\,\nu^{as}_{NH_2}$
3478	41.9	3218	100
1737	820.2	1634	83
1615	337.7	1601	$45\,\delta_{HNH}$, 23
1603	83.5		$35\,\nu^{Ph}_{CH}$, $15\,\delta^{Ph}_{CCC}$, 12
1587	3.1		$30\,\nu^{Ph}_{CH}$, $24\,\delta_{HNH}$, $15\,\nu_{CC}$
1545	58.8	1547	$41\,\nu^{Ph}_{CH}$, $19\,\nu_{CC}$
1477	26.1	1509	$37\,\delta^{Ph}_{CCH}$, $12\,\nu^{Ph}_{CC}$
1430	17.9	1459	$35\,\delta^{Ph}_{CCH}$, $23\,\delta^{Ph}_{CCC}$
1400	90.9	1438	24, $16\,\delta^{Ph}_{CCC}$, 11
1326	23.3	1333	$77\,\nu^{Ph}_{CC}$
1268	1.5		24, 22, $14\,\delta_{CCH}$, 12
1261	27.0	1266	$62\,\delta^{Ph}_{CCC}$
1235	46.1		$23\,\delta^{Ph}_{CCH}$, 17, 14
1159	96.5	1196	$30\,\delta^{Ph}_{CCH}$, 16, 16
1147	21.8	1120	$44\,\delta^{Ph}_{CCH}$, $25\,\nu^{Ph}_{CC}$
1123	6.2		$48\,\delta^{Ph}_{CCH}$
1094	36.1	1077	$13\,\delta_{CNH}$, $11\,\delta^{Ph}_{CCH}$

[a]Scaled by 0.9648.[17]

[b] Vibrational modes: ν, stretching; δ, in plane and out of plane deformations; τ, torsion; The numbers before the mode symbols indicate % contribution (10 or more) of a given mode to the corresponding normal vibration, according to the potential energy distribution matrix.[18]

^{1}H and ^{13}C NMR Spectra

To the best of our knowledge, the full NMR spectra of **2** have not been published yet. Therefore, the experimental and calculated ^{1}H and ^{13}C spectra (Table 4) in this paper were included. The

spectra were assigned with assistance of 1 and 2D (COSY, HMQC and HMBC) NMR spectra. The calculated spectral data were in agreement with the experimental.

Table 4. Calculated (HF/6-31+G**) and experimental ^{1}H (250.13 MHz) and ^{13}C (62.89 MHz) NMR spectral data (chemical shifts, δ in ppm; coupling constants *J* in Hz)

No.[a]	Calc.	Exp.
C1	154.0	153.7
C2	112.6	114.5
C3	123.9	123.0
C4	119.3	123.3
C5	134.7	132.1
C6	117.0	116.8
C7	156.4	155.7
C8	87.0	84.0
C9	156.2	161.8
H3	7.91	7.98 dd (8.3, 1.2)
H4	7.44	7.30 overl.
H5	7.99	7.59 ddd (8.0, 8.0, 1.2)
H6	7.25	7.28 overl.
H8	5.24	5.21s

[a]Numbering according to Figure 1.

UV spectra

The spectra of 4-aminocoumarin in sulfuric acid solutions, reconstructed in the region from 195 to 400 nm (Figure 3), exhibit four bands resulting from $\pi \rightarrow \pi^*$ transitions. With increasing the concentration of the mineral acid, the band with λ_{max} at 209 nm exhibited small hypsochromic and hypochromic effect, *i.e.* it shifted towards shorter wavelengths and decreased in intensity (Table 5). The absorption band at approximately 228 nm in water appeared only as shoulder, while in sulfuric acid solution it exhibited a hyperchromic effect. The absorption band at 250 nm shifted towards longer wavelengths (257 nm) and increased in intensity. In the same time, bands at longer wavelengths (291 and 304 nm in water) showed both hypsochromic and hyperchromic effects. As a result, the absorption band at longer wavelengths could not be clearly recognized, being submerged (hidden) under the high-intensity band with λ_{max} at 287 nm.

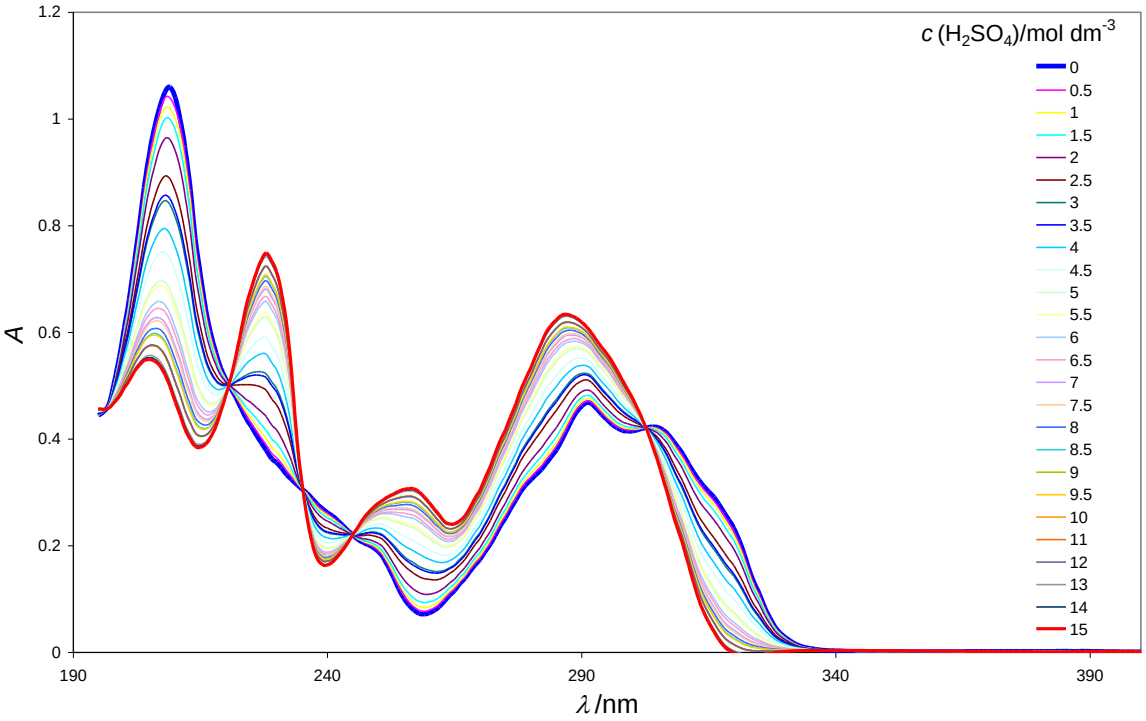


Figure 3. Changes in the reconstructed UV spectra of 4-aminocoumarin as a function of sulfuric acid concentration from 0.0 to 15.0 mol dm^{-3}

Table 5. Experimental transitions in the UV spectra of unprotonated and protonated form of 4-aminocoumarin (c = 4.93·10^{-5} mol dm^{-3})

B	λ_{max}/nm	209	228 (sh)	257 (min)	291	304
	log{ε}	4.57	4.13	3.42	4.21	4.15
BH^+	λ_{max}/nm	205	228	257	287	304 (sh)
	log{ε}	4.07	4.21	3.84	4.15	3.90

sh-shoulder, [ε]= dm^3 mol^{-1} cm^{-1}

Determination of pK_{BH^+}

Acid-base properties of coumarin and its derivatives have been previously studied, but to the best of our knowledge, no protonation data for **2** using UV spectroscopy have been published so far. Structures of protonated forms of coumarin and their hydroxy derivatives have been studied by UV and fluorescence spectroscopy.[19] The acid-base properties of 3-formyl-7-dialkylaminocoumarins[20] and 3-benzazolylcoumarins[21] have been investigated, too. In order to determine the basicity of **2**, the thermodynamic pK_{BH^+} values and solvation parameters were calculated using three different methods: Yates and McClelland[22] (with H_A acidity functions, where $-H_A = m^* \cdot X + \log\{c_{H^+}\}$), Excess Acidity Method[23] and Bunnett and Olsen Method.[24]

Ionization ratios were calculated from the absorbances of the free and protonated base in 26 different sulphuric acid solutions at several selected wavelengths. Also, they were obtained

directly from the coefficients of the first characteristic vector. Characteristic vector analysis was successfully applied to separate the effect of protonation from the medium effect. The first characteristic vector accounts for about 98 % of the variance in the region 195–400 nm.

Protonation parameters (dissociation constant for protonated form of **2** and solvation parameters) calculated from absorbances at reconstructed wavelengths and first characteristic vector are presented in Table 6.

The pK_{BH^+} values calculated with all three methods were determined to be between -1.08 and -1.20. Best correlation was obtained using Bunnett and Olsen Method, where average pK_{BH^+} is -1.11. The slope of the log I vs. H_A (calculated using the m^* = 0.3) was close to 1. The results indicate that the acidity function H_A satisfactorily describes the protonation equilibria for the entire acidity range. The obtained ϕ(1–m*) values presented in Table 6 were positive, as expected for oxygen Brønsted bases. The site of protonation is probably the carbonyl oxygen, according to the previous theoretical studies of coumarin and derivatives.[19]

Table 6. Protonation parameters for **2** calculated from reconstructed wavelengths and first characteristic vector

Method	Protonation parameters	209 nm	228 nm	257 nm	287 nm	characteristic vector c_1
	pK_{BH^+}	-1.14 (0.06)	-1.20 (0.06)	-1.20 (0.06)	-1.21 (0.06)	-1.20 (0.06)
YMC	m	1.05 (0.03)	1.07 (0.04)	1.07 (0.04)	1.08 (0.04)	1.08 (0.04)
M	r (n=24)	0.9888	0.9875	0.9860	0.9870	0.9874
	pK_{BH^+}	-1.10 (0.05)	-1.14 (0.05)	-1.14 (0.05)	-1.15 (0.05)	-1.14 (0.05)
EAM	m^*	0.31 (0.02)	0.32 (0.02)	0.32 (0.02)	0.32 (0.02)	0.32 (0.02)
	r (n=24)	0.9688	0.9645	0.9600	0.9622	0.9638
	pK_{BH^+}	-1.08 (0.05)	-1.12 (0.06)	-1.12 (0.06)	-1.13 (0.06)	-1.12 (0.06)
BOM	ϕ	0.70 (0.02)	0.69 (0.02)	0.70 (0.02)	0.69 (0.02)	0.69 (0.02)
	r (n=24)	0.9926	0.9910	0.9904	0.9904	0.9908

The value of the pK_{BH^+} of **2** was between values of the pK_{BH^+} of benzamide (-1.43[25]) and acetamide (-0.66[26]), both with very weak nucleophilic properties of NH_2 group. 3-Aminocoumarin (pK_a = 1.0[27]), aniline (pK_a = 4.6[28]), 1-naphthylamine (pK_a = 3.9[29]) and 2-naphthylamine (pK_a = 4.2[29]) are weak bases too, but unlike previous compounds they are with positive pK_a values, have sufficiently nucleophilic properties to react with alkyl halogenides, carboxylic acid anhydrides, acyl halides, sulfonyl chlorides, etc.

Conclusions

The structure of **2** was determined with single crystal X-ray analysis. The full data from NMR and IR spectra were reported for the first time. The calculated values with quantum chemical methods were in accordance with the experimental. The C7-N1 bond distance indicates a considerable degree of double bond character. The conjugation of NH_2 is additionally confirmed by the infrared spectra. This is most probably the reason for very low nucleophility of nitrogen atom in molecule of **2**. Moreover, the values of pK_{BH}^{+} correlate with the week nucleophilic properties of **2**.

Considering the above mentioned and our experience in performing reactions with **2,** an attempt to synthesize N-substituted 4-aminocoumarins from **2** would be bad strategy.

Experimental Section

General. Ammonium acetate and 4-hydroxycoumarin were purchased commercially and used without further purification. Melting points were determined on a Reichert hot-stage apparatus.

The crystallographic analysis was carried out on an Enraf–Nonius CAD4 diffractometer, using graphite monochromated Mo-Kα radiation (λ = 0.71073 Å) at room temperature. An orange irregular block was cut off from a large crystal and selected for measurement of the intensities. Unit cell parameters were determined from centering 22 reflections in the θ range (17.94–19.58)º and refined by the least-squares method. Maximum 2θ was 27.98º and scan mode: $\omega/2\theta$. Three standard reflections were monitored every 500 reflections during data collection and no significant intensity decay was observed. All diffracted intensities were corrected for Lorentz and polarization effects.[30] No absorption correction was employed. After merging of equivalent reflections, 1836 independent reflections were obtained (R_{int} = 0.0896), which were used for the solution and refinement of the structure. The structure was solved by direct methods and was refined by the full-matrix least-squares method using SHELXS97 and SHELXL97 computer programs,[31] respectively, in the space group C 2/c (no. 15). All non-hydrogen atoms were refined with anisotropic displacement parameters. H atoms were placed at idealized positions using standard geometric criteria. The final refinement of the structure converged to the final indices R1 = 0.0578 and *w*R2 = 0.1538 for 1836 reflections with [I > 2σ(I)]. The ORTEP program[32] was used to generate the ellipsoid plot and the figures involving H-bonds and packing were drawn using Mercury.[33] Further relevant crystallographic data are summarized in Table 7.

The FTIR spectra (4000-400 cm^{-1}) were recorded at ambient temperature as KBr pellets on Perkin-Elmer System 2000.

The NMR spectra were run on a Bruker DRX 250 spectrometer using standard Bruker software in solvent DMSO-d_6. The residual solvent signal was used as an internal standard for the ^1H (δ = 2.5 ppm) and ^{13}C (δ = 39.5 ppm) NMR spectra.

The UV spectra of the **2** (altogether 26 samples) and appropriate blanks were recorded in a range of sulfuric acid solutions from 0.0 to 15.0 mol dm^{-3}. The UV spectra were recorded, immediately after preparing the solutions, on a Varian Cary 50 Spectrophotometer in 1 cm quartz cell, with resolution of 1 nm, in the range from 190 to 400 nm, at room temperature. Since the absorption spectra are affected by medium effects (well-defined isosbestic points have not been observed), corrections were made by means of the characteristic vector analysis using the developed procedure in MathCad environment, on preprocessed experimental data (all normalized to unit area under the curves).

Table 7. Crystal data and structure refinement for 4-aminocoumarin

Crystal formula	$C_9H_7NO_2$
Formula weight	161.16
Crystal dimensions (mm)	0.20x0.18x0.14
Temp (K)	290(2)
Crystal system	Monoclinic
Space group	C 2/c
a (Å)	10.830(4)
b (Å)	10.758(4)
c (Å)	13.213(5)
α (º)	90.0
β (º)	93.12(2)
γ (º)	90.0
V ($Å^3$)	1537.1(1)
Z; D_{calc}, (g m^{-3})	8; 1.393
F(000)	672
Range of θ (º)	2.7-27.98
μ (MoKα) (mm^{-1})	0.10
Reflections collected	3596
Independent reflections	1836 (R_{int} = 0.0896)
Absorption correction	none
$R[F^2 > 2\sigma(F^2)]$/R*w* (F^2)	0.0578/0.1538
GOF	0.94
Final shift	0.000
$(\Delta\rho)_{min}$, $(\Delta\rho)_{max}$, (e $Å^{-3}$)	-0.21/0.16

The *ab initio* restricted Hartree–Fock (RHF) method and DFT are used to obtain equilibrium geometry of 4-aminocoumarin molecule. All calculations have been performed with the standard GAUSSIAN software (AIX, version 1998).[34] DFT method, employed in the present study is B3LYP—Becke's three parameter hybrid method[35] using the correlation functional of Lee, Yang and Parr.[36] The standard 6-31+G** basis set was applied in all calculations. The local minimum

was verified by establishing that the matrix of the energy second derivatives (Hessian) has no negative eigenvalues. The theoretical vibrational spectra were interpreted by means of potential energy distributions (PEDs) using VEDA 4 program.[18] For a better correspondence between experimental and calculated values, we modified the results using the empirical scaling factors.[17] 1H and 13C NMR chemical shifts were calculated by using the GIAO method[37] at the HF/6-311+G** level of theory (reference compound TMS was calculated at the same level); a solvent was not considered.

4-Aminocoumarin (2). A mixture of well powdered 4-hydroxycoumarin (1,07 g, 0,0066 mol) and ammonium acetate (7,87 g, 0,1 mol) was melted in an oil bath (max. 130 ºC). Liquid mixture was stirred 3 hours and was left to cool to ambient temperature. At the cooled mixture, water was added. Crude product (max. 74 %) was isolated as yellow crystals by simple filtration. First purification was made by dissolving the crystals in ethanol and precipitation with water. Melting point 226-228 ºC (from ethanol). Various melting points were found in the literature, 161.5-162 ºC,[38] 199 ºC,[13a] 232-234 ºC,[12a,39] 241-243 ºC.[40] Anal.Calcd. for $C_9H_7NO_2$: C, 67.07%; H, 4.38%; N, 8.69%. Found: C, 66.94%; H, 4.61%; N, 8.61%.

Reactions of 2 with 3 (Scheme 1) were performed in different solvents (H_2O, dioxane, tetrahydrofuran, pyridine, DMSO and DMF), without and with presence of triethylamine, Na_2CO_3 or pyridine. Also, same reactions were performed at room temperature and by heating the reaction mixture. In addition, two reactions were performed by refluxing the solution of **2** in acetic anhydride or ethyl acetate.

Supplementary material

CCDC 754032 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033).

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