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Revision of the structure and stereochemistry of the 2-naphthol–acetaldehyde 2:2 condensation product. A study by X-ray crystallography and the AM1 method

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ABSTRACT: The structure of the 2:2 condensation product of 2-naphthol and acetaldehyde, 1-(1-methyl-2,3-dihydro-1*H*-benzo[*f*]chromen-3-yl)-2-naphthol, revised by X-ray crystallography, is presented. A moderate intramolecular hydrogen bond is found between the phenolic OH and chromene oxygen atom both in the solid state and in solution. In the crystal structure, the naphthyl groups are oriented in parallel with a π–π stacking distance of 354 pm. AM1 studies are used to explain the formation of one of the four possible stereoisomers for the title compound. Comparison of the experimental and calculated coupling constants indicates that the molecule adopts exclusively the solid-state structure in solution. Copyright © 2001 John Wiley & Sons, Ltd.

KEYWORDS: 2-naphthol; acetaldehyde; phenols; X-ray crystallography; AM1 calculations; intramolecular hydrogen bonding; π–π stacking; condensation

INTRODUCTION

The reaction of substituted phenols and aldehydes under controlled conditions has been used to build up supramolecular compounds, the most important ones being calixarenes.[1–5] 2-Naphthol reacts with aromatic aldehydes to produce 14-aryl-14*H*-dibenzo[*a*,*j*]xanthenes, which could be used as anti-inflamatory agents.[6] One of the first reports on the reaction of 2-naphthol with aliphatic aldehydes was on the product of the reaction of 2-naphthol with acetaldehyde by Claisen.[7] He reported that 2-naphthol and paraldehyde react to form a compound to which he attributed the structure **1**, the 1-[1-(2-hydroxy-1-naphthyl)ethyl]-2-naphthol or dinaphthyl acetal of acetaldehyde (Fig. 1), m.p. 200–201 °C. About a century later Van Allen *et al.*[8] under similar conditions separated a compound, m.p. 198–200 °C, to which they assigned the structure **2**, 1-(3-methyl-2,3-dihydro-1*H*-benzo[*f*]chomen-1-yl)-2-naphthol (Fig. 1). It was shown later that the structure of the condensation product depends on the ratio of 2-naphthol to acetaldehyde. With a molar ratio of 1:1.3 (2-naphthol:acetaldehyde), the same product (**2**) is obtained, whereas with a ratio of 2:1 a mixture of **2** and 14-methyl-14*H*-dibenzo[*a*,*j*]xanthene (**3**) is obtained[9] (Fig. 1). The dibenzo[*a*,*j*]xanthene **3** has been obtained by using either paraldehyde or acetaldehyde diethyl acetal.[10,11]

We have become interested in the 2-naphthol–acetaldehyde 2:2 condensation product as a possible building block for constructing some types of supramolecular compounds such as tweezers.[12,13] Careful examination of the spectroscopic data of the condensation product, especially the sharp band at 3300 cm^{-1} in the Fourier transform (FT) IR spectrum, indicated an intramolecular hydrogen bond, difficult to be present in structure **2** as the model indicates. To solve the problem with certainty, a single crystal of the condensation product was prepared and used for X-ray crystallographic determination of the structure; it turned out that the structure is **4** (Fig. 1) and not **2**. The results of the studies are reported in this paper. The stereochemistry of the formation of the condensation product is taken into the consideration and addressed by AM1 calculations.

RESULTS AND DISCUSSION

Crystal structure of 1-(1-methyl-2,3-dihydro-1*H*-benzo[*f*]chromen-3-yl)-2-naphthol (4)

Compound **4** crystallizes in the monoclinic system with space group $P2_1/c$ (No. 14). The asymmetric unit cell consists of one crystallographically independent molecule (Fig. 2). The angle between the plane of the two naphthyl rings in **4** is 56.8° and the distance between the

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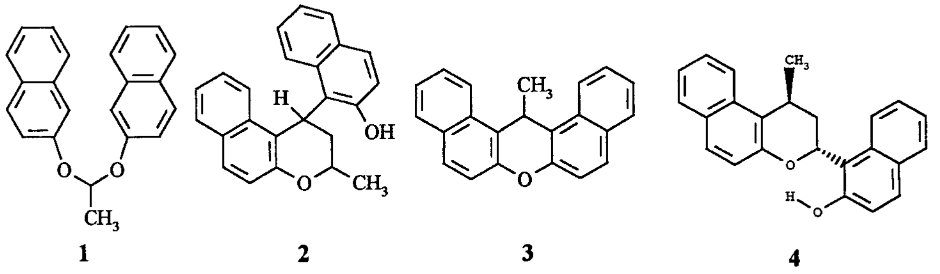


Figure 1. Proposed structures of **1**,[7] **2**,[8] by-product **3**[9] and **4** (this work)

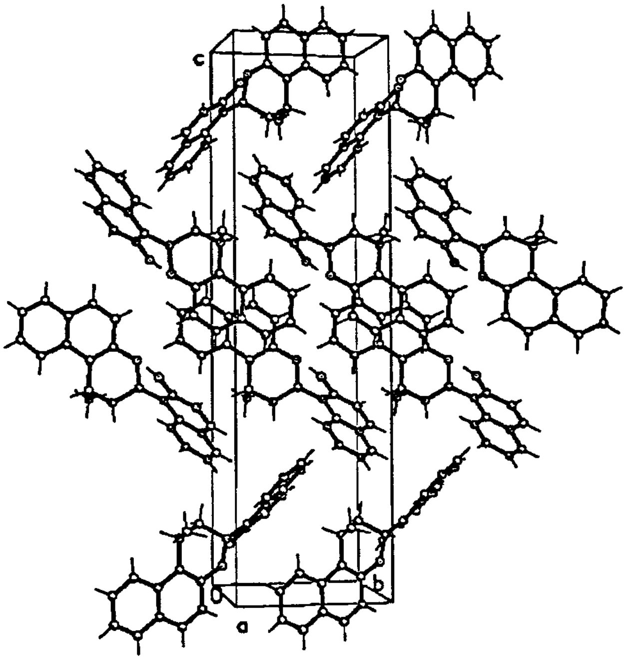


Figure 2. The unit cell in crystal structure of **4**

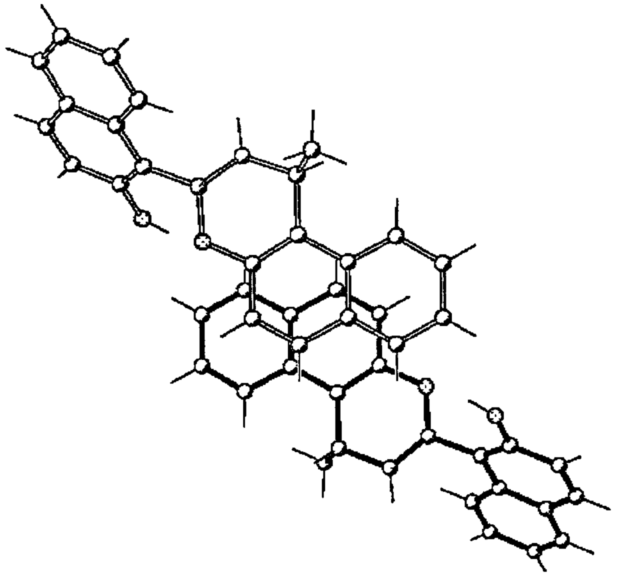


Figure 3. The π–π stacking of the naphthyl group in the solid-state structure of **4**

plane of parallel naphthyl rings of the molecules in successive layers in the crystal structure is 3.54 Å (Fig. 3), a value reported to be suitable for π–π stacking.[14]

In the molecular structure of **4**, the naphthoyl group at the 3-position is arranged such that the second aromatic ring of the 2-naphthoyl group is on the upper side of the chromene six-membered ring and close to the methyl group at the 1-position. The shortest HH distance of naphthoyl-Me [H(29)···H(41)] is 2.66 Å (Fig. 4). The phenolic OH group is located on the opposite side to the methyl group in such a way as to make a moderate internal hydrogen bound[15] to the oxygen atom in the chromene six-membered ring (see Fig. 4). The distances of the donor-H, acceptor···H, donor···acceptor and donor-H···acceptor angles are presented in Table 1 together with the AM1-calculated values. The selected bond lengths and bond angles are listed in Table 2 and compared with the AM1-calculated values.

STEREOCHEMISTRY

The conformation of the chromene six-membered ring in **4** is half-chair with the methyl and 2-naphthoyl groups in a *trans* orientation. Furthermore, the methyl group at the 1-position is pseudoaxial and 2-naphthoyl group at the 3-position is pseudoequatorial, henceforth denoted **4a′e′**. Efforts to obtain the *cis* diastereomer of **4** was not

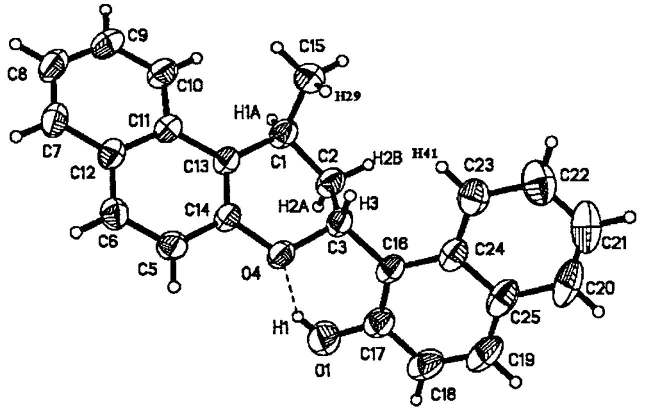


Figure 4. X-ray structure of **4**; the methyl and naphthoyl substituents are in a *trans* orientation

Table 1. The experimental (X-ray) hydrogen bond distances (Å) and OHO angles (°) and the values calculated by the AM1 method in **4a′e′**.[a]

Method	*d*(O—H)	*d*(OH···O)	*d*(O···O)	OHO angle
X-ray	0.82	1.95	2.64	142.2
AM1	0.97	2.03	2.73	127.4

[a] It should be noted that the locations of hydrogen atoms are not accurately determined by X-ray crystallography.

Table 2. Selected bond lengths (Å) and bond angles (°) in **4a′e′**: comparison of computed (AM1) with X-ray crystallographic data

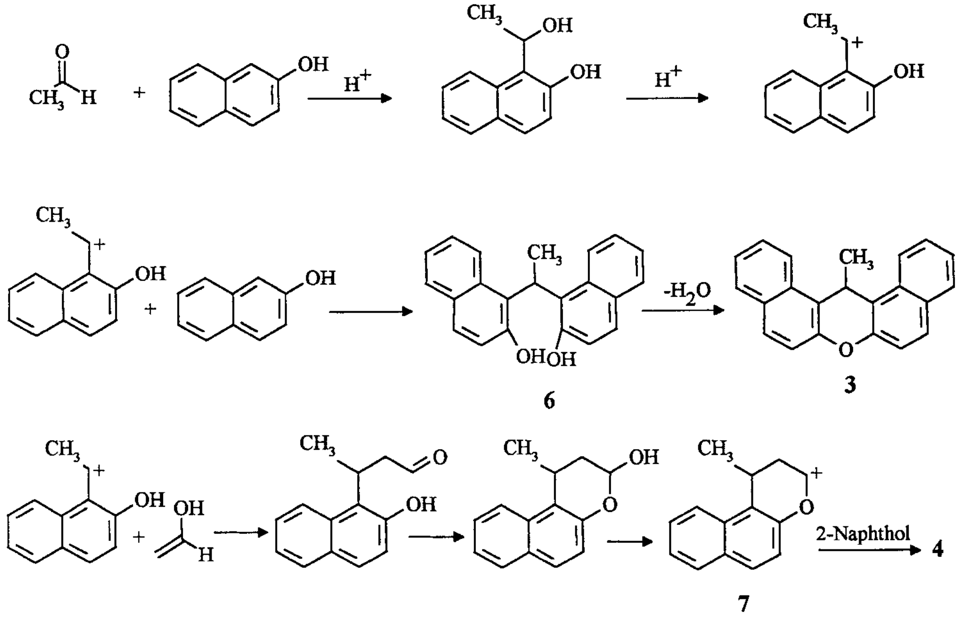
Bond length or angle	X-ray	AM1[a]
O_4—C_3	1.447	1.446
C_3—C_2	1.519	1.523
C_2—C_1	1.529	1.523
C_1—C_{13}	1.520	1.495
C_{13}—C_{14}	1.373	1.385
C_{14}—O_4	1.394	1.383
C_1—CH_3	1.523	1.518
O_4—C_3—C_2	109.4	110.8
C_3—C_2—C_1	110.4	111.0
C_2—C_1—C_{13}	109.7	110.6
C_1—C_{13}—C_{14}	121.4	120.6
C_{13}—C_{14}—O_4	123.1	124.6
C_{14}—O_4—C_3	115.6	115.2
C_2—C_1—CH_3	115.5	110.7

[a] The third digit in the bond lengths calculated by AM1 is included for comparison with X-ray values.

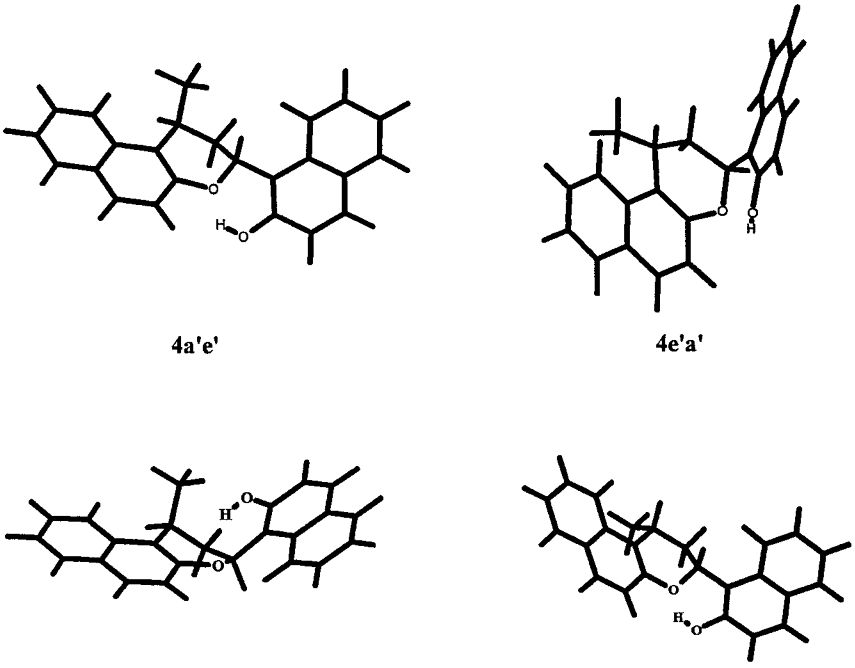
successful; by variation of the reaction conditions a mixture of **3**, **4** and **6** was obtained (see Scheme 1). Formation of products similar to **3** and **6** has been reported before.[10,11,16]

To find out the reason behind the observed stereochemistry, the heats of formation and the structure of **4a′e′** and the most stable form of the *cis* diastereomer **5e′e′** were calculated by the AM1 semiempirical[17] method. The ring-inverted conformers of **4a′e′** (i.e. **4e′a′**) and **5e′e′** (i.e. **5a′a′**) were also included in the AM1 studies (see Fig. 5). The heats of formation and selected dihedral angles of **4a′e′**, **4e′a′**, **5e′e′** and **5a′a′** are given in Table 3, together with the values for dihedral angles from the X-ray structure. As indicated in Table 3, the difference in heats of formation of **4a′e′**–**5e′e′** and **4a′e′**–**5a′a′** are 1.6 and 3.2 kcal mol^{-1}, respectively (1 kcal = 4.184 k J). The difference in the H_f values of **4a′e′** and **5e′e′** at equilibrium corresponds to a population ratio of 9:1, so it is expected that **5e′e′** would be formed if the reaction proceeds under thermodynamic control conditions. *trans*-**4a′e′** and *cis*-**5e′e′** may be formed by an electrophilic aromatic substitution of 2-naphthol by the oxenium **7** (Fig. 6), as an intermediate (see Scheme 1). The formation of an oxenium intermediate such as **7** from hemiacetals under acidic conditions is established in the litrature.[18] The stereochemistry of **7** should control the stereochemistry of the σ-complex intermediates and products. The methyl group in **7** could be oriented in either a pseudoaxial or pseudoequatorial position, but starting from different geometries ends up with the one having a methyl group in a pseudoaxial position (Fig. 6).

Two different σ-complexes could be formed by the attack of **7** on 2-naphthol, a *trans*-**8** and a *cis*-**9** complex (Fig. 6). The relative stabilities of **8** and **9** were calculated by the AM1 method. It is calculated that **8** is 2 kcal mol^{-1} more stable than **9** (Table 4). Also, the dipole moment[19]



Scheme 1



4a'e' **4e'a'**

5a'a' **5e'e'**

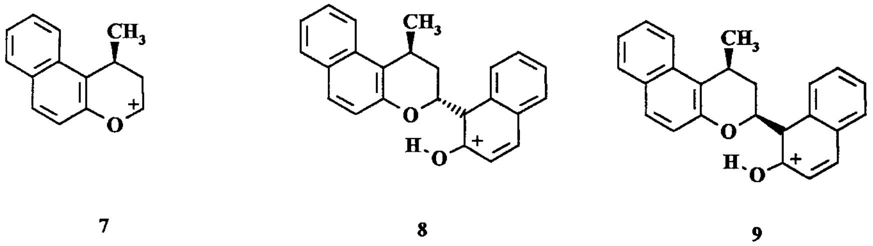
Figure 5. All possible stereoisomers of **4** and **5**, calculated by the AM1 method

Table 3. Computed (AM1) heats of formation (H_f) (kcal mol^{-1}) and comparison of selected dihedral angles (°) in all possible stereoisomers of **4** and **5** with X-ray structures (for numbering see Fig. 4)

Compound	O_4—C_{14}—C_{13}—C_1	C_{14}—C_{13}—C_1—C_2	C_{13}—C_1—C_2—C_3	C_1—C_2—C_3—O_4	C_2—C_3—O_4—C_{14}	C_3—O_4—C_{14}—C_{13}	O_4—C_3—C_{16}—C_{17}	H_f
X-ray	−3.0	17.0	−45.9	63.3	−49.0	19.6	37.1	—
4a′e′	−2.1	17.3	−45.1	60.3	−44.6	16.3	40.1	−0.68
4e′a′	10.2	3.5	−33.6	51.2	−38.0	8.5	−11.7	6.40
5e′e′	6.2	−5.8	−25.1	56.7	−57.0	26.5	41.6	0.94
5a′a′	6.6	27.9	−45.2	30.3	4.7	−24.6	−25.4	2.53

of **8** is calculated to be one 1 D greater than that of **9** (Table 4). It is expected that in a polar solvent such as ethanol–water, used for running the reaction, **8** is better solvated than **9** and the difference in their relative stabilities increases in favor of **8**, which might result in the exclusive formation of **4a′e′**. Complex **8** is converted to **4a′e′** but **9** is converted to **5a′a′**, which is 3.2 kcal mol^{-1} less stable than **4a′e′**. **5a′a′** could be ring inverted to the more stable form **5e′e′**. Ring inversion in the cyclohexene ring is found in the range 5–6 kcal mol^{-1}.[20,21]

The question of conformational equilibrium between two conformers (**4a′e′** and **4e′a′**) in solution was addressed by comparison of the experimental and computed coupling constants. For this purpose, the dihedral angles between aliphatic protons in the chro-



7 8 9

Figure 6. The structure of oxenium **7** and sigma complexes **8** and **9** computed by the AM1 method

Table 4. Calculated heats of formation and dipole moments of σ-complexes

Complex	Heat of formation (kcal mol^{-1})	Dipole moment (D)
8	162.5	10.7
9	164.5	9.5

Table 5. Comparison of the experimental and calculated coupling constants (Hz) between H1a–H2a, H1a–H2b, H2a–H3 and H2b–H3 protons in **4a**′**e**′ and **4e**′**a**′ conformational stereoisomers[a]

Compound	$\Phi_{H1a–H2a}$	$^3J_{calc}$	J_{exp}	$\Phi_{H1a–H2b}$	$^3J_{calc}$	J_{exp}	$\Phi_{H2b–H3}$	$^3J_{calc}$	J_{exp}	$\Phi_{H2a–H3}$	$^3J_{calc}$	J_{exp}
4a′**e**′	75.9	1.30	1.5	−42.5	5.76	5.0	66.0	1.59	2.1	−176.6	11.27	12.3
4e′**a**′	−37.2	6.92	—	−153.9	10.36	—	−76.7	0.89	—	39.8	6.91	—

[a] Torsion angle for **4a**′**e**′ is derived from the X-ray structure and for **4e**′**a**′ from the AM1 calculations. For the assignment of protons, see Fig. 4.

mene six-membered ring of **4a**′**e**′ and **4e**′**a**′ derived from the x-ray structure (for **4a**′**e**′) and estimated by the AM1 method (for **4e**′**a**′) were used to calculate the ^{1}H NMR coupling constants by using Hassnoot *et al.'s* equation[22] (Table 5). The estimated coupling constants indicate that **4e**′**a**′ should not be present in equilibrium with **4a**′**e**′.

EXPERIMENTAL

All reagents were obtained from Merck and used without further purification. Uncorrected melting-points were determined with a Buchi apparatus. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 or 80 MHz spectrometer. FT-IR spectra were obtained with a Shimadzu 4300 spectrophotometer.

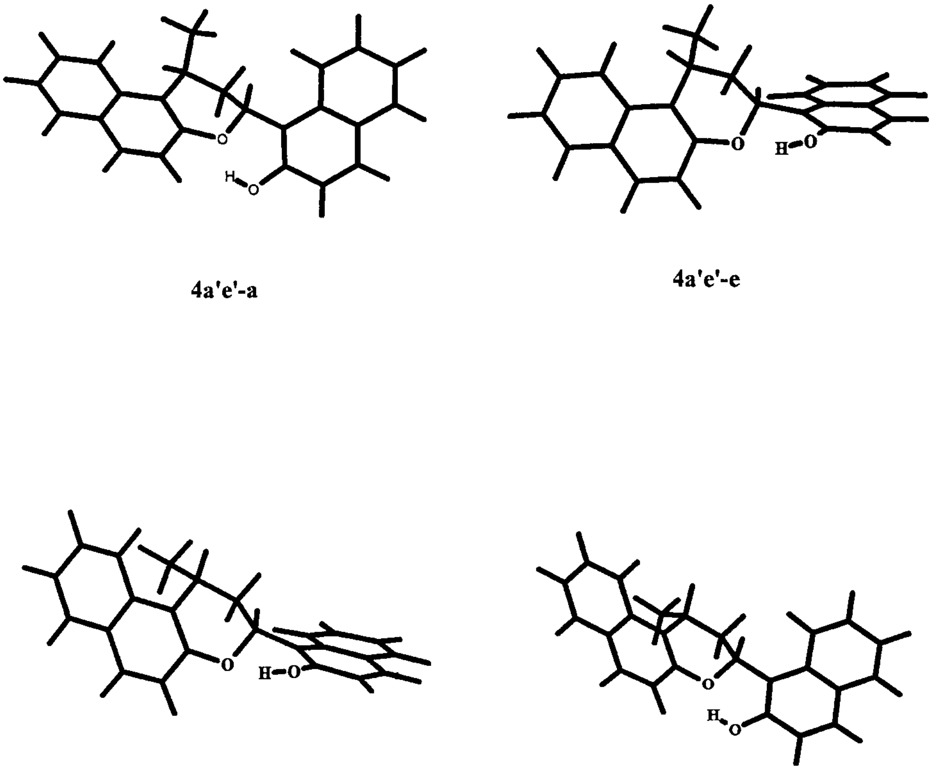
Synthesis of benzo[f]chromene (4). A 2.00 g (13.9 mmol) amount of 2-naphthol was dissolved in 10 ml of 1:1 ethanol–concentrated HCl and 0.62 g (14 mmol) of acetaldehyde was added. The reaction mixture was heated in an oil-bath at 70 °C for 2h. The resulting oily brown liquid was separated and triturated with small amounts of diethyl ether and the precipitate was filtered off. The white precipitate washed with small amounts of cold diethyl ether and dried under vacuum. A mixture of **3**, **4** and **6** was obtained, which was chromatographed on silica gel with light petroleum–ethyl acetate (80:20) as eluent, to give **4** in 80% yield, m.p. 205 °C. FT-IR (KBr): ν cm^{-1} 3350 s; 3062 w, 2960 w; 1622 s, 1591 s, 1514 s, 1458 s; 1398 s, 1240 b, 1215 s, 956 b, 800 b, 742 b. ^{1}H NMR (DMSO-d_6, 400 MHz): (ppm) 1.50 (d, J = 6.9 Hz, 3H); 1.88 (d, J = 13.5 Hz, 1H); 2.84 (dt, J = 13.5 and 5.2 Hz, 1H); 3.68 (m, 1H); 6.37 (dd, J = 12.44 and 2.30 Hz, 1H); 8.23–7.00 (m, 12H); 9.97 (s, 1H). ^{13}C NMR (DMSO-d_6, 80MHz): (ppm) 22.33, 25.49, 32.89, 67.56, 116.15, 117.37, 118.59, 119.02, 122.03, 122.07, 122.33, 124.16, 126.46, 126.63, 128.00, 128.59, 128.67, 128.93, 129.67, 132.28, 132.66, 151.44, 152.53.

Crystal structure determination. A colorless crystal with dimensions 0.40 × 0.12 × 0.10 mm was used for data collection at 297 K using a Siemens SMART CCD diffractometer with Mo K radiation (λ = 0.71073 Å, graphite monochromator). A full sphere of reciprocal lattice was scanned in 0.3° steps in with a crystal-to-detector distance of 3.97 cm and an exposure time of 60 s per frame; for details, see Table 6. A preliminary orientation matrix was obtained from the first frames using SMART. The collected frames were integrated using the preliminary orientation matrix which was updated every 100 frames. Final cell parameters were

Table 6. Crystallographic and refinement data for *4*

Empirical formula	$C_{24}H_{20}O_2$
Formula weight	340.40
Crystal system, space group	Monoclinic, $P2_1/c$ (No. 14)
a (Å)	7.56720(10)
b (Å)	7.97840(10)
c (Å)	28.80290(10)
β (°)	92.4410(1)
V ($Å^3$)	1737.37(3)
Z	4
T (K)	297(2)
Density (calc.) (g cm^{-3})	1.301
μ (mm^{-1})	0.081
F (000)	720
θ range (°)	1.42–28.28
Index ranges	$-10 \leq h \leq 10$ $-10 \leq k \leq 10$ $-38 \leq l \leq 38$
Reflections collected	23177
Independent reflections	4312
R(int.)	0.0416
Reflections obs. [$I > 2\sigma(I)$]	3021
Data/restraints/parameters	4312/237
$G_{oo}F$ (F_o^2)	1.036
$R1/wR2^a$ for obs. reflections	0.0495/0.1083
$R1/wR2$ for all data	0.0800/0.1233
Weighting scheme[b] x/y	0.0467/0.4993
Larg. res. peak/hole (e, $Å^{-3}$)	0.199/−0.174

[a] $R1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$, $wR2 = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma(F_o^2)^2\}^{\frac{1}{2}}$.
[b] $w = 1/[\sigma^2(F_o^2) + (xP)^2 + yP]$, $P = (F_o^2 + 2F_c^2)/3$.



4a′e′-a

4a′e′-e

5e′e′-e

5e′e′-a

Figure 7. Computed (AM1) internal hydrogen bonds with axial- and equatorial-oxygen lone pairs in **4a**′**e**′ and **5e**′**e**′

obtained by refinement on the positions of 8192 reflections with $I > 10\sigma(I)$ after integration of all the frame data using SAINT.[23] The data were empirically corrected for absorption and other effects using SADABS[24] (min./max. transmission = 0.9682/0.9919) based on the method of Blessing.[25] The structure was solved by the direct method and refined by full-matrix least-squares analysis on all F^2 data using SHELXTL.[26] The non-H atoms were refined anisotropically and the hydrogen atoms isotropically with restrained bond distances.

Computational. Initial estimates of the geometry of structures, for semiempirical calculations, were obtained by the MMX molecular mechanics method implemented in PCMODEL software (Serena Software, Bloomington, IN, USA). Full minimization was done by using the semiempirical AM1 Hamiltonian,[17] implemented in the MOPAC 6.0 program.[27] All the structures were characterized as stationary points and true minima on the potential energy surface using the FORCE keyword. A stationary point is described if the first derivatives of the energy with respect to changes in the geometry are zero. The criterion for a minimum is that all eigenvalues of the Hessian matrix are postive.[28] AM1 was chosen as it has been shown to produce the geometry of internal hydrogen bonds better than PM3.[29]

A half-chair conformation of the chromene six-membered ring was selected and the methyl at the 1-position and the naphthoyl at the 3-position were put either in pseudoaxial or pseudoequatorial orientation. The conformational space for the methyl and naphthoyl in each orientation was searched by rigid rotation. The local minima thus found were subjected to AM1 calculations. Two different orientations for the hydrogen bond were found possible for **4a**′**e**′ and **5e**′**e**′, one between the OH and the axial lone pair of oxygen (**4a**′**e**′**-a** and **5e**′**e**′**-a**) and the other between the OH and the equatorial lone pair of oxygen (**4a**′**e**′**-e** and **5e**′**e**′**-e**), the former being the more stable. The different orientations of hydrogen bonds in **4a**′**e**′ and **5a**′**e**′ are given in Fig. 7.

SUPPLEMENTARY DATA

Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Center as supplementary publication No. CCDC 143902. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. Fax, (44) 1223 336 033; E-mail, depositccdc.cam.ac.uk.

The *.arc files of all the AM1 calculations for the given structures are available from the corresponding author via E-mail.

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