

Configuration and conformational equilibrium of (±)-*trans*-1-oxo-3-thiophen-2-yl-isochroman-4-carboxylic acid methyl ester

Milen G. Bogdanov,^a Iliya S. Todorov,^b Pavlina G. Manolova,^c
Diana V. Cheshmedzhieva^a and Mariana D. Palamareva^{a,*}

^aSofia University, Faculty of Chemistry, 1, J. Bouchier Ave., 1164 Sofia, Bulgaria

^bDepartment of Chemistry and Biochemistry, University of Notre Dame, 257 Nieuwland Science Hall, Notre Dame, IN 46556, USA

^cBulgarian Academy of Sciences, Institute of Organic Chemistry, Acad. G. Bontchev Street, Bl, 1113 Sofia, Bulgaria

Received 23 July 2004; revised 30 August 2004; accepted 7 September 2004

Available online 25 September 2004

Abstract—The X-ray analysis of 1-oxo-3-thiophen-2-yl-isochroman-4-carboxylic acid methyl ester **1** confirmed its *trans*-configuration and a conformation with diaxial H-3 and H-4 atoms in solid state. NMR experiments indicated that *trans*-**1** exists in solution in both expected conformers. In CDCl₃ and especially in CD₃OD or DMSO, the conformational equilibrium is shifted towards the conformer with diequatorial H-3 and H-4, which was also determined by 2D NOESY experiments. The shift is due to the greater polarity of that conformer deduced by ab initio calculations.

© 2004 Elsevier Ltd. All rights reserved.

The dihydroisocoumarin (isochroman) fragment is the core of various natural compounds,^{1,2} which exhibit a wide variety of pharmacological activities.^{1–8} Most of these natural 3,4-disubstituted dihydroisocoumarins possess an aryl substituent in position 3. The relative configuration can be defined on the basis of the value of the vicinal coupling constant (³J_{3,4}) between H-3 and H-4 atoms in the ¹H NMR spectra. In general, values of 3–4.4 Hz^{9–13} suggest *cis* configuration and preferred synclinal (*sc* or *gauche*) conformation and values of 8–13 Hz^{9–13} suggest *trans* configuration and preferred antiperiplanar (*ap* or *trans*) conformation. The synthesis of 3,4-dihydroisocoumarins has been achieved by different methods.^{8–18} We recently reported¹⁸ a diastereoselective reaction between homophthalic anhydride and thiophene-2-carboxaldehyde leading to one isomer of 1-oxo-3-thiophen-2-yl-isochroman-4-carboxylic acid. The *trans* configuration was proposed for its methyl ester **1**¹⁸ on the basis of ³J_{3,4} (6.3 Hz in CHCl₃).

In this letter we continue studying the configuration of compound **1** owing to its intermediate value of ³J_{3,4} within the relevant values for the *cis* and *trans* diastereomers of this type. The conformation of **1** in the solid state and conformational equilibrium in solvents of different polarity is discussed. The study is based on data from X-ray diffraction, ¹H NMR, 2D NOESY spectra and quantum chemical ab initio calculations and is related to our recent studies on reactions of homophthalic anhydride.^{18–20}

Compound *trans*-**1** is one of the possible racemic diastereomers. It is a conformationally flexible compound existing as two conformers: **1a** and **1b** (see Fig. 1). According to the Karplus equation,^{21,22} **1a** with antiperiplanar H-3 and H-4 (torsion angle 180°) is expected to show a high ³J_{3,4} of about 13 Hz. Alternatively, ³J_{3,4} for **1b** with synclinal H-3 and H-4 (torsion angle 60°) should be small (about 3–4 Hz). The values of ³J_{3,4} observed will depend on the conformational equilibrium, that is, on the individual values ³J_{3,4(1a)} and ³J_{3,4(1b)} of any conformer and its mole fraction *n*_{(1a)}} or *n*_{(1b)}}.^{23,24}}}

$${}^3J_{3,4} = n_{(1a)}J_{1a} + n_{(1b)}J_{1b} \quad (1)$$

The structure and *trans* configuration of **1** were characterized by a single-crystal X-ray diffraction study (see

Keywords: Crystal structure; *trans*-Isochroman; Conformational equilibrium; Dihydroisocoumarin.

* Corresponding author. Tel.: +359 2 8161 221; fax: +359 2 962 54 38; e-mail: mpalamareva@chem.uni-sofia.bg

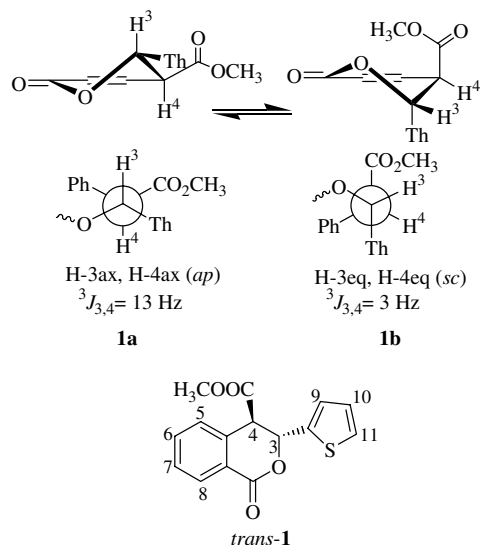


Figure 1. Structure and conformational equilibrium of *trans-1*. For simplicity, the pseudoaxial and pseudoequatorial positions are shown as axial and equatorial, respectively.

Fig. 2). The molecules are packed into two separate layers along the *b*-axis and are stabilized by intermolecular O3...H10–C10 hydrogen bonds (see **Fig. 3**) with a length of 2.507 Å. The crystal structure contains only molecules of **1** without any solvent. The pyranone ring is in a distorted twist conformation. Note that the hydrogen atoms at C10 and C11 are in an *ap* conformation and the thiophenyl and methoxycarbonyl groups occupy equatorial and pseudoequatorial positions, respectively.

The angle between the plane of the equatorial thiophene ring at C10 and the plane of the fused benzene ring is 78°, that is, both planes are almost perpendicular to each other. Each of the stereogenic atoms C10 and C11 is in *R* configuration in the enantiomer used for refinement. The torsion angle H10–C10–C11–H11 is 179.0(1)°. This angle is in agreement with the expected value of about 13 Hz for ${}^3J_{10,11}$ (or ${}^3J_{3,4}$).^{24,25} Thus in the solid state, *trans-1* exists entirely in conformation **1a**.

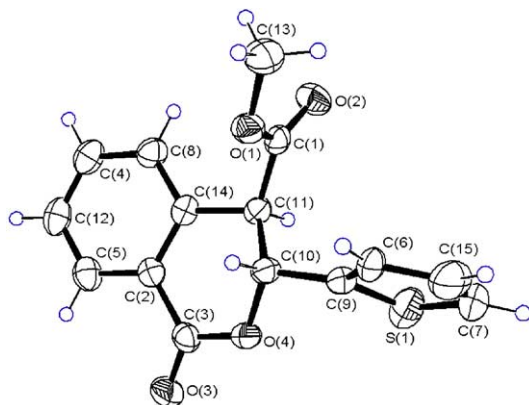


Figure 2. ORTEP plot and numbering of *trans-1*. The thermal ellipsoids are scaled to the 40% probability level.

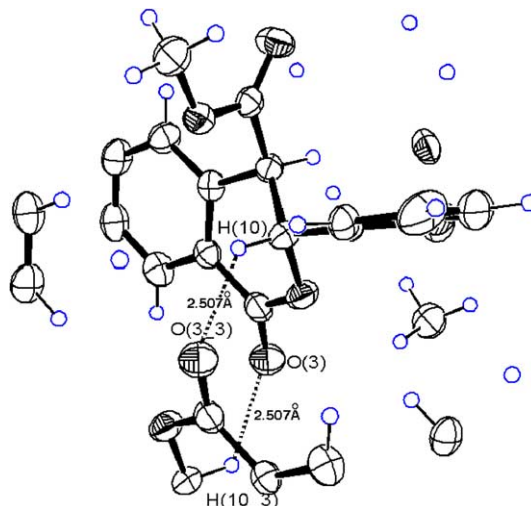


Figure 3. Part of the crystal packing for *trans-1* showing the presence of intermolecular hydrogen bonds and surrounding atoms and functional groups.

The conformational equilibrium of *trans-1* in solution was studied by ${}^1\text{H}$ NMR spectra in different solvents: CDCl_3 , CD_3OD and $\text{DMSO-}d_6$, these solvents being nonpolar aprotic, polar protic and polar aprotic, respectively. The data observed are shown in **Table 1**. The difference in the chemical shift ($\Delta\delta$) within the three solvents is almost negligible for the methoxycarbonyl group and smaller or greater for the individual protons. This indicates that the chemical shift of the OCH_3 protons is more suitable for configuration assignments than those of H-3 and H-4^{9–11} having greater $\Delta\delta$ values. Usually, the signals of the OCH_3 protons in *cis* esters appear about 0.2 ppm at a higher field than in *trans* esters. The most interesting result from **Table 1** is the solvent induced decrease of ${}^3J_{3,4}$ from 6.3 to 4.5 Hz the latter value being characteristic for the *cis* configuration in *sc* conformation. Thus, if we had first taken the NMR spectrum of **1** in DMSO we would erroneously propose the *cis* configuration. A hypothetical question can arise: could the small ${}^3J_{3,4}$ in DMSO be attributed to an epimerization of *trans-1* in this solvent. The answer is negative since in the isochroman series the *trans* isomers are thermodynamically more stable than the relevant *cis* isomers.^{11,14,15} These data show that attention should be paid in ascribing configuration of isochromanones when the values of ${}^3J_{3,4}$ correspond to *sc* conformation both for *cis* and *trans* isomers, namely 2–6 Hz.¹³

The observed values of ${}^3J_{3,4}$ allowed us to characterize quantitatively the conformational equilibrium of *trans-1* in the three solvents on the basis of Eq. 1 and $n_{(1a)} + n_{(1b)} = 1$. Concerning ${}^3J_{3,4(1a)}$ and ${}^3J_{3,4(1b)}$, we took into account the data for 1-oxo-3-phenylisochroman¹⁶ where the values of couplings for diastereotopic H-4 protons (*ax* and *eq*) were 13 and 3 Hz, respectively. The calculations (deviation range $\pm 10\%$) showed the presence of 67% of **1b** in chloroform and a greater shift of the conformational equilibrium to **1b** for methanol (81%) and especially for DMSO (85%).

Table 1. ^1H NMR parameters of 1-oxo-3-thiophen-2-yl-isochroman carboxylic acid methyl ester (**1**) at room temperature in different solvents

Solvent	$J_{3,4}$	Chemical shifts (ppm), multiplicity and coupling constants (Hz)									
		H-3	H-4	H-5	H-6	H-7	H-8	H-9	H-10	H-11	OCH ₃
CDCl ₃	6.3	6.19	4.35	7.30 d 7.7	7.64 dt 1.5; 7.8	7.51 dt 1.0; 7.5	8.16 dd 1.5; 7.8	7.05 dd 1.2; 3.5	6.93 dd 3.5; 5.0	7.27 dd 1.2; 5.0	3.76 s
CD ₃ OD	4.9	6.30	4.58	7.43 d 7.8	7.69 dt 1.5; 7.5	7.53 dt 1.0; 7.5	8.05 dd 1.3; 7.8	7.08 dd 1.0; 3.5	6.94 dd 3.5; 5.0	7.36 dd 1.3; 5.3	3.74 s
DMSO- <i>d</i> ₆	4.5	6.36	4.79	7.47–7.50 m	7.73 dt 1.5; 7.5	7.55 dt 1.3; 7.8	7.97 dd 1.5; 7.8	7.15 dd 1.0; 3.5	6.98 dd 3.5; 5.0	7.47–7.50 m	3.69 s
$\Delta\delta$		0.17	0.44	0.18	0.09	0.04	0.19	0.10	0.05	0.21	0.07

Table 2. Energy difference ($\Delta\epsilon$), dipole moments (μ in D) and percentage of conformers of *trans*-**1** in gas phase

	$\Delta\epsilon^a$	μ_{1a}	μ_{1b}	% _{1b}
HF/3-21G	1.64	3.72	4.37	66
HF/6-31 + G(d,p)	1.59	4.13	5.04	65

^a $\Delta\epsilon = \epsilon_{1b} - \epsilon_{1a}$ in kJ mol^{-1} .

In an attempt to rationalize the shift of the conformational equilibrium of *trans*-**1**, ab initio calculations at HF/3-21G and HF/6-31 + G(d,p) approaches were performed. The calculations showed that the diequatorial conformer **1b** is more stable than the diaxial **1a** and the difference in $\Delta\epsilon$ of their minimum conformational energies is about 1.6 kJ mol^{-1} (see Table 2). The values of $\Delta\epsilon$ allowed us to determine the conformer population using Eq. 2.

$$\Delta\epsilon = -RT \ln K \quad (2)$$

where $K = n_{(1b)}/n_{(1a)}$ is the equilibrium constant, R is the gas constant ($8.33 \times 10^{-3} \text{ kJ mol}^{-1} \text{ K}^{-1}$) and T is the temperature (298.5 K). The data obtained from the theoretical calculations are summarized in Table 2.

In addition, both basis sets used showed that **1b** is more polar than **1a**. These data agree with the position of the equilibrium. The nonpolar chloroform shifts it to a smaller extent than the polar methanol and DMSO. The latter two solvents will solvate **1b** better, having the larger dipole moments. For methanol with lower polarity than DMSO, solvation by intermolecular hydrogen bonds is mainly to be expected.

The configurational and conformational assignments for *trans*-**1** were also made on the basis of 2D NOESY spectra, which proved that **1b** is the preferred conformer in solution. The correlation observed in the NOESY spectra of *trans*-**1** made it possible to estimate the through-space interactions of H-4 with H-3 and H-5. The NOESY spectrum in DMSO-*d*₆ showed cross-peaks between these protons, being more intensive than in the case of CDCl₃. It is worth noting that a NOE was observed⁶ between the equatorial H-4 and the aromatic H-5 proton, while such an effect between the axial H-4 and H-5 was not seen. The NOE established in the case of *trans*-**1** both in CDCl₃ and DMSO proved the equatorial orientation of H-4 in these solvents.

Ab initio computations were carried out with the GAUSSIAN 98 program package.²⁶ The theoretical calculations

were performed at the HF/3-21G²⁷ and HF/6-31 + G(d,p)²⁸ level of theory. The structures **1a** and **1b** were further characterized by analytic computations of harmonic vibrational frequencies at the same level/basis sets.

Crystal data for *trans*-1: Clear, colourless single crystals were obtained by slow evaporation of a chloroform–ethyl acetate solution of **1**. C₁₅H₁₂O₄S, $M = 288.31$, monoclinic, $P2_1/c$, $a = 8.5027(10)$, $b = 20.8161(10)$, $c = 8.6174(10)$, $\beta = 118.971(10)^\circ$, $V = 1334.4(2) \text{ \AA}^3$, $Z = 4$, $D_x = 1.435 \text{ g cm}^{-3}$. Crystals of **1** were checked for singularity and an X-ray diffraction data set was collected for the best crystal ($0.2 \times 0.19 \times 0.12 \text{ mm}$) on an Enraf-Nonius CAD-4 diffractometer with monochromated MoK α radiation ($\lambda = 0.71073 \text{ \AA}$) at room temperature (half of a sphere, ω - 2θ scans, $\theta_{\text{max}} = 25.8^\circ$). The raw data were corrected for absorption with the aid of the average of three ψ -scans. The structure was solved and refined on F2 by means of SHELXTL-v5.1 software package.²⁹ Direct methods provided all sulfur and oxygen positions while the carbons were later identified from difference Fourier maps. The positions of hydrogen atoms were calculated and included as fixed contributors to the structure refinement. A total of 2629 independent reflections were measured in the range $2 < \theta < 25.8$.

Full crystallographic details, excluding structure factors, have been deposited at the Cambridge Crystallographic Data Centre (CCDC). Any request to the CCDC for this material should quote the full literature citation and the reference number 226895.

Conclusions

The X-ray analysis of (\pm)-*trans*-1-oxo-3-thiophen-2-yl-isochroman-4-carboxylic acid methyl ester confirmed its configuration and conformation as **1a**. In contrast, in solution the conformational equilibrium is shifted to **1b** in agreement with the ab initio calculations performed and NOESY experiments. The data for $^3J_{3,4}$ in the three solvents show a decrease in the order chloroform, methanol and DMSO and the value for the latter coincides with the value characteristic for the *cis* isomers of isochromans.

References and notes

- Hill, R. A. Naturally Occurring Isocoumarins. In *Progress in the Chemistry of Natural Products*; Herz, W.;

- Grisebah, H., Kirbi, G. W., Tamm, Ch., Eds.; Springer: Vienna; Vol. 49, pp 1–78, and references cited therein.
- Rahman, I.; Arfan, M.; Khan, G. A. *J. Chem. Soc. Pak.* **1998**, *20*, 76–87, and references cited therein.
 - Nozawa, K.; Yamada, M.; Tsyda, Y.; Kawai, K. *Chem. Pharm. Bull.* **1981**, *29*, 2689–2691.
 - Koshino, H.; Yoshihara, T.; Okuno, M.; Sakamura, S.; Tajima, A.; Shimanuki, T. *Biosci. Biotechnol. Biochem.* **1992**, *56*, 1096–1099.
 - Yoshikawa, M.; Shimada, H.; Yagi, N.; Murakami, N.; Shimoda, H.; Yamahara, Y.; Hisashi, M. *Chem. Pharm. Bull.* **1996**, *44*, 1890–1898, and references cited therein.
 - Koshino, H.; Muroi, M.; Tajika, T.; Kimura, Y.; Takatsuki, A. *J. Antibiot.* **2001**, *54*, 494–500.
 - Kokubun, T.; Veitch, N.; Bridge, P.; Simmonds, M. *Phytochemistry* **2003**, *62*, 779–782.
 - Nepolitano, E. *Org. Prep. Proced. Int.* **1997**, *29*, 633–664, and references cited therein.
 - Haimova, M.; Stanoeva, E.; Ivanova, S.; Palamareva, M.; Spassov, S. *Commun. Dept. Chem., Bulg. Acad. Sci.* **1977**, *10*, 489–509.
 - Boyd, G. B.; Monteil, R. L.; Lindlei, P. F.; Mahmaud, M. *M. J. Chem. Soc., Perkin Trans. 1* **1978**, 1351–1360.
 - Nozawa, K.; Yamada, M.; Tsuda, Y.; Kawai, K. *Chem. Pharm. Bull.* **1981**, *29*, 3486–3493.
 - Kaji, H.; Yamada, M.; Nozawa, K.; Kawai, K.; Nakajima, S. *Org. Prep. Proced. Int.* **1986**, *18*, 253–262.
 - Hutchings, M. G.; Chipendale, A. M.; Ferguson, I. *Tetrahedron* **1988**, *44*, 3727–3734.
 - Hutchings, M. G.; Chipendale, A. M.; Shucla, R.; McPartlin, M. *Tetrahedron* **1991**, *47*, 7869–7874.
 - Okunaka, R.; Honda, T.; Kondo, M.; Tamura, Y.; Kita, Y. *Chem. Pharm. Bull.* **1991**, *39*, 1298–1301.
 - Azzena, U.; Demartis, S.; Melloni, G. *J. Org. Chem.* **1996**, *61*, 4913–4919.
 - Niefang, Y.; Poulain, R.; Tartar, A.; Gesquire, J. *Tetrahedron* **1999**, *55*, 13735–13740.
 - Bogdanov, M. G.; Palamareva, M. D. *Tetrahedron* **2004**, *60*, 2525–2530.
 - Kozekov, I. D.; Koleva, R. I.; Palamareva, M. D. *J. Heterocycl. Chem.* **2002**, *39*, 229–235.
 - Stoyanova, M. P.; Kozekov, I. D.; Palamareva, M. D. *J. Heterocycl. Chem.* **2003**, *40*, 795–803.
 - Karplus, M. *J. Chem. Phys.* **1959**, *30*, 11–15.
 - Karplus, M. *J. Am. Chem. Soc.* **1963**, *85*, 2870–2871.
 - Elieil, E. L.; Wilen, S. H.; Mander, L. N. *Stereochemistry of Organic Compounds*; John Wiley and Sons: New York, 1994, pp. 690–692.
 - Kraszni, M.; Szakacs, Z.; Noszlas, B. *Anal. Bioanal. Chem.* **2004**, *378*, 1449–1463, and references cited therein.
 - Contreras, R. H.; Peralta, J. E. *Prog. NMR Spectrosc.* **2000**, *37*, 321–425, and references cited therein.
 - Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, J. A.; Montgomery, Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Rabuck, A. D.; Raghavachari, K.; Malick, D. K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M.; Johnson, W. B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Andres, J. L.; and Pople, J. A. *Gaussian 98, Revision A.7*; Gaussian, Inc.: Pittsburgh PA, 1998.
 - Pietro, W. J.; Francl, M. M.; Hehre, W. J.; Defrees, D. J.; Pople, J. A.; Binkley, J. S. *J. Am. Chem. Soc.* **1982**, *104*, 5039–5048.
 - Petersson, G. A.; Tensfeldt, T. G.; Montgomery, J. A., Jr. *J. Chem. Phys.* **1991**, *94*, 6091–6101.
 - Sheldrick, G. M. *SHELXTL PC, SHELXTL/PC User's Manual. Version 5.1*; Bruker Axs Inc.: Madison, WI, USA, 1999.