Preparation, structural and conformational study of cyclobis[(*R*,*R*)-α,α′-bis(trifluoromethyl)-9,10-anthracenedimethylsulphite]

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Abstract—The macrocycle cyclobis[(*R*,*R*)-α,α′-bis(trifluoromethyl)-9,10-anthracenedimethylsulphite) has been prepared and the two possible arrangements have been identified and are described. A conformational study was carried out using NMR and molecular modelling techniques and X-ray diffraction analysis has allowed full assignment of the crystal structure. © 2002 Elsevier Science Ltd. All rights reserved.

1. Introduction

The identification and quantification of enantiomeric mixtures is an important part of the analysis of organic compounds. The use of NMR with the aid of chiral auxiliaries, such as chiral solvating agents (CSAs), is an essential methodology in organic chemistry and constitutes one of the most useful and frequently employed methods to determine the composition of enantiomeric mixtures.

The search for new, highly effective and universal CSAs is a very important research target within this field. Moreover, the complex of a chiral substrate with a CSA constitutes a simple model for receptor–substrate interactions where the chirality of the substrate is one of the most important selection factors.

Recently, we presented the preparation and the study of α,α′-bis(trifluoromethyl)-9,10-anthracenedimethanol **1**,[1] which, in enantiomerically pure form, behaves as a very effective CSA. The presence of two chemical functionalities increases the discrimination between the enantiomers, possibly as a result of geometric factors that also modify the kinetics of the process. The formation of an association complex, where enantiodifferentiation originates, could be favoured if a host–guest complex is formed. The difunctional compound **1** represents a good starting point to build chiral macrocycles that can lead to stable associations and thus allow chiral recognition.

Anthracenophanes are cyclophanes containing anthracene rings. Most of them are connected at the 9 and 10 positions. The ([2,2](9,10)-anthracenophane), the simplest homologue, is obtained[2] by dimerization of 9,10-di(chloromethyl)anthracene. Some researchers[3] have combined anthracene rings with ether bonds giving cyclophane-crown ether hybrid macrocycles. Disulphide and disulphone derivatives[4] are used as precursors for 9,10-dihydro-9,10-dimethyleneanthracene. The anthracene ring can also be used[5] as a spacer that determines the length of the macrocycle.

We have published[6] the preparation and structural study of di[(*S*)-1-(9-anthryl)-2,2,2-trifluoroethyl]sulphite where the perpendicular disposition of the anthracene rings was demonstrated, giving an attractive intramolecular edge-to-face aromatic interaction.[7] Herein, we present the preparation and structural study of similar regioisomeric macrocyclic derivatives of **1**.

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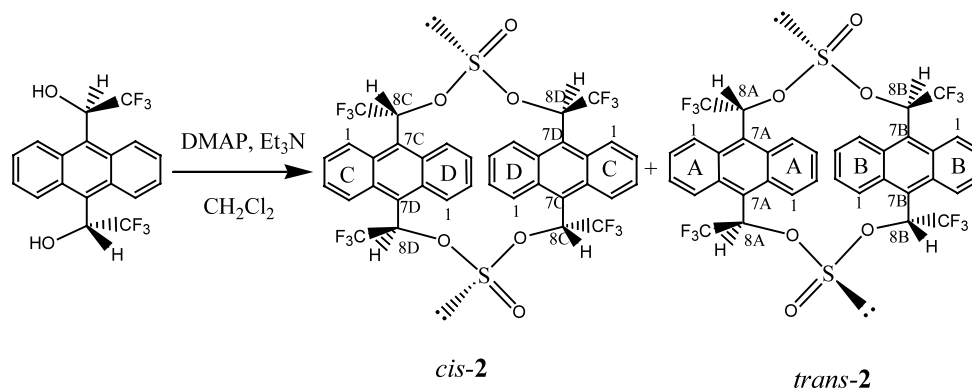
Scheme 1. Preparation of cyclobis[(*R,R*)-α,α′-bis(trifluoromethyl)-9,10-anthracenedimethyl sulphite.
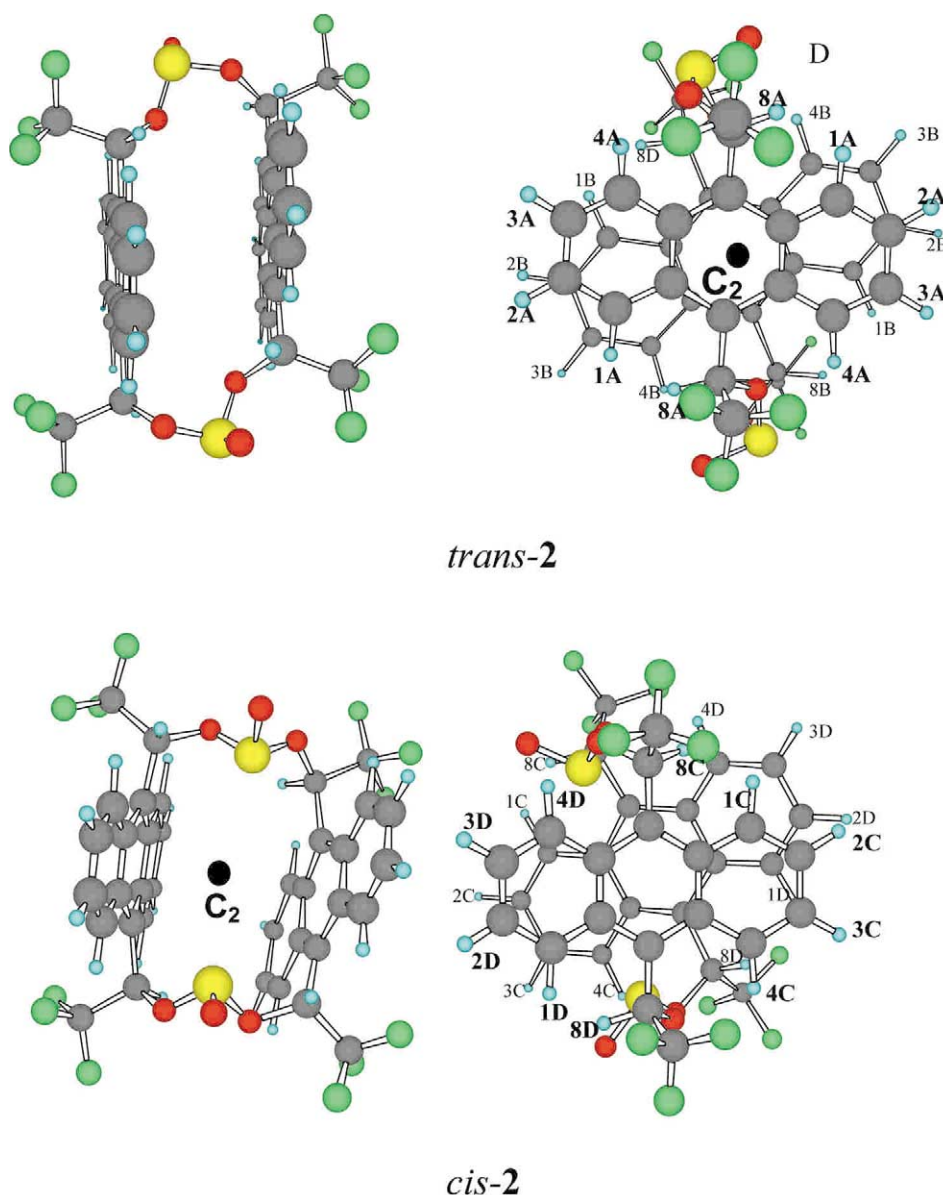

Figure 1. The most stable conformers for each of the two isomers of **2**, *cis* and *trans*, as obtained by Monte-Carlo multiple minimum. Two views of each isomer are shown and the C_2-symmetry axes are indicated.

2. Results and discussion

The reaction of (R,R)-α,α'-bis(trifluoromethyl)-9,10-anthracenedimethanol **1** with an excess of thionyl chloride in the presence of Et$_3$N and dimethylaminopyridine, using CH$_2$Cl$_2$ as a solvent, afforded cyclobis[(R,R)-α,α'-bis(trifluoromethyl)-9,10-anthracenedimethyl sulphite][8] **2** (44% yield) (Scheme 1). The relative position of the two S=O bonds (at the same side of the macrocycle,[9] *cis* or at the opposite side, *trans*) define two isomers that can also be named from the absolute configuration of the sulfur atom. In this way the *cis*-isomer corresponds to the (RR)-configuration and the *trans*-isomer to the (SS)-configuration at the sulfur centers.[10] The cyclization reaction afforded the two isomers in a ca. 1:1 ratio. During chromatographic purification, some eluted fractions showed a ratio between the isomers slightly different from unity.

Molecular modelling of the two isomers allowed us to define two structures that are represented in Fig. 1. In the *cis* derivative, the C$_2$-symmetry axis lies along the cavity, whereas in the *trans*-isomer this C$_2$ axis is perpendicular to both anthracene rings. The ^{1}H NMR spectrum (Fig. 2) showed the presence of the stereoisomers that we have identified. A complete assignation is carried out after considering their symmetry.

Four different 4-spin subsystems were found, which were denoted A, B, C and D. Furthermore, each of these subsystems have five types of protons 1, 2, 3, 4 and 8. It is worth mentioning here that two subsystems belong to the *cis* stereoisomer and the others to the *trans*-isomer.

Four H$_8$ protons were first identified as quartets. Each isomer presents two well differentiated H$_8$ signals. Two (H$_{8A}$ and H$_{8D}$), those that are near to the S=O bond, absorb in the aromatic zone (at high frequency) and the other two (H$_{8B}$ and H$_{8C}$), those further away from the S=O bond, at 6.7–6.8 ppm (at lower frequency). The nearest nucleus to the sulfoxide moiety suffers a strong deshielding effect.[11]

The first identified aromatic protons were those of the type H$_1$ by its NOE with H$_8$. The other signal assignments were achieved with the aid of COSY, TOCSY and NOESY NMR spectroscopy. TOCSY analysis afforded the necessary information about which proton belongs to the described subsystems. The chemical shifts are listed in Table 1.

Table 1. Proton chemical shifts in cyclobis[(R,R)-α,α'-bis(trifluoromethyl)-9,10-anthracenedimethyl sulphite] in CDCl$_3$

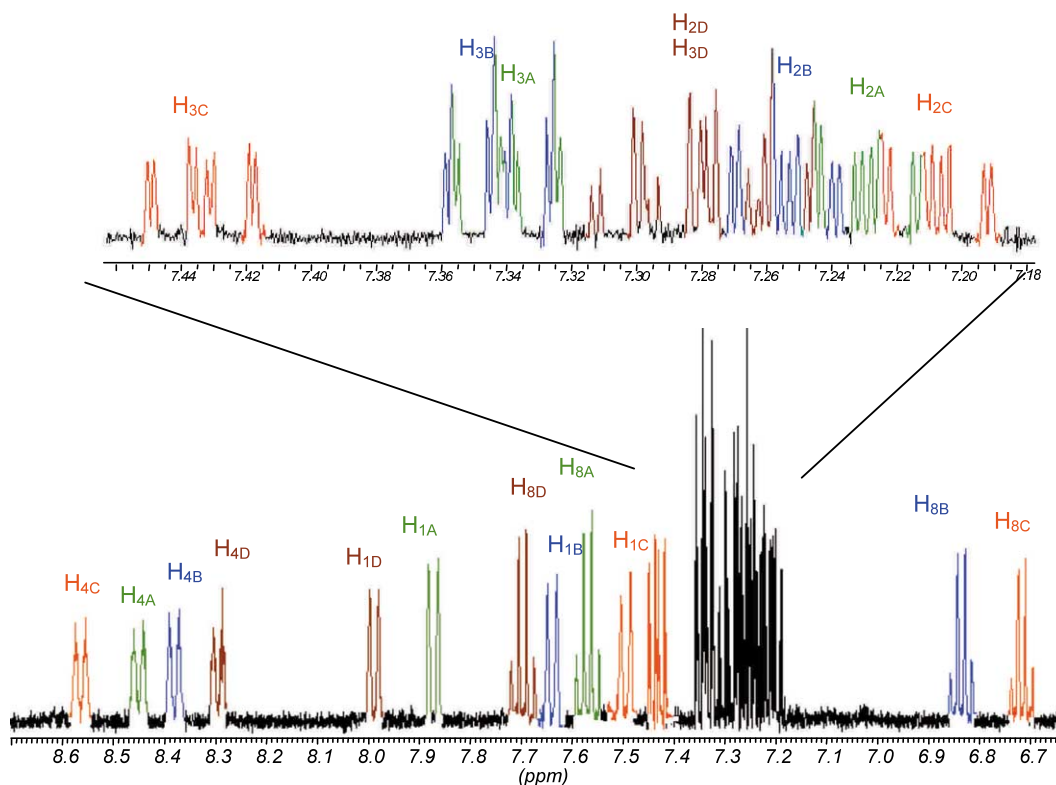| H	δ (ppm)	H	δ (ppm)
	cis		*trans*
H$_{1D}$(d)	7.981	H$_{1A}$(d)	7.874
H$_{2D}$(ddd)	7.280	H$_{2A}$(ddd)	7.230
H$_{3D}$(ddd)	7.280	H$_{3A}$(ddd)	7.340
H$_{4D}$(d)	8.294	H$_{4A}$(d)	8.452
H$_{8D}$(q)	7.699	H$_{8A}$(q)	7.569
H$_{1C}$(d)	7.490	H$_{1B}$(d)	7.639
H$_{2C}$(ddd)	7.208	H$_{2B}$(ddd)	7.254
H$_{3C}$(ddd)	7.435	H$_{3B}$(ddd)	7.343
H$_{4C}$(d)	8.565	H$_{4B}$(d)	8.382
H$_{8C}$(q)	6.721	H$_{8B}$(q)	6.837

Figure 2. ^{1}H NMR spectrum (500 MHz) of cyclobis[(R,R)-α,α'-bis(trifluoromethyl)-9,10-anthracenedimethyl sulphite] **2** (298 K, CD$_2$Cl$_2$).

The chemical shifts (Table 2) of the carbon atoms were assigned using phase sensitive HSQC and HMBC experiments. In order to achieve maximum resolution in the F1 dimension, a bond-selective 2D version[12] was used, in which a semi-selective REBURP pulse (centered on the aromatic carbon atom region) of 5 ms was applied. This last experiment allowed us to identify each isomer, pairing two of the four spin systems. In a first step one can localize each of the carbon atoms that are attached to the stereogenic carbon atom via each of the H_8 protons: C_{7C} and C_{7D} from H_{8C} and H_{8D} in the *cis*-isomer and C_{7A} and C_{7B} from H_{8B} and H_{8A} in the *trans*-isomers (see Fig. 3). In the *cis*-isomer, each of these carbon atoms must show connectivity with four protons that belong to two different spin systems. Thus, C_{7C} shows coupling with H_{1C} and H_{4D} and C_{7D} with H_{1D} and H_{4C}, confirming that the C and D spin systems belong to the *cis*-isomer. On the other hand, in *trans*-**2**, HMBC gave a correlation peak between C_{7A} and two protons of the A subsystem (H_{1A} and H_{4A}), while the atom C_{7B} gave a correlation peak for the B ring (H_{1B} and H_{4B}).

A conformational study was carried out with the aid of molecular mechanics and dynamics techniques and nuclear Overhauser spectroscopy. NOE spectra were obtained in one (Fig. 4) and two dimensions via gradient selections (DPFGE-NOE[13] and 2D NOESY[14]). We have studied[15] the conformations of Pirkle alcohol and other similar derivatives[16] and we have shown the possibility of measuring the energy of rotation of a bond from the study of the transferred NOE between two exchanged protons. In the present case we observed an important NOE between the H_{8s} and each of the H_{1s}. We also observed relaxation between H_{8C} with H_{4C} and H_{8B} with H_{4B}. This possibly corresponds to proximity between the two rings. Moreover, these two protons
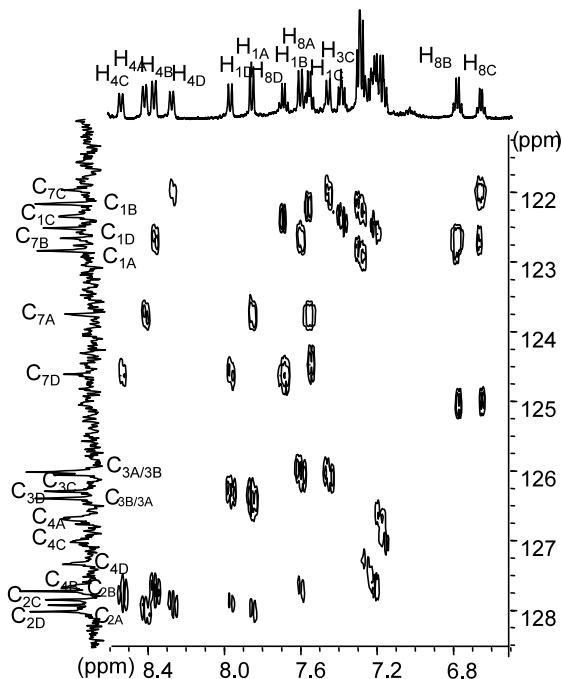

Figure 3. HMBC spectrum (400 MHz) of cyclobis[(*R*,*R*)-α,α′-bis(trifluoromethyl)-9,10-anthracenedimethyl sulphite] **2** in CDCl₃.

(H_{8C} and H_{8B}) give NOEs with H_{4D} for the *cis*-isomer and with H_{4A} for the *trans*-compound, respectively. Partial rotation of the C_7–C_8 bond (together with that of the sulphite bridge) would bring these nuclei closer, justifying these phenomena. In fact, in an open structure these H_4 protons could be considered as the conversion of H_1 from the rotation of C_7–C_8 bond.

The conformational behavior of compounds *trans*-**2** and *cis*-**2** was studied by molecular modelling techniques. A conformer search was carried out using the Monte-Carlo multiple minimum option within the Macromodel program.[17] The selected force field was MM3* (the implemented version of Allinger's MM3 force field[18]). Several conformers were found for each studied molecule, but the most stable (Fig. 1) is always at least 12 kJ/mol lower in energy than the next most stable one. The population of these stable conformers is thus near to 100%.

Computations indicate that *cis*-**2** is about 9 kJ/mol more stable than *trans*-**2** (415.7 and 424.8 kJ/mol, respectively). Careful analysis of the contributions given by the different energy terms indicates that compound *trans*-**2** has about 9 kJ/mol higher energy of bending than the *cis*-isomer. All of this strain is centered in the S–O–C bond angles.

These two compounds generate a cavity, which is too small to include any guest molecule. The distances between the two anthracene units (computed as the distance between the middle points of the central benzene rings) are 3.6 and 4.4 Å for *trans*-**2** and *cis*-**2**, respectively.

Table 2. Chemical shift for carbon atoms in cyclo-bis[(*R*,*R*)-α,α′-bis(trifluoromethyl)-9,10-anthracenedimethyl sulphite] **2** in CDCl₃

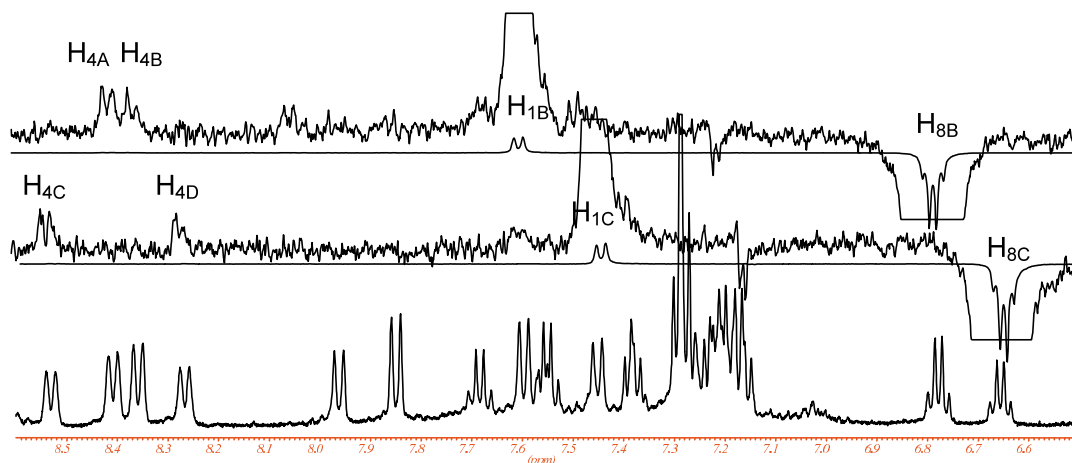| C_n	δ (ppm)	C_n	δ (ppm)
	cis		*trans*
C_{1C}	122.4	C_{1A}	122.9
C_{2C}	127.9	C_{2A}	128.0
C_{3C}	126.1	C_{3A}	126.1/126.4
C_{4C}	127.1	C_{4A}	126.7
C_{5C}	129.7	C_{5A}	130.7
C_{6C}	129.8	C_{6A}	130.3
C_{7C}	122.3	C_{7A}	123.9
C_{8C}	70.9	C_{8A}	63.2
C_{1D}	122.6	C_{1B}	122.1
C_{2D}	127.9	C_{2B}	127.8
C_{3D}	126.3	C_{3B}	126.4/126.1
C_{4D}	127.4	C_{4B}	127.7
C_{5D}	129.9	C_{5B}	129.4
C_{6D}	130.0	C_{6B}	130.2
C_{7D}	124.7	C_{7B}	122.7
C_{8D}	63.1	C_{8B}	70.6

Figure 4. DPFGE–NOESY spectra (CDCl$_3$) of **2** after saturation of H$_{8C}$ and H$_{8B}$.

Molecular dynamics simulations were also carried out using the most stable structures from the Monte–Carlo search as starting points. The results from the long simulations (productive runs of 1000 ps, with 1.5 fs time step at 300 and 700 K) indicate that the system is rather rigid. No significant conformational changes were detected during the simulation time. Minor changes in the relative orientation between both anthracene rings were observed but no rotation around the Csp^2–Csp^3 bonds at the 9 and 10 positions of the anthracene rings were detected.

The molecular dynamic simulations allow us to analyze the geometry of the system with time. Table 3 contains the evolution of the average distances between each H$_8$ and the two *peri* protons (H$_1$ and H$_4$) of its anthracene system. It is worth mentioning here that although H$_1$

Table 3. Average distances (Å) between each unique H$_8$ atom and the four nearer protons (both its *peri* protons H$_1$ and H$_4$ and the two other *peri* protons of the other anthracene ring) existing in compounds *trans*-**2** and *cis*-**2**, as obtained from the MD simulations at 300 K

Isomer	Fragment	H$_{8i}$/H$_{1i}$	H$_{8i}$/H$_{4i}$	H$_{8i}$/H$_{1j}$	H$_{8i}$/H$_{4j}$
2-*trans*	i=A, j=B	1.8	3.7	5.8	3.7
	i=B, j=A	1.8	3.7	5.8	3.5
2-*cis*	i=C, j=D	1.8	3.7	5.7	3.6
	i=D, j=C	1.8	3.7	5.9	3.4

and H$_4$ are distant from each other (they have a *para* relationship) the equivalents can always be found either in the other anthracene ring across the cavity (*cis*-**2**) or in the other half of the anthracene ring (*trans*-**2**).
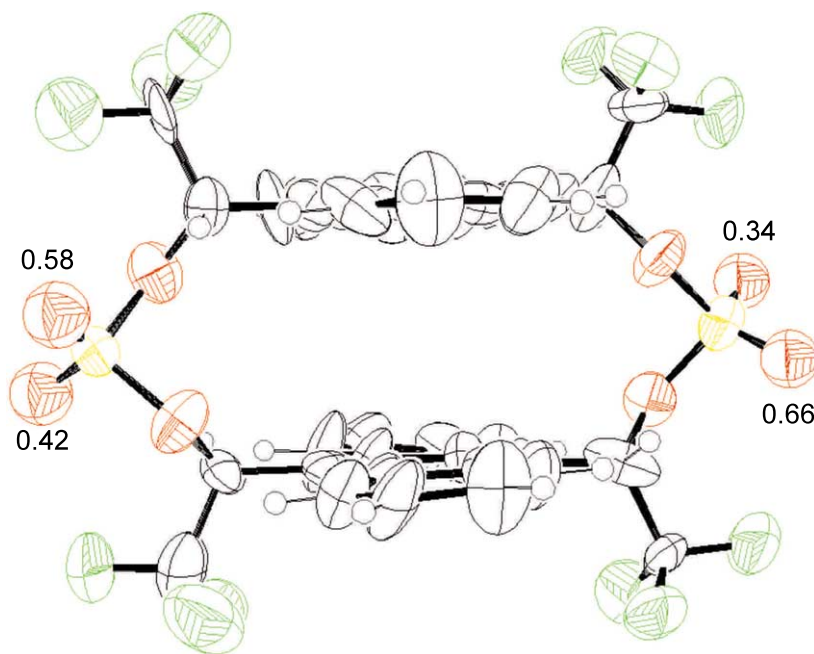

Figure 5. Average molecule found in the X-ray diffraction analysis **2** that corresponds to a 1:1 co-crystal of *cis*- and *trans*-isomers. Site occupation factors for disordered oxygens are included. The displacement ellipsoids are drawn at 50% level.

Clearly, each H_{8i} proton is very near to its corresponding H_{1i} proton, while the *peri* H_{4i} proton is at the limit of the distance for an NOE to occur. However, the H_{4j} (equivalent to H*4i* by symmetry) is always at a slightly shorter distance than H*4i*. Consequently, it may receive some NOE from saturation of H*8*. Crystallization of the isomeric mixture from chloroform at room temperature yielded crystals, one of which was studied by X-ray diffraction. The crystal has a solid solution structure and displays substitutional disorder: on a molecular site in the crystal, either *cis*- or *trans*-isomer can be found. Moreover, orientational disorder is also observed: each isomer can present two orientations related by a 180° rotation.

Therefore, X-ray diffraction analysis detects an average molecule by the superimposition of four molecules located in the same crystallographic position of the average unit cell. The two oxygen atoms linked by a double bond to sulphur are the most involved in this structural disorder and the average molecule has two pairs of disordered oxygen atoms with site occupation factor values of 0.58(1)/0.42(1) and 0.66(1)/0.34(1), respectively (Fig. 5). The crystal used in the X-ray experiment was analyzed by ^{1}H NMR, which indicated an equivalent distribution of two isomers.

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