Pergamon

Tetrahedron: *Asymmetry* 12 (2001) 1737–1740

TETRAHEDRON: *ASYMMETRY*

Di[(*S*)-1-(9-anthryl)-2,2,2-trifluoroethyl]sulphite, a case of diastereotopic anthracene groups

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Received 28 May 2001; accepted 20 June 2001

Abstract—The conformation of di[(*S*)-1-(9-anthryl)-2,2,2-trifluoroethyl]sulphite **1** was determined from NMR data and Monte-Carlo conformational search and molecular dynamics calculations. The two diastereotopic ring systems adopt an almost perpendicular relative position.

Pirkle alcohol **2** is a very useful chiral solvating agent[1] (CSA), which is often used to differentiate enantiomers in racemic mixtures of amines, acids, sulfoxides, etc. The enantiodifferentiation is based on two different properties of the complexes formed between the substrate and the CSA: the different binding constants and the distinct influence of the surroundings over the several nuclei observed in the NMR spectrum. Pirkle alcohol affords a very high magnetic anisotropy due to the anthracene ring, which appears to be the main reason for the enantiodifferentiation.

Pirkle alcohol **2** presents a restricted rotation[2] around the C(9)–C(11) bond ($\Delta G^{\#} = \sim 14$ kcal mol^{-1}) observed in ^{1}H NMR by the broadening of the H(1) (the *peri* proton nearest to H(11)) and H(8) (the *peri* proton nearest to OH) signals. The energy of this rotational barrier is increased to almost 20 kcal mol^{-1} when the alcohol group is converted to an ester functionality. Similarly, sulfite esters[3] will also present this high conformational barrier which will be increased by the presence of two anthracene rings in the same molecule.

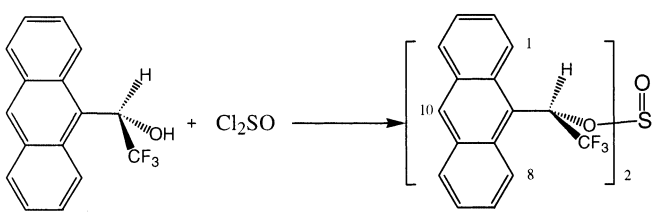
The reaction of thionyl chloride with (*S*)-1-(9-anthryl)-2,2,2-trifluoroethanol (*S*)-**2** (2/1 molar ratio in CH_2Cl_2 and Et_3N) gave di[(*S*)-1-(9-anthryl)-2,2,2-trifluoroethyl]sulphite[4] **1** (Scheme 1). Since the sulfur atom of the sulfite group is pyramidal it can be prochiral or chiral when is symmetrically or unsymmetrically disubstituted, respectively. In our case, the two substituents are homochiral with (*S*) configuration, the sulfur atom being a prochiral center and the anthracene rings diastereotopic and consequently anisochronous.

Fig. 1 presents the ^{1}H NMR spectrum (500 MHz) of di[(*S*)-1-(9-anthryl)-2,2,2-trifluoroethyl]sulphite **1**.

Signal assignments were achieved with the aid of COSY (Fig. 2) and NOE NMR spectroscopy. The first proton identified was H(1*R*) and H(1*S*) by its NOE with H(11). Table 1 contains the chemical shift for each diastereotopic proton, the observed difference and the chemical shift of the corresponding proton of the Pirkle alcohol under the same conditions (CD_2Cl_2, 300 K).

The maximum anisochronism for proton pairs is observed for H(1) and is also very marked for H(11).

The chemical shifts for the carbon atoms were assigned using HMQC and HMBC spectra (Table 2). A major differential influence on the C(1) and C(11) was also observed in this case.



(*S*)-**2** **1**

Scheme 1.

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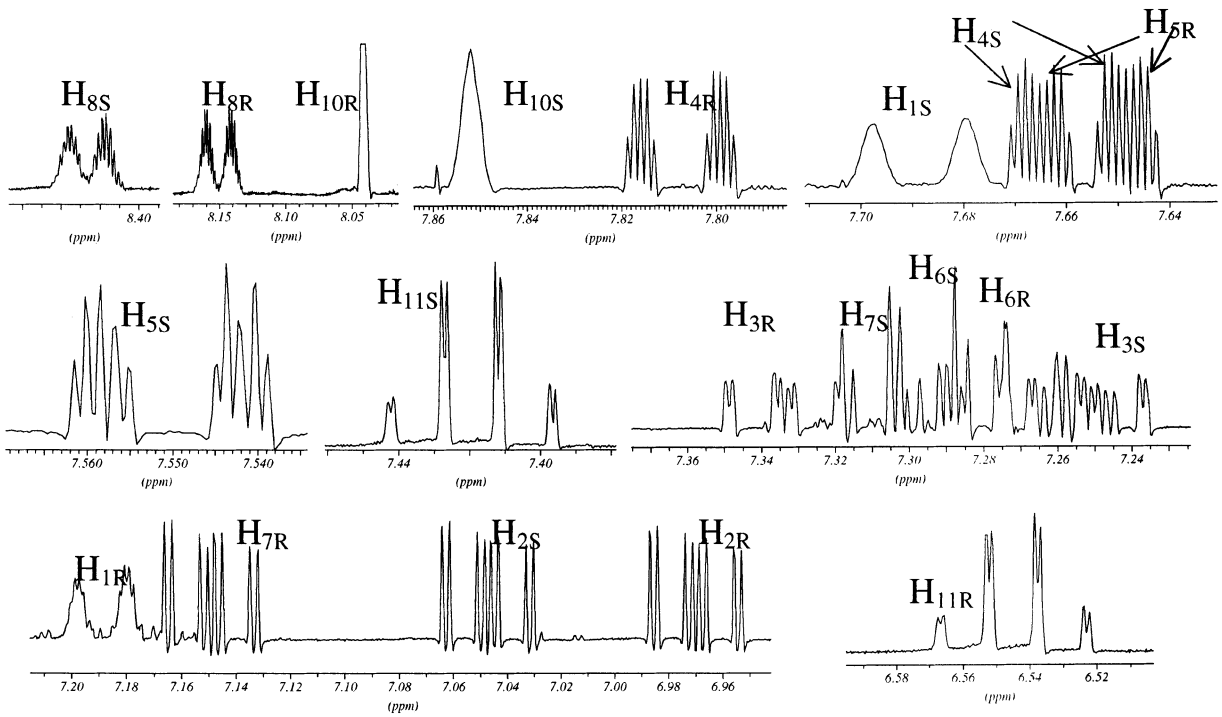

Figure 1. Parts of the ^{1}H NMR spectrum (500 MHz) of di[(*S*)-1-(9-anthryl)-2,2,2-trifluoroethyl]sulphite **1** (300 K, CD_2Cl_2).

The degree of differentiation of the two diastereotopic groups depends mainly on the environment of each group, which in this case, should be principally controlled by the degree of stabilization of a relative parallel position of anthracene rings by π,π-stacking forces (conformation **B**, Fig. 3). However, conformation **B** would give similar influences on each pair of diastereotopic protons and their chemical shifts would be very similar (Fig. 3).

A theoretical study of the conformational behaviour of this molecule was carried out to determine the most stable conformation. Monte-Carlo calculations (MacroModel package,[5] using the MM3* force field[6]) for the systematic search of all conformers obtained by random change of the dihedral angles contained in the C(sp^2)-C(sp^3)-*O*-S-*O*-C(sp)-C(sp^2) molecular fragment gave 385 different structures. The graphical analysis gave four representative conformers, where **A** (Fig. 3) was the most stable and **B** was only 6.8 kJ/mol above it. This energy difference represents a relative population of 95:4. The other conformers each have a less than 1% population.

Interestingly, conformer **B** is stabilized by van der Waals interactions but it suffers from severe bending deformations which together with the electrostatic interactions make **B** less stable than **A**. It is worth mentioning here that conformer **A** presents the two anthracene rings in T-type disposition, while in **B** the rings are parallel.

Molecular dynamics simulations (MacroModel package, MM3* force field, 298 K, 1000 ps, and $CHCl_3$ as solvent[7]) were performed using conformers **A** and **B** as starting coordinates. The conformation is well stabilised in both cases, but changes in geometry are observed for **B**. Conformer **A** keeps the same T-type geometrical disposition for the anthracene rings, but conformer **B** rapidly changes from the parallel to the T-type disposition, i.e. changes conformation to the more stable **A** at the very beginning of the MD simulations. Figs. 4 and 5 show the variation of the C(9*R*)–C(11*R*)···C(11*S*)–C(9*S*) dihedral angle along the MD simulations starting from conformer **A** and **B**, respectively.

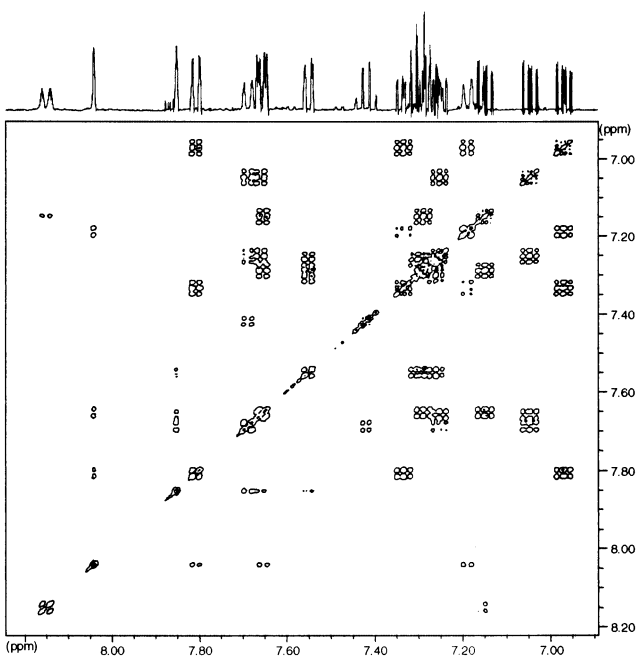

Figure 2. COSY spectra of di[(*S*)-1-(9-anthryl)-2,2,2-trifluoroethyl]sulphite **1**.

Table 1. Chemical shift of proton atoms of **1** and **2**

C(*n*)H	Chemical shift/ppm			
	H_R of **1**	H_S of **1**	**2**	$\Delta\delta$ (δ_{HS}–δ_{HR})
1	7.189	7.688	8.960	0.499
2	6.970	7.047	7.578	0.077
3	7.334	7.252	7.508	−0.082
4	7.807	7.659	8.060	−0.148
5	7.564	7.550	8.060	−0.014
6	–	–	7.508	–
7	7.149	7.301	7.578	0.152
8	8.150	8.426	8.180	0.276
10	8.041	7.852	8.586	−0.189
11	6.545	7.414	6.720	0.869

Table 2. Chemical shift of carbon atoms of **1** ($CDCl_3$, 300 K)

Carbon no.	*pro-R*	*pro-S*	$\Delta\delta$ (δ_S–δ_R)
1	121.00	120.28	−0.72
2	127.06	127.21	0.15
3[a]	–		
4	129.10	128.82	−0.28
5	128.92	129.24	0.32
6[a]	–	–	
7	125.97	126.23	0.26
8	125.83	125.62	−0.21
10	130.98	130.78	−0.20
11	70.30	64.34	−5.96

[a] 124.23, 124.29, 124.34, 124.67 are non-assigned peaks.

Thus, the existence of only conformer **A** should be considered for the studied molecule. This conformer explains the differentiation experimentally observed. The biggest differentiation is observed between pairs of protons labelled as H(11), and H(1) (see Table 1). Fig. 3 clearly denotes that H(1*R*) and H(11*R*) protons are subjected to strong magnetic shielding from the *pro-S* anthracene ring, and both protons have smaller δ than the corresponding *pro-S* protons. Computed distances between these two protons and the geometrical center of the *pro-S* anthracene are of 3.632 and 3.755 Å, respectively. Protons H(7*R*) and H(8*R*) also have very different environments to H(7*S*) and H(8*S*), but here it is the S=O bond which induces the magnetic anisotropy and their chemical shifts are also smaller than those for H(7*S*) and H(8*S*). In contrast, H(4*R*) and H(10*R*) suffer from greater deshielding with respect to H(4*S*) and H(10*S*). Very probably, they are far enough from the *pro-S* anthracene ring to observe any shielding influence from it.

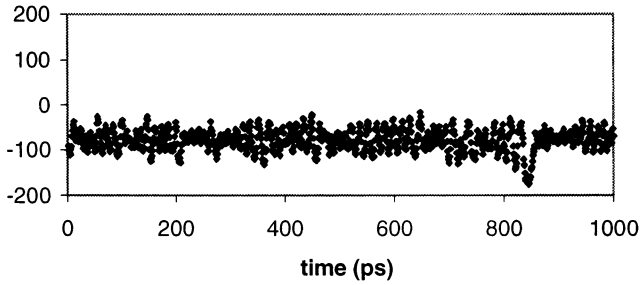

Figure 4. Variation of the C(9*R*)–C(11*R*)···C(11*S*)–C(9*S*) dihedral angle along the MD simulation of conformer **A**.

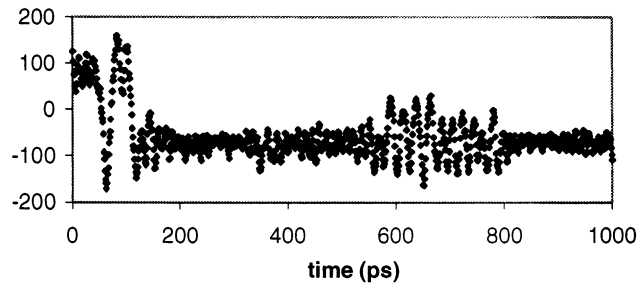

Figure 5. Variation of the C(9*R*)–C(11*R*)···C(11*S*)–C(9*S*) dihedral angle along the MD simulation of conformer **B**.

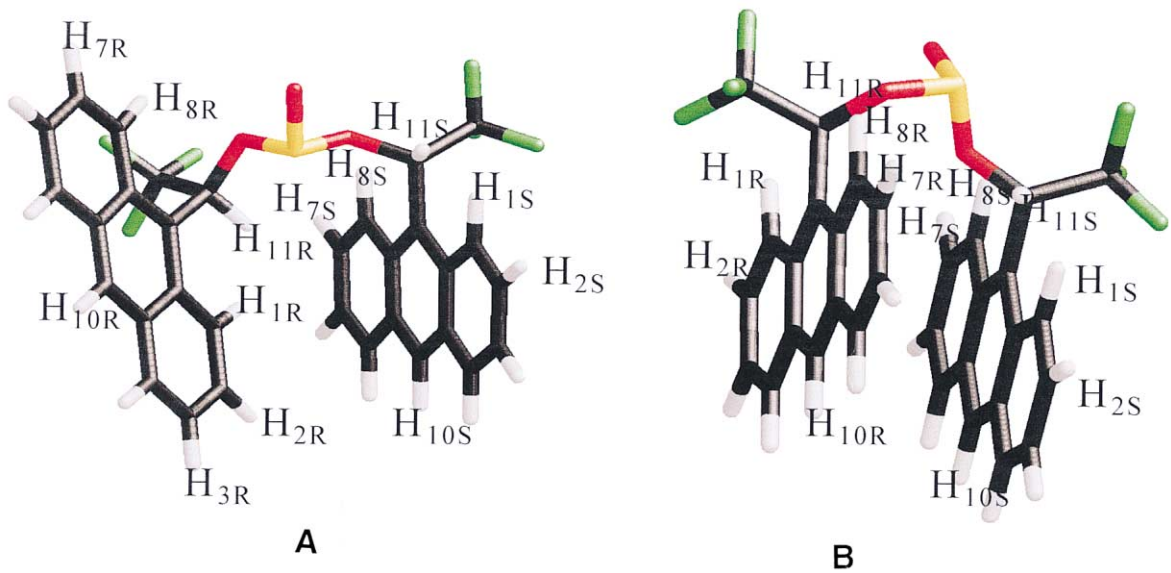

Figure 3. The two most stable conformations of **1** as obtained by MC and MD calculations.

Interestingly, the ^{13}C chemical shifts present significant differences (Table 2). Both C(1) and C(11) are those with the largest differences. However, carbons *pro-S* appear at higher field (smaller δ) than the *pro-R* carbons. The relative position respect to the anthracene ring for C(1) and to the S=O group for C(11) seems to be the reason. C(1*R*) is just above the *pro-S* anthracene ring, suffering from strong shielding. C(11*R*) is farther from the S=O group than C(11*S*). Calculated distances to the sulphite O atom are 3.438 and 2.986 Å for C(11*R*) and C(11*S*), respectively. Moreover, the C(11)-O-S=O dihedral angles are −156.6 and −100.0°, indicating a significantly different location with respect to the region of anisotropy.

Acknowledgements

Financial support from CICYT (project PPQ2000-369) is gratefully acknowledged.

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