Conformational Analysis of Methylsulphinyl Derivatives of Furan and Thiophene by Employing Nuclear Magnetic Relaxation and Lanthanide Induced Shifts

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Relaxation parameters such as nuclear Overhauser effect (NOE) and spin–lattice relaxation times (T_1) were applied to the conformational analysis of methylsulphinyl derivatives of furan and thiophene. Correlation times for molecular tumbling, τ_c, and for methyl reorientation, τ_i, were obtained. The τ_i values for the different molecules examined are nearly the same, the τ_c are twice as large in derivatives that also contain an iodine substituent in the heterocyclic ring. From non-selective, selective and bi-selective T_1 measurements and NOE values, relative to ^{1}H nuclei, and a best-fit procedure, the most probable conformational intervals for the methylsulphinyl group were located. Owing to the pyramidal structure of sulphoxides, the preferred conformers could not be fixed unambiguously. From the Lanthanide Induced Shift (LIS) technique on ^{1}H and ^{13}C nuclei, intervals of preferred orientations of the S–O bond with respect to the heterocyclic ring were found. Reliable conclusions about the conformational behaviour of these molecules have been drawn by matching the two sets of results. Relaxation parameters turn out to be useful for conformational analysis of small molecules when employed as a complementary tool with other experimental approaches.

The preferred orientations of the S–O bond in the ground-states of methylsulphinyl derivatives of furan and thiophene, compounds **1**–**4**, have been studied with MO *ab initio* methods[1] and, in solution, by employing an experimental integrated approach[2] based on ^{1}H, ^{13}C and ^{17}O chemical shifts and long-range ^nJ(C,H) coupling constants. Solid-state molecular structures obtained by X-ray diffraction for the molecules also containing halogen atoms were employed[2] as references for the conformational tests in solution.

Owing to the pyramidal structure of the sulphur atom of the sulphoxides, the conformation of the methylsulphinyl group cannot be unambiguously assigned when only the torsional angle of the methyl group, or that of the S–O bond with respect to the heterocyclic ring, are known. Approximate information on these torsional angles can be obtained from ^{1}H, ^{13}C and ^{17}O chemical shifts.[2] The long-range ^nJ(C,H) coupling constants, where the carbon nucleus refers to the methyl group, have proved[2–4] to depend on the conformation of the methylsulphinyl group, and, those over four bonds,[2] provided useful indications of the preferred orientation of the methyl group in the derivatives of furan and thiophene.

Stereochemical relationships between groups having nuclei active in nuclear magnetic resonance can, in principle, also be obtained from measurements of spin–lattice relaxation times[5] (T_1) and NOEs (nuclear Overhauser effects). For compounds **1**–**4**, relaxation of ring protons should be influenced[5,6] by the position in the ring and preferred orientations of the substituent containing the methyl group. Nevertheless, application of these techniques to conformational analysis is not straightforward owing to a number of limiting factors. Firstly, in a multi-spin system the spin–lattice pathway of each proton cannot be solved simply by a non-selective experiment (T_1^{ns}) but mono- (T_1^s) and bi-selective (T_1^{bs}) modes are also required, in order to obtain proton–proton distances and correlation times. Secondly, in the molecules examined here, internal rotation of the methylsulphinyl group around the exocyclic C–S bond and rotation of the methyl group have to be accounted for in view of the correlation times involved in these internal motions and in molecular tumbling.

Since applications of relaxation parameters to conformational equilibria of small molecules in solution are seldom reported, our intention here is to contribute towards verifying the applicability of these techniques to a number of problems of this kind. At the same time the results will be a useful test for the conformational conclusions obtained[2] from chemical shifts and long-range coupling constants in these systems.

Complexation in the presence of lanthanide ions should occur at the oxygen atom of the S–O group, and simulation of the lanthanide induced shifts[7,8] on ^{1}H and ^{13}C nuclei should provide information on the most probable conformational range of the S–O bond with respect to the heterocyclic ring. These results, when coupled with the orientation of the methyl group from relaxation parameters, should define the orientation of the methylsulphinyl group.

Relaxation Parameters and Outlines of Calculations.—Three relaxation times can be defined and measured for a multi-spin proton system and, referred to proton i, in the approximation of the initial rate conditions,[5,9] namely, T_{1i}^{ns} (non selective), T_{1i}^{s} (selective) and T_{1i}^{bs} (bi-selective). In the extreme narrowing limit, the direct relaxation, ρ_{ij}, and cross-relaxation, σ_{ij}, terms between protons i and j are defined by eqns. (1) and (2), holding

$$\rho_{ij} = \left(\frac{\mu_0}{4\pi}\right)^2 \gamma_H^4 \hbar^2 \tau_c r_{ij}^{-6} \tag{1}$$

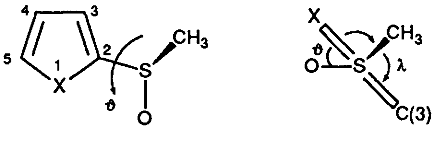
$$\sigma_{ij} = \frac{1}{2}\left(\frac{\mu_0}{4\pi}\right)^2 \gamma_H^4 \hbar^2 \tau_c r_{ij}^{-6} \tag{2}$$

for rigid molecules subjected to isotropic molecular tumbling. In these equations γ_H is the proton magnetogyric ratio, r_{ij} the distance between protons i and j, and τ_c the correlation time for molecular tumbling.

Since it follows that $\sigma_{ij} = (1/2)\,\rho_{ij}$, the relaxation time T_{1i}^{ns} can be written:

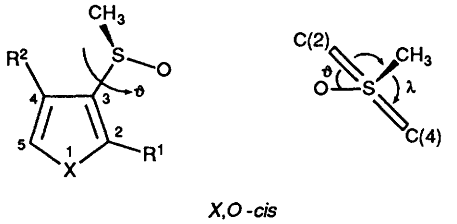
$$\frac{1}{T_{1i}^{ns}} = R_{1i}^{ns} = \frac{3}{2}\sum_j \rho_{ij} + \rho^* \tag{3}$$

The steady-state NOE for identical nuclei is expressed by eqn. (4), where k and i are the irradiated and observed nuclei respectively.



X,O-cis

1 X = O
2 X = S



X,O-cis

3a X = O R^1 = R^2 = H
3b X = O R^1 = H; R^2 = I
3c X = O R^1 = I; R^2 = H
4a X = S R^1 = R^2 = H
4b X = S R^1 = H; R^2 = I
4c X = S R^1 = I; R^2 = H
4d X = S R^1 = Br; R^2 = H

$\lambda \equiv \vartheta + 74.5$

Fig. 1

$$\eta_i(k) = \frac{1}{2}\sum_k \frac{\rho_{ik}}{\sum_j \rho_{ij} + \rho^*} - \frac{1}{2}\sum_{j \neq k} \frac{\rho_{ij}}{\sum_j \rho_{ij} + \rho^*}\eta_j(k) \qquad (4)$$

In compounds **1**–**4** two internal rotational motions, that around the exocyclic C–S bond and that around the C(H$_3$)–S bonds, must be explicitly considered in addition to molecular tumbling. Rotation around the exocyclic C–S bond is characterized by two minima in the energy profile, separated by energy barriers in the order of 4–6 kcal mol^{-1},* as emerges from MO *ab initio* calculations.[1] These molecules should therefore be found mainly in their ground-states (relative to this internal degree of freedom) and jumps from one minimum to the other should occur. This process should not significantly contribute to the effective correlation time for the interaction between any pair of spins in the molecule (for the two processes correlation times are of the order of 10^{-8}–10^{-9} s compared with 10^{-11} s). Internal rotation of the methyl group around the S–C(H$_3$) bond should be faster and the relative correlation time, denoted by τ_i, of the order of magnitude of τ_c.

In employing eqns. (1)–(4) it is therefore necessary to account explicitly for molecular tumbling (assumed to be isotropic) and for internal rotation of the methyl group. This can be performed by substituting proper expressions[10] for τ_c/r_{ij}^6 terms.

From the experimental T_1 and NOE values for the different protons, the unknowns τ_c, τ_i, ρ^* and a factor λ (see Fig. 1) closely related to the molecular structure (changing in the different conformations) should be estimated. By employing equations relating T_{1i}^{ns}, T_{1i}^{s} and T_{1i}^{bs} to these unknowns,[5,9,10] they can be determined by minimizing the deviations between calculated and experimental quantities by a least-squares procedure and employing eqn. (5). In this equation the Y values

$$F = [\Sigma(Y^{obs} - Y^{calc})^2/\Sigma(Y^{obs})^2]^{\frac{1}{2}} \qquad (5)$$

are T_{1i}^{ns}, T_{1i}^{s}, T_{1i}^{bs} and NOE values for the different protons. The T_1 values for the methyl group were not employed since a reliable treatment of this group is feasible only in the case of very fast and very slow internal motion.[11]

In order to extract well-defined values of all the variables from the experimental data, the system should be over-determined, but in our case owing to the small number of observables this is not possible. Therefore we restricted the use of relaxation parameters of ^{1}H nuclei to the calculation of the unknowns ρ^* and λ, introducing τ_c and τ_i values obtained, for each molecule, from T_1 and NOE measurements relative to ^{13}C nuclei.

In the assumption of isotropic molecular tumbling, τ_c can be obtained from T_1 values of protonated carbons of the heteroatomic ring.[9] For these protons the measured NOE values are a maximum (1.988). This should exclude spin rotation contributions to the relaxation mechanism, which should be of highly dipolar character ($T_1 \cong T_{1DD}$). τ_i can be estimated from the ratio $T_{1DD}(CH)/T_{1DD}(CH_3)$ by assuming that for the internal reorientation of the methyl group, the model randomly jumps between equivalent positions.[12,13]

Conformational Results from Relaxation Parameters.—Relaxation times and NOE values for ^{1}H nuclei are reported in Table 1, and relaxation times for ^{13}C nuclei in Table 2. For compound **2** only T_1^{ns} values, relative to ^{1}H, could be obtained owing to the small chemical shift separation of the ring protons.

Correlation times τ_c and τ_i were obtained from the relaxation times of ^{13}C nuclei. In Table 2 the standard deviations of these estimates in the approximation of isotropic molecular tumbling are also reported. The interval is small for τ_c values, whereas the error is slightly larger for the τ_i values. Nevertheless, by employing τ_i and an approximate formula,[10] the barrier for internal reorientation of the methyl group is 2.3–2.8 kcal mol^{-1}, quite in agreement with estimates of the same barrier in dimethyl sulphoxide.[15]

It was found that two distinct sets of τ_c values characterize the molecules with and without the iodine atom: for the former compounds larger correlation times are found. Furthermore, an increase in the correlation time τ_c is observed in 3- methylsulphinyl derivatives when the iodine atom is in position 2 (compounds **3c** and **4c**) with respect to the compounds with iodine in position 4 (compounds **3b** and **4b**). The values of τ_c and τ_i were then employed for calculating ρ^* and λ, minimizing the F values given by eqn. (5). This has been performed by altering λ, which appears in the expressions of T_{1i}^{ns}, T_{1i}^{bs}, T_{1i}^{bs} and NOE, through r_{HH} bond-distances, over the whole rotational circuit of the methylsulphinyl group (in 10° steps). Molecular geometries were built from averages of bond-angles and bond-distances obtained from the X-ray molecular structures of a number of these compounds.[2] Two solutions are possible as regards $\lambda(\pm\lambda)$ corresponding to two sets of identical r_{HH} values, and thus θ (defined in Fig. 1) can assume the values $\lambda - 74.5$ and $285.5 - \lambda$. For example, if $\lambda = \pm 74.5°$, one solution corresponds to $\theta = 0°$ and the other to $\theta = 211°$: the former is the X,O-*cis* conformer with the S–O bond coplanar with the ring, and the latter a twisted X,O-*trans* conformer.

The most probable values of λ and θ for the compounds examined are those reported in Table 3. This table also includes the ρ^* terms and these should represent relaxation contributions from interactions other than intramolecular interactions.[16]

For compounds **1**, **2**, **3a** and **4a** the smallest value of F was obtained for $\lambda = \pm 74.5°$, *i.e.* a coplanar X,O-*cis* and twisted X,O-*trans* conformer are equally probable. Mixtures of these forms reproduce the experimental data equally well. The results clearly indicate that conformers different from these are less probable, but not which of these forms is the preferred one. For

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* 1 cal = 4.184 J.

Table 1 Spin–lattice relaxation times[a] T_1/s and NOE values[b] for ^1H nuclei of compounds **1**–**4**

Compound		H_2	H_3	H_4	H_5	CH_3
1	T_1^{ns}	—	63.0 (0.8)	58.2 (0.8)	89.3 (1.3)	7.7 (0.1)
	T_1^{s}	—	73.6 (1.1)	73.0 (1.1)	119.1 (2.1)	—
	NOE	—	0.112	−0.019	0.023	—
2	T_1^{ns}	—	42.1 (0.6)	34.1 (0.5)	66.1 (1.2)	7.4 (0.1)
	NOE	—	0.067	−0.014	0.015	—
3a	T_1^{ns}	118.1 (1.5)	—	49.0 (0.5)	74.5 (0.8)	7.3 (0.1)
	T_1^{s}	140.8 (1.8)	—	60.8 (0.7)	91.9 (1.1)	—
	T_1^{bs}	148.4 (2.0)	—	—	90.0 (1.0)	—
	NOE	0.083	—	0.132	−0.025	—
3b	T_1^{ns}	69.6 (1.1)	—	—	120.5 (2.1)	5.2 (0.1)
	T_1^{s}	86.6 (1.6)	—	—	162.9 (2.6)	—
	T_1^{bs}	73.6 (1.2)	—	—	123.8 (2.3)	—
	NOE	0.082	—	—	−0.028	—
3c	T_1^{ns}	—	—	30.3 (0.4)	59.3 (0.6)	4.6 (0.1)
	T_1^{s}	—	—	38.3 (0.5)	70.0 (0.8)	—
	NOE	—	—	0.135	−0.057	—
4a	T_1^{ns}	110.4 (1.8)	—	41.7 (0.7)	56.0 (0.8)	7.4 (0.1)
	T_1^{s}	146.3 (3.6)	—	58.9 (1.1)	77.4 (1.7)	—
	NOE	0.078	—	0.099	−0.029	—
4b	T_1^{ns}	108.3 (1.5)	—	—	113.3 (1.5)	4.8 (0.1)
	T_1^{bs}	118.9 (1.6)	—	—	145.4 (2.1)	—
	NOE	0.120	—	—	0.090	—
4c	T_1^{ns}	—	—	30.9 (0.3)	43.1 (0.5)	3.8 (0.1)
	T_1^{bs}	—	—	37.9 (0.4)	59.6 (0.8)	—
	NOE	—	—	0.155	−0.030	—

[a] Estimates of the precision of T_1 values according to Weiss and Ferretti (ref. 14, see text) are reported in parentheses. [b] Obtained on irradiating the Me protons.

Table 2 Spin–lattice relaxation times[a] T_1/s for ^{13}C nuclei and estimates of τ_c and τ_i correlation times for compounds **1**–**4**

	T_1/s						
Compound	C_2	C_3	C_4	C_5	CH_3	$\tau_c/10^{-11}$ s	$\tau_i/10^{-11}$ s
1	—	13.05 (0.31)	9.48 (0.14)	12.43 (0.24)	5.50 (0.16)	0.39 ± 0.05	1.4 ± 0.5
2	—	13.24 (0.33)	10.83 (0.26)	9.75 (0.23)	5.34 (0.12)	0.40 ± 0.04	1.3 ± 0.5
3a	12.52 (0.31)	—	13.05 (0.18)	9.16 (0.19)	5.59 (0.12)	0.39 ± 0.06	1.2 ± 0.3
3b	5.28 (0.08)	—	—	5.57 (0.07)	3.98 (0.09)	0.81 ± 0.02	0.77 ± 0.02
3c	—	—	4.56 (0.12)	5.22 (0.15)	3.34 (0.10)	0.91 ± 0.06	1.00 ± 0.08
4a	12.15 (0.14)	—	11.62 (0.10)	9.93 (0.17)	5.34 (0.10)	0.39 ± 0.03	1.2 ± 0.2
4b	5.51 (0.34)	—	—	5.32 (0.32)	3.37 (0.18)	0.81 ± 0.01	1.12 ± 0.03
4c	—	—	4.58 (0.24)	4.51 (0.26)	3.06 (0.16)	0.969 ± 0.007	1.11 ± 0.01

[a] Estimates of the precision of the T_1 values according to Weiss and Ferretti (ref. 14, see the text) are reported in parentheses. [b] The deviation reported on these values accounts for our having assumed for molecular tumbling an isotropic model.

Table 3 Values[a] of λ and θ (see Fig. 1) and ρ^* for compounds **1**–**4** derived from relaxation parameters

Compound	λ/°	θ/°	$\rho^*/10^{-2}$ s^{-1}
1	±74.5	0; 211	0.30
2	±74.5	0; 211	—
3a	±74.5	0; 211	0.48
3b	±104.5	30; 181	0.65
3c	±64.5	350; 221	0.13
4a	±74.5	0; 211	0.61
4b	±64.5	350; 221	0.65
4c	±74.5	0; 211	0.05

[a] Defined within 10°.

the compounds having an additional iodine substituent in the ring, **3b**, **4b**, **3c** and **4c** conformers of X,O-*cis* and X,O-*trans* type, differing in the degree of twist of the S–O bond, are also preferred. For these molecules, one of the two conformers should nevertheless be considered significantly less probable than the other, in line with previous evidence.[2] Measurements of ^1H, ^{13}C and ^{17}O chemical shifts and $^nJ(C,H)$ long-range coupling constants in solution, and X-ray molecular structures in the solid-state assign a very low preference to the form having the S–O bond facing the iodine (or, in general, a halogen) substituent (X,O-*trans* for **3b** and **4b**, X,O-*cis* for **3c** and **4d**).

LIS (*Lanthanide Induced Shift*) *Simulation*.—The preferred

Table 4 Pseudocontact shifts (ΔM) for ^{1}H nuclei and corrected for diamagnetic shifts ($\Delta M - \Delta D$) for ^{13}C nuclei in compounds **1**–**4**

Compound	C_2	C_3	C_4	C_5	CH_3	H_2	H_3	H_4	H_5	CH_3
1	39.00	20.40	11.73	13.60	41.80	—	16.12	6.79	8.93	28.69
2	39.70	20.40	11.08	11.40	42.60	—	17.90	6.60	7.10	28.70
3a	21.80	40.90	23.12	12.30	42.20	18.05	—	20.80	7.20	28.98
3b	27.86	42.96	19.66	12.17	42.25	28.49	—	—	7.32	29.53
3c	21.60	41.30	26.60	13.40	43.60	—	—	26.60	7.44	29.20
4a	22.70	39.60	21.56	11.27	40.02	23.27	—	20.67	6.67	27.66
4b	30.40	42.70	18.80	11.24	42.10	37.82	—	—	6.99	29.51
4d	19.60	40.90	28.60	13.10	42.60	—	—	34.30	7.01	29.20

Table 5 Results of the analyses of the LIS. R, φ, ψ and pop % refer to the localization of the lanthanide atom, R_{cryst} is an agreement factor (see ref. 8)

Compound	R/Å	φ/°	ψ/°	pop %	R_{cryst}	Conformer amount (%)	θ/°
1	3.40	40	145	5	0.019	90	0
	3.30	70	115	5	0.019	100	±60
2	3.40	30	150	0	0.009	80	0
3a	3.10	65	125	10	0.022	30	0
	3.10	65	125	10	0.022	70	211
3b	2.60–2.80	60–65	150–175	0–30	0.016–0.017	100	0 ± 30
	2.75	65	155	25	0.015	90	0
3c	3.30	55	130	10	0.016	10	0
	3.30	55	130	10	0.016	90	180 ± 30
4a	3.10	70	125	10	0.017	50	0
	3.10	70	125	10	0.017	50	211
4b	2.95–3.05	55	155	25–30	0.012	100	0
4d	3.10–3.35	45–65	130–135	10	0.012–0.014	100	180 ± 30

orientation of the S–O bond with respect to the heterocyclic ring can, in principle, be obtained by employing reagent shifts.[7] The simultaneous use of LIS on ^{1}H and ^{13}C nuclei, with the precaution of removing diamagnetic shifts, has given quantitative answers[8] on the conformer isomerism and structures of aromatic aldehydes and ketones. The pseudocontact shift ΔM was obtained from Yb(fod)$_3$ reagent and the diamagnetic corrections ΔD with La(fod)$_3$: the $\Delta M - \Delta D$ values for ^{13}C nuclei and ΔM for ^{1}H nuclei are reported in Table 4. The experimental LIS values were simulated with the LIRAS-3 package,[8] assuming a 1:1 substrate–lanthanide complex and a four-site complexation model. The molecular geometries were those employed in the simulation of relaxation parameters. Complexation was assumed to occur at the oxygen atom of the S–O bond, in view of previous evidence.[17] The results of LIS analyses are collected in Table 5.

The simulation model assumed for the lanthanide–substrate complex provided the same agreement factor (R_{cryst}) for ±θ. Simulation was carried out either on single conformations as a function of θ or on combinations of two conformations with different θ values. In a number of cases different solutions gave the same minimum of R_{cryst}. Before examining comparatively the results from LIS simulation and from relaxation parameters in order to attempt conformational conclusions, some immediate information can be obtained from a qualitative survey of the LIS values reported in Table 5. The relative magnitude of the induced shift indicates, approximately and within the same molecule, the distance between the oxygen atom of the S–O bond and the ^{13}C or ^{1}H nucleus. The comparison between the LIS values of compounds **3b** and **3c**, which should have[2] opposite orientations of the S–O bond, shows that for C-4 and C-2 these amount to nearly 20 and 28 ppm, respectively, in compound **3b**, and this trend is reversed in compound **3c**. These shifts are in qualitative agreement with the orientation of the S–O bond opposite to the iodine substituent. The same occurs for compounds **4b** and **4e**. For compounds **3a** and **4a** the LIS values on C-2 and C-4 (and on H-2 and H-4) are similar and this may indicate that, for these molecules in chloroform solution, an equilibrium mixture of rapidly interchanging conformers should be present. From theoretical calculations[1] the presence of about 60% of the X,O-*cis* conformer is predicted in chloroform solution and this form becomes less preferred in more polar solvents. For compounds **1** and **2** direct comparison of induced shifts is less indicative since results relative to compounds with a fixed orientation of the S–O bond are lacking. Nevertheless a prevailing X,O-*trans* orientation can be excluded.

Conformational Conclusions from Relaxation Parameters and LIS Analysis.—The simultaneous use of the conformational indications obtained from the experimental techniques enables conclusions to be drawn on the conformational behaviour of compounds **1**–**4** in solution. These are summarized in Table 6.

For compound **1** the common solution from the two approaches indicates a prevailing presence of the O,O-*cis* conformation, with the S–O bond coplanar with the ring. An alternative orientation, with the S–O bond highly twisted, fits LIS simulation. According to MO calculations,[1] two ground-state conformations are present for this molecule, the O,O-*cis* conformation with θ = 62° and the O,O-*trans* conformation with θ = 175°, the latter is more stable in the vapour phase. In polar solvents, according to theoretical predictions,[1] two O,O-*cis* conformers become stable (equally twisted above and below the heterocyclic plane, θ ≅ ±60°), and together are

Table 6 Summary of the conformational indications from relaxation parametrs and LIS analyses and comparison with the most probable conformational results obtained in other approaches

Compound	λ from relaxation parameters/°	θ from LIS simulation/°	Common solution (θ/°)	Other approaches
1	±74.5	0 ±60	0 (prevailing O,O-*cis*)	Predominant O,O-*cis* conformation probably highly twisted[a]
2	+74.5	0	0 (prevailing S,O-*cis*)	Predominant S,O-*cis* conformation slightly twisted[a]
3a	±74.5	220 (100% O,O-*trans*) 180 (70% O,O-*trans*)	211–220 (prevailing O,O-*trans*)	Prevailing O,O-*trans* conformation slightly twisted[a]
3b	±104.5	0 ± 30 (100% O,O-*cis*) 0 (90% O,O-*cis*)	30 (prevailing O,O-*cis*)	Prevailing O,O-*cis* conformer with a low twist.[a] Solid-state[b] θ = 9
3c	±64.5	180 ± 30 (100% O,O-*trans*) 180 (90% O,O-*trans*)	210–220 (prevailing O,O-*trans*)	Prevailing O,O-*trans* conformer with significative twist[a] Solid-state[b] θ = 231
4a	±74.5	0 (50% S,O-*cis*)	0 and 211 (mixture of S,O-*cis* and S,O-*trans* conformers)	Equilibrium mixture of S,O-*cis* and S,O-*trans* conformers with the latter prevailing[a]
4b	±64.5	0	−10–0 (prevailing S,O-*cis*)	Prevailing S,O-*cis* conformation with a low twist[a] Solid-state[b] θ = 3
4c	±74.5		210 (prevailing S,O-*trans*)	Prevailing S,O-*trans* conformer with significative twist[a]
4c		180 ± 30		

[a] Ref. 2, results obtained in solution from ^{1}H, ^{13}C and ^{17}O chemical shifts and ^{n}J(C, H) long-range coupling constants. [b] Ref. 2, X-ray analysis.

more abundant than the O,O-*trans* form. Simulating the relaxation parameters which such a mixture of conformers, the F value did not turn out to be higher than that corresponding to one conformer with $\lambda = \pm 74.5°$. On the basis of these experimental results it would seem impossible to differentiate the situation corresponding to a prevailing O,O-*cis* planar conformation from that of a prevailing mixture of the two equally twisted conformers. Compound **2** should be preferentially in the S,O-*cis* form with a low degree of twist, confirming the results of previous approaches.[2]

For compounds **3a** and **4a**, the equilibrium mixture of the two conformers, evidenced previously,[2] emerges again from this study, yet their amount is not well defined, in view of the fact that changes occur in different solvents.[2] The X,O-*trans* form should nevertheless be higher than 50%. The halogen atom in the ring determines a clear orientation of the S–O bond away from the former substituent. For compounds **3a** and **4a** the preferred conformer is in agreement with the solid-state structure.[2]

In conclusion, these results show that relaxation parameters can provide useful indications of the conformational trend in solution even in the case of molecules of relatively small size. Nevertheless, for reaching conclusive results for the orientation of substituents such as the methylsulphinyl group, complementary information from other experimental approaches is necessary. NMR techniques including LIS simulation, chemical shifts of ^{1}H, ^{13}C and ^{17}O nuclei and long-range coupling constants, when conformationally dependent, provide valuable auxiliary answers.

Experimental

The syntheses of the compounds have been reported in a previous paper.[2]

NMR Measurements.—The relaxation parameters were obtained with a Bruker WP-80 spectrometer. For T_1 measurements on ^{1}H, solutions in [^{2}H$_6$]acetone (0.1 mol dm^{-3} or less) were employed. The samples were repeatedly degassed at 5×10^{-3} mbar after being kept overnight on molecular sieves (4 Å) previously dried in an oven at 400 °C for 5 h. The non-selective relaxation times, T_1^{ns}, were obtained from the conventional inversion-recovery method: D–P_{180}–V_D–P_{90}–A_t, in which 10–16 V_D values were included in the analysis of the data and the delay was at least five times the longest T_1 value. The selective, T_1^{s}, and bi-selective, T_1^{bs}, values were measured by applying selective P_{180} pulses with the decoupling unit. Apparent bi-selective pulses were obtained by applying separate successive pulses when the chemical shift of the protons to be irradiated are sufficiently separated, or a pulse able to invert two nuclei simultaneously in the case of small chemical shift separation (< 10 Hz). The precision of the values $\sigma(T_1)$ was estimated according to Weiss and Ferretti.[14]

Differential NOE measurements were obtained from the samples used in T_1 experiments, with acquisition of 128 + 128 (or 256 + 256) transients in groups of eight. The methyl group was irradiated on- and off-resonance. Before each group of eight transients, 2–4 dummy scansions were performed and a relaxation delay between each transient of $3T_1$–$5T_1$ (T_1 is the longer relaxation time) was employed. The relaxation times and NOE values of ^{13}C nuclei were measured by employing non degassed samples in [$^2H_6$]acetone solution (0.5 mol dm^{-3}) and a Varian XL-200 spectrometer.

Lanthanide induced shifts were measured for ^1H and ^{13}C nuclei on the same sample using the Bruker WP-80 spectrometer. The shift reagent employed is Yb(fod)$_3$, dried *in vacuo* (phosphorous pentaoxide) added in known and increasing amounts to [^2H]chloroform solutions (0.3 mol dm^{-3}) of the substrate examined. The maximum molar ratio between Yb(fod)$_3$ and the substrate was 0.1. The correlation coefficients for the plots relating chemical shifts to the lanthanide/substrate ratio were always found $\geqslant 0.999$ and the intercepts identical with the unshifted spectra.

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