Conformational Analysis. Part 23.[1] A Lanthanide-induced Shift Investigation of Some Cyclic and Acyclic Sulfoxides

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A lanthanide-induced shift (LIS) analysis of methyl phenyl sulfoxide **1**, diphenyl sulfoxide **2**, thiane 1-oxide **3**, thiolane 1-oxide **4** and 1,3-dithiane 1-oxide **5** is reported. The appropriate lanthanum–sulfoxide complexation model was investigated using **1** and **2** as substrates. A three-site binding model with variable populations of the three sites using the LIRAS4 program gives the best agreement factor. This model is then used to determine the conformations and conformational equilibria in the five- and six-membered ring sulfoxides. In the multi-functional 1,3-dithiane 1-oxide the lanthanum complexes exclusively with the SO group, and there is no evidence of any complexation with the 3-sulfur atom. The percentage of O equatorial conformer in thiane 1-oxide and 1,3-dithiane 1-oxide was determined as 45 and 95% respectively, in general agreement with the results of low temperature NMR studies, which are in solvents of different polarity. The large solvent dependence of these conformational equilibria is given a quantitative explanation in terms of classical solvation theory. Molecular mechanics calculations on thiolane 1-oxide predicted a novel envelope conformation of the five-membered ring which gives very good agreement for the LIS shifts.

It is concluded that the application of the LIS method *via* LIRAS4 to sulfoxide conformations and structures is a promising novel development in this area.

The conformational analysis of sulfoxides continues to be of considerable interest, both synthetically as sulfoxides are now often key chiral precursors in asymmetric synthesis,[2] and theoretically in that the SO bond provides a crucial test of present theoretical methods.

The remarkable conformational properties of sulfoxides were first unambiguously determined by Johnson and McCants,[3] and Martin and Uebel.[4] Direct equilibration of 4-*tert*-butylthiane 1-oxides in decalin at 190 °C gave equilibrium mixtures (*cis* : *trans*) of 80 : 20,[3] and similar equilibrium mixtures were obtained for the 4-methyl and 4-*p*-chlorophenyl compounds at room temp.,[3] giving free energy differences in favour of the axial SO conformer [Fig. 1(*a*)] of *ca.* 1.0 kcal mol^{-1}.† Subsequently Lambert[5,6] and Barbarella *et al.*,[7] from low temperature NMR measurements showed the large solvent dependence of this equilibrium and they also noted the contrasting effects of the 4,4- and 3,3-dimethyl substituents on this equilibrium. Similar measurements on 1,3-dithiane 1-oxide [Fig. 1(*b*)][8–10] and on 1,3-oxathiane 1-oxide[9–12] and their 5,5-dimethyl derivatives have been reported.

The conformational analysis of thiolane 1-oxide has been much less investigated. The complete analysis of the ^{1}H NMR spectrum of 3,3-dimethylthiolane 1-oxide was reported by Barbarella *et al.*[13] who proposed an envelope conformation for this molecule with the sulfur atom at the flap and the oxygen axial [Fig. 1(*c*)], mainly from their observation of a long range $^4J_{HH}$ coupling between two of the α protons. Barbarella also gave force field calculations (MMS) and ^{13}C chemical shifts for thiolane 1-oxide and several methyl derivatives.[14]

The calculations showed that the ring conformation depended critically on the methyl substitution pattern. In thiolane 1-oxide the half-chair and the envelope conformations with sulfur at the flap and the oxygen axial were calculated to be of equal energy and a similar envelope conformer with oxygen equatorial was only 0.4 kcal mol^{-1} higher energy. They however appeared only to consider symmetric conformations.

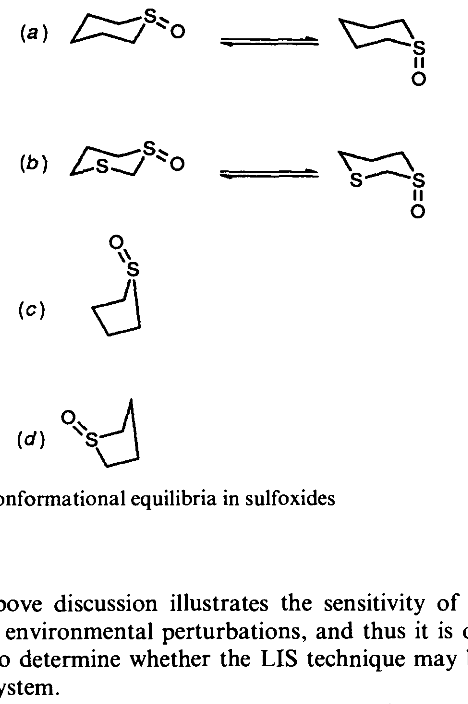

Fig. 1 Conformational equilibria in sulfoxides

The above discussion illustrates the sensitivity of the SO group to environmental perturbations, and thus it is of some interest to determine whether the LIS technique may be used for this system.

A number of LIS investigations on sulfoxides have been recorded. The possible complexation models for lanthanide binding to aromatic sulfoxides were examined by Montaudo *et al.*[15] using a simple one-site model and subsequently Caccamese *et al.*[16] developed a three-site model arising from the three oxygen lone pairs. Also Kodama *et al.*[17] proposed a simple one-site monodentate complexation model in which the oxygen–lanthanide bond extends outwards along the S=O axis. In all cases only ^{1}H LIS data were obtained, thus there was insufficient data to both obtain the lanthanide binding model and determine the substrate geometry.

LISs were used to determine the ring conformations of 3-substituted thietane 1-oxides,[18] but again Eu(dpm)$_3$ was used

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† 1 kcal mol^{-1} = 4.184 kJ mol^{-1}.

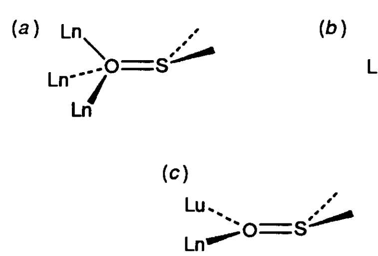

Fig. 2 Possible models for coordination of the lanthanide ion to the sulfoxide group: (*a*) three-site, (*b*) one-site and (*c*) two-site models

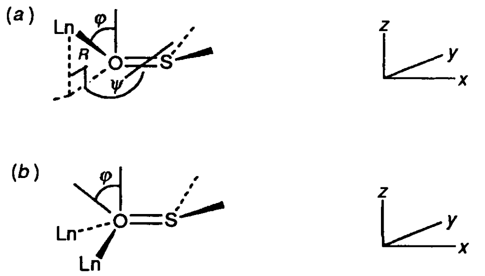

Fig. 3 Parameters used in (*a*) LIRAS3 and (*b*) LIRAS4

Table 1 Diamagnetic shift (ΔD) values for diphenyl sulfone, diphenyl sulfoxide and methyl phenyl sulfoxide

	Previous work	This work	
	$(Ph)_2SO_2$[17]	$(Ph)_2SO$ **2**	MePhSO **1**
i-C	−1.72	−5.53	−6.95
o-C	0.17	0.38	1.39
m-C	0.15	−0.03	0.18
p-C	0.53	0.58	1.10
CH_3	—	—	−3.85

to measure the LIS giving ΔM values only for hydrogen as this reagent has large contact shifts on the carbon nuclei.

An authoritative NMR and LIS investigation on methyl phenyl sulfoxides was reported by Taddei and co-workers,[19] using the recommended procedure for obtaining LIS and the LIRAS3 program[20] for their analysis. Their results were substantiated by further NMR experiments and subsequently by an X-ray[21] and *ab initio*[22] investigations. They showed conclusively that both in the solid state and solution the conformations of methyl phenyl sulfoxides with none or one *ortho*-substituent is that with the phenyl ring coplanar with the SO bond, and this agrees with the conformation of diphenyl sulfoxide, in the solid and gas phase.[23] We will use these important results subsequently to check on the applicability of the LIRAS4 program[24] to the LIS of sulfoxides.

Theory.—The successful simulation of LIS values for any molecule is dependent on obtaining the correct geometry for the lanthanide binding position in the lanthanide–substrate complex.[25] The models of lanthanide complexion to be considered are (*i*) the three-site model,[16] in which the binding sites are arranged in staggered conformation with respect to the atoms bonded to sulfur, and are separated from each other by a rotation angle of 120° [Fig. 2(*a*)]; (*ii*) the one-site model[17] [Fig. 2(*b*)]; and (*iii*) a two-site model [Fig. 2(*c*)] with variations in site population. With the increase in data by using both ^{13}C and ^{1}H shifts, it is possible to remove the assumptions made previously with the above models, and allow variation of such parameters as the Ln–O distance, the Ln–O–S angle and the percentage populations in the various sites.

The program LIRAS3[20] can only simulate the complexation of Fig. 2(*b*, *c*). LIRAS4,[24] is a development of LIRAS3, and calculates shift agreement factors in a similar way to LIRAS3. The lanthanide coordinates (R, φ and ψ) are defined as for LIRAS3 [Fig. 3(*a*)], but ψ is fixed at 180°, forcing the initial position of the lanthanide to be in the *xz*-plane. This position is defined as site 1; sites 2 and 3 are then obtained by rotation through 120° about the *x*-axis, clockwise (site 2) and anticlockwise (site 3). Thus all three sites have the same *x* coordinate. Site 1 can be rotated β about the *x*-axis, but sites 1, 2 and 3 always retain their three-fold symmetry about the *x*-axis [Fig. 3(*b*)]. Variable site populations are also allowed.

Experimental

Methyl phenyl sulfoxide, diphenyl sulfoxide and thiolane 1-oxide were supplied by Aldrich and recrystallised prior to use. Thiane 1-oxide was kindly provided by Professor M. Novi (Department of Chemistry, University of Genoa, Italy) and 1,3-dithiane 1-oxide by Dr. P. C. B. Page (Chemistry Department, University of Liverpool, UK).

LIS experiments were carried out using the incremental weighing method in which weighed amounts of the two shift reagents, $Yb(fod)_3$ and $La(fod)_3$,* are added to a known mass of substrate.[20]

^{1}H and ^{13}C spectra were recorded at 400 MHz on a Bruker AMX400 spectrometer at ambient temperature. All chemical shifts were referenced to Me_4Si.

The sulfoxides and shift reagents were dried *in vacuo* over P_2O_5 for 24 h before use. The solvent, $CDCl_3$, was dried over molecular sieves (3 Å size), which had been baked to 300 °C.

Assignments of the ^{13}C *Spectra*.—Assignments of the ^{13}C spectra of diphenyl sulfoxide,[26] methyl phenyl sulfoxide,[27] thiolane 1-oxide[13] and thiane 1-oxide[7] were taken from the literature. The assignment of the ^{13}C spectrum of 1,3-dithiane 1-oxide is the same as that given by Juaristi *et al.*,[12] with one exception. C-4 is to low field of C-5, the opposite to that of reference 12. This assignment was suggested by the larger value of the pseudo-contact shift (Table 6) and confirmed unambiguously by a ^{1}H–^{13}C HETCOR experiment, the correlation between 5ax-H and C-5 being observed very clearly.

Diamagnetic complexation shifts were measured for both the carbon and hydrogen nuclei. The values for the latter were, as usual for saturated compounds so small as to be within the experimental error and these were not included in the LIRAS analysis.

Assignments of ^{1}H *Spectra*.—The proton spectrum of diphenyl sulfoxide at 400 MHz is an ABB′XX′ spin system with the X nuclei (the *ortho* protons), well separated from the AB portion. This spectrum was simulated using the PANIC routine,[28] taking the coupling constants from the literature[29] and varying the chemical shifts until agreement with observed spectrum was obtained.[30] The chemical shifts obtained are given in Table 2. In the case of methyl phenyl sulfoxide an analogous procedure was used, and the chemical shifts are given in ppm in Table 3.

For thiolane 1-oxide, Barbarella *et al.*[14] reported but did not analyse the high field proton spectrum. The proton spectrum at 400 MHz shows three complex multiplets at δ 2.87, 2.46 and 2.03 of intensity 2:1:1, respectively. Our assignment (Table 4) is based on H_α being to low field of H_β and also the protons *cis* to the oxygen having much larger ΔM values than the protons *trans* to the oxygen.

The complete assignment of the proton spectrum of thiane 1-oxide has not been given previously. Our assignments for the 2,6

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* fod = 1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane-4,6-dione.

and 3,5 protons are based on the proton *cis* to the oxygen in each CH_2 group being to the low field of the *trans* oriented proton, and this is supported by the larger ΔM values for the *cis* oriented protons. Both these effects are particularly noticeable for the H-3,5 protons, as is to be expected from the proximity of the *cis* protons to the oxygen atom in the axial conformation. These assignments agree with results of Lambert and Keske.[5] The 4-H protons are not resolved separately under any of the conditions of these experiments and give one complex multiplet and one ΔM value (Table 5).

The assignments of the proton spectrum of 1,3-dithiane 1-oxide followed from a COSY experiment. The C_2–H AB quartet, with a long range coupling from H_{2e} to H_{4e}, as noted by Cook and Tonge[8] and Juaristi *et al.*,[12] considerably assists the assignment. Our assignment agrees with that of Cook and Tonge[8] for those protons they were able to assign. They were unable to clearly resolve the C-4 and C-5 protons at 200 MHz, but at 400 MHz they can all be assigned unequivocally.

Results and Discussion

Observed chemical shifts (δ), diamagnetic shifts (ΔD), LIS values (ΔM), and pseudo-contact shifts ($\Delta M - \Delta D$) for **1**, **2**, **3**, **4** and **5** are given in Tables 2–6, respectively.

The π electron distribution in sulfone and sulfoxide complexes may be compared from the diamagnetic shift (ΔD) values (Table 1).

The use of diamagnetic shifts to observe π electron delocalisation has been reported previously.[31] Comparison of the ΔD values for diphenyl sulfone with **2** and **1**, respectively, shows that the values are much larger in the sulfoxides, indicating increased interaction between the benzene rings and the sulfur atom in the sulfoxide complex.

Lanthanide–Sulfoxide Complexation Model.—It is first necessary to determine the most appropriate complexation model for the lanthanide sulfoxide complex, and a similar procedure to that of ref. 24 was used. Methyl phenyl sulfoxide was taken as the conformationally fixed model, following the results of Taddei *et al.*, [19,22] which show conclusively that the stable conformation of the molecule is that with the phenyl ring coplanar to the sulfoxide group, and these also provide an accurate geometry for this molecule, given in Table 7.

There are four possible monodentate complexation models for the sulfoxide to consider. These are (*i*) the one-site model with the lanthanide along the SO axis, proposed by Kodama *et al.*,[17] [Fig. 2(*b*)], (*ii*) a two-site model analogous to the model used for CO groups[24] with reflections about the *xz*-plane [Figs. 2(*c*) and 3(*a*)], (*iii*) a three-site model with equal populations in all three sites [Fig. 2(*a*)] and (*iv*) the three-site model with unequal populations.

The results of these analyses using the data for methyl phenyl sulfoxide are shown in Table 8, and are of some interest.

The simple one-site model with a linear Ln–O–S geometry is clearly not acceptable, with a large value of the agreement factor (AF). More surprisingly the three-site model with equal populations of the three sites is also incapable of giving a good solution. If the geometry is allowed to relax completely, keeping the three equally populated sites, the solution degenerates into the one-site model above with a linear Ln–O–S geometry. If the Ln–O–S angle is fixed at 130° the results in Table 8 are obtained, which are unacceptable. In contrast both the two-site and the three-site models with varying site populations give very reasonable agreement.

The reason for this is clearly seen on considering the site populations. In both cases the lanthanum is situated at the sterically least-crowded position, essentially eclipsed to the sulfur lone pair, and well removed from the bulky phenyl and methyl groups. This interpretation is confirmed by the very

Table 2 Observed ^{13}C and ^1H shifts (δ), diamagnetic shifts (ΔD), intercept values (δ_{int}), LIS values (ΔM) and pseudo-contact shifts ($\Delta M - \Delta D$) for diphenyl sulfoxide (in ppm)

Parameter	C-1(*i*)	C-2(*o*)	C-3(*m*)	C-4(*p*)
δ	145.55	124.73	129.30	131.04
δ_{int}	145.54	124.73	129.30	131.04
ΔM^a	40.67	28.64	12.89	10.77
ΔD^b	−5.33	0.38	−0.03	0.58
$\Delta M - \Delta D$	46.20	28.26	12.92	10.19
		(*o*)-H	(*m*)-H	(*p*)-H
δ		7.648	7.442	7.421
δ_{int}		7.643	7.443	7.419
ΔM^a		31.26	7.31	5.80

[a] Four additions of $Yb(fod)_3$, ρ = 0.0216, 0.0688, 0.1105, 0.1552. [b] Four additions of $La(fod)_3$, ρ = 0.0285, 0.0594, 0.0958, 0.1235.

Table 4 Observed ^{13}C and ^1H shifts (δ), diamagnetic shifts (ΔD), intercept values (δ_{int}), LIS values (ΔM) and pseudo-contact shifts ($\Delta M - \Delta D$) for thiolane 1-oxide (in ppm)

Parameter		C-2/5	C-3/4	
δ		54.58	25.57	
δ_{int}		54.55	25.54	
ΔM^a		37.77	26.98	
ΔD^b		−3.63	0.33	
$\Delta M - \Delta D$		41.40	26.65	
	2-H(c)	2-H(t)	3-H(c)	3-H(t)
δ	2.874	2.874	2.466	2.036
δ_{int}	2.890	2.861	2.474	2.037
ΔM^a	36.31	21.58	25.09	15.50

[a] Three additions of $Yb(fod)_3$, ρ = 0.0281, 0.0655, 0.1164. [b] Three additions of $La(fod)_3$, ρ= 0.0156, 0.0381, 0.0551.

Table 3 Observed ^{13}C and ^1H shifts (δ), diamagnetic shifts (ΔD), intercept values (δ_{int}), LIS values (ΔM) and pseudo-contact shifts ($\Delta M - \Delta D$) for methyl phenyl sulfoxide (in ppm)

Parameter	C-1(*i*)	C-2/6(*o*)	C-3/5(*m*)	C-4(*p*)	C-7(methyl)
δ	145.68	123.44	129.32	130.99	43.93
δ_{int}	145.65	123.42	129.31	130.99	43.90
ΔM^a	40.17	29.79	13.39	11.46	45.81
ΔD^b	−6.95	1.39	0.18	1.10	−3.85
$\Delta M - \Delta D$	47.12	28.40	13.21	10.36	49.65
	(*o*)-H	(*m*)-H	(*p*)-H	(methyl)-H	
δ	7.654	7.525	7.504	2.874	
δ_{int}	7.629	7.520	7.498	2.698	
ΔM^a	33.22	8.61	6.85	34.63	

[a] Three additions of $Yb(fod)_3$, ρ = 0.0271, 0.0470, 0.0662. [b] Three additions of $La(fod)_3$, ρ = 0.0222, 0.0454, 0.0666.

reasonable agreement obtained for the one-site model in which the Ln–O–S angle is allowed to relax (Table 8). The lanthanide position in this one-site model corresponds to that in the predominantly populated site for the two-site and three-site models. This is similar to the model proposed earlier by Caccamese *et al.*,[16] except that they selected the single lanthanide site from steric considerations as being *trans* (*anti*) to the phenyl ring.

Table 5 Observed ^{13}C and ^{1}H shifts (δ), diamagnetic shifts (ΔD), intercept values (δ_{int}), LIS values (ΔM) and pseudo-contact shifts ($\Delta M - \Delta D$) for thiane 1-oxide (in ppm)

Parameter	C-2/6(α)	C-3/5(β)	C-4(γ)		
δ	48.87	19.10	24.64		
δ_{int}	48.90	19.12	24.65		
ΔM^a	33.92	22.92	17.86		
ΔD^b	−4.97	−2.07	−0.68		
$\Delta M - \Delta D$	38.89	24.99	18.54		
	2/6-H(c)	2/6-H(t)	3/5-H(c)	3/5-H(t)	4-H
δ	2.888	2.767	2.238	1.663	1.601
δ_{int}	2.859	2.829	2.250	1.678	1.603
ΔM^a	29.66	22.64	25.71	13.97	12.22

[a] Four additions of Yb(fod)$_3$, ρ = 0.0174, 0.0304, 0.0516, 0.0698. [b] Four additions of La(fod)$_3$, ρ = 0.0187, 0.0317, 0.0583, 0.0778.

The lanthanide site obtained here by allowing the geometry to relax completely is somewhat different, as both the methyl and phenyl substituents have considerable steric effects, and the result is one which appears to minimise the total steric interaction, which indeed is only to be expected. The LIRAS4 three-site analysis is significantly better than the one-site and two-site models and will be used subsequently. The observed and calculated shifts for this model are shown in Table 9.

Diphenyl Sulfoxide.—The geometry of diphenyl sulfoxide (Table 7) was taken from electron diffraction data[23] with the phenyl rings almost orthogonal to the CSC plane (see earlier). This geometry with the observed pseudo-contact shifts (Table 2) and the above complexation model gave a very low agreement factor of 0.57% together with the complex geometry shown in Table 10, and calculated and observed shifts in Table 9. The almost exact agreement is pleasing, but probably fortuitous. Owing to the symmetry of the molecule there are only seven distinct pseudo-contact shifts. As the normalisation factor plus lanthanum position require four parameters to define them the

Table 6 Observed ^{13}C and ^{1}H shifts (δ), diamagnetic shifts (ΔD), LIS values (ΔM) and pseudo-contact shifts ($\Delta M - \Delta D$) for 1,3-dithiane 1-oxide (in ppm)

Parameter	C-2	C-4	C-5	C-6	2e-H	2a-H
	50.35	28.24	27.05	52.76	4.022	3.666
δ_{int}	50.30	28.23	27.03	52.70	3.992	3.643
ΔM^a	42.60	15.42	21.11	43.12	29.51	37.68
ΔD^b	−3.00	−0.63	2.36	−3.38		
$\Delta M - \Delta D$	45.60	16.05	18.75	46.50		
	4eH	4a-H	5e-H	5a-H	6e-H	6a-H
δ	2.568	2.679	2.528	2.212	3.337	2.629
δ_{int}	2.559	2.678	2.525	2.212	3.334	2.627
ΔM^a	9.615	12.53	12.98	15.19	32.32	41.01

[a] Four additions of Yb(fod)$_3$, ρ = 0.0114, 0.0290, 0.0454, 0.0667. [b] Four additions of La(Fod)$_3$, ρ = 0.0127, 0.0246, 0.0399, 0.0605.

Table 7 Geometry parameters used in the LIRAS4 analysis

Parameter	Ph_2SO	MePhSO	$(CH_2)_4SO$	$(CH_2)_5SO$	$(CH_2)_3SOCH_2S$
Bond length/Å					
S=O	1.49	1.49	1.49	1.48	1.48
C–S	1.80	1.80	1.82	1.81	1.81
Bond angle/°					
CSC	98.0	98.0	94.7	97.3	
OSC	106.0	106.0	104.0	107.1	105.4
C(1)C(2)S	120.0	120.0	106.7	109.47	
HCC	120.0	(120.0_{ring}) (109.47_{methyl})	109.5	109.47	109.47

Table 8 Summary of LIRAS3–LIRAS4 analysis of methyl phenyl sulfoxide using various lanthanide–sulfoxide complexation models

Fig.	Site model	Agreement factor (%)	Ln–O/Å	Ln–O–S/°	Site population (%)		
					1	2	3
2(*b*)	1-site[b]	6.882	2.80	180	100	0	—
2(*c*)	2-sites[b]	1.872	3.00	129	10	90	—
2(*a*)	3-sites[a]	19.42	3.60	130	33	33	33
2(*a*)	3-sites[a]	1.197	2.99	118	0	10	90
2(*b*)	1-site[a]	2.143	2.50	110	0	0	100

[a] LIRAS4. [b] LIRAS3.

system is not very well determined. However, both the lanthanum position and the site populations agree well with those for methyl phenyl sulfoxide, which is encouraging.

Also, because of the low degree of over-determination of this solution the AF was not very dependent on the geometry of the molecule. Thus further refinement of the ED geometry used, in particular the orientation of the phenyl rings, was not performed.

Conformational Analysis.—The determination of the appropriate model for the lanthanide–sulfoxide complexation allows the investigation of the structures and conformations of more complex molecules by the LIS technique. It is important to recall at this point the caveat noted previously in such determinations of molecular structures.[32] Because the LIS method gives only one measured quantity for each nucleus, for which of course a complete positional definition would require three parameters, the most efficient use of this technique is to identify one or two unknown molecular variables to be determined rather than attempt a total molecular structure determination, and this is the strategy adopted here.

Thus the primary geometries (*i.e.* bond lengths and angles) of the molecules to be investigated were first obtained either from literature data or from molecular mechanics calculations, *i.e.* PCMODEL[33] and NEMESIS.[34] The secondary conformational aspects, in particular the conformational equilibria and ring puckering, were then investigated by the LIS method as follows.

Thiane 1-*oxide*. The primary structure of this molecule was obtained from molecular mechanics (NEMESIS) calculations and is given in Table 7 and Fig. 4. Thus the unknown molecular parameters to be investigated were the conformational equilibrium of this molecule and if possible the refinement of the angle of buckle of the six-membered ring. The conformational equilibrium considered was that between the axial and equatorial SO group in the chair conformations [Fig. 1(*a*)], and no other conformation needs to be considered in this case. The geometry given above was input together with the LIS data of Table 5 into LIRAS4 with the three-site complexation model. The only restriction on the three-site model was that, because of the symmetry of this molecule sites two and three were equally populated and $\beta = 0$.

Table 9 Observed and calculated LIS (ΔM) for **1** and **2**

	1		**2**	
Nucleus	Obs.	Calc.[a]	Obs.	Calc.[b]
C-1	47.1	47.5	46.2	46.2
C-2,6	28.4	28.5	28.3	28.3
C-3,5	13.2	12.9	12.9	12.7
C-4	10.4	10.9	10.2	10.0
C-Me	49.7	49.2		
o-H	33.2	33.3	31.3	31.3
m-H	8.6	8.1	7.3	7.5
p-H	6.8	7.3	5.8	5.9
Me-H	34.6	34.6		

[a] $r = 2.99$ Å, $\varphi = 28°$, $\beta = 10°$, population 0:10:90, $R_x = 1.197\%$. [b] $r = 3.30$ Å, $\varphi = 35°$, $\beta = 5°$, population 5:5:90, $R_x = 0.571\%$.

This iteration converged to a very good value of the agreement factor of 2.0 for 54% of the axial conformer. Fig. 5 shows the AF(R_x) as a function of the % axial conformer. Table 11 gives the observed and calculated pseudo-contact shifts for the best solution, and the complexation parameters for the best solution are given in Table 10. Interestingly, although the site populations were allowed to vary freely within the symmetry imposed restriction above, the best solution was obtained with zero population of site 1. Thus the lanthanide occupies an essentially equatorial bonding orientation with respect to the oxygen atom, *i.e. gauche* to the sulfur lone pair. Again this would appear to be intuitively reasonable, this being the less hindered face of the sulfoxide bond in both the axial and equatorial conformer.

The percent axial conformer obtained here will be discussed later. The agreement obtained for the best solution is well within the recommended level of acceptability for such studies, which is for an AF of < 5% with all calculated shifts to be within 1.0 ppm of the observed shifts.[35] Also varying the angle of buckle of the rings did not produce any dramatic improvement in the AF thus further refinement of the molecular geometry was not performed. Note that this is a multi-dimensional function in

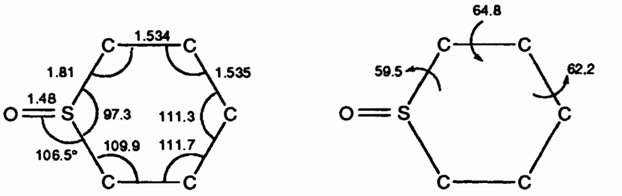

Fig. 4 Bond lengths (Å), bond angles (°) and torsional angles (°) in thiane 1-oxide

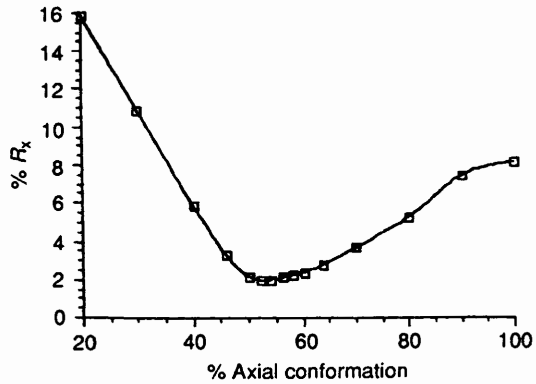

Fig. 5

Table 10 Summary of the LIRAS4 analysis for **1**, **2**, **3**, **4** and **5**

	Model	Agreement factor (%)	Ln–O/Å	Ln–O–S[a]/°	Site population (%) 1	2	3
MePhSO	3-site	1.197	2.99	118	0	10	90
Ph_2SO	3-site	0.572	3.30	125	5	5	90
$(CH_2)_5SO$ (54:46, ax:eq)	3-site	2.03	2.70	132	0	50	50
$(CH_2)_4SO$	3-site	0.40	2.82	126	0	50	50
$(CH_2)_3SCH_2SO$ (95:5; eq:ax)	3-site	2.88	3.05	120	3	34	63

[a] The Ln–O–S angle equals φ + 90° (Fig. 3).

Table 11 Observed and calculated LIS (ΔM) values for **3**, **4** and **5**

	3		**4**		**5**	
Nucleus	Obs.	Calc.[a]	Obs.	Calc.[b]	Obs.	Calc.[a]
C-2	38.9	39.2	41.4	41.5	45.6	45.8
C-3	25.0	24.3	26.7	26.6		
C-4	18.5	18.4			16.0	15.5
C-5					18.8	20.0
C-6					46.5	46.7
2t-H	22.6	23.5	36.3	36.3	29.5	29.4
2c-H	29.7	29.0	21.6	21.6	37.7	38.5
3c-H	25.7	26.0	25.1	24.9		
3t-H	14.0	13.7	15.5	15.6		
4-H	12.2	12.5				
4a-H					12.5	14.1
4e-H					9.6	9.4
5e-H					13.0	12.6
5a-H					15.2	15.3
6e-H					32.3	32.3
6a-H					41.0	39.1

[a] r = 2.70 Å, φ = 42°, β = 0°, population 0:50:50, R_x = 2.02%. [b] r = 2.82 Å, φ = 36°, β = 0°, population 0:50:50, R_x = 0.40%. [c] r = 3.05 Å, φ = 30°, β = −14°, population 3:34:63, R_x = 2.88%.

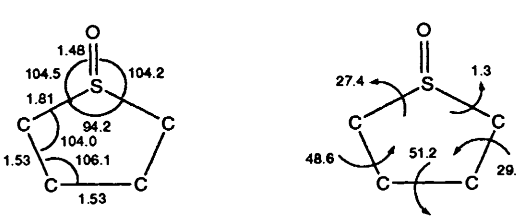

Fig. 6 Bond lengths (Å), bond angles (°) and torsional angles (°) in the thiolane 1-oxide ring

this case as there are four distinct flap angles in the two equilibrating conformers, thus the excellent solution with the above geometries does not imply that the geometries are not capable of further refinement by other techniques.

Thiolane 1-*oxide*. Barbarella *et al.*[13] have suggested that 3,3-dimethylthiolane 1-oxide is conformationally homogeneous and proposed a symmetric envelope conformation with the sulfur at the flap and the oxygen axial. Subsequent molecular mechanics calculations by the same group[14] for methyl substituted thiolane oxides showed the ring conformation to be greatly influenced by the number and position of the methyl substituents. They only considered symmetrical conformations.

Encouraged by this, the NEMESIS modelling program was used to obtain an initial geometry for thiolane 1-oxide, Fig. 6. It was found that no matter what conformation was input the program always iterated to a non-symmetrical envelope conformation with a β carbon atom at the flap and the oxygen axial [Fig. 1(*d*)].

It was of interest to see whether this conformation, or a refinement of it, could give a satisfactory solution to the observed shift data. Thus this geometry was input into LIRAS4 using the three-site model together with the observed data from Table 4. In this case the conformation does not possess C_2 symmetry, but as the environment about the SO complexing site is very similar to that in thiane 1-oxide the model used above in which sites 2 and 3 were equally populated and β equals zero was retained. Note that the effective C_2 symmetry observed in the NMR spectrum is due to averaging between the equivalent conformers and this is reproduced in the LIRAS4 analysis by averaging the non-identical protons. For example the two C-3β protons are non-identical in the proposed conformation, but the calculated pseudo-contact shifts for these two protons are averaged in the LIRAS4 analysis.

This conformation gave an excellent solution with LIRAS4

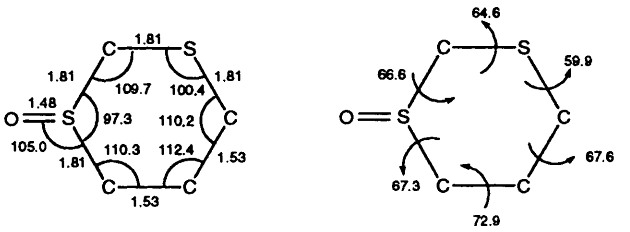

Fig. 7 Bond lengths (Å), bond angles (°) and torsional angles (°) in the 1,3-dithiane 1-oxide ring

with an agreement factor of 0.4%. The observed and calculated shifts are given in Table 11. The complexation geometry, given in Table 10 is also entirely reasonable with again zero population in site 1. This encouraged us to investigate the conformation further by LIS. Varying the flap angle showed that the conformation deduced was indeed the best solution for LIRAS4. The AF was < 0.5% for all conformations with flap angles of 125–135°. Outside these limits the AF increased rapidly. It should be noted that this solution is not particularly well determined with only six pseudo-contact shifts to be measured. A less symmetrical ligand would have provided a much more stringent test of the applicability of the LIS technique, but this was not available to us.

1,3-*Dithiane* 1-*oxide*. The analysis of the pseudo-contact shifts for this molecule follows closely the pattern of the thiane 1-oxide analysis. The molecule is interconverting between the two chair conformations, thus of primary interest is the determination of the conformer percentages, and in this case also the complexation geometry, as the lanthanide atom could complex with either (or both) the oxygen atom or the S3 sulfur atom.

The molecular geometry for both the axial and the equatorial SO conformers was obtained initially from the NEMESIS program and is given in Table 7 and Fig. 7. These geometries were then input together with the observed shifts in to the LIRAS4 program. This molecule has no symmetry and therefore the appropriate non-symmetrical complexation of the lanthanide atom was used, *i.e.* with non-equal populations of the three sites together with optimisation of the rotational parameter β.

The LIRAS4 analysis converges readily to give an excellent agreement factor and reasonable lanthanide-substrate geometry (Table 10).

In 1,3-dithiane 1-oxide, in contrast to thiane 1-oxide, the conformational equilibrium is heavily biased towards the SO equatorial conformer, and the LIRAS analysis converges to a minimum at 95% of the equatorial form, with an agreement factor of 2.9%. The calculated pseudo-contact shifts are given for this best solution in Table 11. Comparison of the observed and calculated shifts shows that all the observed shifts are well reproduced, even for this unsymmetric molecule. This demonstrates that the lanthanide complexes exclusively with the S–O group and not at all to the sulfur atom. If the latter were complexing to any significant extent, one would not expect such good agreement with a 'one-group' complexing model. Inspection of the lanthanide–substrate complexation also supports this thesis. The lanthanide atom complexes to the least hindered lone pair of the oxygen atom, *i.e. anti* to the S–C bond and *cis* to the sulfur atom. The lone pair *cis* to the thiane ring is very disfavoured, as would be expected on steric grounds.

Conclusions

The results obtained above on the conformational equilibrium of thiane 1-oxide **3** and 1,3-dithiane 1-oxide **5** agree very

Table 12 Solvation energies for **3** and **5** conformers

			Solvation energy/kcal mol^{-1}					
			3			**5**		
Solvent	T/°C	ε	eq.	ax.	δE(eq − ax)	eq.	ax.	δE(ax − eq)
Decalin	190	2.0	1.95	1.60	0.35	—	—	—
$CDCl_3$	20	4.8	3.89	3.21	0.67	3.16	3.48	0.32
$CDCl_3$	−75	7.0	4.56	3.76	0.80	3.86	4.26	0.40[a]
CD_2Cl_2	−75	14.4	5.52	4.56	0.96	4.54	5.03	0.49
Acetone	−75	33.2	6.56	5.44	1.12	5.42	5.99	0.57
THF[b]	−75	38.9	6.78	5.63	1.15	6.09	6.73	0.64[c]

[a] $CHClF_2$ at −96 °C, dielectric constant (ε) 7.5. [b] THF = tetrahydrofuran. [c] Methanol at −80 °C, dielectric constant (ε) 54.0.

well with those of previous workers, *e.g.*, the value of 54% axial conformer for **3** in $CDCl_3$ solution obtained here compares well with that of 45% obtained by Barbarella[7] in the same solvent at −75 °C.

Similarly, the value of 95% equatorial conformer for **5** obtained here, compares with the value of 84% obtained by Juaristi[12] by low temperature ^1H NMR (−80 °C) in [$^2H_4$]methanol solution, and a similar value obtained by Lambert[6] in $CHClF_2$ solution at −96 °C.

The skew conformation deduced for thiolane 1-oxide **4** from our molecular mechanics studies which is consistent with the LIS data differs considerably from the conformation proposed previously for the 3,3-dimethyl derivative,[13,14] which is a symmetric envelope conformation [Fig. 1(*c*)]. However, these authors also noted that methyl substitution considerably affects the conformational equilibrium in this ring system, so that comparisons between the parent compound and the 3,3-dimethyl derivative may not be entirely appropriate.

The results obtained do demonstrate conclusively that the LIS method and the LIRAS4 program can be applied very profitably to investigate conformational and structural problems in sulfoxides.

Comparisons between the conformer populations determined by the LIS method, *i.e.*, in a moderately polar solvent at room temp., and those determined by low temperature NMR, in often very polar solvents, need to be corrected for any solvation effects on the conformational equilibrium. In the case of thiane 1-oxide the low temperature measurements of Barbella *et al.*[7] demonstrated clearly the considerable effect of solvation on this equilibrium. Thus it was of interest to calculate the solvation dependence of these conformational equilibria. This was done using the MODELS program,[36] which incorporates a reaction-field model of solvation which has been shown to provide an accurate model for the calculation of the solvent dependence of a variety of rotational and conformational equilibria.[37] Using the NEMESIS geometries and the CHARGE3[38] calculated partial atomic charges for the conformers the calculated solvation energies are given in Table 12 for the appropriate solvents and temperatures.

For thiane 1-oxide the calculated dipole moments from the above geometries and partial atomic charges are 4.39 and 4.17 D for the equatorial and axial conformers respectively, which compared well with the observed (average) value of 4.19 D.[39] For 1,3-dithiane oxide the calculated values are 4.08 (eq) and 4.65 D (ax), which also compare well with the observed, averaged value of 3.93 D, and with the observed values for the corresponding 2-*tert*-butyl derivatives (3.58 and 4.39 D).[8] The latter compounds are conformationally homogeneous, but the *tert*-butyl group will perturb the molecular conformation and hence resultant dipole moment. However, the trends in dipole moments are exactly mirrored by the calculated values. The solvation energies given in Table 12 are thus the quantitative expression of the well known rule that the conformer with the larger dipole moment is stabilised in more polar media, and they can be compared directly with the observed trends. It is however important to remember that these are solvation energy differences and thus they can only be compared with the observed trends in the conformer energies with solvent.

For thiane 1-oxide the equatorial conformer is predicted to be favoured by polar solvents compared to non-polar ones by *ca.* 0.8 kcal mol^{-1}.

The comparison with the observed values of this conformer energy is intriguing. The conformer free energy difference (ΔG), which may be considered to approximate to $\Delta E(E_{eq} - E_{ax})$, is given for the solvents and the temperatures given in Table 12, as +1.0 kcal mol^{-1} (decalin),[3] 0.2 ($CDCl_3$), 0.0 (CD_2Cl_2), 0.5 (acetone), 0.55 (THF).[7] Whereas the increase in the percentage of the equatorial conformer in going from the non-polar (decalin) to moderately polar solvents ($CDCl_3$, CD_2Cl_2) is correctly predicted by the theory, the axial conformer becomes *more* favoured in solvents of high dielectric constant, in direct contrast to the theoretical predictions. These results are from low temperature C-13 measurements[7] and are absolute given that the assignments of the C-13 resonances of the equatorial and axial conformers is unequivocal, based on the values of the *cis* and *trans* 4-*tert*-butyl analogues.[40] Certainly reversing these assignments would give results in very good agreement with the theoretical predictions, but there seems no real justification to do this.

For 1,3-dithiane 1-oxide Table 12 shows that the calculated solvation energy differences are much smaller and in this case the less populated axial conformer is now favoured by more polar solvents. Thus the conformer solvation energy difference $\delta E(E_{ax} - E_{eq})$, only varies from 0.32 kcal mol^{-1} in $CDCl_3$ solution to 0.64 kcal mol^{-1} in CD_3OD solution. This is consistent with the results of the few observed values of this conformer energy difference, *i.e.*, 1.8 (±0.5) kcal mol^{-1} ($CDCl_3$ solution, these studies), 0.66 kcal mol^{-1} ($CHClF_2$ and CD_3OD solutions, −80 °C)[6,12] and 0.6 kcal mol^{-1} (Me_2SO solution, 84 °C).[41]

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References

1 Part 22, R. J. Abraham, E. J. Chambers and W. A. Thomas, *J. Chem. Soc., Perkin Trans. 2*, 1994, 949.
2 P. C. B. Page, S. M. Allin, E. W. Collington and R. A. E. Carr, *J. Org. Chem.*, 1993, **58**, 6902.

3 C. R. Johnson and D. McCants, *J. Am. Chem. Soc.*, 1964, **86**, 2935.
4 J. C. Martin and J. J. Uebel, *J. Am. Chem. Soc.*, 1964, **86**, 2936.
5 J. B. Lambert and R. G. Keske, *J. Org. Chem.*, 1966, **31**, 3429.
6 J. B. Lambert, D. S. Bailey and C. E. Mixan, *J. Org. Chem.*, 1972, **37**, 377.
7 G. Barbarella, P. Dembech and V. Tugnoli, *Org. Magn. Reson.*, 1984, **22**, 402.
8 M. J. Cook and A. P. Tonge, *J. Chem. Soc., Perkin Trans. 2*, 1974, 767.
9 L. Van Acker and M. Anteunis, *Tetrahedron Lett.*, 1974, 225.
10 S. A. Khan, J. B. Lambert, O. Hernandez and F. A. Carey, *J. Am. Chem. Soc.*, 1975, **97**, 1468.
11 K. Bergesen, M. J. Cook and A. P. Tonge, *Org. Magn. Reson.*, 1974, **6**, 127.
12 E. Juaristi, J. Guzman, V. V. Kane and R. S. Glass, *Tetrahedron*, 1984, **40**, 1477.
13 G. Barbarella, A. Garbesi and A. Fava, *J. Am. Chem. Soc.*, 1975, **97**, 5883.
14 G. Barbarella, S. Rossini, A. Bongini and V. Tugnoli, *Tetrahedron*, 1985, **41**, 4691.
15 G. Montauda, S. Caccamese, V. Librando and P. Maravigna, *Gazz. Chim. Ital.*, 1975, **105**, 85.
16 S. Caccamese, P. Finocchiaro, P. Maravigna, G. Montaudo and A. Recca, *Gazz. Chim. Ital.*, 1977, **107**, 163.
17 Y. Kodama, K. Nishihata and M. Nishio, *J. Chem. Res. (S)*, 1977, 102.
18 D. J. H. Smith, J. D. Finlay and C. R. Hall, *J. Org. Chem.*, 1979, **44**, 4757.
19 R. Benassi, U. Folli, D. Iarossi, A. Mucci, L. Schenetti and F. Taddei, *J. Chem. Soc., Perkin Trans. 2*, 1989, 517.
20 R. J. Abraham, D. J. Chadwick and F. Sancassan, *J. Chem. Soc., Perkin Trans. 2*, 1984, 1037.
21 U. de la Camp and H. Hope, *Acta Crystallogr., Sect. B*, 1970, **26**, 846.
22 S. Ianelli, A. Musatti, M. Nardelli, R. Benassi, U. Folli and F. Taddei, *J. Chem. Soc., Perkin Trans. 2*, 1992, 49.
23 *Structure Data of Free Polyatomic Molecules*, ed. K. H. Hellwege, Springer Verlag, Berlin, 1976, vol. 15.
24 R. J. Abraham and I. S. Howarth, *Magn. Reson. Chem.*, 1988, **26**, 252.
25 O. Hofer, *Top Stereochem.*, 1976, **9**, 111.
26 M. S. Chauhan and I. W. J. Still, *Can. J. Chem.*, 1975, **53**, 2880.
27 G. W. Buchanan, C. Reyes-Zamora and D. E. Clarke, *Can. J. Chem.*, 1974, **52**, 3895.
28 PANIC Aspect 2000/3000 Bruker Software.
29 K. Hayamizu and O. Yamamoto, *J. Mol. Spectrosc.*, 1968, **25**, 422.
30 L. Pollock, M.Phil. Thesis, University of Liverpool, 1994.
31 R. J. Abraham, H. A. Bergen, D. J. Chadwick and F. Sancassan, *J. Chem. Soc., Chem. Commun.*, 1982, 998.
32 R. J. Abraham, A. E. Rowan, J. M. Bakke and J. E. Brearden, *J. Chem. Soc., Perkin Trans. 2*, 1991, 1471.
33 PCMODEL, Version 4.0 Serena Software, 1990.
34 NEMESIS, Version 1.1, Oxford Molecular Ltd, 1992.
35 R. J. Abraham, D. J. Chadwick and P. E. Smith, *J. Chem. Soc., Perkin Trans. 2*, 1989, 1377.
36 R. J. Abraham and B. A. Richards, *Tetrahedron*, 1983, **39**, 4201.
37 R. J. Abraham and E. Bretschneider, *Internal Rotation in Molecules*, ed. W. J. Orville-Thomas, Academic Press, New York, 1974, ch. 13.
38 R. J. Abraham, G. H. Grant, I. S. Howarth and P. E. Smith, *J. Comp. Aided Mol. Design*, 1991, **5**, 21.
39 A. L. McClelland, *Tables of Experimental Dipole Moments*, W. H. Freeman and Co., 1963, vol. 1.
40 G. W. Buchanan and T. Durst, *Tetrahedron Lett.*, 1975, 1683.
41 M. J. Cook and A. P. Tonge, *Tetrahedron Lett.*, 1973, 849.

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