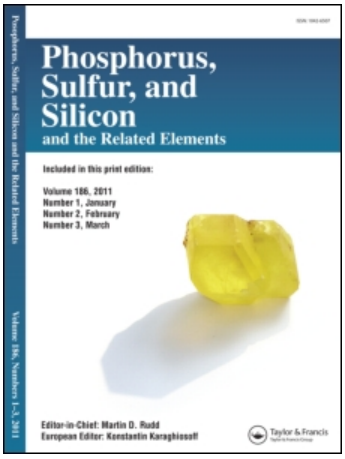

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OXYGEN-17 NMR STUDIES OF HETEROCYCLIC SULFONES AND *trans*-2-(ALKYLSULFONYL)CYCLOHEXANOLS UTILIZING THE LANTHANIDE SHIFT REAGENT, Eu(fod)$_3$

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Abstract: Complexes between paramagnetic metal ions and sulfones bearing diastereotopic oxygens are examined through ^{17}O NMR spectroscopy of heterocyclic sulfones and *trans*-2-(alkylsulfonyl)cyclohexanols in the presence of Eu(fod)$_3$, as well as through *ab initio* calculations on Li· complexes of 3,4-epoxythiolane 1,1-dioxide.

The application of ^{17}O NMR spectroscopy in the structural elucidation of oxidized organosulfur compounds has provided new insights into conformational and stereochemical attributes of sulfoxides and sulfones.[1-3] Oxygen-17 NMR has been employed to distinguish between diastereotopic sulfonyl oxygens in both cyclic and acyclic organosulfur compounds.[2,3] This report summarizes our efforts in determining if diastereotopic oxygens have different binding affinities for metal complexes. We have examined the influence of the lanthanide shift reagent Eu(fod)$_3$ on the oxygen-17 NMR shifts of several sulfones.[4,5]

The induced shift in an ^{17}O NMR resonance is equal to the fraction of substrate, S, which is bound to Eu^{+3} ($[Eu^{+3}\cdot S]/[S]$) times the bound shift Δ_b (the induced contact shift of a hypothetical complex in which 100% of the substrate S is bound to Eu^{+3}):

$$\delta_{ind} = \Delta_b [Eu^{+3}\cdot S]/[S] = \Delta_b K_b [Eu^{+3}] \qquad (1)$$

where K_b is the binding constant between Eu^{+3} and one of the two diastereotopic oxygens.[6] Thus, if we assume that the S=O oxygens have similar contact shifts, the ratio of the induced shifts becomes the ratio of the binding constants between Eu^{+3} and each of the two anisochronous sulfonyl oxygens, or the equilibrium constant K_{eq} between the two

TABLE 1 Oxygen-17 LSR studies on thiadecalin sulfones.

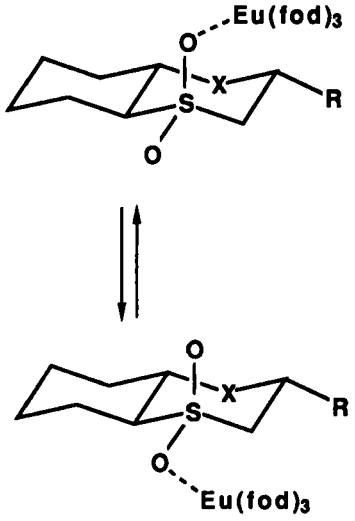
Cmpd	Concen. (M)	Oxygen	^{17}O Chemical Shift (ppm)[a,b]	Induced Shift (ppm/M LSR)	K_{eq}
1	0.32	eq. S=O	139.6	1337	1.64
		ax. S=O	125.6	815	
2	0.10	eq. S=O	141.1	1377	1.00
		ax. S=O	128.6	1371	
3	0.29	eq. S=O	142.6	959	0.89
		ax. S=O	126.2	1073	
4	0.32	eq. S=O	145.9	538	0.68
		ax. S=O	133.3	792	

a) All ^{17}O NMR spectra were recorded at 32°C for **1**, **3** and **4** and 23°C for **2** on a Varian XL-400 spectrometer operating at 54.2 MHz. b) In the absence of $Eu(fod)_3$.

diastereomeric complexes:

$$\delta_1/\delta_2 \approx (K_{b,1}/K_{b,2}) = K_{eq} \qquad (2)$$

To test the applicability of this approach, we examined the influence of $Eu(fod)_3$ on the oxygen-17 NMR spectrum of 1-thiadecalin 1,1-dioxide (**1**), 1,4-dithiadecalin 1,1-dioxide (**2**), 1,4-oxathiadecalin 4,4-dioxide (**3**), and 2a-ethoxy-1,4-oxathiadecalin 4,4-dioxide (**4**).[4] All four compounds exhibited two sulfonyl ^{17}O resonances separated by 12-15 ppm, and in each case, the high-field resonance was assigned to the axial oxygen (see Table 1). Generally, axial sulfinyl or sulfonyl oxygens experience more γ-gauche interactions with the proximal CH and CH_2 groups, resulting in a significant shielding responce.[3] For each sulfone, both sulfonyl oxygens responded to the presence of Eu^{+3} ions. In sulfone **1**, the equatorial oxygen was more sensitive to the presence of $Eu(fod)_3$ than the axial oxygen (See Figure 1). On the other hand, the axial oxygen of the oxathiadecalins **3** and **4** showed the greater sensitivity to



SCHEME 1.

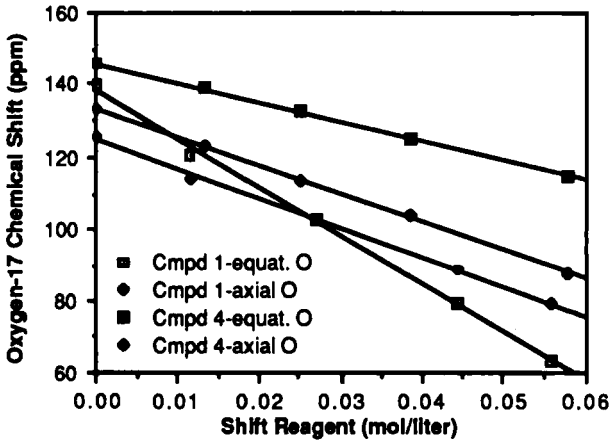


FIGURE 1. Oxygen-17 LSR studies of thiadecalin sulfones **1** and **4**.

$Eu(fod)_3$. Finally, in dithiadecalin **2**, both oxygens show identical sensitivity to $Eu(fod)_3$. It is assumed that a facile and dynamic equilibrium is established between two complexes (see Scheme 1), one in which the europium ion is bound to the sulfone through the axial oxygen and one in which the metal ion is bound through the equatorial oxygen. Using equation (2), the equilibrium constant (K_{eq}) between these complexes can be determined. For sulfone **1**, K_{eq} is 1.64, favoring the equatorial complex, while for **3** and **4**, the axial complexes are favored (K_{eq} = 0.89 and 0.68, respectively). For sulfone **2**, K_{eq} is 1.00. The reversal of binding preference upon substitution of an oxygen atom for C_4 appears to be a result of puckering about the carbon-oxygen bonds, which in turn influences the geometry of the sulfonyl group.

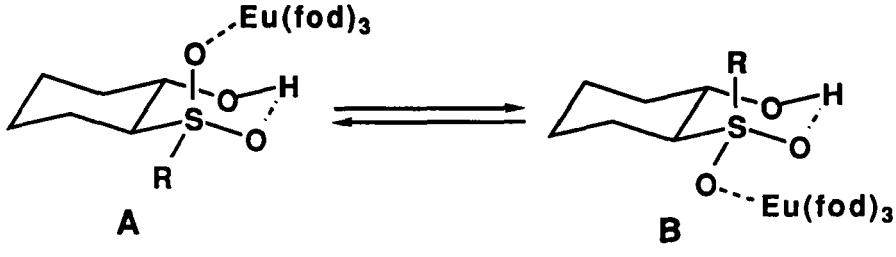
We have also studied a series of acyclic sulfones, the 2-(organosulfonyl)cyclohexanols **5-7**. The methyl and *t*-butyl organosulfur compounds (**5** and **7**, respectively) in this series each exhibited individual ^{17}O resonances for the diastereotopic oxygens, although in *n*-propyl sulfone **6**, the sulfonyl resonances are coincident (see Table 2). Just as in the thiadecalins, the diastereotopic oxygens respond differently to the presence of $Eu(fod)_3$. It is noteworthy that as the steric bulk of the alkyl group increases, the equilibrium constant between diastereomeric

TABLE 2. Oxygen-17 LSR studies on 2-(alkylsulfonyl)cyclohexanols.

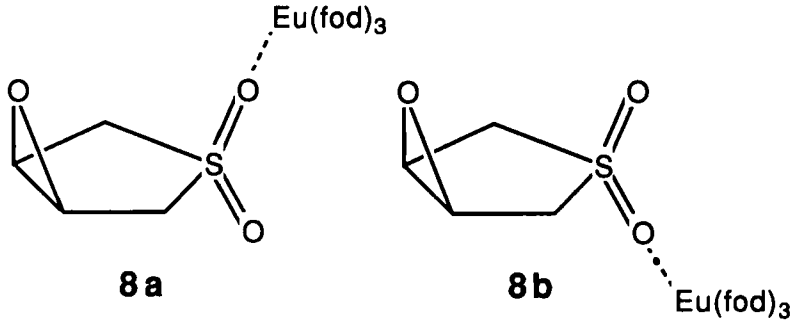
Cmpd.	Concen. (M)	Oxygen	^{17}O Chemical Shift (ppm)[a,b]	Induced Shift (ppm/M LSR)[b]	K_{eq}
5	0.26	$S=O_a$	149.1	-1112.7	1.32
		$S=O_b$	151.3	-840.5	
6	0.48	$S=O_a$	140.7	-803.0	2.26
		$S=O_b$	140.7	-355.9	
7	0.47	$S=O_a$	130.5	-908.4	44±13
		$S=O_b$	126.9	-20.3	

a) All ^{17}O NMR spectra were recorded at 32°C on a Varian XL-400 spectrometer operating at 54.2 MHz. b) In the absence of $Eu(fod)_3$.

complexes, determined from the ratio of induced shifts (*vide supra*), also increases, going from a minimum of 1.32 for the methyl sulfone **5** to a maximum of 44±13 for the *t*-butyl sulfone **7**. The equilibrium constant for sulfone **6** is an intermediate value of 2.26. This wide range of values is probably due to the presence of conformational effects (see Scheme 2). The results of MM2 calculations[7] indicate that intramolecular hydrogen bonding between the C_1 hydroxyl and the sulfonyl oxygens may be important in determining the ground-state structure of these compounds. There are two possible sulfone-$Eu(fod)_3$ complexes (**A**, **B**) in which



SCHEME 2.



simultaneous intramolecular hydrogen bonding and metal ion ligation are possible. 2-(Alkylsulfonyl)cyclohexanols with relatively small alkyl groups (*i.e.*, methyl, *n*-propyl) can populate both structures to significant extents. On the other hand, it seems unlikely that the bulky *t*-butyl group in sulfone **7** will adopt a conformation in which the *t*-butyl group is *gauche* to two CH or CH_2 groups (*i.e.*, **B**). Thus, in this latter instance, we speculate that diastereomeric complex **A** is probably preferred.

In order to determine whether the approximation that the bound shifts for the two sulfonyl oxygens are equal is accurate, studies were also carried out on 3,4-epoxythiolane 1,1-dioxide (**8**). The oxygen-17 NMR spectrum of sulfone **8** shows two sulfonyl resonances at δ 183.7 ($S{=}O_{cis}$) and δ 174.4 ($S{=}O_{trans}$). Just as in the thiadecalins **1-4**, the S=O resonances respond differently to the presence of Eu(fod)3, with the high field resonance shifting upfield significantly more rapidly than the low field signal. When the ratio of the induced shifts for these resonances is calculated, the equilibrium constant K_{eq} between a Eu(fod)3 complex of the *cis* sulfonyl oxygen of **8** (**8a**) and the diastereomeric complex of the *trans* sulfonyl oxygen (**8b**) is determined to be 2.36, favoring the *trans* complex. Since this value could in principle be due to differences in the bound shifts, quantum mechanical calculations[8] using a 3-21G* basis set were carried out on paramagnetic metal complexes of sulfone **8** in an effort to determine the fractional spin f_s in the *s*-orbitals of the complexed oxygens. Since f_s is known to be directly proportional to the bound shift Δ_b,[9] the ratio of the spin densities on the complexed oxygens in **8a** and **8b** must be close to unity for equation (2) to be valid. In actual fact, the spin density on the metal-bound oxygen in **8a** [$f_{s(8a)}$] was determined to be 1.11 x

10^{-3}, while the spin density on the complexed oxygen in **8b** [$f_{s(8b)}$] was 1.29 x 10^{-3}. Therefore, the ratio of spin densities [$f_{s(8a)}/f_{s(8b)}$] is close to one (1.16), suggesting that K_{eq} arises from actual differences in binding affinities of the diastereotopic oxygens, and not simply from inherent differences in their bound contact shifts. However, some care must be used in the interpretation of these results. No basis set for Eu^{+3} was available, so another paramagnetic species, the lithium atom, had to be used as a model for the complexing agent.

In summary, we have developed a potentially valuable protocol for determining equilibrium constants between diastereomeric metal complexes of organosulfur compounds in solution.

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