Heteroatom Chemistry
Volume 3, Number 1, 1992

Oxygen-17 Nuclear Magnetic Resonance Spectroscopy of Organosulfur Compounds. Part III. ^{17}O NMR Lanthanide-Induced Shifts (LIS) of Diastereotopic Oxygen Atoms in *trans*-2-[Alkyl(aryl)sulfonyl]cyclohexanols

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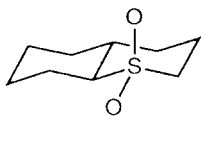
Received 12 August 1991.

ABSTRACT

The ^{17}O NMR diastereotopicity or chemical shift differences of diastereotopic sulfonyl oxygens in a series of trans-2-[alkyl(aryl)sulfonyl]cyclohexanols have been determined. From a comparison of their sulfonyl oxygen ^{17}O NMR lanthanide-induced shifts, equilibrium distributions between diastereomeric sulfonyl oxygen-Eu(fod)$_3$ complexes were determined and found to be sensitive to both the steric size of the $-SO_2R$ substituent as well as the proximity of the C1 hydroxyl group.

INTRODUCTION

Oxygen-17 NMR diastereotopicity ($\Delta\delta = \delta(O_1) - \delta(O_2)$) of monocoordinate oxygens has been previously observed in both cyclic and acyclic substrates [1–3]. For example, conformationally homogeneous *trans*-thiadecalin 1,1-dioxide (**1**), having both axial and equatorial oxygens, exhibits ^{17}O NMR chemical shifts for the diastereotopic sulfonyl oxygens at δ 125.6 and 139.6 ppm [2a]. In acyclic sulfones, where the sulfonyl group is proximal to a stereogenic center, ^{17}O NMR diastereotopicity of the sulfonyl oxygens is substituent-controlled and significantly reduced compared to the ^{17}O NMR chemical shifts in conformationally restricted sulfones. For example, in 2-(phenylsulfonyl)butane (**2**), the ^{17}O NMR shifts of the diastereotopic oxygens are isochronous, appearing at δ 141 ppm, whereas in 1,2-diphenyl-1-(phenylsulfonyl)ethane (**3**), two distinguishable resonances are observed at δ 140.3 and 145.4 ppm [3].



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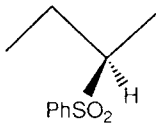

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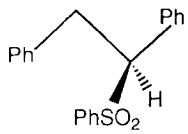

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Herein, we report our findings on the binding between the lanthanide shift reagent (LSR), Eu(fod)$_3$, and the diastereotopic sulfonyl oxygens in a series of acyclic sulfones. Equilibrium constants between diastereomeric sulfonyl oxygen-Eu^{3+} complexes were ascertained by comparing the magnitudes of the lanthanide-induced shifts (LIS) for each diastereotopic sulfonyl oxygen, as described previously for the cyclic systems, 1-thiadecalin 1,1-dioxides and 4-heterothiane 1,1-dioxides [2]. The ^{17}O NMR LIS's are primarily the result of the contact shift, arising from a covalent interaction between the oxygen atom and the Eu^{3+} ion, with transmission of unpaired electron spin density to the complexed atom [4a]. The pseudocontact shift, originating from non-

Dedicated to Ernest L. Eliel on the occasion of his seventieth birthday.

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bonded, through-space interactions, and the complex formation shift, influenced by structural changes in the substrate upon complexation to Eu(fod)$_3$, may also be influential [4b]. Quantum mechanical calculations on paramagnetic complexes of sulfones indicate that spin density is transmitted very poorly from a complexed sulfonyl oxygen to the free oxygen [2b]; thus, only an oxygen atom that is directly complexed should exhibit sizeable ^{17}O NMR shifts.

The observed LIS (Equation 1) is equal to the fraction of substrate bound to Eu^{3+} times the bound contact shift (i.e., the contact shift for a hypothetical complex in which 100% of the substrate is bound to Eu^{3+}) [2c]:

$$\text{LIS} = \Delta_c[Eu^{3+}\cdot S]/S_0 \quad (1)$$

where S_0 is the total substrate concentration. At low shift reagent/substrate ratios, S_0 is approximately equal to the concentration of free substrate (Equation 2); consequently,

$$\text{LIS} = \Delta_c K_b[Eu^{3+}] \quad (2)$$

where K_b is the association constant between the substrate (i.e., sulfonyl oxygen) and Eu^{3+}.

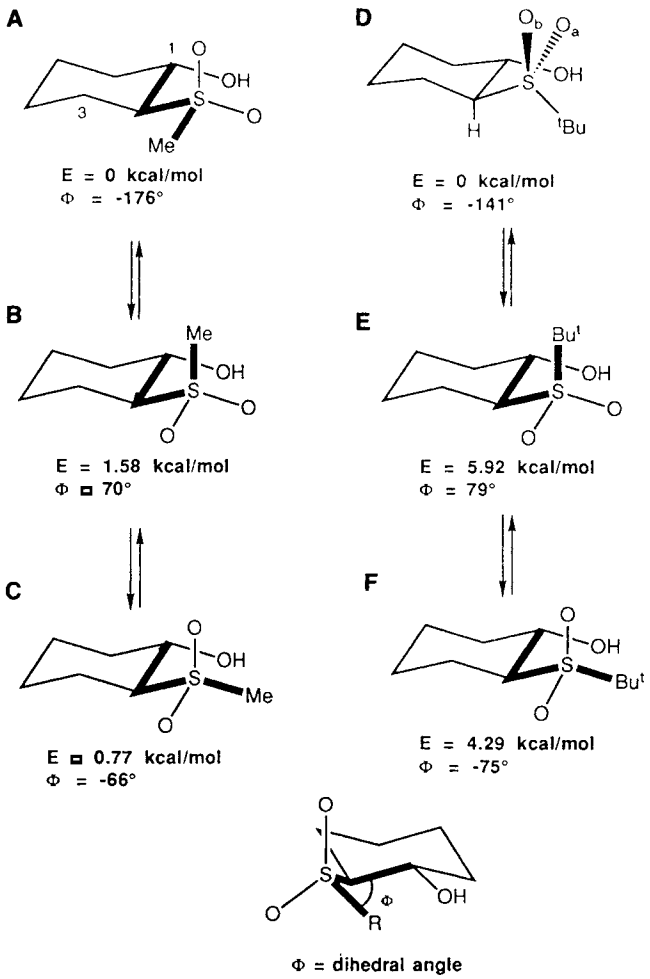
For diastereotopic oxygens, different ^{17}O NMR LIS's (i.e., LIS_1, LIS_2) are expected for each sulfonyl oxygen atom. The ratio of these ^{17}O NMR LIS's allows for cancellation of $[Eu^{3+}]$, affording the expression (Equation 3):

$$LIS_1/LIS_2 = (\Delta_{c1}/\Delta_{c2})(K_{b1}/K_{b2}) = (\Delta_{c1}/\Delta_{c2})(K_3) \quad (3)$$

Assuming that the bound shifts of similarly hybridized oxygen atoms are essentially equivalent when they are individually complexed to the same metal [2,5], this ratio reduces to the ratio of individual binding constants (i.e., K_{b1}/K_{b2}) or K_3, the equilibrium constant between diastereomeric complexes (Scheme 1).

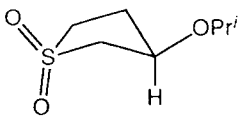
Several recent reports suggest that ^{17}O NMR LIS's, particularly those obtained using Eu(fod)$_3$, possess remarkable potential for identifying and understanding the structural complexities and dynamic properties of molecules containing oxygen heteroatoms [6,7]. Assuming that Δ_c is the major shielding determinant of the ^{17}O nucleus, an increase in $[Eu^{3+}]$ will increase the proportion of Eu^{3+} coordinated to the diastereotopic sulfonyl oxygens. Progressive *upfield* shifts of the coordinated oxygen nuclei with increasing LSR are expected, and the magnitude of these shifts should serve as a probe for assessing the relative binding ability of nonequivalent oxygens.

We previously reported that the diastereotopic sulfonyl oxygens in 3-*iso*-propoxythiolane 1,1-dioxide (**4**) have essentially identical ^{17}O NMR resonances [7]. However, in the presence of Eu(fod)$_3$, both oxygens are shielded, with the cis oxygen (cis to the alkoxy group) exhibiting less shielding than the trans



SCHEME 1 Preferred Rotamers of Acyclic Sulfones **5** and **10**, Derived from MM2 calculations.

oxygen. Furthermore, the ^{17}O NMR resonance width ($W_{1/2}$) of the Eu^{3+}-coordinated trans sulfonyl oxygen is larger than that of the cis S=O. Since the ^{17}O NMR shifts are time-averaged under the fast-exchange limit, the larger $W_{1/2}$ for the trans S=O probably arises from a greater time-averaged correlation time, τ_c, associated with the larger mole fraction of the trans S=O·Eu^{3+} complex. The axial and equatorial sulfonyl oxygens in the 1-thiadecalin 1,1-dioxides also bind differently to Eu(fod)$_3$ and exhibit similar $W_{1/2}$ characteristics [2].



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RESULTS AND DISCUSSION

In this study, six *trans*-2-[alkyl(aryl)sulfonyl-cyclohexanols (**5–10**) were examined, with the alkyl

or aryl groups varying in steric bulk from methyl to *tert*-butyl. The ^{17}O NMR spectra of these compounds exhibited several interesting features. As the steric bulk of the R group is increased, the ^{17}O diastereotopic sulfonyl oxygens are shielded. For example, *trans*-2-(methylsulfonyl)cyclohexanol (**5**) exhibited ^{17}O NMR resonances at δ 151.3 and 149.1 ppm, while *trans*-2-(*tert*-butylsulfonyl)cyclohexanol (**10**) displayed resonances at δ 130.5 and 126.9 ppm (Table 1). This shielding trend for the sulfonyl oxygens is undoubtedly a response to the well-documented "γ-methyl effect" in ^{17}O NMR [8a]. The ^{17}O NMR shifts of the hydroxyl resonances in **5–10**, ranging from δ 26 to 30 ppm, were relatively insensitive to the electronic or structural nature of the R groups, indicating that they are not, on time-average, in close steric proximity to the C1 hydroxyl group [8a, 9].

5 R = CH_3
6 R = CH_2CH_2Cl
7 R = $CH_2CH_2CH_3$
8 R = C_6H_5
9 R = $CH_2C_6H_5$
10 R = $C(CH_3)_3$

Also, the diastereotopic sulfonyl oxygens are not completely resolvable in the ^{17}O NMR in all cases. For example, methyl sulfone **5** and *trans*-2-(2-chloroethylsulfonyl)cyclohexanol (**6**) possess small alkyl groups and their sulfonyl oxygen resonances are distinguishable (in **5**, $\Delta\delta(SO_2)$ = 2.2 ppm; in **6**, $\Delta\delta(SO_2)$ = 2.3 ppm). Similarly, the sulfonyl oxygens in *tert*-butyl sulfone **10** are also resolvable ($\Delta\delta(SO_2)$ = 3.6 ppm). However, *trans*-2-(*n*-propylsulfonyl)cyclohexanol (**7**) and *trans*-2-(benzylsulfonyl)cyclohexanol (**9**), possess alkyl groups of intermediate size and each exhibit isochronous sulfonyl ^{17}O resonances.

The importance of various rotameric distributions within the **CH–SO$_2$R** fragment in sulfones **5** and **10** (where rotational differences are likely to be exaggerated as a result of the large disparity in steric bulk) was established using the results of molecular mechanics (MM2) [10] calculations. In sulfone **5**, the methyl group prefers to be anti to the C1–C2 bond in the cyclohexane ring (Scheme 1; rotamer A). Other rotamers in which the methyl group is gauche to the C1–C2 bond are only slightly

TABLE 1 Oxygen-17 LSR Studies on 2-[Alkyl(aryl)sulfonyl]cyclohexanols

Compound	Concn (M)	Oxygen	^{17}O Chemical Shift (ppm)[a]	Induced Shift (ppm/M LSR)[b]	K_3
5	0.26	S=O_a	149.1	−1112.7	1.32
		S=O_b	151.3	−840.5	
		R–OH	29.2	−1492.9	
6	0.41	S=O_a	142.4	−868.9	2.50
		S=O_b	144.7	−348.5	
		R–OH	28.5	−989.1	
7	0.48	S=O_a	140.7	−803.0	2.26
		S=O_b	140.7	−355.9	
		R–OH	28.6	−843.7	
8	0.47	S=O_a	144.8	−843.1	2.71
		S=O_b	137.5	−310.2	
		R–OH	26.5	−1034.9	
9	0.50	S=O_a	141.5	−765.0	2.98
		S=O_b	141.5	−256.3	
		R–OH	29.2	−871.0	
10	0.47	S=O_a	130.5	−908.4	44.8 ± 13
		S=O_b	126.9	−20.3	
		R–OH	27.9	−633.0	
15	0.21	S=O_a	148.4	−1245.2	1.64
		S=O_b	143.5	−755.5	
		R–OH	27.0	−1998.5	
20	—[c]	S=O_a	150.6	−901.7	1.37
		S=O_b	145.7	−657.2	
21	0.42	S=O_a	134.5	−739.6	1.14
		S=O_b	134.5	−646.2	

[a] In the absence of $Eu(fod)_3$.
[b] Induced shift projected to a 1.0 M solution of $Eu(fod)_3$.
[c] ca. 0.15–0.30 M.

less stable (rotamers B and C) [11]; consequently, in the absence of severe hindrance to C–S bond rotation, a reasonable population of rotamers A–C is guaranteed. On the other hand, the MM2 results indicate that the *tert*-butyl group in sulfone **10** prefers rotamer D (exclusively!) where the *tert*-butyl group is nearly eclipsed with the C2–H bond (Scheme 1). This preference is a consequence of the severe repulsive van der Waals interactions between the pseudo-synaxial **S**-*tert*-butyl group and the C1 and C3 hydrogens (rotamer E) as well as the pseudo-1,3-synaxial repulsive interaction between the **S**-*tert*-butyl and C1 OH groups in rotamer F.

From a perusal of the data in Table 1, it is clear that the magnitude of the ^{17}O NMR diastereotopicities of the acyclic sulfonyl groups in sulfones **5–10** are particularly sensitive to the steric encumbrance of the $-SO_2\mathbf{R}$ substituents that tend to alter the time-averaged rotational preferences. However, in the absence of stereospecific ^{17}O isotopic labeling in the sulfonyl group to facilitate a convincing configurational assignment, speculation on the relative configuration of the diastereotopic sulfonyl oxygens would not be useful.

In the ^{17}O NMR LIS studies involving Eu(fod)$_3$ and dichloromethane solutions of sulfones **5–10**, one sulfonyl oxygen atom was more responsive to Eu^{3+} than the other (Figure 1). This differential LIS behavior of the sulfonyl oxygens was considered as indicative of an *unequal* concentration of the two diastereoisomeric sulfonyl oxygen–Eu(fod)$_3$ complexes [1b, 2, 7]. Furthermore, the sulfonyl oxygen that experiences the *most shielding* (O_a) also exhibits the larger *increase* in its ^{17}O line width ($W_{1/2}$), indicating that its time-averaged correlation time increases more rapidly than that of the other sulfonyl oxygen (O_b) with increasing Eu(fod)$_3$ concentration [7]. These observations also support the hypothesis that there is a larger mole fraction of the $S{=}O_a{\cdot}Eu^{3+}$ complex than there is of the $S{=}O_b{\cdot}Eu^{3+}$ complex. Differential Eu^{3+} ligation and line broadening are most pronounced with *tert*-butyl sulfone **10** (Table 2). As $[Eu^{3+}]$ increases, the combined $W_{1/2}$ for the partially resolved sulfonyl oxygens decreases until the resonances are coincident. The resonances then separate again, and one ^{17}O sulfonyl resonance experiences both a rapid increase in $W_{1/2}$ and a large upfield shift. The other ^{17}O resonance exhibits a considerably smaller change in $W_{1/2}$ and essentially no variation in its ^{17}O NMR chemical shift position.

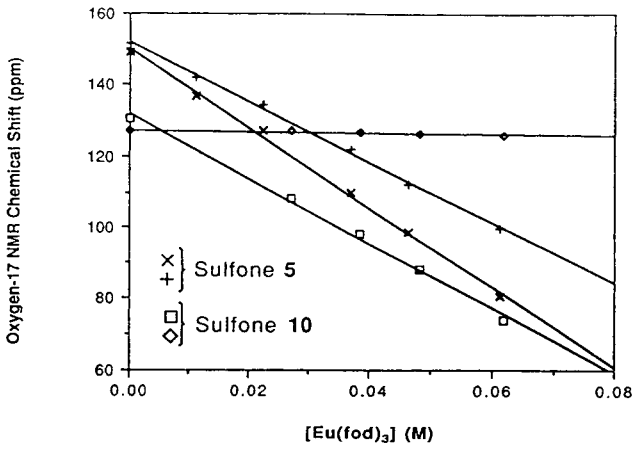


FIGURE 1 LIS studies on sulfones **5** and **10**.

TABLE 2 Dependence of ^{17}O NMR Chemical Shifts and Linewidths on Eu(fod)$_3$ Concentration for Sulfone **10**

Eu(fod)$_3$ (M)	S=O$_a$ (δ, ppm)[a]	($W_{1/2}$, Hz)	S=O$_b$ (δ, ppm)[a]	($W_{1/2}$, Hz)
0.0000	130.5	380[b]	126.9	380[b]
0.0116	126.9	298[c]	126.9	298[c]
0.0270	108.5	447	126.9	173
0.0386	98.4	391	126.4	199
0.0482	88.4	650	125.8	256
0.0617	74.0	749	125.8	272

[a] Uncertainty in ^{17}O chemical shift is ca. 2 ppm.
[b] Combined linewidth; resonances are not baseline resolved.
[c] Isochronous resonances.

From the relationship between $W_{1/2}$ and correlation time (τ_c) in the extreme narrowing limit [8b]:

$$W_{1/2} = (12\pi/125)(1 + \eta^2/3)\,\chi^2\tau_c \qquad (4)$$

where the nuclear quadrupole coupling constant, χ, is ca. 6.7 MHz and the asymmetry parameter, η, is ca. 0.25 [12], the change in τ_c for each oxygen as the Eu(fod)$_3$ concentration increases can be estimated. Assuming that $W_{1/2}$ for each sulfonyl resonance in the absence of Eu(fod)$_3$ is ca. 150 Hz ($W_{1/2} \leq 173$ Hz (Table 2)), the correlation time for a sulfonyl oxygen is ca. 1.1×10^{-11} s or 11 ps. In a 0.062 M solution of Eu(fod)$_3$, τ_c for the more strongly bound sulfonyl oxygen in sulfone **10** ([**10**] = 0.47 M) increases by a factor of five ($\tau_c \approx 5.5 \times 10^{-11}$ s or 55 ps). The time-averaged correlation time of the other oxygen increases by less than a factor of two ($\tau_c \approx 2.0 \times 10^{-11}$ s or 20 ps), suggesting that it does, in fact, spend less time complexed to Eu^{3+}.

The determination of the equilibrium constant, K_3, between the diastereomeric complexes, requires access to the ratios of the ^{17}O LIS's of the sulfonyl oxygens from Equation 5:

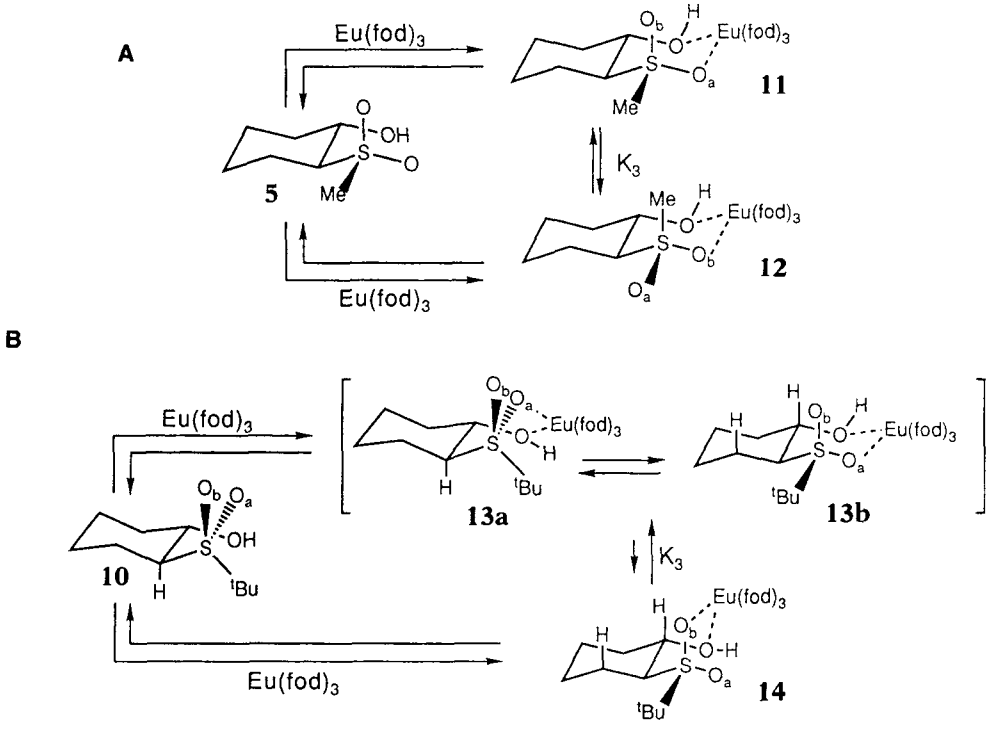
$$LIS_1/LIS_2 = [LSR{\cdot}S]_1/[LSR{\cdot}S]_2 = K_3 \qquad (5)$$

where K_3 is the equilibrium constant between the diastereomeric lanthanide complexes, $LSR{\cdot}S_1$ and $LSR{\cdot}S_2$. The equilibrium constant exhibits a marked dependence on the steric size of the alkyl group. In methyl sulfone **5**, the alkyl group is small and K_3 is quite low ($K_3 = 1.32$). Thus, the stability of both diastereomeric sulfonyl oxygen–Eu^{3+} complexes are essentially equivalent. Sulfones **6**, **7**, and **9** are all

alkyl- or arylmethyl sulfones (R = CH_2X; X = CH_2Cl, CH_2CH_3, C_6H_5) and this moderate increase in the size of the alkyl group (cf. methylsulfone **5**) favors an increased preference for ligation to one diastereotopic sulfonyl oxygen over the other (K_3 = 2.25–3.0). In sulfone **10**, the bulky *tert*-butyl group leads to a large K_3 (K_3 = 44.8 ± 13), indicating that only one sulfonyl oxygen is capable of binding to Eu^{3+} efficiently [13]. Based on the magnitude of K_3 (K_3 = 2.50), the phenyl substituent in *trans*-2-(phenylsulfonyl)cyclohexanol (**8**) appears to be sterically similar to a monosubstituted methyl group.

Since the hydroxyl group and the sulfonyl oxygens in sulfones **5–10** experience similar LIS's (Table 1), *bidentate binding* of $Eu(fod)_3$ through both a sulfonyl oxygen and the C1 OH group is feasible, forming an octacoordinate lanthanide complex [14, 15]. Representative Eu^{3+}-chelated complexes involving sulfones **5–9** are best viewed as diastereomeric "decalin-type" structures, where the alkyl group can occupy either an pseudoequatorial or pseudoaxial array (Scheme 2a). For methyl sulfone **5**, two diastereomeric complexes (**11** and **12**) are anticipated and both sulfonyl oxygens (O_a, O_b) are expected to experience measurable LIS's. Minimum restriction to rotation about the **C**2–**S**O_2 bond, while possible in the "free" sulfone [11], is unlikely in a bidentate complex involving $Eu(fod)_3$; rather, chelation should require greater rigidity within the C1–OH and C2–SO_2 fragments of the substrate. Clearly, some contribution of complex formation shifts, Δ_{cf}, to the total LIS is expected; however, it is uncertain what fraction of these shifts will arise from alteration of the rotameric distribution of the substrate, and what fraction from polarization of the electron density in the sulfonyl bonds by Eu^{3+} [4b].

On the basis of MM2 calculations, sulfone **10** is predicted to exist largely or exclusively as rotamer D, with the *tert*-Bu group nearly synperiplanar to the C2–H bond (dihedral angle, Φ, (Me_3**C**–**S**–**C**2–**C**HOH) = 141°). Accordingly, the sulfonyl bonds are very nearly eclipsed with the C1–C2 and C2–C3 bonds. If rotamer D of sulfone **10** serves as a bidentate ligand, the two preferred conformations of the major complex involving $Eu(fod)_3$ (i.e., a boat-shaped metallocycle (**13a**) or a chair-shaped ring (**13b**)) are envisioned (Scheme 2b). While chair **13b** would normally be expected to be more stable, the MM2 results suggest that boat **13a** has smaller steric interactions between the *tert*-butyl group and the C3 methylene group. Without additional input, a clear description of the preferred conformation(s) of complex **13** is not easily attainable; nevertheless, chelation to Eu^{3+} is expected to increase the binding constant by at least an order of magnitude [17, 18], and the chelated oxygen (O_a) should show a much larger shift than the other oxygen (O_b), in agreement with the experimental ^{17}O NMR results. Diastereomeric complex **14** can be envisioned but it must experience both the repulsive interactions between the C3



SCHEME 2 Bidentate Complexation of *trans*-2-(Alkylsulfonyl)cyclohexanols by $Eu(fod)_3$. (**A**) Complexation of *trans*-2-(Methylsulfonyl)cyclohexanol (**5**). (**B**) Complexation of *trans*-2-(*t*-Butylsulfonyl)cyclohexanol (**10**).

methylene group and $C(CH_3)_3$ (cf. MM2) and the higher energy associated with a boat-shaped ring. Consequently, this species should be significantly less favored than complex **13**.

In order to secure firm evidence of bidentate versus monodentate binding, ^1H NMR LIS studies were performed on sulfone **10** and sulfide **10a**. Generally, sulfenyl sulfur (i.e., divalent sulfur) binds poorly to shift reagents [19]; consequently, **10a** is expected to bind Eu^{3+} only through the C1 OH group. Sulfone **10**, on the other hand, is expected to bind weakly through the sulfonyl oxygens ($K_b \approx 10$–50 for simple sulfones [20]) and more strongly through the hydroxyl group ($K_b > 50$ for simple alcohols [17]). If monodentate binding between **10** and $Eu(fod)_3$ occurs largely through the hydroxyl group, then **10** and **10a** should exhibit similar binding constants since the major mode of binding, that is, ligation to the OH group, is similar for the two compounds. Bidentate binding of sulfone **10** to Eu^{3+} is expected to lead to a sizeable increase in the binding constant [17]. When the binding constants for these compounds were determined by the equimolar method (see Experimental) [17, 21], it was found that K_b between sulfide **10a** and Eu^{3+} was 1.75×10^2, whereas K_b for sulfone **10** was 4.83×10^3 (Figure 2). The 20-fold increase in K_b between **10a** and **10** is viewed as support for the contention that β-hydroxy sulfones actually *chelate* to $Eu(fod)_3$.

Because one sulfonyl oxygen in **10** (presumably, the S=O, which is synperiplanar to the C2–C3 bond and cannot chelate) exhibited little or no LIS, monodentate complexes of sulfone **10** may, in fact, not be present in significant quantity. The LIS experience with sulfone **10** may be unique; consequently, monodentate coordination cannot be discounted for the other sulfones reported here.

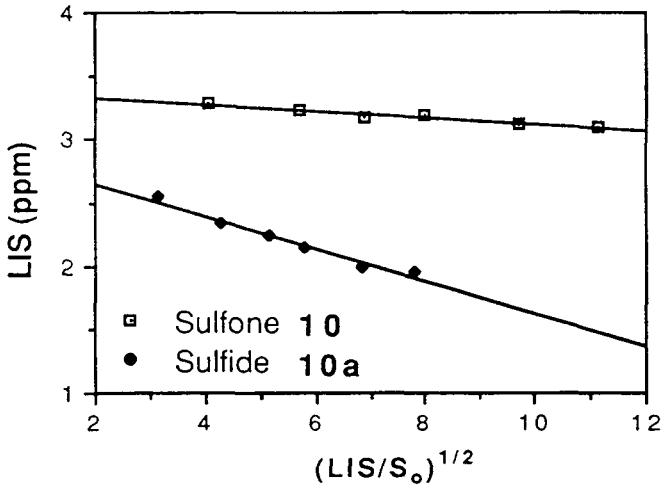
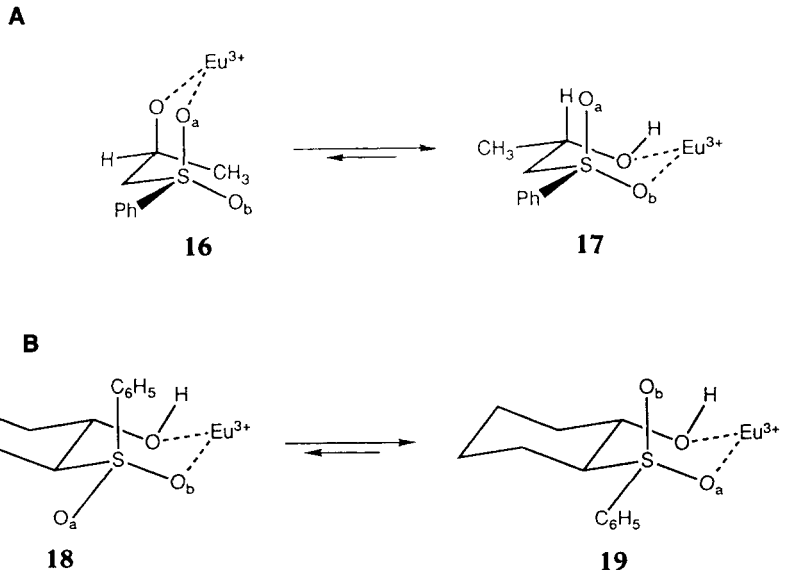


FIGURE 2 $LIS = \Delta_0 - (LIS/S_0)^{1/2}(\Delta_0/K_b)^{1/2}$; where Δ_0 = the bound shift and S_0 = [substrate]. For sulfide **10a**, Δ_0 = 2.91 ppm and K_b = 175 M^{-1}; for sulfone **10**, Δ_0 = 3.39 ppm and K_b = 4827 M^{-1}.

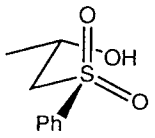
10a R = $C(CH_3)_3$

A comparison of the results of an ^{17}O NMR LIS study of the acyclic analogue, 1-(phenylsulfonyl)-2-propanol (**15**), with those of sulfone **8** indicates that the magnitude of K_3 is also dependent on the cyclohexyl substructure. The absence of this ring leads to a decrease in K_3 from 2.71 in sulfone **8** to 1.64 in sulfone **15**. Here, an increase in the rotational freedom about the C1–C2 bond provides easy access to two bidentate complexes with "pseudoequatorial" phenyl groups (**16** and **17**; Scheme 3). Complex **16**, with a "pseudoaxial" methyl group, is disfavored



SCHEME 3 Diastereomeric $Eu(fod)_3$ Complexes of (**A**) 1-(Phenylsulfonyl)-2-propanol. (**B**) 2-(Phenylsulfonyl)cyclohexanol.

because of steric interactions with the axial sulfonyl oxygen. Phenyl sulfone **8**, which apparently lacks this rotational freedom, forms one complex with a "pseudoaxial" phenyl group (**18**) and another with a "pseudoequatorial" phenyl (**19**); complex **18** is more strongly disfavored by interactions between the phenyl group and the synaxial hydrogens on C1 and C3 of the cyclohexane ring.



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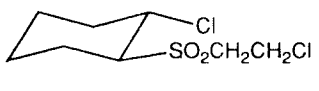
Oxygen-17 NMR LIS studies were performed on *trans*-1-[(2-chloroethyl)sulfonyl]-2-chlorocyclohexane (**20**) to determine whether a proximal hydroxyl group is required to observe differential binding of Eu(fod)$_3$ to diastereotopic sulfonyl oxygens. Halogen atoms attached to carbon are not viewed as serious binding candidates to lanthanide shift reagents [19]. In the absence of polar solvents, the C–Cl and C–OH groups exhibit comparable steric requirements in the cyclohexyl system [22]. When K_3 was determined for dichlorosulfone **20** and compared to that of hydroxysulfone **6**, it was found that replacement of the C1 OH of **6** with Cl led to a significant decrease in K_3, from 2.50 to 1.38. Although the difference in the K_3's for **6** and **20** is relatively small, it is apparent that the hydroxyl group is properly positioned to influence Eu^{3+} binding to the sulfonyl group through chelation [17]. However, *monodentate binding* plays a significant role in the observed differential binding of Eu^{3+} to sulfonyl oxygens, because sulfonyl diastereotopicity is observed in sulfone **20**, in the absence of a second binding site. 2-*exo*-(Phenylsulfonyl)norbornane (**21**), with no β-substituents on the alkyl group, also exhibits differential binding of Eu(fod)$_3$ to the sulfonyl oxygens (K_3 = 1.14).



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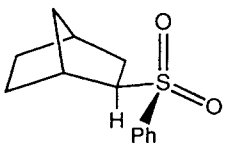

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CONCLUSIONS

From our analysis, the observed ^{17}O NMR LIS's result primarily from an equilibrium between two diastereomeric bidentate complexes. Further, it appears that the relative amounts of these complexes are strongly dependent on the steric requirements of the alkyl- or arylsulfonyl group. Since monofunctional sulfones also exhibit differential LIS's for the sulfonyl oxygens, the presence of smaller quantities of monodentate complexes cannot, however, be neglected. Thus, the total formulation of the LIS for the sulfonyl oxygens in **4–9** is best expressed as:

$$\text{LIS} = \alpha\text{LIS}_{(\text{chel})} + \beta\text{LIS}_{(\text{monodent})}; \qquad \alpha > \beta \quad (6)$$

The LIS's of each sulfonyl oxygen are influenced by the concentration and inherent shielding properties of both bidentate ($\text{LIS}_{(\text{chel})}$) and monodentate ($\text{LIS}_{(\text{monodent})}$) complexes. The major contributor to the ^{17}O LIS is the contact shift (Δ_c), which involves direct binding between the observed sulfonyl oxygen (S=O_a) and the Eu^{3+} ion; however, since chelation influences the rotameric distribution of the substrate, complex formation shifts may affect the position of the S=O_a ^{17}O NMR absorption.

EXPERIMENTAL

The oxygen-17 NMR spectra were obtained using a Varian XL-400 NMR spectrometer (54.2 MHz), operating with a sweep width of 24 kHz (50 Hz linebroadening). Samples were prepared in 10-mm (o.d.) NMR tubes as solutions containing 80–300 mg of the sulfone in 2–3 mL solvent. The number of transients required to obtain adequate spectra ranged from 3×10^4 to 10^5. Tap water was used as an external reference (H_2 ^{17}O, δ = 0.00 ppm). All ^{17}O NMR spectra were obtained at 32 ± 1°C.

Carbon-13 and ^1H NMR spectra were recorded at ambient temperature (20–25°C) using the XL-400 NMR spectrometer (operating at 100 MHz for ^{13}C; 400 MHz for ^1H) and a Bruker AC-200 NMR (operating at 50 MHz for ^{13}C; 200 MHz for ^1H). For all nuclei examined, a positive δ value is downfield of the reference.

Oxygen-17 NMR LIS studies were performed by adding several weighed increments of Eu(fod)$_3$ to CH_2Cl_2 solutions containing known concentrations of sulfones. New ^{17}O NMR spectra were obtained after each addition. ^1H NMR LIS studies were performed on solutions containing equimolar amounts of substrate and Eu(fod)$_3$ in anhydrous $CDCl_3$ (for **10**, initial concentration = 0.20 M; for **10a**, initial concentration = 0.26 M). These solutions were then diluted by the addition of known volumes of pure solvent, and new NMR spectra were obtained. The LIS of the *tert*-butyl resonance for each spectrum was determined by comparison with a spectrum of pure substrate, and the binding constants (K_b) and bound shifts (Δ_0) were determined by application of Equation 7 [21]:

$$\text{LIS} = \Delta_0 - (\text{LIS}/S_0)^{1/2}(\Delta_0/K_1)^{1/2} \quad (7)$$

Sulfones **6**, **8**, **20**, and **21** and 1-(phenylthio)-2-propanol were available from previous work [23]. Other sulfones were prepared by oxidation of the corre-

sponding sulfide, as described below. Dichloromethane was purified by distillation from phosphorus pentoxide, except where noted. The remaining chemicals, including $Eu(fod)_3$ (Norrell Chemical Co., mp 192–196°C), were used without additional purification. The melting points are uncorrected.

Preparation of trans-2-(Alkylthio)-cyclohexanols

General Procedure. Potassium hydroxide (2.7–2.8 g, 0.048–0.050 mol) was dissolved with stirring in 50 mL dry ethanol. The reaction mixture was then cooled (ice water bath), and the desired alkanethiol (≥ 0.04 mol; see below for exact quantities) was poured into the alcoholic KOH solution. Neat cyclohexene oxide (4.0 mL, 0.04 mol) was then added to the alcoholic solution, and the resulting reaction mixture was allowed to stir overnight. Water (50 mL) was then added to the reaction mixture and the organic fraction was subsequently extracted with three 20-mL portions of diethyl ether. The organic layers were combined, and the ether and ethanol were removed (rotary evaporator). If some residual water remained, the residue was extracted again with hexanes (40 mL) and dried ($MgSO_4$). Removal of the solvent (rotary evaporator) afforded the thioethers in crude yields as yellow oils. *trans*-2-(Methylthio)cyclohexanol and *trans*-2-(*n*-propylthio)cyclohexanol were purified by distillation under high vacuum while *trans*-2-(benzylthio)cyclohexanol and *trans*-2-(*t*-butylthio)-cyclohexanol were purified by column chromatography over silica (4″ high × 1″ diameter; hexanes were used as eluent). A layer of decolorizing carbon was added to the column before chromatographic purification of *trans*-2-(*t*-butylthio)cyclohexanol; this compound was subsequently distilled under high vacuum.

trans-*2*-(*Methylthio*)*cyclohexanol.* *trans*-2-(Methylthio)cyclohexanol was prepared from the reaction of methanethiol (4.0 mL; 0.08 mol) and cyclohexene oxide. The product was a clear oil (1.0 g, 17%): bp 104°C (12 mm Hg); ^{13}C NMR (100 MHz, $CDCl_3$) δ 71.11 (*C*HOH), 53.16 (*C*HS), 33.82, 31.49, 26.22, 24.49, and 11.41 ppm (SCH_3) (lit. [24], ^{13}C NMR (acetone-d_6) δ 72.83, 53.24, 35.09, 31.88, 26.34, 24.77, and 13.01 ppm); ^1H NMR (400 MHz, $CDCl_3$) δ 3.3 (m, 1H, C*H*OH), 3.05 (s, 1H, CHO*H*), 2.2–2.3 (m, 1H, C*H*S), 2.0–2.15 (m, 2H), 2.05 (s, 3H, SCH_3), 1.65–1.8 (m, 2H), 1.35–1.5 (m, 1H), and 1.2–1.35 ppm (m, 3H).

trans-2-(n-*Propylthio*)*cyclohexanol.* *trans*-2-(*n*-Propylthio) cyclohexanol was prepared from the reaction of *n*-propanethiol (4.0 mL; 0.04 mol) with cyclohexene oxide. The product was a clear oil (3.3 g, 48%): bp 120–122°C (12 mm Hg) (lit. [25], bp: 96–97°C (3 mm Hg)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 72.42 (*C*HOH), 53.64 (*C*HS), 34.03, 33.22, 32.22, 26.55, 24.68, 23.90, and 13.75 ppm (CH_2CH_3); ^1H NMR (400 MHz, $CDCl_3$) δ 3.25 (m, 1H, C*H*OH), 2.93 (s, 1H, CHO*H*), 2.48 (t, 2H, SCH_2), 2.27–2.37 (m, 1H, C*H*S), 1.98–2.10 (m, 2H), 1.60–1.75 (m, 2H), 1.55 (m, 2H, CH_2CH_3), 1.32–1.45 (m, 1H), 1.15–1.30 (m, 3H), and 0.94 ppm (t, 3H, CH_2CH_3). Anal. Calcd for $C_9H_{18}OS$: C, 62.02; H, 10.41. Found: C, 61.55; H, 10.47.

trans-*2*-(tert-*Butylthio*)*cyclohexanol* (**10a**). *trans*-2-(*tert*-Butylthio)cyclohexanol was prepared from the reaction of *tert*-butylmercaptan (4.5 mL; 0.04 mol) and cyclohexene oxide. The product was a clear oil (3.8 g, 50%): bp 250°C; ^{13}C NMR (100 MHz, $CDCl_3$) δ 72.12 (*C*HOH), 50.94 (*C*HS), 43.54 ($C(CH_3)_3$), 35.90, 33.56, 31.65 ($C(CH_3)_3$), 26.55, and 24.48 ppm; ^1H NMR (400 MHz, $CDCl_3$) δ 3.1–3.2 (m, 2H, C*H*OH and CHO*H*), 2.3–2.4 (m, 1H, C*H*S), 2.0–2.15 (m, 2H), 1.6–1.8 (m, 2H), 1.2–1.5 (m, 4H), and 0.94 ppm (s, 9H, $C(CH_3)_3$). Anal. Calcd. for $C_{10}H_{20}OS$: C, 63.77; H, 10.70. Found: C, 63.88; H, 10.33.

trans-*2*-(*Benzylthio*)*cyclohexanol.* *trans*-2-(Benzylthio)cyclohexanol was prepared from the reaction of benzylmercaptan (5 mL; 0.04 mol) with cyclohexene oxide. The crude product was divided into two portions, each of which was purified by column chromatography over silica as described above. The products recovered from each chromatographic separation were combined, affording 2.5 g (25%) of a yellow oil: bp 148°C (0.25 mm Hg) (lit. [25], bp: 158–160°C (3 mm Hg)); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.80, 129.04, 128.84, 127.35 (C_6H_5); 72.65 (*C*HOH), 53.37 (*C*HS), 35.00, 34.20, 32.94, 26.44, and 24.63 ppm; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.55 (m, 5H, C_6H_5), 3.95 (dd, 2H, $CH_2C_6H_5$), 3.4–3.55 (m, 1H, C*H*OH), 3.05 (s, 1H, CHO*H*), 2.5–2.65 (m, 1H, C*H*S), 2.1–2.3 (m, 2H), 1.8–1.95 (m, 2H), and 1.3–1.7 ppm (m, 4H).

Preparation of β-Hydroxysulfones

trans-*2*-(tert-*Butylsulfonyl*)*cyclohexanol* (**10**). Sulfide **10a** (1.51 g, 0.008 mol) was added dropwise to glacial acetic acid (25 mL). After the sulfide had dissolved, 30% hydrogen peroxide (2.5 mL, 0.025 mol H_2O_2) was added (via syringe) and the reaction mixture was allowed to stir overnight. The acetic acid was removed under reduced pressure (vacuum pump), to afford a yellowish solid. This material was recrystallized from dichloromethane and hexanes solvents to give a colorless, crystalline solid (0.51 g, 29%): mp 122°C; ^{13}C NMR (100 MHz, $CDCl_3$) δ 68.37 (*C*HOH), 63.03 ($CHSO_2$), 61.25 ($C(CH_3)_3$), 34.49 (CH_2CHOH), 28.02 (CH_2CHSO_2), 25.46, 24.06, and 23.57 ppm ($C(CH_3)_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 3.96–4.04 (m, 1H, C*H*OH), 3.12–3.22 (m, 1H, C*H*SO_2), 2.30–2.38 (m, 1H), 2.08–2.18 (m, 1H), 1.80–2.00 (m, 4H), 1.35–1.65 (m, 3H), and 1.42 ppm

(s, 9H, C(CH_3)$_3$). Anal. Calcd. for $C_{10}H_{20}O_3S$: C, 54.51; H, 9.15. Found: C, 54.79; H, 9.12.

trans-*2*-(n-*Propylsulfonyl*)*cyclohexanol* (**7**). *trans*-2-(*n*-Propylthio)cyclohexanol (1.5 g, 0.0086 mol) was added dropwise to glacial acetic acid (10 mL). After the sulfide had dissolved, 30% hydrogen peroxide (2.7 mL, 0.026 mol H_2O_2) was added by syringe and the reaction mixture was allowed to stir overnight. The reaction mixture was then extracted with ether and the ethereal solution was washed with 5% sodium bicarbonate to remove any residual acetic acid. The ether solution was concentrated to dryness (rotary evaporator). Any remaining traces of water and acetic acid were removed by placing the residue under high vacuum overnight. An oily solid was obtained and was subsequently purified using column chromatography employing silica (6″ high × 1″ in diameter; 50:50 hexanes/ethyl acetate eluent) to afford a colorless, crystalline solid (0.41 g, 23%): mp 94–96°C; ^{13}C NMR (100 MHz, $CDCl_3$) δ 69.04 (*C*HOH), 66.51 (*C*HSO$_2$), 55.16 (SO$_2$*C*H$_2$), 35.04 (*C*H$_2$CHOH), 24.87, 24.60, 24.02, 15.50 (*C*H$_2$CH$_3$), and 13.48 ppm (CH$_2$*C*H$_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.9–4.05 (m, 1H, C*H*OH), 3.40 (s, 1H, CHO*H*), 3.07 (t, 2H, *C*H$_2$CH$_2$CH$_3$), 2.8–2.9 (m, 1H, C*H*SO$_2$), 2.05–2.2 (m, 2H, CH$_2$*C*H$_2$CH$_3$), 1.82–1.95 (m, 3H), 1.75–1.82 (m, 1H), 1.45–1.6 (m, 1H), 1.15–1.45 (m, 3H), and 1.07 ppm (t, 3H, CH$_2$*C*H$_3$). Anal. Calcd. for $C_9H_{18}O_3S$: C, 52.40; H, 8.80. Found: C, 52.22; H, 8.72.

trans-2-(*Benzylsulfonyl*)*cyclohexanol* (**9**). Sulfone **9** was prepared in the same manner as sulfone **10**, starting from *trans*-2-(benzylthio)cyclohexanol (1.5 g, 0.0068 mol) and 30% hydrogen peroxide (2.2 mL, 0.0214 mol H_2O_2). Purification of the solid product was achieved through recrystallization from dichloromethane and hexanes to give a colorless, crystalline solid (0.72 g, 42%): mp 117°C (lit. [26], mp 122°C); ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.08, 128.94, 127.90 (*C*$_6$H$_5$), 69.21 (*C*HOH), 64.19 (*C*HSO$_2$), 60.38 (*C*H$_2$C$_6$H$_5$), 34.99 (*C*H$_2$CHOH), 24.56, 24.07, and 23.81 ppm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25–7.65 (m, 5H, C$_6$*H*$_5$), 4.45 (dd, 2H, C*H*$_2$C$_6$H$_5$), 4.0–4.05 (m, 1H, C*H*OH), 3.2 (s, 1H, CHO*H*), 2.8–2.9 (m, 1H, C*H*SO$_2$), 2.0–2.2 (m, 2H), 1.6–1.9 (m, 2H), 1.4–1.6 (m, 1H), and 1.1–1.4 ppm (m, 3H).

trans-*2*-(*Methylsulfonyl*)*cyclohexanol* (**5**). Sulfone **5** was prepared in the same manner as sulfone **10**, starting from *trans*-2-(methylthio)cyclohexanol (1.0 g, 0.0068 mol) and hydrogen peroxide (2.1 mL, 0.020 mol H_2O_2). The product of the reaction was a clear oil that was determined by ^{13}C NMR to be a mixture of sulfone **5** and the corresponding sulfoxides. Homogeneous sulfone **5** was obtained as a colorless, crystalline solid (0.10 g, 8.3%) by chromatographic separation on a silica column (6″ × 1″ diameter; 50:50 hexanes/ethyl acetate eluent): mp 92–93°C (lit. [25], mp 95–96°C); ^{13}C NMR (50 MHz, $CDCl_3$) δ 69.14 (*C*HOH), 67.89 (*C*HSO$_2$), 41.55 (*C*H$_2$CHOH), 34.88 (*C*H$_2$CHSO$_2$), 24.57, 24.16, and 23.85 ppm; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.8–4.0 (m, 1H, C*H*OH), 3.3 (s, 1H, CHO*H*), 3.0 (s, 3H, SC*H*$_3$), 2.85 (m, 1H, C*H*SO$_2$), 2.0–2.3 (m, 3H), 1.7–1.9 (m, 2H), and 1.2–1.6 ppm (m, 3H).

trans-*1*-(*Phenylsulfonyl*)-*2*-*propanol* (**15**). *trans*-1-(Phenylsulfonyl)-2- propanol was prepared in the same manner as sulfones **5** and **10**. Hydrogen peroxide (2.7 mL of a 30% solution, 0.026 mol H_2O_2) and (2-hydroxypropylthio)benzene (1.5 g, 0.009 mol) were used as starting materials. The product obtained was a clear oil, from which the desired sulfone was isolated as a colorless oil by column chromatographic separation over silica (6″ × 1″ diameter; 50:50 hexanes/ethyl acetate eluent). Over the course of a week, this oil slowly solidified into a colorless, crystalline solid (80 mg, 4.4%): mp 39–42°C (lit. [27], 44–45°C); ^{13}C NMR (50 MHz, $CDCl_3$) δ 134.10, 129.52, 127.96 (*C*$_6$H$_5$), 63.41 (*C*HOH), 62.37 (*C*H$_2$SO$_2$), and 22.58 ppm (*C*H$_3$); ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.95 (d, 2H, ortho-C$_6$*H*$_5$), 7.5–7.8 (m, 3H, meta, para-C$_6$*H*$_5$), 4.3 (s, 1H, CHO*H*), 3.25 (dd, 2H, C*H*$_2$SO$_2$), 3.2 (d, 1H, C*H*OH), and 1.2 ppm (d, 3H, C*H*$_3$).

ACKNOWLEDGMENTS

We thank the National Science Foundation for the support of this research and the University of North Carolina Board of Governors for a fellowship to TAP. Finally, we are grateful to Dr. Paul Kropp for a generous sample of sulfone **21**.

REFERENCES

[1] (a) J. C. Dyer, D. L. Harris, S. A. Evans, Jr., *J. Org. Chem., 47,* 1982, 3660. (b) G. Lowe, S. J. Salamone, *J. Chem. Soc., Chem. Commun., 1983,* 1392.

[2] (a) T. A. Powers, S. A. Evans, Jr., *Tetrahedron Lett., 31,* 1990, 5835. (b) T. A. Powers, L. G. Pedersen, S. A. Evans, Jr., *Phosphorus, Sulfur,* 1991, *59,* 205–210. (c) T. A. Powers, S. A. Evans, Jr., K. Pandiarajan, J. C. N. Benney, *J. Org. Chem.,* 1991, *56,* 5589–5594.

[3] (a) K. Kobayashi, T. Sugawara, H. Iwamura, *J. C. S. Chem. Commun., 1981,* 479. (b) M. Manoharan, E. L. Eliel, *Magn. Reson. Chem., 23,* 1985, 225.

[4] (a) F. Inagaki, T. Miyazaya, *Prog. NMR Spectrosc., 14,* 1981, 67. (b) J. A. Peters, M. S. Nieuwenhuizen, D. J. Raber, *J. Magn. Reson., 65,* 1985, 417.

[5] It is known that the fractional spin shows relatively small dependence on the nature of the metal: J. Reuben, D. Fiat, *J. Chem. Phys., 51,* 1969, 4909.

[6] D. W. Boykin, A. L. Baumstark, Mehdizadeh, M. K. Venkatramanen, *Magn. Reson. Chem., 28,* 1990, 305.

[7] T. H. Sammakia, D. L. Harris, S. A. Evans, Jr., *Org. Magn. Reson., 22,* 1984, 747.

[8] (a) S. A. Evans, Jr.: In D. W. Boykin (ed): *^{17}O NMR Spectroscopy in Organic Chemistry,* CRC Press, Inc., Boca Raton, FL, 1990. (b) C. Brevard: In P. Laszlo,

(ed): *NMR of Newly Accessible Nuclei*, Vol. 1, Academic Press, New York, pp. 1–19 (1983).

[9] Proximity of an alkyl group to oxygen (e.g., diaxial relationships between methyl groups and sulfonyl oxygens in substituted thiane 1,1-dioxides) leads to a compression effect at the oxygen atom and a subsequent deshielding effect. G. Barbarella, P. Dembech, V. Tugnoli, *Org. Magn. Reson., 22*, 1984, 402.

[10] N. L. Allinger, Y. H. Yuh, *QCPE, 11*, 1980, 395.

[11] The results of MM2 calculations indicate that several potential conformers experience significant stabilization (ca. 3.5 kcal/mol) from intramolecular hydrogen bonding. However, FT IR spectroscopic studies of sulfone **6** failed to reveal clear evidence of an intramolecular hydrogen bond between 2800–3200 cm^{-1} (ν(OH) = 3520 cm^{-1} in 0.08 M CH_2Cl_2 solution; ν(OH) = 3540 cm^{-1} in 0.005 M CCl_4 solution). Consequently, the energies that result from intramolecular hydrogen bonding were subtracted from the total energies calculated by MM2.

[12] C. P. Cheng, T. L. Brown, *J. Am. Chem. Soc., 102*, 1980, 6418.

[13] One of the sulfonyl oxygens in sulfone **6** exhibited large upfield shifts in the presence of increasing Eu(fod)$_3$. The ^{17}O NMR LIS for the other sulfonyl oxygen was essentially zero and the ^{17}O absorption remained well within experimental error (<3 ppm upfield shift).

[14] Reports of such chelation are discussed in (a) M. R. Wilcott III, R. E. Davis: In R. E. Sievers (ed): *Nuclear Magnetic Resonance Shift Reagents*, Academic Press, New York, p. 159 (1973). (b) R. N. Warrener, I. G. Pitt, R. A. Russell, *J. C. S. Chem. Commun., 1982*, 1195.

[15] The existence of octacoordinate lanthanide species has been confirmed from the results of X-ray analysis: (a) J. G. Leipoldt, L. D. C. Bok, S. S. Basson, A. E. Laubscher, J. S. van Vollenhoven, *J. Inorg. Nucl. Chem., 39*, 1977, 301. (b) R. A. Lalancette, M. Cefola, W. C. Hamilton, S. J. LaPlaca, *Inorg. Chem., 6*, 1967, 2127.

[16] F. A. Cotton, G. Wilkinson: *Advanced Inorganic Chemistry*, 4th Ed., Wiley-Interscience, New York, 1980; Chapter 3.

[17] D. J. Raber: In T. C. Morrill, (ed): *Lanthanide Shift Reagents in Stereochemical Analysis*, VCH Publishers: New York, p. 55 (1986).

[18] (a) D. M. Rackham, *Spectrosc. Lett., 14*, 1981, 117. (b) J. W. M. de Boer, C. W. Hilbers, E. de Boer, *J. Magn. Reson., 25*, 1977, 437. (c) R. N. Warrener, I. G. Pitt, R. A. Russell, *J. Chem. Soc., Chem. Commun., 1982*, 1195.

[19] T. J. Wenzel: *NMR Shift Reagents*, CRC Press: Boca Raton, FL., pp. 58–64 (1987).

[20] The binding constant between *cis*-3,5-diphenyl-4-methyl-tetrahydro-1,4-thiazine 1,1-dioxide and Eu(fod)$_3$ is 10.6 M^{-1} (Ref. [2c]); the binding constant between 3-sulfolene and Eu(fod)$_3$ = 64 M^{-1} (T. A. Powers, S. A. Evans, Jr., Unpublished results).

[21] J. Bouquant, J. Chuche, *Bull. Soc. Chim. Fr., 1977*, 959.

[22] (a) E. L. Eliel, N. L. Allinger, S. J. Angyal, G. A. Morrison, *Conformational Analysis*, Interscience Publishers, New York, pp. 44–47, 433–442 (1965). (b) J. A. Hirsch, *Top. Stereochem., 1*, 1967, 199–222.

[23] (a) C. N. Barry, Doctoral Dissertation, The University of North Carolina, Chapel Hill, 1980. (b) J. W. Kelly, Doctoral Dissertation, The University of North Carolina, Chapel Hill, 1986.

[24] C. Carreno, E. Dominguez, J. L. Garcia-Ruano, A. Rubio, *J. Org. Chem., 52*, 1987, 3619.

[25] C. D. Nenitzescu, N. Scarlatescu, *Chem. Ber., 68*, 1935, 587.

[26] M. E. Ali, N. G. Kardouch, L. N. Owen, *J. Chem. Soc., Perkin 1*, 1975, 748.

[27] I. W. J. Still, F. J. Ablenas, *Synth. Commun., 12*, 1982, 1103.