Oxygen-17 Nuclear Magnetic Resonance Spectroscopy of Organosulfur Compounds. 2. ^{17}O NMR Lanthanide-Induced Shifts (LIS) of Diastereotopic Sulfonyl Oxygens in Substituted Six-Membered-Ring Sulfones

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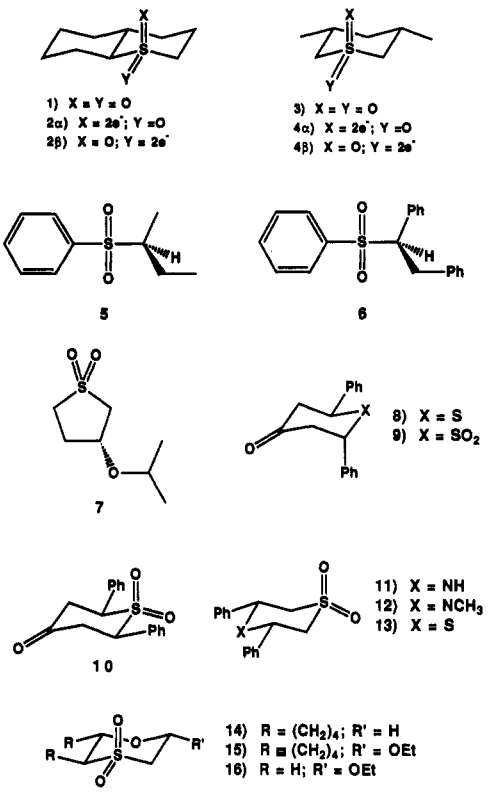
The ^{17}O NMR shifts of diastereotopic sulfonyl oxygens within a series of conformationally homogeneous six-membered-ring organosulfur compounds have been determined. Their lanthanide-induced shifts (LIS), resulting from competitive complexation with the europium metal ion (i.e., $Eu(fod)_3$), provide structural insights into the relative binding potential of the attached diastereotopic sulfonyl oxygens.

Introduction

The importance of ^{17}O NMR spectroscopy in the structural elucidation of organosulfur compounds containing the sulfinyl (—S=O) and sulfonyl (—SO_2—) groups has been well-documented.[1-6] These reports are highlighted by correlating relative ^{17}O NMR chemical shift differences caused by the influence of substituents (i.e., α-, β-, and γ-substitutent effects) and differential steric shielding effects caused by conformer differences in diastereomeric relationships.

The ^{17}O NMR diastereotopicity or chemical-shift nonequivalence ($\Delta\delta = \delta_1 - \delta_2$) of sulfonyl oxygens has been previously observed employing ^{17}O NMR spectroscopy in both cyclic[1-4] and acyclic sulfones.[5,6] For example, conformationally homogeneous *trans*-thiadecalin 1,1-dioxide (**1**), possessing both axial and equatorial monocoordinated oxygens in a six-membered chair conformation, exhibits ^{17}O NMR chemical shifts for these sulfonyl oxygens at δ 123.9 and 138.9, reflecting a shift difference ($\Delta\delta(SO_2)$) of 15 ppm (see Table I).[2] By analogy with the ^{17}O NMR shifts of the isomeric *trans*-thiadecalin 1-oxides, **2α** (δ-($S{=}O_{eq}$) = 5.6 ppm) and **2β** ($\delta(S{=}O_{ax})$ = −11.4 ppm), where the high-field resonance characterizes the axial sulfinyl oxygen, the axial oxygen in sulfone **1** is assigned to δ 123.9.[2] In 3,5-dimethylthiane 1,1-dioxide (**3**), $\Delta\delta(SO_2)$ is 10 ppm between the axial and equatorial oxygens. On the basis of the ^{17}O NMR chemical shifts of the "configurationally secure" sulfoxides, **4α** ($\delta(S{=}O_{eq})$ = 7 ppm) and **4β** ($\delta(S{=}O_{ax})$ = −14 ppm), the high-field ^{17}O NMR resonance in sulfone **3** is also assigned to the axial oxygen.[1g,h]



In the acyclic sulfones where the sulfonyl oxygens are proximal to a stereogenic center, the magnitude of the ^{17}O NMR sulfonyl diastereotopicity is both substituent and rotamer controlled and significantly diminished compared to the ^{17}O NMR shifts in conformationally restricted sulfones. For example, in 2-(phenylsulfonyl)butane (**5**) the diastereotopic oxygens are isochronous, appearing at δ 141,[5,6] while the ^{17}O NMR spectrum of sulfone **6** clearly exhibits diastereotopic oxygens at δ 140.3 and 145.4.[5]

Theory

The derivation of the equilibrium constants between the complexes of the diastereotopic sulfonyl oxygens in 4-heterothianes and $Eu(fod)_3$ is best understood from a brief

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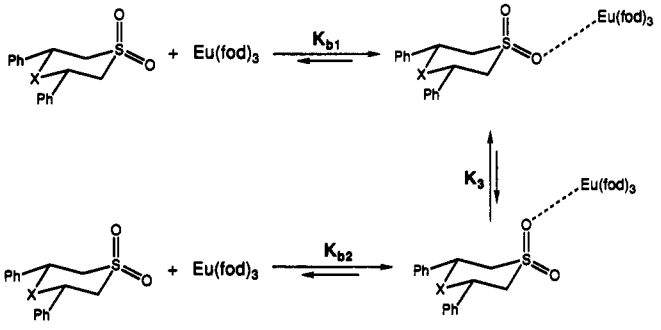
Table I. Oxygen-17 NMR Chemical Shift Data for *S*-Oxides and *S*,*S*-Dioxides

compd	solvent	temp (°C)	δ ^{17}O (±2 ppm)	$W_{1/2}$ (Hz)	SO/SO$_2$ orientation[a]
1[c]	$CDCl_3$	30	123.9	139	ax
			138.9	146	eq
2α	CH_2Cl_2	amb	5.6		eq
2β	CH_2Cl_2	amb	−11.4		ax
3[c]	$CHCl_3$	35	139		ax
			149		eq
4α	CH_2Cl_2	35	7		eq
4β	CH_2Cl_2	35	−14		ax
5[b]	toluene	100	141.0	100–200	
6[c]	toluene	100	140.3	100–200	
			145.4	100–200	
7[c]	toluene	100	172.3	163[d]	trans
			171.0	163[d]	cis
9[b]	CH_2Cl_2	30	134.8	430	
10[c]	CH_2Cl_2	30	122.1	285	ax
			135.7	430	eq
11[c]	CH_2Cl_2	30	140.6	320	ax
			155.1	400	eq
12[c]	CH_2Cl_2	30	135.9	320	ax
			150.3	480	eq
13[c]	CH_2Cl_2	30	143.4	480	ax
			154.1	480	eq
14[c]	CH_2Cl_2	30	126.2	162	ax
			142.6	147	eq
15[c]	CH_2Cl_2	30	133.3	251	ax
			145.9	255	eq
16[c]	CH_2Cl_2	30	149.0	160	ax
			157.1	170	eq

[a] ax = axial oxygen; eq = equatorial oxygen; trans = oxygen trans to 3-isopropoxy group; cis = oxygen cis to 3-isopropoxy group. [b] The ^{17}O NMR shifts for the sulfonyl oxygens are isochronous. [c] The sulfonyl oxygens are diastereotopic and exhibit separate ^{17}O NMR resonances. [d] Combined line width—signals are not base-line resolved.

Scheme I. Equilibria between Sulfones 11–13 and Eu(fod)$_3$



description of the origin of lanthanide-induced shifts (LIS).[7]

Each conformationally restricted sulfone described in this report possesses one distinct axial and one equatorial sulfonyl oxygen. Thus, two diastereomeric Ln·sulfone complexes of 1:1 stoichiometry (Ln·S) are possible (Scheme I), assuming that the sulfonyl moiety does not function as a bidentate ligand.[8] Complexes of 1:2 stoichiometry (i.e., Ln·S$_2$) are also viable;[9] however, for weakly bound substrates, the concentrations of Ln·S$_2$ species are normally negligible at low Ln to S ratios.[10] The approximation that *only* 1:1 complexes are formed between Ln^{3+} and sulfonyl oxygens significantly reduces the complexity of the multistep equilibria involving the Ln^{3+} ion and the substrate, S.

The origin of the observed LIS is best understood by considering a hypothetical 1:1 complex with 100% of the substrate bound to Ln^{3+}. The LIS is described as a sum of three components (eq 1): a contact shift (Δ_c), a pseudocontact shift (Δ_{pc}), and a complex formation shift (Δ_{cf}).[7]

$$\mathrm{LIS} = \Delta_c + \Delta_{pc} + \Delta_{cf} \quad (1)$$

For ^{17}O NMR, Δ_{pc}, arising from nonbonded through-space interactions, and Δ_{cf}, caused by electron polarization at the oxygen induced by the metal as well as changes in the molecular conformation of Ln·S, are expected to be much smaller than Δ_c for Eu(fod)$_3$.[11] Thus, it seems justified to assume that the contact shift term is largely responsible for the induced shifts in ^{17}O NMR (i.e., $\Delta_c > \Delta_{pc}, \Delta_{cf}$).

Contact shifts originate from a covalent interaction between oxygen and the lanthanide ion, involving transfer of some electron density to the coordinated oxygen. The contact shift arising (δ_i) the complexed substrate, or the *bound shift*, can be described mathematically by the expression in eq 2 where ν and γ are the Larmor frequency

$$\Delta_c = \frac{-2\pi\beta\nu A J(J+1) g_L (g_L - 1)}{3kT\gamma} \quad (2)$$

and the gyromagnetic ratio of the ^{17}O nucleus, respectively, β is the Bohr magneton, J is the electronic spin angular momentum, and g_L is the Lande g value. A, the scalar coupling in Hz, is dependent on the fractional electron spin occupancy, f_s, at the oxygen nucleus, which results from delocalization of unpaired electron density from the lanthanide ion to the bound oxygen atom (eq 3) where A_s is

$$A = f_s A_s / 2S \quad (3)$$

the coupling constant arising from one unshared electron in an oxygen s orbital and $2S$ is the number of unpaired electrons on the metal ion. By using this expression, the following proportionality can be derived (eq 4):

$$\Delta_c \propto f_s A_s / \gamma \quad (4)$$

A ratio of bound contact shifts for two different oxygen atoms can be equated to a ratio of their spin densities:

$$\Delta_{c1}/\Delta_{c2} = f_{s1}/f_{f2} \quad (5)$$

Reuben and Fiat[12] demonstrated that the fractional spin, f_s, on the ^{17}O nucleus in a series of rare-earth aquo complexes M(H$_2$O)$_9^{3+}$ varied by less than a factor of 3 as M^{3+} was varied. Thus, it seems reasonable that the fractional spin should be approximately the same for similarly hybridized oxygen atoms that are complexed to the same lanthanide ion. Therefore, the ratio of the bound contact shifts should approximate unity.

Since the substrate is present in large excess over Ln in the actual experiment, only a small fraction of substrate is actually complexed. Therefore, the observed shift (δ_i) is equal to the bound shift times the fraction of substrate that is actually bound to Ln^{3+} where S_0 is the total sub-

$$\delta_i = \Delta_c[\mathrm{Ln{\cdot}S}]/S_0 \quad (6)$$

(7) Inagaki, F.; Miyazawa, T. *Prog. NMR Spectrosc.* **1981**, *14*, 67–111.
(8) Wrobel, J. T.; Kabzinska, K.; Ruszkowska, J.; Wrona, P. K. *J. Mol. Struct.* **1977**, *41*, 287.
(9) It is well-established that Ln(fod)$_3$ reagents possess an inherently higher Lewis acidity than other Ln^{3+} reagents and consequently exhibit a stronger propensity to form LnS$_2$ complexes as well as the "expected" LnS complexes.[7]
(10) Raber, D. J.; Hardee, L. E. *Org. Magn. Reson.* **1974**, *6* 544.
(11) (a) Reuben, *J. Prog. NMR Spectrosc.* **1973**, *9*, 1. (b) Peters, J. A.; Nieuwenhuizen, M. S.; Raber, D. J. *J. Magn. Reson.* **1985**, *65*, 417. (c) Raber, D. J.; Peters, J. A.; Nieuwenhuizen, M. S. *J. Chem. Soc., Perkin Trans. 2* **1986**, 853.
(12) Reuben, J.; Fiat, D. *J. Chem. Phys.* **1969**, *51*, 4909.

strate concentration and [Ln·S] is the concentration of shift reagent–substrate complex.[13] At low Ln/S ratios, S_0 is approximately equal to the concentration of free substrate ([S]), thus

$$\delta_i = \Delta_c([Ln{\cdot}S]/S_0[Ln])[Ln] = \Delta_c K_b[Ln] \quad (7)$$

where K_b is the association constant between Ln^{3+} and substrate. The ratio of experimental LIS's for two nonequivalent oxygens then becomes

$$\delta_{i1}/\delta_{i2} = (\Delta_{c1}/\Delta_{c2})(K_{b1}/K_{b2}) = (f_{s1}/f_{s2})(K_{b1}/K_{b2}) \quad (8)$$

$$\delta_{i1}/\delta_{i2} = (K_{b1}/K_{b2}) = K_3 \quad (9)$$

where K_3 is the equilibrium between the chemically different Ln·S complexes (see Scheme I). The free energy difference between the two complexes can then be calculated from eq 10, and the ratio of the binding constants

$$K_3 = e^{-\Delta G^\circ/RT} \quad (10)$$

for each oxygen to Ln^{3+} can be ascertained from the ratio of their LIS values.

Assuming that the contact shift contribution dominates the observed ^{17}O shift increments, increasing the Eu^{3+} concentration should result in progressive *upfield* shifts of the coordinated oxygen nucleus and thus serve as a probe for assessing steric inhibition of oxygen to metal binding. Finally, several previous reports suggest that lanthanide-induced ^{17}O NMR shifts (e.g., Eu^{3+}) possess remarkable potential for understanding structural complexities as well as dynamic properties of molecules containing heteroatoms.[3,4]

Results and Discussion

We previously reported[3] that the intrinsic diastereotopic sulfonyl oxygens of 3-isopropoxythiolane 1,1-dioxide (**7**) exhibit essentially identical ^{17}O NMR shifts. However, in the presence of $Eu(fod)_3$ both oxygens are shifted upfield to different extents and, more importantly, the more sterically encumbered cis sulfonyl oxygen (cis to the isopropoxy group) experiences less shielding compared to the trans sulfonyl oxygen. Furthermore, the resonance width at half-height ($W_{1/2}$) of the more strongly coordinated *trans*-S=O is larger than that of the coordinated *cis*-S=O, suggesting that the the larger equilibrium concentration (or mole fraction) of the *trans*-S=O complex may correlate with a longer correlation time, τ_c, for this oxygen. In this present report, we describe a quantitative analysis of competitive Eu^{3+} binding to diastereomeric sulfonyl oxygens in conformationally rigid heterocycles.

The ^{13}C NMR spectrum of *trans*-2,6-diphenyl-4-oxothiane (**8**) indicates that the benzylic carbons are equivalent (δ(PhCHS) = 48.55 ppm), and the ^{17}O NMR spectrum for *trans*-2,6-diphenyl-4-oxothiane 1,1-dioxide (**9**) affords a single resonance at δ 134.8 ppm for the sulfonyl group. These data indicate that these *trans*-2,6-diphenylthianes probably exist as rapidly equilibrating, isoenergetic chair conformers with one phenyl group axial and the other one in the equatorial position. Parenthetically, contributions from boat or twist-boat conformers cannot be completely dismissed. Nevertheless, the ^{13}C and ^{17}O NMR spectra for **8** and **9** are the consequence of rapid time averaging on the NMR time scale.

cis-2,6-Diphenyl-4-oxothiane 1,1-dioxide (**10**) occupies a single chair conformation with diequatorial phenyl groups, and the sulfonyl group gives two ^{17}O NMR resonances at δ 122.1 and 135.7 ($\Delta\delta(SO_2)$ = 13.6 ppm). Presumably, the high-field sulfonyl oxygen, shielded by the γ-gauche interactions between the sulfonyl oxygen and the C3,5 methines,[2] exists in the axial conformational array, as in sulfones **1** and **3**.

Table II. Oxygen-17 NMR Shifts, Ln·S Equilibrium Constants, and Binding Sensitivity Slopes

sulfone	sulfonyl oxygen	α (eq ax)[a]	K_3 (M^{-1})	$\delta^{17}O$[b]
11	eq	−459.0 ± 18	2.20 ± 0.12	155.0
	ax	−209.3 ± 8		142.1
12	eq	−534.6 ± 11	4.02 ± 0.11	149.8
	ax	−132.9 ● 3		136.4
13	eq	−452.3 ± 11	2.89 ± 0.17	153.4
	ax	−156.5 ± 9		144.1
16	eq	−119.7 ± 7	0.57 ± 0.04	157.8
	ax	−210.2 ± 7		150.0

[a] Induced shift extrapolated to [Eu(fod)$_3$] = [substrate]. [b] Extrapolated to [Eu(fod)$_3$] = 0.

The ^{17}O NMR parameters of a series of conformationally rigid *cis*-3,5-diphenyl-4-heterothiane 1,1-dioxides were also examined. For example, *cis*-3,5-diphenyltetrahydro-1,4-thiazine 1,1-dioxide (**11**) affords shifts at δ 140.6 and 155.1; *cis*-3,5-diphenyl-4-methyltetrahydro-1,4-thiazine 1,1-dioxide (**12**) exhibits shifts at δ 135.9 and 150.3, and the sulfonyl oxygens in *cis*-2,6-diphenyl-1,4-dithiane 4,4-dioxide (**13**) occur at δ 143.4 and 154.1. Again, by analogy with the ^{17}O NMR spectra of other conformationally homogeneous sulfones, it seems reasonable to suggest that the high-field sulfonyl oxygens are axial.

The most interesting feature of this work is the differential ^{17}O NMR LIS's of the diastereotopic sulfonyl oxygens in the *cis*-3,5-diphenyl-substituted sulfones (see Table II). When incremental quantities of $Eu(fod)_3$ are added to dichloromethane solutions of sulfones **11–13**, their ^{17}O resonances experience varying degrees of differential shielding where the axial oxygens are less responsive than the equatorial oxygens (see Figure 1). When the incremental shifts for each oxygen are plotted against the Ln^{3+}/substrate mole ratio, two slopes, α_1(eq) and α_1(ax) ppm, afford the LIS values expected from an equimolar solution of shift reagent and substrate. For **11**, α_1(eq) = 459.0 ppm and α_1(ax) = −209.3 ppm; for **12**, α_1(eq) = −534.6 ppm and α_1(ax) = −132.9 ppm; for **13**, α_1(eq) = −452.3 ppm and α_1(ax) = −156.5 ppm. The slopes, α_1, represent the relative sensitivities of axial and equatorial oxygens toward binding to Eu^{3+}. From these data, it is clear that Eu^{3+} binding to the equatorial sulfonyl oxygen is significantly stronger than Eu^{3+} binding to the axial sulfonyl oxygen.

An estimate of the actual binding constant between Eu^{3+} and methylazathiane **12** was obtained from a ^1H NMR shift study using the reciprocal method.[13] While this experiment could not provide individual association constants for each oxygen, it did afford a net binding constant between **12** and $Eu(fod)_3$ of 10.6 ± 1.8 M^{-1} (Figure 2). This comparatively low value[13] supports the assumption that 1:2 complexes do not form to a significant extent for the low Ln^{3+}/substrate ratios (≤0.3) employed here.

The ratio, α_1(eq)−α_1(ax), can be effectively translated into K_3 affording valuable dynamic information on the Eu^{3+}–sulfonyl oxygen complexes. The K_3's for **11–13** are 2.20, 4.02, and 2.89, respectively, and suggest that binding to the equatorial sulfonyl oxygen is favored. In fact, assuming that the Eu^{3+}–sulfonyl oxygen exchange is rapid on the NMR time scale and that equilbrium between the diastereomeric complexes is established almost instantaneously, these K_3's can be converted to ΔG°'s. The ΔG°'s

(13) Raber. D. J. The Nature of the LSR-Substrate Complex. In *Lanthanide Shift Reagents in Stereochemical Analysis*; Morrill, T. C., Ed.; VCH Publishers: New York, 1986.

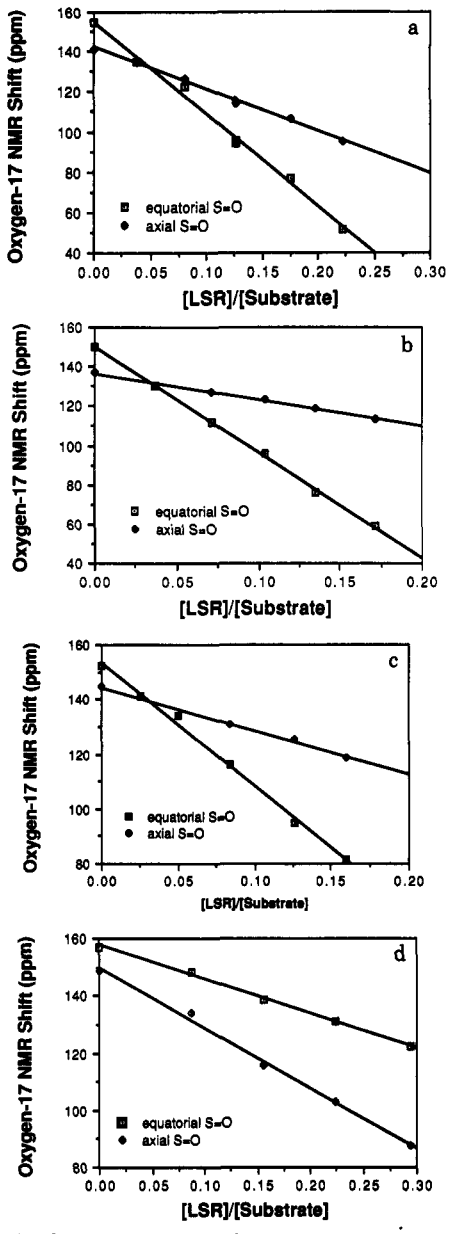


Figure 1. (a) Oxygen-17 LIS study on sulfone 11. (b) Oxygen-17 LIS study on sulfone 12. (c) Oxygen-17 LIS study on sulfone 13. (d) Oxygen-17 LIS study on sulfone 16.

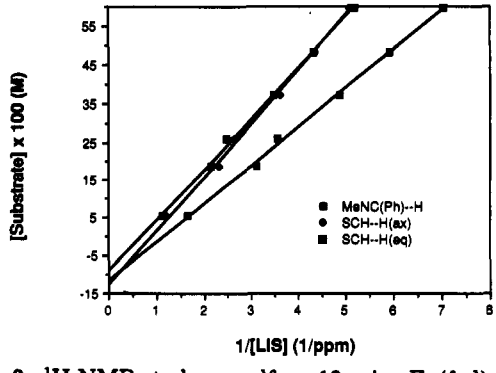
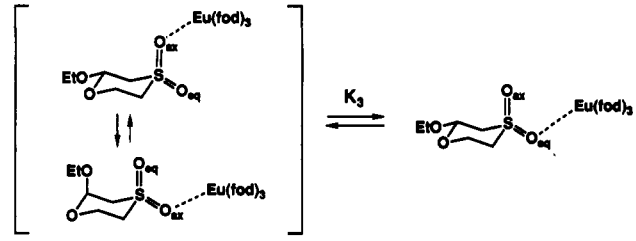


Figure 2. ^{1}H NMR study on sulfone 12 using Eu(fod)$_3$: Y-intercept = [LSR]Δ; slope = ([LSR] + K^{-1}); [LSR] = 0.013 M; Δ = bound shift.

for 11–13 indicate that the complex between the lanthanide and the equatorial sulfonyl oxygen (i.e., $-SO_{eq}-Eu^{3+}$) is more stable than $-SO_{ax}-Eu^{3+}$ by 0.48 kcal/mol for 11, 0.84 kcal/mol for 12, and 0.64 kcal/mol for 13. In the absence

Scheme II. Equilibria between the Major Eu(fod)$_3$ Complexes of Sulfone 16



of reliable structural information (i.e., MM2 or X-ray structural data) on these sulfones, comparative interpretation of these $\Delta G°$'s with emphasis on subtle structural variations may be premature. Nevertheless, earlier work on 4-hetero-1-thiadecalin 1,1-dioxides[14] does suggest that the percentage of axially bound Eu(fod)$_3$ complex increases as the the C–SO$_2$–C fragment of thiadecalin is flattened relative to the remainder of the ring. Consequently, the axial oxygen moves away from the 1,3-syn axial hydrogens and becomes increasingly more accessible to the shift reagent. This distortion involving the axial sulfonyl oxygen increases the availability for metal coordination and a reversal in binding selectivity to Eu(fod)$_3$ results. For example, 1-thiadecalin 1,1-dioxide (1) prefers binding to Eu(fod)$_3$ through the equatorial oxygen (K_3 = 1.62), while 1,4-oxathiadecalin 1,1-dioxide (14) and 2-(α-ethoxy)-1,4-oxathiadecalin 1,1-dioxide (15) prefer binding through their axial oxygens (K_3 = 0.89 and 0.68, respectively).

In an effort to determine whether this reversal of binding selectivity was observed in *monocyclic* oxathianes as well, the ^{17}O LIS's of 2-ethoxy-1,4-oxathiane 4,4-dioxide (16) were examined (vide supra; Figure 1d). Since the 2-ethoxy group prefers the equatorial position by ca. 0.8–1.0 kcal/mol,[15] the axial sulfonyl oxygen is reasonably assigned the ^{17}O NMR resonance at δ 149.0 and the equatorial sulfonyl oxygen appears at δ 157.1 ($\Delta\delta(SO_2)$ = 8.1 ppm) as compared to $\Delta\delta(SO_2)$ = 12.6 ppm for sulfone 15 and $\Delta\delta(SO_2)$ = 10 ppm for sulfone 3. For sulfone 16, the axial oxygen showed the greater sensitivity to Eu(fod)$_3$ (α_1(ax) = −210.2 ppm; α_1(eq) = −119.7 ppm). The equilibrium constant, K_3, between the axial and equatorial oxygen Eu^{3+} complexes of sulfone 16 was 0.57, favoring $-S{=}O_{ax}-Eu^{3+}$. This agrees well with the K_3's for oxathiadecalin sulfones 14 and 15 and is radically different from K_3 for sulfone 1. Molecular modeling studies using MM2[16] were employed to determine whether this binding selectivity could arise from differences in steric variations. The C_3–C_2–O–C_6 (C_9) torsional angles, ϕ, in sulfones 14–16 are similar and fairly large (in 14, ϕ = 69.9°; in 15, ϕ = 70.8°; in 16, ϕ = 71.2°), while the corresponding ϕ in sulfone 1 is significantly diminished (C_2–C_3–C_4–C_{10} in 1, ϕ = 62.4°). Sulfones 14–16 respond to ring puckering by increasing the flattening about the sulfonyl group, and this appears to lead to an increased preference for axial binding. However, the equilibria between sulfone 16 and Eu(fod)$_3$ may be complicated by the presence of ca. 15–20% of the other chair conformer or a twist-boat form.[15] The conformer where the ethoxy group is axial or pseudoaxial can also bind to Eu^{3+} through the least hindered equatorial (or pseudoequatorial) sulfonyl oxygen, so at least three complexes may contribute to K_3 (Scheme II).[17] Thus, while this technique

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(15) (a) Lee, D.; Keifer, J. C.; Rooney, R. P.; Garner, T. B.; Evans, Jr., S. A. *J. Org. Chem.* **1979**, *44*, 2580. (b) Harris, D. L.; Evans, Jr., S. A. *J. Org. Chem.* **1982**, *47*, 3355.
(16) Allinger, N. L.; Yuh, Y. H. *QCPE* **1980**, *11*, 395.

can be applied to flexible systems, the results must be interpreted with some caution since organosulfones capable of possessing small conformational interchange through relatively low energy barriers may be uniquely influenced by $Eu(fod)_3$ complexation.

It is conceivable that the endocyclic heteroatoms (S, N, or O) in these 4-heterothianes may also ligate to Eu^{3+}; however, our ^{17}O NMR shift data suggest that such contributions are probably very minor. For example, when an LIS study was performed on sulfone **14**, no shift in the ethereal resonance (δ 31.8) was observed.[14] The steric proximity of the C-3,5 phenyl groups in **11–13** should discourage Eu^{3+} binding to the endocyclic heteroatom (X = NH, NCH_3, or S).

In summary, we have demonstrated the utility of $Eu(fod)_3$ coupled with ^{17}O NMR in studying the propensity of $Eu(fod)_3$ to bind and distinguish between diastereotopic sulfonyl oxygens in solution. Further, we have demonstrated that ^{17}O NMR spectroscopy, when coupled with lanthanide shift reagents, is a useful probe for identifying subtle structural variations in conformationally homogeneous organosulfur compounds.

Experimental Section

Samples, in 10-mm (o.d.) NMR tubes, were prepared for ^{17}O NMR studies by dissolving 300–500 mg of the organosulfur compound in 3 mL of anhydrous dichloromethane (CH_2Cl_2) or acetonitrile (CH_3CN) solvent. Spectra were initially recorded over a sweep width of 100 kHz, but ultimately the sweep width was reduced to 24 kHz for the lanthanide-shift determinations. The number of transients required for reliable data presentation ranged from 3×10^4 to 3×10^5. All ^{17}O NMR shifts were recorded at 32 ± 2 °C and referenced to the ^{17}O NMR shift of external tap water ($H_2{}^{17}O$ = δ 0.00). ^1H and ^{13}C NMR spectra were obtained at 20–25 °C from deuteriochloroform ($CDCl_3$) solutions containing 25–50 mg of sample in a 5-mm (o.d.) NMR tube.

Lanthanide-Induced-Shift (LIS) Studies. The LIS ^{17}O NMR studies involved the initial measurement of the ^{17}O NMR shifts of 0.40 ± 0.02 M CH_2Cl_2 solutions of sulfones **11–13** and of a 0.14 M solution of **16** in the absence of the lanthanide-shift reagent (LSR), tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyloctane-3,5-dionato)europium [$Eu(fod)_3$]. Weighed increments of $Eu(fod)_3$ were added to the solutions and allowed to dissolve, and new ^{17}O NMR shifts were obtained. This process was repeated until at least six data points characterizing differing LSR concentrations were acquired for each of the sulfones. The ^{17}O NMR shifts were then plotted against the $Eu(fod)_3$–substrate mole ratio, and the linear dependence of ^{17}O NMR shifts of the diastereotopic sulfonyl oxygens versus the LSR concentration was established through linear least-squares analyses. For each conformationally homogeneous sulfone, at least one ^{17}O NMR spectrum exhibited overlapping ^{17}O NMR resonances in the presence of $Eu(fod)_3$.

The ^1H NMR LIS study involving sulfone **11** was accomplished by adding weighed increments of sulfone **11** to a deuteriochloroform ($CDCl_3$) solution (1 mL) of $Eu(fod)_3$ (13 mg). The LIS involving the ring ^1H NMR resonances were the major focus of this study, and they were determined by comparing the observed shifts (δ_i) of the target hydrogens with those of sulfone **11** in the absence of LSR (δ_0) for each determination (LIS = $\delta_i - \delta_0$), and the reciprocals of the LIS for each ^1H NMR resonance were then plotted against the substrate concentration S_0. The impact of the bound shift (Δ) on each hydrogen as well as the binding constant between $Eu(fod)_3$ and sulfone **11** can be determined from a least-squares fit to[13]

$$S_0 = L_0\Delta(\mathrm{LIS})^{-1} - (L_0 + K^{-1}) \qquad (11)$$

(17) Steric encumbrance to axial binding of $Eu(fod)_3$ to sulfone **16** when the ethoxy group is axial is expected to be large, disfavoring formation of this complex.

Syntheses of the Organosulfur Compounds. The preparations of organosulfur compounds **1–7** and **14–16** have been previously described.[1e,3,5,6,15,18] The other cyclic organosulfur compounds described in this report were synthesized using published procedures, and they are described below.

***trans*-2,6-Diphenyltetrahydrothiopyran-4-one (8).** Hydrogen sulfide gas was bubbled into a refluxing solution of sodium acetate (15 g, 0.17 mol) and 1,5-diphenyl-1,4-pentadien-3-one[19] (dibenzylideneacetone; 5.0 g, 0.02 mol) in 80 mL of 95% ethanol. The solution was cooled, separated from any resinous material that was formed, and then placed a refrigerator for 1 day to allow for crystallization of *trans*-2,6-diphenyltetrahydrothiopyran-4-one. The resulting solid was collected by filtration and dried to afford (4.0 g, 70%) of thiopyran-4-one **8**. Recrystallization of **8** from petroleum ether (bp 60–80 °C) gave homogeneous material: mp 234–235 °C (lit.[19] mp 234–235 °C); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 208.6 (*C*=O), 140.4, 128.7, 127.7, 127.5 (C_6H_5), 48.6 (C_2, C_6), 43.9 (C_3, C_5).

***trans*-2,6-Diphenyltetrahydrothiopyran-4-one 1,1-Dioxide (9).** Excess 30% hydrogen peroxide was added slowly to a solution of *trans*-2,6-diphenyltetrahydrothiopyran-4-one (2.0 g, 0.0075 mol) in acetic acid (20 mL) with constant shaking until the solution became turbid. The resulting solution was maintained at ambient temperature for 3 days and diluted with water. Sulfone **9** was collected by filtration and recrystallized from a benzene–petroleum ether (bp 60–80 °C) mixture to afford homogeneous **9** (1.7 g, 70%): mp 87–88 °C (lit.[19] mp 88 °C).

***cis*-2,6-Diphenyltetrahydrothiopyran-4-one 1,1-Dioxide (10).** *cis*-2,6-Diphenyltetrahydrothiopyran-4-one was oxidized with 30% hydrogen peroxide employing the method previously described for the preparation of sulfone **9**. Crude dioxide **10** was obtained in >99% yield, and recrystallization from a benzene–petroleum ether (bp 40–60 °C) solution afforded homogeneous material: mp 193 °C (lit.[19] mp 196 °C); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.3–7.5 (m, 10 H, C_6H_5), 4.53 (dd, 2 H, C-2,6 C*H*), 3.72 (t, 2 H, C-3,5 CH_2), 2.94 (d, 2 H, C-3,5 CH_2).

3,5-Diphenyltetrahydro-1,4-thiazine 1,1-Dioxide (11). A mixture of sulfonyldiacetic acid (2.0 g, 0.011 mol), benzaldehyde (30 g, 0.028 mol), and ammonium acetate (900 mg, 12.0 mmol) in glacial acetic acid (10 mL) was refluxed for 0.25 h. The exothermic release of carbon dioxide followed by a change of coloration to brownish yellow indicated the completion of the reaction. The reaction mixture was cooled to ambient temperature then extracted with 30 mL of diethyl ether. Dry hydrogen chloride gas was bubbled through the ethereal solution and thiazine hydrochloride precipitated. The solid material was collected by filtration and then washed with ether and dried to afford crude **11**·HCl (1.2 g, 34%). Recrystallization from an ethanol–ether mixture gave homogeneous **11**·HCl mp 268–270 °C dec. Dissolution of **11**·HCl in aqueous ammonia followed by dilution with water gave crude dioxide **11**, which was recrystallized from ethanol to give homogeneous material: mp 202–203 °C (lit.[20] mp 205–206 °C); ^{13}C NMR (CH_2Cl_2, 67.5 MHz) δ 143.3, 131.6, 131.1, 129.4 (C_6H_5), 61.7 (C_3, C_5), 61.0 (C_2, C_6); ^1H NMR ($CDCl_3$, 250 MHz) δ 7.25–7.45 (m, 10 H, C_6H_5), 4.40 (dd, 2 H, C-3,5 C*H*), 3.10–3.21 (m, 4 H, C-2,6 CH_2), 2.15 (s, 1 H, N*H*).

3,5-Diphenyl-4-methyltetrahydro-1,4-thiazine 1,1-Dioxide (12). A mixture containing sulfonyldiacetic acid (2.7 g, 0.015 mol), a 25% aqueous methylamine solution (1.4 mL), and benzaldehyde (3.2 g, 0.03 mol) was refluxed in glacial acetic acid (5 mL) for 1.5 h. The reaction mixture was cooled to ambient temperature and extracted with diethyl ether (50 mL). Dry hydrogen chloride gas was passed through the ether solution, and the solution was allowed to stand overnight. The hydrochloride of **12** that separated (700 mg, 14%) was isolated by filtration, washed with dry ether, and recrystallized from an ethanol–ether mixture, mp 255–257 °C. Dissolution of **12**·HCl in ethanol followed by the addition of liquid ammonia then water gave crude **12**, which was subsequently recrystallized from ethanol to afford homogeneous **12**: mp 178–179 °C (lit.[20] mp 178–179 °C); ^{13}C NMR (CH_2Cl_2,

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67.5 MHz) δ 143.7, 131.6, 130.8, 129.8 (C_6H_5), 69.6 ($CHNCH_3$), 59.8 (CH_2SO_2).

2,6-Diphenyl-1,4-dithiane 4,4-Dioxide (13). Hydrogen sulfide gas was passed into a refluxing solution of bisstyryl sulfone (10 g, 0.04 mol) and sodium acetate (10 g, 0.13 mol) in 90% ethanol (200 mL) for 2 h. The reaction mixture was poured into water, and the separated solid material was removed by filtration, washed with water, and recyrstallized from benzene to afford dioxide 13: mp 186 °C (lit.[21] mp 184-85 °C); ^{13}C NMR (CH_2Cl_2, 67.5 MHz) δ 140.2, 131.6, 131.2, 129.9 (C_6H_5), 60.5 (C_2, C_6), 48.5 (C_3, C_5); ^1H NMR ($CDCl_3$, 250 MHz) δ 7.29-7.47 (m, 10 H, C_6H_5), 4.67 (dd, 2 H, C-3,5 C*H*), 3.60 (m, 4 H, $(J_{AX} + J_{BX}) = 14.2$ Hz, C-2,6-CH_2).

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Registry No. 1, 71989-44-1; 2α, 67530-09-0; 2β, 70561-54-5; 3, 91146-68-8; 4α, 67512-93-0; 4β, 67530-08-9; 5, 34009-06-8; 6, 95158-93-3; 7, 17200-23-6; 8, 18456-45-6; 9, 34379-72-1; 10, 27798-81-8; 11, 135228-17-0; 11·HCl, 135228-20-5; 12, 135228-18-1; 12·HCl, 135228-21-6; 13, 135228-19-2; 14, 62015-76-3; 15, 131814-30-7; 16, 82338-32-7; 1,5-diphenyl-1,4-pentadien-3-one, 538-58-9; *cis*-2,6-diphenyltetrahydrothiopyran-4-one, 18456-44-5; sulfonyldiacetic acid, 123-45-5; benzaldehyde, 100-52-7; bisstyryl sulfone, 4973-50-6; hydrogen sulfide, 7783-06-4.

Indolizines. 5. Preparation and Structural Assignments of Azaindolizinols

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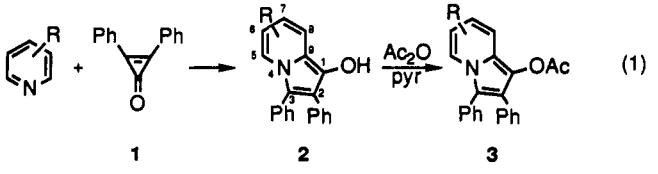
Diphenylcyclopropenone reacts smoothly with a variety of aromatic N-heterocycles to provide aza- and benzazaindolizinols. Although known in the literature, these compounds had been assigned incorrect structures. The preparation and physical properties of a number of derivatives, along with unequivocal assignments of structure based on a variety of NMR techniques, is described herein.

Introduction

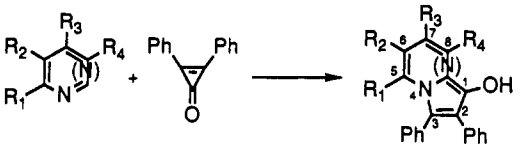
In our papers describing the preparation of 1- and 3-indolizinols and their esters from a variety of pyridines and cyclopropenones,[1,2] we observed that the literature had misassigned the structure of **2** (eq 1, R = H) as a 3-indolizinol.[3,4] Since the structural assignments of many related compounds were subsequently based on the incorrect assignment of **2** as a 3-indolizinol, we felt that a careful reexamination of the structural assignments from the older indolizinol literature using modern NMR techniques was imperative.



(1)

1 **2** **3**

For ease of discussion, and in order to facilitate comparisons of the cyclopropenone/pyridine adducts (indolizinols) with the cyclopropenone/N-aromatic adducts presented herein, the products containing more than one nitrogen in the six-membered ring will be referred to as azaindolizinols and numbered as simple indolizinols (eq 2). Similarly, the adducts derived from bicyclic aromatic



(2)

N-heterocycles will be designated as benzoindolizinols or benzazaindolizinols. The IUPAC numbering and designations for all new compounds are found in the Experimental Section.

In attempts to reproduce the literature azaindolizinols, we were often unable to obtain materials with physical or spectral constants compatible with those described.[3] Since our previous experience has shown that the corresponding esters or ethers of indolizinols are more stable and more crystalline than the free alcohols,[2] we prepared the esters or ethers of the corresponding azaindolizinols (Table I). The use of a nonhydroxylic solvent (method 2, Experimental Section) allowed the direct preparation of the esters in a one-pot operation. Typically, equimolar amounts of diphenylcyclopropenone, **1**, and the appropriate aromatic N-heterocycle were dissolved in dioxane, heated to reflux under argon until the 1850 cm^{-1} IR band of **1** disappeared, and acetylated with a mixture of acetic anhydride/pyridine to yield the azaindolizinol acetates. The corresponding ethers were prepared via the original literature method by treatment of the isolated azaindolizinols with triethyloxonium tetrafluoroborate.[3] In order to demonstrate that the choice of solvent was not a factor in determining the regiochemical outcome of addition products, the free alcohols **7**, **10**, **13**, **15**, and **20** were prepared both in methanol and dioxane and subsequently acetylated to obtain the

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