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CONFORMATIONAL PREFERENCE OF THE S=O GROUP .3. CONTINUED EVIDENCE FOR A VERY STRONG S-S=O ANOMERIC INTERACTION FROM THE NMR SPECTROSCOPIC STUDY OF 4,4,5,5-TETRAMETHYL-1,2--DITHIANE 1-OXIDE.[1]

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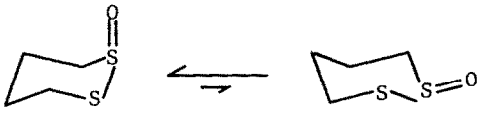
Abstract - The ^{1}H and ^{13}C NMR behavior of the title compound (4) was studied in order to determine the conformational preference of the S=O group in this heterocycle. The NMR spectra were assigned by a combination of homo- and heteronuclear double irradiation, as well as nuclear Overhauser enhancement experiments. From the results of variable temperature, solvent effects and shift reagent experiments, it is concluded that the axial conformer dominates the equilibrium to such an extent that no contribution of the equatorial isomer is recorded. This result suggest that ΔG° (4-ax $\rightleftharpoons$ 4-eq) $\geq$ 1.7 kcal/mol, and because the axial conformer suffers from a syn-diaxial Me/S=O interaction, a $\Delta G^{\circ} \geq 3.0$ kcal/mol for the conformational equilibrium in the parent 1,2-dithiane mono-S-oxide (1) can be extrapolated. Some discussion of the possible mechanism responsible for such strong anomeric effect is presented.

Introduction.

Thiosulfinates, RSS(O)R, are well-known compounds of current interest.[2] Natural products containing the thiosulfinate moiety have also been reported,[3-6] e.g. allicin, the antibacterial principle of garlic.[3] Of particular interest are the biological activities of some of these compounds.[3-5,7] Thiosulfinates may also be formed on oxidation of proteins containing cystine residues.[2,6] The biochemical consequences of such oxidation by atmospheric pollutants may be important. This paper presents evidence for a previously unrecognized stereoelectronic effect in thiosulfinate groups.

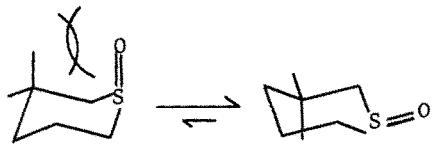
In this respect, 1,2-dithiane-1-oxide (1) has been found to show a great preference for the axial conformer[8-11] (Equation 1).



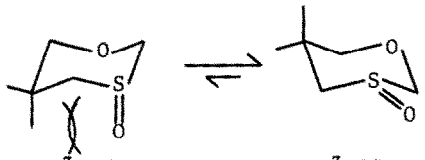
1-ax 1-eq (1)

In fact, the equilibrium 1-ax $\rightleftharpoons$ 1-eq is so much tilted to the left that the participation of the equatorial isomer is too small to permit a quantitative measure-

ment of the equilibrium constant. However, it has been suggested by Lambert, et al.,[12] that a syn-diaxial $CH_3/S{=}O$ repulsive interaction in 3,3-dimethylthiane oxide (2; Equation 2) is worth at least 1.9 kcal/mol, although a smaller value of 1.3 kcal/mol for such an interaction was found by van Acker and Anteunis[13] in 5,5-dimethyl-1,3-oxathiane mono-S-oxide (3; Equation 3).

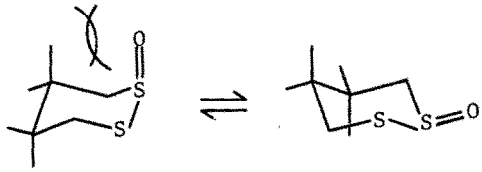


2-ax 2-eq (2)



3-ax 3-eq (3)

In this paper we describe the NMR spectroscopic analysis of 4,4,5,5-tetramethyl-1,2-dithiane-1-oxide (4), prepared[1] with the idea that the syn-diaxial $CH_3/S{=}O$ interaction present in 4-ax would produce an equilibrium closer to unity in equation 4, therefore allowing a more precise determination of the conformational preference of the S=O group in 4, and, indirectly, in 1.



4-ax 4-eq (4)

Results.

A. Assignment of the ^1H NMR spectrum of 4.

Figure 1 shows the 250 MHz proton spectrum of 4. In addition to four distinct singlets for the diastereotopic methyl groups, two doublet of doublets are observed. These AB patterns, ascribable to the methylene groups, differ substantially in shape: one of them, centered at 3.05 ppm, shows $\Delta\delta$ = 1.45 ppm, whereas the other has $\Delta\delta$= 0.05 ppm.

The very large difference in chemical shifts for the hydrogens in one of the methylene groups ($\Delta\delta$ = 1.45 ppm) can only be reasonably attributed to a predominantly axial conformation in 4, in which H(3ax) experiences a strong deshielding effect by the syn-diaxial sulfinyl group.[14] The resonance at δ= 3.78 ppm is therefore assigned to H(3ax); irradiation of this signal caused the collapse of the doublet at 2.32 ppm into a singlet, which is then ascribed to H(3eq).

Subsequent assignment of the proton spectrum was facilitated by the high-resolution observation of a long-range W-coupling constant between H(3ax) and the methyl signal at δ = 1.14 ppm. Indeed, irradiation of this methyl signal resulted in the loss of the small coupling in the doublet of quartets at 3.78 ppm (J_{gem} = = 14.51 Hz; J_W = 0.84 Hz. See Figure 1). The chemical shift of 1.14 ppm is then ascribed to the axial methyl group at C(4) in 4-ax; the hydrogen atoms in this substituent are the only ones that can adopt a W orientation with H(3ax).

The same line of reasoning allowed for the identification of H(6ax) and H(6eq). At high resolution the long-range coupling between the higher-field half

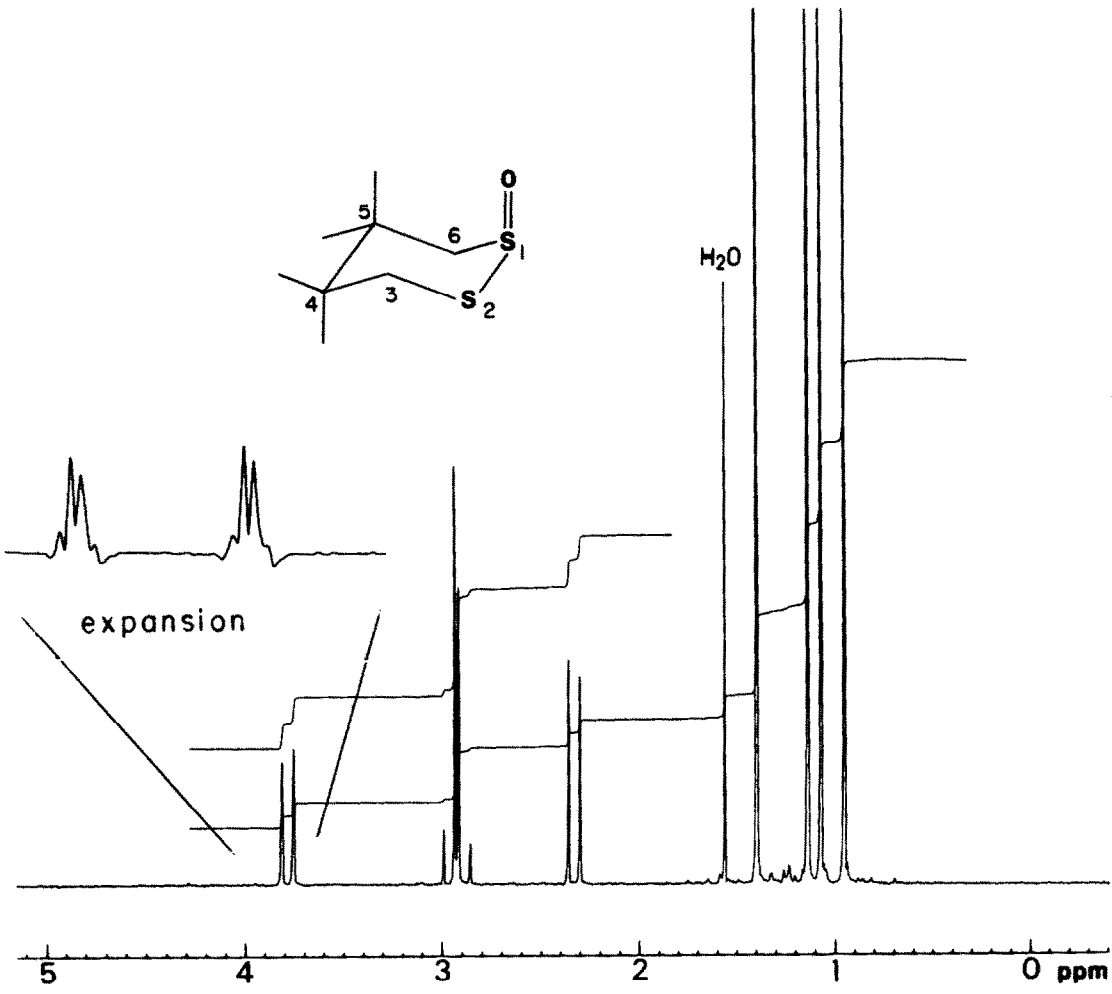


Figure 1. The observed 250-MHz proton spectrum of 4,4,5,5-tetramethyl-1,2-dithiane mono-S-oxide (4) in $CDCl_3$ at 22°C, and expansion showing the long-range W coupling of H(3ax) with the axial methyl group at C(4).

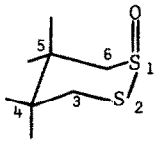
of the AB pattern, centered at 2.90 ppm, and the methyl group at 1.39 ppm [syn-diaxial to the S=O group, and therefore identified as axial CH_3-C(5)] are related by a 0.62 Hz coupling constant. Again, irradiation of the methyl at 1.39 ppm resulted in loss of the W-coupling for the doublet of quartets at 2.90 ppm, which collapsed into a doublet with J_{gem} = 14.09 Hz. This signal was therefore assigned to H(6ax), and the doublet at δ = 2.95 ppm was then attributed to H(6eq).

At this point, the last two signals to be assigned in the ^{1}H NMR spectrum of 4 are the methyl singlets at 0.95 and 1.07 ppm. These resonances were identified by means of nuclear Overhauser enhancement (NOE) techniques. In particular, subtraction of the free induction decay (FID) spectrum with irradiation of a particular methyl signal from the FID in the absence of such irradiation, followed by Fourier transformation afforded the desired NOE effects. It was then observed that irradiation of axial CH_3-C(5) (δ = 1.39 ppm) produced NOEs in the three remaining methyl signals, with relative magnitudes δ0.95 > δ1.07 > δ1.14 ppm. Since the NOE is inversely proportional to the distance between nuclei,[15] it is apparent that the signal at δ 0.95 ppm must correspond to the methyl group geminal to the one under irradiation; i.e., equatorial CH_3-C(5). By the same argument, the relative effect experienced by the signal at 1.07 ppm agrees for the gauche-oriented methyl:

equatorial CH_3-C(4). In a confirmatory experiment, irradiation of equatorial CH_3-C(5) at 0.95 ppm caused NOEs in the order δ 1.39 > δ 1.07 > δ 1.14; i.e., NOE at geminal methyl larger than NOE at gauche methyls.

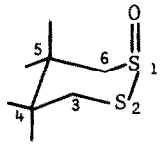
Tables I and II summarize the chemical shifts and coupling constants in the proton NMR spectrum of 4.

Table I. 250 MHz ^1H NMR Chemical Shifts (ppm) for 4 in $CDCl_3$ and Benzene-d_6.



Nuclei	Solvent: $CDCl_3$	C_6D_6
H(3ax)	3.78	3.56
H(3eq)	2.32	1.66
axial CH_3-C(4)	1.14	0.69
equat CH_3-C(4)	1.07	0.55
axial CH_3-C(5)	1.39	1.25
equat CH_3-C(5)	0.95	0.40
H(6ax)	2.90	2.18
H(6eq)	2.95	2.26

Table II. Coupling Constants for the Hydrogens in 4.



Coupled Nuclei	J (Hz)
H(3ax)/H(3eq)	14.5
H(3ax)/ax CH_3-C(4)	0.8
H(3eq)/H(3ax)	14.5
ax CH_3-C(4)/H(3ax)	0.8
ax CH_3-C(5)/H(6ax)	0.6
H(6ax)/H(6eq)	14.1
H(6ax)/ax CH_3-C(5)	0.6
H(6eq)/H(6ax)	14.1

B. Assignment of the ^{13}C NMR Spectrum of 4.

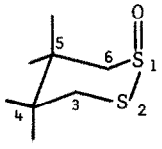
Seven signals are recorded in the broad-band proton decoupled 62.9 MHz carbon spectrum of 4. Off-resonance as well as attached proton test (APT)[16] experiments confirmed the preliminary assignment (based on signal intensities and anticipated shifts) as follows: δ 22.64, 25.03, 25.03 and 26.52 are the methyl carbons; δ 34.18 and 36.36 are the quaternary carbons; δ 34.54 and 59.42 ppm correspond to the methylenic carbons. A more specific classification was then achieved by $^{13}C\ \{^1H\}$ heteronuclear double resonance experiments, taking advantage of the fact that the proton signals had been completely identified (vide supra).

Indeed, when the methyl signal at δ 0.95 ppm was irradiated in the proton NMR region, the off-resonance carbon spectrum of 4 suffered a change at δ 22.64 ppm; this quartet became a singlet and was therefore identified as the equatorial methyl at C(5). By the same token, sequential irradiation in the proton region of the methyl signals at δ 1.39, 1.07 and 1.14 ppm caused the quartets at δ 25.03, 25.03 and 26.52 ppm to coalesce into singlets, allowing for the assignment of these signals as axial CH_3-C(5), equatorial CH_3-C(4), and axial CH_3-C(4), respectively.

Finally, irradiation in the proton region of the signals at δ 2.93 ppm caused the triplet at δ 59.42 ppm in the off-resonance carbon spectrum to transform into a singlet, while irradiation of either signal at δ 2.32 or 3.78 ppm transformed the triplet at δ 34.54 ppm into a doublet. These observations permit the assignment of the carbon signal at δ 59.42 ppm as C(6), and δ 34.54 as C(3).

The quaternary carbons at δ 34.18 and 36.36 ppm were ascribed to C(5) and C(4), respectively, in view of the known[8] shielding effect by a β-sulfinyl group. Nevertheless, the relatively small difference in chemical shifts ($\Delta\delta$ = 2.18 ppm) found here suggests a weaker than normal shielding contribution.[8,17] Table III contains the chemical shifts observed for the carbon atoms present in 4.

Table III. ^{13}C NMR Data for Monosulfoxide 4 in CD_2Cl_2, at 62.9 MHz.

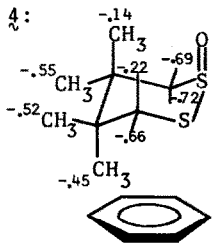


Carbon	T(°C):	22[a]	0	-20	-40	-60	-80
C(3)		34.54	34.42	33.95	33.55	33.16	32.82
C(4)		36.36	36.41	36.10	35.83	35.58	35.33
C(5)		34.18	34.27	33.95	33.77	33.57	33.34
C(6)		59.42	59.42	58.80	58.30	57.80	57.33
axial $\underline{C}H_3$-C(4)		26.52	26.44	26.22	26.00	25.81	25.57
equat $\underline{C}H_3$-C(4)		25.03	24.96	24.72	24.51	24.31	24.08
axial $\underline{C}H_3$-C(5)		25.03	24.96	24.72	24.51	24.31	24.08
equat $\underline{C}H_3$-C(5)		22.64	22.54	22.29	22.07	21.87	21.62

[a] In $CDCl_3$

C. Conformation of 4.

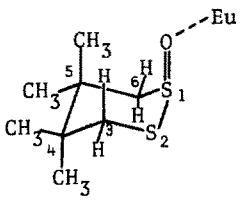
Comparison of the ^1H NMR chemical shifts for 4 in $CDCl_3$ and in benzene-$\underline{d}_6$ (Table I) shows that most signals are significantly shifted upfield in C_6D_6, by an average of ca. 0.6 ppm.[18] The only signals that remain relatively unchanged are those due to H(3ax) and axial CH_3-C(5). These induced shifts (Δ ASIS) clearly indicate the formation of a collision complex[19,20] between the aromatic solvent and the axial conformer of sulfoxide 4:



Further evidence in support of the predominance of the axial conformation of 4 was obtained from its ^{1}H NMR spectrum after the sequential addition of Eu(fod)$_3$ in CD_2Cl_2 (Table IV). The lanthanide-induced shifts (LIS) decreased in the order H(6eq) ≈ H(3ax) >> H(3eq) ≈ H(6ax) >> equat CH_3C(5) ≈ equat CH_3-C(4) ≈ axial CH_3C(5) >> axial CH_3-C(4), which suggests the complex as shown below for 4.

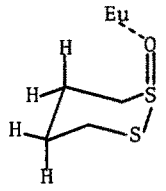
Table IV. Lanthanide-Induced Shifts (LIS) (δ) on the ^{1}H NMR (250 MHz) Spectrum of 4 after the Addition of Eu(fod)$_3$ in $CDCl_3$ at 22°C.

Eu(fod)$_3$,equiv.	H_{3ax}	H_{3eq}	H_{6ax}	H_{6eq}	Me_{4ax}	Me_{4eq}	Me_{5ax}	Me_{5eq}
0	3.78	2.32	2.90	2.95	1.14	1.07	1.39	0.95
0.08	4.78	2.76	3.32	4.00	1.10	1.33	1.45	1.24
0.19	5.99	3.28	3.82	5.26	1.10	1.65	1.82	1.59
0.35	7.69	4.00	4.52	7.04	1.09	2.08	2.35	2.10
Δδ	3.91	1.68	1.62	4.09	-0.05	1.01	0.96	1.15



4·Eu(fod)$_3$

vs.



1·Eu(fod)$_3$

This complex differs from the one with the unsubstituted 1,2-dithiane mono-S-oxide (1), in which the europium Lewis acid is situated inside the ring.[11] This isomeric form would be congested in the tetramethyl analogue due to steric interaction with the axial methyl at C(5). Surprisingly however, the LIS data for the carbon NMR spectra show that axial $\underline{CH_3}$-C(5) is significantly affected by the complexation to Eu(fod)$_3$ (Table V).

Table V. Lanthanide-Induced Shifts (LIS) (δ) on the ^{13}C NMR (62.9 MHz) Spectrum of 4 after the Addition of Eu(fod)$_3$ in $CDCl_3$ at 22°C.

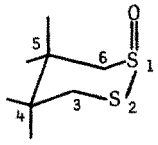
Eu(fod)$_3$ equiv.	C(3)	C(4)	C(5)	C(6)	Me_{4ax}	Me_{4eq}	Me_{5ax}	Me_{5ax}
0	34.60	36.36	34.25	59.47	26.55	25.05	25.05	22.67
0.01	34.71	a	34.30	59.53	26.59	25.07	25.18	22.72
0.04	34.95	36.77	34.48	59.65	26.65	25.13	25.42	22.79
0.08	35.24	37.18	34.66	59.78	26.71	25.25	25.76	22.90
0.10	35.54	37.37	34.83	59.95	26.77	25.35	26.07	23.01
Δδ	0.94	1.01	0.58	0.48	0.22	0.30	1.02	0.34

[a]Obscured by the baseline noise.

In an attempt to observe different signals for the individual conformers in 4-axial ⇌ 4-equatorial, the spectra were recorded at -80°C in CD_2Cl_2. The proton spectrum (Table VI) is the same at this temperature and room temperature (Δδ for all hydrogens ≤0.1 ppm), and the carbon spectra are also little changed at low

temperature (Table III). This, together with the additional information collected, indicates that the participation of 4-equatorial in the equilibrium is not significant: K in equation 4 ≥ 95/5: $\Delta G° \geq 1.7$ kcal/mol. Because the Me/S=O syn-diaxial interaction present in 4-ax amounts to at least 1.3 kcal/mol,[12,13] the conformational free energy difference in the equilibrium 1-ax ⇌ 1-eq is estimated as $\Delta G° \geq 3.0$ kcal/mol.

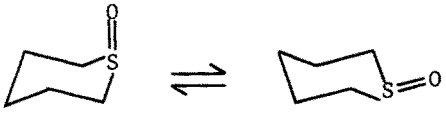
Table VI. Low-Temperature 250 MHz ^{1}H NMR Chemical Shifts (ppm) for 4 in CD_2Cl_2.



Temperature (°C)	H(3ax)	H(3eq)	H(6ax)	H(6eq)	axial CH_3-C(4)	equat CH_3-C(4)	axial CH_3-C(5)	equat CH_3-C(5)
0	3.75	2.35	2.89	2.96	1.13	1.06	1.36	0.94
-20	3.74	2.33	2.88	2.95	1.11	1.04	1.34	0.92
-40	3.72	2.32	2.87	2.93	1.09	1.02	1.31	0.90
-60	3.70	2.31	2.86	2.93	1.06	1.00	1.29	0.88
-80	3.68	2.29	2.84	2.91	1.03	0.97	1.26	0.85
Δδ	0.07	0.06	0.05	0.05	0.10	0.09	0.10	0.09

Discussion.

The classical papers of Johnson and Martin showed, almost 25 years also, that the S=O group in thiane oxide (5) prefers an axial arrangement.[21] A quantitative determination of the equilibrium depicted in equation 5 was accomplished by Lambert and Keske,[22] suggesting a conformational free energy difference of 0.175 kcal/mol.

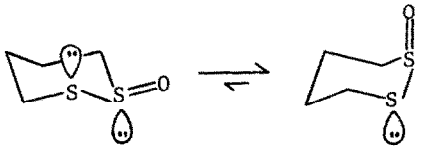


5-ax 5-eq (5)

Replacement of an α methylene in 5 by sulfur (5 → 1) results in a much greater preference for the axial conformer; indeed, a lower value of $\Delta G° \geq 1.7$-2.0 kcal/mol has been proposed for the conformational equilibrium in equation 1.[8-11] The new lower limit determined in this report [$\Delta G°$ (4-ax ⇌ 4-eq) ≥ 3.0 kcal/mol] indicates that the axial preference of the S=O group in 1,2-dithiane mono-S-oxide 1 is at least ca. 20 times greater than in thiane oxide 5. Such an augmented effect in thiosulfinate 1 (and 4) cannot be explained solely on the basic of the attractive van der Waals interaction proposed[12,21a,23] to account for the predominance of 5-ax over 5-eq.

It is suggested that stereoelectronic effects contribute to the unusual stability of 1-ax relative to 1-eq. One such effect is the well-known "anomeric effect" in which electronegative substituents prefer the axial configuration at C(1) of pyranoses due to stabilization by lone pair-σ^*_{C-X} interaction with this anti-

periplanar arrangement of lone pair orbital on oxygen and the axial C-X bond.[24] Such interaction is possible in 1-ax, but not 1-eq as seen in the drawings of equation 6 . In addition to this effect, the destabilizing antiperiplanar arrangement of lone pairs in 1-eq and stabilizing antiperiplanar arrangement of lone pair on the sulfoxide sulfur atom and the C-S bond in 1-ax, which permits lone pair σ^*(C-S) interaction, are expected to be important factors.[25] While the relative importance of each of these stereoelectronic factors needs to be assessed there is no question that stereoelectronic effects contribute to the remarkable stability of 1-ax.



(6)

Experimental.

The compound subject of this study, 4,4,5,5-tetramethyl-1,2-dithiane mono-S--oxide was prepared as described in a separate report.[1]

The ^1H and ^{13}C NMR spectra were recorded on a Bruker WM-250 spectrometer at 250 and 62.9 MHz, respectively, and are reported in ppm from internal tetramethylsilane (TMS) on the δ scale.

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17. A carbon-carbon connectivity NMR (INADEQUATE) experiment designed to confirm the assignment of C(4) and C(5) failed in our hands due to the limited availability of compound 4.
18. The assignment of the methyl groups was not as rigorously done as in $CDCl_3$ solvent (see Section 4); however, mixtures of $CDCl_3$ with increasing amounts of C_6D_6 show comparably gradual shifts, so as to make a change in the relative order unlikely.
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