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FORCE FIELD AND MULTINUCLEAR NMR STUDY OF THE CONFORMATIONAL PROPERTIES OF THIOLANE-1-OXIDE AND ITS MONO AND DIMETHYL DERIVATIVES

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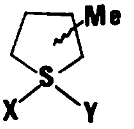
Abstract. Force field calculations and ^{1}H, ^{13}C and ^{17}O NMR data are reported for thiolane S-oxide and several of its mono and dimethyl derivatives. For comparison carbon-13 and oxygen-17 chemical shifts of the corresponding S-dioxides are also reported. According to force field calculations and NMR data the conformation of S-oxides depends on the number and on the position of ring substituents. Oxygen-17 chemical shifts of thiolane S-oxides are apparently not very sensitive to ring substitution and to the configuration of the sulfinyl group. This is however the result of conformational changes which cannot be easily predicted. For 2-methyl derivatives $\delta_{^{17}O}$ allows an easy identification of the cis and trans isomers.

Our interest in the conformational properties of system 1 arised from the observation that for S-methylthiolanium cations (X=Me and Y=lone-pair) the hydrogen-deuterium base-catalysed exchange of the diastereotopic protons alpha to sulfur, was highly stereospecific[1]. Thus we prompted a ^{1}H and ^{13}C NMR investigation on the conformational and configurational factors which may be at the origin of this phenomenon[2]. We showed that S-methylthiolanium cations are sufficiently well described in terms of an equilibrium between two 'half-chair' conformations, 2A and 2B, with ring methyls tending to be equatorial[2b]. A behaviour similar to that of thiolanium cations, either with respect to kinetic acidity or to conformational properties, was expected for thiolane-S-oxides (X=S-O,Y=lone-pair),as the sulfinyl (S-O) and the sulfonium ($\overset{+}{S}$-CH_3) functions are both pyramidal and with a high barrier to pyramidal inversion[3,1c]. Contrary to expectations thiolane-1-oxides show little if any differential acidity of alpha protons[1c]. Moreover for the only compound extensively studied, i.e. 3,3-dimethylthiolane-1-oxide, a conformation (3A with X=O and Y=lone-pair) different from that of the corresponding sulfonium salt was proposed and it was suggested that the difference in the ground state conformation may be precisely at the origin of the lack of stereospecificity in the H/D exchange[1c]. Up to now no systematic studies have been carried out on the conformational properties of thiolane S-oxides. Furthermore a knowledge of the conformational properties of these compounds is of some interest also in view of the fact that they are part of several biologically important products (c.f. the sulfoxides of biotine or neothiobinupharidine of ref.4 and 5). The determination of the configuration of the sulfinyl group in these compounds is a major problem and generally requires ^{1}H and ^{13}C NMR studies of selected classes of model compouds^{4,5}. The present possibility of obtaining ^{17}O spectra suggests that $\delta_{^{17}O}$ allows a direct determination of configuration of the sulfinyl group in these compounds. In this paper we report a theoretical (force field)and a multinuclear (^{1}H, ^{13}C, ^{17}O) NMR study of thiolane-S-oxide and several of its mono and dimethyl ring substituted derivatives. For comparison some data on the corresponding S-dioxides are also reported. Force field calculations were extended to thiolanes and S-methylthiolanium cations to test the validity of the method with classes of compounds whose conformational properties were established by other ways and ,more important, to derive the trends for geometrical and energetical variations following the functionalisation of the sulfur atom of a thiolane ring.



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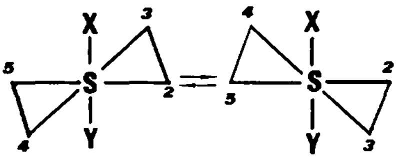
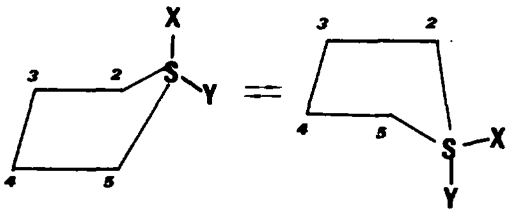


2A 2B



3A 3B

RESULTS

Table 1 gives the 300 MHz proton NMR parameters of *cis-3,trans-4*-dimethylthiolane-1-oxide. A complete stereochemical assignment of ring protons was possible on the basis of the comparison of the spectra in CDCl$_3$,C$_6$D$_6$ and in CDCl$_3$ with Eu(dpm)$_3$^{6}. Since even at high field the proton spectrum of thiolane-1-oxide was not interpretable, two selectively deuteriated derivatives, *3,3-d$_2$* and *3,3-4,4-d$_4$* thiolane-1-oxide were examined. In CDCl$_3$ the high field proton spectrum of *3,3-4,4-d$_4$* -thiolane-1-oxide gives only one line at 2.9 ppm. Addition of Eu(dpm)$_3$ (about 0.15 M) to the solution leads to an AB spectrum with J_{AB}= 14.0 Hz. The lines of B protons are about 2 Hz broader than those of A protons. In C$_6$D$_6$ an AB spectrum is obtained with δ_A =2.5ppm and δ_B = 2.2ppm and J_{AB}= 14.0 Hz. The lines of the B part of the AB spectrum are again about 2 Hz broader than those of the A part. On the basis of the comparison of proton spectra in CDCl$_3$ and C$_6$D$_6$ and in CDCl$_3$ with Eu(dpm)$_3$, B protons are identified as being those trans to the oxygen atom. The high field spectrum of *3,3-d$_2$*-thiolane-1-oxide consists of four poorly resolved multiplets centered at 2.5ppm (two protons) , 2.2 ppm (two protons), 2.0 ppm (one proton) and 1.4 ppm (one proton). ^{13}C and ^{17}O data for S-oxides and S-dioxides are reported in tables 2 and 3 . The data for 2- and 3-methyl-thiolane-S-oxides are relative to mixtures of isomers. For the bicyclic compound, *trans*-thiahydrindan S-oxide, 10, the attribution of resonances for C(2),C(5) was made by analogy with the corresponding sulfonium salt since, owing to the ring trans fusion, the conformation of the five-membered ring must be the same for both compounds and moreover S-O and $\overset{+}{S}$-CH$_3$ have similar magnetic anisotropies^7 . There is a large chemical shift difference for alpha ($\delta_{C(2)}$ - $\delta_{C(5)}$= 3.5 ppm) and beta ($\delta_{C(3)}$ - $\delta_{C(4)}$=2.5 ppm) carbons of 10, which can be viewed as arising from the beta and gamma effects of the oxygen atom . On going from S-oxides to S-dioxides it is found that alpha carbons are <u>shielded</u>

Table 1. Proton chemical shifts[1] and coupling constants[1] of *cis-3,trans-4*-dimethylthiolane-1-oxide

Solvent	H(1)	H(2)	H(3)	H(4)	H(5)	H(6)	Me(1)	Me(2)
C_6D_6	3.23	2.79	2.33	2.20	1.83	1.14	0.90	0.78
$CDCl_3$	3.72	3.07	2.52	2.40	2.32	1.64	1.21	1.14
$CDCl_3$ + Eu(fod)$_3$	3.77	3.33	2.70	2.70	2.37	1.75	1.20	1.25

1) In ppm and in Hz, respectively 2) 0.15 M

Table 2. ^{13}C and ^{17}O chemical shifts[1] of thiolane-1-oxide and its mono and dimethylderivatives

Substituent	C(2)	C(3)	C(4)	C(5)	CH_3	^{17}O
(4) None	54.3	25.4	25.4	54.3		11 (16,15)[2]
(5a) *trans* 2-methyl	64.4	33.1	24.7	52.4	15.1	17
(5b) *cis* 2-methyl	58.5	32.4	24.9	54.8	11.5	- 7
(6a) *trans* 3-methyl	60.4	34.6	33.7	54.8	18.3	15
(6b) *cis* 3-methyl	62.4	35.7	34.0	53.8	19.9	15
(7) 2,2-dimethyl	64.9	38.4	24.1	52.2	22.2 20.1	15
(8) 3,3-dimethyl	65.7	42.2	39.8	52.5	29.4 27.6	15
(9) *cis-3,trans-4*-dimethyl	63.6	42.3	40.4	60.7	16.5	
(10) *trans-2*-thiahydrindan-2-oxide	62.8	45.6	43.1	59.3		9

1) ± 0.2 ppm in $CDCl_3$ with respect to TMS as internal reference for carbon-13 and ±1 ppm in $CHCl_3$ with respect to H_2O as external reference for oxygen-17 2) Values given in ref. 16a,b.

Table 3. ^{13}C and ^{17}O chemical shifts[1] of thiolane-1,1-dioxide and its mono and dimethylderivatives

Substituent	C(2)	C(3)	C(4)	C(5)	CH_3	^{17}O
(11) None	51.2	22.7	22.7	51.2		164(165,164)[2]
(12) 2-methyl	56.0	30.7	19.9	50.5	12.3	150 158
(13) 3-methyl	58.2	31.5	30.9	52.6	19.3	168
(14) 2,2-dimethyl	63.6	48.5	36.6	57.8	17.0	145
(15) 3,3-dimethyl	63.9	37.3	36.9	51.9	28.2	171
(16) *trans-2*-thiahydrindan-2,2-dioxide	58.9	42.2	42.2	58.9		169

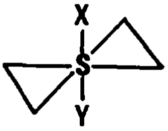
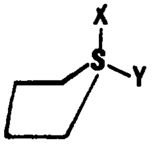
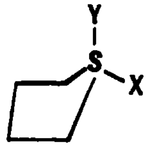
1) ∓0.2 ppm in $CDCl_3$ with respect to TMS as internal reference for carbon-13 and ∓1 ppm in $CHCl_3$ with respect to H_2O as external reference for oxygen-17 2) values given in ref. 16 a,b.

and not deshielded as it would be expected on the basis of the electronegativity of the second oxygen atom. This has also been observed for thiane-S-dioxides[8]. The phenomenon has been discussed but it has not yet received a satisfactory explanation[9]. For thiolane-1-oxide the ^{13}C chemical shift and the one bond coupling constant, $^1J_{CH}$ = 139 Hz , for the alpha carbons was measured in the temperature range $-80 \leq T \leq 100\,^{\circ}C$, with $CDCl_3$ as the solvent for the low and DMSO-d_6 for the high temperatures. No variation of both parameters was observed in the limits of the experimental error, ∓ 0.2 ppm for the chemical shift and ∓ 1 Hz for the coupling constant. The linewidth of ^{17}O lines was about 10 ppm for all compounds. The oxygen atom of five-membered rings , either S-oxides or S-dioxides, is deshielded by several ppm with respect to that of the corresponding six-membered ones[8]. Tables 4,5,6 and 7 give the results of force field calculations. The MM2 force field was employed with new parameters for SO and SO_2 functions kindly furnished by Professor Allinger[11].

DISCUSSION

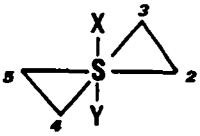
It is known that five-membered rings are generally very flexible and do not possess sharp energy minima[12]. The barriers to conformational interconversion , either by inversion through a planar skeleton or by pseudorotation[12c] are small and freezing of the conformational equilibrium is not attained even at low temperatures. Thus the conformational analysis of these compounds is not straightforward, compared with that of six-membered rings, for which low temperature proton and carbon-13 NMR allow quantitative estimates of the conformational equilibrium. For thiolane the most stable conformation is the half-chair (2) with maximum staggering between adjacent groups at C(3),C(4)[12e]. The barrier to pseudorotation was estimated to be about 3 $kcalmol^{-1}$ from thermodynamic data[12f]. Room temperature proton and carbon-13 NMR indicates that the half-chair is the preferred conformation also for ring methylated thiolanes[2a] and S-methylthiolanium cations[2b]. Instead for 3,3-dimethylthiolane-1-oxide, 8 , an envelope conformation with the S-O bond axial was proposed on the basis of proton data[1c]. In the envelope conformation , 3 , the region of maximum staggering between adjacent groups is at C(2),S,C(5). It was argued that if the envelope with a small torsional angle at C(3),C(4) is the preferred conformation for 3,3-dimethylthiolane-1-oxide in spite of the geminal methyls at C(3), with greater reason the unsubstituted compound should have the same conformation[1c]. On these arguments the question arises whether the envelope with an axial S-O bond is a well defined energy minimum for thiolane-S-oxides as the half-chair is for S-methylthiolanium cations[2b] . For a better understanding of the conformational properties of thiolane-S-oxides we carried out force field calculations of the energy and the geometry of these compounds. The data in table 4 indicate that the half-chair is an energy minimum in all cases, including thiolane-1-oxide. When the sulfur atom bears a substituent, either methyl or oxygen, the preference for this conformation is drastically reduced with respect to the unsubstituted compound. When sulfur bears one methyl group (thiolanium cation) there is still about 1 $kcalmol^{-1}$ energy difference between the half-chair and the more stable of the envelope forms , the axial one. However when sulfur bears one oxygen atom (thiolane-1-oxide) there is no significant energy difference between the half-chair and the more stable of the envelope forms, again the axial one. In considering the envelope forms it is found that, as for six-membered ring S-oxides, force field calculations do not support the existence of attractive interactions between the axial oxygen and the nearly syn-axial hydrogens at C(3) as the determining factor for the axial preference. All data suggest that the axial preference of the envelope forms depends on minor changes on the whole geometry of the molecule arising from that 'squeezing effect' on equatorial substituents characteristic of these calculations[10]. For the half-chairs there is a perfect symmetry in torsional angles for the sulfide and the S-dioxide, whereas introduction of a single substituent on sulfur leads to some distorsions. These are more accentuated when the substituent is an oxygen atom, although the trend is the same for oxygen and methyl. The puckering at C(3),C(4) is the same for the S-methyl cation and the S-oxide and is rather accentuated, in agreement with what has been observed by electron diffraction data of thiolane[14] and X-ray data of S-methylthiolanium cations[15]. As far as torsional angles of the envelope forms are concerned, it is seen that the angle between the two planes, the one defined by C(2),C(3),C(4),C(5)

Table 4. Calculated conformational energies[1] for thiolane, S-methylthiolanium cation, thiolane-1-oxide and thiolane-1,1-dioxide for the envelope and half chair forms

X	Y			
l.p.	l.p.	4.96	7.24	7.24
m.	l.p.	9.19	10.20	11.06
o.	l.p.	7.59	7.60	7.99
o.	o.	8.53	9.09	9.09

1) In kcal mol^{-1} 2) l.p.=lone pair , m.=methyl , o.=oxygen

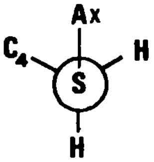
Table 5. Torsional angles φ^1 in half chair forms

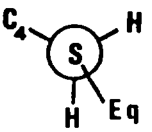


X	Y	φ 1234	2345	3451	4512	5123	321X
l.p.	l.p.	- 38	50	- 38	14	14	--
m.	l.p.	- 40	50	- 37	12	16	- 83
o.	l.p.	- 41	50	- 36	10	18	- 91
o.	o.	- 38	51	- 38	14	14	129,- 101

1) φ in (°) 2) l.p.=lone pair , o.=oxygen , m.=methyl

and the one defined by C(2),S,C(5), is larger for axial substituents than for equatorial ones. The trend is more accentuated for S-methylthiolanium cations than for S-oxides. Looking along the S,C(5) (or S,C(2)) bond it is seen that for envelope forms axial substituents gives rise to an almost perfect gauche arrangement whereas this is not the case for equatorial ones. Qualitatively the situation is depicted in the figure reported below:





In table 7 the conformational energies for monomethyl substituted compounds are reported for the envelope and chair forms. Calculations for all dimethyl substituted compounds are reported separately. Table 7 shows that equatorial or pseudo-equatorial positions are favoured over axial ones. The preference for the equatorial position is higher at C(3),C(4) than at C(2),C(5) in the half-chair conformation. For thiolanes and S-methylthiolanium cations this is in agreement with ^{13}C data[2a,b]. It appears that the conformational preference of monomethyl thiolane-S-oxides is determined by the possibility for the methyl groups of occupying equatorial positions, in agreement with what has been observed for methylcyclopentanes[10c].

In comparing the results of force field calculations with experimental data, solvent effects should be taken into account. For six-membered ring S-oxides we showed that solvent effects on conformational equilibria may be not negligible[8]. We have now recalculated the conformational energy difference between the axial and the equatorial forms of thiane-1-oxide using the new Allinger's parameters for SO[11]. We found ΔE = 0.18 $kcalmol^{-1}$ in favour of the *equatorial* form, the same result as that obtained by low temperature ^{13}C NMR in $CDCl_3$[8]. Thus all our data are relative to $CDCl_3$ as the solvent. Let us now examine case by case the results of NMR and force field calculations.

For unsubstituted thiolane-1-oxide, 4 , proton data rule out the possibility that the compound exists as an equilibrium $\underline{2A}\rightleftarrows\underline{2B}$ between two equivalent half-chair conformations ,contrary to the corresponding S-methylthiolanium cation[1a]. Indeed, if this were the case, $^2J_{gem}$ for the alpha protons should be the average of the two values, 12 and 13 Hz, measured for the rigid half chair of the bicyclic compound, 10. On the contrary a much higher value, $^2J_{gem}$ =14.0 Hz, is observed. Moreover the rapid, on the NMR scale, switching of the two half-chair forms should make the beta protons isochronous. On the contrary , for 3,3-d_2-thiolane-1-oxide a 0.6 ppm difference in the chemical shift of the protons at C(4) is observed. Both criteria, the large value of the geminal constant of alpha protons and the large chemical shift difference of beta protons, define the axial orientation of a sulfinyl group for six-membered as well as for five-membered ring sulfoxides[4,6]. Thus proton data indicate that , if the envelope with S-O axial may not be the only existing form, it must be present to a large extent in the conformational equilibrium of thiolane-1-oxide in solution. An equilibrium between the half chair and the envelope conformation as suggested by force field calculations cannot be excluded but it is difficult to prove. Variable temperature ^{13}C NMR shows that there are no changes in the chemical shifts and in the $^1J_{CH}$ couplings for alpha carbons for this compound between -80 and +100 °C but this could be due either to the compound being conformationally homogeneous or to these parameters being the same for both conformations. Before commenting the ^{17}O chemical shift of this compound let us turn to the chemical shift of S-dioxides. It is known that for several classes of compounds beta, gamma and delta effects exerted by methyl groups on oxygen follow the same trend as for ^{13}C[16]. The ^{17}O chemical shift of S-dioxides can be explained on the basis of these effects. Indeed the 2-methyl, 12, is shielded and the 3-methyl, 13, deshielded as expected for the presence of a gamma and delta methyl, respectively. The same trend is observed for the *gem*-dimethyl substituted compounds, 14 and 15. The bicyclic S-dioxide, 16 is deshielded by 5 ppm with respect to the parent compound, owing to the delta effect exerted by the C(3)-C(6) and C(4)-C(9) bonds. In the bicyclic S-oxide, 10, only one delta bond is cis to the sulfinyl group and a smaller deshielding effect with respect to the parent compound 4 is expected However 10 is shielded by 2 ppm with respect to 4. This can only be explained by a change in

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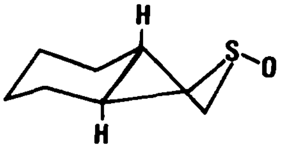

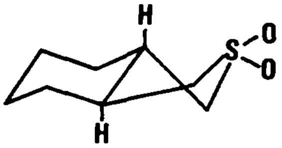

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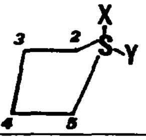
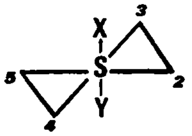
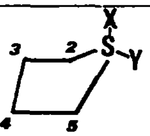
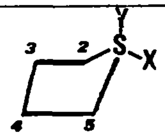
Table 6. Torsional angles φ^1 in envelope forms



X	Y	φ 1234	2345	3451	4512	5123	321X
l.p.	l.p.	- 30	0	30	- 42	42	--
m.	l.p.	- 26	0	26	- 36	36	65
l.p.	m.	- 34	0	34	- 48	48	-149
o.	l.p.	- 31	0	31	- 43	43	65
l.p.	o.	- 33	0	33	- 46	46	-154
o.	o.	- 29	0	29	- 42	42	157,- 71

1) φ in (°) 2) l.p.=lone pair , o.=oxygen , m.= methyl

Table 7. Calculated conformational energies for monomethyl substitution of thiolane, thiolane-1-oxide, thiolane-1,1-dioxide and S-methylthiolanium cation

										
X	Y		C(2)	C(3)	C(4)	C(5)	C(2)	C(3)	C(2)	C(3)
l.p.	l.p.	*eq*	5.69	5.08			8.22	(7.65)		
		ax	6.28	6.31			8.84	(8.06)		
l.p.	o.	*eq*	8.56	7.74	7.78	8.30	8.76	(8.49)	8.49	(8.04)
		ax	9.20	9.21	9.36	9.31	(10.28)	(9.17)	9.54	(8.96)
l.p.	m.	*eq*	10.34	9.31	9.29	9.82	11.50	11.44	10.91	10.68
		ax	10.98	(12.22)	10.71	(12.24)	14.23	11.96	11.77	(12.52)
o.	o.	*eq*	10.06	8.73	10.50	(9.67)				
		ax	10.92	10.17	(11.36)	(10.43)				

1) Numbers are the conformational energies in kcalmol^{-1} for a methyl group in the corresponding position. 2) Values in parenthesis were obtained by minimisation with fixed torsional angles 3) l.p.=lone pair , o.=oxygen , m.=methyl

conformation on going from the bicyclo to the parent compound, in agreement with the presence of a large amount of the envelope form as indicated by proton data and force field calculations.

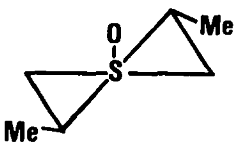
As for the corresponding six-membered rings[8] the cis and trans isomers of 2-methylthiolane-1-oxide can easily be distinguished by ^{13}C and ^{17}O NMR since, owing to the mutual γ_{cis} effect, the resonances of oxygen and methyl for the cis isomer are at higher field than those for the trans isomer. The effect experienced by oxygen is generally more important than that experienced by carbon[16]. For several classes of compounds a scale factor of about 2.5 was found[16]. In the present case a much higher scale factor of about 5 would result (see table 2). This suggests that the conformation of the two compounds may not be the same. Force field calculations support this hypothesis. For *cis* 2-methyl thiolane-1-oxide ,5b, the half-chair and the envelope conformation are equally probable (table 7), a situation similar to that of the parent compound . Then ^{13}C data of both compounds are comparable. Indeed it is found that the chemical shifts of C(4) and C(5) are very close for both compounds. This also implies that the methyl group is largely equatorial; if this were not the case both carbons for 5b should be at higher field owing to the γ effect exerted by an axial methyl. According to force field calculations (table 7), for *trans*-2-methylthiolane-1-oxide,5a, the half chair is the most probable conformation, however the envelope with an equatorial S-O bond has also to be taken into account. If it is assumed that as for six-membered ring S-oxides , also for five-membered ones the oxygen of an axial S-O bond is more shielded than that of an equatorial one, the large deshielding observed for the 5a with respect to 4 can be explained by the presence of a non negligible amount of an equatorial envelope form.

For both isomers of 3-methylthiolane-1-oxide, 6a and 6b, force field calculations indicate the half-chair with the methyl group equatorial,2A for the trans and 2B for the cis, to be the preferred conformation. The calculated overall energy of both compounds for the preferred conformation is the same.This can explain why these compounds cannot be separated either by distillation or chromatography, a mixture 60:40=cis:trans being always obtained (see experimental). This also explains why, in the limits of experimental errors, both isomers have the same ^{17}O chemical shift.

The proton NMR spectrum of 3,3-dimethylthiolane-1-oxide,8, and *trans* thiahydrindane *S*-oxide

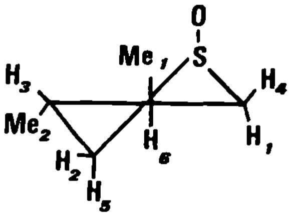
,10, has already been reported[1c] . The key parameter in assessing the conformation of 8 (3A with X=O and Y=lone pair) was the long-range, four bonds coupling constant $^4J_{HH}$ = 1.4 Hz between the two equatorial alpha protons at C(2) and C(5), both cis to the oxygen atom . This implied a nearly planar setting of the H_{eq}-C(2)-S-C(5)-H_{eq} fragment[1c].On the other hand the axial orientation of the S-O bond was indicated by the large value ,13.7 and 14.0 Hz, of the geminal coupling constants for the alpha protons[1c] .In the corresponding S-methylthiolanium cation, which is instead half-chair, a similar four bonds long-range coupling constant was found between the two equatorial protons at C(2) and C(4),both trans to the methyl group, indicating that the region of maximum puckering was at C(3),C(4) and the conformation 2A (with X=Me and Y=lone-pair).

Cis-3,trans-4-dimethylthiolane-1-oxide, 9, may be considered to be equivalent to the bicyclic S-oxide, 10, as far as the stereochemistry of the substituents at C(3),C(4) is concerned, free however of adjusting its conformation even by rotation around C(3),C(4). Table 1 shows that there is a long-range , four bonds coupling constant $^2J_{H(2),H(4)}$ = 1.5 Hz between the two equatorial alpha protons both cis to oxygen. Moreover large $^2J_{gem}$ values,14.0 and 13.5 Hz ,are found for the alpha protons. Thus on the basis of the arguments applied to 3,3-dimethylthiolane-1-oxide an envelope with the S-O bond axial should be considered the preferred conformation .However ^{13}C data are not in agreement with this assumption. Indeed compound 9 has ($\delta_{C(2)} - \delta_{C(5)}$) = 2.9 ppm and ($\delta_{C(3)} - \delta_{C(4)}$) = 1.9 ppm .These chemical shift differences are similar to those found for the bicyclic compound ,10. If it is assumed that these differences arise from beta and gamma effects of the substituents on C(2),C(5) and C(3),C(4), respectively, they are related to the orientation of the substituent with respect to these atoms; then for an envelope conformation a much lower,if any, differece is expected a priori. Moreover the chemical shift of the oxygen atom for 9 is the same as that of the rigid compound . Force field calculations for 9 do not indicate an energy minimum corresponding to the envelope with sulfur at the tip and the S-O bond axial. Instead conformations C and D, close in energy, have to be taken into accout, all other conformations being of much higher energy. C is the usual half chair conformation with maximum puckering at C(3),C(4) whereas D geometrically resembles to an half chair with sulfur in the region of maximum puckering and the oxygen atom axial .Our proton data exclude that C may be the only conformation present in solution since it is not compatible with the existence of a long range coupling constant between two equatorial alpha protons cis to oxygen. On the contrary geometrical considerations indicate that D is in agreement with both ^{1}H and ^{13}C data.



C

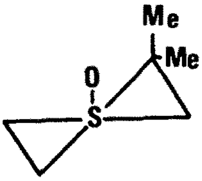
(8.6 kcal mol^{-1})



D

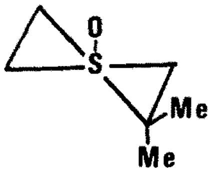
(8.9 kcal mol^{-1})

A conformation similar to D is indicated by force field calculations also for 3,3-dimethylthiolane-1-oxide . Again the calculations do not indicate the existence of an energy minimum corresponding to the envelope with the sulfur atom at the tip and the S-O bond axial as proposed for this compound (3A with X=O and Y=lone-pair). For 8 the situation is more complicated as there are several energetically similar and geometrically different conformations which have to be taken into account, as shown below:



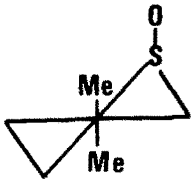
C'

(9.6 kcal mol^{-1})



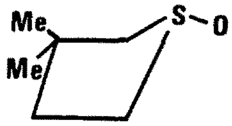
C''

(9.7 kcal mol^{-1})



D'

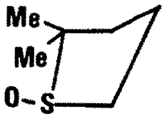
(9.4 kcal mol^{-1})



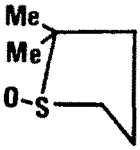
E

(9.8 kcal mol^{-1})

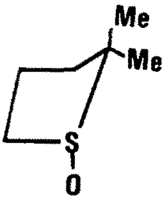
However of all these conformations D' is the only one in agreement with the observation of the proton-proton long range coupling constant $^4J_{H(3),H(4)}$. What is to be pointed out is that force field calculations indicate the existence of a conformation which was not taken into account in the previous study but which is also compatible with proton data. Also for 2,2-dimethyl-thiolane-1-oxide , 7 , a very flat energy profile is found. According to our calculations several geometrically different and energetically similar conformations are found:



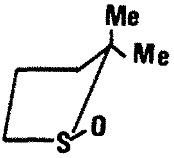
(10.2 kcal mol^{-1})



(10.3 kcal mol^{-1})



(10.4 kcal mol^{-1})



(10.8 kcal mol^{-1})

It may be suggested that since the oxygen atom is prevalently in an equatorial or nearly equatorial orientation, this accounts for the deshielding of the oxygen atom with respect to the unsubstituted compound in spite of the presence of the two gamma methyls. On the other hand, contrary to six-membered ring S-oxides[8], it is difficult to rationalise the ^{17}O chemical shifts of 7 as well as of all other compounds of table 2 as they are clearly the result of small geometry variations which cannot be easily related to shift increments. Probably ^{33}S chemical shifts would give more reliable conformational informations owing to the position of the sulfur atom inside the ring skeleton. In a recent paper we found that the ^{33}S chemical shift of 2,2-dimethylthiolane-1,1-dioxide,14, is several ppm lower than expected and we attributed this to a conformational change wih respect to the parent compound[17]. Force field calculations indicate that this is indeed the case as the geminal methyls oblige the ring to assume an envelope conformation with the sulfur atom in the most flat region of the ring[18]. Work is in progress in this direction.

CONCLUSIONS

Force field calculations do not support the idea that the envelope with sulfur at the tip and the S-O bond axial is the preferred conformation for all five-membered ring S-oxides. Instead the overall conformational preference depends on the position and on the number of substituents, a situation which recalls more that of 1,3-dioxolanes[12] than that of the corresponding S-methylthiolanium cations[2b]. This makes difficult the conformational analysis of these compounds and it appears that investigation on a single parameter such as $^4J_{HH}$ or $\delta_{^{17}O}$ may not lead to a satisfactory description of the conformational properties. The use of a variety of techniques and force field calculations among them, seems more appropriate to have a correct insight on their ambiguous conformational features. The apparent lack of sensitivity of $\delta_{^{17}O}$ on ring substitution is the result of conformational changes and contributions which make difficult to relate this parameter to the configuration of the sulfinyl group, contrary to the corresponding six-membered ring compounds[8]. However for compounds bearing a single substituent at C(2), $\delta_{^{17}O}$ allow an easy identification of the cis and trans isomers on the basis of the strong gamma effect exerted on oxygen by the substituent. This is not without interest insofar as for several biologically important sulfoxides , such as those of biotine[4] , the five-membered ring moiety bears just a substituent on the carbon alpha to sulfur. Finally the conformational variability of five-membered ring S-oxides is likely to be at the origin of the lack of stereospecificity on the H/D base-catalysed exchange of alpha protons[1c]. Force field calculations support indeed Fava's hypothesis according to which '..the lack of stereospecificity... may be due to the system being sufficiently mobile to be able to adjust the conformation at the transition state so as to minimise at nearly the same level the overall energy barriers for exchange...'[1c].

EXPERIMENTAL

Compounds 4, 11 and 14 are commercial products. Compounds 10[1c], 8[1c], 6[19], 12[19] have been already described . Sulfoxides 6,7,9 and sulfones 14 , 15, 16 were obtained by oxidation of the corresponding sulfides either with hydrogen peroxide at 0-4°C(ice-bath) in acetone or with m-chloroperbenzoic acid at 0-4°C(ice-bath) in methylene chloride (ref.20,21). All sulfides are known compounds (ref.2a). For all compounds MS, IR and NMRparameters were in agreement with the proposed structure. In particular sulfoxides showed the characteristic IR absorption at 1050 cm^{-1} and sulfones at 1300 and 1150 cm^{-1}. The sulfoxide obtained by oxidation of 3-methylthiolane is a mixture of about the same amount of cis and trans isomers, b.p. 80-90°C (8 mmHg). The same mixture was obtained by oxidation of 3-methylthiolane with acylnitrates[22]. Distillation with an annular still (Perkin Elmer 251) leads only to a moderate enrichment in one isomer (60:40=cis:trans). The same mixture was obtained by chromatography on a silicagel column (Et_2O : MeOH = 90:10). The identificationof the cis and trans isomers was made by comparison of the proton chemical shifts of the methyl groups in $CDCl_3$, C_6D_6 and $CDCl_3$ with $Eu(dpm)_3$.

Methyl chemical shifts(300 MHz) of the cis isomer : 0.83 ppm(C_6D_6), 1.28($CDCl_3$), 2.26($CDCl_3$ + $Eu(dpm)_3$ 0.097M). Methyl chemical shifts(300 MHz) of the trans isomer : 0.57 ppm(C_6D_6), 1.17($CDCl_3$), 1.85($CDCl_3$ + $Eu(dpm)_3$ 0.097 M).

2,2-dimethylthiolane-1-oxide, b.p. 115 -117°C(18 mmHg); proton chemical shifts(first order,300MHz): a) in C_6D_6 , 2.56(1H), 2.36(1H), 1.86(1H), 1.97(1H), 1.34(1H), 1.21(1H), 1.23(3H), 0.63(3H) ppm b) in $CDCl_3$, 3.27(1H) , 2.75(1H), 2.38(1H), 2.25(1H), 2.02(1H), 1.81(1H), 1.42(3H), 1.14(3H) ppm c) in $CDCl_3$ with $Eu(fod)_3$ 0.15 M, 3.37(1H), 3.03(1H), 2.5(2H), 2.13(1H), 1.95(1H), 1.65(3H), 1.22(3H) ppm

Cis-3,trans-4-thiolane-1-oxide, b.p. 128 -130°C (15 mmHg) ; *trans-2*-thiahydrindan-2,2-dioxide, m.p. 90°C ; 2,2-dimethylthiolane-1,1-dioxide, m.p. 35°C ; 3,3-dimethylthiolane-1,1-dioxide, b.p. 76 -77°C (0.1 mmHg). Melting and boiling points are uncorrected. 3,3-4,4-d_4- and 3,3-d_2-thiolane-1oxides were prepared according to Lambert *et al.*(ref.23).

NMR spectra- Proton noise decoupled C-13 spectra were recorded at 20 MHz with a Varian FT-80 spectrometer using 10 mm tubes, 0.3-0.5 M solutions in $CDCl_3$ and TMS as internal standard. Typical conditions were: 3000 Hz sweep width, 1.5s acquisition time , 8k data point and 40 -60° pulse width. Proton spectra were recorded at 300 MHz on a Bruker CXP-300 spectrometer with 5mm tubes, 0.1 M solutions in $CDCl_3$ or C_6D_6 and TMS as internal standard. Typical conditions were : 3000 Hz sweep width, 4.7s acquisition time, 32k data point and 45° pulse width. Oxygen-17 spectra were recorded with a CXP-300 spectrometer using the high power probe (no spinning,no lock) with a solenoid insert at 40.06 MHz. Solutions were 0.5 M in $CHCl_3$ and the chemical shift was measured with respect to H_2O as external reference. All samples were repeatedly evaporated with dried C6H6 before the oxygen-17 spectra were recorded. Typical conditions were: 20000 Hz sweep width, 2k data point, 50ms acquisition time and 90 pulse width.

Computational details. Force field calculations were carried out using the 1977 Force Field MM2 program by N.L.Allinger and Y.H.Yuh(quantum chemistry program exchange n° 395) on a Vax 11/780. All structures were energy minimised until 0.018 kcal mol^{-1}. In table 7 values in parenthesis were obtained by minimisation with fixed torsional angles.

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