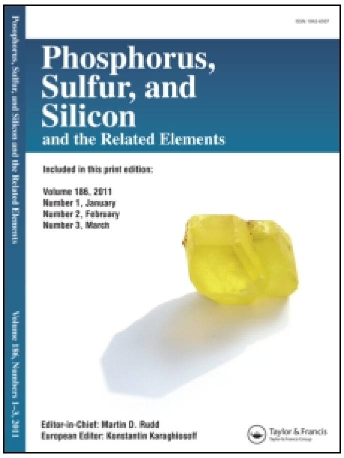

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Stereoelectronic Effects in Sulfur Heterocycles. Thiosulfonium Ions

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STEREOELECTRONIC EFFECTS IN SULFUR HETEROCYCLES. THIOSULFONIUM IONS

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Abstract The conformational and configurational preferences of a novel type of sulfur heterocycle (cyclic thiosulfonium ions) have been studied by high field NMR. Six-membered S-methyl-1,2-dithianium cations were prepared as fluoroborate salts by the methylation of corresponding 1,2-dithianes with $Me_3O^+ BF_4^-$. Methylation produced only one of two possible diastereomers in the cases studied, and the products displayed fixed conformations in which the S^+Me group is axial. In contrast, methylation of 1,2-dithiolanes produced S-methyl-1,2-dithiolanium ions nonselectively. Proton and C-13 NMR revealed a dynamic process involving S-methyl-1,2-dithiolanium ions and methyl sulfide which rapidly interconverted configurational isomers (enantiomers and diastereomers). The process is attributed to sulfide-induced ring-opening by $S-S^+$ cleavage that is both rapid ($>10^5$ sec^{-1} l. mole^{-1}) and reversible. The equilibrium position strongly favors ring closure. Ring strain effects are therefore unimportant. A similar sulfide-induced ring-opening was observed with S-methyl-1,2-dithianium, which interconverted enantiomers, but a comparable process with ring-substituted dithianium ions is invisible. The conclusion is reached that the conformations and preferred configurations are controlled by a stereoelectronic or anomeric effect of the neutral ring sulfur on the exocyclic polar S^+Me bond. The ready polymerization-depolymerization of 1,2-dithiolanes under electrophilic conditions is explained in terms of ring activation through dithiolanium ion formation rather than through relief of ring strain. The possibility that lipoic acid owes its reactivity to 1,2-dithiolanium ion formation is suggested.

INTRODUCTION

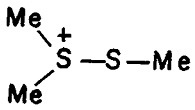
In comparison with sulfonium ions R_3S^+, which are well known and easily prepared by alkylation of sulfides, thiosulfonium ions R_2S^+SR are relatively unknown. They can be prepared in some instances by the alkylation of disulfides [1,2] and in this manner we have successfully prepared several five and six-membered cyclic thiosulfonium ions as fluoroborate salts. Provided that nucleophilic solvents and nucleophilic counterions are avoided, methylated 1,2-dithianium and 1,2-dithiolanium salts can be isolated as crystalline solids or oils upon methylation of the corresponding 1,2-dithiane or 1,2-dithiolane. The conformational preferences of these novel heterocycles are of interest, especially in comparison with related sulfur heterocycles, and a conformational study of ions **1**-**7** by high field NMR is the main topic of this paper. The reactions of these ions with nucleophiles, notably sulfides and alkenes [1a,3] are also remarkable, and we take this opportunity to summarize our findings.

RESULTS AND DISCUSSION

Methylation of 1,2-Dithianes

Conformational analysis of 1-methylthianium ions has been well studied [4,5] and it is known that the energy difference between the axial and equatorial conformers of the 1-methylthianium cation **10** is small. In solution, the equatorial forms is favored by only 0.0 - 0.6 kcal/mole depending on the temperature and the presence of other groups [4a]. In fact, the conformer distribution for ring-substituted thianium ions is determined more by other ring substituents than by the ^+SMe group. It was therefore surprising to find that the related 1-

THIOSULFONIUM IONS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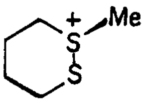
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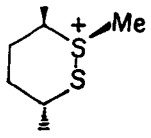
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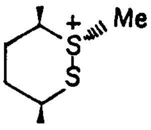
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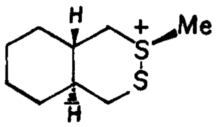
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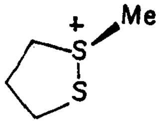
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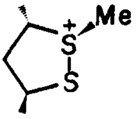
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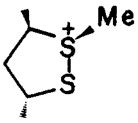
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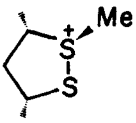
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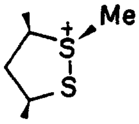
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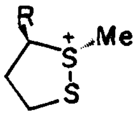
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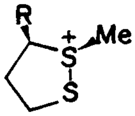
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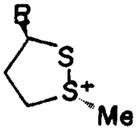
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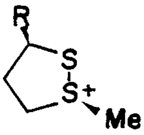
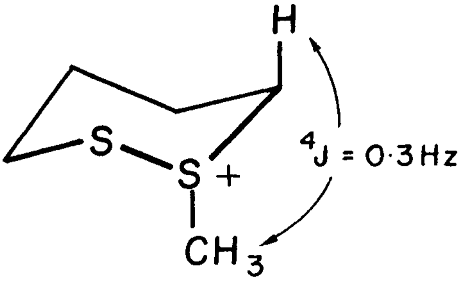

9b
(18)

R = $(CH_2)_4CO_2Me$

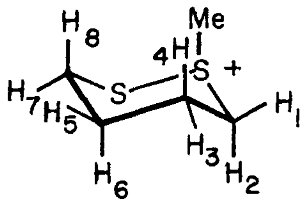
(Bracketed numbers are parent disulfide) methyl-1,2-dithianium cation **1** is evidently conformationally homogeneous and noninverting at $300^{\circ}K$ - at least on the NMR time scale. Thus the 500 MHz proton spectrum of **1** in CD_3NO_2 showed all eight ring protons to be well resolved with coupling constants indicative of an undistorted chair (see Table 1). The dihedral angle $\psi_{\alpha\beta}$ at $\overset{+}{S}C_{\alpha}-C_{\beta}$ is calculated from the coupling parameters to be $58^{\circ}C$, which is not remarkably different from the value of 56° in cyclohexane.

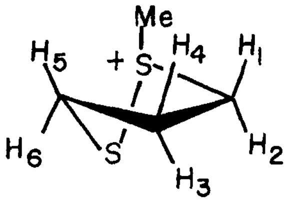
Another surprise was that the methyl resonance is a narrowly spaced doublet (0.3 Hz). Double resonance confirmed that this is due to spin coupling of the methyl protons with the axial proton at C6. A similar long-range coupling is documented for conformationally rigid steroids and terpenes wherein an axial (angular) methyl group is coplanar with an axial proton four bonds removed [6]. We conclude that the ^{+}SMe group in **1** is similarly fixed in an axial orientation to the axial proton at C6.



It was anticipated that methylation of ring-substituted 1,2-dithianes **12**-**14** would give mixtures of diastereomers in a kinetically controlled reaction, by analogy with the methylation of related monothianes [4a]. Surprisingly though, only one diastereomer was obtained in each case. The proton NMR spectra of the products **2**-**4** (Table 1) indicate that each is conformationally and configuratio-

TABLE 1 Proton NMR (500 MHz) Chemical Shifts of 1-Methyl-1,2-dithianium and 1-Methyl-1,2-dithiolanium Fluoroborates in CD_3NO_2





Salt[a]	H1	H2	H3	H4	H5	H6	H7	H8	^+SMe	^+SCMe	SCMe
1[b]	3.53	3.75	2.28	2.37	2.28	2.10	3.12	3.68	3.38		
1[c]	3.64	3.64	2.32	2.32	2.19	2.19	3.40	3.40	3.37		
2[b]		3.91	2.32	2.24	2.36	1.92		3.75	3.25	1.56	1.40
2[c]		3.87	2.32	2.21	2.36	1.91		3.73	3.24	1.56	1.40
3	3.80		2.20	2.60	2.06	2.00		3.75	3.38	1.77	1.39
3[c]	3.80		2.20	2.58	2.06	2.00		3.75	3.37	1.76	1.40
4[f]	3.43	3.45		1.87		2.15	2.95	3.44	3.37		
4[c]	3.43	3.45		1.87		2.15	2.95	3.44	3.37		
5[d]	4.06	4.06	(3.02)	(2.91)	(3.80)	(3.96)			3.09		
5[c]	4.06[e]	4.06[e]	2.97	2.97	3.88	3.88			3.09		
20[g]	3.99	3.99	2.74	2.74	3.75	3.75					

Salt[a]	H1	H2	H3	H4	H5	H6	^+SMe	^+SCMe	SCMe
6a	4.67		(3.04)	(2.70)		4.80	3.18	1.65	1.71
6b		4.80	(2.89)	(2.78)	4.67		2.97	1.77	1.56
6c	4.70	4.70	(2.95)	(2.76)	4.79	4.79	3.11	1.69	1.66
7a	4.55		3.24	2.15	4.56		3.22	1.80	1.61
7b		4.61	3.24	2.39		4.43	3.03	1.76	1.65
7c	4.58	4.58	3.24	2.26	4.50	4.50	3.12	1.78	1.63

a. Shifts are in ppm. Numbering of resonances is as shown in structures at top of table. Assignment of values in parenthesis is uncertain.

b. J in Hz for **1** are $J_{1,2}=14$, $J_{1,3}=3.5$, $J_{1,4}=3.5$, $^4J_{Me,H2}=0.3$, $J_{2,3}=3.4$, $J_{2,4}=12$, $J_{7,8}=14.5$, $J_{5,8}=2.3$, $J_{6,8}=12$; For **2** are $J_{2,3}=3.0$, $J_{2,4}=12$, $J_{5,8}=2.0$, $J_{6,8}=11.5$, $J_{Me,H}=6.8$, 7.0.

c. $(CD_3)_2S$ added

d. at 254°K

e. broadened

f. proton shifts in carbocyclic ring are 1.23(2), 1.47(2), 1.69, 1.74, 1.82(2); $J_{7,8}=14.5$, $J_{6,7}=3.0$, $J_{6,8}=12.0$

g. 1-Ethyl-1,2-dithiolanium fluoroborate (ref 12) nally homogeneous, although the actual stereochemistry cannot be deduced from this data alone. The C-13 NMR spectra (Table 2) are more informative, and comparisons with C-13 spectra of corresponding thianium ions proved to be useful. In a comprehensive C-13 study of thianium salts, Eliel and Willer established a dependence of the SMe^+ chemical shifts on the position and orientation of ring methyl substituents [4b]. Using this data, we have calculated the SMe^+ shifts for the possible stereoisomers of 2-4 (Table 3). The calculated and observed shifts are in reasonable agreement for axial SMe^+ in every case.

The shifts of the ring carbons are also dependent on the orientation of SMe^+. In fact Barbarella et al. have reported values for the differences between the chemical shifts of ring carbons in S-methylthianium ions and the parent thianes as a funtion of the SMe^+ orientation [5]. Assuming that these values also apply to S-methyldithianium ions and the corresponding dithianes, we have calculated the shifts of C4, C5 and C6 for the possible stereoisomers of 2-4 (Table 3). Again, the agreement with the observed shifts is best for the axial orientation of SMe^+. Assignment in the case of 3 is uncertain based on the calculated SMe^+ shifts alone (compare 3a and 3b in Table 3) but taken in conjunction with the calculated ring carbon shifts, the best fit is with configuration 3a in which the methyl groups at S^+ and C6 are both axial.

The observed preference for the axial orientation in 1-4 is in striking contrast to the conformational mobility of the corresponding S-methylthianium ions; particularly 10 and 19.

Replacing the C2 ring carbon with a heteroatom clearly

TABLE 2. Carbon-13 NMR Chemical Shifts of 1,2-Dithianes, 1,2-Dithiolanes, and Their S-Methyl Analogs as Fluoroborate Salts in CD_3NO_2 25°.

Compound	Comp.[b] %	Chemical Shift[a] C3	C4	C5	C6	$^{+}$SMe	(5)6-Me	3-Me
11		34.80	28.90	28.90	34.80			
1	100	26.70	23.50	17.50	40.10	25.00		
12[c]		41.00	37.80	37.80	41.00		21.00	21.00
2	100	36.10	34.70	27.40	50.20	20.70	(18.90)	(19.90)[d]
13[c]		38.00	32.70	32.70	38.00		19.70	19.70
13[e]		35.00	30.60	33.80	42.50		17.50	22.00
3	100	37.70	(27.50)	(26.10)[d]	47.00	28.20	17.00	21.60
14[f]		39.50	44.90	44.90	39.50			
4[g]	100	31.00	40.60	33.50	44.80	25.20		
15[c]		35.80	27.20	35.80				
5	100	42.70	33.70	54.00		33.30		

(Table 2 continued)

Compound	Comp. %	C3	C4	C5	$^{+}$SMe	(5)6-Me	3-Me
16[c]		49.60	50.10	49.60		20.50	20.50
6a	65	56.40	45.60	68.30	34.70	20.30	16.70
6b	35	54.30	44.90	63.50	26.40	13.20	23.30
17[c]		51.30	51.00	51.30		20.40	20.40
7a	52	56.00	50.00	72.00	33.40	20.10	18.30
7b	48	55.50	45.30	65.60	27.60	13.40	17.40
18[h]		38.20	39.80	56.00			
8a[i]	26	40.80	37.40	73.90	32.70		
8b[i]	11	39.50	35.00	70.60	26.00		
8[j]		40.40	36.70	72.90	30.70		
(9a)[id]	33	52.00	37.80	60.70	32.80		
(9b)[id]	30	52.90	36.80	62.40	33.00		
9[j]		52.00	37.30	61.40	32.90		

(Table 2 continued)

Compound	^+SMe	SMe
MeSSMe		22.00
Me_2S^+SMe	31.80	17.80
Me_2S^c		19.30
Me_3S^+	26.20	

a. ppm relative to TMS

b. Composition of mixture obtained on methylation of disulfide

c. $CDCl_3$

d. Assignments in parentheses could be reversed

e. $(CD_3)_2CO$ at -70°, noninverting conformation

f. ref 20; shifts in carbocyclic ring are 26.6 and 34.15 ppm

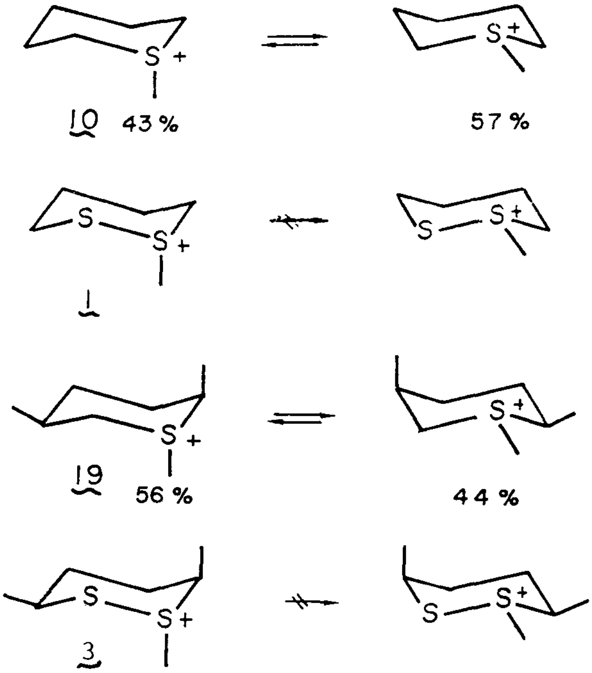
g. Shifts in carbocyclic ring are 27.1, 28.1, 33.3, 34.4 ppm

h. ref 23; shifts are for the parent acid

i. CO= 175.7, OCH_3= 51.8, CH_2= 24-34 ppm

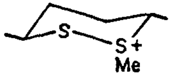
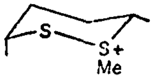
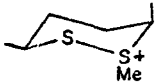
j. With added $(CD_3)_2S$

has a significant effect on conformational preference and ring mobility, as has been noted before for cyclic sulfites, sulfinates and thiosulfinates[7,8,20]. This may be attributed to a stereoelectronic (anomeric) effect of the heteroatom on the orientation of the adjacent S^+-C bonds[7]. Ab inito molecular orbital calculations confirm that axially protonated 1,2-dithiane



is energetically favored over the equatorial form by about 3 kcal/mole[9]. The origin of this relative stabilization may be associated with repulsive lone-pair interactions which are minimized in the axial form (compare A and B). Alternatively or additionally, stabilization may be due to favorable lone-pair interaction between neutral sulfur and the antibonding orbital of an antiperiplanar S^+-Me bond (as in A). Similar calculations on related systems which are isoelectronic with thiosulfonium ions, such as sulfur ylides (S^+-C^-), likewise indicate that a π-type lone pair orbital interacts favorably with an

TABLE 3. Estimated C-13 Chemical Shifts in 1-Methyl-1,2-dithianium Ions

Structure		Chemical Shifts[a,b]				
		C3	C4	C5	C6	MeS$^+$
 1	Calc eq-SMe	--	26	24.5	45.9	34.0[a]
	Calc ax-SMe		24.8	18.9	40.6	25.0[a]
	Found[c]	26.7	23.5	17.5	40.1	25.0
 2	Calc eq-SMe		34.9	33.4	52.1	32.9
	Calc ax-SMe		33.7	27.8	46.8	20.9
	Found[c]	36.1	34.7	27.4	50.2	20.7
	Calc eq-SMe 3c		30.9	26.2	46.1	31.6
	Calc ax-SMe 3d		29.7	20.6	40.8	<20
 3	Calc eq-SMe 3b		27.7	29.4	53.6	29.8
	Calc ax-SMe 3a		26.5	23.8	48.3	27.9
	Found[c]	37.7	(27.5)	(26.1)	47.0	28.2

(Table 3 continued)

Structure		C3	C4	C5	C6	MeS^{+}
	Calc eq-SMe		42.0	40.5	50.6	34.1
	Calc ax-SMe		40.8	34.9	45.3	25.4
	Found [c]	31.0	40.6	33.5	44.8	25.2
4						

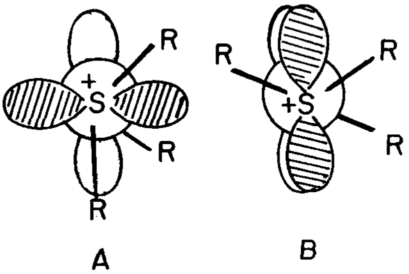
Footnotes to Table 3

a. $^{+}$SMe shifts were estimated from the shielding effect of ring methyls on the base shift values of ax-$^{+}$SMe as 25.0 ppm and eq-$^{+}$SMe as 34.0 ppm by analogy with 1-methylthianium ions (ref 4b). To the value of 25.0 ppm for ax-$^{+}$SMe was added 2.26 for 6-Me-ax, -4.72 for 6-Me-eq, 0.63 for 3-Me-eq or 5-CH_2-eq, -0.18 for 4-CH_2-eq; to the value of 34.0 ppm for eq-$^{+}$SMe was added -4.28 for 6-Me-ax, -2.02 for 6-Me-eq, -0.38 for 3-Me-ax, 0.11 for 3-Me-eq or 5-CH_2-eq, and 0.03 for 4-CH_2-eq.

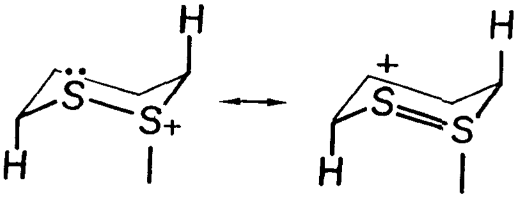
b. Shifts of ring carbons were estimated by adding to the observed C-13 shifts of the corresponding 1,2-dithiane (Table 2) the shielding effect of $^{+}$SMe-eq as 11.1, -4.4, -2.9 ppm for α(C6), β(C5), and γ(C4) carbons, respectively; and for $^{+}$SMe-ax as 5.8, -10.0, and -4.1 for α(C6), β(C5), and γ(C4), as given in ref.5. Estimated values at C3 were considered less reliable due to additional ring sulfur.

c. As fluoroborate salts in CD_3NO_2 relative to TMS at 25°C.

antibonding (σ^*)orbital of the adjacent polar bond when the latter is oriented as in A[10].



Evidence in support of the $n_\pi - \sigma^*$ hyperconjugative interaction as a source of the stereoelectronic effect may also be found in the proton chemical shifts of S-methyldithiolanium ions (Table 1). In every case, the chemical shift of the axial proton at C3 (adjacent to neutral sulfur) is deshielded almost as much as the axial proton at C6 (adjacent to positive sulfur). The charge must therefore be extensively delocalized over both sulfurs and has the greatest influence on neighboring axial protons that maintain an antiperiplanar orientation with the interaction orbitals.



Methylation of 1,2-Dithiolanes

Results obtained on methylation of five-membered 1,2-dithiolanes were interestingly different. Unlike the six-membered dithianes, methylation of 1,2-dithiolanes

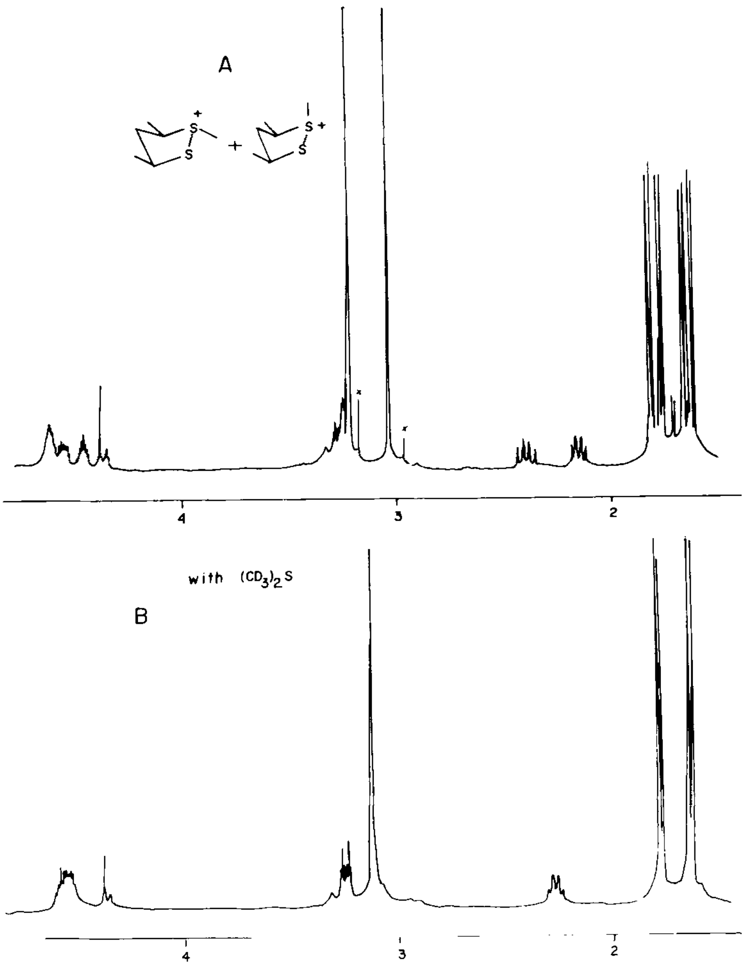


Figure 1 a) 5oo MHz proton NMR Spectrum of a 1:1 mixture of **7a** and **7b** in CD_3NO_2 at 25°. The mixture also contains about 1o% of the other pair of diastereomers, **6a** and **6b**, as can be seen from the $^+$SMe singlets marked with x.

b) spectrum with added $(CD_3)_2S$

16-18 proceeded with little stereoselectivity or regioselectivity. Diastereomers were obtained in a 2:1 and 1:1 ratio from 16 and 17 respectively, and methyl lipoate 18 gave all four possible S-methylated isomers in the ratio 11:26:30:33. In order to assign configuration to the products, we relied on an earlier observation by Barbarella and Dembech [11] that the chemical shift of S^+Me in methylated monothiolanes is shielded by an adjacent cis methyl substituent by 6.8 ppm but is affected little by substituents at other ring positions. Accordingly, the spectral assignments were made as shown in Table 2.

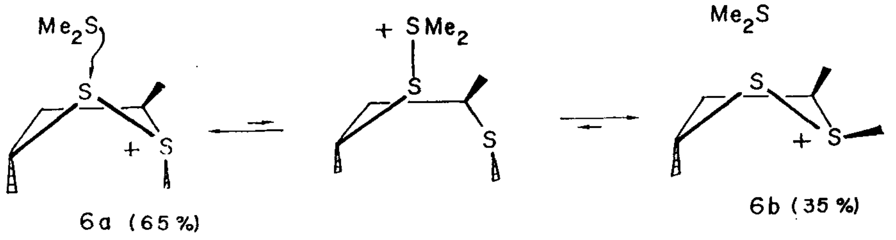
The proton spectrum of the parent S-methyl-1,2-dithiolanium ion 5 deserves special comment since it was deceptively simple. At room temperature, the methylene protons at each ring carbon were equivalent, consistent with a ring with reflection symmetry. Similar ring symmetry is suggested by a literature notation of the proton spectrum of the corresponding S-ethyl derivative [12]. Furthermore the spectrum of 5 was temperature dependent and, at − 30°C, resonances for six non-equivalent ring protons were broad but adequately resolved. These results imply that inversion at the pyramidal sulfur of 5 is rapid, but it seems very unlikely that a direct physical inversion at sulfur is involved. A chemically induced inversion seems more likely, especially since the coalescence temperature was poorly reproducible and varied widely with the age of the sample. The possibility that impurities such as sulfide or disulfide nucleophiles could be responsible was suggested by earlier studies in which rapid exchange was demonstrated between acyclic thiosulfonium ions and sulfur nucleophiles [1b,13] (eq.1).

$$Me_2S^+SMe + (CH_3)_2S \rightleftharpoons Me_2S + (CH_3)_2S^+SMe \quad (1)$$

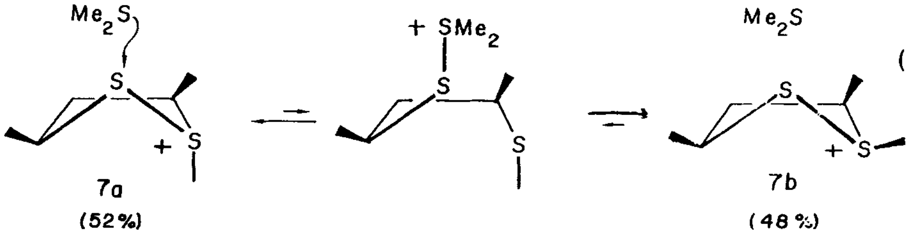
In fact, addition of *trace* amounts of methyl sulfide to **5** at -30° had a dramatic effect on the proton spectrum. The diastereotopic protons of **5** instantly became enantiotopic. Likewise, addition of sulfide to a 1:1 mixture of **7a** and **7b** caused the pair of S-methyl resonances to collapse to a singlet of intermediate shift, and the four C-methyl doublets to collapse to two doublets (Figure 1). In the C-13 spectrum, the twelve carbon resonance of **7a** and **7b** collapsed to six. The trans isomers **6a** and **6b** behaved similarly (see Table 1). The four S-methyl singlets of S-methylated lipoic ester collapsed to two corresponding to a 2:1 ratio of two regioisomers **8** and **9**, and the C-13 spectrum revealed the same dynamic effect since the resonance of the four isomeric esters coalesced to those of two isomers on addition of methyl sulfide (Table 2). No net chemical change occurred on addition of methyl sulfide because the diastereomeric mixtures could be recovered with no change in the initial composition. At long time intervals and with stoichiometric amounts of added sulfide, a slow demethylation occurred with regeneration of the parent 1,2-dithiolanes.

Evidently, methyl sulfide induces a rapid reaction which effectively destroys the chirality of the pyramidal sulfur in the S-methylated dithiolanes. We conclude that the process is a rapid and reversible ring-opening reaction in which the neutral sulfide attacks the neutral ring sulfur to cleave the S-S^+ bond.

Chirality at S^+ is thereby lost and reclosure of the ring can form either of two stereoisomers. The result is the interconversion of enantiomers in the case of **5** and diastereomers in the case of **6**-**9** (eqs. 2-3).



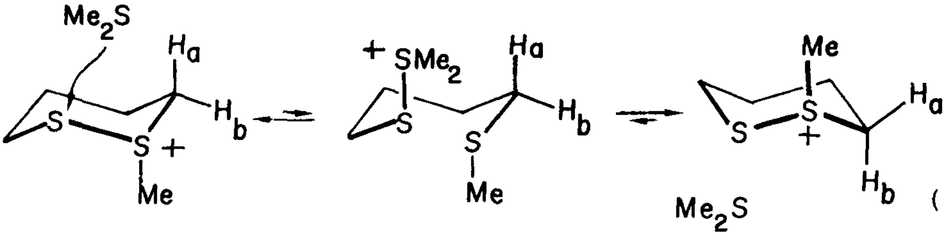
(2)



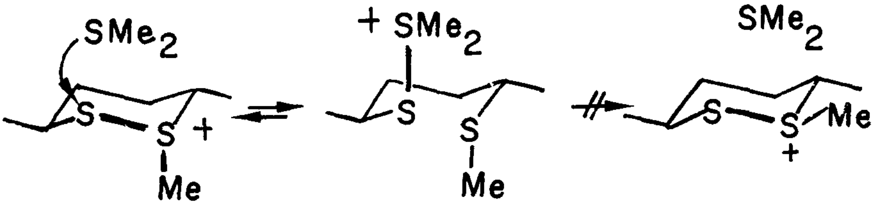
(3)

Equilibration of Dithianium Ions

The question now arises whether sulfide-induced ring-opening is restricted to 1,2-dithiolanium ions or whether 1,2-dithianium ions behave similarly. Addition of methyl sulfide to ring-substituted salts 2-4 had essentially no effect on their proton or C-13 spectra apart from very slight changes in chemical shift. However, addition of sulfide to the unsubstituted salt 1 in CD_3NO_2 caused the eight ring proton resonances to collapse to four as the diastereotopic protons became effectively enanthiotopic (Table 1). Clearly then, the S-methyl-1,2-dithianium ring undergoes rapid interconversion of enantiomeric configurations induced by added sulfide, presumably by the reversible ring-opening reaction of eq. 4.

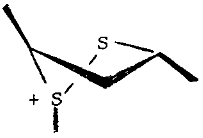

(4)

It is reasonable to expect the ring-substituted analogs to behave similarly. The reaction is not visible, however, because the diastereomeric configurations of 3 (and 4) must differ sufficiently in energy such that only one is formed upon ring closure. Formation of the other would require an equatorial orientation of S^+Me. Since the equatorial isomer is not formed under equilibrium conditions, the axial isomer must clearly be more stable, presumably because it enjoys a stereoelectronically favorable $n_\pi - \sigma^*$ interaction.

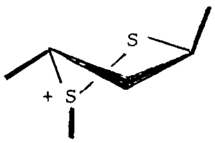


In view of the rapid equilibration of dithianium and dithiolanium isomers brought about even by trace amounts of added sulfide it seems highly probable that the methylation reactions used to prepare the ions from the parent disulfides are also under equilibrium control. The fact that the product ratios are unaffected by added sulfide confirms that equilibrium is reached during methylation. Unfortunately, we have no way of knowing from the present results what the kinetic selectivity might be in the methylation of cyclic disulfides.

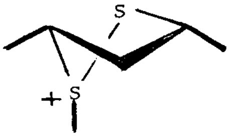
As mentioned, we attribute the diastereoselectivity observed in the methylation of substituted 1,2-dithianes to the stereoelectronic advantage associated with an axial $S^{+}Me$. In contrast, diastereoselectivity in the methylation of 1,2-dithiolanes is low. This does not necessarily mean, however, that stereoelectronic effects are insignificant. Rather it suggests that the 1,2-dithiolanium ring system is conformationally flexible, as are other five-membered rings [14], and can evidently adopt twist conformations such as **6a**-**7b** (shown below) which alleviate repulsive interactions between substituents on the same face of the ring without sacrificing the stereoelectronic advantage of a pseudoaxial $S^{+}Me$. The difference in energy between diastereomers is thereby minimized.



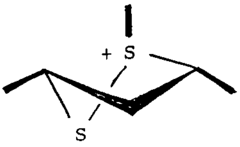
6a 65%



6b 35%



7b 48%



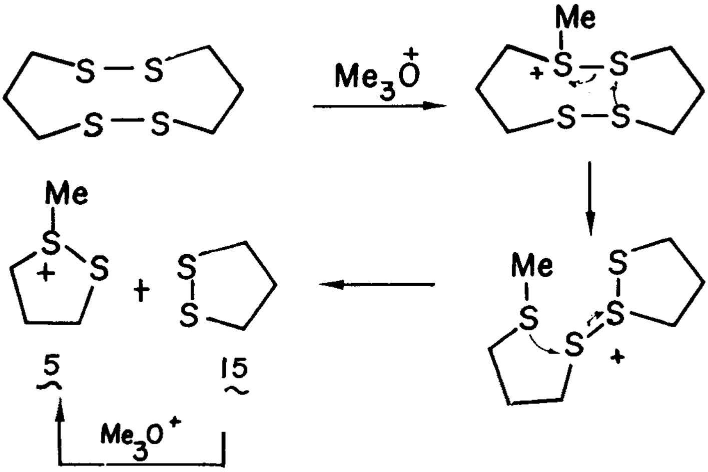
7a 52%

Ring Strain

It is important to note that the ring-opening equilibria of equations **2**-**4** favor ring closure. No products of ring opening were observed in the reactions with methyl sulfide, and no NMR evidence was forthcoming that the open chain products were populated to any detectable extent. There is a modest entropic advantage to ring closure, but this would be completely overshadowed by ring strain effects if these were as severe as reported for 1,2-dithiolanes [15]. Thus, the high reactivity of 1,2-dithiolanes is generally attributed to the strain of incorporating a disulfide function into a five-membered ring. If indeed the preferred dihedral angle of 90° for disulfides is compressed to 26° in 1,2-dithiolanes, this would increase electronic strain through increased repulsion between adjacent lone pairs [15]. It is therefore remarkable that comparable strain effects are inconsequential in related dithiolanium ions. The latter clearly are highly reactive and rapidly cleaved by nucleophiles, yet equilibrium conditions favor ring closure. This suggests that S-methylation stabilizes the ring, perhaps because it trades a relatively unfavorable stereoelectronic effect in the neutral disulfide for a favorable one in the ion. Alternatively, strain in 1,2-dithiolanes may be overestimated because of a confused association of high reactivity with ring strain. Our results clearly demonstrate that the reactivity of the 1,2-dithiolane ring is greatly enhanced by methylation whereby the $S-S^+$ bond becomes more susceptible to cleavage by nucleophiles. Nevertheless, equilibrium favors ring closure. The driving force for ring cleavage in 1,2-dithiolanium ions is therefore the high reactivity of the $S-S^+$ bond rather than relief of ring strain.

Depolymerization Reactions

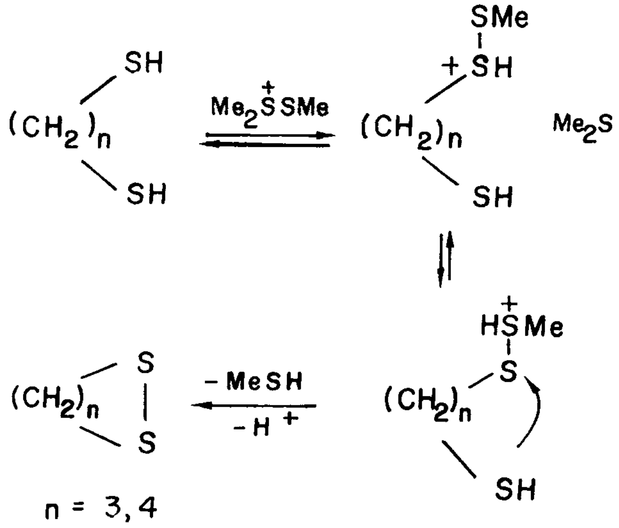
The ready polymerization of 1,2-dithiolanes can also be understood in terms of ring activation. As an example, 1,2-dithiolane **15** readily polymerizes and cannot be isolated as a stable monomer [16]. Depolymerization can be realized by prolonged heating and by treatment with electrophiles (I_2, HOAc)[16] but the conditions are not satisfactory as a source of monomer **15** for the preparation of the S-methylated ion **5**. However, we succeeded in preparing 5 by methylation of the polymer. The steps involved are illustrated in Scheme 1 for a cyclic dimer of 15[17].



Scheme 1

The first step is activation of one S-S bond by S-methylation. This is followed by a sequence of S-S^+ cleavage reactions through intramolecular attack of the other disulfide function. The process is terminated by irreversible methylation of the monomer 15 which is released in the penultimate step. The sequence readily extends to polymerization-depolymerization of polymer chains and larger rings.

A related reaction was discovered in attempts to prepare disulfide heterocycles from alkanedithiols. We found that methylthiolation of alkanedithiols with dimethylmethylthiosulfonium fluoroborate gave good yields of 1,2-dithiane (n=4) and 1,2-dithiolane (n=3; isolated as polymer). Cyclization is rationalized by the steps in Scheme 2.



Scheme 2

The physiological action of lipoic acid has also been attributed to the high reactivity of the 1,2-dithiolane ring. The role of lipoic acid in biologically important acyl transfer reactions from α-ketoacids (e.g. pyruvate) to coenzyme A (eq. 5) is not completely understood but lipoic acid is known to cycle between oxidized (cyclic) and reduced (open-chain) forms.[15b,18].

$$RCOCO_2H + CoASH + NAD^+ \longrightarrow RCOSCoA + CO_2 + NADH + H^+ \quad (5)$$

It is tempting to consider that lipoic acid reactivity is associated with intermediate formation of thiolanium ions at some juncture in the complex sequence of reactions underlying eq. 5. An earlier suggestion that acyl transfer might occur through S-acylated 1,2-dithiolanes seems to have drawn little attention[19]. We will end then on a speculative note by suggesting that serious consideration be given to the possibility that 1,2-dithiolanium (thiosulfonium) ions may play a role in lipoic acid mediated acylation of coenzyme A.

EXPERIMENTAL

The cyclic disulfides employed in this study are all known compounds and were prepared by previously published procedures. The method of choice involved the conversion of the appropriate alkanediol to the ditosylate or dimsylate followed by cyclization to the disulfide effected by $Na_2S.9H_2O$ and sulfur in DMF [20,21,22]. Yields were in the range of 60-80%.

Cyclization of dithiols. A new route to 1,2-dithiane and 1,2-dithiolane was found which utilized dimethylmethylthiosulfonium fluoroborate 1 as the reagent to cyclize the corresponding alkanedithiol. Addition of $Me_2S^+SMe\ BF_4^-$ to a molar equivalent of 1,4-butanedithiol in CH_2Cl_2 at 0-5°C followed by treatment with a saturated $NaHCO_3$ solution produced 1,2-dithiane 10, mp 29-31 in yields of 70-90%. The same procedure applied to 1,2-propanedithiol produced a yellow solution of 1,2-dithiolane monomer which was isolated as a polymer - a white powder of mp 70-76° - on removal of the solvent. Anal. for $C_3H_6S_2$: Calc. C 33.93, H 5.69, S 60.38; Found C 33.83, H 5.52, C 60.14. Solid state C-13 NMR by "magic angle spinning" of material mp 71-76° showed three resonances at 35.87, 33.0 and 27.24 ppm (TMS). 1,2-Dithiolane polymer was also prepared from 1,3-propanedithiol on treatment with iodine in chloroform [17], or lead tetraacetate and sulfur in benzene.

Methylation of Cyclic Disulfides. To prepare fluoroborate salts **1**-**4** and **6**-**9**, trimethyloxonium fluoroborate in nitromethane or acetonitrile was added to an equivalent of the appropriate cyclic disulfide dissolved in dichloromethane. The solution was maintained at 0°C under a nitrogen atmosphere for 1-2 hr or until all the oxonium salt had been consumed. The product was precipitated from the solution by addition of dry ether. Purification was achieved by dissolving the crude product in nitromethane and reprecipitating with ether. No satisfactory recrystallization procedure was found. 1-Methyl-1,2-dithianium fluoroborate **1** was obtained in 92% yield as a white powder mp 162-4°C (dec) stable in air. 1,3t,6c-Trimethyl-1,2-dithianium and 1,3t,6t-trimethyl-1,2-dithianium fluoroborates, **2** and **3**, were each obtained in 85-o8% yield as a glassy solid which did not crystallize. 2-Methyl-2,3-dithia-*trans*-decalin **4** had mp 176-8°C (90%). 1-Methyl-*trans*-3,5-dimethyl-1,2-dithiolanium fluoroborate was obtained as a 65:35 mixture of diastereomers **6a** and **6b** of mp 88-101° (86%), and 1-methyl-*cis*-3,5-dimethyl-1,2-dithiolanium fluoroborate as a 52:48 mixture of **7a** and **7b** (oil, 85%). The latter was also obtained by methylation and desulfurization of *cis*-4,6-dimethyl-1,2,3-trithiane which was obtained as a dimesylate of *meso*-2,4-pentanediol.

The most convenient procedure for the preparation of 1-methyl-1,2-dithiolanium fluoroborate **5** was as follows: Polymeric 1,2-dithiolane (mp 70-76°C, 1.06 g, 10 mmole) and trimethyloxonium fluoroborate (1.48 g, 10 mmole) in 20 ml each of CH_3NO_2 and CH_2Cl_2 were stirred at room temperature until the solution became free of undissolved solids. Filtration of the slightly cloudy solution into cold ether (100 ml) gave **5** as a white hygroscopic solid in 75-85% yield which, when dry, had mp 141-5°C (dec). The procedure was equally satisfactory with higher molecular weight $(C_3H_6S_2)_n$ polymers present as suspended solids in the reaction mixture.

ACKNOWLEDGEMENT

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