CONFORMATIONAL STUDIES ON SEVEN-MEMBERED
RINGS CONTAINING THE DISULFIDE AND TRISULFIDE GROUPS

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The barrier to ring inversion in medium sized carbocyclic rings may be in-
creased substantially by the introduction of heteroatoms in place of the com-
ponent carbon atoms.[1,2] The extension of this concept to seven-membered rings
systems containing the disulfide and trisulfide groups is of interest because
of the relatively high torsional barrier associated with these units as well
as their preferred 90° torsional angle.[3,4] To this end we have studied the
temperature dependence of the nmr spectra of the natural product lenthionine(1)
(1,2,3,5,6-pentathiepane)[5] and 1,2,4,6-tetrathiepane(2).[6] The low temperature
nmr spectrum of 1,2,3-trithiepane(3) has already been reported.[7]

1   2   3
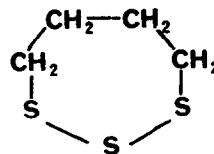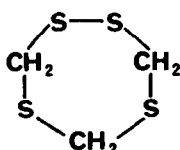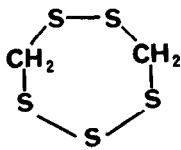
As expected the nmr spectrum of 1 showed at 30° only one sharp singlet peak

at δ=4.33. As the temperature was decreased, this resonance gradually broadened. The coalescence temperature was -60°. At -90° two sharp singlet peaks were observed separated by 10.3Hz.

This behavior is consistent with the occurrence of ring inversion between two conformational isomers such as <u>4</u> and <u>5</u>, which possess non-equivalent sets of


<p align="center">4   5</p>
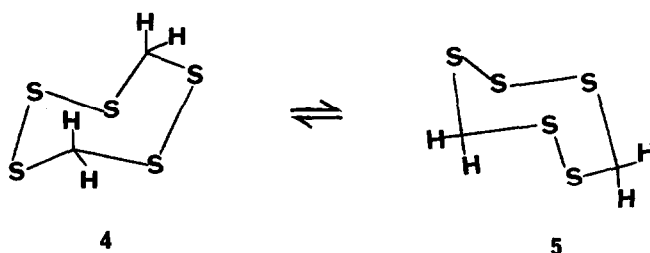
methylene groups. From related systems such as 1,2-dithiane(<u>6</u>)[3] and 1,2,3,4,5 pentathiepane(<u>7</u>)[8] a geminal coupling constant of 13 to 14Hz has been reported. The non-observation of a geminal coupling constant in the lower temperature spectrum of <u>1</u> indicates the incursion of a second rate process, namely, pseudorotation, which rapidly equilibrates the geminal protons.

The nmr parameters for compound (<u>1</u>) over the temperature range -45° to -80° are listed in Table 1. Total line shapes, including the positions of the resonances and their halfwidths were utilized to obtain the first order rate constants for ring inversion.[9] These in turn yielded from a plot of log k <u>versus</u> 1/T, an Arrhenius activation energy of 12.9 ± 0.4 kcal.

In the crystalline state lenthionine was shown to possess structure <u>4</u> by means of X-ray diffraction.[10]

The nmr spectrum of 1,2,4,6-tetrathiepane(<u>2</u>) showed two sharp resonances at δ=4.14 and 4.18 with an intensity ratio of 2:1 at room temperature. The spectrum did not change significantly when the temperature was reduced to -90°. The two resonances correspond to the structurally non-equivalent methylene groups. Conformations <u>8</u> and <u>9</u> may be drawn using 90° torsional angles for the disulfide group.

8   **9**
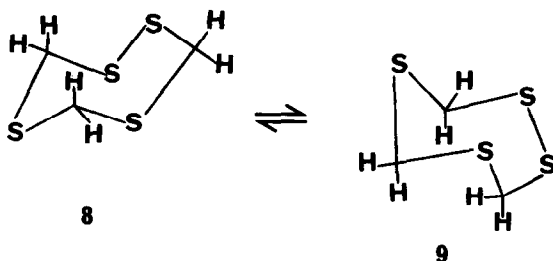
The energy barrier for equilibration of the three sets of non-equivalent methylene groups in these conformations is lower than that in lenthionine(1). This barrier is a composite consisting of both ring inversion and pseudorotation. Furthermore Kabuss et al.[7] report a coalescence temperature of -130° for 1,2,3-trithiepane(3) which corresponds to a very low barrier for ring inversion.

The point which emerges from these relative variations in energy barriers is that the very low barrier for pseudorotation in cycloheptane of 2-3 kcal[11] is not increased significantly in the sulfur analogs 1, 2 and 3 eventhough in the case of lenthionine(1) a fairly high barrier for ring inversion occurs. The tri-sulfide group in 3 serves to raise the barrier to approximately 6-7 kcal/mole. Introduction of the disulfide and sulfide groups as in 2 does not cause a very large increase in the barrier for ring inversion. This is understandable in terms of the expectedly low torsional contribution for the C-S-C bond.
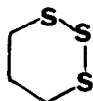
An analogous progressive increase in barrier height for successive replace-ment of the ring carbons by sulfur atoms occurs in the six-membered ring.

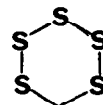|	**6**	**10**	**7**
Tc	-43°	-8°	23° (ref 8)
G kcal/mole	11.6 (ref 3)	13.2 (ref 7)	

The difference in Tc of -130° for the seven-membered trisulfide 3 compared to -8° for the six-membered trisulfide 10 in another manifestation of the "floppiness" of the seven-membered ring which is ultimately due to facile pseudorotation in the former. The six-membered pentasulfide 7 has a very high barrier and is essentially locked in a chair form.

A similar, but limited comparison, may be made for the pair of five-membered compounds 1,2-dithiolane(11) and 1,2,4-trithiolane(12).[6]

11   **12**
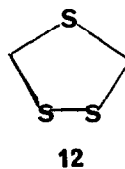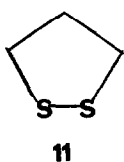
The latter compound shows a singlet resonance at δ=4.11 which remained unchanged upon cooling to -90°. This is in agreement with a very low barrier for pseudorotation. Although 1,2-dithiolane was not measured in this study Bergson and Schotte[12] report a torsional barrier of 14.2 ± 0.2 kcal/mole for the S-S bond in 1,2-dithiolane-4-carboxylic acid.

Finally, the torsional angles for the S-S bonds in 4 and 5 may be close to 90° as revealed by inspection of models while the S-S torsional angle has been found by Foss et al.[13,14] to be 60.3 ± 1.5° for the six membered racem-1,2-dithane-3,6-dicarboxylic acid and only 26.6° ± 1° in the five-membered racem-1,2-dithiolane-4-carboxylic acid.

Table 1[a]

NMR Parameters of Lenthionine (1)

as a Function of Inversion Frequency

temp°C	Line width (Wl/2) (Hz)	$\tau(sec^{-1})$
-45	1.0	0.005
-55	5.0	0.026
-60	coalescence	0.05
-70	2.1	0.17
-80	0.4	0.80

a) Spectra were determined on a Varian Ha-100
    spectrometer at 100 MHz. Carbon disulfide
    was used as solvent. Temperatures for the
    rate determinations are considered accurate
    to ± 0.5°. τ is related to k by k= $\frac{1}{2\tau}$.

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