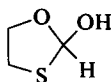


## The ring-opening of an unsymmetrical tetrahedral intermediate – 2-hydroxy-1,3-oxathiolane

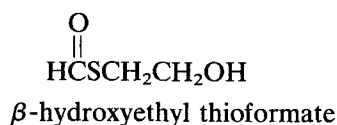
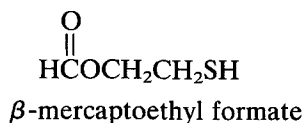
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*Ab initio* calculations were performed on 2-hydroxy-1,3-oxathiolane:



and the two products of its breakdown:



Complete geometry optimizations were performed at minimal (STO-3G) and split-valence (3-21G) basis set levels. In addition, a single point calculation was performed at 6-31G\* level with *d* orbitals added on sulfur only. The conformation of the oxathiolane intermediate and its stability relative to the breakdown products was investigated. The STO-3G basis set gave an envelope form while 3-21G gave the twist form of the five-membered ring as the most stable. For all three basis sets the ester product was more stable than thioester.

**Key words:** *Ab initio* calculations—tetrahedral intermediate—2-hydroxy-1,3-oxathiolane—sulfur-containing compounds

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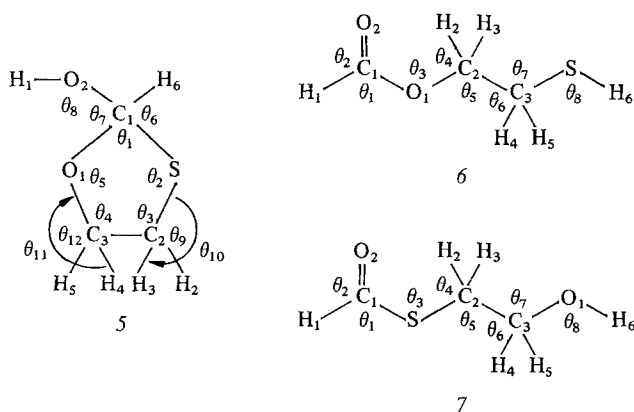
## 2. Computational details

*Ab initio* calculations were performed on a SEL 32/75 and an IBM 3033/N8A at the University of Toronto. The computer program used was MONSTER-GAUSS [4]. The program incorporates the integral and SCF routines from GAUSS80 [5]. The analytical SCF gradients were calculated with the routine FORCE [6]. The optimization method used was OC [7].

Complete geometry optimizations were carried out at the STO-3G [8] and 3-21G [9] levels. In addition, single point calculations were performed at 6-31G\* [9] with *d* orbitals added on sulfur.

## 3. Results and discussion

Fig. 1 shows the definition of geometric parameters considered in the geometry optimization of the three molecules. The geometries calculated with STO-3G



**Fig. 1.** Definition of geometry parameters for the cyclic tetrahedral intermediate and the two products. The torsional angles are defined as follows

- |  |   |
|--|---|
| <p><b>5</b></p> <p><math>\phi_1 = \text{TORS}(C_2, S, C_1, O_1),</math><br/> <math>\phi_3 = \text{TORS}(O_2, C_1, O_1, S),</math><br/> <math>\phi_5 = \text{TORS}(H_6, C_1, O_1, S),</math><br/> <math>\phi_7 = \text{TORS}(H_3, C_2, S, C_3),</math><br/> <math>\phi_9 = \text{TORS}(H_5, C_3, O_1, C_2)</math></p>       | <p><math>\phi_2 = \text{TORS}(C_3, C_2, S, C_1)</math><br/> <math>\phi_4 = \text{TORS}(H_1, O_2, C_1, S)</math><br/> <math>\phi_6 = \text{TORS}(H_2, C_2, S, C_3)</math><br/> <math>\phi_8 = \text{TORS}(H_4, C_3, O_1, C_2)</math></p>     |
| <p><b>6</b></p> <p><math>\phi_1 = \text{TORS}(H_2, C_2, O_1, C_1),</math><br/> <math>\phi_3 = \text{TORS}(H_4, C_3, C_2, O_1),</math><br/> <math>\phi_5 = \text{TORS}(C_3, C_2, O_1, C_1),</math><br/> <math>\phi_7 = \text{TORS}(O_2, C_1, O_1, C_2),</math><br/> <math>\phi_9 = \text{TORS}(H_6, S, C_3, C_2)</math></p> | <p><math>\phi_2 = \text{TORS}(H_3, C_2, O_1, C_1)</math><br/> <math>\phi_4 = \text{TORS}(H_5, C_3, C_2, O_1)</math><br/> <math>\phi_6 = \text{TORS}(S, C_3, C_2, O_1)</math><br/> <math>\phi_8 = \text{TORS}(C_2, O_2, C_1, H_1)</math></p> |
| <p><b>7</b></p> <p><math>\phi_1 = \text{TORS}(H_2, C_2, S, C_1),</math><br/> <math>\phi_3 = \text{TORS}(H_4, C_3, C_2, S),</math><br/> <math>\phi_5 = \text{TORS}(C_3, C_2, S, C_1),</math><br/> <math>\phi_7 = \text{TORS}(O_2, C_1, S, C_2),</math><br/> <math>\phi_9 = \text{TORS}(H_6, O_1, C_3, C_2)</math></p>       | <p><math>\phi_2 = \text{TORS}(H_3, C_2, S, C_1)</math><br/> <math>\phi_4 = \text{TORS}(H_5, C_3, C_2, S)</math><br/> <math>\phi_6 = \text{TORS}(O_1, C_3, C_2, S)</math><br/> <math>\phi_8 = \text{TORS}(C_2, O_2, C_1, H_1)</math></p>     |

**Table 1.** Optimized geometries of the three molecules shown in Fig. 1

Parameters	5		6		7	
	STO-3G	3-21G	STO-3G	3-21G	STO-3G	3-21G
C <sub>1</sub> —O <sub>1</sub>	1.434	1.385	1.387	1.347	—	—
C <sub>1</sub> —O <sub>2</sub>	1.430	1.405	1.214	1.199	1.217	1.197
C <sub>1</sub> —S	1.835	1.916	—	—	1.773	1.837
O <sub>1</sub> —C <sub>3</sub>	1.436	1.457	—	—	1.435	1.441
C <sub>2</sub> —C <sub>3</sub>	1.549	1.551	1.545	1.519	1.546	1.520
O <sub>1</sub> —C <sub>2</sub>	—	—	1.441	1.459	—	—
S—C <sub>2</sub>	1.799	1.886	—	—	1.806	1.895
S—C <sub>3</sub>	—	—	1.805	1.896	—	—
C <sub>1</sub> —H <sub>1</sub>	—	—	1.104	1.076	1.104	1.080
C <sub>1</sub> —H <sub>6</sub>	1.108	1.074	—	—	—	—
C <sub>2</sub> —H <sub>2</sub>	1.088	1.075	1.096	1.079	1.088	1.076
C <sub>2</sub> —H <sub>3</sub>	1.087	1.077	1.096	1.079	1.088	1.076
C <sub>3</sub> —H <sub>4</sub>	1.097	1.077	1.089	1.077	1.098	1.083
C <sub>3</sub> —H <sub>5</sub>	1.093	1.077	1.089	1.077	1.098	1.083
O <sub>2</sub> —H <sub>1</sub>	0.991	0.965	—	—	—	—
O <sub>1</sub> —H <sub>6</sub>	—	—	—	—	0.991	0.966
S—H <sub>6</sub>	—	—	1.330	1.351	—	—
$\theta_1$	109.7	104.6	124.9	124.4	125.6	123.4
$\theta_2$	91.8	85.2	125.6	125.7	122.2	125.5
$\theta_3$	104.9	105.8	112.3	118.3	98.8	98.0
$\theta_4$	108.5	109.8	110.5	109.6	110.6	108.1
$\theta_5$	109.1	113.5	107.5	104.6	110.2	108.9
$\theta_6$	109.1	109.7	108.5	110.2	109.6	110.2
$\theta_7$	104.1	108.7	110.1	107.9	107.7	104.2
$\theta_8$	104.3	111.9	95.0	97.6	103.9	111.0
$\theta_9$	111.7	107.5	—	—	—	—
$\theta_{10}$	111.0	108.7	—	—	—	—
$\theta_{11}$	110.8	105.9	—	—	—	—
$\theta_{12}$	107.4	109.0	—	—	—	—
$\phi_1$	-5.048	42.48	59.4	59.9	59.37	59.36
$\phi_2$	-17.59	-31.97	-59.4	-59.9	-59.37	-59.36
$\phi_3$	122.2	116.5	58.19	61.1	58.75	59.99
$\phi_4$	-73.78	-59.33	-58.19	-61.1	-58.75	-59.99
$\phi_5$	-120.0	-117.5	180.0	180.0	180.0	180.0
$\phi_6$	119.5	118.8	180.0	180.0	180.0	180.0
$\phi_7$	-119.7	-120.4	0.0	0.0	0.0	0.0
$\phi_8$	120.7	120.5	180.0	180.0	180.0	180.0
$\phi_9$	-121.2	-120.9	180.0	180.0	180.0	180.0

and 3-21G basis sets are given in Table 1. The energies calculated for the three molecules are tabulated in Table 2.

### 3.1. Geometrical results

The tetrahedral intermediate examined in the present study is of interest from a geometric point of view because it is a five-membered ring – a 1,3-oxathiolane.

**Table 2.** Energies<sup>a</sup> calculated for the three molecules shown in Fig. 1. At optimized geometries except where noted

Basis set	5	6	7
STO-3G	-656.586893	-656.551894	-656.540303
3-21G (STO-3G geometry)	-660.858822	-660.879916	-660.851149
3-21G	-660.876731	-660.888418	-660.859143
6-31G <sup>*b</sup>	-664.181129	-664.198949	-664.180825
6-31G <sup>*c</sup>	-664.171219	-664.194137	-664.179528

<sup>a</sup> In hartrees.<sup>b</sup> With polarization on sulfur. Done at 3-21G geometry.<sup>c</sup> Same as b except STO-3G geometry.

The conformation of five-membered rings has been an area of considerable interest.

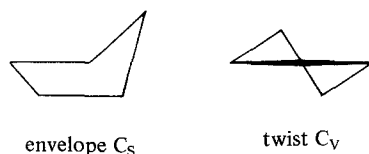
Several studies have been made on the conformation of 1,3-oxathiolane rings – utilizing generally nmr techniques.

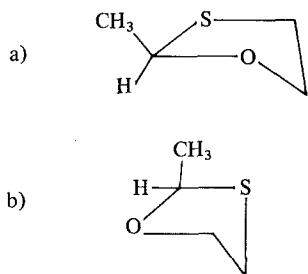
Pasto, Klein and Doyle [10] studied a series of 2-substituted-1,3-oxathiolanes. They found that the preferred conformation is a slightly distorted envelope (see Fig. 2) with the oxygen atom at the “flap” position. Their results also indicated no pseudo-rotation in these molecules, i.e. they were conformationally semi-rigid.

This view was refuted by Wilson, Huang and Bovey [11] who also carried out an nmr study and concluded that an envelope structure was preferred but the “flap” atom was C-5. They also deduced that rapid pseudo-rotation was taking place.

Keskinen, Nikkilä and Pihlaja [12], also on the basis of nmr studies, concluded that the oxathiolane ring is less flexible and more puckered than 1,3-dioxolane. They proposed that although envelope conformations with either O or C-5 as the “flap” are highly favored, the minimum energy conformation may in fact be intermediate between these two and distorted towards the half-chair or twist form (see Fig. 2). They concluded that the conformation depends on the substitution.

Wilson [13] has done conformational energy calculations on 1,3-oxathiolanes. He found two minima, the first corresponding to an envelope with C-5 as the “flap” atom and a secondary minimum 1 kcal/mole higher in energy with C-4 as the “flap” atom (see Fig. 3). In addition, he found half-chair conformations

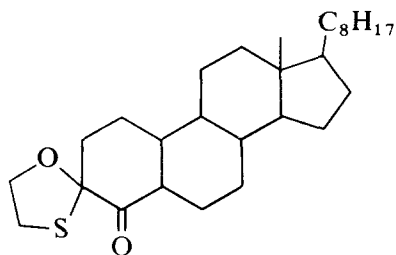
**Fig. 2.** Two possible conformations of a five-membered ring



**Fig. 3.** The two conformations found by Wilson in his conformational energy studies [13]; a) minimum energy and b) secondary minimum 1 kcal/mole higher in energy

with C-4 or C-5 and one heteroatom lying above and below the plane defined by the other three atoms with essentially the same energy as the corresponding envelopes.

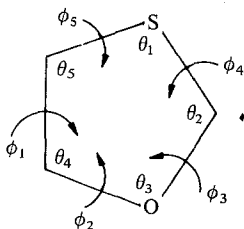
These results can be compared with an X-ray crystal structure [14] of cholestan-4-one-3-spiro-(2,5-oxathiolane).



This showed the oxathiolane ring to have a slightly distorted envelope conformation with the methylene carbon adjacent to oxygen lying  $0.5 \text{ \AA}$  out of the plane defined by the other four atoms and with a torsional angle of  $34.3^\circ$  between the two carbon atoms.

Table 3 gives a comparison between the STO-3G and 3-21G geometries obtained in this study and the results of Wilson along with the parameters obtained from the X-ray crystal structure of cholestan-4-one-3-spiro-(2,5-oxathiolane).

It is interesting to note that the STO-3G geometry is quite close to that of the minimum of Wilson's calculations and the structure determined for the cholestanone derivative.



**Fig. 4.** Bond and torsional angles used for Table 3

**Table 3.** Geometry comparison between STO-3G, 3-21G and experimental values for a 1,3-oxathiolane (Fig. 4)

Angle	STO-3G <sup>a</sup>	3-21G <sup>a</sup>	B <sup>b</sup>	C <sup>c</sup>	D <sup>d</sup>
$\phi_1$	37.38	16.23	-39.0	38.0	34.3
$\phi_2$	-17.59	-31.97	22.8	-16.6	-13.5
$\phi_3$	-5.05	42.48	2.3	-8.1	-10.4
$\phi_4$	28.51	-42.27	-21.3	33.0	34.0
$\phi_5$	-42.91	17.56	40.9	-48.0	-46.3
$\theta_1$	109.1	113.5	112.9	111.0	112.0
$\theta_2$	109.7	104.6	107.5	106.4	106.0
$\theta_3$	91.82	85.2	91.8	91.9	91.9
$\theta_4$	104.9	105.8	103.5	104.0	105.2
$\theta_5$	108.5	109.8	109.0	108.0	107.8

<sup>a</sup> This study.<sup>b</sup> Wilson, Ref. 13. +1 kcal minimum of conformational energy map.<sup>c</sup> *Ibid*, minimum energy of conformational energy map.<sup>d</sup> Ref. [14]. Cholestan-4-one-3-spiro-(2,5-oxathiolane).

The 3-21G geometry, on the other hand, resembles more closely a twist or half-chair conformation. From the discussion above, there probably is very little energy difference between the two conformations, and the STO-3G basis set prefers an envelope while 3-21G prefers the twist form.

**Table 4.** Geometry comparison between STO-3G, 3-21G and experimental

Parameter	Compound	STO-3G	3-21G	expt'l	reference
C—O	6	1.441	1.459	1.46	16
C—O	7	1.435	1.441	1.46	16
C—S	6	1.805	1.896	1.819	17
C—S	7	1.806	1.895	1.819	17
C=O	6	1.214	1.199	1.203	9
C=O	7	1.217	1.197	1.203	9
C—C	6	1.545	1.519	1.529	18
C—C	7	1.546	1.520	1.529	18
C—H	6	1.104	1.076	1.097	19
C—H	7	1.104	1.080	1.097	19
O—H	7	0.991	0.966	0.963	9
S—H	6	1.330	1.351	1.329	16
C—O—C	6	112.3	118.3	113	16
C—S—C	7	98.8	98.0	105	16
C—C—O	6	110.5	109.6	—	
C—C—O	7	107.7	104.2	—	
C—C—S	6	110.1	107.9	108.6	18
C—C—S	7	110.2	108.9	108.6	18
C—O—H	7	103.9	111.0	109	20
C—S—H	6	95.0	97.6	96.5	17
O—C—O	6	124.9	124.4	124	16

Cremer and Pople [15] found much the same thing when they studied the geometry of 1,3-dioxolane at STO-3G and 4-31G levels. STO-3G gave the envelope while the 4-31G basis set predicted a twist form.

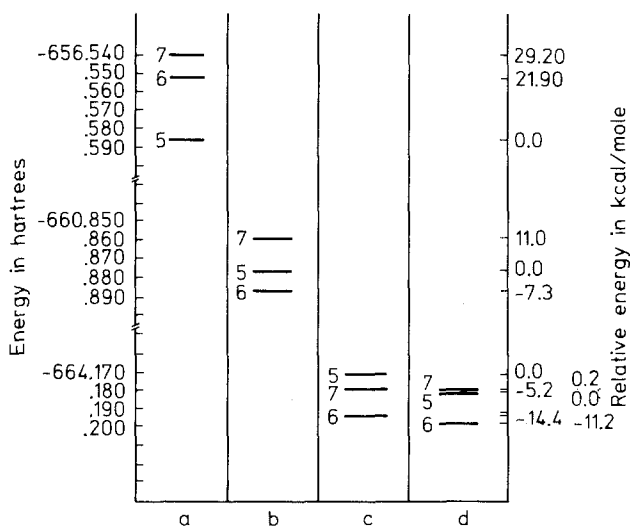
Table 4 shows a comparison between STO-3G, 3-21G and (where available) some typical experimental values obtained for various geometric parameters in the ester products.

Examination of the Table indicates that the 3-21G basis set gives better values for C—O, C=O, O—H bond lengths and CCS, COH, and OCO bond angles. STO-3G seems to give closer results for C—S, C—H, S—H bond lengths and COC bond angles. C—C bond lengths and CSH bond angles appear to be approximately intermediate between the values given by the two basis sets. Neither basis set seemed to be close to the experimental value for a CSC bond angle.

The largest discrepancy was noted for the C—S bond length from the higher level 3-21G basis set.

The 3-21G basis set is a relatively new one [9a]. Results for the second-row elements have only recently been published [9b]. The results obtained in the present study are in excellent agreement with those found by Pople et al. For first-row elements, 3-21G gives better results, but it does not do as well as the STO-3G basis set with sulfur in particular.

From the values of the energies obtained from the single point 6-31G\* calculations at the STO-3G and 3-21G geometries, it can be seen that even though the 3-21G



**Fig. 5.** Relative energies of the Intermediate and Products with a) STO-3G (optimized geometry), b) 3-21G (optimized geometry), c) 6-31G\* (STO-3G geometry) and d) 6-31G\* (3-21G geometry)



geometry gave some bond lengths and bond angles which do not seem reasonable, overall it was a better geometry for all three molecules since the energies were all lower.

### 3.2. Energetic results

Fig. 5 shows the relative ordering of the energies for the three molecules at STO-3G, 3-21G, 6-31G\* (at STO-3G geometry) and 6-31G\* (at 3-21G geometry).

At the STO-3G level, the cyclic tetrahedral intermediate was considerably stabilized relative to the ester and thioester (21 and 28 kcal/mole respectively). This is a general feature of the minimal basis set – it tends to overestimate the stability of a cyclic isomer over an acyclic isomer [21]. With the split-valence basis set, 3-21G, this problem was at least partially corrected and the tetrahedral intermediate came between the two products in energy. The single point calculation with 6-31G\* led to a further raising of the oxathiolane energy with respect to the products. Using the STO-3G geometry, the intermediate actually had a higher energy than either product although at 3-21G geometry it was still slightly lower than the thioester.

The more important point for the purposes of this study was the relative ordering of the energies of the two products. With the minimal basis set, the  $\beta$ -mercaptoethyl formate was more stable than the  $\beta$ -hydroxyethyl thioformate by 7.4 kcal/mole. With the 3-21G basis set, the difference was 18 kcal/mole. This is a sizable energy difference. From the single point calculations at 6-31G\* the ester was again lower in energy, by 9.2 kcal/mole at STO-3G geometry and by 11.4 kcal/mole at the 3-21G geometry, still a large energy difference.

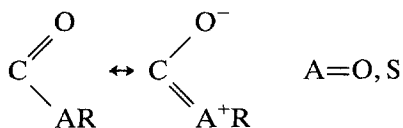
This result can be compared with some *ab initio* calculations performed by Hayes, Kenyon and Kollman [22] who studied hydrolysis of esters and thioesters. They considered the isodesmic (same number and types of bonds on either side of the equation) reactions:

	$\Delta E$ (STO-3G)	$\Delta E$ (STO-3G*)
$\text{CH}_3\text{COOCH}_3 + \text{H}_2\text{O} \rightarrow \text{CH}_3\text{COOH} + \text{CH}_3\text{OH}$	+4.03	—
$\text{CH}_3\text{COSCH}_3 + \text{H}_2\text{O} \rightarrow \text{CH}_3\text{COOH} + \text{CH}_3\text{SH}$	-4.56	-3.20

They found  $\Delta E$  for thioacetate hydrolysis more exothermic than acetate hydrolysis by about 9 kcal/mole. Although comparative solution phase  $\Delta H$  values for the two reactions are not known, available evidence indicates that the relative free energies parallel the relative enthalpies [22]. Thus, their calculations qualitatively agreed with the observation that the free energy of hydrolysis of thioacetate is about 3 kcal/mole more negative than that of acetate in solution. Again one can only draw qualitative comparisons with the present study's finding that the ester is 11 kcal/mole more stable than the thioester in the gas phase, but if one considers the effect of putting the two esters into solution, one would expect that

the  $\beta$ -hydroxyethyl thioformate would participate in hydrogen bonding with solvent much better than the  $\beta$ -mercaptoethyl formate which would decrease the energy difference in solution, bringing it closer to the 3 kcal/mole difference.

Hayes, Kenyon and Kollman [22] considered the energy difference found to be due primarily to a resonance effect:



Oxygen can participate better in this resonance than sulfur.

From these results one may expect that the formate ester should be the thermodynamically favored product. This is currently being tested by hydrolyzing orthoester in 1.0 M acid where the kinetically favored product is the thioformate. Preliminary results seem to indicate that by letting it stand, slow isomerization to formate occurs [23].

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