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Investigation of Sulfur Extrusion from a Cyclic Dialkoxy Disulfide

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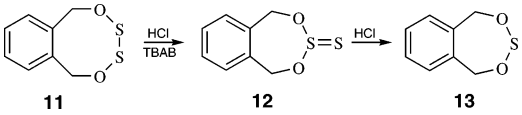

The relationship of cyclic dialkoxy disulfide **11**, its thionosulfite isomer **12**, and the related sulfoxylate **13** has been examined. Investigations demonstrate an interconversion between thionosulfite **12** and sulfoxylate **13**. This sequential transformation brings evidence that a branched-bond sulfur structure is likely involved in sulfur extrusion.

The extrusion of sulfur from the ubiquitous disulfide structure **1** to give the resulting sulfide **2** (Figure 1a) has been known and well-documented for over a century.[1] The mechanism by which this transformation occurs (catalyzed or uncatalyzed) is, however, still unclear and has been the subject of considerable debate. Over 50 years ago, Foss[2] reviewed the evidence for the existence of the sulfur branched-bond and underscored the role that thiosulfoxide structure **3** might play as an intermediate in the extrusion of elemental sulfur. Study of the sulfur monofluoride structures[3] **4** and **5** in 1964 and the discovery of thionosulfites[4] (e.g., compound **6**, Figure 1b) further supports the existence of the sulfur branched-bond. This structural arrangement for the thionosulfites was conclusively demonstrated in 1980 with an X-ray single-crystal structure analysis of **7**.[5]

The rearrangement of allylic disulfides[6a] (*e.g.*, rearrangement of disulfide **8** to **9,** possibly *via* branch-bonded **10**) as well as reports on the desulfurization of polysulfides[1,7] and the conversion of diallyl sulfide to diallyl disulfide[6b] with S_8 as well as

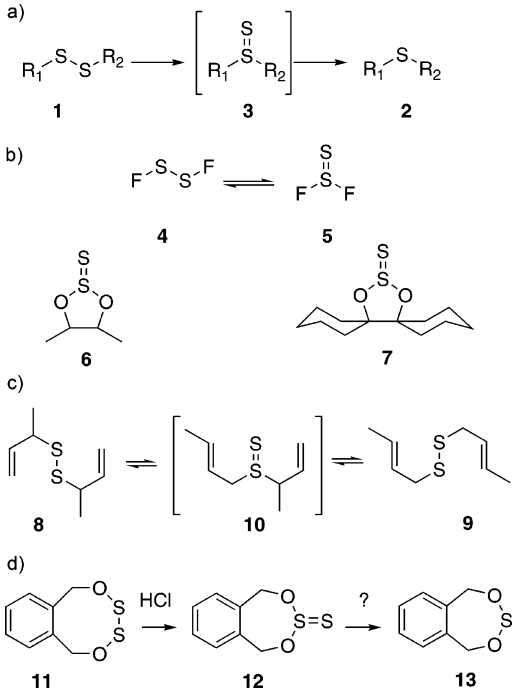

FIGURE 1. Examples of branched-bond sulfur-containing molecules and sulfur extrusion reactions. (a) Proposed sulfur extrusion sequence via thiosulfoxide structure **3** although barriers are calculated to be high.[9] (b) Sulfur monofluoride structures **4**−**5** and thionosulfite structures **6** and **7**. (c) Rearrangement of allylic disulfide **8** to **9** via possible thiosulfoxide **10**. (d) Possible sulfur extrusion mechanism from dialkoxy disulfide **11**.

sulfur extrusion from thiiranes[6c] constitute other evidence for possibly implicating branch-bonded structures as transient intermediates in sulfur extrusion/insertion processes. Attempts to detect a thiosulfoxide structure by spectroscopic means have been carried out.[7,8] Theoretical studies have also been published on the isomerization of disulfide bonds,[9] although in aliphatic cases, the branch-bonded intermediates are judged to be high-energy species. Such is not the case, however, for thionosulfites (like **12**). In this context, our recent work on cyclic dialkoxy disulfides[10] was promising as it could possibly illustrate how sulfur might be lost in such a ring system.

Indeed, cyclic dialkoxy disulfide **11** was found to isomerize to its thionosulfite isomer **12** under acidic conditions with

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(10) Zysman-Colman, E.; Nevins, N.; Eghbali, N.; Snyder, J. P.; Harpp, D. N. *J. Am. Chem. Soc.* **2006**, *128*, 291.

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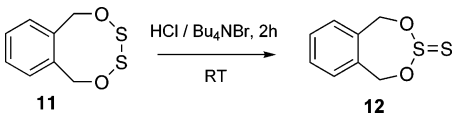
TABLE 1. Transformation of Dialkoxy Disulfide 11 to Its Structural Isomer Thionosulfite 12



entry[a]	T (°C)	reaction time (h)	HCl gas (mL)	additive	NMR yield (%)
1	25	2	-	-	0
2[b]	90	2	-	-	0
3	25	2	0.2	-	0
4	25	24	0.2	-	0
5	25	60	0.2	-	4
6	25	366	0.2	-	7
7	65	2	0.2	-	15
8	25	2	2.0	-	0
9	25	2	0.2	Et_3NHCl	61
10	25	2	0.2	Bu_4NCl	63
11	25	2	0.2	Bu_4NBr	65
12	25	2	0.2	Bu_4NOAc	0
13	25	1	0.2	Bu_4NBr excess	67

[a] All reactions were performed in toluene-d_8, with a 5 mg/mL (0.025 mM) solution of the dialkoxy disulfide, a catalytic amount of HCl gas (0.3 equiv, 0.0075 mM), and a stoichiometric amount of salt. [b] Benzene-d_6 was used as solvent and refluxed for 2h.

TABLE 2. Formation of Sulfoxylate 13 from Thionosulfite 12

entry[a]	T (°C)	reaction time (min)	conditions	NMR yield (%)
1	90	120	-	0
2	25	120	HCl (g)	15
3	25	2	HCl (g)	15
4	65	2	HCl (g)	10
5	25	120	HCl (g)/Bu_4NCl	10

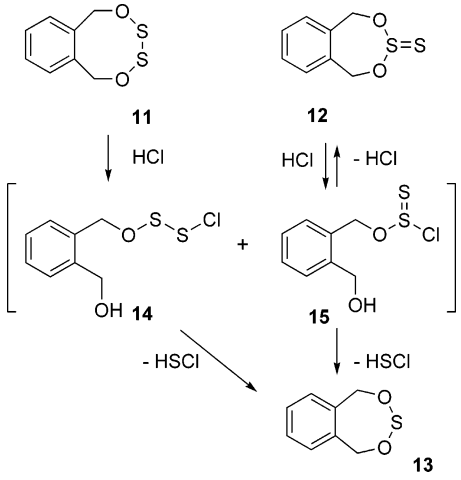
[a] All reactions were performed in toluene-d_8 with a 5 mg/mL (0.025 mM) solution of thionosulfite, catalytic amount of HCl gas and a stoichiometric amount of salt.

concomitant formation of small quantities of the corresponding sulfoxylate **13** (Figure 1d).[10] In this paper, we propose a possible mechanism by which sulfur is extruded from **12** and use thionosulfite **12** as a model to examine the chemistry of branch-bonded sulfur species. The results are presented in Tables 1 and 2.

A detailed analysis of the information contained in Tables 1 and 2 clearly underscores the importance of hydrochloric acid in this reaction. Since triethylammonium hydrochloride formed as a byproduct in the *in situ* acid-catalyzed conversion of **11** to **12**,[10] we investigated whether the salt promoted the transformation. To test this proposal, combinations of acid and ammonium salts were formulated in a series of experiments (entries 9 to 13, Table 1). The addition of either triethylammonium hydrochloride or tetrabutylammonium chloride under acidic conditions promoted the conversion of the dialkoxy disulfide **11** to thionosulfite **12** in moderate yield. Polymerization or partial decomposition is believed to be one of the major side-reactions observed during this transformation.

We suggest the possibility of a rearrangement of the dialkoxy disulfide (Scheme 1, intermediate **15**). Protonation of **11** followed by ring opening to give intermediates **14** and **15** and

SCHEME 1. Possible Mechanistic Pathway from 11 to 12 and 13



by subsequent closure to give thionosulfite **12** is a reasonable working hypothesis. In our recent paper,[10] calculations revealed that the energies of **11** and **12** were comparable thus it is not unreasonable to portray **14** and **15** in this pathway.

The salt would serve as a source of nucleophilic chloride ion, speeding up the reaction. Evidence of its nucleophilic character has been observed under other circumstances. For instance, when 1,3-diphenyl-1,3-propandiol was subjected to the original reaction conditions (S_2Cl_2, Et_3N), a significant amount of the corresponding 1,3-dichloropropane was isolated.[11] Precipitation of the salt ($Et_3N{\cdot}HCl$) as it forms suppressed the formation of dichloropropane. Interestingly, the use of a non-halogen counteranion did not promote the transformation (entry 12). This would be in agreement with the proposed mechanism as halogens have properties as both nucleophiles and leaving groups.

Acidic conditions were similarly applied to cyclic thionosulfite **12**. As expected, a small amount of the cyclic sulfoxylate **13** was quickly produced instead of the dialkoxy disulfide **11**. No other product was observed with these conditions; results are summarized in Table 2 and Scheme 1. Although elemental sulfur was recovered at the end of the reaction, the actual process by which the sulfur atom is lost remains unknown; the formation of HSCl could be involved with its decomposition leading to the release of S_8 and HCl. A control experiment based on the use of lead acetate was also performed to detect any potential release of H_2S, but no characteristic precipitation was observed.

These results clearly demonstrate that in the presence of hydrochloric acid, cyclic thionosulfite **12** is partially converted to the corresponding sulfoxylate **13**. Reports of sulfoxylate formation during previous experiments[10] might therefore be the result of a sulfur extrusion from a branched-bond structure. The existence of other pathways in the desulfurization of the dialkoxy disulfide **11** cannot be ruled out.

The stability of the cyclic thionosulfite and the rearrangement between structural isomers **11** and **12** brings strong evidence that a sulfur-branched bond can indeed be involved in a desulfurization process.

Finally, a sample of sulfoxylate **13** was subjected to identical acidic conditions as in the previous reaction. Although the yield

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was not high, ~3% of thionosulfite **12** could clearly be detected by ^{1}H NMR with use of an internal standard. Carrying out this same reaction in the presence of elemental sulfur did not increase the yield of **12**. The mechanism behind this interesting transformation is unclear as the origin of the extra sulfur atom has yet to be determined. However, this evidence brings better insight into thionosulfite chemistry as well as into the sulfur insertion hypothesis.

Foss[2] postulated that a sulfoxylate might be the most favorable structure to accept an extra sulfur atom. Our results are indeed in agreement with this suggestion. Moreover, our group reported the use of the monoatomic sulfur transfer reagent thiobisbenzimidazole to generate directly the *two*-sulfur-containing thionosulfite via a likely sulfoxylate intermediate;[12] the method is still recognized as an appropriate route for the synthesis of those compounds.[13] Mechanistic speculations pointed toward the preliminary formation of sulfoxylate, which is further supported by our finding.

We have demonstrated that isomerization of **11** to **12** required the presence of ammonium salts of halogens. We have also shown that under these conditions, the desulfurization of **12** to **13** can be catalyzed, albeit to a limited extent. Finally, we have also shown that a sulfoxylate can acquire a sulfur atom giving thionosulfite. The involvement of hydrochloric acid is necessary to promote these conversions. Although an interconversion between the isomers might be possible, the reverse process from **12** to **11** could not be achieved.

Experimental Procedures

Conversion of Dialkoxy Disulfide 11 to Thionosulfite 12. A pure sample of **11** (5 mg, 0.025 mmol) was dissolved in 1 mL of toluene-d_8 containing a stoichiometric amount of tetrabutylammonium bromide (8 mg, 0.025 mmol). 1,3,5-Tri-*tert*-butylbenzene (2 mg) served as the internal standard. After taking the ^{1}H NMR spectrum, the dialkoxy disulfide solution was transferred to a vial and the experiment was initiated by dropwise addition of 0.4 mL of a HCl/toluene-d_8 solution (0.2 equiv). The solution was mixed and replaced in the NMR tube. Relative amounts of both dialkoxy disulfide **11** and thionosulfite **12** were estimated by integrating the methylene protons after 2 h. Characteristic ^{1}H NMR peaks for cyclic dialkoxy disulfide **11**: 4.94 (d, 2H, J = 12 Hz). Characteristic ^{1}H NMR peaks for thionosulfite **12**: 6.61 (d, 2H, J = 14.2), 4.49 (d, 2H, J = 14.2 Hz).

Conversion of Thionosulfite 12 to Sulfoxylate 13. A pure sample of thionosulfite **12** (5 mg, 0.025 mmol) was dissolved in 1 mL of toluene-d_8. 1,3,5-Tri-*tert*-butylbenzene (2 mg) served as the internal standard. After taking the ^{1}H NMR spectrum, the thionosulfite solution was transferred to a vial and the experiment was initiated by dropwise addition of 0.4 mL of a HCl/toluene-d_8 solution (0.2 equiv). The solution was mixed and replaced in the NMR tube. Relative amounts of both thionosulfite **12** and sulfoxylate **13** were estimated by integrating the methylene protons after 2 h. ^{1}H NMR for thionosulfite **12**: δ 7.32 (m, 4H), 6.61 (d, 2H, J = 14.25 Hz), 4.49 (d, 2H, J = 14.25 Hz); ^{13}C NMR 62.9, 128.4, 129.5, 136.9. ^{1}H NMR for sulfoxylate **13**: δ 7.28 (m, 4H), 5.54 (s, 4H); ^{13}C NMR δ 88.7, 128.4, 129.8, 138.6.

Conversion of Sulfoxylate 13 to Thionosulfite 12 in the Presence of Elemental Sulfur. A pure sample of sulfoxylate **13** (5 mg, 0.03 mmol) was dissolved in 1 mL of toluene d_8. 1,3,5-Tri-*tert*-butylbenzene (2 mg) served as the internal standard. A stoichiometric amount of elemental sulfur (8 mg, 0.03 mmol) was added to the solution. After taking the ^{1}H NMR spectrum, the sulfoxylate solution was transferred to a vial and the experiment was initiated by dropwise addition of 0.4 mL of a HCl/toluene-d_8 solution (0.2 equiv). The solution was mixed and replaced in the NMR tube. The relative amount of thionosulfite **12** was estimated by integrating the methylene protons after 15 min (ca. 3%). ^{1}H NMR for thionosulfite **12**: δ 7.32 (m, 4H), 6.61 (d, 2H, J = 14.25 Hz), 4.49 (d, 2H, J = 14.25 Hz); ^{13}C NMR 62.9, 128.4, 129.5, 136.9. ^{1}H NMR for sulfoxylate **13**: δ 7.28 (m, 4H), 5.54 (s, 4H); ^{13}C NMR δ 88.7, 128.4, 129.8, 138.6.

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Supporting Information Available: Experimental procedures and compound characterizations. This material is available free of charge via the Internet at http://pubs.acs.org.

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