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Crossover Point between Dialkoxy Disulfides (ROSSOR) and Thionosulfites ($(RO)_2S{=}S$): Prediction, Synthesis, and Structure

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Abstract: Isomeric preference between cyclic dialkoxy disulfides and thionosulfites is governed by the ring size of the heterocycle. Rings smaller than seven atoms prefer the thionosulfite connectivity, whereas larger rings or acyclic analogues favor the unbranched dialkoxy disulfide structure. Density functional calculations were employed to predict the crossover point at which both constitutional isomers are of comparable stability. Follow-up synthesis provides the previously unknown eight-membered ring dialkoxy disulfide **14** and seven-membered ring thionosulfite **15** *from the same reaction*. X-ray crystallography for all but one of the reaction products and complementary NMR analysis furnishes insights into both solid-state and solution conformations. A long-standing issue regarding the concerted *vs* catalyzed isomerization pathway between XSSX and $X_2S{=}S$ has been addressed for $X = RO$ and shown to be acid dependent.

Introduction

Two classes of compounds containing the branch-bonded $R_2S{=}S$ motif have been experimentally verified: FS(S)F[2−6] and a small group of thionosulfites,[7−10] compounds containing the OS(S)O moiety. Over fifty years ago Foss[11] first proposed a basis for the stability of compounds containing a hypervalent[12] sulfur atom ($R_2S{=}$) bonded to an adjacent, branched sulfur (${=}S$). He suggested that the sulfur atoms are bonded by $S_{3d}-S_p$ orbital interactions and that these are only stabilized when the branched sulfur is attached to an electronegative group.[11,13] Though many others[14−16] have suggested the existence of the thiosulfoxide species bound to less electronegative groups as transient intermediates, to our knowledge none of these have been

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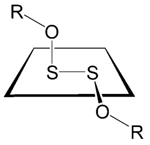
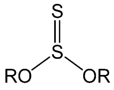
10.1021/ja0559395 CCC: $33.50 © 2006 American Chemical Society

captured as stable species within the temperature ranges common to solution chemistry.[17]

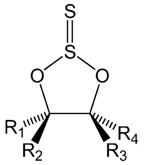
Of particular interest is the fact that not only do compounds with the formula S_2F_2 and $R_2S_2O_2$ exist in their branched configurations but also in the latter case they commonly exist as their unbranched dialkoxy disulfide isomers, **1** vs **2a**.[18−20]



1



2a



2b

In the oxygen-containing family, the known branched isomers are universally embedded in a five-membered ring, **2b**.[7−10,21,22] We sought to answer two questions: (1) What are the factors that govern the isomeric preference between dialkoxy disulfides **1** and thionosulfites **2a**; and (2) with this knowledge, can features be designed that broaden the structural base of each of the thionosulfite and dialkoxy disulfide families?

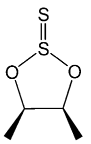
We report a density functional theory (DFT) study of the structural factors that influence relative $R_2S_2O_2$ isomeric stability. In particular, we have made predictions employing ring size and angle strain as guides to modulation of the relative energies of the **1**/**2** pair. This has led to a favored crossover point at which the isomeric OS_2O moieties should show comparable stability. The projections were followed by synthesis and structural characterization of compounds in which the S_2O_2-containing moieties embedded in medium-sized rings break the literature's historical pattern.

Results and Discussion

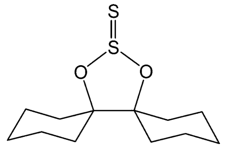
Results are divided into three sections: the first presents DFT calculations and discusses a testable prediction regarding the relative stability of isomers **1** and **2a**; second, target synthesis and structural characterization of previously unknown variations of the latter are described; finally we comment on the validity and generality of the predictions in light of the experimental outcome.

Computational Predictions. An important issue concerning the relationship of dialkoxy disulfides (ROSSOR) **1** and the isomeric thionosulfite (ROS(S)OR) **2a** is whether the two forms can interconvert by means of an uncatalyzed equilibrium. A number of experiments with S_2F_2 have been interpreted to suggest that the two isomers are present in such an equilibrium at temperatures well below room temperature,[3,5] although other studies imply a catalytically mediated rearrangement.[5] To our knowledge the same question has been addressed for the ROSSOR system only briefly in a computational context.[19,23]

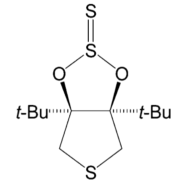
As a first step, we were interested in modeling the relative ground-state stabilities of analogues of **1** and **2a**. As mentioned above, all previous structural determinations for the former were acyclic while the latter portray the thionosulfite functionality as part of a five-membered ring (e.g., **2c**−**e**).[7−10,21,22,24] A



2c

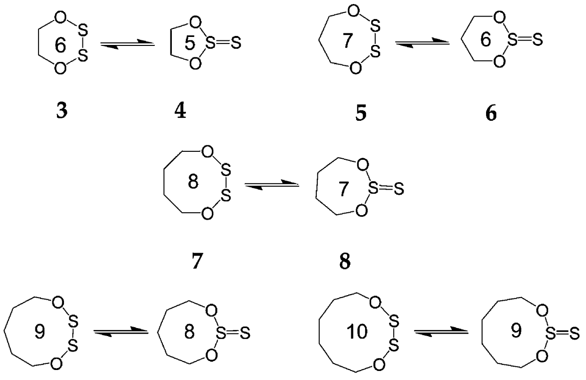


2d



2e

common conformational feature of two crystal structures containing the latter ring[8,9] is the presence of a 40°−45° twist in the τ(O−C−C−O) dihedral angle accompanied by unequal τ(C−O−S−S) angles of 95.6° and −127.4°. We hypothesized that obligating the ring to adopt another geometry, perhaps with greater conformational flexibility, might influence the relative ground-state stabilities of cyclic isomers of **1** and **2a**. A straightforward strategy to test this idea focuses on ring size as a means of relieving strain, while simultaneously permitting both torsional and bond angles an opportunity to vary. Accordingly, the conformational surfaces of five isomeric pairs of model compounds, **3**−**12**, were examined in a two-step procedure.



3 **4** **5** **6**

7 **8**

9 **10** **11** **12**

To locate the lowest energy conformations for the OS_2O isomers, we performed a 3000-step Monte Carlo search with the MM3* force field in MacroModel[25] for each of the 10 structures. All fully optimized conformations within 3 kcal/mol from the MM3* global minimum were subsequently submitted for a single-point energy evaluation at the B3LYP/6-31G(2d)

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[17] Recently, it has been shown via tandem mass spectrometry that in the gas phase thiosulfoxides are stable entities both as radical cations and as neutral species. See: Gerbaux, P.; Salpin, J.-Y.; Bouchouxb, G.; Flammang, R. *Int. J. Mass Spectrom.* **2000**, *195/196*, 239−249.

[18] For examples where the acyclic dialkoxy disulfide (ROSSOR) connectivity has been structurally resolved, see: Steudel, R.; Gleiter, R.; Hyla-Kryspin, I.; Schmidt, H. *Chem. Ber.* **1993**, *126*, 2363. Koritsanszky, T.; Buschmann, J.; Schmidt, H.; Steudel, R. *J. Phys. Chem.* **1994**, *98*, 5416. Steudel, R.; Schmidt, H.; Baumeister, E.; Oberhammer, H.; Koritsanszky, T. *J. Phys. Chem.* **1995**, *99*, 8987. Harpp, D. N.; Tardif, S. L.; Williams, C. R. *J. Am. Chem. Soc.* **1995**, *117*, 9067. Tardif, S. Ph.D. Thesis, McGill University, 1997. Harpp, D. N.; Priefer, R.; Farrell, P. G. *Tetrahedron Lett.* **2002**, *43*, 8781.

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[22] Thompson, Q. E. U.S. Patent No. 3,357,993; United States Patent Office: United States of America, 1967, 4.

[23] Though there is no experimental evidence to suggest the existence of branched isomer **2a** (R = Me), it was nevertheless found to be 1.9 kcal/mol more stable than unbranched **1** (R = Me) at B3LYP/6-311G* + ZPE with an MP2/6-311G(3d) unimolecular interconversion barrier between **1** (R = Me) and **2a** (R = Me), of 37.5 kcal/mol.[19]

[24] Thompson, Q. E. U.S. Patent No. 3,376,322; United States Patent Office: United States of America, 1968, 8.

[25] Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. *J. Comput. Chem.* **1990**, *4*, 440. We have modified the MM3* force field to include new atom types and parameters to handle the OSSO and OS(S)O functionalities. For example, the X-ray structures of **14** and **15** (Figure 2) are virtually superimposable with the MM3* geometries; Nevins, N.; Zysman-Colman, E.; Harpp, D. N.; Snyder, J. P. Unpublished results.

Table 1. Single-Point DFT Energies (B3LYP/6-31G(2d)) for **3**−**12** Optimized with the MM3* Force Field

1 or **2**	*E*(ROSSOR)^{a,b}	*E*(ROS(S)OR)^{a,b}	Δ*E*^{c}
3	−1025.382 63		Δ*E*(**4**−**3**)
4		−1025.392 60	−6.3
5	−1064.705 44		Δ*E*(**6**−**5**)
6		−1064.710 18	−3.0
7	−1104.022 48		Δ*E*(**8**−**7**)
8		−1104.019 82	1.7
9	−1143.335 50		Δ*E*(**10**−**9**)
10		−1143.328 65	4.3
11	−1182.648 87		Δ*E*(**12**−**11**)
12		−1182.639 72	5.7

[a] B3LYP/6-31G(2d)//MM3*. [b] Hartrees. [c] kcal/mol.

level of DFT theory.[19,26] The lowest energy conformations from MM3* did not uniformly translate into the lowest energy conformations by DFT, although the Δ*E* between the two methods was no greater than 1.5 kcal/mol. The relative DFT energy differences between isomeric forms (Table 1) as a function of ring-size are graphically portrayed in Figure 1.

As is evident from Table 1 and Figure 1, the DFT/MM3* protocol predicts that modifying the ring size monotonically influences the relative ground-state stabilities between dialkoxy disulfide **1** and thionosulfite **2a**. Small ring compounds are predicted to be thionosulfites, whereas medium and large ring structures as well as acyclic compounds (i.e., an infinitely large ring) are predicted to adopt the dialkoxy disulfide form. The trend suggests that the crossover point in isomeric stability occurs as the seven-membered thionosulfite ring in **8** is expanded to the eight-membered dialkoxy disulfide ring in **7**. The 1.7 kcal/mol energy difference between **7** and **8** implies that the compounds should coexist in an approximate 95:5 ratio at room temperature, if they are either interconvertible or generated from a common precursor.

The predicted crossover phenomenon can be understood as a consequence of two opposing effects; one stabilizing, the other destabilizing. For ROSSOR, the calculated, strained disulfide dihedral angles of **3** and **5** (64.8° and 78.6°, respectively) are well below the experimental values observed for acyclic analogues (85°−95°).[18−20] The eight-membered ring **7** is the minimum ring size required to adopt an optimal τ(OS−SO) dihedral angle (94.3°). For the $(RO)_2S{=}S$ system with axial S═S bonds, the near-cis and near-trans LP—O—S═S torsion angles (estimated from heavy atom angles: **4**, 15/−39° and 154/−179°; **6**, 162° (two trans); **8**, −147, 167° (both trans)) contribute to maximum orbital overlap between the oxygen lone pairs and the $\sigma^*_{S=S}$ antibonding orbital (see the Supporting Information for a structural representation), resulting in stabilization of this isomer by negative hyperconjugation.[12,27] Larger rings and acyclic forms elicit less favorable LP-$\sigma^*_{S=S}$ angular interactions. The two effects converge at ring sizes of eight and seven, respectively.

A breakdown of the computational results for structures **7** and **8** in terms of the three lowest energy conformations (**7a**−**c** and **8a**−**c**, respectively) is provided in Table 2. Within the DFT energy context, both systems are posited to exist as a mixture of three conformations. Thionosulfite **8** presents three forms with similar populations (23−45%), while dialkoxy disulfide **7** is predicted to be dominated by a single conformer (94% population). When taken as a total mixture of potentially equilibrating forms, **7** and **8** are estimated to coexist in an approximate 4:1 ratio at ambient temperature (Table 2).

The predictions summarized in Table 1 and Figure 1 are compelling. We next turned to identification of a suitable series of substrates that would permit us to test them experimentally.

Synthesis of the Crossover System. The compound 1,2-benzenedimethanol **13** was chosen as the starting material for the synthesis of the **7**/**8** isomer pair. The diol is ideal as it is not only readily available, but the benzene ring adds sufficient molecular bulk to simplify eventual crystal structure analysis.

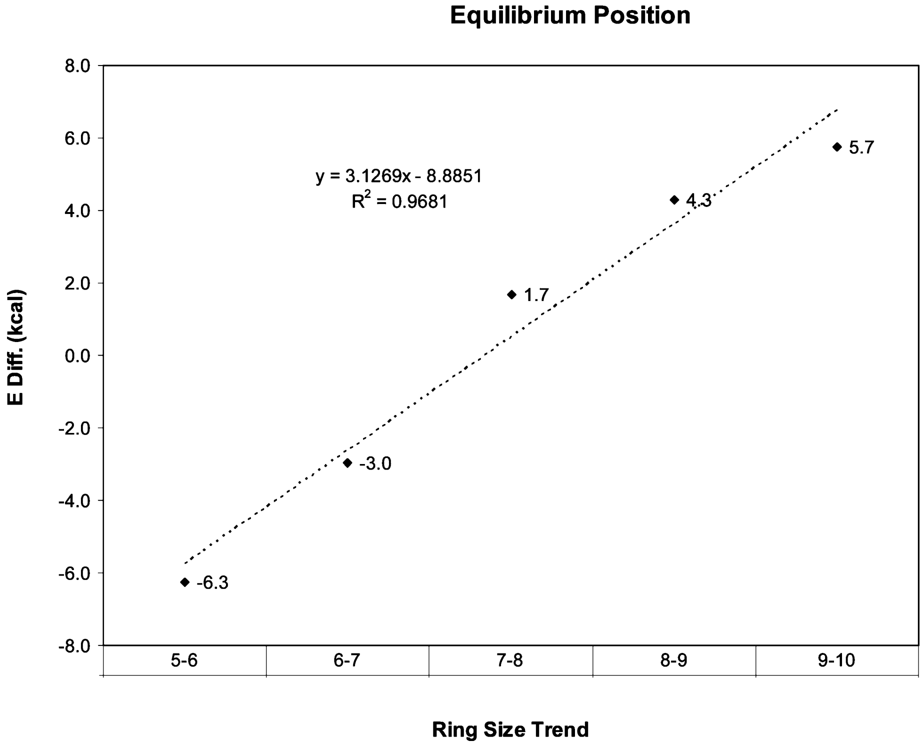
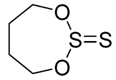
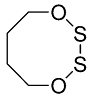


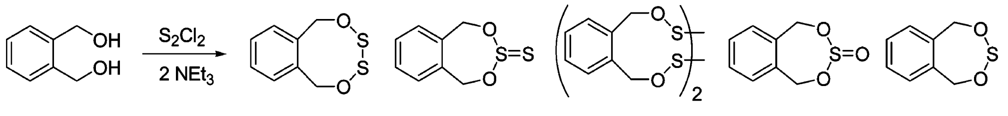
Figure 1. Ring-size trend in DFT Δ*E*’s (B3LYP/6-31G(2d)) for **3**−**12**. A positive value indicates that the dialkoxy disulfide isomer is the more stable.

Table 2. Boltzmann Population Analysis for Conformations of the **7**/**8** System at 298 K; DFT Energies

		B3LYP/6-31G(2d)//MM3*[a]	ΔE[b]	Weight	Pop (%)[c]	ΔE[d]	Total Pop (%)[c,f]	Weighted Total Pop (%)[c,f]
	**8a**	-1104.01920	0.4	2	22.9	2.1	2.4	4.4
	8b	-1104.01982	0.0	2	45.0	1.7	4.8	8.6
	8c	-1104.01943	0.2	2	32.1	1.9	3.4	6.0
								19.0
	**7a**	-1104.02248	0.0	1	93.7	0.0	83.8	75.1
	7b	-1104.01982	1.7	1	5.3	1.7	4.8	4.3
	7c	-1104.01822	2.7	2	1	2.7	0.9	1.6
								81.0

[a] Atomic units. [b] Relative energy difference within a given conformational family, kcal/mol. [c] Boltzmann population, 298 K. [d] Energy difference relative to **7a**, kcal/mol. [f] Combined Boltzman populations, 298 K.

Table 3. Coupling of S_2Cl_2 with Diol **13**

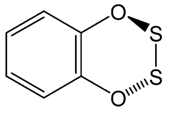


13 **14** **15** **16** **17** **18**

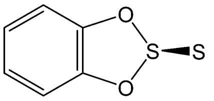
							yield[d] (%)				
entry[a]	[S_2Cl_2] (M)	equiv of S_2Cl_2	addn time (min)	time (h)	solvent	temp[c] (°C)	**14**	**15**	**16**	**17**	**18**
1	0.1	1	5	5	CH_2Cl_2	0	93 (94)	0	7	0	0
2[b]	0.1	1	9	5.5	CH_2Cl_2	0	96 (96)	0	4	0	0
3	0.1	1	35	6	CH_2Cl_2	−78	94	0	4	2	0
4	0.1	1	12	5	CH_2Cl_2	23	58	33 (22)	5 (>1)	2	1
5	0.02	1	50	5	CH_2Cl_2	0	96 (79)	0	4	0	0
6	1.0	1	2	5	CH_2Cl_2	0	92	0	8	0	0
7	0.2	2	13	5.3	CH_2Cl_2	0	13	0	0	87	0
8	0.1	1	3	5	THF	0	88	1	10 (9)	2	0
9	0.1	1	3	5	CH_3CN	0	0	9	0	87	4

[a] The concentrations of **13** and NEt_3 were 0.1 and 0.2 M, respectively, in all cases. [b] **13** and S_2Cl_2 were simultaneously added to 10 mL of CH_2Cl_2. [c] Refers to the temperature maintained during the addition of S_2Cl_2. [d] By ^1H NMR with isolated yields in parentheses.

We reasoned that the extra element of unsaturation would have minimal impact on the relative ground-state energies based on calculations for the unsaturated 5/6-ring structures **3a**−**4a**. At



3a



4a

the B3LYP/6-31G(2d) level there was no effect on the isomer preference and only an inconsequential change in the energy gap when a second degree of unsaturation was added (ΔE(**4**−**3**) −6.3 kcal/mol; ΔE(**4a**−**3a**) −7.0 kcal/mol).[28] Recently, we reported an improved preparation for acyclic dialkoxy disulfides.[29] Using the corresponding reaction conditions as a starting point, we investigated the coupling of S_2Cl_2 to the model diol **13**. The results are summarized in Table 3.

In most cases, dialkoxy disulfide **14** was the major product formed and isolated. To our knowledge, this represents the *first* example of a stable and fully characterized *cyclic* dialkoxy disulfide. We were able to influence the ratio of **14**/**15** by increasing the S_2Cl_2 addition temperature to 23 °C (entry 4). Thompson indicated in his patent[22] that thionosulfites could be preferentially formed with simultaneous diol and S_2Cl_2 addition. In our hands, these conditions (entry 2) produced the same ratio of products and isolated yield of **14** as addition of a solution of S_2Cl_2 to **13** (entry 1). Moreover, no thionosulfite **15** was detected.

It has been proposed that intermediates similar to **20** (ROSSCl) might be stabilized at lower temperatures.[30] To test the possibility that this phenomenon might affect the yields of products, the temperature of S_2Cl_2 addition was decreased to −78 °C and the addition time was lengthened. However, the latter changes had little effect on the relative amounts of monomer **14** and dimer **16** formed. Either increasing the concentration of S_2Cl_2 (entry 6) or changing the solvent to THF (entry 8) promoted an increase in the yield of **16** relative to **14**, whereas employing the more polar CH_3CN solvent (entry 9) resulted in formation of unwanted sulfite **17**. Similar results were observed with the use of 2 equiv of S_2Cl_2 in CH_2Cl_2 (entry 7).

Apparently, under these conditions 7-*exo-tet* ring closure to form sulfoxylate **18** and subsequent oxidation in the workup to furnish sulfite **17** are preferred over 8-*exo-tet* ring closure to give dialkoxy disulfide **14**. Trace acid- or base-catalyzed decomposition of **14** to **17** cannot be ruled out.[31] Decreasing

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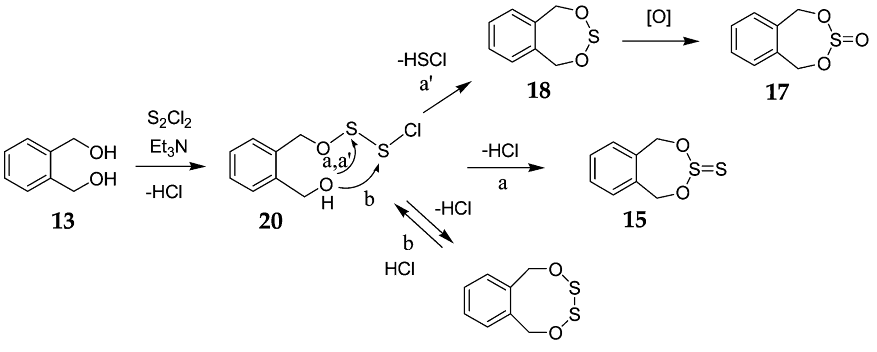
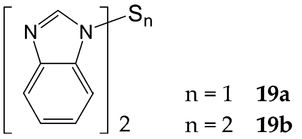
(26) Balcells, D.; Maseras, F.; Ujaque, G. *J. Am. Chem. Soc.* **2005**, *127*, 3624.
(27) Reed, A. E.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1990**, *112*, 1434.
(28) See Supporting Information for details.
(29) Zysman-Colman, E.; Harpp, D. N. *J. Org. Chem.* **2005**, *70*, 5964.
(30) Steudel, R.; Schmidt, H. *Z. Naturforsch.* **1990**, *45B*, 557.
(31) The acid- and base-catalyzed decomposition of MeOSSOMe **1a** has been documented. See: Kobayashi, M.; Minato, H.; Shimada, K. *Int. J. Sulfur Chem., A* **1971**, *1*, 105.

Scheme 1. Proposed Cyclization Routes for the Formation of Either **14** or **15**



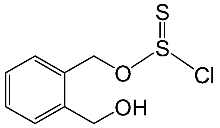
the concentration of S_2Cl_2 in solution from 1 to 0.02 M while increasing the addition time from 2 to 50 min slightly increased the yield of **14** over dimer **16** (entries 5 and 6). Compound **15** could only be synthesized at rt (entry 4), while **14** could be obtained at lower temperatures (*e.g.*, entries 1−3, 5, 6). Taken with the fact that **14** converts to **15** as described in a subsequent section, while the reverse conversion was not observed, it is reasonable to suggest that **14** may be the kinetic product whereas **15** is thermodynamically more stable. The isolation of **15** represents the *first* synthesis of a *non*-five-membered ring thionosulfite.

Altering the base from NEt_3 to pyridine resulted in decreased yields and increased product impurity. Compounds **19a** and **19b** have been shown to be useful sulfur transfer reagents in the formation of five-membered thionosulfites.[9,10] Replacement of S_2Cl_2 with either reagent in the present experiments proved ineffective in the formation of **14**−**18** from diol **13**; only complex mixtures of products were obtained.



What factors determine the formation of **14** and **15**? Initially, it was not clear whether **15** was the result of an isomerization process from **14** or whether **15** formed independently from **14** in the reaction mixture. Based on experiments described below, we propose the synthetic scheme above (Scheme 1).

The first hint that acid was involved in the transformations of Scheme 1 arose when pure **14** stored at 0 °C in $CDCl_3$ for 2 weeks delivered 5% of **15**, presumably by slow and incomplete isomerization under the influence of traces of acid from the solvent. Under similar conditions, the reverse isomerization of **15** to **14** at 0 °C was not detected, nor was it observed at temperatures up to 150 °C. Experiments described below in a separate section on the acid promoted conversion of **14** to **15** provide definitive evidence for the role of HCl and rule out dynamic isomerization between the two compounds. Although the possibility of an S_N2' mediated ring closure to form **15** from **20** cannot be discounted, the appearance of trace **17** and **18** is consistent with the current mechanism. Moreover, in these initial experiments we were unable to find conditions delivering >33% of **15** (see below, Table 6). However, much higher yields (65−75%) could be obtained by adjusting the $[Et_3N]/[S_2Cl_2]$ ratio to a value of 1.7 in order to release a small quantity of free HCl (see below; Table 6). Although it has been proposed that branch-bonded products arising from treatment of various compounds with S_2Cl_2 emanate from traces of S_2Cl_2 in the branch-bonded form ($Cl_2S{=}S$),[16] there is little evidence to suggest this is the case at the addition temperatures employed here.[32,33] Finally, while there is precedent[30] for compounds incorporating the unbranched OSSCl connectivity as pictured in the proposed intermediate **20**, we are unaware of evidence to support the formation of isomeric **21**, a potential alternative intermediate for the direct formation of **15** from **13**.[34]



21

Solid-State Structures from X-ray Crystallography. X-ray crystal structures for all but one of the compounds derived from S_2Cl_2 treatment of diol **13** (Table 3) have been obtained, thereby verifying the connectivity of structures **14**−**17** and identifying the corresponding solid-state conformations.

A capped stick representation of dialkoxy disulfide **14** in the solid state is shown in Figure 2. It possesses no symmetry (C_1). The eight-membered ring adopts a pseudo-saddle geometry[35] with limited conformational flexibility occasioned by both unsaturation in the fused benzene ring and the OS−SO moiety. The result contrasts with that for most eight-membered rings

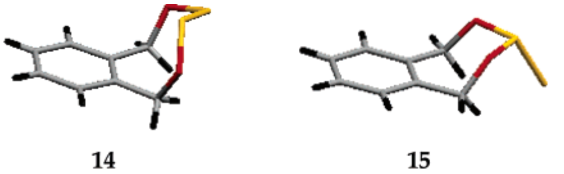


Figure 2. X-ray crystal structures of dialkoxy disulfide **14** in an asymmetric twist-chair−chair conformer (C_1 symmetry) and thionosulfite **15** presenting a seven-membered ring chair and an axial exocyclic S=S bond (C_S symmetry).

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(32) Spong, A. H. *J. Chem. Soc.* **1934**, 485. Palmer, K. J. *J. Am. Chem. Soc.* **1938**, *60*, 2360. Beagley, B.; Eckersley, G. H.; Brown, D. P.; Tomlinson, D. *Trans. Faraday Soc.* **1969**, *165*, 2300. Hirota, E. *Bull. Chem. Soc. Jpn.* **1958**, *31*, 130. Chadwick, B. M.; Grzybowski, J. M.; Long, D. A. *J. Mol. Struct.* **1978**, *48*, 139.

(33) Bock, H.; Solouki, B. *Inorg. Chem.* **1977**, *16*, 665.

(34) Branched sulfur species have been proposed as intermediates in desulfurization, sulfurization, and isomerization reactions. See for instance: Baechler, R. D.; Hummel, J. P.; Mislow, K. *J. Am. Chem. Soc.* **1973**, *95*, 4442.

(35) Evans, D. G.; Boeyens, J. C. A. *Acta Crystallogr. B* **1988**, *44*, 663.

17a **17b**

Figure 3. X-ray crystal structures obtained from the deconvoluted X-ray diffraction pattern for sulfite **17**; the major chair conformation **17a**; the minor twist conformation, **17b**; ratio 9:1, respectively.

which adopt either a boat−chair or a twist-boat−chair conformation in the solid state with a potential for interconversion into the higher energy crown conformation.[35,36] Perhaps more relevant, while cyclooctene can exist in both chair and boat conformations, a considerably less strained twist-chair−chair conformer has been calculated to be the lowest in energy,[37] a prediction confirmed by clustering of X-ray data.[38] The twisted unsymmetrical conformer **14** shown in Figure 2 sustains an OS−SO torsion of 93.2°, a value within the 85°−95° window observed for acyclic dialkoxy disulfides.[18−20]

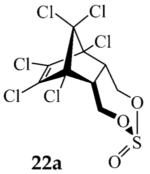
Thionosulfite **15** (Figure 2) is found exclusively in a chair conformation characterized by C_s symmetry. In this conformation each pair of benzylic hydrogens directs its axial C−H bond parallel to the S═S (or $S^{\delta+}$−$S^{\delta-}$) bond, while the other proton resides in a pseudoequatorial orientation. From a more general perspective, simple cycloheptenes are known to adopt a chair conformation stabilized by 0.6−3.5 kcal/mol over the twist and boat conformations.[39,40] At the same time, replacement of the C═C double bond with a benzene ring to give benzocycloheptenes has been suggested to preferentially stabilize the chair form[41] relative to the twist conformer as a consequence of α-hydrogen C_{sp2}/H eclipsing of the type observed in toluene.[40,42] The stability supposition has been subsequently confirmed for the all-carbon 7-rings by analysis of X-ray structures found in the Cambridge Crystallographic database.[43]

The solid-state conformational energy profile for sulfite **17** is somewhat more complex. The solid-state X-ray diffraction pattern has been deconvoluted to provide a 9:1 mixture of chair and twist forms (Figure 3). In this case, the more abundant chair conformer (**17a**) possesses a plane of symmetry similar to crystalline **15**, while the low population twist form (**17b**) is asymmetric. A comparison of the annelated O_2SX structures from the viewpoint of possible α-hydrogen eclipsing does not provide a basis for understanding the formation of the twist form in the sulfite crystal compared with its absence in **15**. In the latter and in both **17a** and **17b**, the $(C_{sp2})H\text{- - -}H(C_{bn})$ distances (i.e., between protons: $HC{=}C{-}CH_2$) range from 2.26 to 2.30 Å. Consequently, we attribute the formation of both chair and twist in sulfite **17** to similar energies (i.e., $\Delta E = 1-2$ kcal/mol) coupled with polar effects in the crystal. In agreement, a 9:1 ratio at 298 K corresponds to a 1.3 kcal/mol free energy difference.

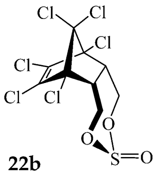
16

Figure 4. X-ray crystal structure of dialkoxy disulfide dimer **16**.

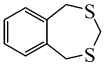
Interestingly, the two conformations in the solid state for a related sulfite, the insecticide thiodan (**22a** and **22b**), are found as chairs with axial S═O bonds.[44] The related bis-thioethers[45] **23a** and **23b** also exist exclusively as chairs, while trisulfide **24** presents as an 85:15 ratio of chair/twist-boat conformations in CS_2.[46]



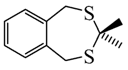
22a



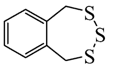
22b



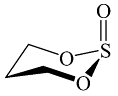
23a



23b



24



25

The sum of the θ(O−S−O) and two θ(O−S−S) bond angles in **15** (319.2°) is comparable to the sum of the three θ(O−S−O) angles in **17a** (317.1°) indicating the pyramidal nature of the branch-bonded sulfur. The two stereoelectronic $n_O \rightarrow \sigma^*_{S=O}$ donor−acceptor interactions[12,27] in **17a** and the analogous pair of $n_O \rightarrow \sigma^*_{S=S}$ interactions in **15** contribute to a lengthening of the respective S═O and S═S bonds. The S═S bond length in **15** is 1.936 Å, slightly longer than that in **2d** (1.901 Å).[8] Similarly, the S═O bond in **17a** (1.595 Å) is also much longer than that found in **25** (1.45 Å).[47]

Compound **16**, a formal dimer of dialkoxy disulfide **14**, is a novel 16-membered macrocycle. Its X-ray structure (Figure 4) reveals a conformation possessing C_2 symmetry and two chiral OS−SO units. The O−S−S−O torsion angles at 87.6° are comparable to those found for acyclic dialkoxy disulfides (85°−95°).[18−20] The conformation corresponds to (M,M)/(P,P)[48] and possesses two different benzylic-CH_2 groups. All four benzylic hydrogens are chemically and magnetically distinct, the consequences of which will be discussed below in connection with the proton NMR.

Each of the solid state conformations for **14**−**16** can exist in other competing conformers. Below, we present analyses of the NMR spectra for the series and elaborate on the corresponding conformational energy profiles.

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(36) Setzer, W. N.; Glass, R. S. *Conformational Analysis of Medium-Sized Heterocycles*; VCH: 1988; p 151. Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons: Toronto, 1994.

(37) Traetteberg, M. *Acta Chem. Scand., Sect B* **1975**, *29*, 29.

(38) Allen, F. H.; Howard, J. A. K.; Pitchford, N. A. *Acta Crystallogr., Sect. B* **1996**, *52*, 882.

(39) Favini, G.; Buemi, G.; Raimondi, R. *J. Mol Struct.* **1968**, 137.

(40) Allinger, N. L.; Sprague, J. T. *J. Am. Chem. Soc.* **1972**, *94*, 5734.

(41) Kabuss, S.; Friebolin, H.; Schmid, H. *Tetrahedron Lett.* **1965**, 469.

(42) Burkert, U.; Allinger, N. L. *ACS Monograph 177*; American Chemical Society: Washington D.C., 1982; p 339.

(43) Allen, F. H.; Garner, S. E.; Howard, J. A. K.; Pitchford, N. A. *Acta Crystallogr., Sect. B* **1994**, *50*, 395.

(44) Byrn, S. R.; Siew, P. Y. *J. Chem. Soc., Perkin. Trans. 2* **1977**, 144.

(45) Friebolin, H.; Mecke, R.; Kabuss, S.; Lüttringhaus, A. *Tetrahedron Lett.* **1964**, *29*, 1929.

(46) Kabuss, S.; Lüttringhaus, A.; Friebolin, H.; Mecke, R. *Z. Naturforsch.* **1966**, *21b*, 320.

(47) Altona, C.; Geise, H. J.; Romers, C. *Recl. Trav. Chim. Pays-Bas* **1966**, *85*, 1197.

(48) S−S torsion angles can be defined in terms of their helical twist using the Cahn−Ingold−Prelog nomenclature. A positive dihedral angle corresponds to the P conformation, while a negative dihedral angle is denoted by the M conformer. See: Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons: Toronto, 1994.

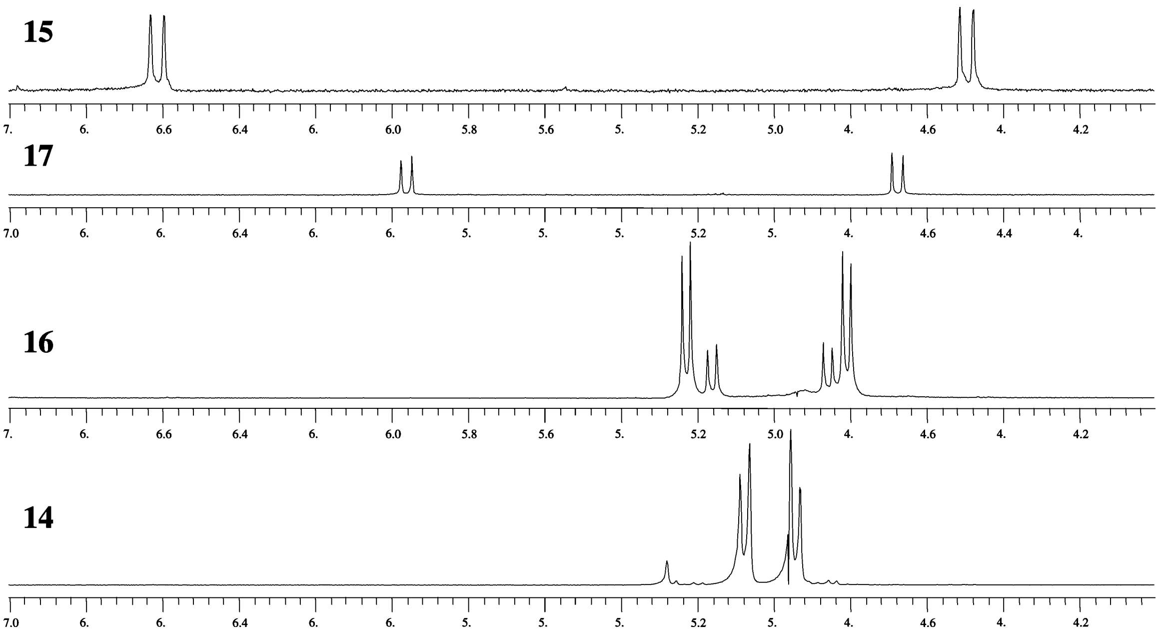
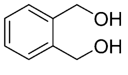
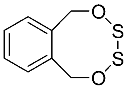
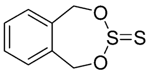
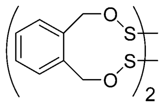
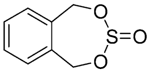
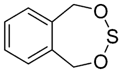


Figure 5. ^{1}H NMR spectra (300 MHz) of the benzyl protons in **14**−**17** in CDCl$_3$ at rt.

Table 4. Selected ^{1}H and ^{13}C Observables for **13**−**18**

Compounds		Chemical Shifts,[a]			^2J (Hz)
		^{1}H NMR		^{13}C NMR	
	**13**	4.65	-	64.01	-
	**14**	4.94	5.07	72.27	-12.00
	**15**	4.49	6.61	62.92	-14.25
	**16**	4.84	5.26	75.31	-11.00[b]
		4.89	5.20	75.35	-12.00[c]
	**17**	4.68	5.96	62.72	-14.00
	**18**	5.54	-	88.73	-

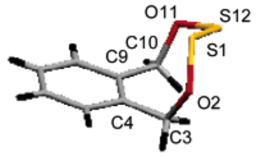
NMR Analysis of Solution Conformation. The ^{1}H NMR spectra of the benzyl protons in **14**−**17** all show either an AB or AX pattern and are clearly distinct from one another as depicted in Figure 5. The one exception to the geminal splitting pattern is sulfoxylate **18**, which presents a singlet at 5.54 ppm in CDCl$_3$ at rt. Selected NMR parameters are provided in Table 4.

The second-order geminal ^{1}H splitting pattern for the benzyl protons of **14** is characteristic of dialkoxy disulfides in that the two protons are anisochronous. The diastereotopicity results from the high barrier to rotation about the chiral axis associated with the OS−SO moiety, indicating that in solution **14** is a racemic mixture of two enantiomeric atropisomers separated by a free energy barrier of 18−19 kcal/mol.[4,19,20,29] The sense of helicity is defined by viewing down the S−S bond. A clockwise rotation is designated P(+), and a counterclockwise rotation is designated M(−). The doublet of doublets is characteristic of the compound class and implies exchange between the benzylic positions on the NMR time scale.[4,19,20,29]

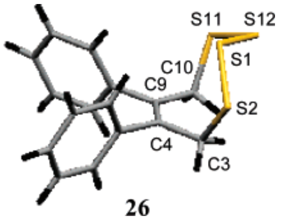
The crystal structure of **14** depicted in Figure 2 portrays a molecule in which all four benzylic protons are chemically distinct. Thus, there are two "inner" protons (H$_{ia}$ and H$_{ib}$) and two "outer" ones (H$_{oa}$ and H$_{ob}$). This contrasts with the picture provided by the AB splitting pattern observed in the ambient NMR spectrum of Figure 5 reflecting the presence of only two different protons. Dynamic averaging of the benzylic centers explains the appearance of the solution spectrum. It might be concluded that rotation about all four single bonds in **14** (C−CH$_2$, CH$_2$−O, O−S, and S−S) is necessary to promote averaging.

However, three factors make it clear that the S−S bond is not recruited in the averaging process. First, the energy barrier for OS−SO rotation in other dialkoxy disulfides is 18−19 kcal/mol,[4,19,20,29] a value very similar to that determined for the S−S bond in **14** (see below). The barrier is sufficiently high to preclude rapid S−S rotation at room temperature. Second, the seven-membered ring systems of thionosulfite **15** and sulfite **17** contain no S−S bond, yet the AX spectra of both imply that torsional motions around the C−CH$_2$, CH$_2$−O, and O−S bonds alone are sufficient to cause chemical equivalence of the benzylic CH$_2$ groups. Third, the averaging operation involves bond rotations that move the OSSO unit on one face of the benzene ring in **14** (Figure 2) to the other face. The result is that the inner protons are translated to the outer positions and vice versa. Simultaneously, the H$_{ia}$/H$_{ib}$ and H$_{oa}$/H$_{ob}$ geminal proton pairs become H$_{ib}$/H$_{ia}$ and H$_{ob}$/H$_{oa}$, respectively, as four protons are averaged to two. Were rapid rotation about the OS−SO bond involved, the molecule would experience a virtual

Table 5. Comparison of Low Energy Conformations of **14** and **26**



14



26

dihedral angle[a]	**14**[b,c]	**26**[b,d]	Δ(**14**–**26**) (deg)
C3−C4−C9−C10	−3.4	−3.1	−0.3
C4−C9−C10−X11	−86.7	−101.2	14.4
C9−C10−X11−S12	90.2	88.1	−2.2
C10−X11−S12−S1	−77.9	−72.6	−5.3
X11−S12−S1−X2	93.2	103.6	10.4
S12−S1−X2−C3	−53.9	−65.1	11.2
S1−X2−C3−C4	−46.6	−41.9	−4.8
X2−C3−C4−C9	99.1	105.0	6.0

[a] X = O in **14**, X = S in **26**. [b] Dihedral angles in degrees. [c] Numbering as that of X-ray. [d] Numbering altered from X-ray to facilitate comparisons with **14**.

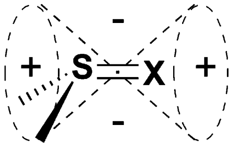


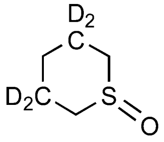
Figure 6. Approximate shielding (+) and deshielding (−) zones of sulfites (X = O) and thionosulfites (X = S).

plane of symmetry leading to a singlet as observed for sulfoxylate **18**.

The X-ray and presumably lowest energy solution conformation of **14** is quite similar to that of tetrasulfide **26**[49] as evidenced by the 0°−15° differences in the corresponding dihedral angles (Table 5). The larger torsion angle deviations are the result of bond angle differences. The X−S−S bond angles are quite similar: θ_{av}(O−S−S) = 108.3° and θ_{av}(S−S−S) = 106.2°. By strong contrast, θ_{av}(C−O−S) (116.9°) is 12.5° larger than θ_{av}(C−S−S) (104.4°). The variation is due to the natural angles sustained by the central atoms of C−X−S. Microwave spectra of dimethyl sulfide[50] and dimethyl ether[51] exhibit C−X−C angles of 98.8° and 111.8°, respectively, a difference of 13.0°. Thus, the C−X−S angle variation is translated into the small but significant torsion angle differences between **14** and **26**.

The proton NMR traces of thionosulfite **15** and sulfite **17** display well-resolved AX spectra (Figure 5). The large chemical shift separation of the geminal protons is characteristic of exocyclic and axial S═X (X = O, S), each proton falling into a different region of the deshielding zones as depicted qualitatively by Figure 6.

While the X-ray crystal structures of **15** and **17a** display the S═X in an axial orientation, equilibration between chair and twist forms (e.g., **17b**, equatorial S═X (Figure 3)) in solution has the potential to tip the balance. It is well-known that the S═O bond in sulfites strongly differentiates between axial and equatorial protons on carbon adjacent to the sulfite moiety.[52] Diagnostic are large geminal coupling constants such as those recorded for **27** (13.7 Hz) and **28** (13.2 Hz), both of which sustain axial or pseudoaxial S═O bonds.[53] Supporting the notion that **15** and **17** likewise possess largely axial S═X bonds in solution are their two bond couplings of 14.3 and 14.0 Hz, respectively (Table 4). Finally, the relative 0.65 ppm downfield shift of the low field doublet in **15** with respect to **17** may indicate an increased polarization of the S═S bond (*i.e.*, S$^+$−S$^-$) similar to that proposed for the S═O bond of sulfites.[54] Steudel and colleagues[55] have performed calculations suggesting that thionosulfite bonds are polarized in the same manner.



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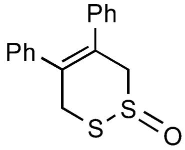

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It is noteworthy that the ^{13}C NMR chemical shifts of the benzyl carbons of dialkoxy disulfides **14** and **16** are 10−13 ppm further downfield than those of **15** and **17** (Table 4). This is a result of a large upfield "γ shift",[56] which in this particular case is an indicator of the strong interaction of an axial S═O bond with *syn*-axial H's.[57] It results in the shielding of the benzyl carbon (ca. 9 ppm) relative to a conformation wherein the S═O bond is equatorial. It is assumed that the γ shift would also apply to the analogous thionosulfite system. Moreover, the benzyl carbons of **18** resonate an additional ca. 13 ppm further downfield from **14** and **16** (Table 4). The origin of this additional shift is unclear.

With respect to the conformational profiles of **15** and **17** in solution, their clean ^{1}H AX spectra (Figure 5) imply that the compounds are best described by either a rapidly equilibrating mixture of chair, twist-boat and boat forms or one of these as a single stable conformer. Inversion around the hypervalent ring sulfur at room temperature can be eliminated immediately since this dynamic feature would result in equivalent geminal protons and lead to a singlet. The outcome is consistent with a calculated barrier above 30 kcal/mol.[19] A definitive answer for **17** has been provided by St-Jacques and co-workers.[58] ^{1}H and ^{13}C DNMR studies in concert with solution IR reveal that the compound consists of a near 1:1 mixture of chair and twist-boat forms in CHF$_2$Cl at −157 °C interconverting over a free energy barrier of 7 kcal/mol. The ratio of conformers is solvent dependent. In the less polar dimethyl ether medium, the chair/twist ratio

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(49) This tetrasulfide was isolated in a trapping experiment between dithiatopazine and 2,3-diphenylbutadiene. See: Nicolaou, K. C.; DeFrees, S. A.; Hwang, C.-K.; Stylianides, N.; Carroll, P. J.; Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 3029.

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(52) Green, C. H.; Hellier, D. G. *J. Chem. Soc., Perkin Trans. 2* **1972**, 458. Albriktsen, P. *Acta Chem. Scand.* **1972**, *26*, 3678. Maroni, P.; Cazaux, L.; Gorrichon, J. P.; Tisnes, P.; Wolf, J. G. *Bull. Soc. Chim. Fr.* **1975**, 1253.

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becomes 2:1. These observations are in accord with the averaged AX spectrum of **17** at room temperature and with the determination of both conformers in the crystal lattice (Figure 3). Although we have not performed low-temperature NMR experiments for thionosulfite **15**, we presume the compound undergoes an averaging process similar to **17**.

The ^{1}H spectrum of dimer **16** displays the benzylic centers as two distinct AB spin systems in an approximate 2:1 ratio. ^{13}C NMR likewise reveals the benzylic carbons in a 2:1 ratio. The connectivity in **16** is that of a 16-membered ring containing two chiral axes within the two OS−SO functional groups similar to that described for dialkoxy disulfide **14**. This implies that **16** can exist in any of three atropisomers: (M,M), (P,P), or (M,P), the latter being the meso form.[48] Dynamic exchange in solution promoted by rotation around single bonds other than S−S is capable of making equivalent the methylene centers and providing a single AB spin pattern for the (M,M)/(P,P) atropisomers. The same behavior for the slightly less stable (M,P) meso form leads to the second, less intense AB spectrum portrayed. A reasonable interpretation of the proton spectrum is that it represents a statistical average of the three atropisomers, each of which can populate a number of conformations. Since the NMR spectra of the (M,M) and (P,P) enantiomers are identical, two sets of doublets of doublets corresponding to the (M,M)/(P,P) and (M,P) forms each with slightly different coupling constants are observed (Table 4). Based on the integrated 2:1 ratio of NMR peak intensities (*ca*. 3:2) and assuming a Boltzmann population distribution at 296 K, the (M,P) conformer is disfavored by *ca*. 0.3 kcal/mol.

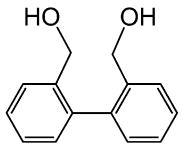
Thermal Stability of Isomers 14 and 15. Whereas thionosulfite **15** decomposes only slowly at 120 °C for several hours in solution (p-xylene-d_{10}), dialkoxy disulfide **14** decomposes within minutes under the same conditions to afford **15**, **17**, **18**, and other unidentified products as monitored by ^{1}H NMR and compared to the chemical shifts of authentic samples. The lack of observable coalescence of the methylene AX signal in **15** (Figure 2) is primarily due to the contribution of a large pyramidal sulfur inversion barrier.[59]

Differential scanning calorimetry (DSC) also provides insight into the relative stabilities of **14**−**16**. Although phase transitions in **14**−**16** were observed (see Supporting Information), the thermodynamic profiles of dialkoxy disulfides **14** and **16** are unique in that they also present an exotherm at higher temperatures (*ca*. 140 °C), absent for **15** and **17**, indicating decomposition. DSC measurements thus provide another tool that easily distinguishes between constitutionally isomeric forms of compounds possessing the OS$_2$O motif.

S−S Rotation Barriers for 14 and 16. The barrier to conformational interconversion of the eight-membered ring in **14** was measured by NMR to be 18.8 ± 0.2 kcal/mol using approximations developed by Gutowsky and Holm.[60] The benzyl proton AB spin system coalesced at 114.6 °C in p-xylene-d_{10}. This barrier is comparable to those measured[4,19,20,29] and calculated[19,61] for acyclic dialkoxy disulfide analogues. While traversing the barrier to effect ring inversion certainly involves rotation about the S−S bond, previous kinetic measurements were uniformly conducted on molecules that interconvert conformational enantiomers through a trans O−S−S−O transition state. The eight-membered ring in **14**, by necessity, switches disulfide chirality by means of a cis transition state. In general, the latter is higher than for the trans pathway.[61] Thus, although the measured barrier for **14** is essentially identical to that obtained from previous dialkoxy disulfide evaluations, the matched values may well be a coincidence. Coupled torsional motions of the C−CH$_2$, CH$_2$−O, and O−S bonds in the medium-sized ring of **14** undoubtedly assist in traversing the cis transition state and lowering its energy. As such, the 18−19 kcal/mol value is most likely an underestimate of the energy cost for cis interconversion in an acyclic system.

Dimer **16** was also heated in p-xylene-d_{10}, but full coalescence could not be achieved even at 140 °C where decomposition sets in. Here the two AB spin systems coalesce into a single, broad doublet. The observation is consistent with rapid rotation about the four pairs of C−CH$_2$, CH$_2$−O, and O−S bonds as discussed above in connection with the averaging process for **14** that promotes equivalence of its two CH$_2$ centers. For **16**, the high-temperature dynamics averages all four CH$_2$ moieties but retains diastereotopicity for the geminal protons. While 140 °C is sufficient to promote S−S rotation in **14**, it may be insufficient to do so for both S−S units in **16**. Conceivably, one of the disulfide centers exerts a rigidifying effect on the 16-membered ring permitting independent permutation of the other. Thus, the high-temperature NMR spectrum for **16** appears qualitatively similar to that for the low-temperature spectrum of disulfide **14**, both incorporating a single stable chiral moiety. At temperatures permitting rapid interchange about both S−S bonds in **16**, the benzylic hydrogens of the atropisomers would coalesce into a singlet representing the full average. Unfortunately, the compound decomposes thermally before such a temperature can be reached. The details of the various conformational processes are under study and will be reported separately.

Synthesis of Cyclic Dialkoxy Disulfide 30. As a departure from medium ring compounds derived from 1,2-benzenedimethanol **13**, we turned our attention to the S$_2$Cl$_2$ coupling of 2,2′-biphenyldimethanol **29**.



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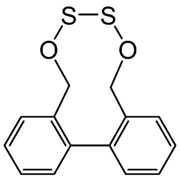

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Reaction conditions used were similar to those found in the literature;[29] the crude solution yielded a complex mixture of products. After chromatography, dialkoxy disulfide **30** was isolated in 25% yield as a clear oil, which subsequently solidified in the freezer. Though we were unable to obtain a crystal

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(59) For a background on the causes of pyramidal inversion, see: Mislow, K.; Rauk, A.; Allen, L. C. *Angew. Chem., Int. Ed. Engl.* **1970**, *9*, 400. For a review on linear free energy correlations of barriers to pyramidal inversion, see: Mislow, K.; Baechler, R. D.; Andose, J. D.; Stackhouse, J. *J. Am. Chem. Soc.* **1972**, *94*, 8060. For a review on calculated and experimental barriers to pyramidal inversion for first- and second-row elements, see: Mislow, K.; Rauk, A.; Andose, J. D.; Frick, W. G.; Tang, R. *J. Am. Chem. Soc.* **1971**, *93*, 6507. For examples of high pyramidal sulfur inversion barriers in sulfites, see: Pritchard, J. G.; Lauterbur, P. C. *J. Am. Chem. Soc.* **1961**, *83*, 2105. Lauterber, P. C.; Pritchard, J. G.; Vollmer, R. L. *J. Chem. Soc.* **1963**, 5307.

structure of **30**, its structural topology was inferred from two pieces of data.[62]

Interestingly, this compound possesses two chiral units: the OS−SO unit and biphenyl moiety. This implies that **30** carries the potential to exist in diastereomeric conformations that may be isolable. In addition, **30** is a ten-membered ring that is predicted by the correlation in Figure 1 to be the sole product from ring closure. Unfortunately, the low 25% yield precludes any conclusion at this time regarding the operation of the crossover principle for this compound.

Conversion of Dialkoxy Disulfide 14 to Thionosulfite 15 with Acid. As mentioned in the computational predictions section, the two isomers of FS_2F (F−S−S−F and $F_2S{=}S$) have been structurally characterized[2−6] and claimed to participate in an uncatalyzed equilibrium well below room temperature (−100 °C).[3,5] Leaving this view in an uncertain state are recent high level calculations which predict that the corresponding unimolecular[6,33,63−65] and bimolecular[66] transition states are associated with 35−45 kcal/mol barriers and studies which suggest that Lewis or Brønsted acids and traces of mineral acid promote the isomerization.[5]

To address this question for the interconversion of dialkoxy disulfide **14** and thionosulfite **15**, we have performed a series of experiments designed to test conditions that promote transformation between the two isomers. Already mentioned is the thermal stability of **15** at 120 °C in *p*-xylene-d_{10} and the initial observation of the formation of **15** from **14** under the same conditions. When acid was rigorously excluded during the reaction (*e.g.*, new glassware or base wash), the conversion of **13** was similar to entries 1 and 2 in Table 3. Namely, no thionosulfite was detected. Excess triethylamine provides the same result with partial decomposition of **14**. Base wash of the glassware likewise leads to some decomposition. In either case, small amounts of dimer **16** (5−10%) are observed even when the reaction is diluted to one-third the normal concentrations. The sensitivity of **14** to base and acid (see below) is consistent with the observation that dialkoxy disulfides are decomposed by both basic and acidic alumina upon chromatography[67] and in the presence of Brønsted or Lewis acids.[31]

A deliberate attempt to introduce acid into the reactions catalogued in Table 1 and depicted by Scheme 1 is summarized in Table 6. Before workup, all reactions were monitored by ^{1}H NMR at the times indicated.

At 25 °C, in the presence of 1 equiv of S_2Cl_2 and 2 equiv of Et_3N, diol **13** provides dialkoxy disulfide **14** within a few minutes in high yield (Table 6, entry 1). The dialkoxy disulfide is stable to longer reaction times (entry 2). Reduction of the concentration of Et_3N to 1.7 equiv permits the liberation of free HCl; early in the reaction (5 min) **14** is produced in high yield, but after 2 h the major product is thionosulfite **15** (75%) (entry 4; Figure 7). A similar result is observed at 0 °C, although the process is slower, as expected (entry 5). Reduction of the Et_3N concentration to 1 equiv causes decomposition, possibly with the formation of oligomeric byproducts. Obviously, the course of the reaction summarized in Scheme 1 is dependent on the concentration of HCl. The important observation is that **14** is unstable relative to **15** in the presence of moderate concentrations of free HCl.

Table 6. Influence of Acidity on the Formation of Dialkoxy Disulfide **14** and Thionosulfite **15** from Treatment of Diol **13** with Varying Ratios of S_2Cl_2/Et_3N

entry	temperature (°C)	reaction time (min)	ratio $[Et_3N]/[S_2Cl_2]$	main product
1	25	5	2	**14**[a,b]
2	25	120	2	**14**[a,b]
3	25	5	1.7	**14**[a,b]
4	25	120	1.7	**15**[c]
5	0	120	1.7	**15**[d]
6	25	5−15	1	*e*

[a] Isolated yields are in the 88−92% range. [b] Minor amounts of dimer **16** were observed as the only side product. [c] Isolated yields are in the 65−75% range. [d] Mixture of **14** (40%) and **15** (45%) by ^{1}H NMR. [e] Decomposition products. ^{1}H NMR broad and characterless.

To substantiate these observations further, the acid-promoted conversion of a purified sample of **14** to **15** was monitored by ^{1}H NMR as depicted in Figure 7. A $CDCl_3$ solution containing the dialkoxy disulfide **14**, tetrabutylammonium bromide, and HCl (0.5:1.0:0.1 ratio, respectively) with 1,3,5-tri-*tert*-butylbenzene as an internal standard was monitored every 15 min by integrating the benzylic protons. The acid-promoted disappearance of dialkoxy disulfide **14** is accompanied by the simultaneous formation of thionosulfite **15** as well as small amounts of diol **13**, sulfite **17** and sulfoxylate **18**. The 3−4% yield of the latter is consistent with its appearance in equally low yields in some of the runs listed in Table 3. The yields for these reactions were reproducible. Similar results were obtained in toluene-d_8.

One implication of these experiments is that thionosulfite **15** is thermodynamically more stable than disulfide **14**. Qualitatively, this is at odds with the B3LYP/6-31G(2d)//MM3* DFT calculations of Tables 1 and 2, which predict the reverse by 0.5 to 1.7 kcal/mol. It is well-known that the ability to accurately predict the experimental energy differences between FS−SX and $F_2S{=}S$ is a challenge. Only with expanded basis sets and significant electron correlation is it possible to invert the stability difference [ΔE(FSSF) − ΔE($F_2S{=}S$)] from +3.5 to −1.7 kcal/mol (e.g., MP4(SDTQ)/6-311G(2d)//MP2/6-311G(2d) and QCISD(T)/6-31+G(d,f)//MP2/631G**, respectively).[63] Although we have not examined the considerably larger structures **14** and **15** with the much higher level calculations, it is likely that a similar stability reversal would be obtained here as well. Despite the uncertainty in the relatively small DFT energy difference between **14** and **15** using the B3LYP/6-31G(2d)//MM3* model, predicted energy differences between other dialkoxy disulfide/thionosulfite pairs are sufficiently large that the crossover correlation (Table 1, Figure 1) is not compromised.

A plausible mechanism for the conversion of **14** to **15** is suggested in Scheme 1. Although dialkoxy disulfide **14** is rapidly formed from **13**, in the presence of acid it reverts to the chloro-

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(60) Gutowsky, H. S.; Holm, C. H. *J. Chem. Phys.* **1943**, *25*, 1228; Kost, D.; Carlson, E. H.; Raban, M. *Chem. Commun.* **1971**, 656.

(61) Snyder, J. P.; Carlsen, L. *J. Am. Chem. Soc.* **1977**, *99*, 2931.

(62) Compound **30** liberated SO under EI MS conditions, a property observed for other dialkoxy disulfides[27] but not for thionosulfites. As well, the splitting pattern observed in the ^{1}H NMR spectrum displays two diagnostic AB spin systems in an approximate ratio of 5:2, ostensibly associated with two distinct atropisomers; the spectra of thionosulfites exhibit AX spin systems. The ratio of the benzyl carbon signals in the ^{13}C NMR corroborates this analysis.

(63) Bickelhaupt, F. M.; Solà, M.; Schleyer, P. v. R. *J. Comput. Chem.* **1995**, *16*, 465.

(64) Torrent, M.; Duran, M.; Sola, M. *THEOCHEM* **1996**, *362*, 163.

(65) Jursic, B. S. *J. Comput. Chem.* **1996**, *17*, 835.

(66) Mestres, J.; Fores, M.; Sola, M. *THEOCHEM* **1998**, *455*, 123.

(67) Thompson, Q. E.; Crutchfield, M. M.; Dietrich, M. W.; Pierron, E. *J. Org. Chem.* **1965**, *30*, 2692.

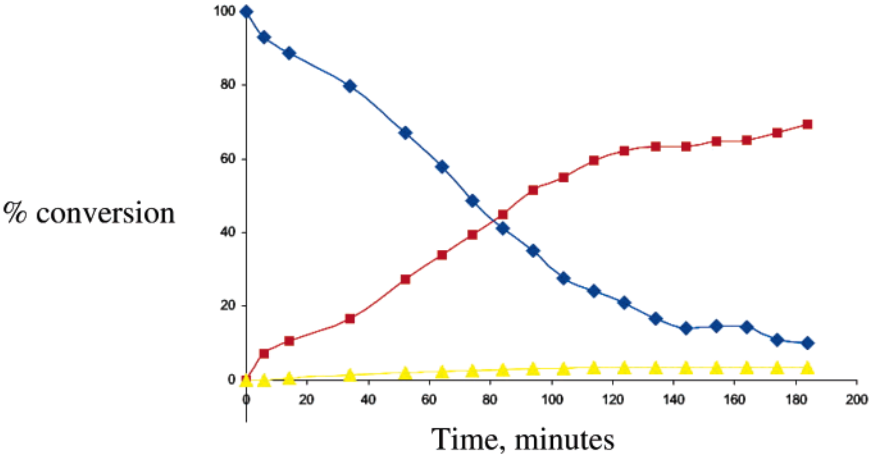

Figure 7. Monitoring the conversion of **14** (blue) to **15** (red) and sulfoxylate **18** (yellow) by ^{1}H NMR ($CDCl_3$, 22 °C) in the presence of HCl and tetrabutylammonium bromide with 1,3,5-tri-*tert*-butylbenzene as an internal standard.

alkoxy disulfide intermediate **20**. Apparently, an acid-promoted 7-*exo-tet* S_N2' mechanism affords **15**. The same functional group transformation has been reported when dialkoxy disulfide is treated with SCl_2 under carefully controlled conditions.[30]

Summary, Conclusions and Future Prospects. It is known that electronegative substituents flanking the disulfide bond in XS—SX can stabilize the constitutional thionosulfite isomer $X_2S{=}S$. The most celebrated case known for over 40 years is FS_2F.[2−6] While indirect evidence exists for the thionosulfite constitution in transient species for various electronegative atoms, the only other documented case is X = O. Dialkoxy disulfides (ROS—SOR) have been known since the turn of the past century,[68] but the first isolable and fully characterized thionosulfite ($(RO)_2S{=}S$), captured in a five-membered ring, appeared 70 years later.[7] Another 23 years passed before additional examples were reported.[8−10] However, once again five-membered rings sustain the rearranged disulfides. This curious ring-size limitation suggested that our understanding of the ROS—SOR/$(RO)_2S{=}S$ relationship was inadequate. Therefore, we undertook a theoretical investigation of the relationship to see if new insights might be gained. Indeed, DFT calculations with a reasonable basis set (B3LYP/6-31G(2d)) pointed to the seven-membered ring thionosulfite as the ideal ring size for approximate energetic equivalence with the corresponding eight-membered ring dialkoxy disulfide (Figure 1). Smaller ring sizes were predicted to favor the thionosulfite structure, and larger, the dialkoxy disulfide.

Choosing 1,2-benzenedimethanol **13** as a convenient starting material, the compound was treated with various bases and sulfur transfer reagents to refine reaction conditions leading simultaneously to the first examples of a stable cyclic dialkoxy disulfide (**14**) and a *non*-five-membered ring thionosulfite (**15**). Fulfilling our theoretical predictions in all particulars, the same reaction yields dimer **16**, sulfite **17**, and sulfoxylate **18** in low yields. X-ray crystal structures of **14**−**17** confirm the connectivities in the solid state, while ambient ^{1}H and ^{13}C NMR provide insights into conformational mobility in solution.

While a deeper analysis may be called for, we speculate that the overriding forces controlling the formation of **14** and **16** from the same reaction appear to be two-fold. For the $(RO)_2S{=}S$ system, the near cis and trans LP—O—S=S torsion angles contribute to maximum orbital overlap between the oxygen lone pairs and the $\sigma^*_{S=S}$ antibonding orbital and thus conformational stability. For ideal values of 0° and 180°, stabilization is a maximum. The corresponding estimated angles for the symmetrical thionosulfite **15** (Figure 2) with two such interactions are 168°. For the RO—S—S—OR system, in contrast to carbon-based disulfides (C—S—S—C), we surmise that small rings induce sufficient strain to render the compounds unstable to facile further transformation. It is noteworthy that the eight-membered ring in **14** represents the minimum ring size required to adopt the optimal τ(OS—SO) dihedral angle near 90°, i.e., 93.2°. The two effects of minimal disulfide ring strain and thionosulfite S=S stereoelectronic stabilization appear to coincide at the ring sizes of eight and seven, respectively (Figure 1, Table 1).

With the present synthetic and structural knowledge in hand, we anticipate that other cyclic 7/8-ring ROS_2OR pairs will soon be synthetically accessible. This projection extends to larger ring cyclic dialkoxy disulfides, one example of which is the 10-membered ring **30**, and the presently unknown six-membered thionosulfite series **6**. We likewise expect that examples of less stable species beyond these boundaries, such as **3**, **5**, and **10**, may be detected as transient intermediates or entities stabilized by heavy substitution.

In addition, we have made an effort to address the potential for rearrangement between the dialkoxy disulfide and thionosulfite isomers. Early literature claimed that interconversion of FSSF and $F_2S{=}S$ is uncatalyzed,[3,5] while other work suggested acid mediation.[5] Experimentally, the situation is not fully resolved. However, recent calculations suggest a barrier of 40−55 kcal/mol for the unimolecular rearrangement[33,63,64] and 40 kcal/mol for a bimolecular reaction channel[66] implying that an uncatalyzed process is beyond reach at room temperature or below where the interconversion is observed to take place. Similar calculations for the unimolecular transition state between MeOSSOMe and $(MeO)_2S{=}S$ yields a $\Delta E^\ddagger$ of 37.5 kcal/mol equally inaccessible at room temperature.[19] We have carefully evaluated the conversion of **14** to **15** under a variety of conditions and demonstrated that the transformation between 0° and 25° requires the presence of at least traces of acid. A plausible mechanistic route is depicted in Scheme 1. Recognition that the dialkoxy disulfide to thionosulfite transformation is acid

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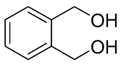
[68] Lengfeld, F. *Ber.* **1895**, *28*, 449.

catalyzed should contribute to the preparation and identification of six- and seven-membered ring systems such as **3** and **5** and other acid sensitive dialkoxy disulfides as well.

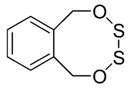
Experimental Section

General Experimental. All reagents were commercially available and were used without further purification save for the following exceptions. Methylene chloride (CH_2Cl_2) and triethylamine (NEt_3) were distilled over calcium hydride. Sulfur monochloride, S_2Cl_2, (135−137 °C) was distilled according to procedures adapted from Fieser and Fieser (100:4:1 S_2Cl_2/sulfur/charcoal).[69] Sulfur dichloride, SCl_2 (59−60 °C), was fractionally distilled over 0.1% phosphorus pentachloride, PCl_5. Both S_2Cl_2 and SCl_2 were used immediately after distillation. All glassware was oven-dried. All reactions were performed under a nitrogen atmosphere (N_2) unless otherwise stated. Flash chromatography[70] was conducted using 230−400 mesh silica gel. NMR spectra were recorded at 400 or 500 MHz for ^1H and 75, 100, or 125 MHz for ^{13}C. Deuterated chloroform ($CDCl_3$), dried over 4 Å molecular sieves, was used as the solvent of record, and spectra were referenced to the solvent peak. Melting points (mp's) were recorded using open end capillaries and are corrected.

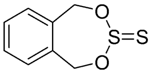
Synthesis of 1,2-Benzenedimethanol 13: To a slurry of $LiAlH_4$ (19.3 g, 0.5 mol, 2.5 equiv) in 315 mL of THF was slowly added a solution of *o*-phthalic acid (33.5 g, 0.2 mol, 1 equiv) in 215 mL of THF at 0 °C under N_2. The flask was equipped with an exit to monitor the production of H_2 gas during the addition. The solution was stirred for 18 h and then quenched according to the literature procedure.[71] This was then stirred for an additional 3 h. The whitish slurry was then vacuum-filtered and washed with excess THF. The organic section was extracted with Et_2O. The solution was dried over $MgSO_4$. The solvent was removed first under reduced pressure and then in vacuo. White crystalline solid. If need be, this can be recrystallized in EtOAc as the solvent and hexanes as the cosolvent. R_f (50% EtOAc/hexanes) 0.35. Yield: 84%. Mp 68−69 °C (lit. mp 62−63 °C,[72] 63−65 °C[73]). ^1H NMR δ 3.44 (s, 2H), 4.65 (s, 4H), 7.30 (m, 4H); ^{13}C NMR δ 64.0, 128.5, 129.7, 139.3; MS (CI) *m/z* 156 ($M^{+\bullet} + NH_4^+$), 139 ($M^{+\bullet} + H^+$), 120, 91; HRMS calcd for $C_8H_{11}O_2$ ($M^{+\bullet} + H^+$): 139.0759. Found: 139.075(3).



Synthesis of Eight-Membered Ring Dialkoxy Disulfide 14: The compound was synthesized using a modification of the literature procedure for the synthesis of acyclic alkoxy disulfides.[29] A solution of diol **13** (138 mg, 1 mmol, 1 equiv) and NEt_3 (280 μL, 2 mmol, 2 equiv) in 10 mL of CH_2Cl_2 was allowed to stir under nitrogen at 0 °C. A solution of S_2Cl_2 (80 μL, 1.0 mmol, 1 equiv) in 50 mL of CH_2Cl_2 was added dropwise over ca. 60 min. The reaction mixture was allowed to stir for a further 4 h. The reaction mixture was quenched with 20 mL of H_2O. The organic phase was washed 3 × 33 mL of H_2O. The organic phase was dried over $MgSO_4$. This mixture was vacuum filtered, and the solvent was removed first under reduced pressure and then in vacuo. Frequently, it was not necessary to chromatograph the product as there was quantitative conversion as detected by TLC and ^1H NMR. Fruity-smelling white crystalline solid. R_f (25% EtOAc/hexanes) 0.47, (25% CH_2Cl_2/hexanes) 0.17. Yield: 94%. Mp 59−60 °C; DSC $T_{onset} = 61.11$, $T_{max} = 64.63$, $\Delta H = 476.2$ J/g; $T_{onset} = 117.98$, $T_{max} = 125.36$, $\Delta H = -404.5$ J/g. ^1H NMR δ 7.43 (m, 4H), ABq system 4.94 (d, 2H, $J_{AB} = 12.00$ Hz), 5.07 (d, 2H, $J_{AB} = 12.00$ Hz); ^{13}C NMR δ 72.3, 130.1, 132.1, 136.1; ^{13}C NMR indirectly detected by HMQC(500 MHz, 125 MHz) δ 72.6, 131.0, 133.0; IR ($CDCl_3$) 531 cm^{-1} (S−S stretch); MS (EI) *m/z* 200 ($M^{+\bullet}$), 152 ($M^{+\bullet}$ − SO); 119 ($M^{+\bullet} - S_2OH$), 104 ($M^{+\bullet} - S_2O_2$). HRMS calcd for $C_8H_8S_2O_2$: 199.9966. Found: 199.997(0). Calcd for $C_8H_8S_2O_2$ − SO: 152.0296. Found: 152.030(0). IR − KBr (cm^{-1}) 1471(w), 1452(w), 1384(w), 1352(w), 1306(w), 1209(w), 1188(w), 1117(w), 956(m), 932(s), 874(w), 848(w), 816(w), 789(w), 760(m), 743(s), 698(w), 676(w), 647(s), 619(m), 590(w), 531(w). Raman (powder − 5000 scans) 3046, 2966, 2920, 1604, 1051, 676 ν(S−O), 518 ν(S−S), 355, 196, 137, 122, 84.



Synthesis of Seven-Membered Ring Thionosulfite 15: A solution of diol **13** (138 mg, 1 mmol, 1 equiv) and NEt_3 (280 μL, 2 mmol, 2 equiv) in 10 mL of CH_2Cl_2 was allowed to stir under N_2 at rt. A solution of S_2Cl_2 (80 μL, 1.0 mmol, 1 equiv) in 10 mL of CH_2Cl_2 was added dropwise over ca. 60 min. The reaction mixture was allowed to stir for a further 4 h. The reaction mixture was quenched with 10 mL of H_2O. The organic phase was washed 3 × 33 mL of H_2O. The organic phase was dried over $MgSO_4$. This mixture was vacuum filtered, and the solvent was removed first under reduced pressure and then in vacuo. The crude solid, which contained a 2:1 mixture of **14**:**15**, was flash chromatographed[70] in 25% CH_2Cl_2/hexanes as the eluant to afford a slightly aromatic white crystalline solid. R_f (25% CH_2Cl_2/hexanes) 0.31. Yield: 22%. Mp 73−74 °C; DSC $T_{onset} = 79.93$, $T_{max} = 80.69$, $\Delta H =$ 78.10 J/g; ^1H NMR δ 7.32 (m, 4H), 6.61 (d, 2H, $J = 14.25$ Hz), 4.49 (d, 2H, $J = 14.25$ Hz); ^{13}C NMR δ 62.9, 128.4, 129.5, 136.9; MS (EI) *m/z* 200 ($M^{+\bullet}$), 170, 135, 119, 90, 78; HRMS calcd for $C_8H_8S_2O_2$: 199.9966. Found: 199.995(9). Calcd for $C_8H_8S_2O_2$ − O: 184.0017. Found: 184.001(6). Calcd for $C_8H_8S_2O_2 - O_2$: 168.0067. Found: 184.005(9). Calcd for $C_8H_8S_2O_2$ − SO: 152.0296. Found: 152.029(4). IR − KBr (cm^{-1}) 1496(w), 1455(m), 1442(w), 1384(w), 1352(w), 1306(w), 1242(w), 1219(w), 1209(w), 1186(w), 1118(w), 956(w), 947(m), 932(s), 893(m), 874(w), 853(w), 848(w), 816(w), 789(w), 774(m), 760(m), 743(w), 739(m), 696(m), 685(m), 676(m), 669(m), 647(w), 632(s), 619(m), 595(m), 590(w), 540(w), 531(w). Raman (powder − 1000 scans) 3047, 2983, 1606, 1220, 1160, 1048, 745, 633 ν(S−O), 540 ν(S═S), 337, 304, 179, 135, 87, 58.



Synthesis of 16-Membered Ring Dimer 16: The following conditions appear to be optimal for the procedure of **16**. A solution of diol **13** (138 mg, 1 mmol, 1 equiv) and NEt_3 (280 μL, 2 mmol, 2 equiv) in 10 mL of THF was allowed to stir under nitrogen at 0 °C. A solution of S_2Cl_2 (80 μL, 1.0 mmol, 1 equiv) in 10 mL of THF was added dropwise over ca. 3 min. The reaction mixture was allowed to stir for a further 5 h. The reaction mixture was quenched with 10 mL of H_2O. The organic phase was extracted in 20 mL of Et_2O. The organic phase was washed 3 × 33 mL of H_2O. The organic phase was dried over $MgSO_4$. This mixture was vacuum filtered, and the solvent was removed first under reduced pressure and then in vacuo. The crude solid, which contained a 10:1 mixture of **14**:**16**, was flash chromatographed[70] in 25% CH_2Cl_2/hexanes as the eluant to afford a slightly aromatic white crystalline solid. R_f (25% CH_2Cl_2/hexanes) 0.13. Yield: 9%. Mp 153−155 °C; DSC $T_{onset} = 92.18$, $T_{max} = 95.80$, $\Delta H = 11.99$ J/g; $T_{onset} =$ 139.88, $T_{max} = 143.19$, $\Delta H = -124.70$ J/g; $T_{onset} = 153.75$, $T_{max} =$ 156.76, $\Delta H = -42.52$ J/g. ^1H NMR δ 7.36 (m, 8H), AX system: 5.26 (d, 4H, $J = 11.00$ Hz), 5.20 (d, 2H, $J = 12.00$ Hz), 4.89 (d, 2H, $J =$ 12.00 Hz), 4.84 (d, 4H, $J = 11.00$ Hz); ^{13}C NMR δ 75.3, 75.4, 128.7, 129.0, 129.7, 134.7, 134.9; ^{13}C NMR indirectly detected by HMQC

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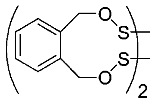
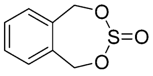
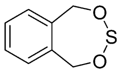
(600 MHz, 151 MHz) δ 75.2, 129.0, 129.7; MS (EI) *m/z* 400 ($M^{+\bullet}$), 352 ($M^{+\bullet} - SO$), 272 ($C_{12}H_{16}O_3S_2$), 255, 200 ($C_8H_8O_2S_2$), 152 (C_8H_8OS), 135, 121, 120 (C_8H_8O), 105, 104 (C_8H_8); HRMS calcd for $C_{16}H_{16}S_4O_4$: 399.9931. Found: 399.99(3)4. IR − KBr (cm^{-1}) 1481(w), 1456(w), 1447(w), 1384(w), 1367(w), 1360(w), 1300(w), 1262(w), 1232(w), 1205(w), 1189(w), 1112(w), 984(m), 974(m), 953(m), 926(s), 874(m), 855(w), 816(m), 763(s), 736(m), 723(m), 697(s), 639(w), 602(w), 514(w).



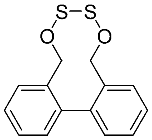
Synthesis of Sulfite 17: To a solution of **13** (141.5 mg, 1 mmol, 1 equiv) and NEt_3 (280 μL, 2 mmol, 2 equiv) in 10 mL of CH_2Cl_2 was added dropwise a solution of 75 μL of $SOCl_2$ in 10 mL of CH_2Cl_2 at 0 °C under N_2. The reaction was stirred for 2.3 h. The reaction was quenched with 20 mL of H_2O. The organic phase was washed 3 × 30 mL H_2O. The solution was dried over $MgSO_4$. The solvent was removed first under reduced pressure and then in vacuo. Brownish crystals. R_f (25% EtOAc/hexanes) 0.38; (25% CH_2Cl_2/hexanes) baseline. Yield: 74%. Mp 33−36 °C; Recrystallized as clear crystals from CH_2Cl_2/hexanes: Mp 34−35 °C; ^{1}H NMR δ 7.27 (m, 4H), 5.96 (d, 2H, J = 14.00 Hz), 4.68 (d, 2H, J = 14.00 Hz); ^{13}C NMR δ 62.7, 128.3, 128.3, 136.1; MS (EI) *m/z* 184 ($M^{+\bullet}$), 119, 91; HRMS calcd for $C_8H_8SO_3$: 184.0194. Found: 184.019(8).



Synthesis of Sulfoxylate 18: A solution of diol **13** (138 mg, 1 mmol, 1 equiv) and NEt_3 (280 μL, 2 mmol, 2 equiv) in 10 mL of CH_2Cl_2 was allowed to stir under nitrogen at 0 °C. A solution of SCl_2 (64 μL, 1.0 mmol, 1 equiv) in 10 mL of CH_2Cl_2 was added dropwise over ca. 10 min. The reaction mixture was allowed to stir for a further 3 h. The reaction mixture was quenched with 20 mL of H_2O. The organic phase was washed 3 × 33 mL of H_2O. The organic phase was dried over $MgSO_4$. This mixture was vacuum filtered, and the solvent was removed first under reduced pressure and then in vacuo. Aromatic light-brown solid. R_f (25% CH_2Cl_2/hexanes) 0.18. Yield: 92%. ^{1}H NMR δ 7.28 (m, 4H), 5.54 (s, 4H); ^{13}C NMR δ 88.7, 128.4, 129.8, 138.6; MS (EI) *m/z* 168 ($M^{+\bullet}$), 160, 138, 135, 119, 104, 78 HRMS calcd for $C_8H_8SO_2$: 168.0245. Found: 168.024(0).



Synthesis of 10-Membered Ring Dialkoxy Disulfide, 30: A solution of 2,2′-biphenyldimethanol **29** (214 mg, 1 mmol, 1 equiv) and NEt_3 (280 μL, 2 mmol, 2 equiv) in 10 mL of CH_2Cl_2 was allowed to stir under nitrogen at 0 °C. A solution of S_2Cl_2 (80 μL, 1.0 mmol, 1 equiv) in 10 mL of CH_2Cl_2 was added dropwise over ca. 10 min. The reaction mixture was allowed to stir for a further 5.5 h. The reaction mixture was quenched with 15 mL of H_2O. The organic phase was washed 3 × 33 mL of H_2O. The organic phase was dried over $MgSO_4$. This mixture was vacuum filtered, and the solvent was removed first under reduced pressure and then in vacuo. The crude mixture was flash chromatographed[70] in 10% CH_2Cl_2/hexanes as the eluant to afford a fruity-smelling clear oil which solidified in the freezer. R*f* (10% CH_2Cl_2/hexanes) 0.09. Yield: 25%. ^{1}H NMR δ 7.51−7.40 (m, 5H), 7.36−7.31 (m, 2H), 7.21−7.12 (m, 2H), 5.15 (d, 0.4H, J = 12.30 Hz), 4.99 (d, 2H, J = 12.60 Hz), 4.59 (d, 2H, J = 12.60 Hz), 4.55 (d, 0.4H, J = 12.30 Hz); ^{13}C NMR δ 70.4, 76.5, 127.6, 127.8, 128.2, 128.9, 129.4, 129.6, 129.8, 131.4, 134.7, 135.8, 139.4, 140.7; 5:1 of two diastereomers as detected by ^{13}C NMR, ^{1}H NMR. MS (EI) *m/z* 276 ($M^{+\bullet}$), 228 ($M^{+\bullet} - SO$) 196 ($M^{+\bullet} - S_2O$); 179 ($M^{+\bullet} - S_2O_2H$), 165 ($M^{+\bullet} - S_2O_2CH_3$). HRMS calcd for $C_8H_8S_2O_2$: 276.0279. Found: 276.027(1).



Isomerization of 14 to 15: A. Preparation of the HCl Solution. Gaseous HCl was generated in a three-neck flask under nitrogen by dropwise addition of concentrated sulfuric acid (20 mmol, 1 equiv) to solid sodium chloride (40 mmol, 2 equiv). Using a plastic syringe, the gas (3 mL, 25 °C) was dissolved in 3 mL of dry $CDCl_3$ (99.8%) at room temperature. The resulting solution was titrated with amidazophene in the presence of dimethyl yellow.[74] Specifically, a sample of the HCl/$CDCl_3$ solution was placed in a 5-mL round-bottom flask under nitrogen. One drop of a 0.1% solution of dimethyl yellow indicator in dry benzene was added to the sample before the solution was titrated with a 0.01 M solution of amidazophene in dry benzene. The solution of amidazophene was slowly added dropwise until the pink color turns slightly yellow. The HCl concentration was determined to be 0.013 M. The $CDCl_3$ used was similarly tested for HCl and found to contain negligible amounts of acid.

B. ^{1}H NMR (500 MHz) Monitoring of the Isomerization. Vials and NMR tubes used below were new and preheated in an oven hours before use. A pure sample of dialkoxy disulfide **14** (5.0 mg, 0.025 mmol, 1 equiv) in 1 mL of $CDCl_3$ containing tetrabutylammonium bromide[75] (17.0 mg, 0.050 mmol, 2 equiv) was prepared. 1,3,5-Tri-*tert*-butylbenzene (2.1 mg, 0.008 mmol, 0.33 equiv) served as the internal standard. After taking the ^{1}H NMR spectrum and integrating the methylene protons for time-zero values, the dialkoxy disulfide solution was transferred to a vial and the experiment was initiated by dropwise addition of 0.4 mL of the HCl/$CDCl_3$ solution (~0.005 mmol, 0.2 equiv). The solution was mixed and replaced in the NMR tube. Relative amounts of both dialkoxy disulfide **14** and thionosulfite **15** were monitored by integrating the methylene protons approximately every 15 min for several hours (delay time: d_1 = 20 s). The NMR device was reshimmed a number of times throughout the experiment. In addition to the loss of **14** and formation of **15**, a peak at 5.5 ppm demonstrated the formation of sulfoxylate **18** over the course of the experiment for a final yield of 3−4%. The experiment was performed at a corrected probe temperature of 22 °C; 500 MHz.

Preparation of 14 and 15 in the Presence of Acid (Table 6): A solution of **13** (1 mM, 1 equiv) and triethylamine (2 mM, 2 equiv) in 20 mL of CH_2Cl_2 was allowed to stir under nitrogen at 25 °C. A solution of S_2Cl_2 (1 mM, 1 equiv) in 30 mL of CH_2Cl_2 was added dropwise over 5 min.

Entry 1: The reaction mixture was immediately worked up with 3 × 30 mL of H_2O. The organic phase was dried over $MgSO_4$ and vacuum filtered. The solvent was removed first under reduced pressure and then in vacuo. A colorless crystalline solid was obtained and purified over neutral alumina (25% CH_2Cl_2/hexanes) to afford **14** as a white solid (92%); Mp 59−60 °C; ^{1}H NMR spectra are in agreement with values reported previously.

Entry 2: The reaction mixture was prepared as in entry 1 and allowed to stir for an additional 2 h at rt. Workup was identical to entry 1 to afford **14** as a white solid (90%); Mp 59−60 °C; ^{1}H NMR spectra are in agreement with values reported previously.

Entries 3, 4, and 5: A solution of **13** (1 mM, 1 equiv) and triethylamine (1.7 mM, 1.7 equiv) in 20 mL of CH_2Cl_2 was stirred under nitrogen at 25 °C and treated with S_2Cl_2 as described above over 5 min.

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(74) Barcza, L. *Talanta* **1963**, *10*, 503. Schulek, E.; Barcza, L. *Acta Pharm. Hung.* **1962**, *32*, 1.

(75) The isomerization is more rapid and complete when this salt is added, apparently providing a higher halide ion concentration to supplement the chloride ion from HCl as pictured in Scheme 1.

Entry 3: With the exception of the reduced amount of Et_3N, the reaction mixture was treated and worked up as in entry 1 to afford **14** as a white solid (89%). Mp 59−60 °C; ^{1}H NMR spectra are in agreement with values reported previously.

Entry 4: The reaction mixture was treated and worked up as in entry 2 to afford **15** a white solid (75%; 65−75% range for different runs); Mp 73−74 °C; ^{1}H NMR spectra are in agreement with values reported previously.

Entry 5: The reaction mixture was allowed to stir for 2 h at 5 °C (ice bath) and worked up as above. Solvent removal yielded a yellow oil that proved to be an approximate 1:1 mixture of **14** and **15** according to ^{1}H NMR (i.e., 40 and 45%, respectively, as monitored by the tri-*t*-butybenzene internal standard); the spectra are in agreement with values reported previously for both compounds.

Entry 6: A solution of **13** (1 mM, 1 equiv) and triethylamine (1 mM, 1 equiv) in 20 mL of CH_2Cl_2 at 25 °C was stirred for 5−15 min. An aliquot of the mixture was taken and analyzed by ^{1}H NMR as above to yield a broad and featureless spectrum.

Computational Methodology. All ab initio calculations were carried out with the GAUSSIAN 94[76] suite of programs. Geometries for the dialkoxy disulfides and their branch-bonded thionosulfites isomers **3**−**12** were calculated based on an appropriately parametrized MM3* force field.[25] Single-point energy calculations were obtained with the B3LYP functional[77] and the 6-31G(2d) Pople double ζ (zeta) split valence basis set.[78]

Acknowledgment. We thank NSERC and FQRNT (formerly FCAR) for funding. E.Z.-C. acknowledges support from FQRNT in the form of graduate and postdoctoral fellowship scholarships. N.N. and J.P.S. are grateful to Professor Dennis Liotta (Emory University) for encouragement and support. We are also grateful to Charles B. Abrams for preliminary work on the project and to Dr. Andrzej Rys (McGill University) for assistance in studying the interconversion of **14** and **15**.

Supporting Information Available: DSC Spectra of **14**−**16**. IR Spectra of **14**−**16**, including zoomed spectra highlighting the region < 1500 cm^{-1}. A composite IR plot of isomers **14** and **15** is provided to aid in the comparison of the spectra. Raman spectra for **14** and **15**. Crystal structures of **14**−**17**. ^{1}H NMR of **30**. This material is available free of charge via the Internet at http://pubs.acs.org.

JA0559395

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