

## Inherently Hindered Rotation about a Disulfide Bond

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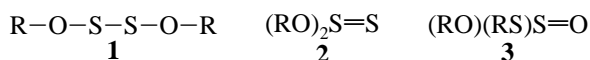
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Compounds with the formula  $S_2(OR)_2$  were first synthesized in 1895,<sup>1</sup> but have been generally overlooked until the past few years.<sup>2–5</sup> It has been recognized since 1935 that  $S_2(OR)_2$  can possibly exist in three isomeric forms, **1–3**.<sup>6</sup> Structure **3** was



readily ruled out by NMR, but the appearance of an ABM pattern for  $S_2(OCH_2CH_3)_2$  has been insufficient to distinguish dialkoxy disulfide **1** from the branch-bonded isomer **2**.<sup>2,7</sup>

Although we have depicted  $S_2(OCH_2Ar)_2$  as the disulfide in our  $S_2$  synthetic work,<sup>5</sup> the persistent presence of diastereotopic methylene protons in the <sup>1</sup>H NMR from –70 to ca. 75 °C, where the peaks coalesce and the compounds decompose, leaves the distinction between **1** and **2** unresolved. To be sure,  $S_2(OCH_2R)_2$  analogues are in the disulfide form in the gas phase<sup>3c</sup> and the solid state.<sup>3b,5</sup> However, the low barriers to rotation about S–O and S–S bonds (6–9<sup>8,9b</sup> and 8–10<sup>2,9,10</sup> kcal/mol, respectively), the existence of isomers for  $S_2F_2$ ,<sup>11</sup> and the capacity for isomerization of FSSF to  $F_2S=S$  above –100 °C<sup>12</sup> continue to suggest the possibility that **1** rearranges to branch-bonded valence isomer **2** in solution.<sup>7b</sup> The latter would display diastereotopic methylene protons at ambient temperature and carries the potential for NMR coalescence due to inversion at S(=S). The branch-bonded dialkoxy disulfide linkage in small rings was justifiably claimed by Thompson as early as 1964,<sup>13</sup>

although only a single example (**4**, Figure 1) has been verified since by X-ray crystallography.<sup>14</sup>

We have performed a combined theoretical and spectroscopic study to show that the structures of the  $S_2(OCH_2Ar)_2$  compounds in solution are definitively dialkoxy disulfides **1** with unusually high barriers to rotation about the S–S bond. The conformers of dimethoxy disulfide (and all other  $S_2(OCH_3)_2$  isomers considered here) were optimized at the MP2/6-311G(3d) and Becke3LYP/6-311G\* levels of theory<sup>15</sup> to obtain geometries/relative energies and vibrational frequencies, respectively. The lowest energy conformer of  $C_1$  symmetry, **5**, is in agreement with the electron diffraction structure and the theoretical studies of Studel.<sup>3c</sup> In sharp contrast to thiosulfoxides,<sup>16</sup> the global minimum conformation of the branch-bonded isomer, **6**, is predicted to be more stable than **5** by 1.9 kcal/mol when zero point energy (ZPE) corrections are included. We conclude that the energies of the isomers are sufficiently close to justify considering transformation between them, although the absolute energy difference is open to question.<sup>17</sup>

To assign the structure, we have calculated various spectra for **1** and **2** and compared them with experiment. MM3 force fields for both ROSSOR and  $(RO)_2S=S$  have been developed from a blend of structural and ab initio data to assist the task.<sup>18</sup> MM3 conformational analysis of **1** and **2** (R = CH<sub>2</sub>Ph) followed by single point Becke3LYP/3-21G\*/GIAO calculations<sup>15a</sup> of the proton chemical shifts of low-energy conformations yields four methylene proton shifts from  $\delta = 3.5–5.0$  and  $4.0–5.5$  ppm, respectively, relative to TMS. The predicted peak positions bracket the experimental ones (CDCl<sub>3</sub>, 4.76, 4.81, 4.87, and 4.93 ppm). Proton NMR is unable to distinguish between the isomers.

Turning to vibrational spectra, we note that dimethoxy disulfide **5** exhibits a band at 525–530 cm<sup>–1</sup> assigned by HF/6-311G\* normal coordinate analysis as the S–S stretch ( $\nu_{SS}(\text{calc}) = 489$  cm<sup>–1</sup>).<sup>3c</sup> The unscaled<sup>15b</sup> Becke3LYP/6-311G\* value from the present work is  $\nu_{SS} = 468$  cm<sup>–1</sup>. With the same method, thionosulfite **6** and the simple five-membered ring analogue of **4** are predicted to possess relatively intense S–S stretches at 639 and 643 cm<sup>–1</sup>, respectively. As a result, we assign the moderately strong frequency of thionosulfite **4** at 650 (IR, Nujol) and 652 cm<sup>–1</sup> (Raman, neat) to the S–S vibration. Compounds **1** (R = CH<sub>2</sub>Ph, CH<sub>2</sub>Ph-*p*-NO<sub>2</sub>) show weak IR and Raman bands from 524–529 cm<sup>–1</sup> in various media including CHCl<sub>3</sub>, but nothing in the higher energy thionosulfite region. Vibrational analysis of optimized conformations by MM3 is confirmatory: **1** and **2** (R = CH<sub>2</sub>Ph),  $\nu_{SS}(\text{calc}) = 505–520$  and 640–665 cm<sup>–1</sup>, respectively.

In the UV, the OSSO moiety for both alkyl and benzylic structures is calculated by ZINDO<sup>19</sup> to be transparent at wavelengths greater than 200 nm. The branch-bonded moiety, however, is predicted to show several O<sub>2</sub>S=S absorption bands from 230 to 275 nm. In pentane, thionosulfite **4** displays peaks

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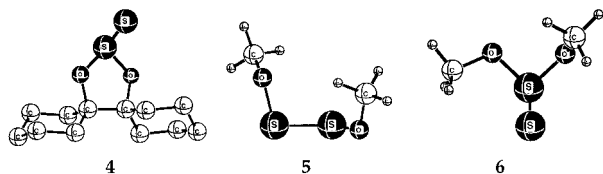
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**Figure 1.** Structures of **4** (X-ray) and **5** and **6** (MP2/6-311G(3d) optimized).

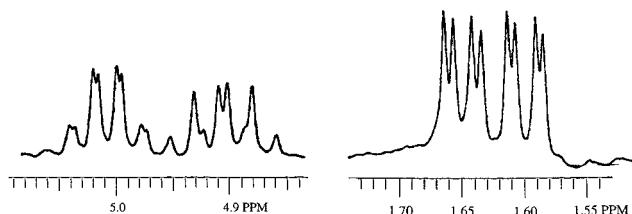
at 250 ( $\epsilon = 2500$ ) and 311 ( $\epsilon = 195$ ), while **1** ( $R = \text{CH}_2\text{Ph}$ ) shows only tailing beyond 196 nm (e.g.  $\lambda_{\text{max}}$  250–260 nm ( $\epsilon < 200$ )).

To assess the dynamic process underlying the observed 75 °C coalescence temperature of **1/2**, three transition states have been examined with MP2/6-311G(3d). The predicted barriers for intramolecular migration of RO in the rearrangement of **1** to **2** ( $R = \text{CH}_3$ ) and the inversion of branch-bonded sulfur in **2** ( $R = \text{CH}_3$ ) are 37.5 and 32.3 kcal/mol, respectively. Neither process can be expected to operate at temperatures at which  $\text{S}_2(\text{OCH}_2\text{Ar})_2$  analogues are thermally accessible. Calculation of the trans torsional barrier<sup>9b</sup> for dimethoxy disulfide corrected for ZPE yields a value of 18.1 kcal/mol. The coalescence of the AB pattern of **1** ( $R = \text{CH}_2\text{Ph}$ ) at 75 °C as it undergoes decomposition likewise translates to an activation barrier of  $E_a = 17.8$  kcal/mol. The experimental and theoretical barrier maxima agree extremely well with one another and require that the Thompson dialkoxy disulfide barrier<sup>2,10</sup> be adjusted upward by 9.2 kcal/mol. The results likewise confirm that Seel's measurement is in fact an S–S torsional barrier.<sup>7,10,20</sup>

The combined measurements and computed spectra are most reasonably interpreted in terms of the exclusive presence of dialkoxy disulfide **1** in solution, while the appearance of diastereotopic protons in the  $^1\text{H}$  NMR is due to hindered rotation around the S–S bond at room temperature. The 8–10 kcal/mol increase in rotation barrier relative to dialkyl disulfides<sup>9</sup> can be attributed to partial S–S double bond character arising from a contracted S–S bond ( $r(\text{S}-\text{S})$ , **1** ( $R = \text{CH}_3$ ) 1.972 (X-ray),<sup>3b</sup> 1.960 (ED),<sup>3c</sup> and 1.990 Å (MP2/6-311G(3d)); MeSSMe 2.038 Å (ED)<sup>21</sup>, a consequence of disulfide substitution by electronegative oxygen atoms.<sup>3c,17</sup> At the trans transition state for rotation, the S–S bond elongates by 0.165 Å to a value of 2.155 Å (MP2/6-311(3d)). Similar to FSSF and CISSF,<sup>17</sup> NBO analysis<sup>22</sup> for ROSSOR (**1**,  $R = \text{CH}_3$ ) ascribes an S–S bond order of 1.17. The value drops to 0.87 at the trans torsional maximum. While restricted rotation about single bonds due largely to steric congestion is well-known,<sup>23</sup> to our knowledge

(20) **Note Added in Proof:** The 18–19 kcal/mol barrier has been confirmed for a number of (ROS)<sub>2</sub> derivatives: Borghi, R.; Lunazzi, L.; Placucci, G.; Cerioni, G.; Foresti, E.; Plumitallo, A. *J. Org. Chem.* **1997**, *62*, 4924.

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**Figure 2.** The  $^1\text{H}$  NMR spectrum of disulfide **1** ( $R = \text{CH}(\text{CH}_3)\text{Ph}$ ) prepared from racemic phenethyl alcohol;  $\text{CHCl}_3$ , 25 °C.

no unambiguous case of atropisomerism<sup>23a</sup> arising entirely from electronic effects has been reported.<sup>24</sup>

The high S–S rotational barrier for ROSSOR relative to RSSR should permit the unprecedented separation and isolation of disulfide torsional enantiomers. As a first step in this direction,  $(\text{PhCH}_2\text{OS})_2$  and  $(p\text{-NO}_2\text{PhCH}_2\text{OS})_2$  have been treated gradually with 1 equiv of the chiral shift reagent  $\text{Eu}(\text{hfc})_3$  in  $\text{CDCl}_3$ . The lower doublet of the AB system centered around 4.9 ppm separates into doublets. Solvent dilution shows the complexation to be reversible. An even more striking effect is evident if the disulfide is prepared from phenethyl alcohol (**1**,  $R = \text{CH}(\text{CH}_3)\text{Ph}$ ). The room-temperature NMR ( $\text{CDCl}_3$ ) of the  $\text{CH}(\text{CH}_3)$  moiety from the  $R(+)$ -alcohol exhibits two equally intense doublets and quartets, while racemic alcohol delivers the expected splitting of all signals (Figure 2); a powerful demonstration of chirality for  $(R\text{-O-S})_2$ .

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**Supporting Information Available:** A summary of calculated vs experimental quantities and the NMR spectra of **1** ( $R = \text{CH}_2\text{Ph}$ ) (+Eu-(hfc)<sub>3</sub>) and  $\text{CH}(\text{CH}_3)\text{Ph}$  (5 pages). See any current masthead page for ordering and Internet access instructions.

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