

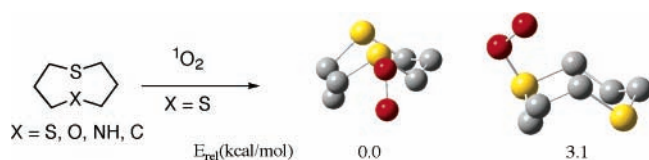
## Natural Bond Orbital Analyses of Persulfide Stabilization by Remote Functional Groups. The Conformationally Induced Electrostatic Stabilization Sulfide Photooxygenation Mechanism

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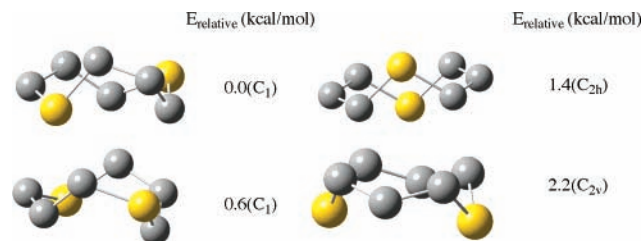
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The conformationally induced electrostatic stabilization (CIES) sulfide photooxygenation mechanism was computationally examined using an ab initio model and extended to the study of new donor atoms. The MP2/6-31G(d) geometries and a natural population analysis of natural lone-pair orbitals on the donor atoms support the mechanism and reveal that oxygen and nitrogen donor groups are more stabilizing than sulfur.

It is well established that decompositions of persulfides, **1**, formed during photooxygenations of organic sulfides, are responsible for the low quantum yields of these reactions.<sup>1</sup> It is also well established that hydrogen bonding to the pendant oxygen<sup>2</sup> and nucleophilic additions to the sulfonium-like sulfur<sup>3,4</sup> stabilize the persulfide, inhibit decomposition to triplet oxygen, and increase the quantum yield.<sup>1</sup> We recently suggested *conformationally induced electrostatic stabilization* (CIES) as yet another mechanism to increase the efficiencies of these reactions.<sup>5</sup> As the name implies, this mechanism involves a conformational change during persulfide formation that places an electron-rich group in a geometry that allows stabilization by noncovalent electron donation into an empty orbital associated with the persulfide sulfur. This stabilization can increase the rate of persulfide formation (anchimeric assistance) and decrease the rate of decomposition by loss of oxygen. The decomposition is inhibited in part by the fact that, as the oxygen departs, the nascent electron-rich-group/sulfur-lone-pair interaction destabilizes the transition state for physical quenching (i.e., loss of oxygen). This new mechanism is more restrictive than the previously suggested mechanisms (vide supra) and only

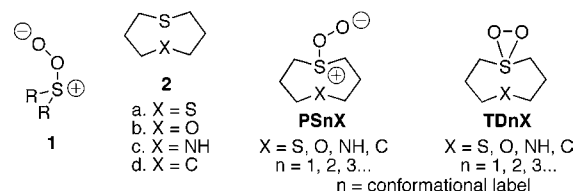
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**FIGURE 1.** Conformational minima for 1,5-dithiocyclooctane and their relative energies and symmetries, with hydrogens removed for clarity.

applies to a subset of organic sulfides. On the other hand, this new mechanism could potentially have far reaching implications during photooxygenations of biological targets that often have suitable electron-donor groups in close proximity to the reaction center.<sup>6</sup>

In this manuscript, we report a computational study of four eight-membered ring sulfides, **2**, and a series of homologous persulfides, **PSnX**, containing a lone-pair donor group or atom, X, ideally situated for through-space electrostatic stabilization. We assess the extent of interaction between the persulfide sulfur and the remote group X using a natural bond orbital analysis (NBO) to provide insight into the relative abilities of X to participate in CIES.



Extensive computational studies of the reactions of singlet oxygen with sulfides have been reported by Jensen,<sup>7–12</sup> by Ishiguro and co-workers,<sup>13</sup> and by McKee.<sup>14</sup> These studies have demonstrated that energetic results are very sensitive to the selection of computational methods. For the number of calculations reported here, it is clearly impractical to use high-level computational methods such as CCSD(T)/6-31G(d) or CCSD(T)/6-311+G(2df), so instead, we have chosen to use the MP2/6-31G(d) method which is known to give good energies and excellent structural results for singlet oxygen sulfide reactions.<sup>7–12</sup> Jensen<sup>12</sup> has also reported calculations that suggest that dimethylpersulfide is stabilized by 13 kcal/mol in acetone. Solvents have not been explicitly taken into account in this work. Consequently, we will restrict our energetic comparisons to

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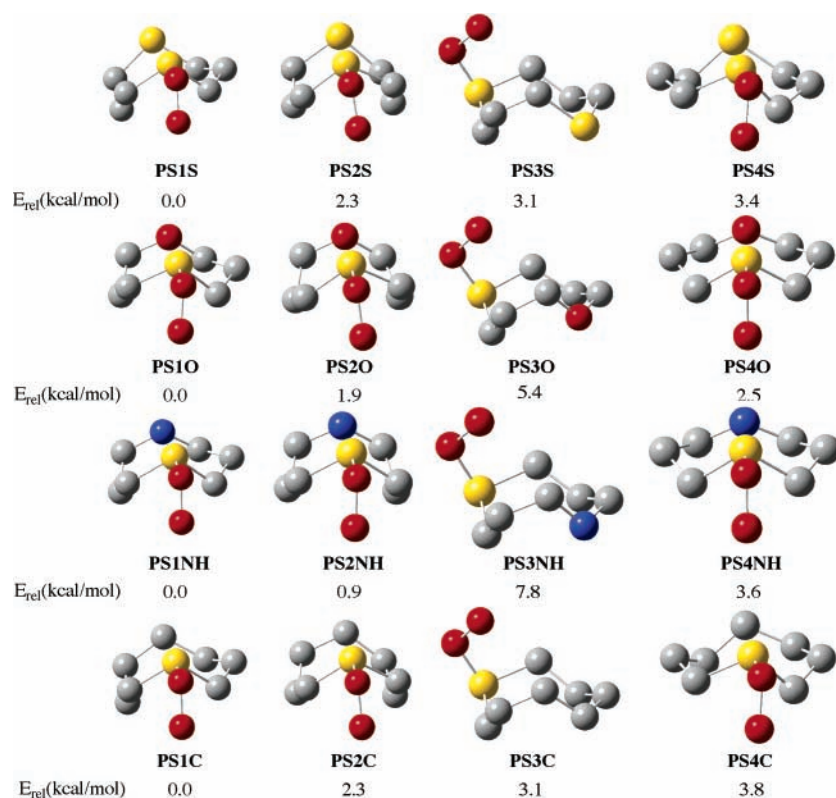


FIGURE 2. Persulfoxide (**PSnS**) and those derived from it (**PSnO**, **PSnNH**, and **PSnC**).

persulfoxide isomers or to thiadioxirane isomers and resist any temptation for cross comparisons (e.g., a comparison of persulfoxide energy to the corresponding thiadioxirane energy) because persulfoxides will be preferentially stabilized in organic solvents.

The conformational surfaces for **2** are very complex, so we have adopted a systematic approach to ensure the location of the most important conformational isomers. This method uses as a starting point the well-established conformations of cyclooctane that have been identified by Anet and others.<sup>15</sup> Two sulfur atoms are introduced to replace two 1,5-disposed carbons in the lowest energy cyclooctane conformation to generate all possible input structures. This procedure is then repeated for all the reported cyclooctane conformations. Geometry minimizations of these input structures generated nine conformations of **2a**. (See Supporting Information for additional structural details.) Four of the conformations (Figure 1) are less than 3 kcal/mol above the global minimum and could potentially have chemical consequences. The global minimum in **2a** is a twist-boat-chair, and the boat-chair conformation, corresponding to the global minimum in cyclooctane, is 0.6 kcal/mol higher in energy. The **2a** conformation at 1.4 kcal/mol is a twist-chair with  $C_{2h}$  symmetry. The analogous conformation in cyclooctane is significantly destabilized by severe H–H eclipsing and H–H transannular interactions which are absent in the  $C_{2h}$  **2a** conformation. The  $C_{2v}$  conformation at 2.2 kcal/mol above the global minimum is a chair-chair conformation characterized by two  $\sigma_v$  planes, one through the two sulfur atoms and the second through  $C_3$  and  $C_7$ .

The input structures for the computations designed to locate persulfoxides **PSnS** were generated by placing the oxygen on the two faces of each conformation of **2a**, with the pendant oxygen either bisecting the C–S–C angle or rotated by 180°. S–O bond lengths and S–O–O bond angles from the minimized structure of dimethylpersulfoxide were used.<sup>10</sup> Minimizations using input structures with the pendant oxygen rotated by 180° often collapsed to a three-membered ring thiadioxirane, **TDnX**, whereas the bisected input geometries successfully resulted in location of persulfoxide stationary points with zero imaginary frequencies. Persulfoxides **PSnO**, **PSnNH**, and **PSnC** were located by minimization of input structures generated by replacing the divalent sulfur in the **PSnS** persulfoxides with oxygen, nitrogen, and carbon, respectively.

These calculations led to the identification of 18 persulfoxides in the **PSnS** and **PSnC** (i.e.,  $n = 1, 2, \dots, 18$ ) and 16 persulfoxides in the **PSnO** and **PSnNH** ( $n = 1, 2, \dots, 16$ ) series. The local geometry around the persulfoxide functional group in all four series (X = S, O, NH, and C) was remarkably uniform. In all cases, the pendant oxygen prefers to reside over the two  $\alpha$ -carbons in a nearly bisected rotamer. The S–O and O–O bond lengths were between 1.59 and 1.65 Å and 1.45 and 1.48 Å, respectively, and the S–O–O angles were  $108^\circ \pm 4^\circ$ . The four most stable persulfoxides, **PSnS** ( $n = 1-4$ ), and those derived from **PSnS** by replacement of the remote sulfur by O, NH, and C are shown in Figure 2.

The ring conformations in the geometry-minimized persulfoxides generated by substitution (e.g., **PSnS**  $\rightarrow$  **PSnO**, **PSnNH**, and **PSnC**) were surprisingly similar to **PSnS** and to one another given the differences in calculated C–X bond lengths (C–S, 1.81–1.83 Å; C–O, 1.42–1.44 Å; C–NH, 1.46–1.47 Å; C–C, 1.53–1.55 Å), the differences in van der Waals radii (S, 1.80

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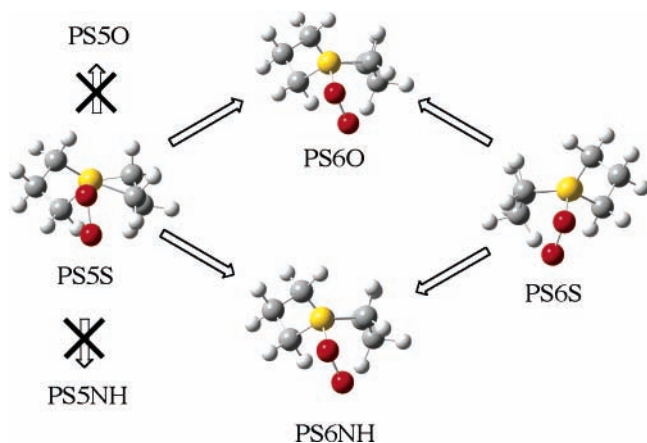


FIGURE 3. PS5X and PS6X conformations.

TABLE 1. Occupancy of Natural Lone-Pair Orbitals on Heteroatom X in Persulfoxides<sup>a</sup>

	PSnS	PSnO	PSnNH
$\Sigma \text{vdW}^b$	3.6 Å	3.3 Å	3.35 Å
<b>PS1X</b>	1.98631, 1.92584	1.97295, 1.94174	1.91835
( $d_{S-X}$ ) <sup>c</sup>	(3.16 Å)	(2.69 Å)	(2.65 Å)
<b>PS2X</b>	1.98361, 1.91137	1.97126, 1.93575	1.90857
( $d_{S-X}$ )	(3.03 Å)	(2.64 Å)	(2.60 Å)
<b>PS3X</b>	1.98020, 1.93316	1.97467, 1.94752	1.94388
( $d_{S-X}$ )	(4.15 Å)	(3.67 Å)	(3.73 Å)
<b>PS4X</b>	1.98020, 1.93316	1.96900, 1.94752	1.91208
( $d_{S-X}$ )	(3.24 Å)	(2.63 Å)	(2.60 Å)
<b>PS10X</b>	1.98889, 1.94173	1.97330, 1.94098	1.92739
( $d_{S-X}$ )	(3.47 Å)	(2.70 Å)	(2.73 Å)

<sup>a</sup> Calculated with NBO 3.0 program: Glendening, E. D.; Reed, A. E.; Carpenter, J. E.; Weinhold, F. found in Gaussian 2003.<sup>18</sup> <sup>b</sup> Sum of van der Waals radii of sulfur and the lone-pair bearing atom in X. <sup>c</sup> Distance in Å between persulfoxide sulfur and the lone-pair bearing atom in X.

Å; O, 1.50 Å; N, 1.55 Å; C, 1.70 Å),<sup>16</sup> and the differences in calculated C–X–C angles (C–S–C,  $102.7^\circ \pm 4.0^\circ$ ; C–O–C,  $115.8^\circ \pm 3.4^\circ$ ; C–N–C,  $116.5^\circ \pm 3.8^\circ$ ; C<sub>4</sub>–C<sub>5</sub>–C<sub>6</sub>  $115.7^\circ \pm 3.2^\circ$ ). However, despite the structural similarities in these substitutional isomers, several subtle conformational changes are noteworthy. For example, to minimize eclipsing interactions, **PS4S** and **PS4C** adopt slightly twisted chair–chair conformations and **PS4O** and **PS4NH**, with shorter C–X bonds, adopt idealized chair–chair conformations with C<sub>s</sub> symmetry (Figure 2; C<sub>s</sub> plane through the four heteroatoms). As a second example, substitution of sulfur in the distorted twist–boat–chair persulfoxide **PS5S** underwent minimization to form undistorted twist–boat–chair persulfoxides **PS6O** and **PS6NH** rather than **PS5O** and **PS5NH** (Figure 3). We also attribute this result to the shorter C–X bond length in the O and NH analogues that cannot accommodate the geometric distortion necessary to form the **PS5X** analogues to the more stable **PS5S** persulfoxide (Figure 3). See the Supporting Information for structural details on all 68 persulfoxides.

Despite the population of similar conformations, the energetic ordering of these conformations in the four persulfoxide series, **PSnS**, **PSnO**, **PSnNH**, and **PSnC**, is very different. These differences in relative energies are most easily observed graphically as shown in Figure 4 and in the Supporting Information. Plots of the relative energies of the **PSnS** persulfoxides vs the energies of the **PSnO**, **PSnNH**, and **PSnC**

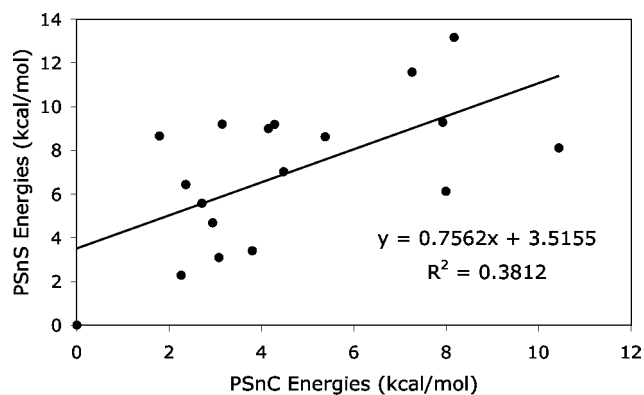


FIGURE 4. PSnS versus PSnC energies

persulfoxides give very poor linear correlations. In contrast, the plot of **PSnNH** vs **PSnO** gives a respectable straight line with a decent correlation coefficient ( $R^2 = 0.9687$ ). These persulfoxides are characterized by similar C–O–C and C–N–C angles ( $\approx 115^\circ$ ) and van der Waals radii of the heteroatom in the X groups (O, 1.50 Å; N, 1.55 Å). On the other hand, sulfur (1.80 Å) and carbon (1.70 Å) have similar van der Waals radii but very different preferred C–X–C angles (C–S–C  $\approx 102^\circ$ ; C–C–C  $\approx 115^\circ$ ) leading to dissimilar energetic ordering of the conformations in the **PSnS** and **PSnC** persulfoxide series (Figure 4).

Scatter in correlation plots is most severe when comparisons to the carbon series, **PSnC**, are involved (see Figure 4). We have previously argued that the energies of the **PSnS** persulfoxides are a composite of the energies of the persulfoxide functional group ( $E_{\text{SOO}}$ ), the ring energies ( $E_R$ ), which are a measure of the intraring bond stretching, angle distortion, torsional, and nonbonded contributions, and a stabilization term ( $E_A$ ), which we attributed to an attractive interaction between the electron-rich lone pair bearing an X group and the sulfonium sulfur in the persulfoxide functional group.<sup>5</sup> This latter contribution,  $E_A$ , is absent in the carbon series, **PSnC**.

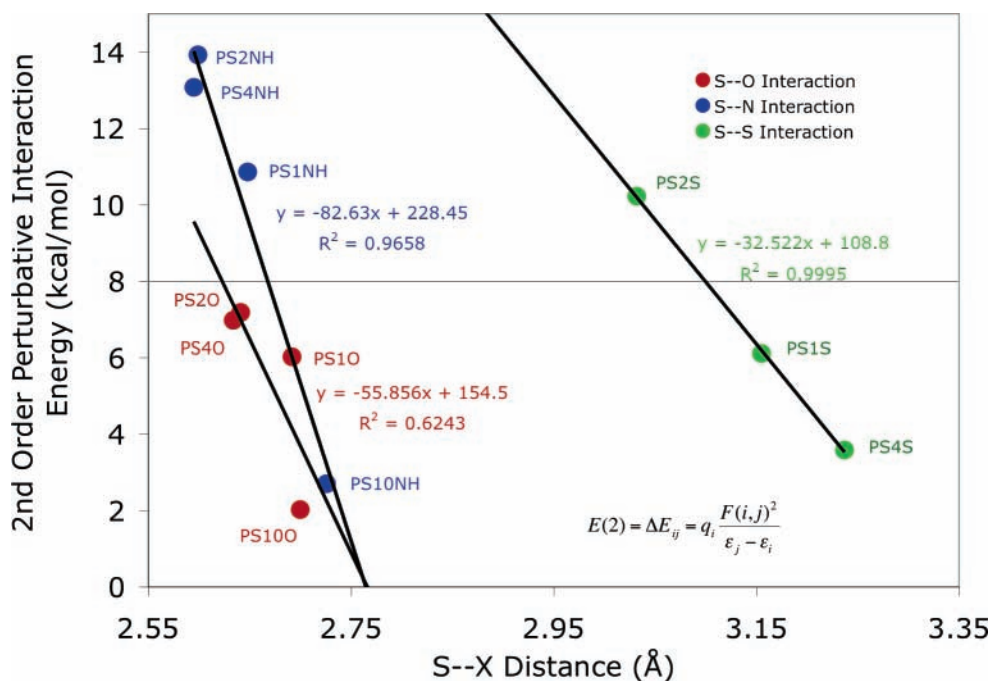
To verify the presence of this attractive interaction and to assess its magnitude, we have conducted a natural bond order analysis<sup>17–18</sup> of the **PSnS**, **PSnO**, and **PSnNH** persulfoxide series. Natural bond order analysis is a procedure for taking the information in the first-order density matrix (i.e., the basis set) and converting it into a series of localized basis sets (NAO, natural atomic orbital; NHO, natural hybrid orbital; NBO, natural bond orbital; and NLMO, natural localized molecular orbitals). The NBOs have been referred to as the “chemist’s

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**FIGURE 5.** Plot of the energies of the donor–acceptor interactions between the remote group X and the persulfoxide sulfur.

basis set” because they closely resemble the localized bond picture we visualize when we draw Lewis dot structures.<sup>17</sup> These orbitals can subsequently be used to perform natural population analysis (NPA). In addition, NBO analysis also leads to orbitals that are not formally occupied in the Lewis structure (antibonding orbitals) and, as a consequence, noncovalent NBO interactions, such as those between the remote heteroatom and the persulfoxide sulfur, can be assessed by second-order perturbation theory.

Table 1 gives the occupancy from a NPA analysis of the natural lone-pair orbitals on the remote heteroatoms in several of the persulfoxides. Examination of this table reveals that, in general, as the distance between the persulfoxide sulfur and the remote heteroatom decreases the occupancy of the natural lone-pair orbitals on the remote heteroatom decreases. In addition, unequal decreases of the occupancy of the two natural lone-pair orbitals on sulfur and oxygen suggest a directional component of the delocalization consistent with cross-ring noncovalent interaction with the persulfoxide sulfur. Examination of the structures of **PS1X**, **PS2X**, and **PS4X** in Figure 2 shows that the S–O persulfoxide bond and the remote heteroatom are collinear, confirming the directional delocalization of the natural lone-pair orbital on the remote heteroatom into an empty orbital localized on the persulfoxide sulfur. We previously attributed the enhanced rate of reaction of singlet oxygen with **2a** to this stabilizing delocalization (anchimeric assistance) that develops concomitantly with a conformational change on the reaction surface for formation of the persulfoxide intermediate.

To assess the magnitude of the donor–acceptor interaction between the group X and the persulfoxide sulfur, we calculated the second-order perturbative interaction energy using the equation depicted in Figure 5. The stabilization energy,  $E(2)$ , associated with the donor–acceptor interaction from the  $i$ th donor to the  $j$ th acceptor NBO is a function of the donor orbital

occupancy,  $q_i$ , the orbital energies,  $\epsilon_i$  and  $\epsilon_j$ , and the off-diagonal Fock matrix element,  $F(i,j)$ . Figure 5 is a plot of the sum of all interaction energies between the lone-pair NBOs on the group X and all the acceptor orbitals centered on the persulfoxide sulfur vs the distance between the interacting groups. As anticipated, the donor–acceptor interaction becomes energetically more favorable as the persulfoxide sulfur X distance decreases. In addition, the larger slopes (i.e., the change in the interaction energy per angstrom) of the **PSnNH** and **PSnO** correlations in comparison to the **PSnS** correlation suggest that NH and oxygen are more potent donors than sulfur in this molecular architecture.

In summary, the study of the CIES sulfide photooxygenation mechanism has been extended to oxygen and NH donor groups. The lowest energy MP2/6-31G(d) persulfoxide conformations with these remote groups were shown to exist in geometries characterized by collinear *donor(X)–acceptor(S)–oxygen* arrays consistent with electrostatic (donor–acceptor) stabilization of the persulfoxide. In addition, natural population analyses of the occupancies of the natural lone-pair orbitals on these donor atoms show a depletion of electron density consistent with their donor function. Finally, a quantitative second-order perturbation treatment of these interactions allowed us to demonstrate that in these particular molecular architectures both donor groups are more effective than sulfur in promoting oxygenation.

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**Supporting Information Available:** Tables of structural data (11 pages). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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