

## Calorimetric and Computational Study of 1,3,5-Trithiane<sup>†</sup>

María Victoria Roux,<sup>\*,‡</sup> Pilar Jiménez,<sup>‡</sup> Juan Z. Dávalos,<sup>‡</sup> Rafael Notario,<sup>‡</sup> and Eusebio Juaristi<sup>#</sup>

Contribution from Instituto de Química Física "Rocasolano", CSIC, Serrano 119, 28006 Madrid, Spain, and Departamento de Química, Centro de Investigación y de Estudios Avanzados del IPN, Apartado Postal 14–740, 07000 México D.F., México

victoriaroux@iqfr.csic.es

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To understand the differences in conformational behavior and reactivity of oxygen- and sulfur-containing 1,3,5-heterocyclohexanes, the enthalpies of formation and sublimation of 1,3,5-trithiane, **1**, have been measured. The numerical value of the enthalpy of formation for this compound in the solid state is  $-8.6 \pm 2.6$  kJ mol<sup>-1</sup>, while the corresponding value in the gaseous state is  $84.6 \pm 2.6$  kJ mol<sup>-1</sup>. The value for the enthalpy of sublimation is  $93.2 \pm 0.2$  kJ mol<sup>-1</sup>. Standard ab initio molecular orbital calculations at the G2(MP2), G2, and G3 levels were performed, and the calculated enthalpies of formation are compared with the experimental data. These experimental and theoretical studies support the relevance of through-space lone pair-lone pair electronic repulsion in the sulfur heterocycle.

### Introduction

Oxygen- and sulfur-containing six-membered heterocycles occupy a fundamental position in organic chemistry.<sup>1</sup> Nevertheless, whereas the chemistry of pyrans (oxanes) constitutes a very large body of knowledge, that of thiopyrans (thianes) has been less extensively investigated.<sup>2</sup> However, the difference in size, electronegativity, and bond polarities associated with oxygen and sulfur, as well as the availability of 3d orbitals in sulfur, are reflected in contrasting structural, conformational, and reactivity behavior for the corresponding heterocycles. Thus, C–O–C bond angles are substantially larger (ca. 113°) than the corresponding C–S–C bond angles (ca. 97°), whereas C–O bonds are significantly shorter (ca. 1.43 Å) than typical C–S bonds (ca. 1.81 Å).<sup>3</sup>

Regarding conformational properties,<sup>4</sup> O–C–C–O segments exhibit a preference for gauche arrangements,<sup>5</sup> whereas S–C–C–S segments generally adopt anti conformations, as a consequence of repulsive gauche interactions.<sup>5b,c,6</sup> Furthermore, the anomeric effect<sup>7</sup> tends to be stronger in O–C–O relative to S–C–S segments.

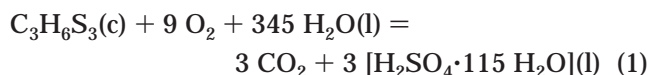
The availability of 3d orbitals in sulfur is apparently the main factor responsible for the contrasting reactivity

behavior of oxygen and sulfur. For example, there is a well-established ability by sulfur to stabilize adjacent carbanions. For example, 1,3-dithiane is readily deprotonated by *n*-butyllithium to give 2-lithio-1,3-dithiane,<sup>8a</sup> whereas 2-lithio-1,3-dioxane is much more difficult to prepare.<sup>8b,c</sup>

Thermodynamic data such as the enthalpy of formation is often helpful in the understanding of the contrasting structural, conformational, and reactivity trends exhibited by oxygen- and sulfur-containing six-membered compounds. We report here the enthalpies of combustion, sublimation, and formation of 1,3,5-trithiane, which complements our recent studies of 1,3-dithiane<sup>9a</sup> and its 1,4-isomer.<sup>9b</sup>

### Results and Discussion

**Experimental Enthalpy of Formation.** Table 1 gives the standard molar energy and enthalpy of combustion and formation of 1,3,5-trithiane, **1**, in the crystalline state at  $T = 298.15$  K, and correspond to the reaction:



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\* To whom correspondence should be addressed. Tel: 34 91 561 94 00. Fax: 34 91 564 24 31.

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<sup>‡</sup> Instituto de Química Física "Rocasolano", CSIC.

<sup>#</sup> Centro de Investigación y de Estudios Avanzados del IPN.

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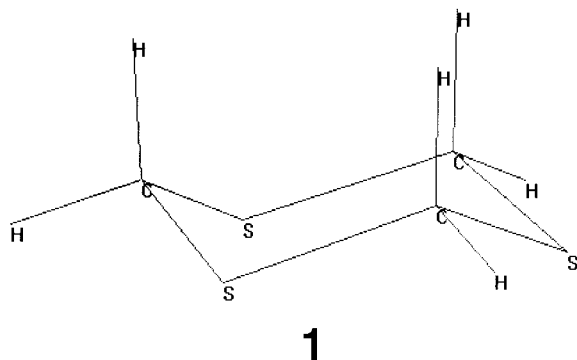
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**Table 1. Standard Molar Energy of Combustion and Enthalpies of Combustion, Sublimation, and Formation at  $T = 298.15$  K**

compound	$\Delta_c U_m^0$ kJ mol <sup>-1</sup>	$\Delta_c H_m^0$ kJ mol <sup>-1</sup>	$\Delta_f H_m^0(\text{cr})$ kJ mol <sup>-1</sup>	$\Delta_{\text{sub}} H_m^0$ kJ mol <sup>-1</sup>	$\Delta_f H_m^0(\text{g})$ kJ mol <sup>-1</sup>
1,3,5-trithiane	-3820.5 ± 2.6	-3835.4 ± 2.6	-8.6 ± 2.6	93.2 ± 0.2	84.6 ± 2.6

**Figure 1.** Chair conformation ( $C_{3v}$ ) of 1,3,5-trithiane.

The uncertainties of the standard molar energy and enthalpy of combustion are twice the final overall standard deviation of the mean and were estimated as outlined by Olofsson.<sup>10</sup>

Vapor pressures were determined at different temperatures and the enthalpy of sublimation was calculated. The standard molar enthalpies of sublimation and formation for both crystalline and gaseous states of 1,3,5-trithiane at  $T = 298.15$  K are also given in Table 1.

No combustion enthalpy for 1,3,5-trithiane has been found for comparison with our results. The enthalpy of sublimation of 1,3,5-trithiane was determined previously by de Wit.<sup>11</sup> The enthalpy of sublimation at  $T = 330.76$  K given by de Wit corrected at  $T = 298.15$  K is 93.9 kJ mol<sup>-1</sup>, in excellent agreement with our value.

**Structure.** Geometry of 1,3,5-trithiane, **1**, both experimental and optimized at the MP2(FULL)/6-31G(d) and MP2(FULL)/6-31G(3df,2p) levels, is presented in Table S6 (see Supporting Information). For comparison purposes, experimental and calculated geometries of another thianes, oxanes, and cyclohexane are included.

The most stable form is the chair conformation, being the symmetry point group  $C_{3v}$  (see Figure 1). The chair structure is similar to that of cyclohexane but is more puckered to accommodate the bond angles and bond lengths characteristic of sulfur. The twist-boat conformer is too a minimum of the potential energy surface of the molecule, but calculations at the HF/6-31G(d) level indicate that it is about 12.7 kJ mol<sup>-1</sup> higher in energy than the chair conformer.

The calculated structural parameters are in good agreement with the experimental ones.

The structural parameters in the oxane and thiane series follow different patterns when the number of heteroatoms in the molecule increases. The bond lengths are practically unaffected with the inclusion of heteroatoms in the six-membered rings, but the most important changes occur in the bond angles. In the case of thiane series all the bond angles increase from thiane to 1,3,5-

trithiane whereas in the oxane series the behavior is the opposite, all the bond angles decrease from oxane to 1,3,5-trioxane.

It has been observed<sup>12,13</sup> that the introduction of a sulfur heteroatom into a six-membered carbon ring increases the ring puckering in comparison with the conformation of cyclohexane.

The relation between torsional angles,  $\varphi$ , and valency angles,  $\theta$ , in a chair form cyclohexane ring is given by:

$$\cos \varphi = -\cos \theta / [1 + \cos \theta] \quad (2)$$

This relation, which holds exactly for cyclohexane,<sup>14</sup> can be used also for deformed chair forms of lower symmetry six-membered rings<sup>15</sup> provided that the individual angles  $\varphi$  and  $\theta$  are replaced by the average of the six torsional angles,  $\Phi$ , and the six valency angles,  $\Theta$ :

$$\cos \Phi = -\cos \Theta / [1 + \cos \Theta] \quad (3)$$

The average torsional angle,  $\Phi$ , which is determined by a delicate balance between valency, torsional, and nonbonded forces, is therefore an easily calculated and convenient index of the puckering in six-membered rings. Calculated and experimental values of  $\Theta$  and  $\Phi$  mean angles for 1,3,5-trithiane and other reference compounds are collected in Table S6.

The  $\Phi$  torsional angle has the highest value for 1,3,5-trithiane, i.e., it exhibits the most puckered ring. Comparing the  $\Phi$  values between the oxane and thiane series, it is clear that the thianes are more puckered than the corresponding oxanes. The increase in the puckering of the ring is more important in thianes than in oxanes when the number of heteroatoms in the ring increase.

It is interesting to compare the variation of the angles between planes in both series of compounds. The optimized values at the MP2(FULL)/6-31G(d) level are shown in Figure 2. The angles in thiane are larger than in oxane, but the situation change when increase the number of heteroatoms in the ring and so angles in 1,3-dithiane and 1,3,5-trithiane are smaller than in 1,3-dioxane and 1,3,5-trioxane, respectively.

The computed vibrational frequencies at the HF/6-31G(d) level for 1,3,5-trithiane are presented in Table S7 (see Supporting Information). As it is indicated above, this compound belongs to the symmetry point group  $C_{3v}$ , and among the 30 fundamental vibrations (7  $A_1$  + 3  $A_2$  + 10 E) only 27 are classified IR and Raman active (7  $A_1$  + 10 E).

The IR and Raman spectra of 1,3,5-trithiane have been studied previously by some authors. Hitch and Ross<sup>16</sup> examined the IR spectrum and made a complete assignment of the IR vibrations by a factor group analysis and normal coordinate analysis, NCT. Klaboe<sup>17</sup> studied the IR and Raman spectra. His vibrational assignments were

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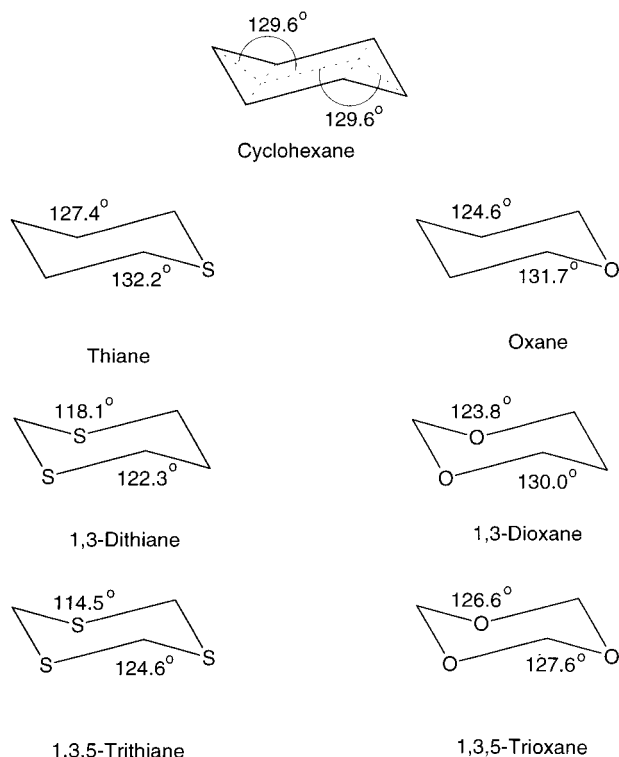
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**Figure 2.** Angles between planes in the oxanes and thianes series. Values calculated at the MP2(FULL)/6-31G(d) level.

based on the calculated force constants and on analogies with similar compounds. Recently, Arca et al.<sup>18</sup> have reinvestigated the IR and Raman spectra of 1,3,5-trithiane on the basis of the selenation effect, and have reassigned to C–S modes some vibrations previously assigned to C–H modes. All the experimental IR and Raman frequencies are also given in Table S7.

The agreement between our results and the experimental values is quite satisfactory. If we plot the calculated vibrational frequencies vs the experimental ones, the correlation (not taking into account the frequencies calculated at 171 and 1109  $\text{cm}^{-1}$ ) is very good, with a slope of 1.007;  $R = 0.9998$ , and a standard deviation of 21  $\text{cm}^{-1}$ .

**Theoretical Enthalpies of Formation.** G2(MP2),<sup>19</sup> G2<sup>20</sup> and G3-calculated<sup>21</sup> energies, at 0 K, for 1,3,5-trithiane, **1**, as well as 1,3,5-trioxane, **2**, as a reference compound, are given in Table S8 (see Supporting Information).

To calculate enthalpy values at 298 K, the difference between the enthalpy at temperature  $T$  and 0 K can be evaluated according to standard thermodynamics.<sup>22</sup> The thermal correction in Gaussian-n theories is made using scaled (0.8929) HF/6-31G(d) frequencies for the vibrations in the harmonic approximation for vibrational energy,<sup>23</sup>

the classical approximation for translation (3/2 RT) and rotation (3/2 RT for nonlinear molecules, and RT for linear molecules), and an additional RT for converting energy to enthalpy (the PV term).

G2(MP2), G2, and G3 enthalpies at 298 K, for the studied compounds, are also collected in Table S8.

It has been reported<sup>24</sup> that the G2 family of computational methods (notably G2(MP2)<sup>19</sup> and G2<sup>20</sup> itself), allows the reliable estimation of the standard enthalpies of formation in the gas phase of a variety of compounds. In many cases, the computed magnitudes agree with the experimental data within about 7.5  $\text{kJ mol}^{-1}$ .<sup>24c</sup> The standard procedure to obtain enthalpies of formation in Gaussian-n theories is through atomization reactions (see Experimental Section), but there has been some evidence in recent years that there is an accumulation of errors in the application of G2 theory (or similar approaches) to larger molecules.<sup>24a,c,25</sup> Glukhovtsev and Laiter<sup>25a</sup> have shown that more accurate heats of formation can be derived using isodesmic or homodesmotic reactions rather than atomization energies as in standard G2 theory.

As Raghavachari et al.<sup>24d</sup> have pointed out, one of the deficiencies of the isodesmic reaction approach is that many different isodesmic reactions can be set up for the same molecule yielding different results. These authors have proposed to use simpler, but better defined reactions to assess the performance of theoretical methods in a more systematic manner. A standard set of isodesmic reactions is “bond separation reactions”,<sup>26</sup> where all formal bonds between nonhydrogen atoms are separated into the simplest parent molecules containing these same kinds of linkages.

We have obtained in this study theoretical values of the enthalpy of formation of 1,3,5-trithiane evaluated at G2(MP2), G2, and G3 levels of theory, using both methods above-mentioned.

As can be seen in Table 2, the  $\Delta_f H_m^0$  value for 1,3,5-trithiane calculated from G2(MP2) energies using atomization reaction scheme is not in agreement with the experimental value, being 20.2  $\text{kJ mol}^{-1}$  lower. The same occurs in the case of 1,3,5-trioxane, being the difference 26.4  $\text{kJ mol}^{-1}$ .

The use of the G3 theory improves the results. Now, as it is shown in Table 2, theoretical  $\Delta_f H_m^0$  values are closer to the experimental ones, but still the difference is high in the case of **1**, 13.0  $\text{kJ mol}^{-1}$ .

Calculations at the more expensive G2 level of theory should be more reliable because the electron correlation effect higher than those of second order could be very important for the sulfur compounds. So, the heat of formation of 1,3,5-trithiane calculated at the G2 level, 77.3  $\text{kJ mol}^{-1}$ , is clearly better than the values obtained at the other two levels, and is only 7.3  $\text{kJ mol}^{-1}$  lower than the experimental value.

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**Table 2.** G2(MP2)-, G3-, and G2-calculated Heats of Formation, at 298.15 K, in kJ mol<sup>-1</sup>, Obtained from Atomization and Bond Separation Isodesmic Reactions<sup>a</sup>

compound	G2(MP2)		G3		G2		exp <sup>c</sup>
	atom. <sup>b</sup>	BS	atom.	BS	atom. <sup>b</sup>	BS	
1,3,5-trithiane, <b>1</b>	64.4 (77.5) [67.6] <sup>d</sup>	68.1	71.6 [72.9] <sup>e</sup>	64.1	77.3 (77.1) [80.4] <sup>f</sup>	66.9	84.6 ± 2.6 <sup>g</sup>
1,3,5-trioxane, <b>2</b>	-492.3 (-468.6)	-463.5	-473.3	-470.9			-465.9 ± 0.4
cyclohexane, <b>3</b>	-113.4 (-124.6)	-121.5	-122.7	-120.4			-123.3 ± 0.8
thiane, <b>4</b>	-61.6 (-64.7)	-65.8	-63.8	-64.8			-63.5 ± 1.0
1,3-dithiane, <b>5</b>	-1.3 (3.7)	-1.5	2.1	-2.1			-2.7 ± 2.1 <sup>h</sup>
oxane, <b>6</b>	-224.8 (-224.4)	-220.6	-224.4	-222.1			-223.4 ± 1.0
1,3-dioxane, <b>7</b>	-352.9 (-340.8)	-336.4	-343.2	-340.7			-340.6 ± 4.2

<sup>a</sup> Calculated values for compounds **3** to **7** are taken from ref 9b. <sup>b</sup> Values in parentheses are those obtained from atomization reaction including the spin-orbit and the isodesmic bond additivity corrections. See text. <sup>c</sup> Unless otherwise noted, all the experimental enthalpies of formation taken from ref 27. <sup>d</sup> G2(MP2)+ level. See text. <sup>e</sup> G3+ level. See text. <sup>f</sup> G2+ level. See text. <sup>g</sup> This work. <sup>h</sup> Ref 9a.

When bond separation isodesmic reaction scheme (see Experimental Section) is used to calculate the heats of formation of the studied molecules, the comparison of the calculated  $\Delta_f H^0$  values, both at G2(MP2) and G3 levels, with the experimental values is very good in the case of **2** and the other reference compounds, but not in the case of **1**. The G3- and G2-calculated values are even worse than the values obtained from atomization reaction.

To obtain a more reliable calculated  $\Delta_f H^0_m$  value for 1,3,5-trithiane we can do some corrections to the values obtained at the G2(MP2) and G2 levels through atomization reactions.

It has previously been noted that the spin-orbit effects are important in calculating the ionization potential of sulfur atom.<sup>28</sup> Curtiss et al.<sup>24c</sup> carried out a study about the importance of including spin-orbit effects in the calculated enthalpies of formation for the G2 test set by adding a spin-orbit correction,  $\Delta E(\text{SO})$ , to the total G2 energies that are used to calculate the atomization energies in eq 4:

$$E_0[\text{G2}_{\text{SO}}] = E_0[\text{G2}] + \Delta E(\text{SO}) \quad (4)$$

They concluded that the overall average absolute deviation for the full G2 test set decreases when spin-orbit corrections are included. The corrections are particularly important for compounds containing S, F, and/or Cl. And so, the same authors have included a correction to take into account the experimental spin-orbit interaction for the atoms in the new G3 theory.<sup>21</sup> This interaction vanishes for closed-shell molecules.

Also Petersson et al.<sup>29</sup> have introduced the experimental spin-orbit interactions for the atoms in their study about the comparison of the Gaussian-2, complete basis set, and density functional methods for computational thermochemistry.

This has prompted us to introduce the spin-orbit correction, SO, in our calculations at the G2(MP2) and G2 levels.<sup>30</sup> The SO corrections for the molecules studied

**Table 3.** Spin-Orbit (SO) and Bond Additivity (BAC) Corrections Applied to the Molecules Studied in This Work (all Values in kJ mol<sup>-1</sup>)

	SO	BAC [G2(MP2)]	SO + BAC
cyclohexane	2.1	-13.3	-11.2
oxane	2.7	-2.3	0.4
1,3-dioxane	3.3	8.8	12.1
1,3,5-trioxane	3.9	19.8	23.7
thiane	4.1	-7.2	-3.1
1,3-dithiane	6.1	-1.1	5.0
1,3,5-trithiane	8.1	5.0 (-8.3) <sup>a</sup>	13.1 (-0.2) <sup>a</sup>

<sup>a</sup> At the G2 level.

in this work are collected in Table 3. The correction is particularly important in the case of 1,3,5-trithiane, 8.1 kJ mol<sup>-1</sup>.

The use of isodesmic reactions to calculate heats of formation has been criticized by Petersson et al.<sup>29</sup> They pointed that the bond separation reaction algorithm is ill conditioned for two reasons: the required heats of formation of the products may be impossible to obtain accurately, and the scheme can yield an unreasonably large number of molecules. They propose the use of isodesmic bond additivity corrections, BAC, employing the assumption that the errors in calculated bond energies are constant for each type of bond and these errors are additive:

$$\Delta_f H^0_{298}(\text{BAC}) = \Delta_f H^0_{298}(\text{calc.}) + \sum N_{ij} \text{BAC}_{ij} \quad (5)$$

The authors<sup>29</sup> have estimated a preliminary BAC data set where are included the bonds involved in the molecules studied here.<sup>31</sup> The BAC corrections for the molecules studied in this work are given in Table 3. The corrections are particularly important in the cases of 1,3,5-trioxane, 19.8 kJ mol<sup>-1</sup>, and cyclohexane, -13.3 kJ mol<sup>-1</sup>.

The heats of formation calculated through atomization reactions and corrected adding the SO and BAC corrections are given in Table 2. There is a marked improve-

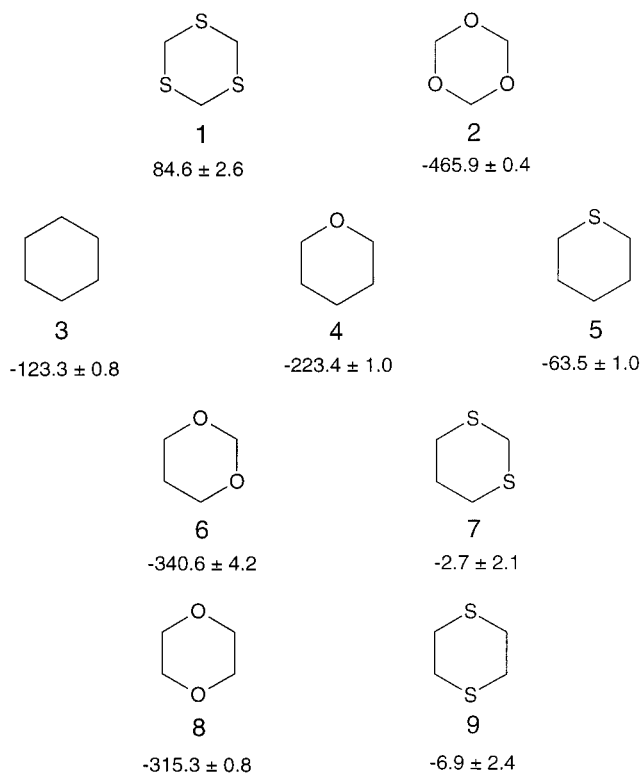
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(30) (a) Spin-orbit corrections for the atoms are taken to be the energy difference between the spin-orbit-coupled ground state and the weighted *J*-averaged state. So, for S and O, the correction is  $\Delta E(\text{SO}) = -\{3/9 [\Delta E(^3P_1 - ^3P_2)] + 1/9 [\Delta E(^3P_0 - ^3P_2)]\}$ ; and for C the correction is  $\Delta E(\text{SO}) = -\{3/9 [\Delta E(^3P_1 - ^3P_0)] + 5/9 [\Delta E(^3P_2 - ^3P_0)]\}$ . From the atomic energy levels in ref. (30b) we obtain the atomic spin-orbit corrections, in kJ mol<sup>-1</sup>: C = -0.354; O = -0.933; S = -2.345.

(31) Bond additivity corrections, in kJ mol<sup>-1</sup> bond<sup>-1</sup>, taken from ref 29 are: C-H = 0.293; C-C = -2.803; C-O = 3.012; C-S = 0.544, at the G2(MP2) level, and C-H = 0.837; C-C = -2.929; C-O = 1.297; C-S = -2.218, at the G2 level.



**Figure 3.** Experimental gas-phase enthalpies of formation, in  $\text{kJ mol}^{-1}$ , for several oxygen- and sulfur-containing heterocycles.

ment in the calculated heats of formation. Now, the  $\Delta_f H_m^0$  value of 1,3,5-trioxane is in very good agreement with the experimental value, whereas the  $\Delta_f H_m^0$  value of 1,3,5-trithiane,  $77.5 \text{ kJ mol}^{-1}$ , is only  $7.1 \text{ kJ mol}^{-1}$  lower than the experimental value,  $84.6 \pm 2.6 \text{ kJ mol}^{-1}$ , measured in this work, and it is of a quality comparable with the value obtained at the G2 level. However, the introduction of SO and BAC corrections to the G2-calculated  $\Delta_f H_m^0$  value does not improve the result, because the correction is very small and negative.

A further step in the obtaining of a reliable theoretical value of  $\Delta_f H_m^0$  of 1,3,5-trithiane is the consideration of a more sophisticated basis set in the optimization of its geometry. As we have pointed in the Introduction, the availability of 3d orbitals in sulfur is the main factor responsible for its reactivity behavior and so, the adequate description of the geometry and electronic properties of sulfur containing compounds would require the inclusion of supplementary d functions in the basis set. We have reoptimized the geometry of 1,3,5-trithiane at the MP2(FULL)/6-31G(3df,2p) level and have also carried out the single point calculations using similar schemes as in the G2(MP2), G3, and G2 formalisms. These approaches will be designed as G2(MP2)+, G3+, and G2+. The  $\Delta_f H_m^0$  values of 1,3,5-trithiane, calculated at these computational levels, are collected in Table 2. The new values are better than those previously obtained. Now, the value obtained at the more expensive G2+ level is only  $4.2 \text{ kJ mol}^{-1}$  lower than the experimental one.

A proper rationalization of the thermodynamic data for 1,3,5-trithiane reported in this paper requires consideration of the corresponding data for the oxygen analogues in the series oxane, 1,3-dioxane, and 1,3,5-trioxane. Figure 3 summarizes the gas-phase enthalpies of formation for the organic compounds of interest.

Relative to cyclohexane, **3**, the enthalpy of formation of tetrahydropyran, **4**, is much more negative,  $-123.3 \text{ kJ mol}^{-1}$  and  $-223.4 \text{ kJ mol}^{-1}$ , respectively. By contrast, the enthalpy of formation of tetrahydrothiopyran, **5**,  $-63.5 \text{ kJ mol}^{-1}$ , is less negative than that for cyclohexane. As discussed by Wiberg and co-workers,<sup>32</sup> the lower electronegativity of sulfur relative to oxygen results in diminished Coulombic attraction between the carbon atom and heteroatom, and thus weaker C–S bonds.

Comparison of the enthalpies of formation for tetrahydropyran, **4**, and 1,3-dioxane, **6**, shows that introduction of the second heteroatom is an even more exothermic event; that is,  $\Delta_f H_m^0(\mathbf{4})$  is  $100.1 \text{ kJ mol}^{-1}$  more negative than  $\Delta_f H_m^0(\mathbf{3})$ ; furthermore,  $\Delta_f H_m^0(\mathbf{6})$  is  $117.2 \text{ kJ mol}^{-1}$  more negative than  $\Delta_f H_m^0(\mathbf{4})$ . Thus, the second substitution of  $-\text{CH}_2-$  for  $-\text{O}-$  (in **4**  $\rightarrow$  **6**) results in  $17.1 \text{ kJ mol}^{-1}$  further stabilization, in agreement with previous observations.<sup>33</sup> The additional stabilization of  $17.1 \text{ kJ mol}^{-1}$  is not observed when the oxygen atoms are not geminal, as evidenced from examination of  $\Delta_f H_m^0(\mathbf{8}) = -315.3 \text{ kJ mol}^{-1}$ , which is only  $91.9 \text{ kJ mol}^{-1}$  more negative than the enthalpy of formation of oxane, **4**. These results can be explained in terms of the so-called “perfluoro effect”,<sup>34</sup> where carbon prefers to bind more than one electronegative heteroatom, to benefit from “double-bond-no-bond” stabilizing stereoelectronic interactions, and/or Coulombic attraction between carbon and the geminal electronegative substituents.<sup>32,34,35</sup>

In line with this discussion, the experimental enthalpy of formation for 1,3,5-trioxane, **2**, is  $125.3 \text{ kJ mol}^{-1}$  more negative than  $\Delta_f H_m^0(\mathbf{6})$ . That is, the third substitution of a “meta” methylene group for oxygen (in **2**  $\rightarrow$  **6**) is  $25.2 \text{ kJ mol}^{-1}$  more stabilizing than the first substitution, in **3**  $\rightarrow$  **4**. Again, this additional stabilization can be rationalized in terms of stereoelectronic and/or Coulombic stabilizing interactions in the O–C–O “anomeric” segments.<sup>32,34,35</sup> Interestingly, there is evidence for a saturation of the effect since the additional stabilization of  $25.2 \text{ kJ mol}^{-1}$  is significantly less than the calculated  $17.1 \times 3 = 51.3 \text{ kJ mol}^{-1}$ , considering that 1,3,5-trioxane, **2**, presents *three* O–C–O segments.<sup>36</sup>

In strong contrast, analysis of the experimental enthalpies of formation for the sulfur-containing heterocycles exhibits a lack of stabilization upon substitution of methylene for sulfur. Indeed,  $\Delta_f H_m^0$  for thiane, **5**, is  $59.8 \text{ kJ mol}^{-1}$  less negative than  $\Delta_f H_m^0$  for cyclohexane, **3**, and  $\Delta_f H_m^0$  for 1,3-dithiane, **7**, is  $60.8 \text{ kJ mol}^{-1}$  less negative than  $\Delta_f H_m^0(\mathbf{5})$ . These thermochemical data can be interpreted in terms of the lower electronegativity of sulfur vis-à-vis oxygen, as well as the longer nature of the C–S bonds relative to C–O bonds—both factors leading to weaker carbon–sulfur bonds, and therefore, less negative enthalpies of formation for thiane and 1,3-dithiane, when compared with  $\Delta_f H_m^0(\text{cyclohexane})$ .

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**Figure 4.** S–S internuclear distances in 1,3,5-trithiane and 1,3-dithiane. Values calculated at the MP2(FULL)/6-31G(d) level.

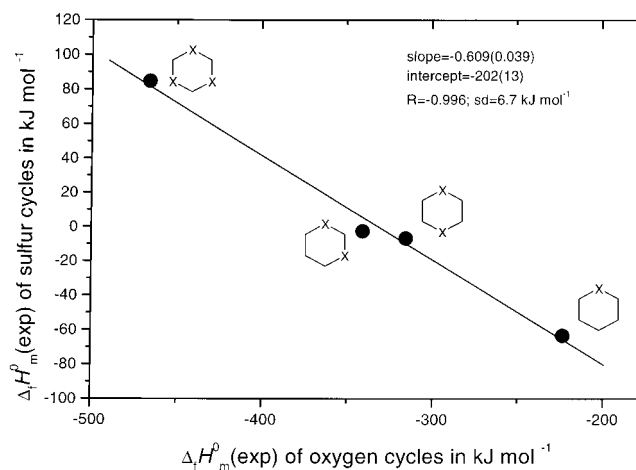
The belittled “gem effect” in the sulfur series (lower electronegativity of sulfur gives rise to diminished Coulombic attraction<sup>32c</sup>) is apparently overpowered by through-space lone pair-lone pair electronic repulsion between sulfurs. Indeed, there is convincing evidence for the existence of significant through-space lone pair-lone pair orbital interactions in 1,3-dithiane and 1,3,5-trithiane. The original evidence came mainly from UV<sup>37a</sup> and photoelectron spectroscopy,<sup>37b</sup> which showed splitting of the bands associated to the sulfur *n* orbitals. Through bond mechanisms for this interaction between sulfurs in a 1,3 (meta) disposition were discarded, based on theoretical considerations.<sup>37b</sup>

The experimentally observed enthalpy of formation of 1,3,5-trithiane (**1**),  $\Delta_f H_m^0 = +84.6 \pm 2.6$  kJ mol<sup>-1</sup> (this work), is 87.3 kJ mol<sup>-1</sup> more endothermic than the enthalpy of formation of 1,3-dithiane, **7**,  $\Delta_f H_m^0 = -2.7 \pm 2.1$  kJ mol<sup>-1</sup>.<sup>9b</sup>

Thus, substitution of a meta methylene group in the **7** → **1** conversion is 26.5 kJ mol<sup>-1</sup> more energetically unfavorable than similar CH<sub>2</sub> → S substitution in the thiane, **5**, to 1,3-dithiane, **7**, transformation,  $\Delta_f H_m^0(\mathbf{7}) - \Delta_f H_m^0(\mathbf{5}) = -2.7 - (-63.5) = 60.8$  kJ mol<sup>-1</sup>. This observation is again interpreted in terms of lone pair-lone pair orbital interaction between sulfurs.

Indeed, both experimental structural measurement<sup>38,39</sup> and calculated data (see Figure 4) confirm the substantial ring puckering and short S/S internuclear distance (3.06–3.07 Å) present both in 1,3-dithiane, **7**, and 1,3,5-trithiane, **1**. Of course, there exist *three* S/S repulsive interactions in trithiane, **1**, whereas there is only *one* in dithiane, **7**, which is congruent with the observed relative magnitude of the enthalpies of formation. Interestingly, a plot of experimental  $\Delta_f H_m^0$  for sulfur six-membered heterocycles versus the corresponding oxygen analogues gives a linear correlation with negative slope (Figure 5), contrasting the stabilization effect in the oxygen series relative to the destabilization effect in the sulfur compounds, upon increasing heteroatom enrichment.

Two products from the theoretical studies undertaken in this project support the relevance of the lone pair-lone pair electronic repulsion advanced above for the sulfur heterocycles, 1,3-dithiane, **7**, and 1,3,5-trithiane, **1**. Figure 6 presents the electrostatic potential distributions for the compounds in the oxane and thiane series. Most relevant, the regions of highest electron density ( $V_{\min}$ ) are easily located and assigned to the lone electron pairs on heteroatoms (oxygen or sulfur). It can clearly be seen that whereas  $V_{\min}$  is essentially constant in the oxane series



**Figure 5.** Plot of experimental  $\Delta_f H_m^0$  values for sulfur six-membered heterocycles vs the corresponding oxygen analogues.

**Table 4.** HOMO and LUMO Calculated Energies<sup>a</sup> and Experimental Ionization Potentials for the Studied Compounds<sup>b</sup>

compound	$E_{\text{HOMO}}$	$E_{\text{LUMO}}$	IP <sup>c</sup>
thiane	-8.96	5.38	8.45
1,3-dithiane	-8.98	4.49	8.54
1,3,5-trithiane	-9.30	4.13	8.76
oxane	-10.88	6.26	9.50
1,3-dioxane	-11.54	6.35	10.1
1,3,5-trioxane	-12.11	6.36	~10.8

<sup>a</sup> Evaluated at the MP2(FULL)/6-31G(d) level. <sup>b</sup> All values in eV. <sup>c</sup> Taken from ref 37b.

(small oxygen lone pairs, so insignificant through-space repulsion between lone pairs), the substantial electronic repulsion between sulfur lone pairs in 1,3-dithiane, **7**, and 1,3,5-trithiane, **1**, causes drastic displacement of  $V_{\min}$ , away from the nuclear framework, to minimize lone pair-lone pair through-space overlap.

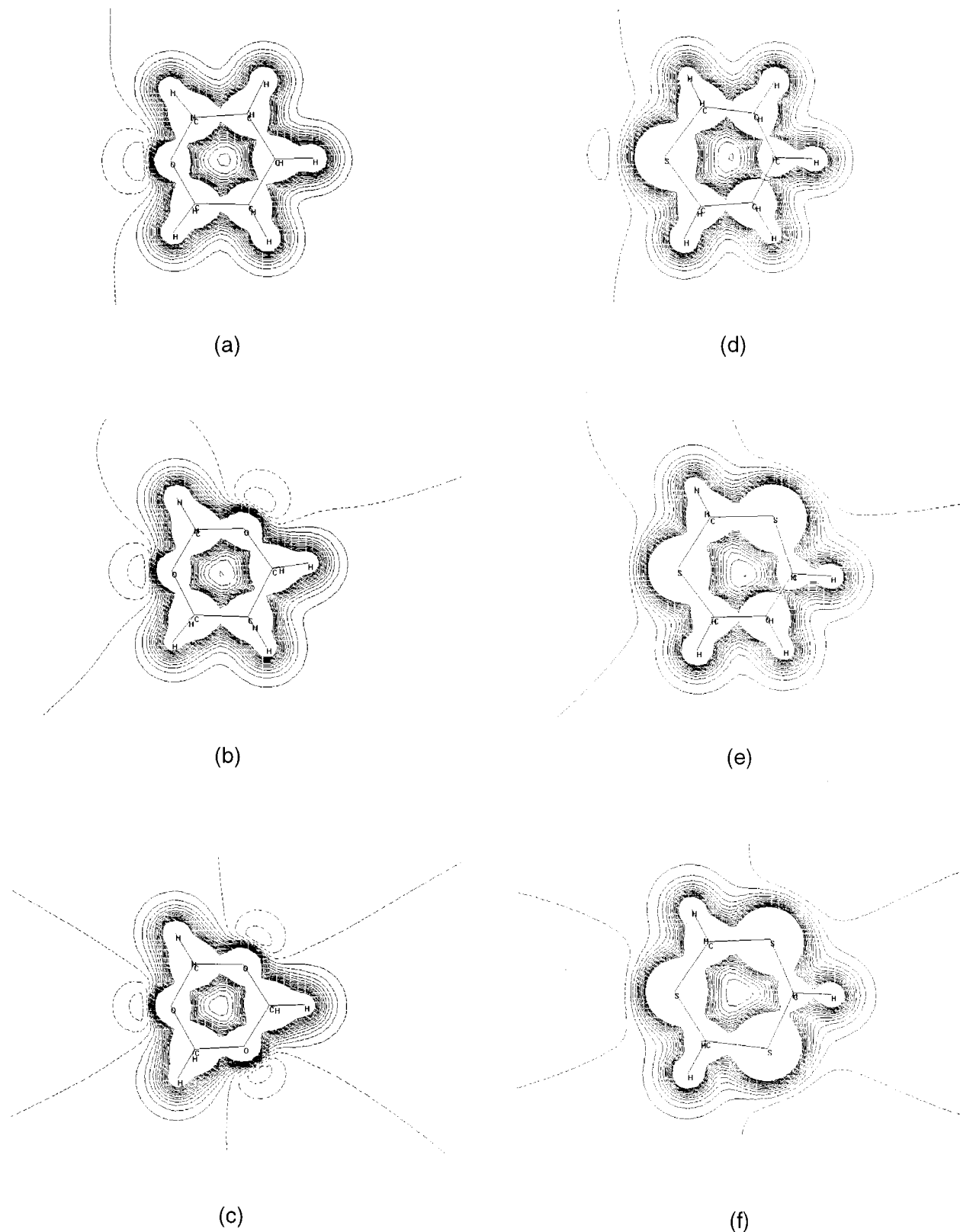
Table 4 collects the MP2(FULL)/6-31G(d)-calculated energies for the molecular orbitals of highest energy (HOMO) in the oxane (**4**, **6**, and **2**) and thiane (**5**, **7**, and **1**) series of interest. Interestingly, the estimated values for  $-E_{\text{HOMO}}$  match very well with the experimentally determined ionization potentials for the same compounds, also included in Table 4.

As anticipated,  $E_{\text{HOMO}}$  decreases in going from oxane ( $E_{\text{HOMO}} = -10.88$  eV) to 1,3-dioxane ( $E_{\text{HOMO}} = -11.54$  eV) to 1,3,5-trioxane ( $E_{\text{HOMO}} = -12.11$  eV), as a consequence of the inductive effect arising from the incorporation of each electronegative oxygen. In contrast, the more erratic variation observed in the thiane ( $E_{\text{HOMO}} = -8.96$  eV), 1,3-dithiane ( $E_{\text{HOMO}} = -8.98$  eV), 1,3,5-trithiane ( $E_{\text{HOMO}} = -9.30$  eV) seems to result from two competing, opposite effects: an energy-lowering inductive effect associated to the introduction of each sulfur atom, and the repulsive overlap between sulfur lone electron pairs, which raises  $E_{\text{HOMO}}$ . Even more interesting is the observation that  $E_{\text{LUMO}}$  remains essentially constant in the oxane-dioxane-trioxane series (+ 6.26, + 6.35, and + 6.36 eV, respectively), whereas  $E_{\text{LUMO}}$  clearly decreases in the thiane-dithiane-trithiane series (+ 5.38, + 4.49, and + 4.13 eV, respectively). The fact that the atomic orbitals at oxygen do not contribute to the composition of the LUMOs in **4**, **6**, and **2**, whereas the atomic orbitals of the sulfur atoms

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**Figure 6.** Electrostatic potential contours calculated for (a) oxane, (b) 1,3-dioxane, (c) 1,3,5-trioxane, (d) thiane, (e) 1,3-dithiane, (f) 1,3,5-trithiane.

do present important contributions to the LUMOs in **5**, **7**, and **1** (see Supporting Information) is again in agreement with the argument that through-space interactions are effective with sulfur atoms, but insignificant with the smaller, tighter oxygen atoms.

To get more information on the net atomic charges and electronic charge densities, the study was completed with two different electron population techniques.

The charge distribution in the studied compounds was analyzed by means of the natural bond orbital (NBO)

**Table 5. Natural Charges, Obtained from a NBO Analysis at the MP2(FULL)/6-31G(d) Level, Located at the Heavy Atoms in Thianes and Oxanes<sup>a</sup>**

	thiane	1,3-dithiane	1,3,5-trithiane
S	+0.216	+0.249	+0.280
C1	-0.589	-0.785	-0.790
C2	-0.441	-0.594	
C3	-0.435	-0.451	
	oxane	1,3-dioxane	1,3,5-trioxane
O	-0.656	-0.661	-0.666
C1	-0.041	+0.304	+0.296
C2	-0.465	-0.049	
C3	-0.437	-0.498	

<sup>a</sup> C1 is the carbon atom adjacent to the S or O atoms, in thiane and oxane, and is the C atom between the two S or O atoms, in 1,3-dithiane and 1,3-dioxane, respectively.

analysis of Weinhold et al.<sup>40</sup> In Table 5 we have collected the natural atomic charges (the nuclear charges minus summed natural populations of the natural atomic orbitals on the atoms), at the heavy atoms for all the compounds in both series, thianes and oxanes.

The results indicate the different behavior of sulfur and oxygen in both homologous series of compounds. The positive charge in thianes is located at the sulfur atoms whereas all the carbon atoms of the ring have negative charge, being more negative in the case of the C atoms directly bonded to the S atoms. In oxanes, the charge distribution is very different as a consequence of the higher electronegativity of oxygen (3.44), compared to that of sulfur (2.58) and carbon (2.55). The negative charge is located at the oxygen atoms whereas the carbon atoms directly bonded to the O atoms have positive or slightly negative charge.

The NBO analysis also describes the bonding in terms of the natural hybrid orbitals. In thianes the hybridization of sulfur atoms is  $sp^5$ , with more than 82% of p character, whereas in oxanes the hybridization of oxygen atoms is between  $sp^2$  and  $sp^3$ , with ca. 71% of p character. Sulfur and oxygen have sp ( $sp^{0.5}$  in the case of S and  $sp^{1.4}$  in the case of O) and p lone pairs which may delocalize into the vicinal antibonding orbitals. Through orbital occupancies and second-order perturbation energy lowering,  $\Delta E^2$ , due to the interaction of the donor and acceptor orbitals, one can fix the exact orbitals that are involved in the charge-transfer process. Occupancies and energy lowerings of the orbitals involved in the delocalization of the lone pairs of S and O in thianes and oxanes, respectively, are shown in Table S9 (see Supporting Information).

Several studies on compounds involving atoms with different types of lone pairs (O, S, Se) have shown that the effect of the charge delocalization should not be analyzed only in the basis of  $p_X \rightarrow \sigma^*_{CX}$  hyperconjugations since orbital interactions involving sp lone pairs, that is,  $sp_X \rightarrow \sigma^*_{CX}$ , are not negligible.<sup>41</sup> This behavior is observed in the studied compounds.

As it has been previously suggested,<sup>42</sup> delocalization energies decrease when moving down through a group, but more notably when passing from the second to the

third row. The  $p_X \rightarrow \sigma^*_{CX}$  hyperconjugation is less effective for higher row substituents because these are poorer  $\sigma$  acceptors and have lower  $\pi$ -donor abilities than their second-row analogues.<sup>43</sup>

We have also carried out a topological analysis of electron charge density,  $\rho(\mathbf{r})$ , and its Laplacian,  $\nabla^2\rho(\mathbf{r})$ , using the AIM theory of Bader.<sup>44</sup>  $\nabla^2\rho(\mathbf{r})$  identifies regions of the space wherein the electronic charge is locally depleted ( $\nabla^2\rho(\mathbf{r}) > 0$ ) or concentrated ( $\nabla^2\rho(\mathbf{r}) < 0$ ). The former is typically associated with interactions between closed-shell systems (ionic bonds, hydrogen bonds, and van der Waals molecules), whereas the latter characterizes covalent bonds, where the electron density concentrates in the internuclear region. Because there are significant exceptions to this general rule, mainly when high electronegative atoms are involved in the bonding,<sup>45</sup> we have also evaluated the local energy density,  $H(\mathbf{r})$ , which does not present these exceptions.<sup>46</sup> In general, negative values of  $H(\mathbf{r})$  are associated with stabilizing charge concentrations within the bonded region, which are associated with covalent interactions.

The bonding characteristics of the bond critical points, BCPs, associated with the C–X bonds in thianes and oxanes, are collected in Table S10 (see Supporting Information).

The AIM-calculated net charges on the heavy atoms follow the same pattern that the NBO natural charges. The sulfur atoms tend to disperse the electron density to the adjacent carbon atoms, to minimize the lone pair-lone pair repulsions.

In Table S11 (see Supporting Information), the values of  $\rho(\mathbf{r})$  and  $\nabla^2\rho(\mathbf{r})$ , as well as  $H(\mathbf{r})$  and the radial distances from the critical points to the heteroatoms, for the nonbonded charge concentrations associated with the lone pairs of S and O for all the studied compounds are shown. We have also calculated the distance between the points of maxima nonbonded charge concentrations, i.e., the separation between the lone pairs of S and O atoms, in thianes and oxanes. The results show that the distance is constant in the oxane series (0.629, 0.628, and 0.628 Å, for oxane, 1,3-dioxane, and 1,3,5-trioxane, respectively), but increase in the thiane series, particularly going from 1,3-dithiane to 1,3,5-trithiane (1.250, 1.255, and 1.441 Å, for thiane, 1,3-dithiane, and 1,3,5-trithiane, respectively). This is again a clear confirmation of the strong through-space lone pair-lone pair electronic repulsion in 1,3,5-trithiane.

## Experimental Section

**Materials.** 1,4-Dithiane, purity >97%, was supplied by Aldrich. The sample was recrystallized two times from toluene and carefully dried under vacuum. Determination of purity, assessed by dsc by the fractional fusion technique<sup>47</sup> indicated that the mole fraction of impurities in the compound was less than 0.001. The sample was studied by dsc over the temperature range between  $T = 258$  K and  $T = 340$  K and no transition in the solid state was observed.

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**Procedure for Thermochemical Measurements.** An isoperibol calorimeter equipped with a rotary bomb and an isothermal water jacket was used for the measurements of the energy of combustion. Apparatus and procedure have been described in ref 9.

A differential scanning calorimeter (Perkin-Elmer, Pyris 1) equipped with an Intracooler unit was used in this research in order to measure the heat capacities of the compound, to control the purity and to study the phase transitions of the sample.

The vapor pressures as a function of temperature of 1,3,5-trithiane were measured by a mass-loss Knudsen-effusion method<sup>48</sup> and the enthalpies of sublimation were deduced from the temperature dependence of the vapor pressures (Clausius–Clapeyron). Full experimental details are given as Supporting Information.

**Computational Details.** Standard ab initio molecular orbital calculations<sup>26</sup> were performed with the Gaussian 98 series of programs.<sup>49</sup> Energies of 1,3,5-trithiane, **1**, and 1,3,5-trioxane, **2**, were calculated using Gaussian-n theories, at the G2(MP2),<sup>19</sup> G2,<sup>20</sup> and the recently proposed<sup>21</sup> G3, levels.

G2(MP2) and G2 corresponds effectively to calculations at the QCISD(T)/6-311+G(3df,2p) level on MP2(full)/6-31G(d) optimized geometries, incorporating scaled HF/6-31G(d) zero-point vibrational energies and a so-called higher-level correction to accommodate remaining deficiencies.

Recently, Curtiss, Pople et al.<sup>21</sup> set forth Gaussian-3 theory (or G3 theory) for the calculation of molecular energies of compounds containing first and second row atoms. This new theoretical procedure modifies G2 theory<sup>20</sup> in several ways including a new sequence of single point energy calculations using different basis sets, a new formulation of the higher level correction, a spin–orbit correction for atoms, and a correction for core correlation. G3 theory was assessed<sup>21</sup> using the G2/97 test set, including enthalpies of formation, and the new procedure corrects many of the deficiencies of G2 theory. Very recently,<sup>50</sup> the G2/97 test set has been expanded to include 75 additional enthalpies of formation of larger molecules. This new set is referred to as the G3/99 test set, and several levels of the G3 theory have been assessed.<sup>50</sup> We have also reoptimized the geometries at the MP2(FULL)/6-31G(3df,2p) level and have carried out the single point calculations using similar schemes as in the G2(MP2), G3, and G2 formalisms. These approaches have been designed as G2(MP2)+, G3+, and G2+.

The bonding characteristics of the different compounds in both series, thianes and oxanes, have been investigated using two different population partition techniques, the natural bond

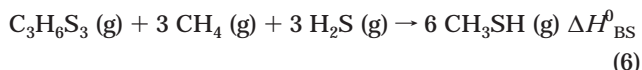
orbital (NBO) analysis of Reed and Weinhold,<sup>40</sup> and the topological analysis of electron charge density and its Laplacian using the atoms in molecules (AIM) theory of Bader.<sup>44</sup> The NBO formalism provides values for the atomic natural total charges and describes the bonding in terms of the natural hybrids centered on each atom. The AIM approach locates the bond critical points (BCPs), i.e., points where the electron density function,  $\rho(\mathbf{r})$ , is minimum along the bond path and maximum in the other two directions.

The NBO analysis have been performed using the NBO program,<sup>51</sup> implemented in the Gaussian98 package, and the AIM analysis have been performed using the AIMPAC series of programs.<sup>52</sup> Both population analyses were carried out on the MP2 charge densities in order to explicitly include electron correlation effects.

**Theoretical Determination of Heats of Formation.** In standard Gaussian-n theories, theoretical enthalpies of formation are calculated through atomization reactions. We have detailed this method in previous studies.<sup>53</sup>

As it is indicated above, Raghavachari et al.<sup>24d</sup> have proposed to use a standard set of isodesmic reactions, the “bond separation reactions”,<sup>26</sup> to derive the theoretical enthalpies of formation. This method is detailed in previous studies.<sup>53</sup>

In the case of 1,3,5-trithiane, the bond separation reaction using its effective valence bond structure, is



## Conclusions

The theoretical value of the enthalpy of formation of 1,3,5-trithiane, 80.4 kJ mol<sup>-1</sup>, evaluated at the more expensive G2+ level, is in very good agreement with the experimental value, 84.6 ± 2.6 kJ mol<sup>-1</sup>.

Calorimetric measurements (enthalpies of combustion and of sublimation) and quantum chemical calculations show that through-space interactions are effective with sulfur atoms, but insignificant with the smaller, tighter oxygen atoms.

**Acknowledgment.** M.V.R., P.J., R.N., and J.Z.D. would like to acknowledge support of the Spanish D.G.E.S. (Projects BQU2000-1479 and BQU2000-1499). R.N. thanks to Centro de Supercomputación de Galicia (CESGA) and CIEMAT for computing facilities. The authors thank to Dr. I. Alkorta and Dr. G. Cuevas for their valuable suggestions.

**Supporting Information Available:** Detailed procedure for thermochemical measurements, including 5 Tables (S1 to S5) and references, Tables S6 to S11, and HOMOs and LUMOs coefficients of thianes and oxanes. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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