

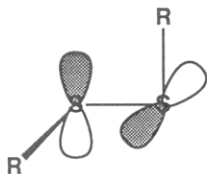
# Diatomic Sulfur

KOSTA STELIOU

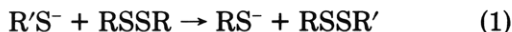
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Sulfur is one of the most ubiquitous elements in nature and has the chemical and physical properties that give it a synthetic versatility that few other elements can equal. The disulfide bond found in cystinyl residues is one of nature's most widely used functional moieties for temporarily or permanently controlling the conformations of proteins during the folding process or in the growing stage.<sup>2</sup> Because the substituents about a sulfur–sulfur bond adopt a 90° torsional orientation to minimize the sulfur–sulfur lone pair energy interactions,<sup>1</sup> any deviation from 90° can exert a profound weakening effect on the disulfide bond. This property

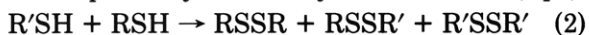


is dramatically reflected in the thiol–disulfide exchange reaction (eq 1), which has been measured to occur over 1000 times faster when the sulfur–sulfur bond is part of a small ring relative to the exchange rate for a geometrically unconstrained disulfide unit.<sup>3</sup> Since the

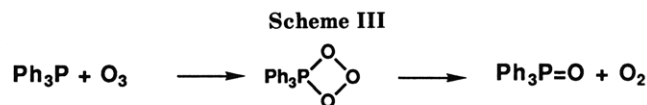
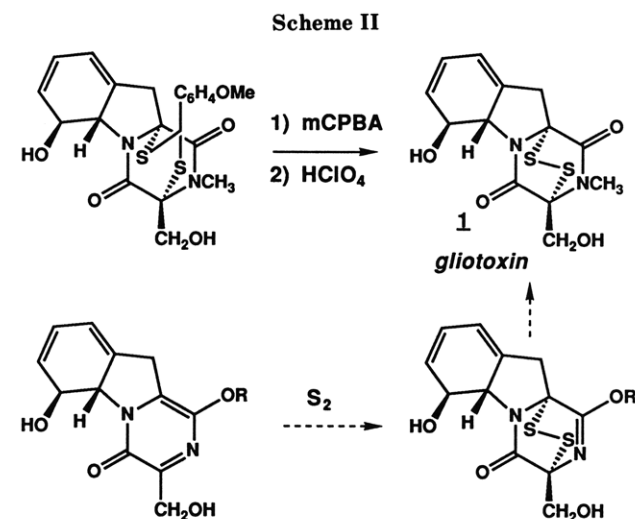
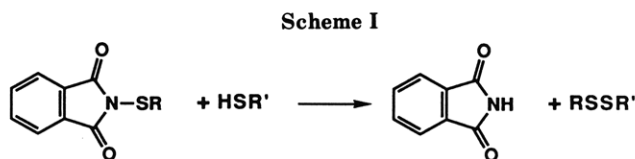


thiol–disulfide interchange is universal in biology,<sup>3b</sup> synthetically influencing the conformation of the disulfide linkage potentially could control the equilibrium direction that this important biochemical process takes.

Incorporating the disulfide moiety into an organic substrate is primarily effected by thiol oxidation (eq 2).



For symmetrically disposed acyclic disulfides, this reaction normally proceeds uneventfully. However, the problem of statistical distribution, inherent in the oxidation process, requires alternative methodology, such as that developed by Harpp and Back<sup>5</sup> (Scheme I), to be used for the unsymmetrical cases. Because oxidation of an  $\alpha,\omega$ -dithiol to form a small cyclic disulfide inevitably would lead to a strained sulfur–sulfur bond, the thermodynamically more stable polymeric material is normally formed. Thus, in the elegant synthesis of the immunosuppressive agent gliotoxin<sup>6</sup> (1, Scheme II), Kishi and co-workers<sup>7a</sup> cleverly used a Pummerer<sup>7b</sup> type rearrangement reaction to generate the disulfide unit. From a synthetic point of view, a Diels–Alder cycloaddition for directly delivering the labile disulfide entity into the dioxopiperazine six-membered-ring system is



attractive. A general approach to six-membered-ring disulfides that would circumvent the problematic coupling of the open-chain mercapto ends is analogous to singlet oxygen chemistry used in the preparation of cyclic six-membered peroxides.<sup>8</sup>

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(4) This footnote was deleted on revision.

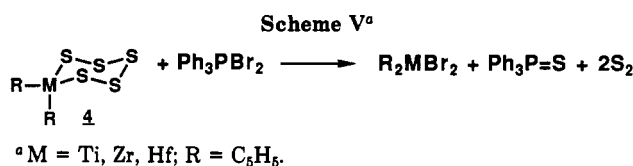
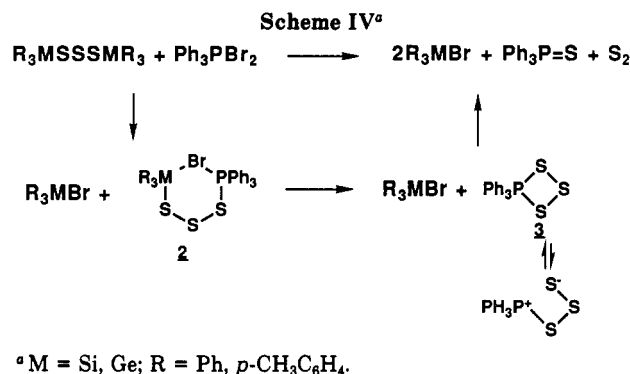
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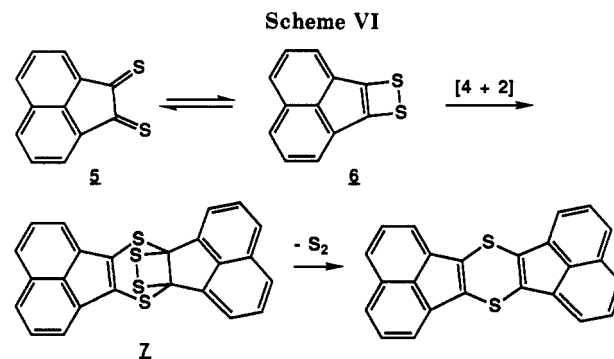
Kosta Steliou was born in Athens, Greece, and grew up in Montreal, Quebec, Canada. He received his B.Sc., M.Sc., and Ph.D. degrees (David N. Harpp) from McGill University (Montreal). After a postdoctoral position with Edward C. Taylor at Princeton University, he was appointed Assistant Professor at the University of Montreal in 1979 and is current Associate Professor. His research interests include heterocyclic chemistry, synthetic organic chemistry, development of new synthetic methods, and application of computational chemistry to synthetic problems.



Before our work, the only known<sup>9</sup> source of diatomic sulfur (spectroscopic evidence) was pyrolysis of octatomic sulfur at 1000 °K. Therefore, we initiated a research program to develop a synthetically useful method for generating singlet diatomic sulfur and to characterize the scope and limitation of its participation, if any, in the Diels–Alder addition to 1,3-dienes. In 1984 we were the first to publish a synthetically useful method for the generation of singlet diatomic sulfur.<sup>10</sup> Since then, a number of workers<sup>11–17</sup> have discovered other sources and are actively helping to define the chemistry of this reactive species. We hope that this Account, summarizing for the first time what is known about diatomic sulfur, will provide impetus for further study in this new and exciting branch of organosulfur chemistry.

### Methods Used To Generate Diatomic Sulfur (S<sub>2</sub>)

**Organometallic and 1,2-Dithietane Routes.** Numerous (unsuccessful) approaches to the preparation of diatomic sulfur have been tried and referenced by Smith.<sup>18</sup> An obvious method, remarkably not previously tried, was to mimic the phosphine ozonide technique routinely used for the generation of singlet oxygen<sup>8</sup> (Scheme III). Enticing as this approach might be, S<sub>3</sub> is not a stable or easily accessible form of elemental sulfur.<sup>19,20</sup> By using group 14 metal sulfide chemistry<sup>21</sup>



(Scheme IV), to our delight in strict analogy to the singlet oxygen chemistry, triphenylphosphine thiozonide (3), or possibly an intermediate such as 2, was produced. As expected, this product spontaneously extruded S<sub>2</sub> (which, in the presence of 2,3-dimethylbutadiene, is efficiently captured as its Diels–Alder adduct) to give the thermodynamically more stable product triphenylphosphine sulfide.<sup>10</sup>

An alternate, but parallel, organometallic route to S<sub>2</sub> using the Shaver–McCall<sup>22</sup> pentasulfide reagents 4 (Scheme V) as the sulfur source was subsequently described by Harpp and MacDonald.<sup>16</sup> Interestingly, in 1985, Cava and co-workers<sup>12</sup> reported S<sub>2</sub> to be a by-product of the decomposition of 1,2-dithietane 7, formed from a Diels–Alder addition of acenaphthenedithione (5) (Scheme VI) with its 1,2-dithiete tautomer 6, although no supporting trapping evidence for its formation was presented. In our hands, the organometallic routes to S<sub>2</sub> were found to be limited to room temperature reactions, which often afforded low yields of Diels–Alder adducts. Further, triphenylphosphine dibromide used in these processes is incompatible with many desirable oxygenated functional groups. Thus, through the use of computer-aided analyses to evaluate enthalpic properties, we predicted that 2,2'-bis(thiobenzoyl)biphenyl (10a) (Scheme VII), if mailable, would undergo an unprecedented head-to-head dimerization to give the 1,2-dithietane 12a, which would then thermally release S<sub>2</sub> en route to the aromatically stabilized 9,10-diphenylphenanthrene (13). Indeed, using thionating methodology<sup>21a</sup> specifically developed for this kind of sulfuration, this Promethean route to S<sub>2</sub> proved fruitful and remains to this date the most efficient means for generating diatomic sulfur, as measured by yields in trapping experiments.<sup>23</sup>

Although the biphenyl route to S<sub>2</sub> and 13 implicates a transient 1,2-dithietane intermediate (12a), our evidence was by inference only; no example of a stable isolated 1,2-dithietane was known. (Only a 1,1'-dioxo derivative (14) had been described by Block and co-workers.<sup>24</sup>) However, support for this hypothesis came from Nicolaou, who prepared and isolated dithiatopazine (15), an intermediate used in the total synthesis of brevetoxin B<sup>25</sup> and the only example of a 1,2-di-

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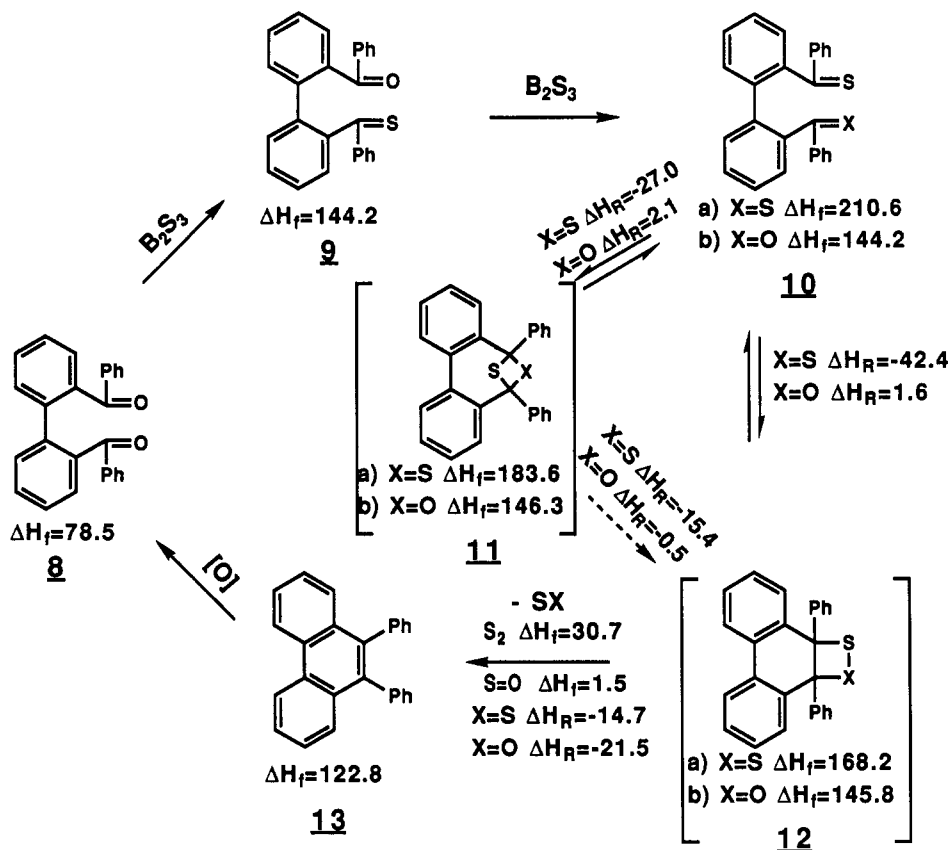
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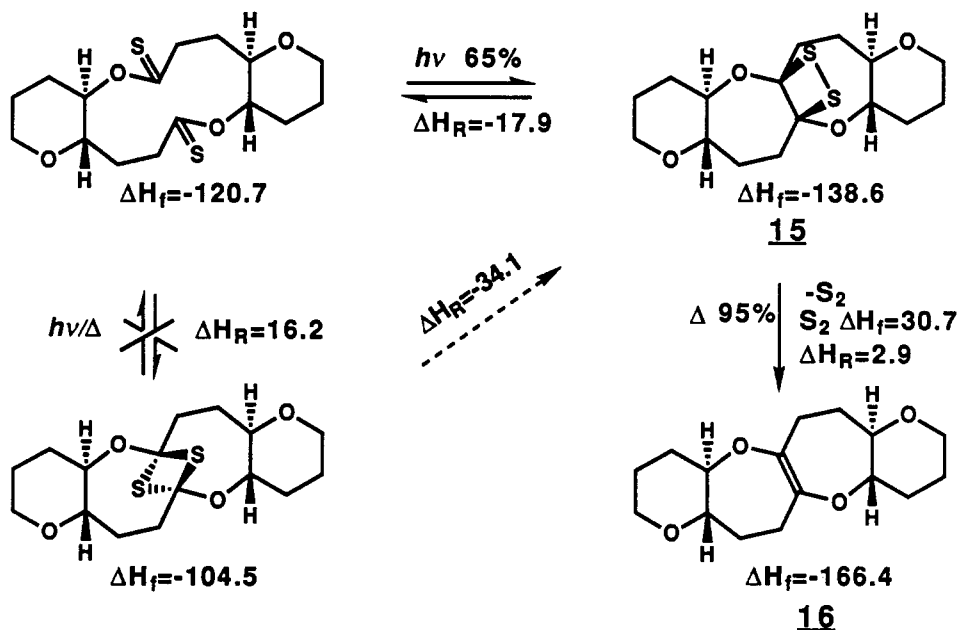
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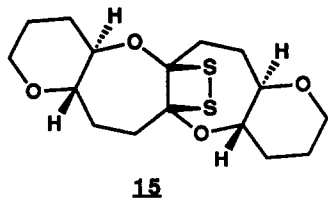
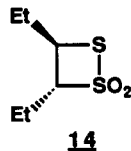
Scheme VII



Scheme VIII



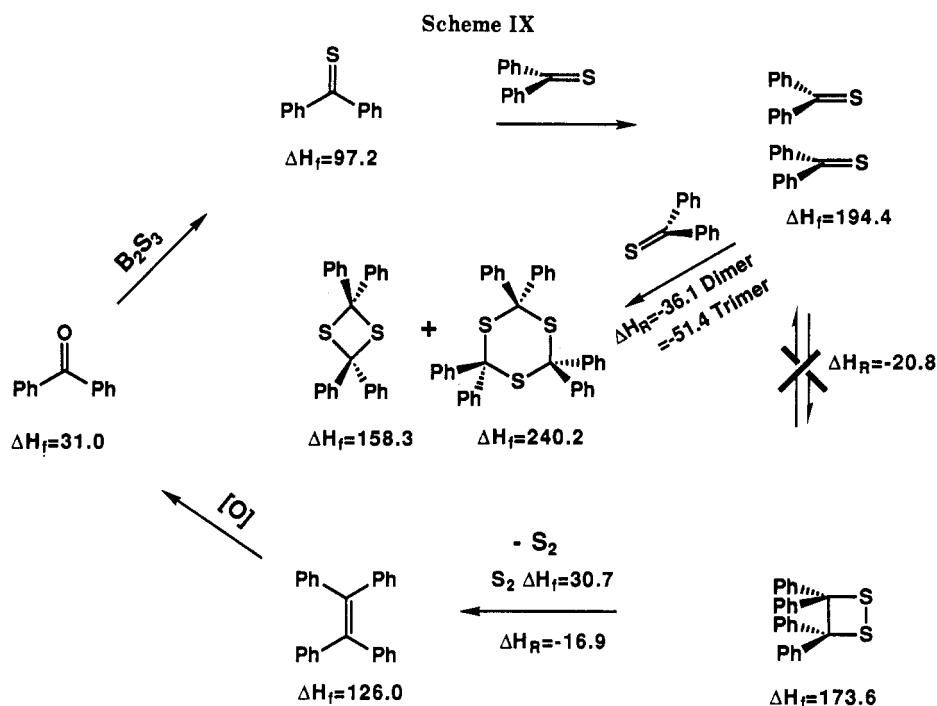
thietane stable enough to be isolated and fully characterized. As projected,<sup>17c</sup> when **15** was photolyzed or



heated to 100 °C, it smoothly extruded  $S_2$  (trapped with 2,3-diphenylbutadiene) to give the desired olefinic material **16** (Scheme VIII). Nicolaou's results gave us impetus to use the computational techniques we developed for the biphenyl system to try to design other stable 1,2-dithietanes that could release diatomic sulfur upon heating.<sup>26</sup>

The computational protocol<sup>17b,c,23</sup> that we are the first to advocate<sup>23</sup> entails the following procedure. Each

(26) Steliou, K.; Salama, P.; Yu, X.-P., submitted for publication.



intermediate is conformationally searched for its global minimum conformer on the MM2<sup>27</sup> based energy hypersurface using the algorithms of the MODEL<sup>28</sup> set of programs. The geometry of this conformer, with no further optimization, is then subjected to an enthalpic evaluation in the AMPAC<sup>29</sup> program using the AM1 Hamiltonian. The significance of this procedure is that, on a Digital micro VAX II work station, it generally takes CPU minutes instead of CPU hours and days if further geometry "optimization" is requested. Importantly, the AMPAC optimized results do not correlate

with the experimental observations as depicted.

The expected preference for the head-to-tail dimerization (11a, Scheme VII) of the thiocarbonyl units in 10a, based on literature precedent,<sup>30</sup> is correctly calculated to be less favored than the head-to-head (1,2-dithietane 12a) dimerization inferred. To verify that the calculated enthalpic stability of the 1,2-dithietanes over the corresponding 1,3 isomers is not coincidental, benzothiofenone (Scheme IX) and adamantanethione (Scheme X), which are known to dimerize and trimerize in strict head-to-tail fashion,<sup>30</sup> were subjected to the

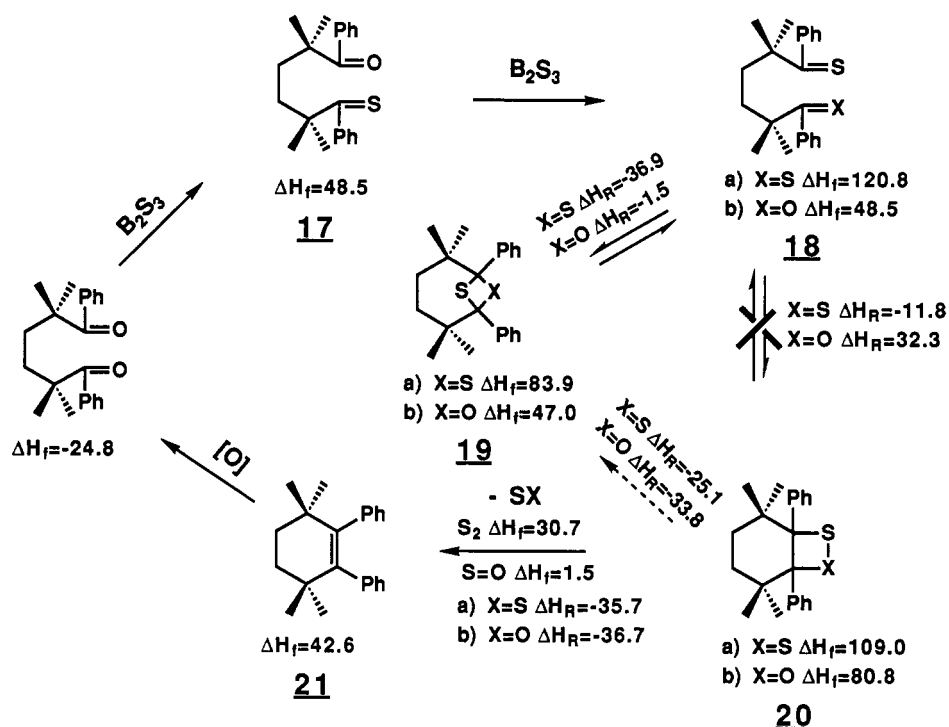
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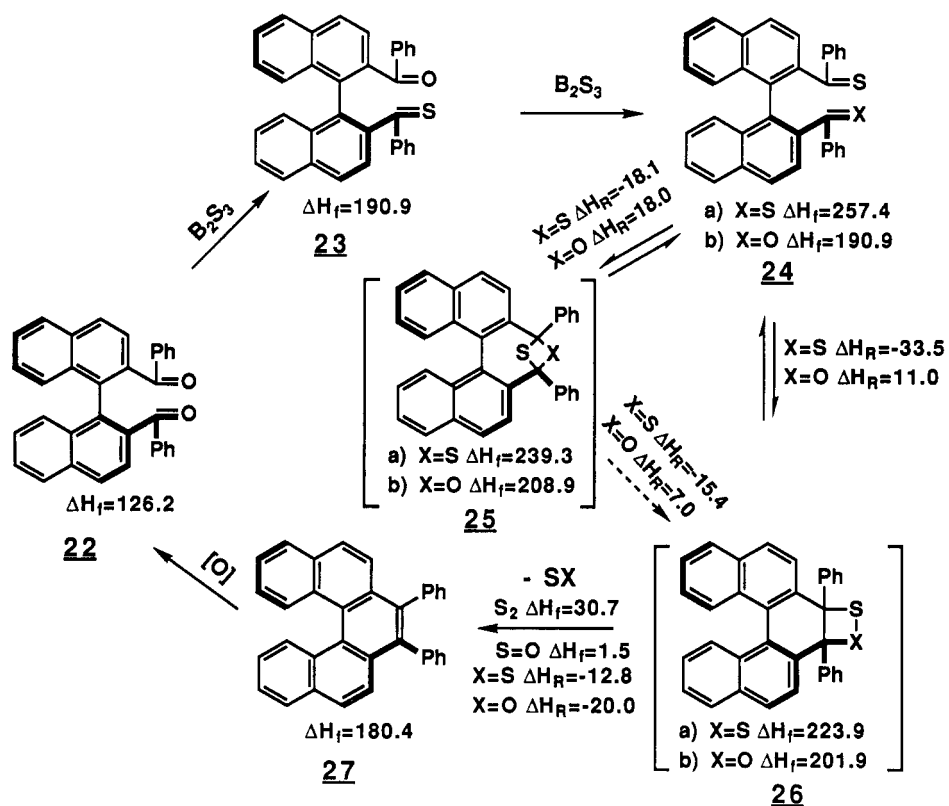
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Scheme XI



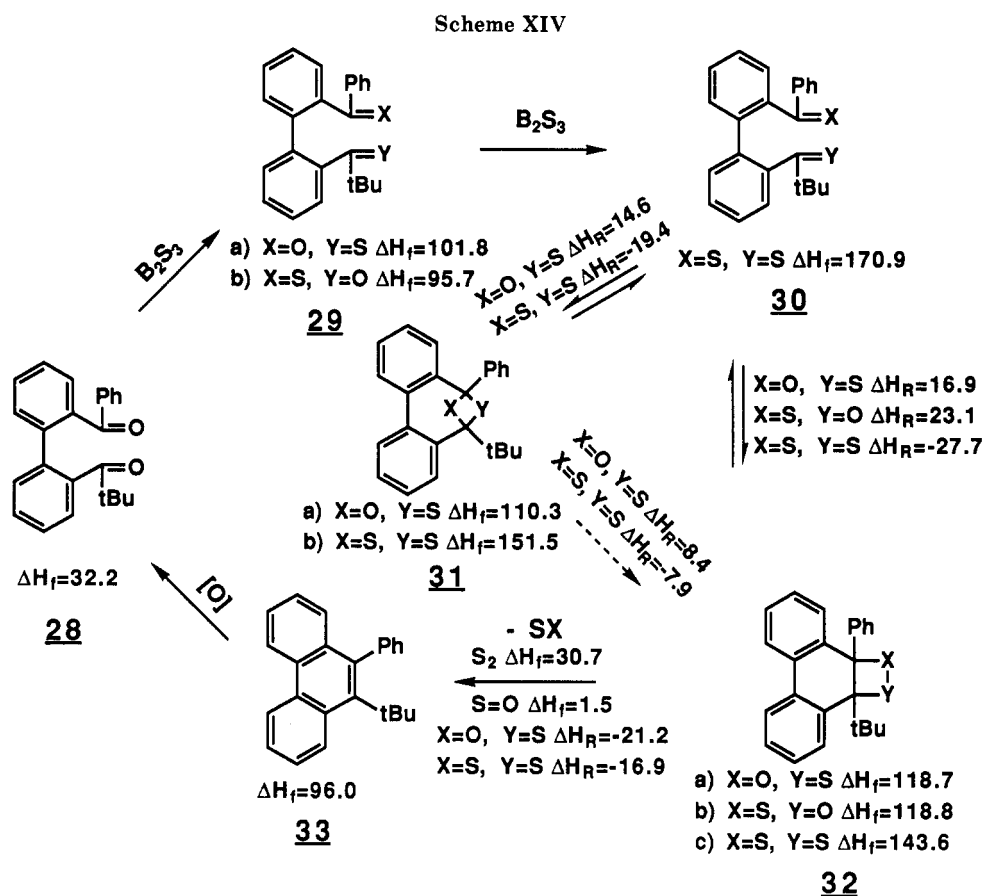
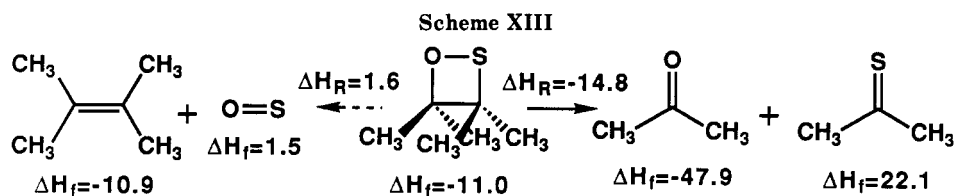
Scheme XII



same computational procedure. Both systems yield the observed products by calculation. To test further the integrity of the computational method, structural modifications (Schemes XI and XII) founded on the successful biphenyl analogy were experimentally undertaken.<sup>26</sup> Whenever the 1,3-dithietane is calculated to be enthalpically more stable than the 1,2 isomer (19a vs 20a, Scheme XI), S<sub>2</sub> extrusion from these systems cannot be experimentally achieved.<sup>31</sup> On the other

hand, in the examples where the 1,2-dithietane (12a vs 11a, Scheme VII, and 26a vs 25a, Scheme XII) is computed to be preferred, S<sub>2</sub> extrusion occurs spontaneously. It is worth noting that the monothiocarbonyl intermediates in these thermally directed reactions can

(31) During the course of our investigation in this series of compounds, an unsuccessful attempt to generate S<sub>2</sub> using this logic was published. See: Ishii, A.; Nakayama, J.; Ding, M. X.; Kotaka, N.; Hishino, M. *J. Org. Chem.* 1990, 55, 2421.



also undergo dimerization, and where they are calculated to be more stable than the uncoupled material (18b vs 19b, Scheme XI), the resulting oxathietane derivatives can indeed be isolated.<sup>31</sup> Although in principle the 1,2-oxathietane coupled product can also extrude S=O, with these examples, this does not take place. The uncoupled material or the 1,3-oxathietane (as calculated) is always found to be the more stable entity. Again, it can be demonstrated that the calculated predictions are not coincidental. Consistent with experimental findings,<sup>32</sup> 3,3,4,4-tetramethyl-1,2-oxathietane is correctly predicted (Scheme XIII) to favor cycloreversion (-14.8 kcal/mol) into acetone and thioacetone. The formation of tetramethylethylene with concomitant S=O extrusion (1.6 kcal/mol) is not observed.

Thus, in each case in which experimental results are available for verification, the computational technique successfully predicts elimination, dimer/trimerization, or cycloreversion. Unfortunately, this method of analysis tends to evaluate only systemic thermodynamic properties and offers no insight as to what the intermediate kinetic or entropic preferences for the ultimate reaction process might be. For example, in our quest

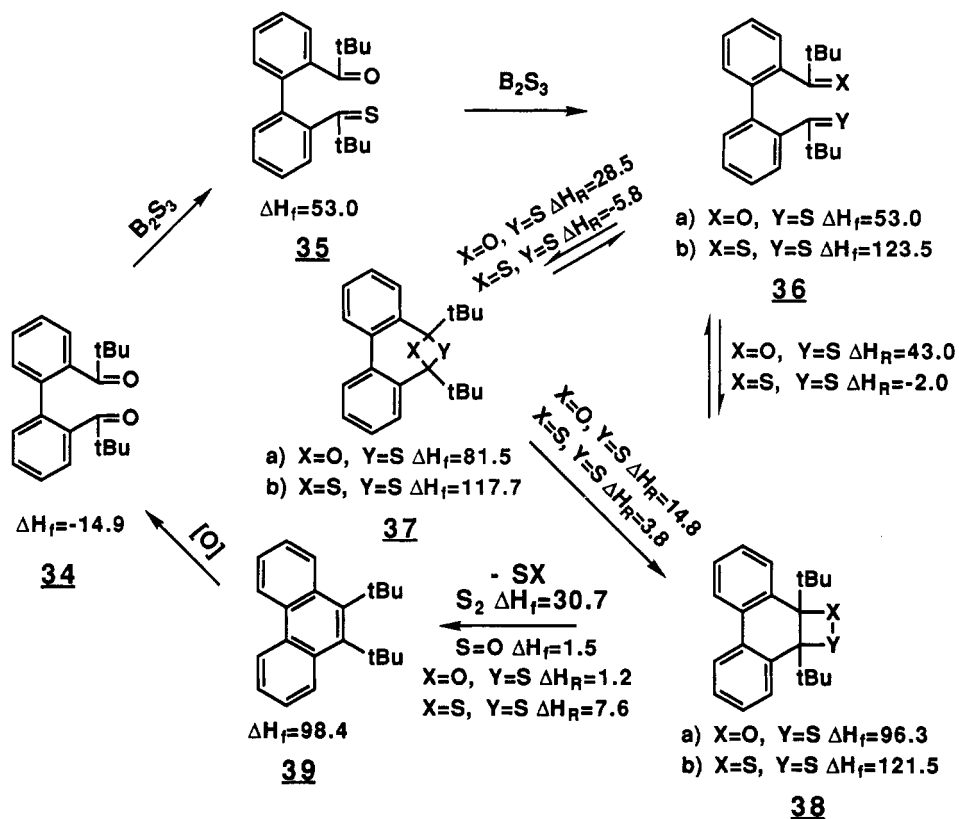
to synthesize an isolable 1,2-dithietane, diketone **28** (Scheme XIV) was prepared. Experimentally, monothionation affords **29a**. This was surprising because it was expected that the benzoylated ketone would thionate preferentially to give **29b** instead. In fact this does occur and the observed product **29a** is formed from the pyrolysis of the 1,3-oxathietane cyclized intermediate **31a**. If thionation is continued, S<sub>2</sub> elimination spontaneously occurs to give **33**. Dithietane **32**, as with previous examples, is too short-lived under the reaction conditions necessary for its formation to be isolable.

The di-*tert*-butyl congener **34** (Scheme XV), on the other hand, is calculated to favor the 1,3-dithietane cyclized product **37b** over 1,2 isomer **38b** by a mere 3.8 kcal/mol. If the 1,2-dithietane derivative **38b** should be formed during the reaction process, an additional 7.6 kcal/mol would be required for S<sub>2</sub> extrusion. Thus, the calculations suggested that this system could, in principle, yield to an isolable 1,3-dithietane derivative which, upon controlled heating, might be equilibrated with the prerequisite 1,2 isomer necessary for S<sub>2</sub> extrusion. Unexpectedly, the ultimate product achieved, in letting the reaction go to completion, is the totally desulfurized novel compound **44** (Scheme XVI). Evidence for this remarkable transformation is provided by the following experimental results.<sup>26</sup> The mono-*tert*-butylthiocarbonyl intermediate **41** can be isolated

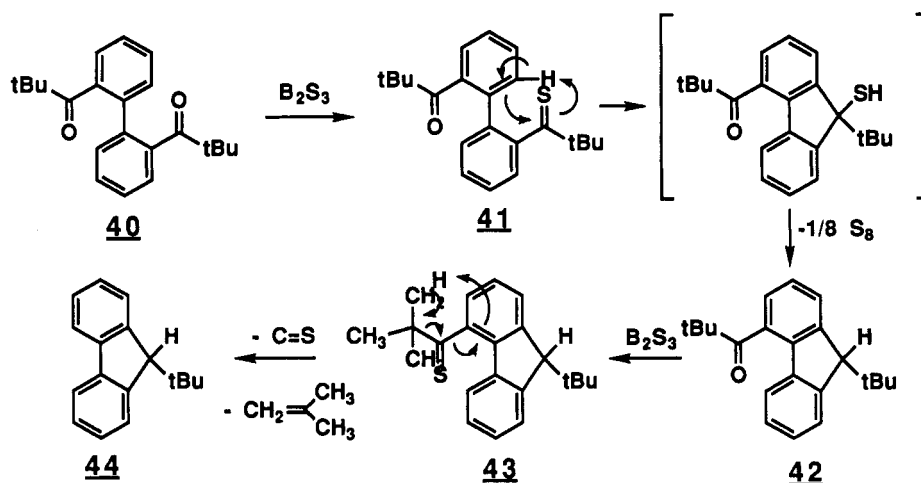
(32) Lown, J. W.; Koganty, R. P. *J. Am. Chem. Soc.* 1986, 108, 3811.

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Scheme XV



Scheme XVI



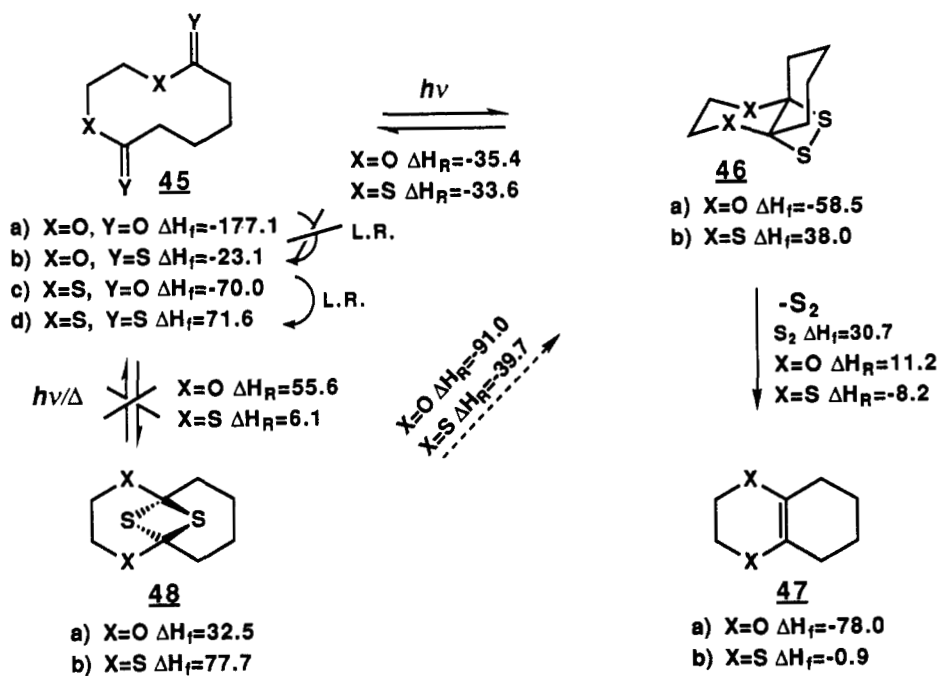
and independently subjected to the reaction process. Similarly both **42** and **43** have been isolated and fully characterized, and the structure of desulfurized compound **44** was assured by X-ray crystallography. Diketone **40** does not by itself undergo these rearrangements.

Since our efforts to prepare an isolable 1,2-dithietane derivative under thermal conditions for subsequent  $S_2$  extrusion did not bear fruit, we turned our attention to the photochemical process which led to the successful preparation of dithiatopazine.<sup>25</sup> A series of synthetically accessible esters were prepared by the coupling of various  $\alpha,\omega$ -diols with acid chlorides.<sup>26</sup> Although all of the esters have the desired computational features, in our hands, thionation of aliphatic esters such as **45a** (Scheme XVII) could not be achieved,<sup>26</sup> and this direction was pursued no further.

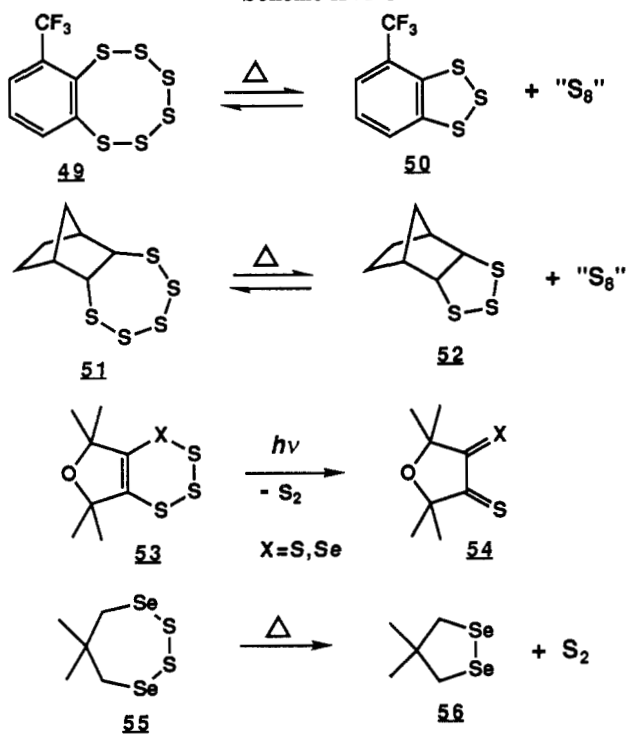
**Chalcogen Ring Contraction Routes.** Chalcogen rings such as **49** (Scheme XVIII) were shown by Chenard and co-workers<sup>34</sup> to be in equilibrium with their corresponding trithiolane derivatives **50** and elemental sulfur. The equilibrium suggests that an  $S_2$  intermediate is involved and that the octaatomic form of elemental sulfur that is formed reflects only the stable end product of  $S_2$  tetramerization. Although the sulfur extruded by such chalcogens can be used to sulfate reactive olefinic material, careful trapping experiments by Bartlett and Ghosh<sup>13</sup> on the norbornene-derived derivatives **51** and **52** with 2,3-dimethylbutadiene is inconsistent with an  $S_2$  intermediate being involved. Ando and co-workers<sup>15a</sup> claim  $S_2$  to be extruded in the

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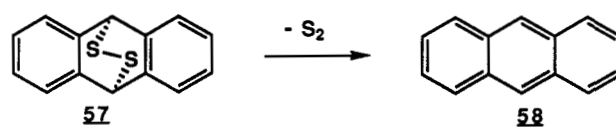
Scheme XVII



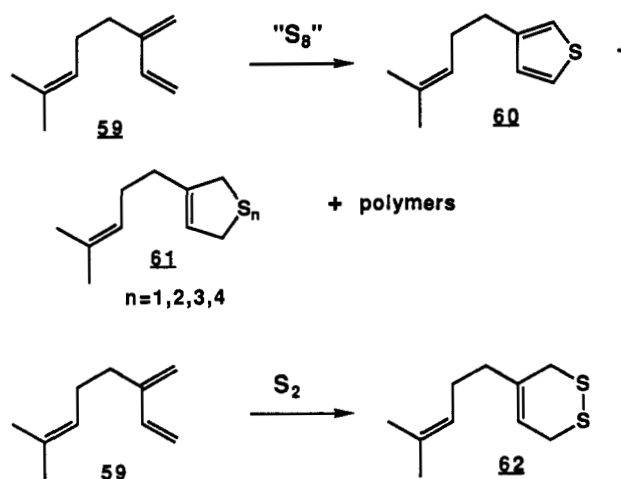
Scheme XVIII



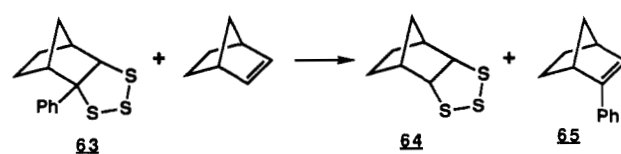
Scheme XIX



Scheme XX



Scheme XXI



photochemical decomposition of **53** into **54**, but again, no trapping evidence is provided. On the other hand, Schmidt and Görli<sup>14</sup> show unequivocally that  $S_2$  is produced during the thermal conversion of **55** into **56**, by trapping it with 2,3-dimethyl-1,3-butadiene.

**Retro-Diels-Alder Routes.** The only reported procedure for  $S_2$  production via a retro-Diels-Alder route comes from Ando's<sup>15b</sup> work (Scheme XIX).

### $S_2$ Additions to Olefins

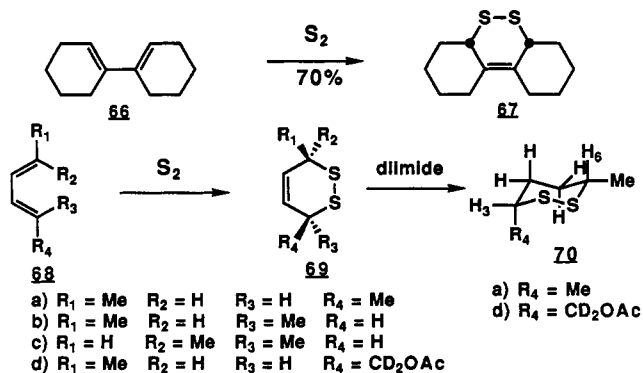
It is important to distinguish the chemistry of  $S_2$  from that of activated elemental sulfur. Additions of activated elemental sulfur ( $S_n$ ,  $n = 1-7$ ) to reactive olefins can be characterized by the multitude of products, in-

cluding  $S_2$  Diels-Alder type adducts with 1,3-dienes, that are obtained. For example, when myrcene is treated with activated elemental sulfur, the Diels-Alder adduct **62** (Scheme XX) is formed in 30% yield.<sup>35</sup> However, the bulk (70%) of the reaction mixture consists of thiophene **60**, polysulfides **61**, and other intractable sulfurated products.<sup>35</sup>  $S_2$  addition to the same

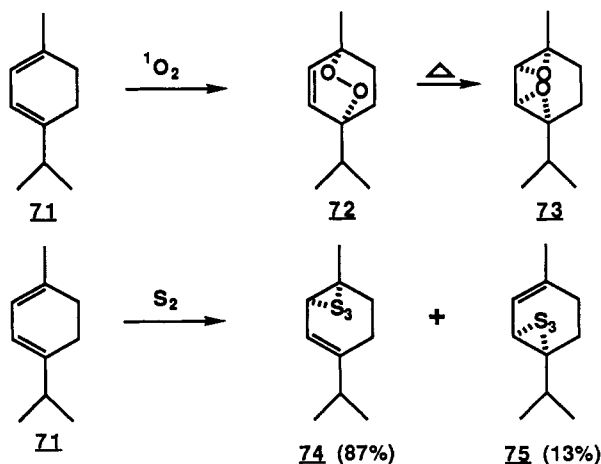
(35) Elvidge, J. A.; Jones, S. P.; Peppard, T. L. *J. Chem. Soc., Perkin Trans 1* 1982, 1089.



Scheme XXII



Scheme XXIII

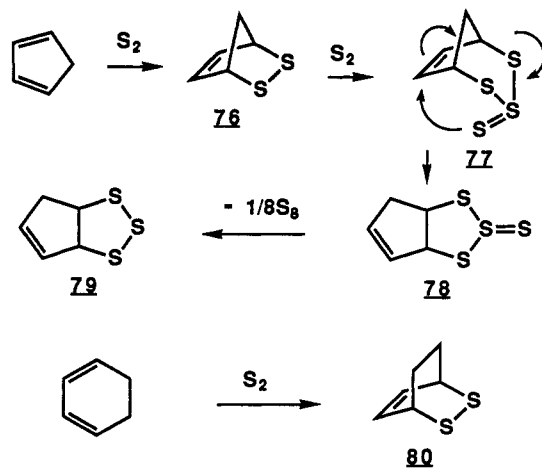


diene affords (75% yield) myrcene disulfide (62) as the only sulfurated product.<sup>23</sup> Also, elemental sulfur need not be the only source for activated sulfur. Ghosh and Bartlett<sup>19</sup> found that norbornane trithiolanes can intermolecularly transfer discrete  $\text{S}_3$  units of sulfur. For example, trithiolane 63 (Scheme XXI) will transfer all of its sulfur content to norbornene to afford 64 and 65 in quantitative yield.

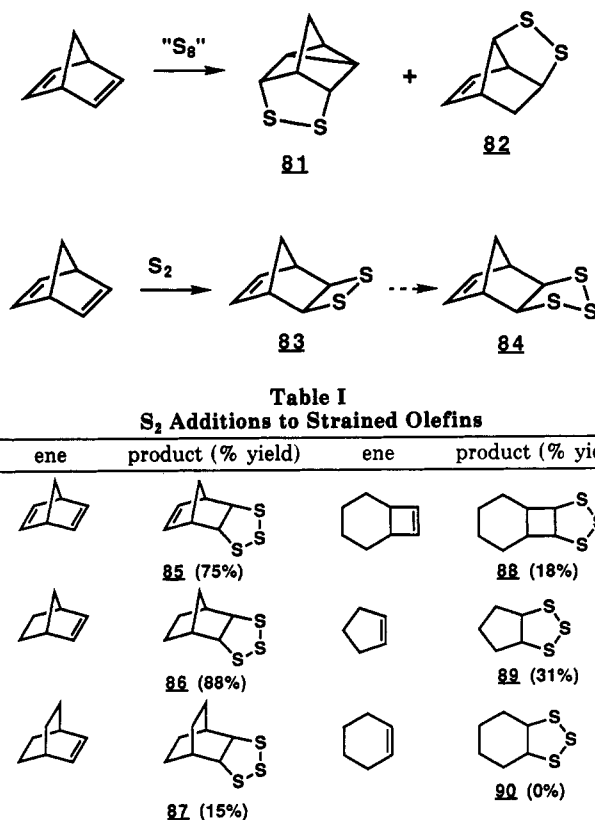
**$\text{S}_2$  Additions to Acyclic and Cyclic 1,3-Dienes.** The anticipated Diels–Alder addition of  $\text{S}_2$  to 1,3-dienes, for general application to the synthesis of 1,2-dithiin six-membered rings, was the basis for our initiating this work. Furthermore, for synthetic utility, it was important to know if such additions were governed by the Woodward–Hoffmann rules.<sup>36</sup> Stereochemical analysis carried out on adducts 67 and 70 (Scheme XXII) indicate that  $\text{S}_2$  additions to acyclic 1,3-dienes 66 and 68 are entirely analogous to the corresponding singlet oxygen additions.<sup>37</sup> However, additions to cyclic 1,3-dienes (Scheme XXIII) generally afford allylic epitrisulfides and not the expected bicyclic bridged disulfide that would be in keeping with an analogous singlet oxygen addition.<sup>37</sup>

Formation of the epitrisulfides is thought to occur via a second  $\text{S}_2$  addition to the strained sulfur–sulfur bond of the bicyclic bridged disulfide intermediate. For example, although cyclopentadiene (Scheme XXIV) ultimately gives allylic epitrisulfide 79, the bicyclic adduct 80 can be isolated from  $\text{S}_2$  addition to 1,3-cyclo-

Scheme XXIV



Scheme XXV

Table I  
 $\text{S}_2$  Additions to Strained Olefins

ene	product (% yield)	ene	product (% yield)
	81 (75%)		88 (18%)
	82 (88%)		79 (31%)
	83 (15%)		80 (0%)

hexadiene. It is proposed<sup>37</sup> that adduct 76 is not isolable because it is more strained than 80 and therefore much more susceptible to further  $\text{S}_2$  addition to give 77, which undergoes a 2,3-sigmatropic rearrangement that leads to thionotrissulfide 78. Thionotrissulfide 78 then deposits elemental sulfur to yield 79. The extreme volatility of bicyclic adduct 80 also accounts for its protection from any further  $\text{S}_2$  addition.

**$\text{S}_2$  Additions to Strained Olefins.** Diatomic sulfur also adds to strained olefins, and the products obtained are different from those obtained by the addition of activated sulfur. For example, whereas norbornadiene gives disulfides 81 and 82 (Scheme XXV) with activated sulfur,<sup>13</sup> trithiolane 84 is the only product obtained by  $\text{S}_2$  addition.<sup>37</sup> Presumably, a second  $\text{S}_2$  addition occurs on the highly strained intermediate 83, which then suffers the same rearrangement and sulfur deposition process outlined in Scheme XXIV for cyclo-

(36) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Verlag Chemie: Weinheim, 1970.

(37) Steliou, K.; Gareau, Y.; Milot, G.; Salama, P. *J. Am. Chem. Soc.* 1990, 112, 7819.

pentadiene.<sup>37</sup> Table I lists other examples of strained olefins that react with S<sub>2</sub> to give trithiolane products.<sup>37</sup> The trithiolane products obtained from these S<sub>2</sub> additions are in sharp contrast to the episulfide and thiophene products or no reaction that Ando and co-workers<sup>15b</sup> report if reagent 57 (Scheme XIX) is used as the "S<sub>2</sub>" source.

### Conclusion

From our many S<sub>2</sub> experiments, S<sub>2</sub> additions to olefins give only disulfide or trisulfide products. The trisulfide products obtained can be explained, in all instances, in terms of addition of a second mole of S<sub>2</sub> followed by a rearrangement process that deposits atomic sulfur in its elemental octaatomic form. In none of our experiments did we find episulfide products, thiophenes, tetrasulfides, or polymeric material. Thus, we conclude that when these latter products are observed in the reaction mixture, the sulfuration was more likely a reaction of activated elemental sulfur and not S<sub>2</sub>.

The recent widespread interest in S<sub>2</sub> chemistry is based on a fundamental point of view and also on possible applications to the synthesis of 1,2-dithiin compounds, many of which show antimicrobial activity, including anti-HIV activity.<sup>38</sup> Thus, we believe that this new area of organosulfur chemistry will be richly explored for many more years to come.

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Registry No. S<sub>2</sub>, 23550-45-0.

(38) (a) Steliou, K.; Gareau, Y.; Milot, G.; Salama, P. *Phosphorus, Sulfur Silicon Relat. Elem.* 1989, 43, 209. (b) Freeman, F.; Kim, D. S. H. L.; Rodriguez, E. *Sulfur Rep.* 1989, 9, 207.

## Thermal Reactions and Properties of Polycyclic Aromatic Hydrocarbons

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### Introduction

Early studies of coal tar and the earliest applications of quantum theory have both dealt extensively with the varied, yet systematic behavior of polycyclic aromatic hydrocarbons (PAHs). They have remained at the center of soot, coal, and carbon chemistry for many years and, more recently, have gained notoriety (and attention) for their cancer-causing potential.<sup>1</sup> Intense and very recent interest in PAHs has developed in the study of diamond synthesis,<sup>2</sup> interstellar space,<sup>3</sup> and carbon cages ("fullerenes").<sup>4</sup>

This Account reviews results of studies on the thermal chemistry and properties of PAHs. While most of this work has been motivated by practical concerns, especially in the areas of coal processing and soot formation, the results illuminate certain fundamental features of PAH chemistry.

Since facile routes are generally not available for building large hexagonal-ring systems characteristic of

PAHs, their ubiquity is largely a consequence of their high-temperature thermodynamic stability. Two separate factors are responsible for this stability. First, the delocalized orbitals in PAHs provide stable repositories for electrons. Second, and equally important, the low H/C ratios of PAHs tie up little hydrogen, serving to increase system entropy.

Some of the notable difficulties in the study of PAHs are low solubility, multisite reactivity, synthesis, and identification. Fortunately, several simplifying factors may also be cited. First,  $\pi$ -electron properties of PAHs are estimable. Moreover, the inherent thermodynamic stability of PAHs limits their energetically accessible reactions. In addition, well-developed predictive methods for free-radical reactions can be applied to PAH reactions.<sup>5,6</sup>

The following discussion examines first properties and then reactions of PAHs and derived radicals. It

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(1) See, for example: *The Proceedings of the Symposium on Polynuclear Aromatic Hydrocarbons*; Battelle Press: Columbus, OH, 1990.

(2) Badziag, P.; Verwoerd, W. S.; Ellis, W. P.; Greiner, N. R. *Nature* 1991, 343, 244-245.

(3) Frenklach, M.; Figelson, E. D. *Astrophys. J.* 1989, 341, 372.

(4) Curl, R. F.; Smalley, R. E. *Sci. Am.* 1991, 265, 54-63.

(5) Stein, S. E. A Fundamental Chemical Kinetics Approach to Coal Conversion. In *New Approaches to Coal Chemistry*; Blaustein, B. D., et al., Eds.; ACS Symposium Series 169; American Chemical Society: Washington, DC, 1981; pp 97-130.

(6) Stein, S. E. Free Radicals in Coal Conversion. In *Chemistry of Coal Conversion*; Schlosberg, R., Ed.; Plenum Press: NY, 1985; pp 13-44.