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Polysulfane Antitumor Agents from *o*-Benzyne. An Odd−Even Alternation Found in the Stability of Products *o*-$C_6H_4S_x$ ($x = 1-8$)

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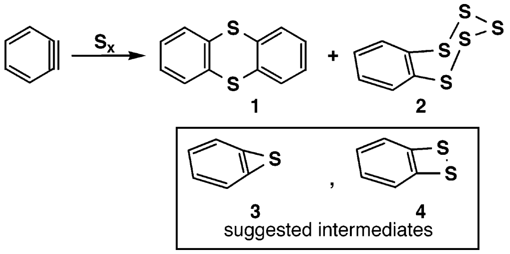
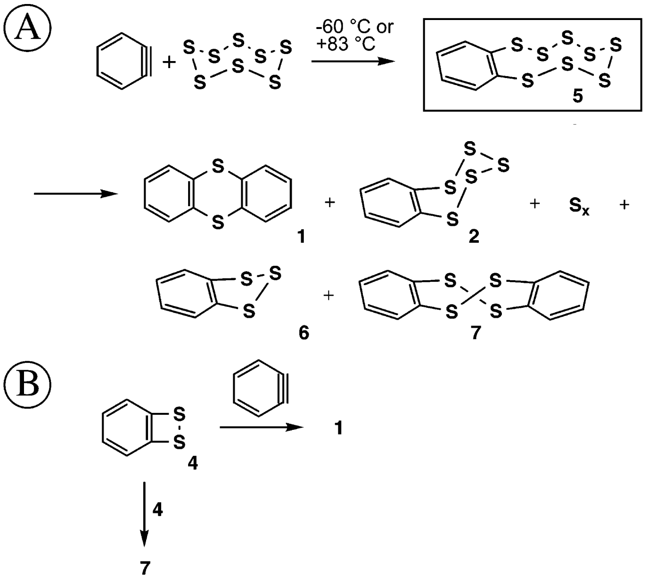
Abstract: Benzyne is shown to add elemental sulfur and give rise to a series of polysulfane compounds. A computational and experimental study is presented. Odd-membered *o*-$C_6H_4S_x$ rings ($x = 1-8$), except $x = 1$, which suffers from ring strain, have enhanced stability compared to even-membered rings. The acquisition of “odd−even” data may shed new light, revealing patterns on polysulfane stability and structure.

We present the study of a reaction that can make ortho-fused polysulfur chemical bonds. *o*-Benzopolysulfanes possess antitumor and antimicrobial activity.[1] Previous research has demonstrated that elemental sulfur can react with unsaturated chemical groups such as benzyne[2,3] and alkynes.[4−6] A reaction where thianthrene (**1**) and benzopentathiepin (**2**, *o*-$C_6H_4S_5$) are formed utilizing *o*-benzyne as a precursor has been established previously by Nakayama et al. (Scheme 1).[2,3] The report suggested an initial formation of benzothiirene (**3**, *o*-C_6H_4S) or benzodithiete (**4**, *o*-$C_6H_4S_2$) intermediates.[2,3] A more detailed study of the *o*-benzyne−elemental sulfur reaction has not yet appeared. The study of *o*-benzyne with elemental sulfur is presented here that provides evidence for the decomposition of an initial *o*-$C_6H_4S_8$ intermediate (**5**) to give thianthrene **1**, pentathiepin **2**, trithiole **6**, and tetrathiocin **7** products (Scheme 2).

SCHEME 1

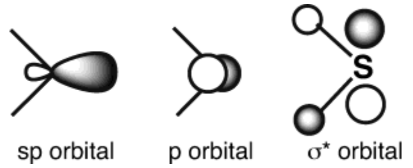


SCHEME 2



Various heterocycles may be expected to arise from the reaction of *o*-benzyne with cyclic S_8. B3LYP/6-31G(d) calculations are used to predict the stability of possible ortho-fused heterocycles, *o*-$C_6H_4S_x$ (where $x = 1-8$). Low-energy conformers of the rings containing up to 8 sulfurs were identified by a search of conformational space. An oscillation pattern emerges in the relative stability of these heterocycles (Figure 1). The odd-membered *o*-$C_6H_4S_x$ rings (except $x = 1$, which suffers from ring strain) have enhanced conformational stability compared to the even-membered rings.

Figure 1 is a measure of the stability of *o*-$C_6H_4S_x$. We compared the energy difference of *o*-$C_6H_4S_8$ **5** relative to *o*-$C_6H_4S_x$ plus a fraction of cyclic S_8’s energy in an isodesmic reaction. Compounds *o*-$C_6H_4S_7$ and *o*-$C_6H_4S_5$ possess staggered lone-pair electrons in the stable crown and chair forms, respectively. The five-membered ring molecule *o*-$C_6H_4S_3$ adopts a stable half-chair conformation. Lone-pair interactions in polysulfur systems are known.[7] Sulfur lone pairs are in nonequivalent orbitals: one pair in the 3p orbital (axial to the plane of the



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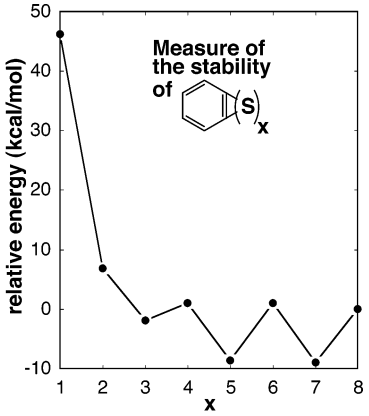


FIGURE 1. Oscillations in the stability of *o*-benzopolysulfanes *o*-$C_6H_4S_x$ gauged by a fraction of cyclic S_8 subtracted from *o*-$C_6H_4S_8$ in an isodesmic reaction, i.e., "relative energy" is the energy of the reaction *o*-$C_6H_4S_8 \rightarrow$ *o*-$C_6H_4S_x + (8 - x)/8$ cyclic S_8. Data shown were obtained with B3LYP/6-31G(d) gas-phase calculations. The temperature sensitivity of the stability of polysulfur compounds appears to be small (see Supporting Information). The perfect linear correlation of energy for $(8 - x)/8$ cyclic S_8, where $x = 1$ to 8, allowed for the study of *o*-$C_6H_4S_x$ heterocycle stability plotted here.

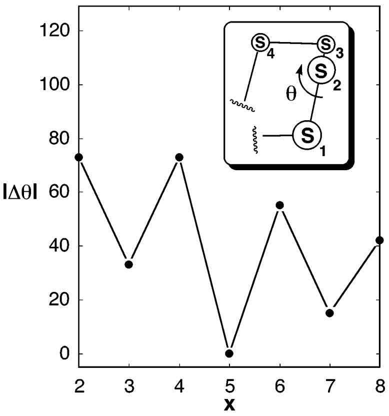
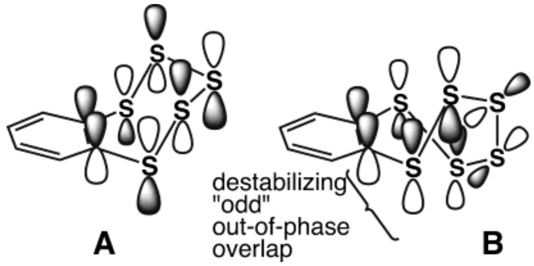


FIGURE 2. Odd–even alternation arising from eclipsing strain measured in *o*-$C_6H_4S_x$ heterocycles based on B3LYP/6-31G(d) calculations. The dihedral angle of pentathiepin *o*-$C_6H_4S_5$ (73.0°) is used as a reference point from which the segment S1–S2–S3–S4 in *o*-$C_6H_4S_x$ (x = 4–8), C–S1–S2–S3 in *o*-$C_6H_4S_3$, and C–C–S1–S2 in *o*-$C_6H_4S_2$ are compared. The difference gives rise to the $|\Delta\theta|$ values.

molecule) and the other in an sp (equatorial) orbital. Sulfur also possesses a vacant σ^* orbital.

The conformations in *o*-$C_6H_4S_x$ (x = 3, 5, 7) can better adopt gauche interactions, whereas eclipsing interactions occur in the even-numbered cases. The extent of eclipsing is measured by comparison of the polysulfur torsion angle (θ = S1–S2–S3–S4) in *o*-$C_6H_4S_x$ as positive or negative to the pentathiepin θ angle of 73.0° as a reference point described as $|\Delta\theta|$. Figure 2 reveals that the conformations for the even-membered rings exhibit enhanced eclipsing strain with higher $|\Delta\theta|$ values. The origin of the oscillating feature in Figure 1 is also likely the result of the overlap in the p-orbitals for the odd- vs even-membered rings. With *o*-$C_6H_4S_x$ (x = 3, 5, 7), an even number of out-of-phase overlaps is achieved, whereas with *o*-$C_6H_4S_x$ (x = 2, 4, 6, 8), an odd number of out-of-phase overlaps is achieved (e.g., compare structures **A** and **B**). Even vs odd out-of-phase overlap in *o*-$C_6H_4S_x$ (x = 1–8) is reminiscent of Hückel and Möbius π electron systems. Similar "odd–even" trends may apply to allotropes of elemental sulfur but are not described in the literature.



Described below is an experimental study of the *o*-benzyne–S_x reaction. The identification of *o*-$C_6H_4S_5$ **2** and *o*-$C_6H_4S_3$ **6** as products is based on an NMR and GC/MS analysis. Formation of *o*-$C_6H_4S_2$ **4** is suggested on the basis of a secondary reaction that traps *o*-benzyne to give thianthrene **1** as well as a *o*-$C_6H_4S_2$ **4** dimerization process to give tetrathiocin **7** (Scheme 2B).

Benzyne was generated by low-temperature (−60 °C reaction of *n*-BuLi with *o*-dihalobenzene in diethyl ether)[8] and elevated-temperature methods (83 °C decomposition of benzenediazonium-2-carboxylate in 1,2-dichloroethane).[9] The production of *o*-benzyne was demonstrated with furan trapping where 1,4-dihydronaphthalene-1,4-endoxide was detected in 80% yields. Elemental sulfur was added to trap the in situ-generated *o*-benzyne and gave thianthrene **1**, pentathiepin **2**, trithiole **6**, and tetrathiocin **7** in low overall yields [**1** (17.2%), **2** (11.9%), **6** (1.3%), **7** (2.6%)]. Acyclic polysulfanes are probably formed concomitantly. One of the byproducts obtained, *o*-C_6H_4ClSH (1%), suggests that the *o*-benzyne precursor, *o*-C_6H_4ClLi, reacts with elemental sulfur and generates thiolates, which can equilibrate polysulfides. Concentrations of **1**, **2**, **6**, and **7** are identical to within experimental error with the *o*-benzyne precursors *o*-C_6H_4ClLi or *o*-C_6H_4-$CO_2^-N_2^+$, which provide evidence for thermodynamic product ratios. Pentathiepin **2** displayed a weak molecular ion peak *m*/*z* 236 [M^+] and a base peak at *m*/*z* 172 [$M^+ - 2S$] representing the loss of two sulfur atoms. The molecular ion of trithiole **6** is abundant and represents the base peak *m*/*z* 172 [M^+]. Mass spectrometry was also used to confirm the presence of thianthrene **1**. ^{1}H NMR data on the *o*-benzyne sulfuration reaction yielded conclusive evidence for the formation of thianthrene **1**, pentathiepin **2**, and tetrathiocin **7**.[10] The expected upfield chemical shifts for trithiole **6** are obscured by the reagent and byproduct peaks. The assignment of **2** is based on two sets of dds: a downfield set at δ 7.85 (2H) and an

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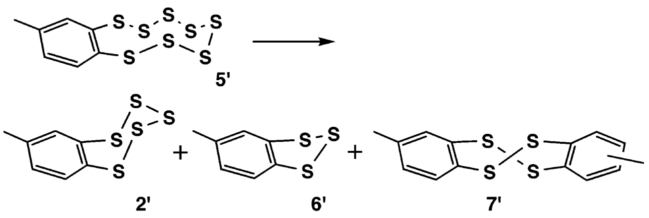
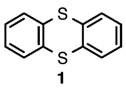
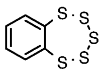
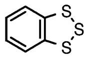
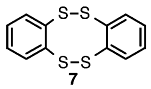
upfield set at δ 7.34 (2H). Similar chemical shifts are found for **1** [δ 7.58 (4H); δ 7.32 (4H)] and **7** [δ 8.66 (4H)].

The reaction shown in Scheme 2 stems from the proposal that benzooctathiecin **5** forms. There was no direct detection of **5** in the benzyne reaction. However, experimental evidence for the decomposition of an octathiecin was obtained by synthesizing **5** and **5′** from the method of Steudel using ZnS_6(TMEDA).[11] In the presence of heat (40 °C) or an added nucleophile *n*-PrSH in dicholormethane, gas chromatographic analyses of the reaction revealed the formation of **2**, **6**, and **7** and **2′**, **6′**, and **7′** from **5** and **5′**, respectively (see Supporting Information). These results provide evidence for the formation of **5** in the benzyne$-S_x$ reaction and are consistent with the idea that heat or nucleophiles can influence the equilibrium between polysulfane compounds,[7a,11−13] which offers a reason for the decomposition of *o*-$C_6H_4S_8$ **5** under the conditions. Formation of stable arene annulated polysulfur products from precursor **5** likely occurs by reversible exchange reactions involving complex mixtures of polysulfanes.



The product distribution also bears on the solubility of elemental S_x in the benzyne system. The yield of thianthrene **1** decreased by 17% when the initial cyclic S_8 concentration is varied from 0.8 to 85 mM (Table 1). Such an effect between *o*-benzyne and cyclic S_8 concentration and the suppression of **1** is consistent with a reduced *o*-benzyne trapping of the dithiete intermediate **4** (Scheme 2B). It follows that the ability of **2**, **6**, and **7** to form from *o*-benzyne is enhanced with higher elemental sulfur concentrations. We find that elemental sulfur is soluble to the extent of 0.0078 g in 10 g of diethyl ether at −60 °C, which leads to the conclusion that amounts of elemental sulfur above ∼10 mM. This result indicates that a heterogeneous process amplifies the production of polysulfanes **2**, **6**, and **7** but not sulfane **1**.

TABLE 1. Product Distribution of *o*-Benzosulfanes that Arise from the Cyclic S_8 Sulfuration of *o*-Benzyne[a−c]

$[\text{Cyclic } S_8]_{\text{init}}$	 **1**	 **2**	 **6**	 **7**
0.8 mM	57	31	3	7
10 mM	52	36	4	8
52 mM	46	41	5	9
85 mM	40	48	4	8

[a] GC/MS and NMR detection of products formed in diethyl ether at −60 °C after addition of cyclic S_8 to *o*-benzyne. [b] *o*-Benzyne concentration in the reaction is approximately 200 mM. Each entry is an average of four runs. [c] Reactions were taken to ∼20% completion.

In conclusion, this study describes a reaction that can make ortho-fused polysulfur bonds. We find that the odd-membered *o*-$C_6H_4S_x$ rings ($x = 3, 5, 7$) have enhanced stability compared to the even-membered rings. The acquisition of odd−even data can reveal patterns on the stability and the structure of cyclic polysulfanes. The mechanism of polysulfane product formation appears to be governed by reversible, equilibrium, exchange processes.

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Supporting Information Available: Experimental section on reactions and product characterizations and descriptions of the geometries of the stationary points and absolute energies. This material is available free of charge via the Internet at http://pubs.acs.org.

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