A New Rigid Sulfur-Bridged Dithiametacyclophane and Its Acyclic Analogue: Direct Observation of the Transannular Bond Formation between the Three Sulfur Atoms and Isolation of Dicationic Salts

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Abstract: A new rigid sulfur-bridged dithiametacyclophane, 1,11-(methanothiomethano)-5*H*,7*H*-dibenzo[*b*,*g*][1,5]dithiocin (**1**), analogous acyclic trithia compounds, 2,6-bis[(methylthio)methyl]phenyl phenyl sulfide (**7**), and the corresponding sulfoxides were prepared by general methods. The transannular bond formation between the three sulfur atoms of **1** was observed in the reaction of sulfide **1** and its sulfoxides (**2**, **3**) with concentrated H_2SO_4 by both ^1H and ^{13}C NMR spectroscopy. A new type of oxygen-transfer reaction via the dication of **1** was found by the hydrolysis of the H_2SO_4 solutions of **1**-**3**. The dicationic salt of **1** was obtained in the reaction of the sulfoxide **3** with trifluoromethanesulfonic anhydride. Evidence for intramolecular sulfur-sulfur interaction between the three sulfur atoms of **7** was found in the reactions of the corresponding sulfoxides (**8**, **9**) with concentrated H_2SO_4. Electrochemical oxidation of trithia compound **7** and mono- and dithioethers was studied by using cyclic voltammetry. Anodic oxidation of **7** was 400 mV easier than that of monothia compound such as diphenyl sulfide because of the intramolecular interaction between the three sulfur atoms in **7**.

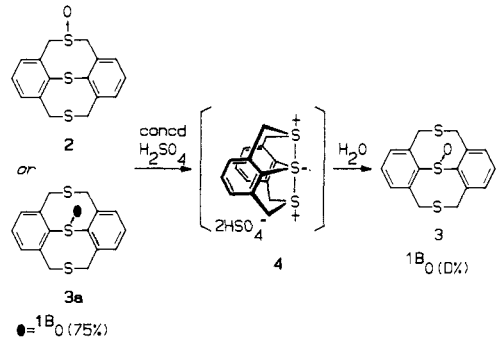
Transannular or intramolecular interaction between bifunctional compounds is a fundamental phenomenon in numerous cyclic or acyclic compounds. In such compounds, if one could generate a cation or a radical on the one group, the other functional group could interact to stabilize the cation or the radical, resulting in the generation of a new functional group. As such an example, di- and polythia compounds would be one of the most attractive substrates, both in view of an investigation of transannular S-S interaction and formation of a new type of functional group, since if the two sulfide groups would form an S-S bond, one could prepare a tetrasubstituted disulfide group. Several procedures

for the generation of either an incipient or a discrete tetrasubstituted disulfide species have been reported involving several devices such as electrochemical oxidation,[1] pulse radiolysis,[2] or treatment with the oxidizing agents[3] of dithia compounds.

Particularly interesting target molecules for formation of the cation radical and the dication by transannular interaction would be 1,5-dithiacyclooctane and related compounds, which have been prepared quite readily. As typical examples, Musker and coworkers reported that the cation radical of 1,5-dithiacyclooctane is formed by oxidation of the sulfide with 1 equiv of nitrosyl tetrafluoroborate. Further oxidation produces a dithioether dication salt, which is assigned its structure by ^{13}C NMR and elemental analyses.[3] They also confirmed formation of the dithioether dication by kinetic investigation for the reduction of the corresponding sulfoxide with aqueous HI.[4]

Recently, we reported the formation and isolation of a dithioether dication of 1,5-dithiacyclooctane in the reaction of the corresponding sulfoxide with concentrated H_2SO_4 and also provided evidence for the formation of the dication in the Pummerer reaction of the sulfoxide with acetic anhydride.[5-8] More recently,

Scheme I



we succeeded in preparation of the dithioether dication 1,5-dithioniabicyclo[3.3.0]octane bis(trifluoromethanesulfonate) as a remarkably stable crystalline salt that was first characterized by X-ray crystallographic analysis.[9] These new sulfur species are of particular interest and become attractive if one could prepare the analogous derivatives bearing multithia centers (tri-, tetra-, etc.), since the multithia cation radical or dication once formed could be stabilized more than the dithia dication and play an important role in development of a new field in organosulfur chemistry. A clear-cut example of transannular interaction between more than three sulfur atoms in multithia compounds has been hitherto unknown, except for our recent result.[10]

We now report the direct observation of transannular sulfur-sulfur bond formation of a new sulfur-bridged dithiametacyclophane, 1,11-(methanothiomethano)-5*H*,7*H*-dibenzo[*b*,*g*]-[1,5]dithiocin (**1**), in the reaction of **1** and its sulfoxides with concentrated sulfuric-d_2 acid (concentrated D_2SO_4) by 400-MHz ^1H and ^{13}C NMR spectroscopy, a new type of acid-catalyzed oxygen transfer in these reactions, and the first isolation of the dicationic salt of **1**. We also describe evidence for an intramolecular sulfur-sulfur interaction of 2,6-bis[(methylthio)methyl]-phenyl phenyl sulfide (**7**) was an acyclic analogue of **1** in the reactions of the corresponding sulfoxides with concentrated H_2SO_4

(1) Wilson, G. S.; Swanson, D. D.; Klug, J. T.; Glass, R. S.; Ryan, M. D.; Musker, W. K. *J. Am. Chem. Soc.* **1979**, *101*, 1040-1042.
(2) Asmus, K.-D. *Acc. Chem. Res.* **1979**, *12*, 436-442.
(3) (a) Musker, W. K.; Wolford, T. L.; Roush, P. B. *J. Am. Chem. Soc.* **1978**, 100, 6416-6421. (b) Musker, W. K. *Acc. Chem. Res.* **1980**, *13*, 200-206.
(4) Doi, J. T.; Musker, W. K. *J. Am. Chem. Soc.* **1978**, *100*, 3533-3536.
(5) Furukawa, N.; Kawada, A.; Kawai, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1151-1152.
(6) Furukawa, N.; Kawada, A.; Kawai, T.; Fujihara, H. *J. Chem. Soc., Chem. Commun.* **1985**, 1266-1267.
(7) Fujihara, H.; Kawada, A.; Furukawa, N. *Heterocycles* **1986**, *24*, 17-20.
(8) Fujihara, H.; Kawada, A.; Furukawa, N. *J. Org. Chem.* **1987**, *52*, 4254-4257.
(9) (a) Fujihara, H.; Akaishi, R.; Furukawa, N. *J. Chem. Soc., Chem. Commun.* **1987**, 930-931. (b) Iwasaki, F.; Toyoda, N.; Akaishi, R.; Fujihara, H.; Furukawa, N., to be submitted.
(10) Fujihara, H.; Chiu, J.-J.; Furukawa, N. *J. Chem. Soc., Chem. Commun.* **1986**, 1359-1360.

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Table I. NMR Data for **1–4** and **6**[a]

compd	chemical shift, δ	
	^{1}H	^{13}C
1	3.89, 4.94 (AB q, J = 14 Hz, 8 H), 7.12–7.20 (m, 6 H)	41.0, 128.5, 130.2, 148.0
2	3.87, 4.93 (AB q, J = 14 Hz, 4 H), 4.29, 5.54 (AB q, J = 12 Hz, 4 H), 7.22 (d, J = 8 Hz, 2 H), 7.28 (t, J = 8 Hz, 2 H), 7.54 (d, J = 8 Hz, 2 H)	40.1, 64.9, 129.8, 130.6, 131.4, 135.3, 138.1, 148.0
3	3.88, 5.00 (AB q, J = 14 Hz, 4 H), 4.52, 4.98 (AB q, J = 14 Hz, 4 H), 7.05–7.21 (m, 6 H)	40.1, 57.1, 129.8, 130.0, 132.8, 134.4, 138.4, 146.7
4	4.11, 4.63 (AB q, J = 17 Hz, 8 H), 7.16 (d, J = 8 Hz, 4 H), 7.38 (t, J = 7 Hz, 2 H)	43.6, 126.3, 134.0, 140.4, 140.7
6[b]	4.65, 5.20 (AB q, J = 17 Hz, 8 H), 7.39–7.98 (m, 6 H)	42.5, 131.4, 137.2, 139.8

[a] ^{1}H NMR (400 MHz, **6** is 60 MHz) data for **1–3** in $(CD_3)_2SO$; **6** in CD_3CN relative to Me_4Si. ^{13}C NMR (25 MHz) data for **1–3** in $CDCl_3$; **6** in CD_3CN relative to Me_4Si. All data for **4** in D_2SO_4 relative to sodium 4,4-dimethyl-4-silapentanesulfonate (DSS). [b] The difference of chemical shifts between **4** and **6** is probably due to a solvent effect.

and in electrochemical oxidation.

Results and Discussion

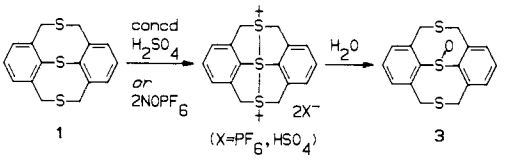
Dication of Cyclic Trithia Compounds. When the sulfoxide **2** was dissolved in concentrated D_2SO_4 (98%) at room temperature, the solution became pale yellow. The reaction was followed by both ^{1}H and ^{13}C NMR spectroscopy. In the ^{1}H NMR spectrum, four methylene signals adjacent to the sulfinyl and the sulfenyl groups for **2** in $(CD_3)_2SO$ disappeared and new AB quartet peaks appeared in D_2SO_4, which must be the benzylic methylene protons of **4**; while in the ^{13}C NMR spectrum, two signals due to the corresponding methylene carbon atoms of **2** in $CDCl_3$ coalesced into one signal in D_2SO_4. These spectra did not change in 24 h at room temperature. The spectral data are listed in Table I. These results indicate that **2** is converted into the dication **4**. Surprisingly, however, on treatment of the D_2SO_4 solution of **2** with ice–H_2O, the sulfoxide **3** was obtained exclusively in 85% isolated yield, and none of the starting sulfoxide **2** was recovered (Scheme I).

Dissolution of the sulfoxide **3** in concentrated D_2SO_4 also led to the formation of the dication **4** as determined by ^{1}H and ^{13}C NMR spectroscopy. Hydrolysis of the D_2SO_4 solution of **3** gave, as expected, the starting sulfoxide **3** in 87% yield. In order to confirm the oxygen exchange by an ^{18}O tracer experiment, ^{18}O-labeled compound **3a** (74.7% ^{18}O excess) was prepared and dissolved in concentrated H_2SO_4. Upon treatment with ice–H_2O, no ^{18}O was found in the recovered *S*-oxide (confirmed by mass spectrometry) (Scheme I). This result demonstrates that the oxygen-exchange reaction actually took place in the reaction.

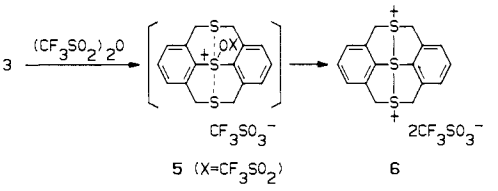
These results reveal that the oxygen migration from the benzylic sulfur to the arylic one in **2** in concentrated H_2SO_4 proceeds via the initial formation of dication **4** on which the H_2O molecule attacks the central arylic sulfur atom. It is a previously unknown type of reaction and a new oxygen-transfer process, since in the previous experiments involving the acid-catalyzed oxygen transfer from sulfoxides to sulfides, the migration took place solely from the arylic sulfur atom to the alkyl sulfur atom.[7,10,11] This unusual behavior of the dication **4** as compared with the other acyclic system **11** (vide infra) or even dibenzodithiocin[7,11c] can be explained in terms of the rigidness of the dication **4**. The S–S–S bond in dication **4** forms a sulfurane structure under the present reaction conditions to give a hypervalent bond. This hypervalent bond as shown in Scheme I is orthogonal to the π-orbitals of the two phenyl rings in **4**. Therefore, the positive charge on the central sulfur atom cannot be stabilized by resonance with the two phenyl rings. Thus, the positive charge should be concentrated preferentially on the central arylic sulfur atom rather than the benzylic sulfur atoms.

The dication **4** was also formed upon reaction of the sulfide **1** with concentrated D_2SO_4, since the ^{1}H and ^{13}C NMR chemical shifts of **1** in concentrated D_2SO_4 observed agreed well with those for **4** obtained from **2** and **3**. ESR signals were not observed from the H_2SO_4 solution of **1**. Treatment of the D_2SO_4 solution of **1** with H_2O afforded again the *S*-oxide **3** in 87% yield, and none of the sulfide **1** or the sulfoxide **2** was obtained (Scheme II). On the other hand, the reaction of **1** with 2 equiv of $NOPF_6$, a one-electron-oxidizing agent, in CH_2Cl_2 also gave the dication $(PF_6)_2$ salt, which on treatment with H_2O again resulted in the formation of sulfoxide **3** (Scheme II). This result suggests that the reaction of **1** with concentrated H_2SO_4 may proceed via a two-electron-transfer process.[12] These findings obviously demonstrate that the three sulfur atoms in the trithia compound participate transannulary in the stabilization of a positive charge developed on the one sulfur atom and, hence, indicate that **1–3** are converted into a common dication such as **4**.

Scheme II



Scheme III

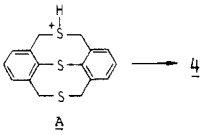


Although we could obtain the crystalline bis(hydrogen sulfate) salt of dication **4**, **4** could not be dissolved in general organic solvents. The dication salt of **1** could also be prepared by adding a solution of trifluoromethanesulfonic anhydride $[(CF_3SO_2)_2O$ (Tf_2O); 1 equiv] in anhydrous CH_2Cl_2 to a solution of sulfoxide **3** (1 equiv) in anhydrous CH_2Cl_2 under argon at −20 °C. This reaction likely proceeds through the initial formation of the trifloxysulfonium cation **5**, which subsequently is converted into the dication salt **6** by an intramolecular nucleophilic displacement of the triflate ion ($CF_3SO_3^-$) by the second remote sulfur atom as shown in Scheme III. The ^{1}H and ^{13}C NMR spectra of **6** in CD_3CN (Table I) are clearly consistent with the assigned structure.

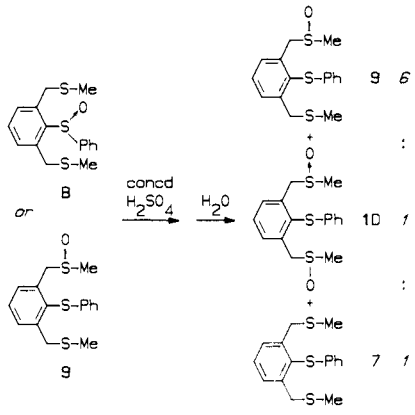
Intramolecular S–S Interaction in Acyclic Trithia Compounds. We have also studied the interaction of sulfur–sulfur atoms in acyclic trithia compounds 2,6-bis[(methylthio)methyl]phenyl phenyl sulfoxide (**8**) and 2-[(methylsulfinyl)methyl]-6-[(methylthio)methyl]phenyl phenyl sulfide (**9**).

(11) (a) Numata, T.; Oae, S. *Int. J. Sulfur Chem., Part A.* **1971**, *1*, 6–11. (b) Ruffato, V.; Miotti, U. *Gazz. Chim. Ital.* **1978**, *108*, 91–96. (c) Ohkata, K.; Okada, K.; Akiba, K. *Tetrahedron Lett.* **1985**, *26*, 4491–4494.

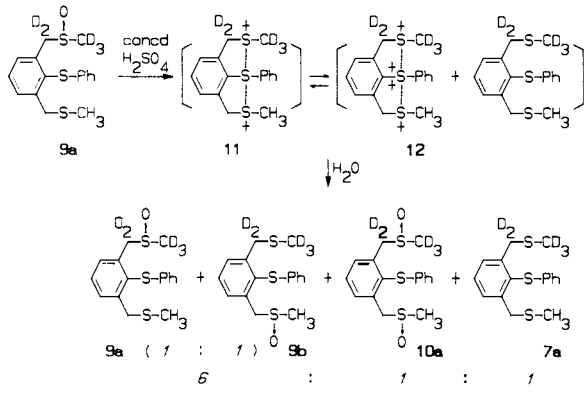
(12) One reviewer pointed out that the other possible mechanism for the formation of the dication **4** in the reaction of **1** with concentrated H_2SO_4 can be explained in terms of the initial generation of sulfidonium cation **A**.



Scheme IV

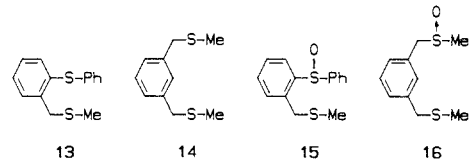


Scheme V



When **8** was treated with concentrated D_2SO_4 (98%) at room temperature, the solution became yellow. The ^1H NMR spectrum of this solution showed signals at δ 2.30–2.90 (br m, 6 H, CH_3), 4.07–4.30 (br m, 4 H, CH_2), and 6.80–7.70 (m, 8 H, ArH). Hydrolysis of the D_2SO_4 solution of **8** gave three products in 80% isolated yield, which were separated by preparative liquid chromatography to give compounds **9**, **10**, and **7** in a 6:1:1 ratio, respectively, and none of the sulfoxide **8** was obtained (Scheme IV).

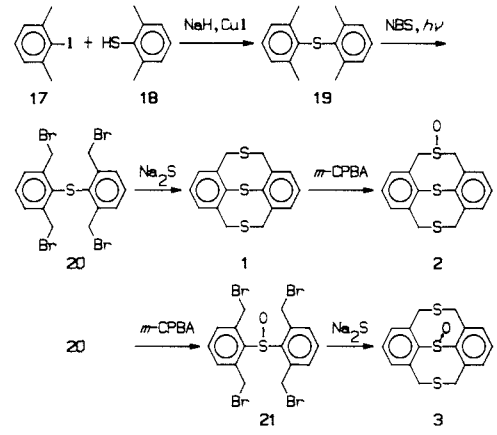
On dissolution of **9** in concentrated D_2SO_4, the ^1H NMR chemical shifts observed were found to be analogous to those of the D_2SO_4 solution of **8**. Similar treatment of the pentadeuteriated monosulfoxide of **9**, **9a**, in D_2SO_4 led to analogous changes in the ^1H NMR spectra and a mixture of monosulfoxide, disulfoxide, and sulfide in a 6:1:1 ratio was obtained by hydrolysis of the D_2SO_4 solution of **9a**. The ^1H NMR spectrum of the monosulfoxide obtained indicated that it was a 1:1 mixture of **9a** and the pentadeuteriated isotopemer **9b** and also that no H–D exchange with the solvent H_2SO_4 took place during the reaction (Scheme V). Dithioether monosulfoxides such as 2-[(methylthio)methyl]phenyl phenyl sulfoxide (**15**) and 1-[(methylsulfinyl)methyl]-3-[(methylthio)methyl]benzene (**16**) were decomposed by concentrated H_2SO_4. These results demonstrate that the three sulfur atoms



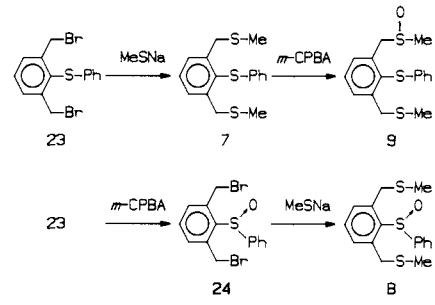
in **8** and **9** participate in the stabilization of a positive charge developed on one sulfur atom and suggest that **8** and **9** are converted initially into a dication **11**. The mechanism for formation of the disulfoxide **10** and the sulfide **7** is ambiguous; however, formation of the tetracation **12** formed by disproportionation of the dication **11** is a possible process (Scheme V).

The importance of neighboring group participation in electrochemical oxidation of sulfides has been demonstrated by Glass

Scheme VI



Scheme VII



and Wilson.[13] They reported that the peak potential is lowered when the neighboring group containing lone electron pairs can interact with the sulfur atom in the sulfide. For example, neighboring sulfide, carboxylate, and alcohol groups facilitate an anodic oxidation of the sulfide in 2-endo-substituted 6-*endo*-(methylthio)bicyclo[2.2.1]heptanes.

In order to further support the existence of an S–S interaction in trithia compound **7**, the electrochemical oxidation of **7** was studied by cyclic voltammetry. Peak potentials of the first oxidation peak were determined at a Pt electrode (200 mV/s scan rate) in acetonitrile–0.1 M *n*-Bu_4NClO_4 vs saturated calomel electrode. The peak potentials (E_p) for **7** and other sulfides showed the following values: **7**, 1.15 V; 2-[(methylthio)methyl]phenyl phenyl sulfide (**13**), 1.34 V; 1,3-bis[(methylthio)methyl]benzene (**14**), 1.82 V; diphenyl sulfide (PhSPh), 1.55 V. All of the oxidations were irreversible at scan rates of 1 V/s. There is a dramatic shift in the peak potential toward more cathodic values for the sulfide **7**. Comparison of the trithia compound **7** with a monothia compound such as diphenyl sulfide shows a peak potential 400 mV more cathodic for the former, indicating that **7** is oxidized more readily. Thus, the trithia compound **7** exhibits large negative potential shifts that are thought to be related to neighboring group interactions.

Experimental Section

^1H and ^{13}C NMR spectra were measured on a Hitachi R-600 FT-NMR or a JEOL JNM GX-400 and FX-100 spectrometer. IR spectra were obtained on a Jasco A-3 spectrometer. Mass spectra were taken with a Hitachi RMU-6MG or a JEOL HX-100 mass spectrometer. Elemental analyses were carried out by the Chemical Analysis Center at this university. For cyclic voltammetry measurements, a Hokuto Denko Co. Model HB-104 electrochemical apparatus was used in conjunction with a Yokokawa Co. Model 3025A X-Y recorder.

All reagents were obtained from Wako Pure Chemical Industries Ltd., Tokyo Kasei Co. Ltd., or Aldrich Chemical Co. [^{18}O]H_2O was supplied by Amersham International plc. Nitrosyl hexafluorophosphate ($NOPF_6$) was supplied by Morton Thiokol, Inc. The reagents used as reaction solvents were further purified by general methods.

(13) (a) Glass, R. S.; Duchek, J. R.; Klug, J. T.; Wilson, G. S. *J. Am. Chem. Soc.* **1977**, *99*, 7349–7350. (b) Glass, R. S.; Coleman, B. R.; Prabhu, U. D. G.; Setzer, W. N.; Wilson, G. S. *J. Org. Chem.* **1982**, *47*, 2761–2764.

2,6-Dimethyliodobenzene (**17**)[14] and 2,6-dimethylbenzenethiol (**18**)[15] were prepared according to the methods reported in the literature. **17**: ^{1}H NMR ($CDCl_3$) δ 2.47 (s, 6 H, CH_3), 7.07 (br s, 3 H, ArH). **18**: ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 6 H, CH_3), 3.20 (s, 1 H, SH), 7.01 (br s, 3 H, ArH).

Synthesis of Cyclic and Acyclic Trithia Compounds. The cyclic trithia compounds **1–3** and the acyclic trithia compounds **7–9** were synthesized by general methods as illustrated in Schemes VI and VII. The X-ray data of **1** and **8** will be reported.[16]

Cyclic Trithia Compound 1. To a solution of 2,6-dimethylbenzenethiol (**18**; 4.76 g, 34.5 mmol) and 60% sodium hydride (NaH; 1.38 g, 34.5 mmol) in hexamethylphosphoric triamide (HMPA; 40 mL) was added CuI (4.55 g) under a nitrogen atmosphere. Then 2,6-dimethyliodobenzene (**17**; 7.15 g, 30.8 mmol) was added to this mixture. After being kept at 105 °C for 17 h, the mixture was poured into water, and the product was extracted with ether. The organic layer was separated and dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was separated by column chromatography (silica gel; eluent, hexane) to give 6.08 g (82% yield) of bis(2,6-dimethylphenyl) sulfide (**19**) [mp 81–82 °C; ^{1}H NMR ($CDCl_3$) δ 2.22 (s, 12 H, CH_3), 7.01 (br s, 6 H, ArH)]. A solution of **19** (8.47 g, 35 mmol) and *N*-bromosuccinimide (NBS; 25 g, 140 mmol) in dry carbon tetrachloride (120 mL) was stirred under a nitrogen atmosphere at 15 °C while being irradiated with a high-pressure mercury lamp for 46 h. The resulting solid was separated by filtration, and the filtrate was concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel; eluent, benzene) to give 9.18 g (47% yield) of bis[2,6-bis(bromomethyl)phenyl] sulfide (**20**) [mp 155–156 °C; ^{1}H NMR ($CDCl_3$) δ 4.61 (br s, 8 H, CH_2), 7.12–7.68 (m, 6 H, ArH)]. To a solution of **20** (7.81 g, 14 mmol) in ethanol (400 mL) was added dropwise a solution of sodium sulfide ($Na_2S{\cdot}9H_2O$; 6.72 g, 28 mmol) in H_2O (50 mL); the mixture was refluxed for 10 h. After evaporation of the solvent, the residue was extracted with $CHCl_3$. The crude product was purified by column chromatography (silica gel; eluent, benzene) to give the cyclic sulfide **1** in 31% yield. The sulfide **1** was further purified by preparative liquid chromatography (Japan Analytical Co. Ltd.; Model LC-09): mp 264 °C; MS, m/z 302 (M^+). Anal. Calcd for $C_{16}H_{14}S_3$: C, 63.53; H, 4.66; S, 31.80. Found: C, 63.38; H, 4.71; S, 31.82. For spectral data, see Table I.

Monosulfoxide 2. To a stirred solution of sulfide **1** (200 mg, 0.66 mmol) in CH_2Cl_2 (35 mL) at 0 °C was added 85% *m*-chloroperbenzoic acid (*m*-CPBA; 161 mg, 0.79 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at room temperature for 3 h and treated with anhydrous ammonia. The resulting solid was separated by filtration, and the filtrate was evaporated in vacuo to afford the crude sulfoxide, which was purified by column chromatography (silica gel; eluent, $CHCl_3$) and further purified by preparative liquid chromatography to give the monosulfoxide **2**: mp 289 °C dec; IR (KBr) 1029 cm^{-1}; exact mass calcd for $C_{16}H_{14}OS_3$ 318.0207, found 318.0198. For spectral data, see Table I.

Monosulfoxide 3. To a stirred solution of bis[2,6-bis(bromomethyl)-phenyl] sulfide (**20**; 4.8 g, 8.6 mmol) in CH_2Cl_2 (80 mL) at 0 °C was added 85% *m*-CPBA (1.75 g, 8.6 mmol) in CH_2Cl_2 (50 mL). The mixture was stirred at room temperature for 4 h. Anhydrous ammonia was bubbled into the reaction mixture. The resulting solid was separated by filtration, and the filtrate was concentrated under vacuum. The mixture was separated by column chromatography (silica gel; eluent, $CHCl_3$) giving bis[2,6-bis(bromomethyl)phenyl] sulfoxide (**21**) as a solid, which was used without further purification: IR (KBr) 1050 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.90 (br s, 8 H, CH_2), 7.25–7.92 (m, 6 H, ArH). To a solution of **21** (7.25 g, 12.6 mmol) in ethanol (500 mL) was added dropwise a solution of sodium sulfide (6.36 g, 26.5 mmol) in H_2O (100 mL); the mixture was refluxed for 10 h. After evaporation of the solvent, the residue was purified by column chromatography (silica gel; eluent, $CHCl_3$) and further purified by preparative liquid chromatography to give the sulfoxide **3**: mp 290–291 °C dec; IR (KBr) 1060 cm^{-1}; exact mass calcd for $C_{16}H_{14}OS_3$ 318.0207, found 318.0185. For spectral data, see Table I.

2,6-Bis[(methylthio)methyl]phenyl Phenyl Sulfide (7). 2,6-Dimethylphenyl phenyl sulfide (**22**) and 2,6-bis(bromomethyl)phenyl phenyl sulfide (**23**) were prepared by the same procedures as **19** and **20**: **22**: liquid; ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 6 H, CH_3), 6.81–7.31 (m, 8 H, ArH). **23**: liquid; ^{1}H NMR ($CDCl_3$) δ 4.69 (s, 4 H, CH_2), 6.85–7.68 (m, 8 H, ArH). A mixture of **23** (6 g, 16 mmol), sodium methanethiolate (2.5 g, 36 mmol), and tetrabutylammonium bromide (100 mg) in benzene (60 mL)–water (40 mL) was stirred at 50 °C for 12 h. The organic layer was separated, washed with water, and dried over $MgSO_4$. After removal of the solvent and column chromatography (alumina; eluent, *n*-hexane–benzene, 3/1) sulfide **7** was obtained as a colorless liquid in 81% yield: ^{1}H NMR ($CDCl_3$) δ 1.99 (s, 6 H, CH_3), 3.88 (s, 4 H, CH_2), 6.83–7.50 (m, 8 H, ArH); MS, m/z 306 (M^+). Anal. Calcd for $C_{16}H_{18}S_3$: C, 62.70; H, 5.91. Found: C, 62.45; H 5.88.

2,6-Bis[(methylthio)methyl]phenyl Phenyl Sulfoxide (8). Preparation of 2,6-bis(bromomethyl)phenyl phenyl sulfoxide (**24**) was performed as described for **21**: **24**: liquid; IR (neat) 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.69, 4.90 (AB q, J = 10 Hz, 4 H, CH_2), 7.31–7.72 (m, 8 H, ArH). A mixture of sulfoxide **24** (3.11 g, 8 mmol), sodium methanethiolate (1.4 g, 20 mmol), and tetrabutylammonium bromide (100 mg) in benzene (50 mL)–water (30 mL) was stirred vigorously at 50 °C for 12 h. The organic layer was separated, washed with water, dried over $MgSO_4$, and evaporated to give the sulfoxide **8** in 83% yield. The sulfoxide was purified by column chromatography (silica gel; eluent, $CHCl_3$) and further purified by preparative liquid chromatography: mp 78–79 °C; IR (KBr) 1050 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.94 (s, 6 H, CH_3), 3.71, 4.18 (AB q, J = 14 Hz, 4 H, CH_2), 7.30–7.73 (m, 8 H, ArH). Anal. Calcd for $C_{16}H_{18}OS_3$: C, 59.58; H, 5.62. Found: C, 59.20; H, 5.65.

2-[(Methylsulfinyl)methyl]-6-[(methylthio)methyl]phenyl Phenyl Sulfide (9). Monosulfoxide **9** and 2,6-bis[(methylsulfinyl)methyl]phenyl phenyl sulfide (**10**) were prepared by the same procedures as **2**. **9**: liquid; IR (neat) 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.00 (s, 3 H, CH_3), 2.46 (s, 3 H, CH_3), 3.89 (s, 2 H, CH_2), 4.08, 4.34 (AB q, J = 13 Hz, 2 H, CH_2), 6.78–7.62 (m, 8 H, ArH); MS, m/z 322 (M^+). **10**: liquid; IR (neat) 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.49 (d, 6 H, CH_3), 4.23 (m, 4 H, CH_2), 6.78–7.62 (m, 8 H, ArH).

2-[(Methylthio)methyl]phenyl Phenyl Sulfide (13) and 2-[(Methylthio)methyl]phenyl Phenyl Sulfoxide (15).[17] Experimental procedures were as described for **7** and **8**. **13**: liquid; ^{1}H NMR ($CDCl_3$) δ 2.03 (s, 3 H, CH_3), 3.87 (s, 2 H, CH_2), 7.18–7.37 (m, 9 H, ArH); MS, m/z 246 (M^+).

1,3-Bis[(methylthio)methyl]benzene (14) and 1-[(Methylthio)-methyl]-3-[(methylsulfinyl)methyl]benzene (16). Compounds **14** and **16** were prepared by the same methods as **7** and **9**. **14**: ^{1}H NMR ($CDCl_3$) δ 1.99 (s, 6 H, CH_3), 3.66 (s, 4 H, CH_2), 7.11–7.32 (m, 4 H, ArH). **16**: IR (neat) 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.00 (s, 3 H, CH_3), 2.46 (s, 3 H, CH_3), 3.67 (s, 2 H, CH_2), 3.97 (s, 2 H, CH_2), 7.12–7.38 (m, 4 H, ArH).

^{18}O-Labeled Sulfoxide 3a. A solution of **4** in H_2SO_4 was poured into cooled anhydrous diethyl ether, and the salt of **4** was obtained as white hygroscopic crystals. Treatment of the salt with $H_2{}^{18}O$ (98.4 atom %) gave the ^{18}O-labeled compound **3a**. The ^{18}O content was 74.7 atom % by mass spectrometry.

Deuteriated Sulfoxide 9a. A mixture of sulfoxide **9** (100 mg) in tetrahydrofuran (2 mL) and a 40% solution of sodium deuterium oxide (20 mL) was stirred under argon at 85 °C for 10 h. The mixture was extracted with chloroform. The organic layer was dried over anhydrous $MgSO_4$. After the solvent was removed, the residue was purified by column chromatography (silica gel, $CHCl_3$) and further purified by preparative liquid chromatography to give the deuteriated sulfoxide **9a**. The content of deuterium atom was more than 95 atom % by ^{1}H NMR spectroscopy.

Reaction of Sulfoxides with Concentrated H_2SO_4. Sulfoxide **2** was dissolved in concentrated D_2SO_4 (98%) at room temperature. The reaction was followed immediately by ^{1}H and ^{13}C NMR spectroscopy. The D_2SO_4 solution was then poured into ice–water, and the solution was neutralized with dilute sodium hydroxide solution. The solution was extracted with chloroform and evaporated in vacuo. The products were purified by preparative liquid chromatography to afford the sulfoxide **3** in 85% yield.

Formation of Sulfoxide 3 in the Reaction of 1 with 2 Equiv of $NOPF_6$. A solution of $NOPF_6$ (23 mg, 0.13 mmol) in CH_2Cl_2 (5 mL) was added to **1** (20 mg, 0.066 mmol) in CH_2Cl_2 (5 mL) at −70 °C, and after 2 h the solution was allowed to come to room temperature and stirred an additional 3 h. After removal of the solvent, the pale yellow solid was treated with a saturated aqueous sodium bicarbonate solution. The resulting mixture was extracted with $CHCl_3$. The combined organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum to afford the monosulfoxide **3**.

Reaction of 3 with $(CF_3SO_2)_2O$. To a stirred solution of sulfoxide **3** (100 mg, 0.31 mmol) in anhydrous CH_2Cl_2 (20 mL) was added dropwise a solution of Tf_2O (89 mg, 0.32 mmol) in anhydrous CH_2Cl_2 (5 mL) at −20 °C. After the addition was complete, the mixture was stirred for 3 h, and the white precipitates were filtered and washed with anhydrous CH_2Cl_2, giving salts **6** in 84% yield: mp 134–135 °C dec; field-desorption (FD) mass spectrum, m/z 601 (MH^+), 451 (M − OTf^+), 302 (M −

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2OTf$^+$), 151 (doubly charged cation). For spectral data, see Table I.

Electrochemical Study. Cyclic voltammetry was performed with 10-mL portions of 2 mM solutions of sulfide in CH_3CN and 0.1 M tetrabutylammonium perchlorate. The CV cell was equipped with a Iwaki Glass SCE reference electrode in a reference well separated from the analyte by a cracked glass bead junction, a Pt wire counter electrode, and a Pt disk working electrode polished before use with alumina. All sulfides studied were purified by preparative liquid chromatography.

Registry No. 1, 112399-00-5; **2**, 112421-52-0; **3**, 112399-01-6; **3a**, 112399-02-7; **4**, 112399-04-9; **6**, 112399-05-0; **7**, 108428-22-4; **8**, 108428-23-5; **9**, 108428-24-6; **9a**, 112399-06-1; **10**, 108428-25-7; **13**, 112399-07-2; **14**, 112399-08-3; **15**, 112335-85-0; **16**, 112399-09-4; **17**, 608-28-6; **18**, 118-72-9; **19**, 52805-90-0; **20**, 112399-10-7; **21**, 112399-11-8; **22**, 54088-93-6; **23**, 112399-12-9; **24**, 112399-13-0; PhSH, 108-98-5; MeSH·Na, 5188-07-8; *o*-$PhSC_6H_4CH_2Br$, 37660-43-8; *m*-$(CH_2Br)_2C_6H_4$, 626-15-3.

Communications to the Editor

A Peroxide Model Reaction for Placental Aromatase

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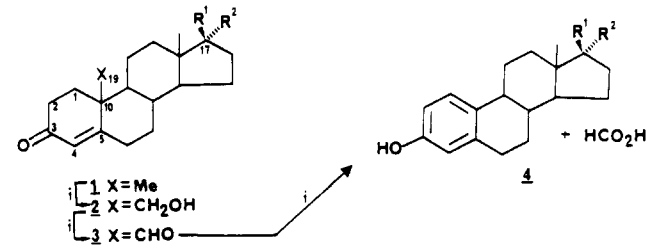
Received October 5, 1987

The conversion of androgens **1** to estrogens **4** is catalyzed by the cytochrome P-450 enzyme system estrogen synthetase (aromatase). The mechanism of this transformation has recently attracted attention both because of the chemical novelty of the reaction and the potential medical importance of aromatase inhibitors.[1] Three separate steps are apparently involved in the transformation (see Scheme I), and formic acid is ultimately produced as a byproduct. Three molar equivalents of NADPH and O_2 are required overall.[2] Two stereospecific hydroxylations occur at C-19 to afford the 19-OH **2** and 19-oxo **3** intermediates. The first equivalent of oxygen consumed is incorporated into compound **3** and eventually formic acid.[3] The third equivalent of oxygen consumed also is incorporated into formic acid[4] as is one of the original C-19 hydrogens. The 1β,2β-hydrogens of compound **3** are lost to the aqueous medium.[5]

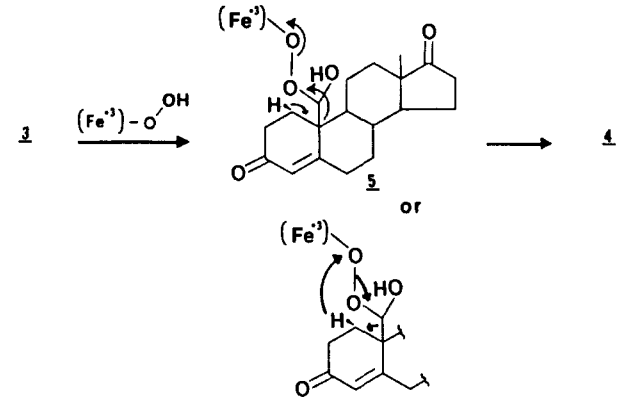
Despite intensive investigation, the nature of the third oxidative step catalyzed by aromatase remains unknown. Theories involving 2β-hydroxylation,[6] Baeyer-Villiger oxygen insertion,[4] and 4,5-epoxidation[7] have been shown to be unlikely. A proposal suggesting heme ferric peroxide attack of the 19-oxo group to yield the corresponding α-hydroxyferric peroxide **5** (see Scheme II) has remained viable but not well studied.[8] The peroxide **5** was envisioned to fragment either by a hydride transfer[8] or proton shift[9]

Scheme I[a]



[a] (i) NADPH, O_2; a: R^1 = O, R^2 = O; b: R^1 = OH, R^2 = H.

Scheme II



pathway to produce the aromatic ring. Recently, we sought to model this intermediate and synthesized the corresponding α-methoxyhydroperoxide **6** by ozonolysis of the appropriate vinyl ether.[10] This relatively unstable compound failed to afford estrone under a variety of conditions. One possible explanation for the observed lack of reactivity was the absence of a driving force for 1β-hydrogen removal. It was hypothesized that concomitant enolization of the 3-ketone could lower this energy barrier.[10] We desired to test this idea by exploring the reactivity of a chemical model such as compound **7**.

It was expected that ozonolysis of the appropriate 10β-vinyl analogue to diene **10** in a manner employed[10] for the synthesis of peroxide **6** would be nonselective. Instead we envisaged the reaction of hydrogen peroxide with the dienol ether **8** as a route to the hydroperoxide **7** (R^1 = TBDMS, R^2 = H).[11] Indeed treatment of the 19-aldehyde **3a** with excess 30% hydrogen peroxide in the absence of strong base (MeOH, $NaHCO_3$, 4 °C, 2 h) led to rapid and stereospecific epoxidation to afford in 60%

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