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A New Type of Reductive Cleavage of Disulfide in Quadruply ortho-Substituted Diphenyl Disulfide by Neighboring Thiolate Anion

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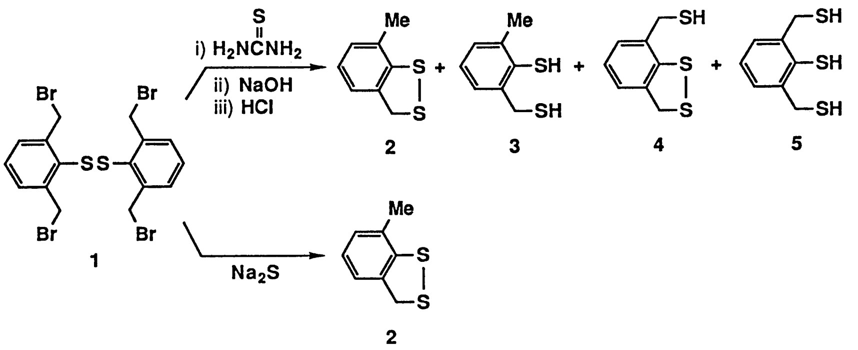
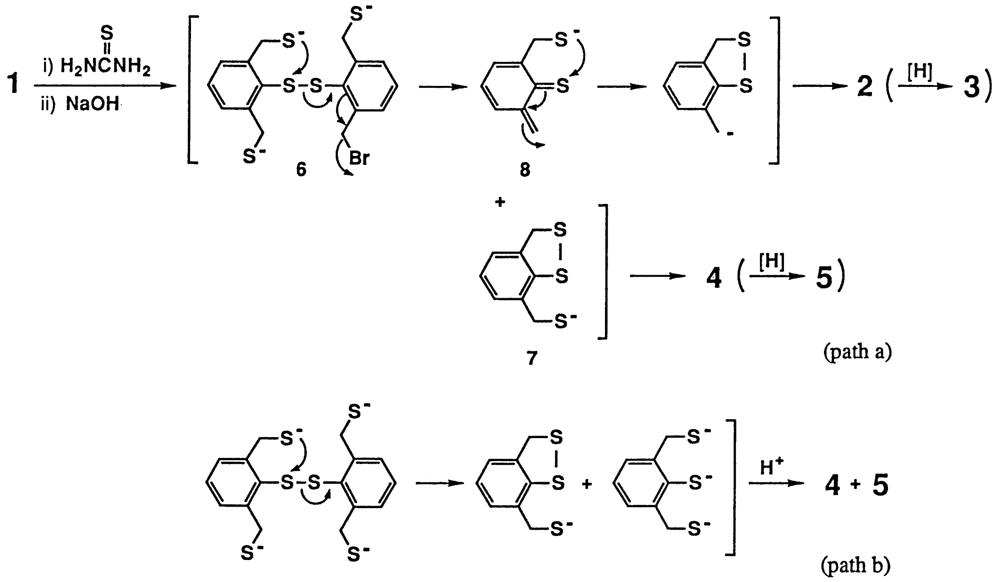
Synopsis. The reaction of bis[2,6-bis(bromomethyl)-phenyl] disulfide with thiourea or sodium sulfide showed an unusual reductive cleavage of disulfide linkage with elimination of bromine by neighboring-group participation of the generated thiolate anion. Its reaction gave the structurally intriguing thiols which indicated the facile anodic oxidation.

Studies of intramolecular interactions and reactions have provided numerous informations on the structures and reactivities of linear and cyclic compounds containing sulfur atoms.1—3) It has been reported that the oxidative cleavage of disulfides having neighboring nucleophiles (e.g., amide) provides a facile route to the formation of heterocyclic intermediates and products.4) The intramolecular redox reactions between disulfides and thiols are of considerable important from a biological point of view.5) Meanwhile, we described an unusual sulfur extrusion in a new quadruply ortho-bridged biphenyl compounds with disulfide linkage, methanodithiomethano-bridged dibenzotrithionin, via the sulfur-sulfur bond formation.6) Its analogous compounds exhibit interesting physical and chemical properties on account of their unique arrangement of functional groups and heteroatoms in space. This paper presents that the reaction of bis[2,6-bis(bromomethyl)phenyl] disulfide (**1**) with thiourea gave the structurally interesting redox products, thiol-disulfide and trithiol, with the elimination of bromine. The electrochemical and chemical oxidations of their thiols are also described.

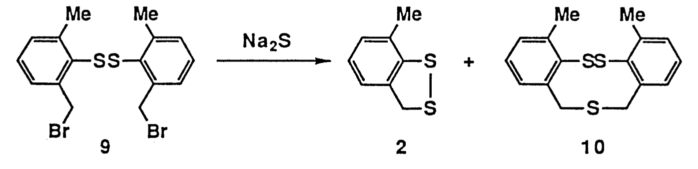
The compound **1** was prepared by photobromination using *N*-bromosuccinimide of bis(2,6-dimethyl-



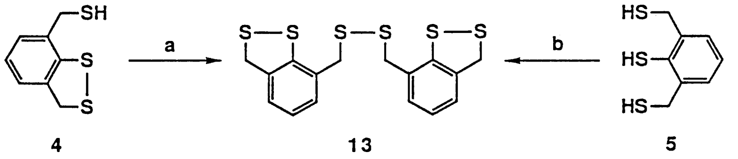
Scheme 1.



Scheme 2.



Scheme 3.



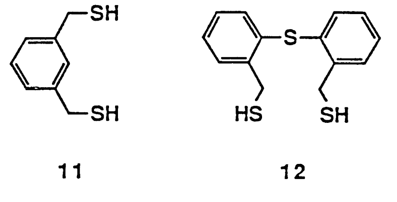
Scheme 4. a) pyridine in $CHCl_3$ under air, b) I_2, Et_3N in $CHCl_3$.

phenyl) disulfide (**14**) which was obtained by oxidation of 2,6-dimethylbenzenethiol with I_2. The reduction of disulfide linkage in **1** was found in the following reactions (Scheme 1). Treatment of **1** with thiourea in ethanol, followed by adding with aqueous sodium hydroxide solution, resulted in formation of four products, disulfide **2** (19%), dithiol **3** (27%), thiol-disulfide **4** (18%), and trithiol **5** (25%). The plausible mechanism for formation of the compounds **2**—**5** can be explained as follows (Scheme 2). The reaction of **1** with thiourea produces the thiol **6** via isothiouronium salt whose third stage proceeds intramolecularly and leads to formation of the cyclic disulfide **7** and thione intermediate **8** like quinodimethane with the elimination of bromine. Subsequently, **8** converts to **2** and **3**, and **7** changes finally to **4** and **5**, respectively (Scheme 2, path a). The path b in Scheme 2 is also conceivable mechanism for the formation of **4** and **5**.

On the other hand, when the compound **1** was allowed to react with Na_2S in the presence of tetrabutylammonium bromide as a phase-transfer catalyst in benzene-water at 80 °C for 8 h, disulfide **2** was obtained in 38% yield (Scheme 1). This reaction may proceed likely as shown in Scheme 2.

Meanwhile, bis(2-bromomethyl-6-methylphenyl) disulfide (**9**) was reacted with Na_2S to give the cyclic disulfide **2** (45%) and the nine-membered ring, dibenzotrithionin **10** (14%) (Scheme 3).

The electrochemical oxidations of thiols (**3**, **5**, **11**, and **12**) were studied by cyclic voltammetry. Peak potentials of the first oxidation peak were determined at a glassy carbon working electrode (scan rate; 100 $mV\,s^{-1}$) in CH_3CN-0.1 M $NaClO_4$ vs. Ag/0.01 M $AgNO_3$ as reference electrode (1 M=1 $mol\,dm^{-3}$). The peak potentials (E_p) showed the following values: 0.78 V for **3**, 0.75 V for **5**, 1.35 V for **11**, and 1.52 V for **12**. These anodic oxidations were irreversible at scan rates of 1 $V\,s^{-1}$. There are dramatic shifts in the peak potentials toward more cathodic values for the thiols **3** and **5**. Comparison of the thiols **5** with **11** showed a peak potential ca. 600 mV more cathodic for the former, indicating that **5** is oxidized more readily.



Structural Formula 1.

The oxidation of **4** in the presence of pyridine in chloroform under air at room temperature gave the oxidative dimer **13** in 74% yield (Scheme 4). Trithiol **5** also afforded the oxidation product **13** in 91% yield upon treatment with I_2 in the presence of triethylamine in chloroform at room temperature.

Experimental

^1H and ^{13}C NMR spectra were measured on Hitachi R-600 FT-NMR and Bruker AM 500 spectrometer. The IR spectra were obtained on JASCO A-3 spectrometer. Mass spectra were taken by Hitachi M-80B mass spectrometer. Elemental analyses were carried out by the Chemical Analytical Center at 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.

Bis(2,6-dimethylphenyl)disulfide (14). To a stirred solution of 2,6-dimethylbenzenethiol[3a)] (44.5 g, 0.32 mol) and triethylamine (32.6 g, 0.32 mol) in chloroform (500 ml) was added a solution of iodine (40.6 g, 0.16 mol) in chloroform (150 ml) at 0 °C. The whole mixture was stirred at room temperature for 1 h. The mixture was washed with aqueous sodium thiosulfate solution and the organic layer was dried over anhydrous $MgSO_4$. After evaporation of the solvent, the residue was purified by silica-gel column chromatography (eluent, hexane) to give the disulfide **14** in 89% yield. The compound **14** was recrystallized from hexane: White crystals; mp 103—104 °C; ^1H NMR ($CDCl_3$) δ=2.22 (s, 12H, CH_3) and 7.02 (br s, 6H, ArH). Found: C, 69.99; H, 6.57; S, 23.40%. Calcd for $C_{16}H_{18}S_2$: C, 70.02; H, 6.61; S, 23.36%.

Bis[2,6-bis(bromomethyl)phenyl]disulfide (1) and Bis(2-bromomethyl-6-methylphenyl)disulfide (9). A solution of disulfide **14** (7 g, 25.5 mmol) and *N*-bromosuccinimide (NBS; 18.2 g, 102 mol) in dry carbon tetrachloride (150 ml) was stirred under an Ar atmosphere at 15 °C while being irradiated with a high-pressure mercury lamp for 7 h. The resulting solid was separated by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica-gel column chromatography (eluent, hexane-$CHCl_3$=1 : 1) to afford the tetrabromide **1** in 11% and bisbromide **9** in 52% yields.

1: White crystals; mp 186.5—187 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ=4.42 (s, 8H, CH_2), 7.38 (t, *J*=8 Hz, 2H, ArH), and 7.45 (d, *J*=8 Hz, 4H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ=31.3, 131.2, 131.6, 134.4, and 143.5. Found: C, 32.60; H, 2.64%. Calcd for $C_{16}H_{14}Br_4S_2$: C, 32.57; H, 2.39%.

9: White crystals; mp 121—121.5 °C; MS *m/z* 432 (M^+); ^{1}H NMR ($CDCl_3$) δ=2.40 (s, 6H, CH_3), 4.25 (s, 4H, CH_2), and 7.22 (s, 6H, ArH). Found: C, 44.11; H, 3.61%. Calcd for $C_{16}H_{16}Br_2S_2$: C, 44.46; H, 3.73%.

Reaction of Bis[2,6-bis(bromomethyl)phenyl]disulfide (1) with Thiourea. A solution of **1** (750 mg, 1.25 mmol) and thiourea (490 mg, 6.40 mmol) in ethanol (500 ml) was stirred for 12 h under reflux. After concentration of the solution, 6% sodium hydroxide solution (1 l) was added to the residue. The mixture was refluxed for 8 h under an Ar atmosphere and then cooled in an ice-water bath; cooled aqueous hydrochloric acid was then added dropwise. The reaction mixture was extracted with chloroform and the extract was dried over $MgSO_4$. After removal of the solvent, the residue was separated by silica-gel column chromatography (eluent, hexane-$CHCl_3$=1 : 1) and further purified by preparative liquid chromatography to give disulfide **2** in 19%, dithiol **3** in 27%, thiol-disulfide **4** in 18%, and trithiol **5** in 25% yields. Yields of **2**—**5** are in 1/2 mol%.

2: Yellow oil; MS, *m/z* 168 (M^+); ^{1}H NMR (500 MHz, $CDCl_3$) δ=2.31 (s, 3H, CH_3), 4.49 (s, 2H, CH_2), 6.96 (d, *J*=7 Hz, 1H, ArH); 7.00 (t, *J*=7 Hz, 1H, ArH), and 7.09 (d, *J*=7 Hz, 1H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ=21.2, 44.1, 122.0, 125.5, 128.4, 132.7, 138.8, and 141.7. Found: C, 56.75; H, 4.75%. Calcd for $C_8H_8S_2$: C, 57.10; H, 4.79%.

3: Yellow oil; MS, *m/z* 170 (M^+); ^{1}H NMR (500 MHz, $CDCl_3$) δ=1.86 (t, *J*=7 Hz, 1H, SH), 2.40 (s, 3H, CH_3), 3.61 (s, 1H, SH), 3.67 (d, *J*=7 Hz, 2H, CH_2), 7.06 (t, *J*=7 Hz, 1H, ArH), 7.10 (d, *J*=7 Hz, 1H, ArH), and 7.13 (d, *J*=7 Hz, 1H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ=22.2, 29.2, 126.0, 127.0, 129.3, 130.1, 138.3, and 139.9. Found: C, 56.46; H, 5.82%. Calcd for $C_8H_{10}S_2$: C, 56.43; H, 5.92%.

4; Yellow oil; MS, *m/z* 200 (M^+); ^{1}H NMR (500 MHz, $CDCl_3$) δ=1.67 (t, *J*=7 Hz, 1H, SH), 3.75 (d, *J*=7 Hz, 2H, CH_2SH), 4.47 (s, 2H, CH_2), 7.04 (t, *J*=7 Hz, 1H, ArH), 7.10 (d, *J*=7 Hz, 1H, ArH), and 7.17 (d, *J*=7 Hz, 1H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ=28.9, 43.7, 123.4, 126.0, 127.2, 136.2, 140.5, and 141.4. Found: C, 47.92; H, 3.89%. Calcd for $C_8H_8S_3$: C, 47.96; H, 4.03%.

5: Yellow oil; MS, *m/z* 202 (M^+); ^{1}H NMR (500 MHz, $CDCl_3$) δ=1.88 (t *J*=7 Hz, 2H, SH), 3.92 (d *J*=7 Hz, 4H, CH_2), 4.10 (s, 1H, SH), 7.14 (t, *J*=7 Hz, 1H, ArH), and 7.21 (d, *J*=7 Hz, 2H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ=29.1, 126.0, 127.0, 128.4, 129.4, and 141.9. Found: C, 47.58; H, 4.94%. Calcd for $C_8H_8S_3$: C, 47.49; H, 4.98%.

Reaction of Bis[2,6-bis(bromomethyl)phenyl]disulfide (1) with Sodium Sulfide. To a solution of **1** (5 g, 8.5 mmol) and tetrabutylammonium bromide (0.27 g, 0.85 mmol) in benzene (1000 ml) and water (50 ml) was added a solution of sodium sulfide (6.36 g, 25.5 mmol) in water (150 ml). The reaction mixture was stirred at 80 °C for 8 h. The organic layer was separated, washed with water, and dried over $MgSO_4$. After removal of the solvent, the residue was separated by silica-gel column chromatography (eluent, $CHCl_3$) and further purified by preparative liquid chromatography to afford disulfide **2** in 38% yield. Yield of **2** is in 1/2 mol%.

Reaction of Bis(2-bromomethyl-6-methylphenyl)disulfide (9) with Sodium Sulfide. The reaction was performed according to the method described in the reaction of **1** with sodium sulfide. The compound **2** and dibenzotrithionin **10** were obtained in 45% and in 14% yields, respectively. Yield of **2** is in 1/2 mol%, while yield of **10** is in mol%.

10: Off white crystals; mp 140—141 °C; MS *m/z* 304 (M^+); ^{1}H NMR ($CDCl_3$) δ=2.64 (s, 6H, CH_3), 4.10 (s, 4H, CH_2), and 6.85—7.34 (m, 6H, ArH). Found: C, 63.39; H, 5.32%. Calcd for $C_{16}H_{16}S_3$: C, 63.12; H, 5.30%.

Oxidation of Thiol-Disulfide 4. A solution of **4** (50 mg, 0.25 mmol) and pyridine (39.5 mg, 0.5 mmol) in chloroform (30 ml) was stirred for 12 h under air. After removal of the solvent, the crude product was purified by preparative liquid chromatography to give the compound **13** in 74% yield: Yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ=3.72 (s, 4H, CH_2), 4.46 (s, 4H, CH_2), 7.01 (d, *J*=7 Hz, 2H, ArH), 7.07 (t, *J*=7 Hz, 2H, ArH), and 7.20 (d, *J*=7 Hz, 2H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ=43.2, 43.8, 123.8, 125.6, 129.1, 132.5, 140.5, and 142.4. Found: C, 47.87; H, 3.41%. Calcd for $C_{16}H_{14}S_6$: C, 48.21; H, 3.54%.

Oxidation of Trithiol 5. The oxidation was carried out according to the same method of the preparation of disulfide **14**. The reaction gave the compound **13** in 91% yield.

Electrochemical Study. Cyclic voltammetry (CV) was performed with 10 ml portions of 2 mM solutions of thiol in CH_3CN and 0.1 M $NaClO_4$. The CV cell was equipped with an Ag/0.01 M $AgNO_3$ in CH_3CN reference electrode in a reference well separated from the analyte by a cracked glass bead junction, a Pt wire counter electrode, and a glassy-carbon working electrode polished before use with alumina.

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