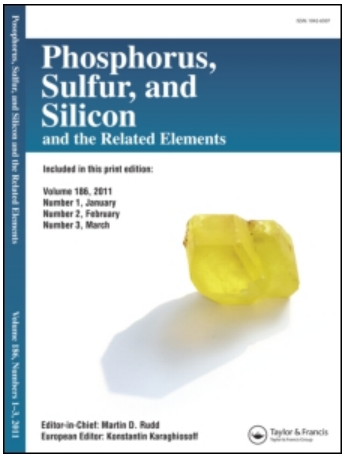


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# RING SIZE CONTROLLED SYNTHESIS AND STRUCTURE OF CYCLIC POLYSULFIDES FUSED TO SUBSTITUTED BENZENE RING

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***We succeeded in the ring size controlled synthesis of stable cyclic benzopolysulfides with five, six, and seven-membered rings. Each sulfur heterocycle has three, four, and five sulfur atoms with S–S bonding. The cyclic structures are characterized by spectroscopic means and X-ray crystallographic analyses.***

**Keywords** Pentathiepin; polysulfide; structure; synthesis; tetrathiin; trithiole



## INTRODUCTION

Considerable current interest has been focused on the synthesis and reactivity of organic cyclic polysulfides containing multisulfur linkages because of their biological activities and chemical properties.[1] Although a number of cyclic polysulfides containing linked three,[2] four,[3] five,[4] seven,[5] eight,[6] nine,[7] and ten[8] sulfur atoms have been reported, there has been no report for the ring size controlled synthesis of cyclic polysulfides due to their conversion into thermodynamically stable ring size, which is attributable to the structure of their molecular framework. Recently, we have succeeded in the systematic and selective synthesis of benzene-fused cyclic polysulfides by the introduction of the substituents on the benzene ring at the proximity position of the sulfur heterocycle.[8] However, in cyclic benzopolysulfides, the different ring size with the different number of sulfur atoms has not so far been synthesized from the same reaction intermediate. In this article, we present the ring size controlled synthesis and structural determination by X-ray crystallographic analysis of the new cyclic polysulfides with multisulfur linkages.

## RESULTS AND DISCUSSION

4,7-Dimethoxy-2,2-dimethyl-1,3,2-benzodithiastannole (**1**),[2] a synthetic equivalent of *ortho* benzenedithiol, was prepared in moderate yield by a sequence of bromination [10],

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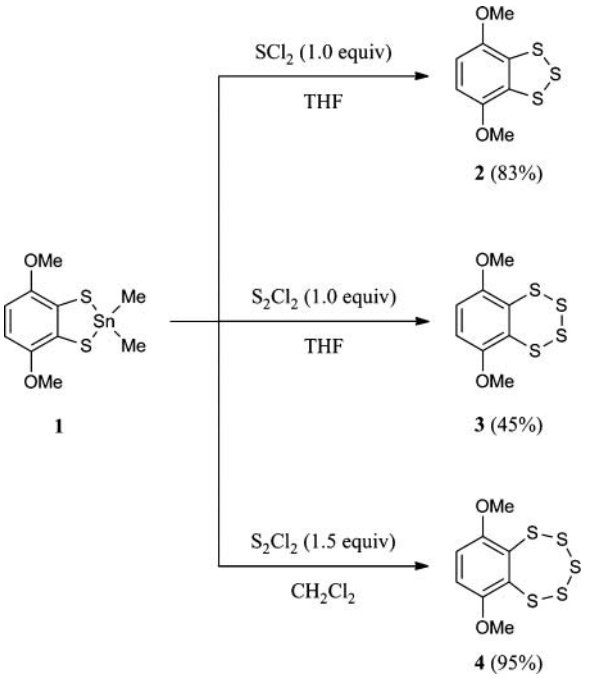
Grignard reaction-thionation,[11] *ortho* lithiation-thionation,[12] and dimethyltin protection.[13] Synthetic intermediates, bromide and thiol derivatives, were obtained in quantitative yields. Ring size controlled transformation into cyclic polysulfides **2**–**4** was successfully carried out by following our original method, namely, by the reaction of 4,7-dimethoxy-2,2-dimethyl-1,3,2-benzodithiastannole (**1**) with electrophiles containing a sulfur unit, sulfur dichloride, or sulfur chloride. Replacement of the thin atom of the stannole **1** by one sulfur atom, synthesis of 4,7-dimethoxybenzotrithiole (**2**), was performed by the reaction of the stannole **1** with 1.0 equivalent of sulfur dichloride in tetrahydrofuran (THF) in good yields. Replacement of the thin atom of the stannole **1** by two sulfur atoms, synthesis of 5,8-dimethoxybenzotetrathiin (**3**), was performed by the reaction of the stannole **1** with 1.0 equivalent of sulfur chloride in THF in good yields. On the other hand, introduction of three sulfur atoms, synthesis of 6,9-dimethoxybenzopentathiepin (**4**), was successfully performed by the reaction of stannole **1** with 1.5 equivalents of sulfur chloride in dichloromethane ($CH_2Cl_2$) in good yields. These results are shown in Scheme 1. In the third reaction, formation of the pentachiepin **4** could explain the initial formation of the tetrathiin **3** and subsequent ring expansion into the pentathiepin **4**. Ring expansion of the tetrathiin **3** could be readily carried out in the presence of residual 0.5 equivalent of sulfur chloride and in situ formation of dimethyltin dichloride as a Lewis acid in $CH_2Cl_2$ instead of THF as a Lewis base. Then the resulting 0.5 equivalent of sulfur dichloride also should be supplied to the ring expansion as the secondary electrophile (Scheme 1).






**Scheme 1**

The structure of tetrathiin **3** has been sufficiently characterized by physical and spectroscopic means, and its crystal structure was confirmed by X-ray crystallographic analysis (Figure 1, Table I). In the solid-state, the S–C–C–S torsion angle of **3** was 5.2(4)°,

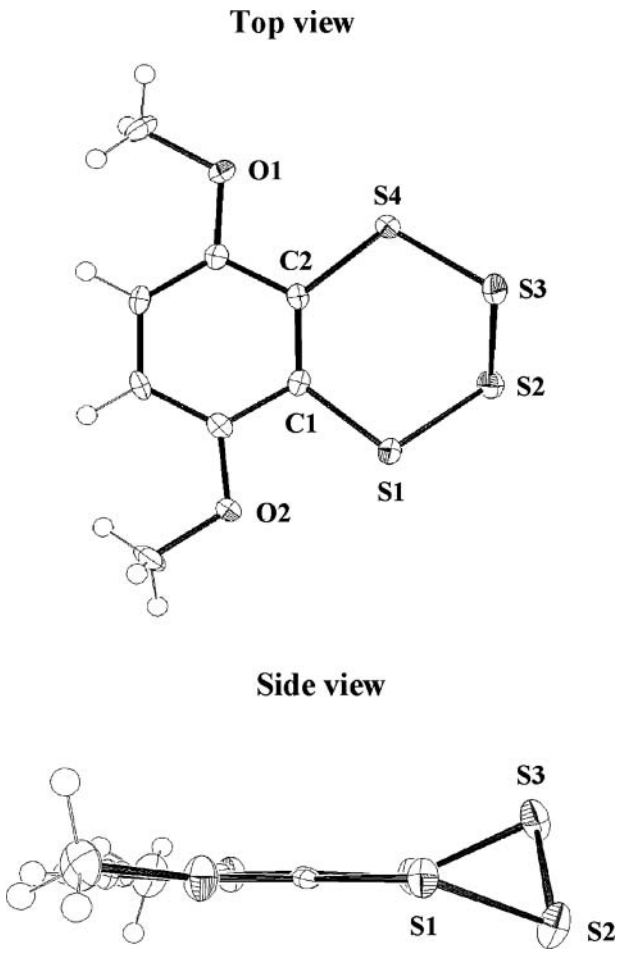





**Figure 1** ORTEP drawing of compound **3**. Thermal ellipsoids are drawn at 50% probability.

the plane of which was located coplanar with the benzene ring, while two sulfur atoms at the 2- and 3-positions deviated from this plane (the C–C–S–S torsion angles are –26.8(2) and –21.8(2)°, respectively) to avoid the benzene moiety. The C–S–S–S torsion angles are 56.23(10) and 60.50(10)°. The S–S–S bond angles of 99.25(5) and 98.60(5)° are between the values of the 5-membered trithiol **2** $(95.5(1)°)^2$ and 7-membered pentathiepin **4** (vide infra). The S–S–S–S torsion angle is –75.77(5)°. The unique distorted twist-boat geometry of the 6-membered tetrathiin ring implies the presence of lone pair–lone pair repulsion of four divalent sulfur atoms.

On the other hand, the structure of pentathiepin **4** also has been sufficiently characterized by physical and spectroscopic means, and its crystal structure was confirmed by X-ray crystallographic analysis (Figure 2, Table II). In the solid-state, the S–C–C–S torsion angle of **4** was 0.6(2)°, the plane of which was located coplanar with the benzene ring, while two sulfur atoms at the 2- and 4-positions were deviated from this plane (the C–C–S–S torsion angles are –78.76(16) and 77.96(16)°, respectively) to avoid the benzene moiety. The S–S–S bond angles of 104.46(3), 102.75(3), 104.24(3)°, the C–S–S–S torsion

**Table I** Selected bond lengths, bond angles, and torsion angles of tetrathiin **3**

| Bond lengths / Å | | Bond angles / ° | |
|---|---|---|---|
| C(1)−S(1) | 1.786(3) | C(2)−C(1)−S(1) | 129.6(2) |
| S(1)−S(2) | 2.0366(10) | C(1)−S(1)−S(2) | 106.03(10) |
| S(2)−S(3) | 2.0678(13) | S(1)−S(2)−S(3) | 99.25(5) |
| S(3)−S(4) | 2.0307(11) | S(2)−S(3)−S(4) | 98.60(5) |
| S(4)−C(2) | 1.794(2) | S(3)−S(4)−C(2) | 105.04(10) |
| | | S(4)−C(2)−C(1) | 128.7(2) |
| | Torsion angles /° | | |
| | S(1)−C(1)−C(2)−S(4) | 5.2(4) | |
| | C(1)−C(2)−S(4)−S(3) | −26.8(2) | |
| | C(2)−C(1)−S(1)−S(2) | −21.8(2) | |
| | C(1)−S(1)−S(2)−S(3) | 56.23(10) | |
| | C(2)−S(4)−S(3)−S(2) | 60.50(10) | |
| | S(1)−S(2)−S(3)−S(4) | −75.77(5) | |

angles of –93.20(8), 91.94(8)°, and the S–S–S–S torsion angles of 74.59(3), –73.48(3)° are in good agreement with those of previously reported benzopentathiepin.[4] The inherent thermal stability of pentathiepin **4** might be attributed to the chair conformation due to avoidance of the repulsion of lone-pair electrons among the neighboring sulfur atoms. The sulfur–sulfur bond lengths of **3** and **4** are similar to those in $S_8$, and the sulfur–carbon($sp^2$) bond lengths of **3** and **4** are marginally longer than those of the general sulfur–carbon($sp^2$) single bond lengths (1.75 Å).

In conclusion, we have developed new ring size controlled synthesis of the stable cyclic benzopolysulfides, 5-membered trithiole, 6-membered tetrathiin, and 7-membered pentathiepin in the reactions of 4,7-dimethoxy-2,2-dimethyl-1,3,2-benzodithiastannole with sulfur-containing electrophiles, sulfur dichloride, and sulfur chloride. The cyclic structures are characterized by spectroscopic means and X-ray crystallographic analyses. The unique geometry of the cyclic polysulfides suggested that the distorted rings with sulfur–sulfur bonding have potent possibilities for the generation of reactive sulfur species.



**Table II** Selected bond lengths, bond angles, and torsion angles of pentathiepin **4**

| Bond lengths / Å | | Bond angles / ° | |
|---|---|---|---|
| C(1)−S(1) | 1.772(2) | C(2)−C(1)−S(1) | 122.78(17) |
| S(1)−S(2) | 2.0460(8) | C(1)−S(1)−S(2) | 104.43(7) |
| S(2)−S(3) | 2.0436(9) | S(1)−S(2)−S(3) | 104.46(3) |
| S(3)−S(4) | 2.0570(9) | S(2)−S(3)−S(4) | 102.75(3) |
| S(4)−S(5) | 2.0533(8) | S(3)−S(4)−S(5) | 104.24(3) |
| S(5)−C(2) | 1.774(2) | S(4)−S(5)−C(2) | 105.07(6) |
| | | S(5)−C(2)−C(1) | 122.32(17) |
| | Torsion angles / ° | | |
| | S(1)−C(1)−C(2)−S(5) | 0.6(2) | |
| | C(1)−C(2)−S(5)−S(4) | −78.76(16) | |
| | C(2)−C(1)−S(1)−S(2) | 77.96(16) | |
| | C(1)−S(1)−S(2)−S(3) | −93.20(8) | |
| | C(2)−S(5)−S(4)−S(3) | 91.94(8) | |
| | S(1)−S(2)−S(3)−S(4) | 74.59(3) | |
| | S(5)−S(4)−S(3)−S(2) | −73.48(3) | |

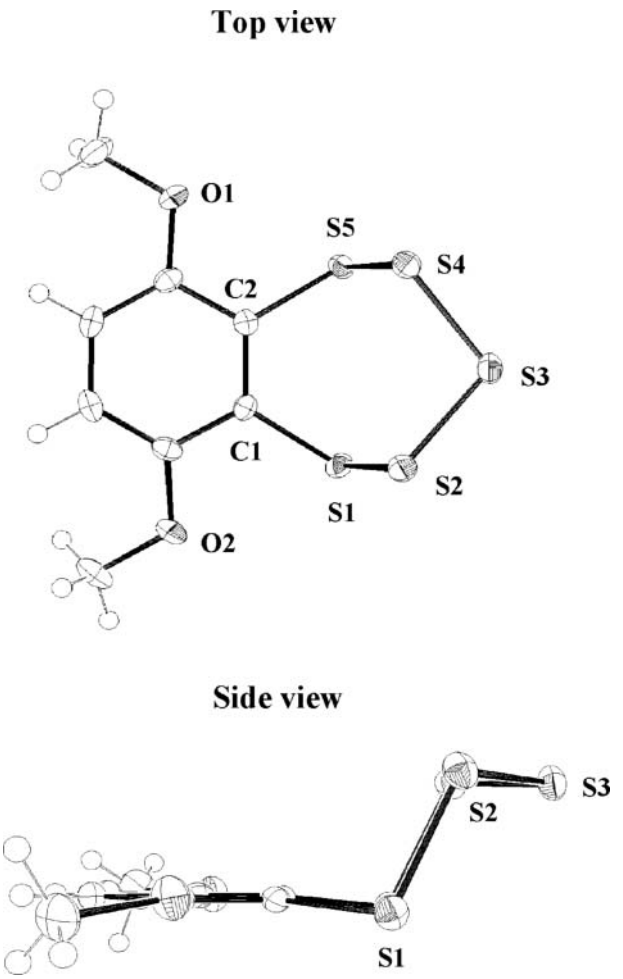



**Figure 2** ORTEP drawing of compound **4**. Thermal ellipsoids are drawn at 50% probability.



## EXPERIMENTAL

Melting points were determined on a MEL-TEMP capillary melting point apparatus and are uncorrected. $^{1}H$ (400 MHz) and $^{13}C$ (101 MHz) NMR spectra were measured on a Bruker AC-400 spectrometer in $CDCl_3$ with $Me_4Si$ as an internal standard. Mass spectra were recorded on a JEOL JMS-700 spectrometer. IR spectra were obtained on a JASCO FT/IR-4200 spectrometer. Silica gel used for column chromatography was Wakogel C-200. Elemental analyses were obtained using Yanaco MT-5 apparatus at Elemental Analysis Division of Iwate University.

### Synthesis of 4,7-Dimethoxybenzotrithiole (2)

To a solution of 4,7-dimethoxy-2,2-methyl-1,3,2-benzodithiastannole **1** (70 mg, 0.2 mmol) in THF (5 mL), $SCl_2$ (0.012 mL, 0.2 mmol) was added at –78°C under nitrogen atmosphere. After 10 min at –78°C, the reaction mixture was poured into water. The

organic layer was extracted with $Et_2O$, dried over anhydrous $MgSO_4$, and filtered. The solution was concentrated in vacuo and purified by column chromatography on silica gel with hexane:$CHCl_3$ (1:1 v/v) mixed solvent as an eluent to give 38 mg (83%) of 4,7-dimethoxybenzotrithiole (**2**) as a orange needles: mp 95.0–96.0°C; $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.82 (s, 6H, $OCH_3$), 6.61 (s, 2H, ArH); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 56.5, 110.9, 130.7, 150.0; IR (KBr) 2993, 2934, 2829, 1585, 1562, 1471, 1428, 1256, 1106, 1044, 1036, 786 cm$^{-1}$; MS (EI) *m/z* 232 ($M^+$); Anal. Calcd for $C_8H_8O_2S_3$: C, 41.35; H, 3.47%. Found: C, 41.23; H, 3.34%.

### Synthesis of 5,8-Dimethoxybenzotetrathiin (3)

To a solution of 4,7-dimethoxy-2,2-methyl-1,3,2-benzodithiastannole **1** (279 mg, 0.8 mmol) in THF (20 mL), $S_2Cl_2$ (0.064 mL, 0.8 mmol) was added at –78°C under nitrogen atmosphere. After 15 min at –78°C, the reaction mixture was poured into water. The organic layer was extracted with $CH_2Cl_2$ and dried over anhydrous $MgSO_4$ and filtered. The solution was concentrated in vacuo and purified by column chromatography on silica gel with hexane:$CHCl_3$ (1:1 v/v) mixed solvent as an eluent to give 95 mg (45%) of 5,8-dimethoxybenzotetrathiin (**3**) as a yellow needles: mp 122–124°C (decomp); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.88 (s, 6H, $OCH_3$), 6.75 (s, 2H, ArH); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 57.0, 107.3, 119.2, 115.1; IR (KBr) 1561, 1449, 1419, 1307, 1257, 1182, 1103, 1040, 787, 709 cm$^{-1}$; MS (EI) *m/z* 264 ($M^+$); Anal. Calcd for $C_8H_8O_2S_4$: C, 36.34; H, 3.05%. Found: C, 36.18; H, 2.95%.



### Synthesis of 6,9-Dimethoxybenzopentathiepin (4)

To a solution of 4,7-dimethoxy-2,2-methyl-1,3,2-benzodithiastannole **1** (307 mg, 0.88 mmol) in $CH_2Cl_2$ (9 mL), $S_2Cl_2$ (0.106 mL, 1.32 mmol) was added at –78°C under nitrogen atmosphere. After 30 min at –78°C, the reaction mixture was poured into water. The organic layer was extracted with $CH_2Cl_2$ and dried over anhydrous $MgSO_4$ and filtered. The solution was concentrated in vacuo and purified by column chromatography on silica gel with hexane:$CHCl_3$ (1:1 v/v) mixed solvent as an eluent to give 248 mg (95%) of 6,9-dimethoxybenzopentathiepin (**4**) as a yellow needles: mp 125°C (decomp); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 3.87 (s, 6H, $OCH_3$), 6.96 (s, 2H, ArH); $^{13}$C NMR (101 MHz, $CDCl_3$) $\delta$ 57.1, 115.4, 134.0, 154.7; IR (KBr) 1577, 1557, 1460, 1440, 1426, 1261, 1180, 1103, 1040, 804 cm$^{-1}$; MS (EI) *m/z* 296 ($M^+$); Anal. Calcd for $C_8H_8O_2S_5$: C, 32.41; H, 2.72%. Found: C, 32.43; H, 2.68%.

### X-Ray Crystallographic Analysis of (3) and (4)

Crystal data for tetrathiin **3**: $M = 264.39$, $C_8H_8O_2S_4$, monoclinic, space group $P2_1/c$ (#14), $a = 16.384(3)$ Å, $b = 6.8414(12)$ Å, $c = 19.076(3)$ Å, $\beta = 98.621(6)$ Å, $V = 2114.1(6)$ Å$^3$, $Z = 8$, $D_{calc} = 1.661$ gcm$^{-3}$. A colorless plate crystal of dimensions 0.60 × 0.40 × 0.10 mm was used for measurement at 123 K on Rigaku R-Axis Rapid diffractometer employing Mo K$\alpha$ ($\lambda = 0.71075$ Å) radiation. The structure was solved by direct methods (SIR97[14]) and expanded using Fourier technique (DIRDIF-99[15]). All calculations were performed using the Crystal Structure 3.8 crystal structure analysis package of Rigaku and Rigaku/MSC. The final cycle of full-matrix least-squares refinement was based on 4837

observed reflections [$I > 2.00\sigma(I)$] and 270 variable parameters with $R_1 = 0.0371$, $wR_2 = 0.0756$ (all data) (CCDC 774740).

Crystal data for pentathiepin **4**: $M = 296.45$, $C_8H_8O_2S_5$, monoclinic, space group $P2_1/n$ (#14), $a = 12.1342(9)$ Å, $b = 16.0096(15)$ Å, $c = 12.5192(11)$ Å, $\beta = 106.808(5)$ Å, $V = 2328.1(3)$ Å$^3$, $Z = 8$, $D_{calc} = 1.691$ gcm$^{-3}$. A colorless plate crystal of dimensions $0.60 \times 0.20 \times 0.20$ mm was used for measurement at 123 K on Rigaku R-Axis Rapid diffractometer employing Mo K$\alpha$ ($\lambda = 0.71075$ Å) radiation. The structure was solved by direct methods (SIR97[14]) and expanded using Fourier technique (DIRDIF-99[15]). All calculations were performed using the Crystal Structure 3.8 crystal structure analysis package of Rigaku and Rigaku/MSC. The final cycle of full-matrix least-squares refinement was based on 5305 observed reflections ($I > 2.00\sigma(I)$) and 288 variable parameters with $R_1 = 0.0289$, $wR_2 = 0.0802$ (all data) (CCDC 774741).

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