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Stereoselective Sulfur Extrusion Reaction of *syn*- and *anti*-10,20-Dibromo-2,3,12,13-Tetrathia[4.4]metacyclophanes to the Corresponding *syn*- and *anti*-Dithia[3.3]metacyclophanes

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ABSTRACT

*A new cyclophane, 10,20-dibromo-2,3,12,13-tetrathia[4.4]metacyclophane (**1**), has been synthesized by the oxidative coupling reaction of 2,6-bis(mercaptomethyl)-1-bromobenzene with I_2. Both syn and anti isomers of **1** can be isolated at room temperature. The thermal sulfur extrusion reaction of anti-**1** with $(Et_2N)_3P$ afforded anti-9,18-dibromo-2,11-dithia[3.3]metacyclophane, while syn-**1** gave 9,19-dibromo-2,11,12-trithia[3.4]metacyclophane. syn-9,18-Dibromo-2,11-dithia[3.3]metacyclophane was produced from the photochemical sulfur extrusion of syn-**1** with $(MeO)_3P$.*

INTRODUCTION

Varieties of cyclophanes have been synthesized, and the structures have been determined by NMR spectroscopy and X-ray crystallographic analysis [1]. The conformational properties of [2.2]metacyclophanes and thia[3.3]metacyclophanes have been extensively studied because, in general, *syn* and *anti* conformations can exist [2]. In contrast, very few thia[4.4]metacyclophanes or larger thiametacyclophanes are known [1]. The potential of tetrathia[4.4]metacyclophanes as useful synthetic precursors of bridged aromatic ring systems has been realized by the conversion of 2,3,12,13-tetrathia[4.4]metacyclophanes into the corresponding 2,11-dithia[3.3]metacyclophanes [3]. We have reported that an unusual sulfur extrusion via transannular S–S bond formation is found in the reaction of a new sulfur-bridged tetrathia[4.4]metacyclophane with concentrated sulfuric acid [4]. As a result of our continued interest in such sulfur extrusion reactions and the properties of metacyclophanes containing sulfur atoms, we recently found that the oxidative coupling of 2,6-bis(mercaptomethyl)-1-bromobenzene (**6**) with iodine affords *syn*- and *anti*-10,20-dibromo-2,3,12,13-tetrathia[4.4]metacyclophanes (**1**) [5]. The thermal sulfur extrusion reaction of each conformer, *syn*-**1** and *anti*-**1**, with $(Et_2N)_3P$ resulted in the formation of *anti*-9,18-dibromo-2,11-dithia[3.3]metacyclophane (*anti*-**2**) from *anti*-**1** and 9,19-dibromo-2,11,12-trithia[3.4]metacyclophane (**3**) from *syn*-**1**, respectively, while the photochemical sulfur extrusion of *syn*-**1** with $(MeO)_3P$ gave *syn*-9,18-dibromo-2,11-dithia[3.3]metacyclophane (*syn*-**2**). This article presents the synthesis, conformational properties, and stereoselective sulfur extrusion of a new type of intra-annularly substituted tetrathia[4.4]metacyclophane **1**.

RESULTS AND DISCUSSION

The oxidative coupling reaction of the dithiol **6** with I_2 afforded the cyclophane **1** (72%) which was sep-

Dedicated to Prof. A. Fava on the occasion of his seventieth birthday.

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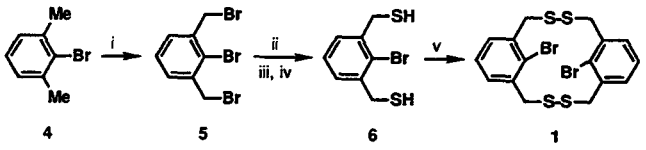


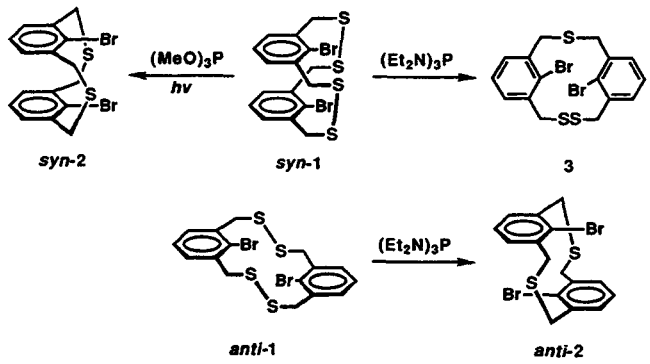
SCHEME 1 (i) NBS, CCl_4, *hv*; (ii) $H_2NC(=S)NH_2$, EtOH, reflux; (iii) *aq* NaOH soln, reflux; (iv) *aq* HCl; and (v) I_2, Et_3N, $CHCl_3$, RT.

arated into two isomeric products, **1a** (mp 202–203°C) and **1b** (mp 209–210°C), in a ratio of 2:1, by preparative liquid chromatography (Scheme 1).

The mass spectrum (EI) of **1** shows the molecular ion peaks at *m/z* 492, 494, and 496 due to the bromine isotopes and the base peak at *m/z* 206 corresponding to tetrahydropyrene. Other abundant fragments (*m/z* 462, 430, 414, and 350) can be rationally explained in terms of loss of sulfur and bromine atoms from the molecular ion.

The conformational properties of **1** were analyzed by ^1H NMR spectroscopy. The ^1H NMR spectrum of one conformer **1a** in $CDCl_3$ at 25°C exhibits an AB quartet at δ 3.52 and 4.16 (J = 14.4 Hz) for the benzylic methylene protons which can be assigned as a *syn*-form, *syn*-**1**. However, the absorption of the methylene protons in the other conformer **1b** appears as a singlet peak at δ 3.76, indicating an *anti*-form, *anti*-**1**. The conformational isomerism between the *syn*- and *anti*-conformers of **1** was confirmed by variable temperature NMR spectroscopy (VT-NMR). When the *anti*-conformer of **1** (in CS_2 containing THF-d_8) was examined by ^1H NMR spectroscopy over the temperature range +25 to −110°C, the methylene signal showed a broadening peak at −90°C and became a multiplet at −110°C; however, no clear splitting of peaks was observed [6]. The conformer, *syn*-**1**, in $CDCl_3$ did not show any temperature dependence from +25 to +100°C, as evidenced by its VT-^1H NMR spectral data [6]. However, *syn*-**1** was converted into *anti*-**1** when heated to 160°C in the solid state. This result clearly indicates that there is a large barrier to conformational flipping in **1**. Thus, the *syn*- and *anti*-conformers of **1** are separable and indicate no tendency for interconversion at room temperature. These results suggest that the interconversion of *syn* and *anti* conformers is restricted, mainly due to crowding of the internally substituted bromines. Analogously, the *syn* and *anti* conformers of 10,20-diphenyl-2,3,12,13-tetrathia[4.4]metacyclophane can be separated [7]. However, 2,3,12,13-tetrathia[4.4]metacyclophane and its 10,20-dimethyl derivative are mobile cyclophanes [3,8].

It is interesting that distinct differences of reactivities between *syn*-**1** and *anti*-**1** were found in the following two types of sulfur extrusion reactions with $(Et_2N)_3P$ [9] and $(MeO)_3P$ [4,10] under



SCHEME 2

photochemical conditions (Scheme 2). Although thermal and photochemical extrusions of sulfur from sulfides and disulfides have been used in cyclophane synthesis, the mechanistic study of their extrusions has received less attention [1].

Treatment of *anti*-**1** with $(Et_2N)_3P$ in benzene under reflux afforded a mixture of the dibromodithia[3.3]metacyclophane and $(Et_2N)_3P$ which, on recrystallization from $CHCl_3$, led to *anti*-9,18-dibromo-2,11-dithia[3.3]metacyclophane (*anti*-**2**) (56%). The ^1H NMR spectrum of *anti*-**2** in $CDCl_3$ at 25°C shows the methylene protons at δ 3.81 as a singlet peak, and the VT-NMR spectra of *anti*-**2** in CS_2 are unchanged from +25 to −90°C [6]. Although intra-annularly substituted dithia[3.3]metacyclophanes (*e.g.*, -Me, -OMe, and -F, -Cl as substituents) are well known [1], the NMR spectral data of dibromo-substituted dithia[3.3]metacyclophane are unknown to our knowledge. In contrast to *anti*-**1**, similar treatment of *syn*-**1** with $(Et_2N)_3P$ gave the trithia[3.4]metacyclophane **3** (52%). On the other hand, it was reported that the thermal sulfur extrusion of 10,20-dimethyl-2, 3, 12, 13-tetrathia[4.4]metacyclophane with $(Et_2N)_3P$ gave a mixture of *syn*- and *anti*-conformers of the corresponding dithia[3.3]metacyclophane in a 1:4 ratio [3].

The photochemical sulfur extrusion reaction of *syn*-**1** with $(MeO)_3P$ afforded *syn*-**2** (49%). The *syn* conformation was confirmed by the methylene proton signals at δ 3.55 and 4.70 (ABq, J = 15.4 Hz) (Scheme 2). However, the analogous reaction of *anti*-**1** with $(MeO)_3P$ gave a complex mixture which was not characterized further. These stereoselective sulfur extrusion reactions may become a useful method for the preparation of *syn*- and *anti*-conformers of intra-annularly substituted dithia[3.3]metacyclophanes.

EXPERIMENTAL

Infrared spectra were obtained on a JASCO FT-IR 3 spectrometer. ^1H and/or ^{13}C NMR spectra were

measured on a Hitachi R-600 FT-NMR or a JEOL FX 100 FT-NMR spectrometer. 500 MHz ^1H and 125 MHz ^{13}C NMR spectra were measured on a Bruker AM 500 spectrometer. Mass spectra were measured with a Hitachi RMU-6MG mass spectrometer. Elemental analyses were carried out by the Analytical Center at this University.

2,6-Dimethyl-1-bromobenzene (**4**)

To a stirred solution of 2,6-dimethylaniline (36.6 g, 0.3 mol) in HCl-H_2O (400 cm^3, 1:1) was added a solution of sodium nitrite (22.8 g, 0.33 mol) in water at 0°C. To this mixture after 1 hour was added CuBr (42.9 g, 0.3 mol) in 48% hydrobromic acid (300 mL). The mixture was stirred at 0°C for 2 hours, and then it was warmed to 80°C for 1 hour. The reaction mixture was extracted with hexane, and the extract was dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was purified by silica-gel column chromatography (eluent, hexane) to give 2,6-dimethyl-1-bromobenzene (**4**) in 26% yield; ^1H NMR ($CDCl_3$) δ 2.36 (s, 6H, CH_3) and 7.14 (s, 3H, ArH). Anal. calcd for C_8H_9Br: C, 51.92; H, 4.90. Found: C, 51.83; H, 4.81.

2,6-Bis(bromomethyl)-1-bromobenzene (**5**)

A solution of 2,6-dimethyl-1-bromobenzene (**4**) (14.5 g, 78.4 mmol) and *N*-bromosuccinimide (NBS; 28 g, 157.3 mmol) in dry carbon tetrachloride (150 cm^3) was stirred under an argon atmosphere while being irradiated with a 400 W high-pressure mercury lamp for 2 hours. The resulting solid was separated by filtration, and the filtrate was concentrated under reduced pressure. The crude residue was recrystallized from hexane to give tris-bromide **5** (37%): mp 88°C; ^1H NMR ($CDCl_3$) δ 4.60 (s, 4H, CH_2) and 7.06–7.55 (m, 3H, ArH). Anal. calcd for $C_8H_7Br_3$: C, 28.03; H, 2.06. Found: C, 28.21; H, 2.17.

2,6-Bis(mercaptomethyl)bromobenzene (**6**)

A solution of 2,6-bis(bromomethyl)-1-bromobenzene (**5**) (2 g, 5.83 mmol) and thiourea (0.89 g, 11.66 mmol) in ethanol (100 cm^3) was stirred for 12 hours under reflux. After concentration of the solution, 6% sodium hydroxide solution (200 cm^3) was added to the residue. The mixture was refluxed for 8 hours under an Ar atmosphere and then cooled in an ice-water bath; cold aqueous hydrochloric acid was then added dropwise. The reaction mixture was extracted with chloroform, and the extract was dried with $MgSO_4$. After removal of the solvent, the residue was purified by silica-gel column chromatography (eluent, $CHCl_3$) to give 2,6-bis(mercaptomethyl)-1-bromobenzene (**6**) in 92% yield; mp 63.5–64.5°C; ^1H NMR ($CDCl_3$) δ 1.99 (t, 2H, SH), 2.87 (d, 4H, CH_2), and 7.26 (s, 3H, ArH). Anal. calcd for $C_8H_9BrS_2$: C, 38.56; H, 3.64. Found: C, 38.71; H, 3.70.

syn- and anti-10,20-Dibromo-2,3,12,13-tetrathia[4.4]metacyclophane (**1**)

To a stirred solution of 2,6-bis(mercaptomethyl)-1-bromobenzene (**6**) (1.33 g, 5.34 mmol) and triethylamine (10 cm^3) in chloroform (150 cm^3) was added a solution of iodine (3.28 g, 12.9 mmol) in chloroform (150 cm^3) at 0°C. The mixture was stirred at room temperature for 2 hours. The mixture was washed with aqueous sodium thiosulfate solution, and the organic layer was dried over $MgSO_4$. After evaporation of the solvent, the residue was purified by silica-gel column chromatography (eluent, $CHCl_3$) and further purified by preparative liquid chromatography (Japan Analytical Industry Co. Ltd.; model LC-09) to give 10,20-dibromo-2,3,12,13-tetrathia[4.4]metacyclophane (72%), *syn*-**1** and *anti*-**1** in a ratio of 2:1.

syn-**1**; mp 202–203°C; MS, *m/z* 492, 494, 496 (M^+); ^1H NMR (500 MHz, $CDCl_3$) δ 3.52, 4.16 (ABq, J = 14.4 Hz, 8H, CH_2), 6.88 (t, J = 7.5 Hz, 2H, ArH), and 6.94 (d, J = 7.5 Hz, 4H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 43.8, 126.7, 127.4, 130.6, and 139.1. Anal. calcd for $C_{16}H_{14}Br_2S_4$: C, 38.88; H, 2.85. Found: C, 39.23; H, 2.87.

anti-**1**: mp 209–210°C; MS, *m/z* 492, 494, 496 (M^+); ^1H NMR (500 MHz, $CDCl_3$) δ 3.76 (s, 8H, CH_2) and 7.05–7.14 (m, 6H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 45.0, 126.4, 126.7, 130.5, and 137.6. Anal. calcd for $C_{16}H_{14}Br_2S_4$: C, 38.88; H, 2.85. Found: C, 39.23; H, 2.88.

Reaction of anti-10,20-Dibromo-2,3,12,13-tetrathia[4.4]metacyclophane (*anti*-**1**) *with Tris(diethylamino)phosphine*

A solution of *anti*-**1** (100 mg, 0.2 mol) and $(Et_2N)_3P$ (99 mg, 0.4 mol) in benzene (30 cm^3) was refluxed for 3 hours. After concentration of the solution, the crude product was purified by preparative liquid chromatography to give a mixture of 2,11-dithia[3.3]metacyclophane and $(Et_2N)_3P$, which was recrystallized from chloroform to afford *anti*-9,18-dibromo-2,11-dithia[3.3]metacyclophane (*anti*-**2**) (56%); mp 182–183°C; MS, *m/z* 428, 430, 432 (M^+); ^1H NMR (500 MHz, $CDCl_3$) δ 3.81 (s, 8H, CH_2), 7.16 (t, J = 7.5 Hz, 2H, ArH), and 7.24 (d, J = 7.5 Hz, 4H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 36.7, 126.7, 127.9, 129.5, and 138.1. Anal. calcd for $C_{16}H_{14}Br_2S_2$: C, 44.67; H, 3.28. Found: C, 44.50; H, 3.11.

Reaction of syn-10,20-Dibromo-2,3,12,13-tetrathia[4.4]metacyclophane (*syn*-**1**) *with Tris(diethylamino)phosphine*

A solution of *syn*-**1** (100 mg, 0.2 mol) and $(Et_2N)_3P$ (99 mg, 0.4 mol) in benzene (30 cm^3) was refluxed

for 3 hours. After concentration of the solution, the crude residue was purified by preparative liquid chromatography to give 9,19-dibromo-2,11,12-trithia[3.4]metacyclophane (**3**) (52%); mp 289–290°C; MS, *m/z* 460, 462, 464 (M^+); ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.54–4.75 (m, 8H, CH_2) and 6.81–7.41 (m, 6H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 34.2, 36.9, 125.9, 126.1, 127.4, 127.7, 129.5, 130.3, 130.8, 131.7, 136.6, and 137.8. Anal. calcd for $C_{16}H_{14}Br_2S_3$: C, 41.57; H, 3.05. Found: C, 41.73; H, 3.18.

Photochemical Reaction of syn-10,20-Dibromo-2,3,12,13-tetrathia[4.4]metacyclophane (syn-1) with Trimethyl Phosphite

A mixture of *syn*-**1** (50 mg, 0.1 mmol) and $(MeO)_3P$ (15 cm^3) was irradiated at 25°C for 18 hours under an Ar atmosphere using a 400 W high-pressure mercury lamp. The mixture was poured into water, and the product was extracted with ether. The extract was dried over $MgSO_4$ and evaporated. The crude product was purified by preparative liquid chromatography to afford *syn*-9,18-dibromo-2,11-dithia[3.3]metacyclophane (*syn*-**2**) (49%) and the recovered *syn*-**1** (37%). *syn*-**2**: mp 170–171°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.55, 4.70 (ABq, J = 15.4 Hz, 8H, CH_2), 6.78 (t, J = 7.5 Hz, 2H, ArH), and 7.08 (d, J = 7.5 Hz, 4H, ArH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 33.9, 126.7, 130.2, 133.3, and 135.9. Anal. calcd for $C_{16}H_{14}Br_2S_2$: C, 44.67; H, 3.28. Found: C, 44.40; H, 3.21.

Photochemical Reaction of anti-10,20-Dibromo-2,3,12,13-tetrathia[4.4]metacyclophane (anti-1) with Trimethyl Phosphite

The reaction was carried out according to the same method as used for the reaction of *syn*-**1** with $(MeO)_3P$. This reaction gave a complex mixture which was not characterized further.

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