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Synthesis, Conformation, and the Stereoselective Sulfur Extrusion Reaction of a New Intraannular Dibromo-Substituted Tetrathia[4.4]metacyclophane

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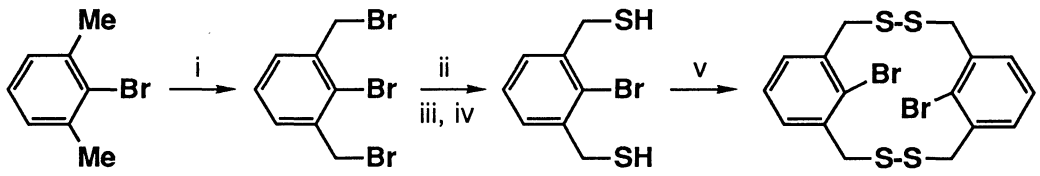
The oxidative coupling of 2,6-bis(mercaptomethyl)bromobenzene using I_2 gave *syn*- and *anti*-10,20-dibromo-2,3,12,13-tetrathia[4.4]metacyclophane (**1**) which can be isolated in the solid state at room temperature. The sulfur extrusion reaction of *anti*-**1** with $(Et_2N)_3P$ afforded the corresponding dithia[3.3]metacyclophane, while *syn*-**1** gave the trithia[3.4]metacyclophane.

A number of studies have been reported on the synthesis and structures of cyclophanes.[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] However, very few thia[4.4]metacyclophanes or larger thiametacyclophanes are known. We have found that the oxidative coupling of 2,6-bis(mercaptomethyl)bromobenzene with iodine afforded *syn*- and *anti*-10,20-dibromo-2,3,12,13-tetrathia[4.4]metacyclophane (**1**). The sulfur extrusion reaction of each conformer, *syn*-**1** and *anti*-**1**, with $(Et_2N)_3P$ resulted in the formation of the corresponding dithia[3.3]metacyclophane from *anti*-**1** and trithia[3.4]metacyclophane from *syn*-**1**, respectively. This communication describes the synthesis, conformational properties, and thermal sulfur extrusion of a new type of intraannular substituted tetrathia[4.4]metacyclophane **1**.

The cyclophane **1** was synthesized as follows (Scheme 1). Tribromide **6** was obtained by photobromination using *N*-bromosuccinimide (NBS) of 2,6-dimethylbromobenzene (**5**) which was prepared by treatment of the diazonium salt of 2,6-dimethylaniline with CuBr. Treatment of **6** with thiourea followed by addition of *aq.* NaOH gave 2,6-bis(mercaptomethyl)bromobenzene (**7**).[3] Finally, dithiol **7** (1.33 g, 5.4 mmol) was treated with iodine (3.27 g, 12.9 mmol) in the presence of triethylamine (10 mL) in chloroform (300 mL) using a high dilution technique at room temperature. The whole mixture was stirred at room temperature for 2 h. After the usual work-up, the crude products were purified by silica-gel column chromatography (eluent, $CHCl_3$) and further separated by preparative liquid chromatography to afford two isomeric products (in 72% yield), **1a** (mp 209-210 °C) and **1b** (mp 202-203 °C) in



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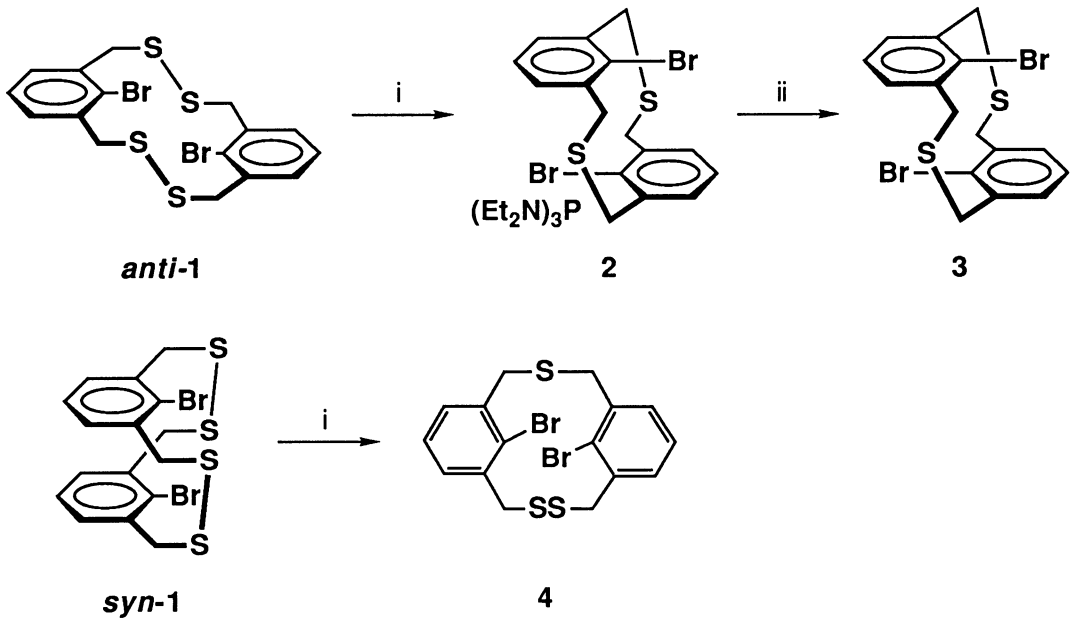
Scheme 1. *Reagents and Conditions*: i, NBS, CCl_4, *hv*; 2 h; ii, $H_2NC(=S)NH_2$, EtOH, reflux, 12 h; iii, *aq.* NaOH soln., reflux, 8 h; iv, 6N-HCl; v, I_2, Et_3N, $CHCl_3$, r.t., 2 h.

a ratio of 1 : 2.[4] The mass spectrum (EI) of **1** exhibits 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 500 MHz ^1H NMR spectrum of one conformer **1a** in $CDCl_3$ at 25 °C shows a singlet peak at δ 3.76 for the benzylic methylene protons which can be assigned as an anti-form, *anti*-**1**, while the absorption of methylene protons in other conformer **1b** appears as an AB system at δ 3.52 and 4.16 (J = 14.4 Hz), indicating a syn-form, *syn*-**1**. The structure of **1** is particularly interesting in view of the conformational isomerism, since inversions between the syn- and anti-conformers are expected to have energy barriers amenable to study by variable temperature NMR spectroscopy (VT-NMR). Compound *anti*-**1** (in CS_2 containing THF-d_8) was examined by ^1H NMR spectroscopy over the temperature range from +25 °C to -110 °C, the methylene signal shows a broadening peak at -90 °C and becomes to a multiplet at -110 °C,[5] however no clear splitting peaks were observed.[6] In *syn*-**1** in $CDCl_3$, an AB quartet for the methylene protons was not temperature dependent over the range from +25 °C to +100 °C.[6] On heating to 160 °C in the solid state, however, *syn*-**1** was converted to *anti*-**1**. This clearly indicates that there is a large barrier to conformational flipping in **1**. Thus, the syn- and anti-conformers in **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 bromine of the internal substituent. In contrast, 2,3,12,13- and 10,20-dimethyl-2,3,12,13-tetrathia-[4.4]metacyclophanes are mobile phanes.[7-9]

Interestingly, the distinct difference of reactivities between *anti*-**1** and *syn*-**1** was observed in the following sulfur extrusion reactions with tris(diethyl-amino)phosphine, $(Et_2N)_3P$,[10] (Scheme 2). A solution of *anti*-**1** (0.2 mmol) and tris(diethylamino)phosphine (0.4 mmol) in benzene (30 mL) was refluxed for 3 h. A 1 : 1 mixture of dibromo-dithia[3.3]metacyclophane and $(Et_2N)_3P$, **2** (mp 108-109 °C), was obtained in 56% yield after concentration of the solution followed by preparative



Scheme 2. i, $(Et_2N)_3P$, benzene, reflux; ii, recrystallization from $CHCl_3$.

liquid chromatography,[11] and then **2** was further recrystallized by several times from chloroform to give 9,18-dibromo-2,11-dithia[3.3]metacyclophane (**3**), mp 182-183 °C, exclusively.[12] However, compound **3** could not be obtained by cyclization using high dilution method of dibromide **6** with dithiol **7** in the presence of cesium carbonate (Cs_2CO_3) in anhydrous DMF. Although intraannular-substituted dithia-[3.3]metacyclophanes (*e.g.*, substituents: -Me, -OMe, -F, -Cl) are well known,[1] the NMR spectral data of dibromo-substituted dithia[3.3]metacyclophane are unknown to our knowledge. The result of the 500 MHz ^1H NMR spectrum [δ 3.81 (s) for CH_2] of **3** in $CDCl_3$ at 25 °C shows an *anti*-conformer, and the VT-NMR spectra of **3** in CS_2 are unchanged from +25 °C to -90 °C.[5,6] In contrast to *anti*-**1**, treatment of *syn*-**1** with $(Et_2N)_3P$ in benzene under reflux led to the unsymmetrical dibromo trithia[3.4]-metacyclophane **4**, mp 289-290 °C, in 52% yield.[13] When **4** was further treated with $(Et_2N)_3P$, **4** was recovered quantitatively. On the other hand, it was found that 2,3,12,13- and 10,20-dimethyl-2,3,12,13-tetrathia[4.4]metacyclophanes gave only the corresponding dithia[3.3]metacyclophanes upon treatments with $(Et_2N)_3P$.[7]

Thus, we observed the distinct difference of the reactivities in thermal sulfur extrusion reactions from the disulfide linkage of *syn*-**1** and *anti*-**1**.[14]

References

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3) **7**: mp 63.5-64.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.99 (t, 2H, SH), 2.87 (d, 4H, CH_2), and 7.26 (s, 3H, ArH).

4) *anti*-**1**: mp 209-210 °C; MS, *m/z* 492, 494, 496 (M^+); ^{1}H 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. Found: C, 39.23; H, 2.88%. Calcd for $C_{16}H_{14}Br_2S_4$: C, 38.88; H, 2.85%.
syn-**1**: mp 202-203 °C; MS, *m/z* 492, 494, 496 (M^+); ^{1}H 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. Found: C, 39.23; H, 2.87%. Calcd for $C_{16}H_{14}Br_2S_4$: C, 38.88; H, 2.85%.

5) The ^{1}H NMR spectra of **1** and **3** in CS_2 at 25 °C are same as those of in $CDCl_3$ at 25 °C.

6) The VT-NMR measurements for **1** and **3** have limitation due to the solubility in suitable solvents.

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10) Disulfides react with $(Et_2N)_3P$ to convert sulfides: D. N. Harpp, J. G. Gleason, and J. P. Snyder, *J. Am. Chem. Soc.*, **90**, 4181 (1968).

11) **2**: mp 108-109 °C; MS, *m/z* 678 (M^+); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.12 (m, 18H, CH_3), 3.06 (m, 12H, CH_2), 3.82 (m, 8H, CH_2), and 7.14-7.27 (m. 6H, ArH).

12) **3**: mp 182-183 °C; MS, *m/z* 428, 430, 432 (M^+); ^{1}H 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.

13) **4**: 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.

14) The photochemical sulfur extrusion reaction of **1** with trimethyl phosphite [$(MeO)_3P$] was carried out as follows.[15,16] Irradition of **1** (50 mg, 0.1 mmol) in $(MeO)_3P$ (15 mL) at 25 °C under argon using 400 W high-pressure mercury lamp for 18 h afforded a complex mixture which was not characterized further.

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