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ISOLATION OF 2,18-DITHIA[3.1.3.1]METACYCLOPHANE AND 2,3,19,20-TETRATHIA[4.1.4.1]METACYCLOPHANE FROM COUPLING REACTIONS DIRECTED TOWARD THE SYNTHESIS OF STRAINED THIACYCLOPHANES

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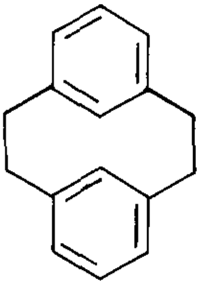
Abstruct - *Intramolecular coupling reactions of bis(3-bromomethylphenyl)methane or bis(3-mercaptomethylphenyl)methane failed to yield the strained thia[3.1]- and dithia[4.1]metacyclophanes respectively. Two previously unknown medium-sized cyclophanes, namely a dithia[3.1.3.1]metacyclophane and a tetrathia[4.1.4.1]metacyclophane, have been isolated and characterized. Variable temperature NMR studies have revealed that both these metacyclophanes have a very high degree of conformational mobility.*

Thiacyclophanes have commonly been used as precursors to novel conjugated aromatic systems.[1] However, the stereochemical and conformational aspects of many of these thiacyclophanes have also been well-studied and proven to be of special interests.[2] As far as the [m.n]metacyclophanes (m=n or m≠n) are concerned, the lowest members known are the [2.2]metacyclophane **1** [3] and [3.1]metacyclophane **2** [4]. The former, **1**, is conformationally very rigid and exists in an *anti*-stepped conformation;[5,6] the latter, **2**, though having the same total number of methylene units in the two bridges as **1**, is conformationally mobile with an observed $\Delta G_c^{\ddagger} = 70\ \mathrm{kJ\ mol^{-1}}$ for the confor-



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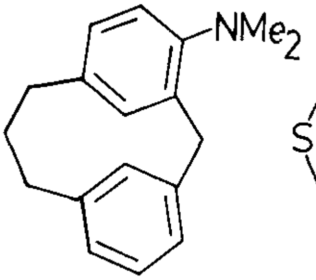

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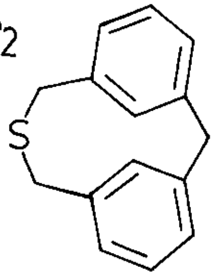

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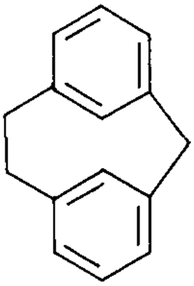

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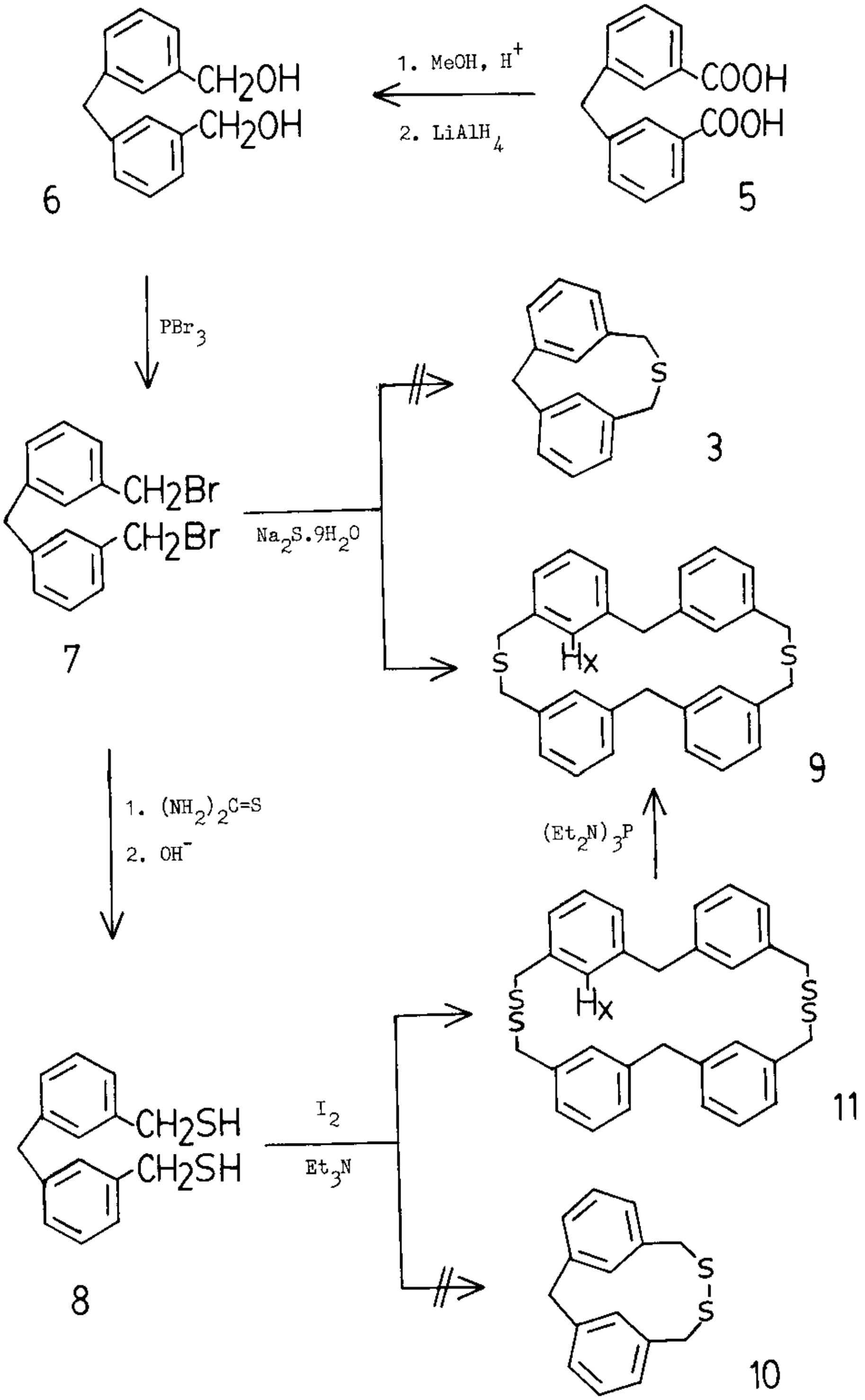
formational inversion process.[4] We believed that the thia[3.1]metacyclophane, 3, due to the longer C-S-C bond and the lower bending energy of a C-S-C bridge, would also be synthetically accessible and provide more conformational flexibility compared to 2. In addition, 3 would be a potential precursor to the highly strained [2.1]metacyclophane 4 via, for example, sulfone pyrolysis.[7,8]

The fact that the sodium sulfide coupling of benzylic bromides has successfully led to the preparations of several thiacyclophanes[9-11] had prompted us to investigate a similar coupling using the dibromide 7 as a possible route to the thia[3.1]metacyclophane 3.

The preparation[12] of the dicarboxylic acid 5, which had been converted[13] to the diol 6, was reported by Schopff[12] in 1894. Conversion of 6 to the dibromide 7 was then readily achieved by treatment of 6 with phosphorus tribromide. The dibromide 7, mp 60-62°C,[14] was obtained in a 63% yield. The ^{1}H-NMR spectrum of 7 expectedly showed the central methylene and the -C$\underline{H}_2$Br protons at δ3.95 and δ4.45 respectively. The structure of 7 was further confirmed by a molecular ion at *m/z* 352 ($C_{15}H_{14}{}^{79}Br_2$) with the 1:2:1 isotope pattern expected for a dibromide.

With the desired precursor now at hand, it was thought that the thiacyclophane 3 could be obtained from the intramolecular coupling of the dibromide 7. Although the sodium sulfide coupling under high dilution conditions has been used successfully in the preparation of thiacyclophanes,[9-11] the result from our attempt in the coupling of

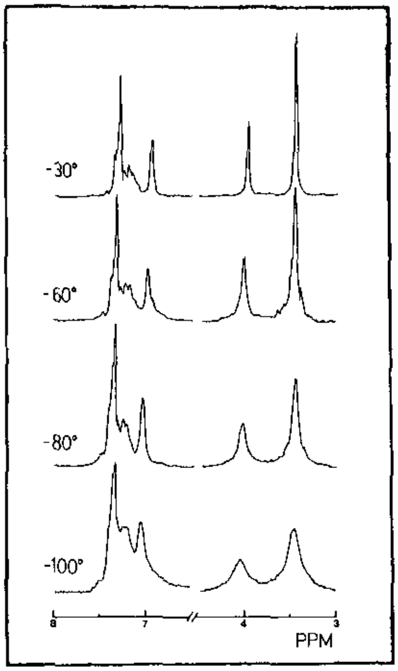

CH2OH
CH2OH
6
1. MeOH, H+
2. LiAlH4
COOH
COOH
5
PBr3
3
S
CH2Br
CH2Br
7
Na2S.9H2O
9
S
Hx
S
(Et2N)3P
1. (NH2)2C=S
2. OH-
11
S
S
Hx
S
S
CH2SH
CH2SH
8
I2
Et3N
10
S
S

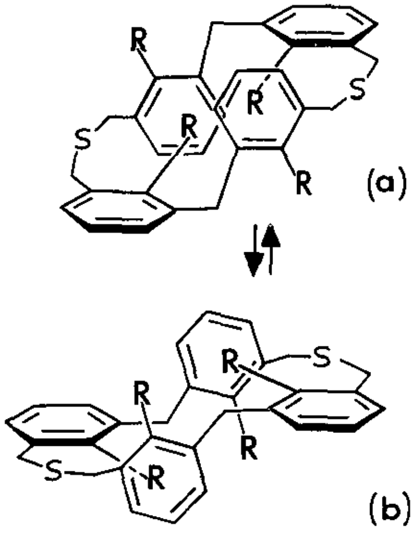
the dibromide **7** under similar conditions was rather unexpected.

Chromatography of the crude product obtained from the coupling reaction isolated a pure fraction (one spot on TLC) of colorless crystals, mp 188-190°C. Its ^{1}H-NMR spectrum indicated the two types of characteristic signals: two singlets at $\delta 3.40$ and $\delta 3.90$ in the ratio of 2:1 for the $ArC\underline{H}_2$-S and $ArC\underline{H}_2Ar$ methylene protons respectively. These data would only be consistent with a thiacyclophane **3** undergoing rapid conformational changes. However, the mass spectrum of the sample obtained confirmed that it was in fact the dimer dithia[3.1.3.1]metacyclophane **9** with a molecular ion at *m/z* 452. Another attempt of the coupling reaction under further dilution still afforded a similar yield of **9**. Chromatographic and mass spectral studies provided no further indication of the presence of **3** in the reaction product.

From the ^{1}H-NMR data mentioned earlier, the dithiacyclophane **9** is undoubtedly conformationally mobile at room temperature. This is not unexpected since a tetramethyl derivative, **12**, is known to behave similarly.[15] It is, however, believed that the equilibrium involves conformers of **9** with the H_x protons projecting toward the benzene cavities as evident by the slightly shielded H_x-signal at $\delta 6.93$ (a value comparable to those reported for other medium-sized metacyclophanes[16]) in the ^{1}H-NMR spectrum of **9** (Figure 1). By analogy to the tetramethyl derivative **12**, the conformational behavior of which has been established (**12a** $\rightleftarrows$ **12b**),[15] the dithia[3.1.3.1]-metacyclophane **9** is also expected to undergo the fluxional process **9a** $\rightleftarrows$ **9b** with two of the H_x protons located in the shielding cones of the two benzene rings leading to a slightly shielded averaged chemical shift as mentioned. An attempt was also made to study the conformational equilibrium in **9** at low temperatures using variable ^{1}H-NMR spectroscopy. Although peak broadening was clearly observed for the $-C\underline{H}_2S-$ and $Ar-C\underline{H}_2-Ar$ protons (see Figure 1), complete coalescence of the peaks was not observed even at -100°C indicating a very high degree of conformational mobility. These results have in fact indicated that the steric effect of the *ortho*-methyl groups in **12** has in fact significantly increased the conformational barrier in the dithia[3.1.3.1]metacyclophane systems to allow studies of the novel fluxional behavior **12a** $\rightleftarrows$ **12b** reported earlier[15] (coalescence temperature = -70°C; $\Delta G^{\ddagger}_{203} = 39$ kJ mol^{-1})

The failure to induce intramolecular coupling of **7**, coupled with the isolation of





9, R=H ; 12, R=CH_3

FIGURE 1. Variable temperature ^{1}H-NMR spectra [$CDCl_3/CD_2Cl_2$ (1:1); 90 MHz)] of the dithia[3.1.3.1]metacyclophane 9 .

9 resulted from the intermolecular coupling of 7 , would suggest that the formation of the thia [3.1]metacyclophane 3 was discouraged due to possibly the angle/steric strains which would be induced in the system. Although [3.1]metacyclophane 2 had been synthesized, the reaction and conditions employed were of entirely different nature. It was thought that addition of another sulfur atom in the bridge such as in the dithia[4.1]-metacyclophane 10 would make the intramolecular coupling more favorable. A method[17] is also known for the possible conversion of dithiacyclophane (such as 10) to a thiacyclophane (such as 3) via desulfurization using tris(diethylamino)phosphine, $(Et_2N)_3P$. An attempt was thus made to investigate the oxidative coupling of the dithiol 8 as a potential route to the dithiacyclophane 10 .

Treatment of the dibromide 7 with two equivalents of thiourea in refluxing tetrahydrofuran gave a quantitative yield of the intermediate bis(thiouronium) salt which after hydrolysis in aqueous potassium hydroxide solution afforded the dithiol 8 as a colorless liquid. Besides an observed molecular ion at m/z 260 in its mass spectrum, the structure of 8 was evident from its ^{1}H-NMR spectrum. The doublet (typical coupling constant J = 8.0 Hz) for the $-C\underline{H}_2S-$ protons at $\delta 3.80$ and the triplet (J = 8.0 Hz) for the -S$\underline{H}$ protons at δ1.80 were characteristic of a benzylic thiol.

An intramolecular oxidative coupling of dithiols to medium-sized cyclic disulfides by titrimetry was recently reported[18] by Musker. A similar coupling of **8** was thus attempted as a possible route to **10**. Separate solutions of the dithiol **8** and iodine were added simultaneously using a syringe pump at a very low rate. The original procedure called for a rate of addition governed by the disappearance of the iodine color. However, the iodine color was not discharged completely after the addition in our attempt and thus the mixture was allowed to stir for 15 h before work-up. The crude product obtained from the reaction was chromatographed on silica gel with dichloromethane/hexane (1:1) as eluent to afford a white solid (one spot on TLC). Its ^{1}H-NMR spectrum, however, showed the presence of a small amount of undesired impurities. Recrystallization from cyclohexane gave a sample of colorless crystals, mp 204-206°C. Its ^{1}H-NMR spectrum indicated the expected singlets at δ3.90 and δ3.20 for the ArC$\underline{H}_2$Ar and -C$\underline{H}_2$S- protons respectively consistent with a conformationally mobile dithiacyclophane **10**. However, the mass spectrum of the sample gave a strong molecular ion at *m/z* 516 indicating the structure of the dimeric tetrathia[4.1.4.1]metacyclophane **11**. We believe that similar reason, namely possible strain induction in the system[§], had discouraged the intramolecular coupling of **8**. The oxidative coupling in our attempt might also be too slow, under the conditions employed, to afford the monomer **10** (thus formation of the dimer **11** was favored) as evident by the slow discharge of the iodine color during the reaction.

Results from studies using variable temperature ^{1}H-NMR sepctroscopy indicated no significant peak broadening of the -C$\underline{H}_2$S- and ArC$\underline{H}_2$Ar proton signals even at -80°C. This is not unexpected since addition of sulfur atom(s) to bridging chain(s) (compare **9** and **11**) is known to increase the conformational mobility of a cyclophane signifi-

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[§] Although [4.1]metacyclophane is known,[8] it was synthesized from a larger dithia[6.1]-metacyclophane via ring contraction. The conformational energy barrier in [4.1]metacyclophane was also found to be unexpectedly high compared to that of [3.1]metacyclophane **3**.

cantly.[2] The ^{1}H-NMR spectrum of **11** at room temperature, however, still showed a slightly shielded singlet for the H_x protons at δ6.88, a value comparable to that of the dithia[3.1.3.1]metacyclophane **9**. A possibility is that the tetrathia[4.1.4.1]-metacyclophane **11**, although having a much lower conformational energy barrier, exhibits a similar fluxional behavior as its dithia-analog **9** (**9a** $\rightleftarrows$ **9b**).

The conversion of **11** to **9** was next investigated. Desulfurization was readily achieved with tris(diethylamino)phosphine[19] to afford a 56% yield of the dithia-[3.1.3.1]metacyclophane **9**. This result suggests that the synthetic route via thiacyclophanes — $-CH_2SSCH_2- \rightarrow -CH_2SCH_2- \rightarrow -CH_2CH_2-$ — is still a potentially very useful sequence *for the preparation of strained cyclophanes (e.g.* **4** *from* **10** *as the* latter becomes available) via ring contraction as shown.

EXPERIMENTAL

Melting points were determined on a Sybron/Thermolyne MP12615 melting point apparatus and are uncorrected. The ^{1}H-NMR spectra were determined in $CDCl_3$ on a Perkin Elmer R32 (90 MHz) spectrometer. The low-temperature ^{1}H-NMR studies were carried out using $CDCl_3$/CD_2Cl_2 (1:1) as solvent. All chemical shifts are reported in ppm downfield from tetramethylsilane as internal standard. The IR spectra were recorded on a Perkin Elmer 1310 spectrophotometer [strong (s) and medium (m) bands are given]. Mass spectra were determined on a VG Micromass 7035 mass spectrometer at 70 eV using electron impact. Microanalyses were performed by the Microanalytical Laboratory of the Department of Chemistry, National University of Singapore.

Bis(3-bromomethylphenyl)methane **7**.

A solution of phosphorus tribromide (3.6 mL; 39 mmol) in dry benzene (20 mL) was added slowly to a vigorously stirred solution of the alcohol **6**[13](6.63 g; 29 mmol) in benzene (80 mL) at room temperature under nitrogen. After 2 h, the mixture was washed successively with water, aqueous $NaHCO_3$ and saturated NaCl solutions. The crude product was chromatographed on silica gel with cyclohexane as the eluent to yield colorless crystals of the dibromide **7**[14] (6.53 g; 63%), mp 60-62°C. ^{1}H-NMR δ7.60-6.95 (m, 8H, Ar$\underline{H}$), 4.45 (s, 4H, -C$\underline{H}_2$Br), 3.95 (s, 2H, ArC$\underline{H}_2$Ar); IR (KBr) 1490(m), 1440(m), 1250(m), 1210(s), 790(m), 700(s), 680(s) cm^{-1}; MS at *m/z* (relative intensity) 352 ($M^{+\bullet}$, 19, correct isotope pattern), 273 (100), 178 (35), 97 (48). HRMS calcd for $C_{15}H_{14}{}^{79}Br_2$, 351.9462;

found, 351.9461.

Sodium sulfide coupling of bis(3-bromomethylphenyl)methane **7** : isolation of 2,18-dithia[3.1.3.1]metacyclophane **9**.

The dibromide **7** (704 mg; 2 mmol) was dissolved in degassed benzene (30 mL). Sodium sulfide nonahydrate (506 mg; 2 mmol) was dissolved in distilled water (10 mL) and was then diluted to 30 mL with degassed absolute alcohol. The dibromide and sodium sulfide solutions were then added simultaneously from syringes using a syringe pump at a rate of 0.15 mL min^{-1}. The resultant mixture was then allowed to stir for an additional 15 h after the addition. The bulk of the solvent was then evaporated and water and dichloromethane were added. The crude product mixture obtained after usual work-up was chromatographed on silica gel using dichloromethane/hexane (3:7) as eluent. The dithiacyclophane **9** was isolated as colorless crystals (0.25 g; 55%), mp 188-190°C. ^{1}H-NMR δ7.40-7.05 (m, 12H, Ar$\underline{H}$), 6.93 (s, 4H, Ar$\underline{H}_x$), 3.90 (s, 4H, ArC$\underline{H}_2$Ar), 3.45 (s, 8H, -C$\underline{H}_2$S-); IR (KBr) 2920(m), 1610(s), 1590(s), 1490(s), 1450(s), 1250(m), 1230(s), 1170(m), 1160(m), 1095(m), 1080(m), 900(m), 880(m), 820(m), 800(s), 760(s), 740(s), 715(s) cm^{-1}; MS at *m/z* (relative intensity) 452 (M$^{+\bullet}$, 83), 387 (83), 226 (100). Anal. Calcd. for $C_{30}H_{28}S_2$: C, 79.60; H, 6.23. Found: C, 79.41; H, 6.50.

Bis(3-mercaptomethylphenyl)methane **8**.

A mixture of the dibromide **7** (2.07 g; 6 mmol), thiourea (0.90 g; 12 mmol) and tetrahydrofuran (100 mL) was heated at reflux for 3 h. After cooling to room temperature, the bulk of the solvent was removed under reduced pressure. The dithiouronium salt was then stirred at reflux with KOH (9.83 g; 175 mmol) in water (50 mL) for 4 h. The reaction mixture was cooled and conc. H_2SO_4/H_2O (1:1; 30 mL) was added to it slowly. The product was then extracted with ether. The organic layer was washed with water, dried and evaporated to give an oil. Filtration through silica gel gave the thiol **8** (1.19 g; 78%) as a colorless liquid. ^{1}H-NMR δ7.50-6.80 (m, 8H, Ar$\underline{H}$), 3.95 (s, 2H, ArC$\underline{H}_2$Ar), 3.80 (d, 4H, J = 8.0 Hz, -C$\underline{H}_2$SH), 1.80 (t, 2H, J = 8.0 Hz , -S$\underline{H}$); IR (neat) 1600(m), 1480(m), 1430(m), 1300(m), 700(s) cm^{-1}; MS at *m/z* (relative intensity) 260 (M$^{+\bullet}$, 15), 227 (70), 226(50), 193 (100), 178 (70), 165 (50), 135 (30). HRMS calcd for $C_{15}H_{16}S_2$, 260.0693; found, 260.0692.

Oxidative coupling of bis(3-mercaptomethylphenyl)methane **8** : isolation of 2,3,19,20-tetrathia[4.1.4.1]metacyclophane **11**.

Triethylamine (0.54 g; 5.30 mmol) dissolved in chloroform (150 mL) was placed in a 500-mL round-bottom flask and stirred at room temperature under nitrogen. Solutions of the dithiol **8** (0.67 g; 2.60 mmol) in chloroform (100 mL) and iodine (0.66 g; 2.60

mmol) in chloroform (100 mL) were added simultaneously to the stirred solution of Et$_3$N at a rate of 0.3 mL min^{-1} using a syringe pump. The reaction mixture was stirred for an additional 15 h after the addition and washed successively with saturated aqueous solution of sodium thiosulfate until the color of the solution appeared only pale yellowish. It was then further washed with 0.1N HCl and water. The organic layer was dried with anhydrous sodium sulfate and evaporated to give a yellow solid. Recrystallization from cyclohexane gave colorless crystals of the tetrathiacyclophane **11** (0.40 g; 60%), mp 204-206°C. ^{1}H-NMR δ7.20-6.90 (m, 12H, Ar$\underline{H}$), 6.88 (s, 4H, Ar$\underline{H}_x$), 3.90 (s, 4H, ArC$\underline{H}_2$Ar), 3.20 (s, 8H, -C$\underline{H}_2$S-); IR (KBr) 1605(s), 1590(s), 1090(s), 900(m), 890 (m), 810(s), 800(s), 760(s), 710(s), 640(m) cm^{-1}; MS at *m/z* (relative intensity) 516 (M$^{+\cdot}$, 60), 451 (100), 418 (20), 385 (24), 266 (28), 179 (85), 178 (85), 105 (55), 104 (43). HRMS calcd for C$_{30}$H$_{28}$S$_4$, 516.1074; found, 516.1074.

Desulfurization of 2,3,19,20-tetrathia[4.1.4.1]metacyclophane **11**.

A solution of the cyclophane **11** (103 mg; 0.2 mmol) and tris(diethylamino)phosphine[19] (99 mg; 0.4 mmol) in benzene (50 mL) was heated at reflux for 4 h. The solution was washed with water, dried and evaporated under reduced pressure. The residue was chromatographed on silica gel using dichloromethane/hexane (3:7) as eluent to yield colorless crystals of dithiacyclophane **9** (51 mg; 56%), identical (mp, ^{1}H-NMR, IR, MS) to the previously obtained sample.

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