Synthesis and Structure of [3.3]Orthocyclophane

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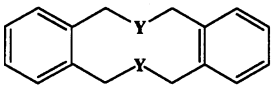
The title compound (**1**) was synthesized by desulfurization of 2,13-dithia[4.4]orthocyclophane. The molecular structure of **1** which has antiperiplanar arrangement of the two benzene rings was obtained by an X-ray crystallographic analysis. Molecular mechanics calculation using MM3 and our MMRS program has indicated that the anti structure found in crystal is the most stable conformer. Variable temperature ^{1}H NMR measurement has disclosed that the contribution of the conformers other than the anti is negligible.

The stereochemical aspects of mobile cyclophanes have been of particular theoretical interest for over the two decades.[1] A cyclophane having long bridges is known to be flexible with many conformational options. [3.3]Metacyclophanes have syn and anti arrangements of the benzene rings with several conformational variations of the bridging chains.[2]

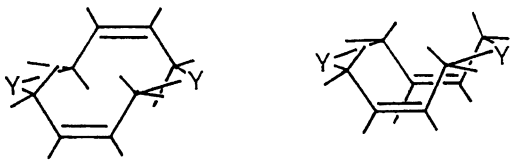
[3.3]Orthocyclophanes might be more flexible because there are two conformers even in a shorter bridging counterpart.[3] The basic skeleton of the [3.3]orthocyclophane is *cis,cis*-1,6-cyclodecadiene (Chart 1). The conformations of this skeleton have been discussed in terms of chair (C) and boat (B) forms (Chart 2).[4] The chair conformer has been claimed to be predominant.[5] However, it is still unclear whether or not the chair form is the only predominant form. The lack of efficient method for the analysis of the conformational behavior in solution is one of the main obstacles in studying a conformationally flexible molecule.

Recently we have developed a new and efficient method to elucidate conformational behavior of flexible molecules containing aromatic rings.[6] It utilizes the combination of molecular mechanics calculation (MM2[7] *inter alia*) and estimation of the secondary induced magnetic field due to an aromatic ring current. The validity of this method has been demonstrated by the successful determination of the most stable conformers of several flexible cyclophanes.[8] The conformational behavior of [3.3]orthocyclophanes having chalcogen atoms at the 2 and 11 positions is also analyzed by this method.[9] The chair-type anti conformer of both dithia and diselena analogues is found to be the most stable one in solution, whereas the conformer having anticlinal orientation of the two benzenes is most stable in the dioxa derivative.[10] The bond dipoles of carbon and chalcogen atoms might play a role controlling their conformations. In order to clarify this factor and to widen the applicability of our ring current method for the conformational analysis of flexible medium-ring compounds we have examined the most stable conformer of [3.3]-orthocyclophane (**1**).



1 Y=CH_2
2 Y=CD_2
7 Y=O
8 Y=S

Chart 1.



chair (C) boat (B)

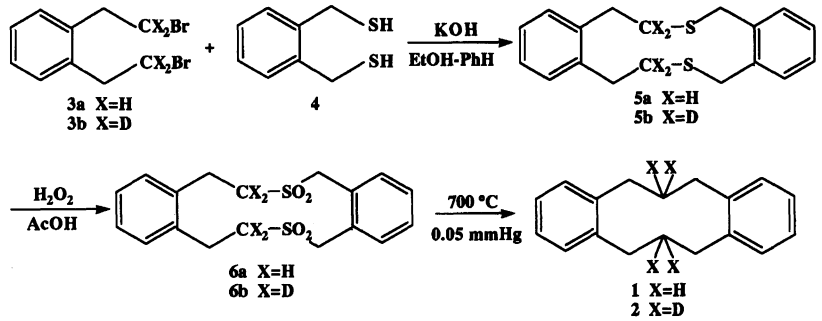
Chart 2.

Results and Discussion

Synthesis of 1. A sulfur extrusion route is usually employed for the synthesis of highly strained cyclophanes.[11] Though the compound **1** is not highly strained, this route was applied for the synthesis. The route consists of coupling a bis(mercaptoalkyl) derivative with a compound having two leaving groups to form a dithiaphane. Desulfurization of the dithia intermediate should give a desired cyclophane.

1,2-Bis(2-bromoethyl)benzene (**3a**) was then coupled in the presence of a base with 1,2-bis(mercaptomethyl)benzene (**4**) to give 2,13-dithia[4.4]orthocyclophane (**5a**) in 58% yield. Oxidation of **5a** with 30% hydrogen peroxide gave the corresponding disulfone (**6a**) in 91% yield. Flash vacuum pyrolysis of the resultant disulfone gave the desired [3.3]orthocyclophane (**1**) in 56% yield. In order to simplify the ^{1}H NMR splitting pattern of the trimethylene bridges of **1**, 2,2,11,11-tetradeuterio[3.3]-orthocyclophane (**2**) was prepared by the same reaction sequence starting from 1,2-bis(2-bromo-2,2-dideuterioethyl)benzene (**3b**) (Scheme 1).

X-Ray Crystallographic Analysis of 1. The ORTEP drawing of **1** is shown in Fig. 1. The compound **1** has antiperiplanar orientation of the two benzene rings in the crystalline state. Similar antiperiplanar conformation has been commonly observed in [3.3]orthocyclophanes having chalcogen atoms at the 2 and 11 positions.[9,10] Small but conspicuous difference of these structures is seen in the top view of **1** when compared to those of dioxa- (**7**) and dithia[3.3]ortho-



Scheme 1.

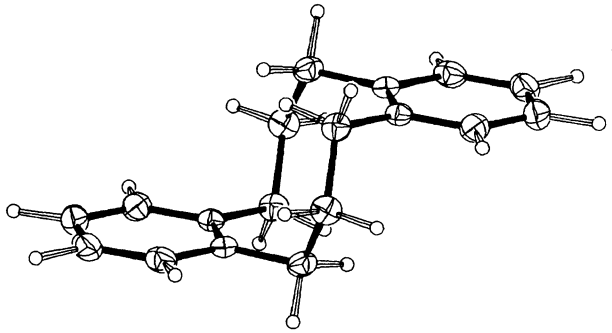


Fig. 1. ORTEP drawing of **1**.

cyclophanes (**8**). Sliding sideways of the benzene ring with respective to the other is common structural feature of [3.3]orthocyclophane with chalcogen atoms. Hydrocarbon analogue on the other hand does not have such sliding. The compound **1** has the highly symmetrical structure (C_{2h}) (Fig. 2). This C_{2h} structure was further supported by molecular mechanics calculation.

Molecular Mechanics Calculation of 1. Although the chair-type antiperiplanar structure is obtained by the X-ray crystallographic analysis, it does not give the conclusive evidence of the most stable structure. It is quite often to find that the structure in solution is different from that in crystal and especially so in case of extremely flexible macrocyclic compounds.[2b,12] In order to obtain information about the structure and conformational energies of **1** in solution, molecular mechanics calculations were performed. By use of the MM3[13] and our MMRS programs, the latter of which generates all the plausible initial geometries,[14] several possible structures are obtained. The structures and the relative energy differences of these conformers are shown in Fig. 3. There are only two syn structures (**S1** and **S2**) within the energy difference of 15 kJ mol^{-1} from the most stable one (**A1**).

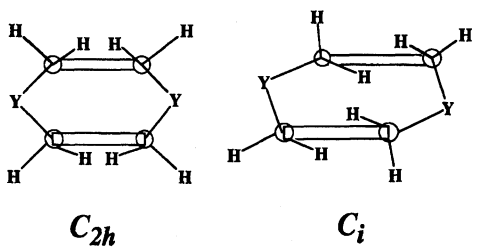


Fig. 2. Schematic presentation of side views of [3.3]-orthocyclophanes.

The structure of the most stable conformer is identical with that in the crystalline state and has highly symmetric C_{2h} form. Though [3.3]metacyclophane[2] has three syn forms, **1** has only two syn structures (**S1**, *syn*-chair-chair; **S2**, *syn*-chair-boat) within this energy limit. Severe steric repulsion between the two central methylene groups of the two trimethylene bridges needs enormous amount of energy cost in *syn*-boat-boat structure (54.56 kJ mol^{-1} from the **A1**). **A2** has anticlinal arrangement of the two benzene rings. **A3** has also anticlinal arrangement and is similar to the most stable conformer of **7** in solution. Again severe transannular steric repulsion between two inner hydrogens at the 2 and 11 positions destabilizes this structure significantly. Since the conformers **A2** and **A3** have extremely high (MM3) steric energies, it is hardly probable that these two conformers play an important role in the conformational equilibrium of **1**.

Conformational Behavior of 1 in Solution. In order to obtain further support of the predominance of the conformer **A1** in solution, magnetically induced shifts of the individual hydrogens of the probable conformers were estimated by the use of our ring current calculation. In accordance with both the X-ray analysis and the molecular mechanics calculations, the predominance of the anti structure was supported by comparison of the ^{1}H NMR chemical shift of the hydrogens of **1** with those of the reference compound, *o*-diethylbenzene. Small observed downfield shifts of the aromatic hydrogens (*o*; 0.12 and *m*; 0.04 ppm) and upfield shift of the bridging chain (0.24 ppm) are compatible with the calculated shifts of the anti structure (Table 1). Since both of the two possible syn structures should have the upfield induced shifts of aromatic hydrogens, it is concluded that the contribution of these two are negligible.

In order to analyze the conformational dynamic process, a sample of **2** was examined by ^{1}H NMR at 500 MHz over the temperature range at -100 to 50°C. When lowering the temperature, the sharp singlet due to the methylene signal became broad at 40°C and then split into AB quartet pattern below 27°C. The splitting pattern of the signals is essentially unchanged below 0°C

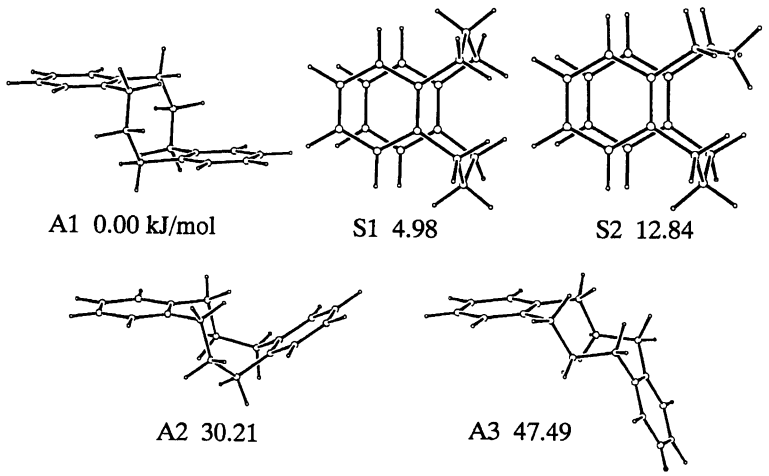


Fig. 3. Relative MM3 steric energies of the conformers of **1**.

Table 1. Induced Chemical Shifts[a] of **1** by Ring Current Method

Structure	CH_2	Aromatic	
		Ortho	Meta
A1	0.46	−0.07	−0.05
S1	0.01	0.43	0.51
S2	0.05	0.46	0.54
Obsd	0.24	−0.12	−0.04

a) A minus sign denotes downfield shift.

suggesting that the conformational dynamic process is slow down below this temperature. There is no signals assignable to a *syn* conformer even at −100°C. Since the chemical shifts of the methylene signals below 0°C are temperature dependent to some extent, the full line shape analysis for this process is not applicable. The free energy of activation of the conformational dynamic process was then estimated by a coalescence temperature method (64 kJ mol^{-1}, T_c=313 K). From the behavior of the temperature dependent signal change, it can be confirmed that the most stable conformation of **1** is the *anti* structure and the conformational dynamic process is the interconversion between the *anti* structure and its mirror image by flipping of the benzene rings. The *syn* structures might be intermediate in this flipping process, however, they could not be detected spectroscopically because of a small energy window (around 12.6 kJ mol^{-1}) of ^{1}H NMR method.

Experimental

All melting points were determined with a micro melting apparatus (Yanagimoto-seisakusho) and are uncorrected. The NMR, IR, and MS spectra were recorded on a JEOL model GSX 270 spectrometer, Hitachi 260-10s infrared spectrophotometer, and Hitachi RMu-6L mass spectrometer, respectively. The chemical shifts of NMR are reported in the δ-scale relative to tetramethylsilane (TMS) as an internal standard.

Material. Thin-layer chromatography (TLC) and flash column chromatography were performed by the use of Merck's aluminium sheets silica gel 60 F254 (Art.5554) and silica gel 60 particle size 0.063—0.200 mm (70—230 mesh ASTM), respectively.

Preparation of 1,2-Bis(2,2-dideuterio-2-hydroxyethyl)benzene (9). A solution of dimethyl 1,2-benzenediacetate[15] (0.50 g, 2.3 mmol) in THF (10 ml) was added dropwise using a dropping funnel into a suspension of $LiAlD_4$ (0.14 g, 3.4 mmol) in THF (20 ml) at 0°C for 1 h. After the addition, the mixture was stirred for 12 h at room temperature. Water (1 ml) was then added slowly. After stirring for 3 h, **9** was obtained by usual work-up, 0.38 g (quant.); colorless oil; MS *m/z* (rel intensity) 152 (M^+-H_2O, 17), 138 (50), 119 (100); ^{1}H NMR ($CDCl_3$) δ= 7.19 (s, 4H), 2.91 (s, 4H); ^{13}C NMR ($CDCl_3$) δ=137.07, 129.86, 126.58, 62.55, 35.29; IR (neat) 3340, 2210, 2110, 1490, 1120, 1095, 975, 955, 750 cm^{-1}; UV λ_{max} (95 % ethanol) 221 (ε 1470), 265 (210), 273 (150) nm. Found: C, 70.49; H, 8.45%. Calcd for $C_{10}H_{10}D_4O_2$: C, 70.58; H, 8.29%.

Preparation of 1,2-Bis(2-bromo-2,2-dideuterioethyl)benzene (3b). To a suspension of **9** (1.50 g, 8.8mmol) in THF (50 ml), triethylamine (4.0 ml, 28.8 mmol) was added slowly at 0°C. Methanesulfonyl chloride (1.7 ml, 22.0 mml) was then added dropwise to the solution over a period of 10 min at the same temperature. After stirring for 20 min, the precipitate was filtered. To the filtrate, lithium bromide (4.00 g, 46.0 mmol) was introduced, and the mixture was refluxed for 8 h. After filtration, the solvent was removed under reduced pressure. The residue was chromatograghed on silica gel with hexane as an eluant to give **3b**: 2.01 g (77%); colorless oil; MS *m/z* (rel intensity) 298 (13), 296 (M^+, 27), 294 (14), 217 (48), 215 (48), 119 (100); ^{1}H NMR ($CDCl_3$) δ=7.22 (m, 4H), 3.19 (s, 4H); ^{13}C NMR ($CDCl_3$) δ=136.92, 129.73, 127.41, 35.73, 31.51; IR (neat) 3030, 2160, 1490, 1105, 985, 760 cm^{-1}; UV λ_{max} (cyclohexane) 222 (ε 1580), 258 (80), 264 (80) nm. Found: C, 40.88; H, 3.91%. Calcd for $C_{10}H_8Br_2D_4$: C, 40.58; H, 4.09%.

Preparation of Dithia[4.4]orthocyclophanes (5a and 5b). A solution of dibromide **3** (0.86 g, 3.0 mmol) and 1,2-bis(mercaptomethyl)benzene **4** (0.50 g, 3.0 mmol) in degassed benzene (100 ml) was added dropwise using a dropping funnel into a well-stirred solution of KOH (0.49 g, 8.7 mmol) in degassed 99% ethanol (300 ml) under a nitrogen atmosphere. After the addition, the mixture was stirred for

12 h at room temperature. The bulk of the solvent was then removed under reduced pressure. CH_2Cl_2 and H_2O (1:1, 100 ml) were added, and the mixture was stirred for 30 min. The organic layer was then separated and the aqueous phase was extracted with CH_2Cl_2 (150 ml). The combined organic layers were washed with water, dried, and evaporated. The residue was chromatographed on silica gel with dichloromethane/hexane (1:1) as an eluant to afford 2,13-dithia[4.4]orthocyclophane (**5a**): 0.51 g (58%); colorless needles, mp 154—156°C (from CH_2Cl_2–EtOH); MS *m/z* (rel intensity) 300 (M^+, 88), 163 (100); ^{1}H NMR ($CDCl_3$) δ=7.59 (m, 2H), 7.23 (m, 2H), 7.11 (s, 4H), 3.87 (s, 4H), 2.80 (m, 4H), 2.71 (m, 4H); ^{13}C NMR ($CDCl_3$) δ=138.37, 137.12, 130.03, 129.79, 127.28, 126.69, 33.64, 33.10, 31.64; IR (KBr) 3060, 3025, 2990, 2910, 1490, 1460, 1415, 1215, 750, 720 cm^{-1}; UV λ_{max} (cyclohexane) 220 (ε 14300), 274 (sh, 470) nm. Found: C, 72.09; H, 6.88%. Calcd for $C_{18}H_{20}S_2$: C, 71.95; H, 6.71%.

3,3,12,12-Tetradeuterio-2,13-dithia[4.4]orthocyclophane (5b): 0.56 g (62%); colorless needles, mp 154—156°C (from CH_2Cl_2–EtOH); MS *m/z* (rel intensity) 304 (M^+, 13), 303 (12), 135 (100); ^{1}H NMR ($CDCl_3$) δ=7.59 (m, 2H), 7.23 (m, 2H), 7.11 (s, 4H), 3.87 (s, 4H), 2.79 (s, 4H); ^{13}C NMR ($CDCl_3$) δ=138.37, 137.14, 130.03, 129.79, 127.28, 126.67, 33.43, 32.48, 31.56; IR (KBr) 3060, 3025, 2990, 2215, 2180, 2125, 1495, 1460, 1240, 1080, 765, 750, 720 cm^{-1}. Found; C, 70.83; H, 6.56%. Calcd for $C_{18}H_{16}D_4S_2$: C, 71.01; H, 6.62%.

Preparation of Disulfones (6a and 6b). To a solution of dithia[4.4]orthocyclophane **5** (100 mg, 0.33 mmol) in acetic acid (5 ml), 0.7 ml (6.9 mmol) of 30% H_2O_2 solution was added at room temperature. After addition, the solution was warmed to 95—105°C and stirred for 5.5 h to give crystalline material. This was filtered, and dried to give disulfone **6**, 110 mg (91%).

2,13-Dithia[4.4]orthocyclophane *S,S,S',S'*-tetraoxide (6a): Colorless crystals, mp >300°C; MS *m/z* (rel intensity) 300 (M^+-SO_2, 7), 208 (10), 163 (8), 132 (27), 117 (54), 104 (100); IR (KBr) 1290, 1130 cm^{-1}. Found: C, 59.59; H, 5.23%. Calcd for $C_{18}H_{20}S_2O_4$: C, 59.32; H, 5.53%.

3,3,12,12-Tetradeuterio-2,13-dithia[4.4]orthocyclophane *S,S,S',S'*-tetraoxide (6b): Colorless crystals, mp >300°C; MS *m/z* (rel intensity) 304 (M^+-SO_2, 5), 211 (7), 167 (8), 136 (50), 119 (38), 104 (100); IR (KBr) 1290, 1130 cm^{-1}. Found: C, 58.97; H, 5.38%. Calcd for $C_{18}H_{16}D_4S_2O_4$: C, 58.68; H, 5.47%.

Preparation of [3.3]Orthocyclophanes (1 and 2). Disulfone **6** was placed in a quarts tube, and pyrolyzed at 700°C under reduced pressure (0.05 mmHg, 1 mmHg= 133.322 Pa) with a fine flow of nitrogen. The product was then chromatographed on silica gel with hexane as an eluant, and recrystallized from CH_2Cl_2–EtOH to give [3.3]-orthocyclophane (**1**) in 56% yield; colorless plates, mp 153—155°C (from CH_2Cl_2–EtOH); MS *m/z* (rel intensity) 236 (M^+, 100), 207 (16), 193 (8); ^{1}H NMR ($CDCl_3$) δ=7.18 (m, 4H), 7.11 (m, 4H), 2.39 (m, 8H), 2.16 (m, 4H); ^{13}C NMR ($CDCl_3$) δ=140.30, 128.87, 125.83, 32.93, 26.95; IR (KBr) 3060, 3025, 2990, 2920, 2855, 1950, 1920, 1490, 1460, 1445, 1355, 1270, 1155, 800, 750 cm^{-1}; UV λ_{max} (cyclohexane) 222 (ε 3590), 276 (880), 268 (920) nm. Found: C, 91.45; H, 8.55%. Calcd for $C_{18}H_{20}$: C, 91.47; H, 8.53%.

2,2,11,11-Tetradeuterio[3.3]orthocyclophane (2): 66% yield; colorless plates, mp 154—156°C (from CH_2Cl_2–EtOH); MS *m/z* (rel intensity) 240 (M^+, 100), 209 (15), 195 (10); ^{1}H NMR ($CDCl_3$) δ=7.18 (m, 4H), 7.11 (m, 4H), 2.38 (s, 8H); ^{13}C NMR ($CDCl_3$) δ=140.28, 128.85, 125.79, 32.17, 26.76; IR (KBr) 3060, 3025, 2990, 2900, 2855, 2200, 2150, 2105, 1490, 1460, 1440, 1290, 1060, 770, 740, cm^{-1}. Found: C, 89.88; H, 9.93%. Calcd for $C_{18}H_{16}D_4$: C, 89.94; H, 10.06%.

X-Ray Analysis of 1. The crystals of **1** belong to a monoclinic system with cell dimensions a=12.665(2), b=6.891(1), c=7.687(2) Å, β=92.44(1)°, and V=670.3(2) Å^3. The space group is $P2_1/n$ and Z=2. The empirical formula is $C_{18}H_{20}$, molecular weight is 236.36, and calculated density is 1.171 g cm^{-3}. The three-dimensional X-ray data were collected by the use of graphitemonochromated Mo $K\alpha$ radiation (λ=0.71073 Å) on a Rigaku AFC-4 automatic four-circle diffractometer up to a maximum 2θ of 55°. The intensity data of 1440 independent reflections were collected and 1223 with $|F_o|>3\sigma|F_o|$ were used in the present X-ray analysis. The structure was solved by the direct method (SHELXS-86). All non-hydrogen atoms were located on the initial E synthesis. Remaining hydrogens were located by the difference Fourier map and included in the further calculations. Block-diagonal least squares refinements with anisotropic 9 non-hydrogen atoms and 10 isotropic hydrogens have converged to a conventional R factor of 0.072. All the calculations were done on a HITAC M-680H computer of Hiroshima University using a structure analysis program system UNICS3.[16] Tables of observed and calculated structure factors, listing of atomic positional and anisotropic thermal parameters of non-hydrogen atoms, atomic parameters of hydrogen atoms, complete lists of bond distances and angles with their estimated standard deviations have been deposited as Document No. 66010 at the Office of the Editor of Bull. Chem. Soc. Jpn.

The measurement of ^{1}H and ^{13}C NMR spectra was made at Instrument Center for Chemical Analysis, Hiroshima University. The present work was partially supported by a Grant-in-Aid for Scientific Research No. 04453026 from the Ministry of Education, Science and Culture.

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