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Synthesis and Conformational Study of 9,18-(Ethylenedioxy)-2,11-dithia[3.3]metacyclophane: The Propelling Behavior of the Three Bridges in a [3.4.3](1,2,3)Cyclophane

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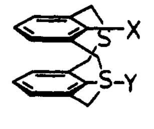
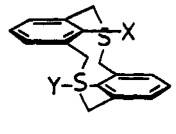
A general approach which involved first the introduction of the central oxy or dioxy bridge and subsequent intramolecular coupling reactions to form the two thia bridges was employed in the syntheses of the 1,2,3-triply bridged cyclophanes **2**, **3**, and **4**. The attempted routes to potential precursors of **2** were unsuccessful while the tetrabromide **16** could be synthesized. Intramolecular cyclizations of the latter, however, failed to yield **4**, possibly due to unfavorable stereochemistry of the intermediate leading to the second intramolecular coupling reaction. The tetrabromide **18**, with a central bridge of an appropriate length, successfully led to the formation of **3**. The conformational behavior of **3** was analyzed by dynamic ^{1}H NMR spectroscopy. The ethylenedioxy bridge is believed to adopt the symmetrical "boat" conformation. All three bridges, however, undergo unrestricted pseudorotation, represented by free conformational interconversion **3b** $\rightleftarrows$ **3c**, at room temperature. A relatively frozen conformation **3b** (**3c**) was observed at the low-temperature limit. Flipping processes of the ethylenedioxy bridge and the two thia bridges are found to be interdependent, resulting in an overall propelling process with a common conformational barrier estimated at ca. 45 kJ mol^{-1}.

Introduction

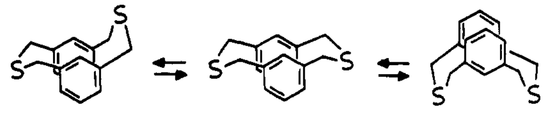
Conformational analysis[1] of the parent 2,11-dithia[3.3]metacyclophane, **1**, which was initially thought to exist in various syn and anti conformations in rapid equilibrium,[2,3] has shown that only the syn conformer, *syn*-**1** (X = Y = H), could be detected in the crystalline state as well as in solution. In fact substitution of H9 with various substituents (X = F,[3,4] CH_3,[5-7] NO_2;[8] Y = H) and even bulky groups (X = $(CH_3)_3C$,[7,9] C_6H_5;[6,10,11] Y = H) still makes *syn*-**1** the preferred conformer. The only known exception seems to be *anti*-**1** (X = NH_2; Y = H).[8] Even in the absence of syn $\rightleftarrows$ anti interconversion, there remain three other interesting aspects in the conformational behavior of *syn*-**1** (X = Y = H): the bridge-wobbling processes, **1a** $\rightleftarrows$ **1b**; the ring-flipping processes, **1b** $\rightleftarrows$ **1c**; and the ring-tilting processes, **1d** $\rightleftarrows$ **1e**. Although the above phenomena could not be studied directly from the conformational analysis[1] of *syn*-**1** (X = Y = H), perhaps due to very low conformational barriers, they could, however, be observed in its derivatives and related cyclophane systems.[7] For example, dynamic ^{1}H NMR study[7] of *syn*-**1** (X = $(CH_3)_3C$; Y = H) gave the first evidence for the bridge-wobbling processes represented by **1a** $\rightleftarrows$ **1b**. Substitution of both X and Y in *syn*-**1** with bulky groups would in principle be expected to favor the conformation **1b** based on steric consideration. The syntheses[12-14] of such derivatives, however, led to only *anti*-**1** or a mixture of anti and syn isomers which in some cases could be separated only with difficulty. The obvious solution to ensure a syn conformation is thus to bridge C9 and C18 in the 2,11-dithia[3.3]metacyclophane system.



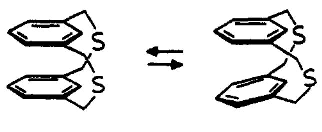
syn-1



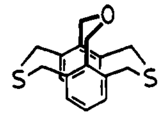
anti-1



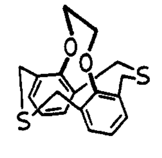
1a 1b 1c



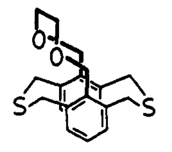
1d 1e



2a



3a



4a

The initial target in our work was to synthesize the three 9,18-bridged systems **2a**, **3a**, and **4a**. The introduction of the heteroatoms has an advantage in that dynamic changes in the bridges could then be observed readily by dynamic ^{1}H NMR spectroscopy due to simpler splitting patterns compared with those of a hydrocarbon bridge. With increasing "bulkiness" of the 8,19-bridge going from **2a** to **3a** to **4a**, if all three were synthetically accessible, a comparative study involving the bridge-wobbling processes represented by **1a** $\rightleftarrows$ **1b** may be possible. In addition, it would be interesting to study the conformational behavior of the central 8,19-bridges in **2a**, **3a**, and **4a**, which may

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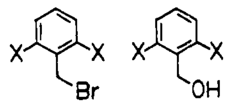
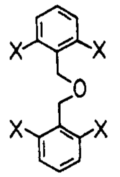
resemble those of the heterocycles tetrahydrofuran (twist conformation),[15-17] 1,4-dioxane (symmetric chair conformation),[18-21] and 1,4-dioxocane (boat-chair conformation),[22] respectively.

Results and Discussion

Attempted Routes to 2 and 4. The general synthetic approach involved first the introduction of the central oxy bridge and a subsequent intramolecular coupling reaction[23] to form the two thia bridges. It was found that hydrolysis (KOH/THF/water) of **5**[24] to **6** could not be achieved. A similar reaction (KOH/dioxane), however, gave **8** from **7**.[25] Nucleophilic substitution of **7** with the alkoxide ion of **8** afforded **11** in a 95% yield. The conversion of **11** to **12** via the von Braun reaction[26] was unsuccessful, presumably due to thermal cleavage of the benzylic linkage leading to decomposition or polymerization similar to some examples reported earlier.[27] Milder reaction conditions, however, resulted in mixtures of inseparable products. In an attempt to prepare **13**, conversion of **9**[24] to **10** again failed. The synthetic approach to **2** was thus in our hands unsuccessful.

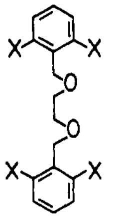


		X
5	6	CN
7	8	Cl
9	10	$COOCH_3$

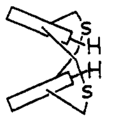


	X
11	Cl
12	CN
13	$COOCH_3$

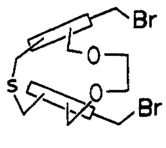
The dianion of ethylene glycol was treated with 2 equiv of **9** to yield **14**, which after reduction with lithium aluminum hydride afforded **15** in a quantitative yield. Treatment of **15** with phosphorus tribromide gave, after chromatography, the tetrabromide **16**. Intramolecular coupling of the latter with sodium sulfide under high dilution conditions[23] was then attempted to introduce the two thia bridges. The results observed were, however, disappointing. A seemingly polymeric product mixture was obtained, and column chromatography did not give any characterizable product either. The preference for *syn*-**1** (X = Y = H) to *anti*-**1** (X = Y = H; which is believed to experience torsional strains in the bridges)[28] could be partly due to the fact that the two flexible bridges and the sterically nondemanding 9,18-protons allow the two aryl rings to tilt at a favorable angle and minimize their unfavorable π-π interaction (see I). However, after the introduction of the first thia bridge via **16**, molecular models show that the longer central dioxy bridge would cause the two aryl rings to tilt as shown in II, thus directing the two bromomethyl groups away from each other and resulting in a more difficult second intramolecular coupling desired. In addition, molecular models also suggest that the presence of the central dioxy bridge would "lock" the two aryl rings in **4** more parallel (see III), leading to more significant but undesirable π-π interaction.



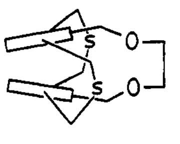
	X
14	CO_2CH_3
15	CH_2OH
16	CH_2Br



I

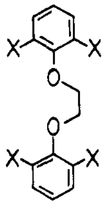


II



III

Dithiacyclophane 3. If the above argument is correct, molecular models would suggest that **18**, with a central bridge of a more appropriate length, would allow more favorable intramolecular coupling reactions to introduce the two thia bridges. Treatment of 1,2-dibromoethane with the phenoxide ion prepared from 2,6-dimethylphenol in refluxing ethanol gave a low yield of **17** (ca. 15%), presumably due to elimination of hydrogen bromide from 1,2-dibromoethane. After much experimentation, good yields (>70%) of **17** could be obtained by using a slight excess of 1,2-dibromoethane with the phenoxide ion added in portions and carrying out the reaction in THF at room temperature. Bromination of **17** with 4 equiv of NBS did not afford the desired product cleanly, but repeated chromatography did, however, lead to isolation of the desired **18** in >30% yield. Intramolecular coupling of **18** was then carried out with sodium sulfide and the dithiacyclophane **3**, which showed a strong molecular ion at m/z 330 in its mass spectrum, was isolated in >40% yield.



	X
17	CH_3
18	CH_2Br

The ^{1}H NMR spectrum (90 MHz) of **3** at room temperature is shown in Figure 1a. The aromatic protons of **3**, unlike those of **1** (X = Y = H[2] or CH_3[12]), are well resolved as an AB_2 system at δ 6.69, 7.02. The B protons are perhaps deshielded slightly by the anisotropic effect of the sulfur atoms (see **3b–e**). The methylene protons in the dioxy bridge appear as a singlet at δ 5.02, clearly indicating unrestricted pseudorotation in the bridge. The methylene protons in the thia bridges, however, are observed as an AB quartet ca. 1.2 ppm apart at δ 3.40, 4.64. These are believed to be the averaged chemical shifts resulting from

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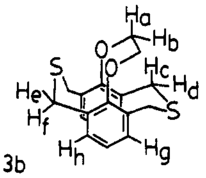
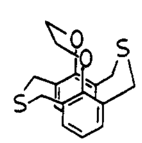
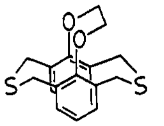


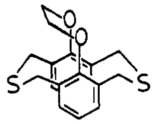
3b



3c



3d



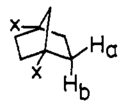
3e

rapid conformational interconversion among **3b–c** (see below) within the NMR timescale. The doublet at δ 4.64 corresponds to the pseudoaxial protons deshielded by the anisotropic effect of the oxygen atoms. This is supported by the fact that the chemical shifts of the corresponding AB quartet in **1** (X = Y = CH_3)[12] are only 0.2 ppm apart while those of **1** (X = Y = F)[3,4] appear at δ 3.43 and 4.34, comparable to values observed for **3**.

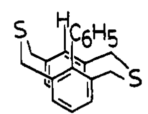
Dynamic NMR Studies of 3. The temperature-dependent ^1H NMR spectra were determined in a mixture of $CD_2Cl_2/CDCl_3$ (1:1) with the lower limit at −80 °C at which gradual percipitation of the sample was observed. As the temperature was lowered from 30 °C (Figure 1a) all signals seemed to broaden, although to different extent. At −50 °C, the inner two signals of the quartet of A protons (δ 7.02) of the aromatic AB_2 system were no longer resolved. The doublet of the B protons (δ 6.69) of the aromatic AB_2 system and that of pseudoequitorial protons (δ 3.40) of the thia bridges were broadened significantly. The singlet (δ 5.02) corresponding to the methylene protons of the dioxy bridge collapsed completely and the doublet of the pseudoaxial protons (δ 4.64) of the thia bridges was barely observable.

The spectrum at −80 °C, at which **3** seems to exist in a relatively frozen conformation, is shown in Figure 1b. Results from decoupling experiments and integration ratios clearly support that there are three sets of AB quartets corresponding to the bridging methylene protons, two pairs of doublets, however, overlap as indicated, and one peak of another doublet was concealed by the solvent signal. As for the aromatic protons, the B protons of the AB_2 system are now resolved into two slightly overlapping broad doublets.

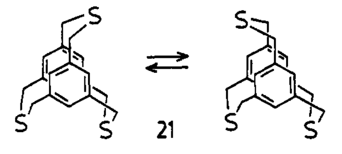
1,4-Dioxane is believed to adopt the symmetrical chair conformation.[18-21] A similar preference in the dioxy bridge as in **3a** would be expected to result in a complicated splitting pattern for the methylene protons. The observed broad AB quartet for H_a and H_b is, however, more consistent with a frozen symmetrical boat dioxy bridge as in **3b**/**3d** or **3c**/**3e**. This is also supported by the fact that H_a and H_b in **19** were also observed (100 MHz) as a broad AB quartet.[29] The singlet at δ 5.04 (Figure 1a) is in fact, within experimental error, at the average position of the AB quartet at δ 4.83, 5.29 (Figure 1b). Due to partial overlap of signals, the exact point at which the AB quartet for H_a and H_b coalesce could not be determined accurately, although it could be estimated at ca. −50 °C. Using the coalescence temperature method,[30,31] the transition state free energy at coalescence, $\Delta G_c^{\ddagger}$, which gives an indication of the conformational barrier, was estimated ($\Delta\nu$ = 40.8 Hz; J = 14.9 Hz) to be ca. 45.2 kJ mol^{-1}.



19 X = Br, I



20



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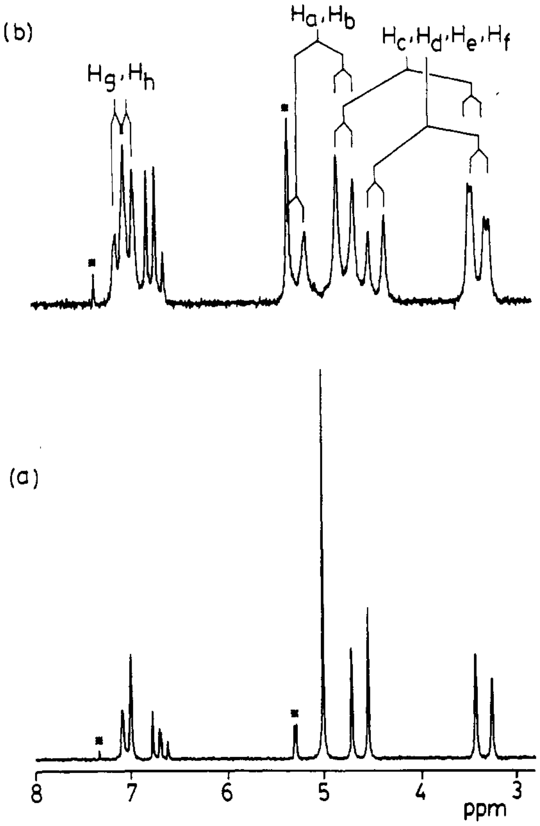

Figure 1. ^1H NMR spectra of 9,18-(ethylenedioxy)-2,11-dithia[3.3]metacyclophane **3** at (a) 30 °C, (b) −80 °C [*: solvent peaks].

The methylene protons in the thia bridges appear as two separate AB systems (δ 3.47, 4.82; δ 3.43, 4.49) which, from measurement of coupling constants (J = 14.9, 14.4 Hz, respectively), could be matched accordingly (Figure 1b). Assignment of H_c, H_d, H_e, and H_f are, however, not practical based on the data available. The above data could correspond to a frozen conformation **3b** (**3c**) or they could be the averaged chemical shifts resulting from the conformational process **3b** ⇄ **3d** (**3c** ⇄ **3e**). The former is supported by the report[6] that **20** exists in the conformation shown both in solid and in solution at the low-temperature limit. On the other hand, bridge-wobbling processes similar to **3b** ⇄ **3d** (**3c** ⇄ **3d**) are known to involve rather low barriers.[3,7] In fact the conformational analysis[32,33] of **21** indicated that one of the thia bridges undergoes the dynamic process even in the crystal state.

From the dynamic ^1H NMR studies, the coalescence of the two doublets at δ 3.43 and 3.47 (Figure 1b) could not be determined due to the very similar chemical shifts; that of the two doublets at δ 4.49 and 4.82 (Figure 1b), which

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seemed to reappear as an averaged doublet at δ 4.64 (Figure 1a), could, however, be estimated at −55 °C. The above data ($\Delta\nu$ = 29.7 Hz) would correspond to a conformational barrier, $\Delta G_c^{\ddagger}$, of 45.3 kJ mol^{-1} for the thia bridges. This is, within experimental error, exactly identical with the value obtained earlier for the ethylenedioxy bridge. Based on the above observation, it is very likely that the conformational behavior of **3** is indeed represented by **3b** $\rightleftarrows$ **3c**. The wobbling processes of the dioxy bridge and the two thia bridges are in fact interdependent, resulting in an overall propelling process involving one common conformational barrier. The frozen conformation is thus **3b** (**3c**) similar to that of **20**.[6] With one of the thia bridges frozen in **3b** (**3c**) at the low-temperature limit, H_g would be expected to experience perhaps a more significant anisotropic effect of the sulfur atom, and thus H_g and H_h are slightly resolved (Figure 1b).

Experimental Section

All melting points were determined using a Sybron/Thermolyne MP 2615 melting point apparatus and were uncorrected. The ^{1}H NMR spectra were determined using $CDCl_3$ on a JEOL FX90Q (90 MHz) Fourier transform spectrometer. All the chemical shifts are reported in ppm downfield from tetramethylsilane as an internal standard. Infrared spectra were recorded on a Perkin-Elmer 1310 infrared spectrometer. Mass spectra were determined on a VG Micromass 7035 mass spectrometer at 70 eV, electron impact being used. Only the molecular ion containing ^{79}Br is given for **18**. A correct isotope pattern was observed. Microanalyses were performed by the Microanalytical Laboratory of the Department of Chemistry, National University of Singapore. All evaporations were carried out under reduced pressure on a rotary evaporator at ca. 40 °C, and all organic layers were washed with water (unless otherwise stated) and dried with anhydrous magnesium sulfate.

1,2-Bis(2,6-dimethylphenoxy)ethane (17). Sodium hydroxide (6.5 g, 164 mmol) was added to a solution of 2,6-dimethylphenol (20.0 g, 164 mmol) in THF (150 mL) to form the corresponding phenoxide ion. 1,2-Dibromoethane (33.8 g, 180 mmol) was then added, and the mixture was stirred for 12 h at room temperature. Another portion of the phenoxide ion (164 mmol) was prepared and added. After being stirred for a further 12 h at room temperature, the mixture was poured into water and the product was extracted into dichloromethane. The organic layer was washed, dried, and evaporated. The crude product mixture was chromatographed on silica gel using chloroform/hexane (1:1) as eluant to give **17**, 32.0 g (72%), as a thick colorless oil: ^{1}H NMR δ 6.9–7.1 (m, 6 H, ArH), 4.10 (s, 4 H, CH_2), 2.33 (s, 12 H, CH_3); IR (neat) 1470, 1370, 1355, 1258, 1190, 1086, 1060, 1020, 915, 810, 765 cm^{-1}; MS ($M^{\cdot+}$) m/z 270 (36), 149 (78), 148 (10), 122 (30), 121 (34), 106 (11), 105 (100); M_r calcd for $C_{18}H_{22}O_2$ 270.1620, found (MS) 270.1603.

1,2-Bis(2,6-bis(bromomethyl)phenoxy)ethane (18). This was prepared by bromination of **17** (a total of 4.67 g, 17.2 mmol) with 4 equiv of NBS (12.27 g, 68.6 mmol) in three separate attempts. In each reaction NBS was added to a solution of **17** in carbon tetrachloride (ca. 150 mL) followed by a catalytic amount of benzoyl peroxide. The mixture was then heated at reflux by irradiation from a 200-W tungsten lamp until all NBS reacted. After being cooled to room temperature, the mixture was filtered, and the filtrate was washed with aqueous $NaHCO_3$ solution and water. The organic phase was dried and evaporated. Repeated chromatography on silica gel was carried out using hexane/dichloromethane (3:1) as eluant. The combined yield of **18** was 3.35 g (33%). Recrystallization from chloroform/cyclohexane gave colorless crystals of **18**: mp 158–159 °C; ^{1}H NMR δ 7.17, 7.42 (AB_2, J = 7.9 Hz, 6 H, ArH), 4.71 (s, 8 H, CH_2Br), 4.59 (s, 4 H, CH_2O); IR (KBr) 1580, 1460, 1445, 1425, 1355, 1230, 1210, 1185, 1065, 1040, 1030, 905, 790, 755 cm^{-1}; MS ($M^{\cdot+}$) m/z 582 (0.6), 503 (4), 305 (25), 225 (20), 199 (15), 147 (13), 146 (30), 119 (100). Anal. Calcd for $C_{18}H_{18}Br_4O_2$: C, 36.90; H, 3.10. Found: C, 36.93; H, 3.01.

9,18-(Ethylenedioxy)-2,11-dithia[3.3]metacyclophane (3). A solution of 95% sodium sulfide nonahydrate (0.60 g, 2.36 mmol) in 95% ethanol (200 mL) and a solution of **18** (0.69 g, 1.18 mmol) in benzene (200 mL) in separate rotaflow dropping funnels were added dropwise simultaneously at the same rate to nitrogen-purged 95% ethanol (1 L) under nitrogen. After the addition, the mixture was stirred for another 15 h and the bulk of the solvent was removed under reduced pressure. Water and dichloromethane were added to the residue, and the mixture was stirred until all solids dissolved. The organic layer was separated, dried, and evaporated. The residue was chromatographed on silica gel using dichloromethane/hexane (1:1) as eluant to yield **3**, 0.17 g (44%). Recrystallization from benzene/cyclohexane gave colorless crystals of **3**: mp >320 °C dec; ^{1}H NMR δ 6.69, 7.02 (AB_2, J = 7.6 Hz, 6 H, ArH), 5.04 (s, 4 H, CH_2O), 3.40, 4.64 (AB q, J = 15.1 Hz, 8 H, CH_2S); IR (KBr) 1445, 1320, 1235, 1215, 1195, 1080, 1040, 940, 905, 865, 790, 740 cm^{-1}; MS ($M^{\cdot+}$) m/z 330 (80), 239 (30), 211 (22), 179 (22), 178 (22), 177 (62), 151 (64), 145 (45), 144 (29), 119 (100), 91 (68). Anal. Calcd for $C_{18}H_{18}O_2S_2$: C, 65.42; H, 5.49. Found: C, 65.29; H, 5.25.

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Supplementary Material Available: Full experimental procedures for the preparation of **8**, **11**, **14**, **15**, and **16** (4 pages). Ordering information is given on any current masthead page.