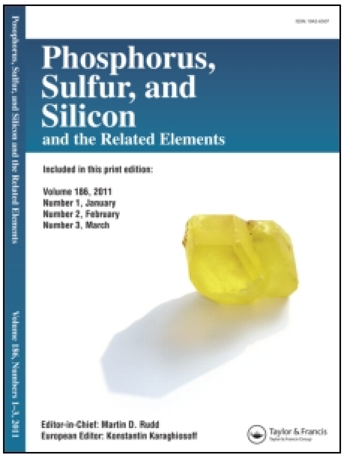

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STEREOCHEMISTRY OF HINDERED CYCLOPHANES. THE CONFORMATIONAL PROPERTIES OF SOME TETRAMERIC METACYCLOPHANES INCORPORATING MESITYLENE UNITS

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STEREOCHEMISTRY OF HINDERED CYCLOPHANES. THE CONFORMATIONAL PROPERTIES OF SOME TETRAMERIC METACYCLOPHANES INCORPORATING MESITYLENE UNITS

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The stereochemistry in solution of 16- to 20-membered metacyclophanes having mesitylene units connected by methylene, sulphide, and/or disulphide linkages, has been investigated by means of ^1H n.m.r. spectroscopy. Depending upon the size of the ring system, *saddle* or *crown* conformation is preferred. Remarkably, within the crown conformation adopted by the 18-membered metacyclophanes with alternating disulphide and methylene or sulphide linkages, *the single bridged dimesityl moieties approach the butterfly configuration.*

The stereochemistry of macrocyclic compounds derived from mesitylene is of interest, because these bulky moieties have been shown to cause severe distortions of the bonds in medium-sized metacyclophanes,[1] to confer a great deal of stereospecificity in particular ring-closure reactions involving the formation of polysulphur bridging chains,[2] and to induce conformational preferences even in larger ring systems.[3]

During the last decade a variety of conformationally interesting (poly)sulphur-bridged macrocycles have been prepared by the one-pot reaction of activated aromatic substrates with sulphur chlorides under catalytic conditions.[4–6] Among these macrocycles, the 18-membered 1,2,16,17-tetrathia- and 1,2,9,16,17,24-hexathia-[2.1.2.1] metacyclophanes **3** and **4** have been obtained from dimesityl methane **6**[5b] and dimesityl sulphide **7**,[5a] respectively. However, the structurally related dimesityl ether failed to give the expected 18-membered macrocycle with alternating disulphide and ether linkages, and steric hindrance effects of methyl substituents have been supposed to play a deleterious role in the crucial cyclization step.[7]

These observations sparked our interest in the stereochemistry of these hindered 18-membered bis-disulphide ring systems, and in this paper we correlated the ^1H n.m.r. spectral data of tetrameric metacyclophanes **1** and **3–5**, having mesitylene

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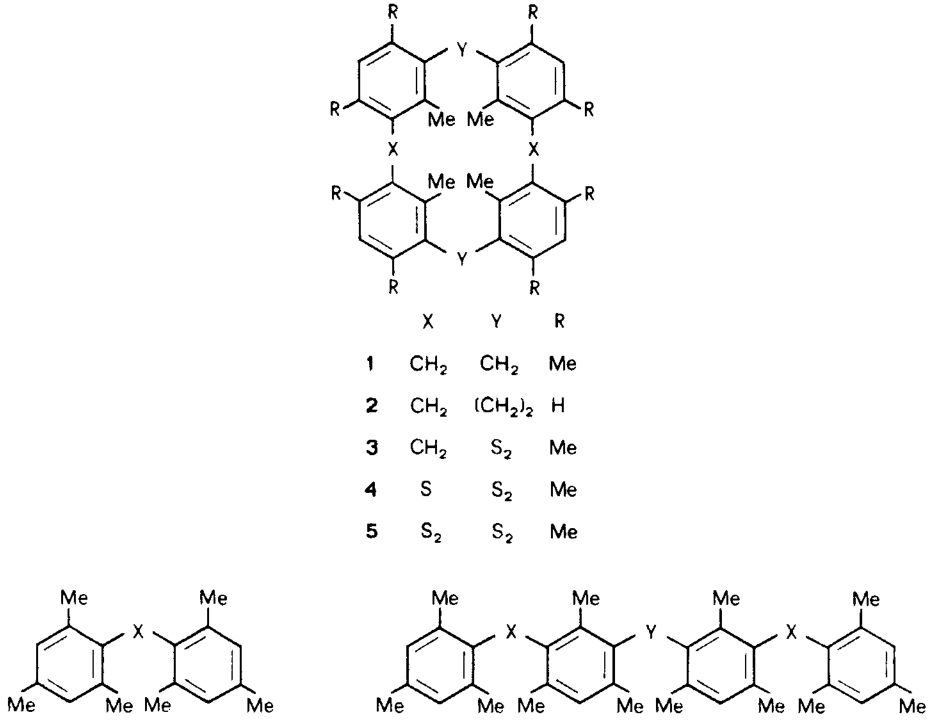
units connected by methylene, sulphide, and/or disulphide linkages, to those of suitable cyclic and open-chain models **2**[8] and **6–10**, in order to define the conformational preferences in solution of **3** and **4**. The compounds investigated are shown in Scheme 1.



	X	Y	R
1	CH_2	CH_2	Me
2	CH_2	$(CH_2)_2$	H
3	CH_2	S_2	Me
4	S	S_2	Me
5	S_2	S_2	Me

	X
6	CH_2
7	S
8	S_2

	X	Y
9	CH_2	CH_2
10	CH_2	S_2

SCHEME 1

RESULTS AND DISCUSSION

The spectral parameters of macrocycles **1–5** are listed in Table I, while those of open-chain model compounds **6–10** are shown in Table II. Because of the sparing solubility of cyclic bis-disulphides **3–5** in most solvents, deuterated nitrobenzene was our solvent of choice; nevertheless, we were able to get their ^1H n.m.r. spectra only at temperatures as high as 150°C. The spectra of the remaining compounds were run in the same solvent at both 35 and 150°C; however, the variation of the chemical shifts with the temperature did not exceed 0.2 ppm (Tables I and II).

TABLE I

Proton magnetic resonance parameters of metacyclophanes **1–5** in $C_6D_5NO_2$

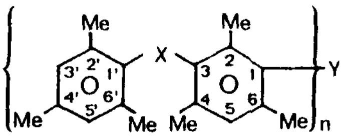
Compound	Temp. (°C)	R	Me	X	Y	ArH
1	35	2.32 $(2.37)^{a}$	0.84 $(1.08)^{a}$	3.58 $(3.93)^{a}$	3.58 $(3.93)^{a}$	6.62 $(6.82)^{a}$
R = Me; X = Y = CH_2	150	2.32	0.98	3.78	3.78	6.71
$\mathbf{2}^{a,b}$	−20	5.9–7.1	1.18, 2.38	3.68	2.5–3.0	5.9–7.1
R = H; X = CH_2; Y = $(CH_2)_2$	120^{c}	6.5–7.0	1.76	3.69	2.95	6.5–7.0
3	150^{d}	2.09	2.27	3.92	—	6.75
R = Me; X = CH_2; Y = S_2						
4	150^{d}	1.98	2.29	—	—	6.65
R = Me; X = S; Y = S_2						
5	150^{d}	2.37	2.46	—	—	6.94
R = Me; X = Y = S_2						

[a] In chloroform.
[b] From Ref. 2.
[c] In hexachlorobutadiene.
[d] Saturated solution.

Inspection of molecular models reveals that the 16-membered hydrocarbon metacyclophane **1** could adopt a *basket* **1a** as well as a *saddle-shape* conformation **1b** (shown in Figure 1). A comparison of the chemical shift of the intra-annular methyl groups in **1** (0.84 ppm at 35°C and 0.98 ppm at 150°C) with those of the corresponding methyl groups in model compounds **6** and **9** (1.99 ppm at 35°C and 2.05 ppm at 150°C) rules out the basket conformation **1a**. In fact, the observed

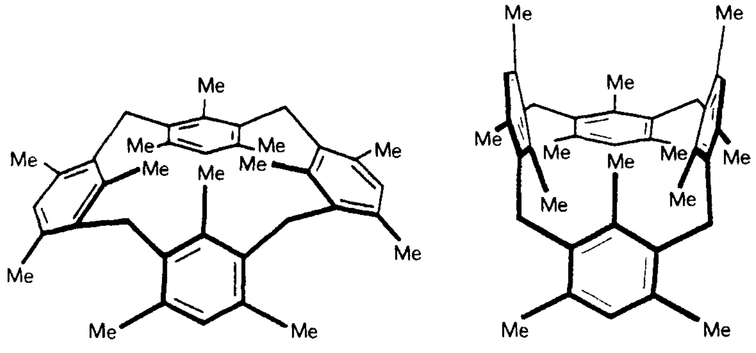
TABLE II

Proton magnetic resonance parameters of bridged di- and tetra-mesityls **6–10** in $C_6D_5NO_2$



Compound	Temp. (°C)	C-2 Me	C-4 Me	C-6 Me	C-2′,6′ Me	C-4′ Me	X	ArH
6	35	1.99	1.99	2.18	1.99	2.18	3.79	6.68
n = 1; X = CH_2; Y = H	150	2.05	2.05	2.20	2.05	2.20	3.94	6.73
7	35	2.12	2.12	2.22	2.12	2.22	—	6.72
n = 1; X = S; Y = H	150	2.20	2.20	2.20	2.20	2.20	—	6.80
8	35	2.17	2.17	2.17	2.17	2.17	—	6.72
n = 1; X = S_2; Y = H	150	2.27	2.27	2.20	2.27	2.20	—	6.83
9	35	1.99	1.99	2.20	1.99	2.20	3.82	6.69
n = 2; X = Y = CH_2	150	2.05	2.05	2.19	2.05	2.19	3.94	6.71
10	35	2.13 (2.20)	2.05	2.24	1.99	2.20 (2.13)	3.83	6.70^{a}, 6.73^{b}
n = 2; X = CH_2; Y = S_2	150	2.22 (2.27)	2.11	2.31	2.07	2.27 (2.22)	3.98	6.74, 6.82

[a] C-3′,5′ H.
[b] C-5 H.



1a **1b**

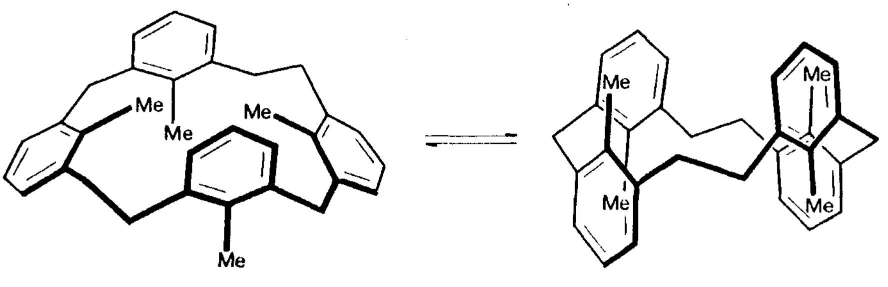
FIGURE 1 Two possible conformations of 16-membered [1.1.1.1]metacyclophane **1**.

upfield shift ($\Delta\delta = 1.15$ ppm at 35°C and 1.07 ppm at 150°C) strongly supports the fixed saddle-shape conformation **1b**, in which each methyl group is shielded by two adjacent phenyl rings. Surprisingly, no temperature dependence has been observed for the methylene signal of **1** down to $-60°$C ($CDCl_3$), thus indicating a residual libration of the mesitylene units.

Interestingly, the isostructural tetraoxa-[9] and tetrathia[1.1.1.1]metacyclophanes[10] have been shown to exist preferentially in the same conformation, while *p-t*-butylphenoxycalix[4]arene, a phenolic [1.1.1.1]metacyclophane, is a rare example of [1.1.1.1]metacyclophane adopting a basket conformation; in this case the stereochemistry is mainly determined by the four intramolecular hydrogen bonds.[11]

In view of the established stereochemistry of compound **1**, we reexamined the ^{1}H n.m.r. data reported for the larger 18-membered [2.1.2.1]metacyclophane **2**.[8] From the molecular models two basic conformations, namely the *saddle* **2a** and the *crown* **2b** become apparent. The ^{1}H n.m.r. spectrum of **2** in $CDCl_3$ at $-20°$C showed two singlets of equal intensity for the methyl groups at δ 1.18 and 2.38, respectively, a not clearly resolved multiplet for the ethylene bridges at δ 2.5–3.0 and an AB pattern for the methylene protons, centered at δ 3.68. At higher temperatures coalescence of these peaks occurred, and at 120°C (hexachlorobutadiene) three apparent singlets were observed at δ 1.76 (methyl groups), 2.95 (ethylene bridges), and 3.69 (methylene bridges). By comparing the low temperature spectrum of **2** with that of **1** in $CDCl_3$, the close chemical shift of methyl groups (Table I) allows to conclude that at $-20°$C compound **2** exists in the frozen conformation **2a**, shown in Figure 2. This conformation is further substantiated by the remarkable upfield shift of a set of aromatic protons, appearing as an AB_2 pattern, due to the "face to face" shielding of two phenyl rings. At higher temperatures the alternative crown conformation **2b**, arising by tilting in opposite directions the two phenyl rings bearing the shielded methyl groups, was populated enough to average the position of all signals. These data are consistent with the fluxional equilibrium **2a** $\rightleftharpoons$ **2b**, shown in Figure 2. For this process $\Delta G^{\neq}_{323} = 15.4$ kcal/mol has been calculated.[8]

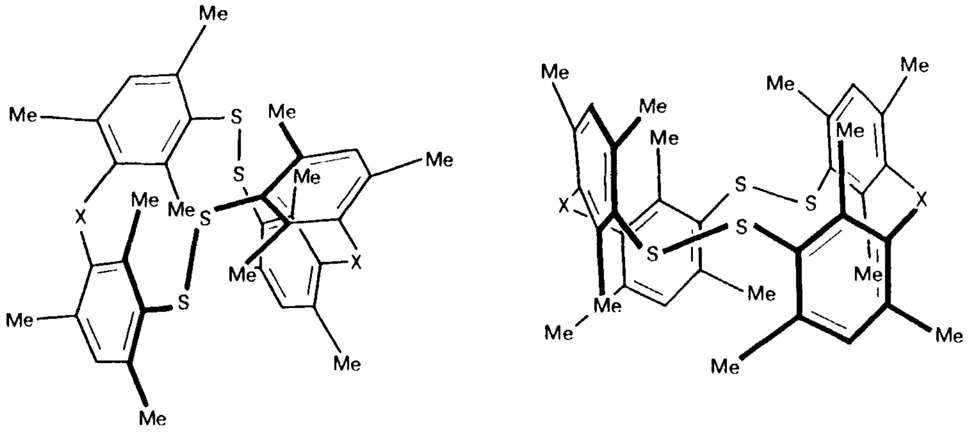
On the analogy of previous studies on the stereochemistry of related 20-membered octathia[2.2.2.2]metacyclophanes,[12] saddle and/or crown conformations, shown in



2a **2b**

FIGURE 2 The saddle-crown conformational equilibrium in 18-membered [2.1.2.1]metacyclophane **2**.

Figure 3, have been considered for bis-disulphides **3** and **4**. However, the former conformation was ruled out on the basis of either steric considerations and experimental evidence. In fact, the intra-annular methyl groups in **3** and **4** resonate at considerably lower field ($\Delta\delta \approx 1.3$ ppm) relative to the shielded methyl groups in **1** and **2** (a possible solvent effect is neglected for the latter compound), while a slight but still significant downfield shift ($\Delta\delta = 0.05$–0.22 ppm) is observed for these protons in comparison with the pertinent protons in open-chain models **6**–**8**, and **10** (Tables I and II). In sharp contrast with the fluxional properties of **2**, these data are suggestive of a *fixed crown conformation* for macrocycles **3** and **4**, owing to the peculiar nature and geometry of the disulphide bridges.[13] Further support to this conclusion was provided by the fairly good agreement of the chemical shifts of intra-annular methyl groups in **3** and **4** (δ 2.27 and 2.29, respectively) with that of **5** (δ 2.46), which has been shown to adopt a crown conformation.[12] The anisotropy



3a X = CH$_2$ **3b** X = CH$_2$

4a X = S **4b** X = S

FIGURE 3 Two possible conformations of 18-membered disulphide bridged [2.1.2.1]metacyclophanes **3** and **4**.

effect of four surrounding sulphur atoms could also account for the higher chemical shift observed in **5**.[14]

Additional points of interest arise from the scrutiny of the crown conformation defined for the 18-membered metacyclophanes **3** and **4**. Their structures consist of two single bridged dimesityls connected by two disulphide linkages. As a result of the various orientations of the phenyl rings, caused by rotation around their bonds to the bridging group, four basic configurations, i.e., *planar*, *butterfly*, *twist* and *skew*, have been considered for bridged diphenyl compounds,[15] but experimental evidence (dipole moment, ^{1}H n.m.r and X-ray techniques) has been provided only for the twist and skew configurations, depending on the nature and number of *ortho*-substituents.[16] In sulphur-bridged macrocycles **3** and **4**, due to the particular steric requirements, *the single bridged dimesityls approach the butterfly configuration.*

This conclusion throw light to our previous unsuccessful attempt to synthesize the analogous 18-membered dodecamethyl-tetrathiadioxa[2.1.2.1]metacyclophane. Although the low temperature ^{1}H n.m.r. spectra of dimesityl ether indicate a free rotation of the mesityl units down to −100°C,[17] the butterfly conformation of the dimesityl-ether units in that particular macrocyclic environment appears to be prevented by severe steric interactions between methyl groups, due to a different geometry of the oxygen with respect to methylene and sulphur bridges.[†]

EXPERIMENTAL

^{1}H n.m.r. spectra were recorded on a Perkin-Elmer R-32 spectrometer operating at 90 MHz in deuterated nitrobenzene. Chemical shifts are in parts per million (δ) from internal TMS. The concentrations used were approximately 15 mg/0.5 ml, unless specified in Table I for compounds **3**–**5**, which were only sparingly soluble. Melting points were determined on a Kofler apparatus and are uncorrected. Elemental analyses were performed by Mr. S. Di Marco in these laboratories.

Macrocycles **1**,[19] **3**,[5b] **4**,[5a] and **5**,[20] and model compounds **6**,[21] **7**,[22] and **8**[23] were prepared following the literature procedures.

Bis-(3-chloromethylmesityl) methane (**11**). To a solution of dimesityl methane (2.52 g, 10 mmol) and chloromethylmethylether (2.4 g, 30 mmol) in CS_2 (25 ml), cooled at −30°C, anhydrous tin(IV) chloride (5.2 g, 20 mmol) in CS_2 (10 ml) was added dropwise with rapid stirring, with the temperature kept below −15°C. The mixture was then stirred for 1 h at −15°C, and for 2 h at room temperature. After pouring into acidulated water, the organic layer was separated and the water layer extracted with CS_2. The combined organic extract was washed (5% $NaHCO_3$, then H_2O) and dried over anhydrous $CaCl_2$. Removal *in vacuo* of the solvent left a solid, which was recrystallized twice from cyclohexane to afford white crystals of the desired compound (1.2 g, 35%), m.p. 125–127°C; ^{1}H n.m.r. (CS_2) δ 2.06 (s, CH_3, 12 H), 2.35 (s, CH_3, 6 H), 4.04 (s, CH_2, 2 H), 4.53 (s, CH_2Cl, 4 H), and 6.82 (s, ArH, 2 H). For $C_{21}H_{26}Cl_2$ calculated: 72.21% C, 7.50% H; found: 72.05% C, 7.45% H.

3,3′-Bis-(2,4,6-trimethylbenzyl)dimesityl methane (**9**). To a solution of **11** (0.348 g, 1 mmol) in mesitylene (5 ml) were added a few drops of anhydrous tin(IV) chloride. The solution was stirred overnight at 50°C in a nitrogen atmosphere. The excess of mesitylene was distilled *in vacuo* to leave a solid, which was washed with methanol–hydrochloric acid (5 : 1), then with water and dried. Recrystallization from ethyl acetate gave white prisms of **9** (0.41 g, 80%), m.p. 134–136°C. For $C_{39}H_{48}$ calculated: 90.64% C, 9.36% H; found: 91.05% C, 9.75% H.

[†] From X-ray studies on a series of bridged diphenyls having mesitylene moieties, the C—O, C—C, and C—S bond distances are respectively 1.41, 1.51, and 1.78 Å, while the C—O—C, C—C—C, and C—S—C bond angles are respectively 118.5, 114.3, and 102.9°.[18]

3,3'-Bis-(2,4,6-trimethylbenzyl)dimesityl disulphide (**10**). Treatment of bis(3-chloromethylmesityl) disulphide[5b] (0.398 g, 1 mmol) with mesitylene (5 ml) in the presence of anhydrous tin(IV) chloride, under conditions identical to those used for **9**, afforded disulphide **10** (0.42 g, 75%), m.p. 183–184.5°C (from ethyl acetate). For $C_{38}H_{46}S_2$ calculated: 80.51% C, 8.18% H; found: 80.89% C, 8.33% H.

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