Conformational Aspects of Some Odd-membered Disulphide-bridged Metacyclophanes derived from *m*-Dimethoxybenzene

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The stereochemistry in solution of three 13- to 17-membered metacyclophanes derived from *m*-dimethoxybenzene (1)—(3), containing sulphide and/or disulphide linkages, has been investigated by means of ^1H n.m.r. spectroscopy. A correlation of the ^1H n.m.r. data of these molecules with those of suitable open-chain and cyclic models (4)—(10) has led to the conclusion that the 13-membered 1,2,9,16-tetrathia[2.1.1]metacyclophane (1) and the 15-membered 1,2,9,10,17,18-hexathia[2.2.2]-metacyclophane (3) adopt a propeller-like conformation, while the 17-membered 1,2,9,16,23-pentathia[2.1.1.1]metacyclophane (2) exists preferentially in the saddle-shaped conformation.

Although the nature and geometry of di- and poly-sulphide chains have been shown to play an important role in determining the conformational behaviour of several polysulphur-bridged metacyclophanes,[1-5] no defined stereochemistry is known for 1,2,9,10,17,18-hexathia[2.2.2]metacyclophanes,[6-8] due to the inaccessibility of suitable models.

Recently, we reported the formation of two new unsymmetrical polysulphur ring systems, *i.e.*, the 13-membered 4,6,11,13,18,20-hexamethoxy-1,2,9,16-tetrathia[2.1.1]metacyclophane (1) and the 17-membered 4,6,11,13,18,20,25,27-octamethoxy-1,2,9,16,23-pentathia[2.1.1.1]metacyclophane (2), from the iron-catalysed reaction of bis-(2,4-dimethoxyphenyl) sulphide with S_2Cl_2.[9] We felt that macrocycles (1) and (2) could be very useful models for the elucidation of the stereochemistry in solution of structurally related compounds.

In this paper, we correlate the ^1H n.m.r. spectral data of disulphide-bridged metacyclophanes (1)—(4), having *m*-dimethoxyphenyl units, to those of pertinent open-chain models (5)—(10) in two different solvents ($CDCl_3$ and [$^2H_6$]DMSO) in order to investigate the conformational preferences of macrocycles (1)—(3) in solution. As a result, 13- and 15-membered cyclic trimers (1) and (3) have been found to adopt a propeller-like conformation, while 17-membered cyclic tetramer (2) exists preferentially in the saddle-shaped conformation.

Experimental

^1H N.m.r. spectra were recorded at room temperature (*ca.* 30 °C) on a Bruker WP-80 or a Perkin-Elmer R-32 spectrometer operating at 90 MHz. Chemical shifts are in p.p.m. (δ) from internal $SiMe_4$. The concentrations used were *ca.* 15 mg per 0.5 ml. Compounds (1)—(10) were available from previous work.[8-11]

Results and Discussion

The ^1H n.m.r. spectral parameters of metacyclophanes (1)—(4) and of model (5) are shown in Figure 1, while those of the remaining open-chain models (6)—(10) are listed in the Table.

The assignment of the aromatic signals to the respective protons followed in a straightforward manner from: (i) the position of the signals [the chemical shift of aromatic protons *ortho* to the (poly)sulphide bridge usually experience a downfield shift, due to the anisotropy effect of sulphur atom(s)],[10-12] (ii) their shape (a small long-range proton–proton coupling between the methoxy-groups and the adjacent aromatic proton occurs, which causes broadening of the corresponding signal) [13] and multiplicity. Further confirmation of the assignments made was given by a striking shift, induced by dimethyl sulphoxide, experienced by the aromatic protons of all the molecules investigated: in general, the absorptions of the protons between the methoxy-groups shifted to higher fields than those measured in $CDCl_3$, while the protons adjacent to the sulphur atom(s) moved in the opposite direction. The magnitude and sign of these shifts for models (6)—(10) are reported in the Table. The assignments of methoxy-signals remain indefinite in most cases (Figure 1 and Table).

Inspection of molecular models reveals that tetrathia[2.1.1]-metacyclophane (1) could adopt a saddle-shape (1a) as well as a propeller-like conformation (1b), shown in Figure 2. In (1a) the intra-annular aryl proton H_a between the two sulphide linkages would project into the shielding regions of the other two aromatic rings, which would be in a *syn*-orientation to each other, with a torsion angle around the S–S bond close to 0°; in (1b) the phenyl rings connected by the disulphide bridge approach a stepped *anti*-orientation with an S–S torsion angle close to 90°, while the third ring is approximately normal to the planes of the other two rings.

The saddle-shape conformation (1a) was ruled out by simple considerations of the nature and geometry of the S–S bridge,[14] and by experimental evidence. In fact, from a comparison of the chemical shifts of the aromatic protons in bis-sulphide (5) with those of sulphides (6) and (7), model (5) is believed to adopt the skew-conformation (5a), depicted in Figure 3, since H_a, resonating at δ 6.44 in $CDCl_3$ and 6.03 in [$^2H_6$]DMSO, shows a remarkable shielding with an upfield shift of −0.64 p.p.m. in $CDCl_3$ and −0.85 p.p.m. in [$^2H_6$]-DMSO to lower values of δ. Further comparison of the ^1H n.m.r. data of (5) with those of (1) suggests that (1) exists predominantly in the propeller-like conformation (1b) in solution, as shown by the deshielding of H_a with a downfield shift of +0.39 p.p.m. in $CDCl_3$ and +0.64 p.p.m. in [$^2H_6$]-DMSO to larger values of δ. Conformation (1b) is also substantiated by the upfield shift experienced by H_b *ortho* to the disulphide bridge relative to the corresponding protons in open-chain models (8)—(10) (Figure 1 and Table), owing to the diamagnetic shielding of the other ring. Also, the averaged signal observed for H_b, instead of the expected two peaks for two magnetically non-equivalent protons in the fixed conformation (1b), could imply conformational mobility of (1) at room temperature.

In order to prove this hypothesis, compound (1) was

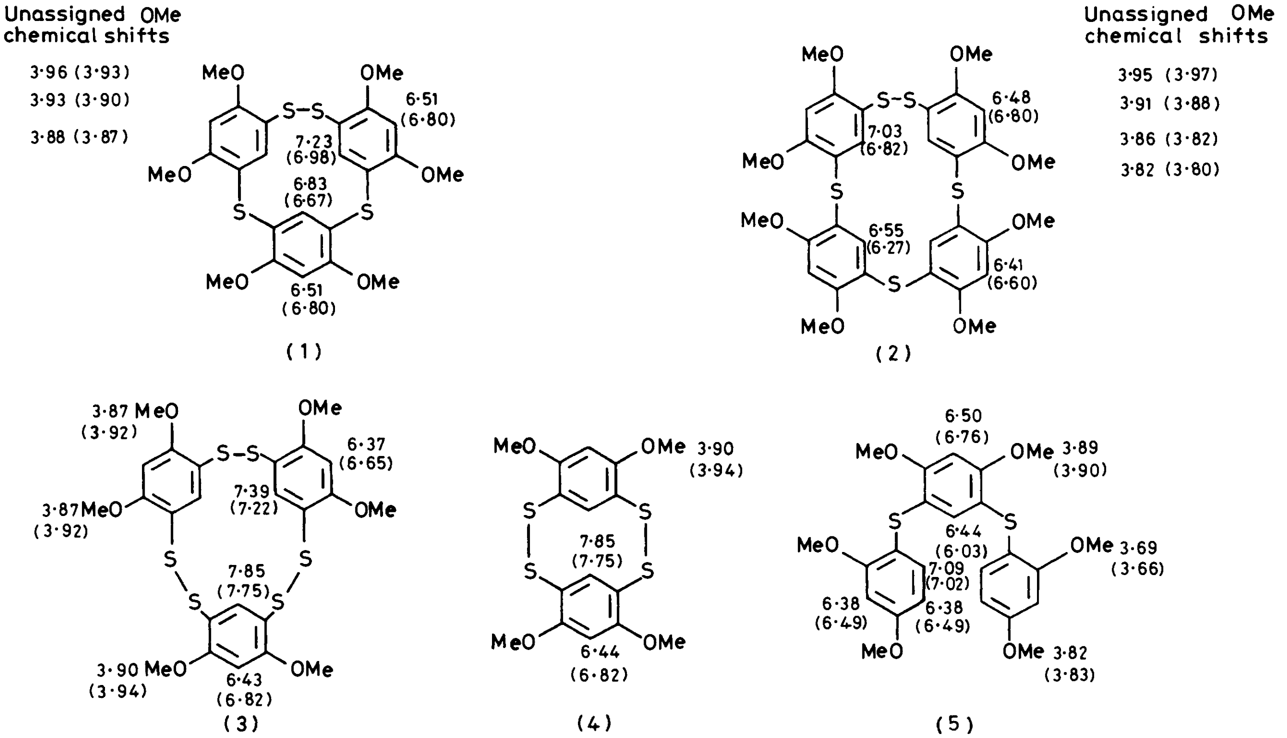
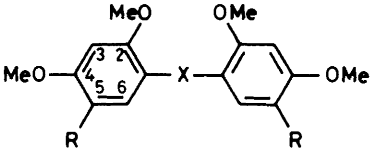


Figure 1. ^1H N.m.r. spectral parameters (δ) in $CDCl_3$ and [$^2H_6$]DMSO for compounds (1)—(5). Values in parentheses refer to [$^2H_6$]DMSO solutions

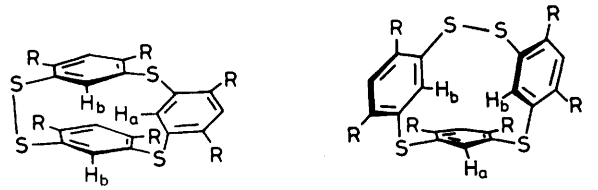
Table. ^1H N.m.r. spectral parameters (δ) of open-chain models (6)—(10)



Compound	Solvent	C(2) OMe [a]	C(3) H	C(4) OMe [a]	C(5) R	C(6) H
(6)	$CDCl_3$	3.90	6.55(d)	3.86	6.47(dd)	7.08(d)
X = S	[$^2H_6$]DMSO	3.78	6.49(d)	3.78	6.61(dd)	6.88(d)
R = H	Δδ (p.p.m.)		−0.06		+0.14	−0.20
(7)	$CDCl_3$	3.92	6.53	3.87		7.08
X = S	[$^2H_6$]DMSO	3.91	6.86	3.85		6.93
R = Cl	Δδ (p.p.m.)		+0.33			−0.15
(8)	$CDCl_3$	3.86	6.51(m)	3.86	6.51(m)	7.53(d)
X = S_2	[$^2H_6$]DMSO	3.80	6.58(d)	3.78	6.53(dd)	7.37(d)
R = H	Δδ (p.p.m.)		+0.07		+0.02	−0.16
(9)	$CDCl_3$	3.91	6.47	3.86		7.59
X = S_2	[$^2H_6$]DMSO	3.93	6.82	3.89		7.49
R = Cl	Δδ (p.p.m.)		+0.35			−0.10
(10)	$CDCl_3$	3.92	6.47	3.86	2.33	7.45
X = S_2	[$^2H_6$]DMSO	3.90	6.71	3.85	2.26	7.21
R = SMe	Δδ (p.p.m.)		+0.24			−0.24

[a] Tentative assignment.

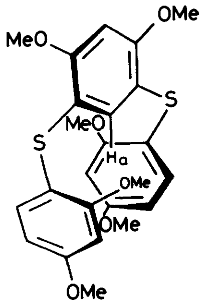
subjected to variable-temperature n.m.r. analysis. No splitting of H_b was observed down to −50 °C ($CDCl_3$); however, H_a was temperature-dependent, moving on cooling progressively to higher fields. At −50 °C four singlets at δ 7.30 (2 H, H_b), 6.64 (1 H, H_a), 6.57 (2 H), and 6.45 (1 H) were detected, due to the contemporary splitting of the broad signal at δ 6.51 (external aryl protons). These data could be interpreted in terms of a rapid interconversion at room temperature among the isomeric forms (1ba)—(1bd), shown in Figure 4. Upon lowering the temperature, the conformational mobility is considerably reduced, and only residual equilibration between (1bb) and (1bc) is still present at −50 °C, as demonstrated by



(1a) (1b)

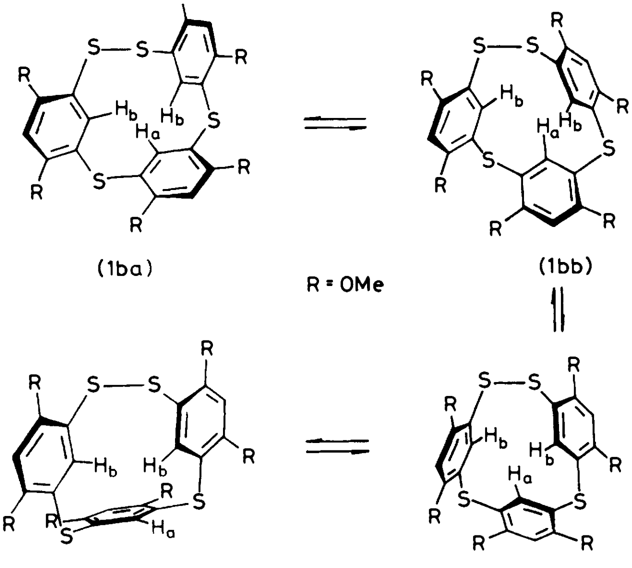
R=OMe

Figure 2. Possible conformations of 1,2,9,16-tetrathia[2.1.1]-metacyclophane (1)



(5a)

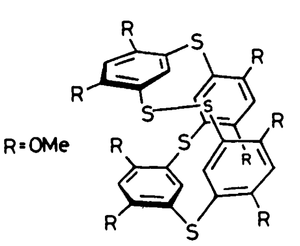
Figure 3. The skew conformation of bis-sulphide (5)



(1ba) (1bb) (1bd) (1bc)

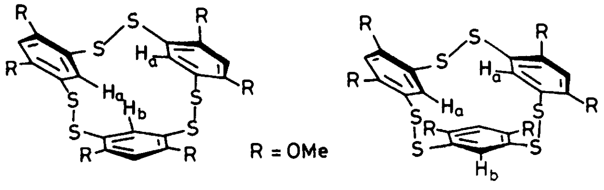
R = OMe

Figure 4. The interconversion process of (1) at room temperature



(2a)

Figure 5. The saddle-shape conformation of 1,2,9,16,23-pentathia-[2.1.1.1]metacyclophane (2)



(3a) (3b)

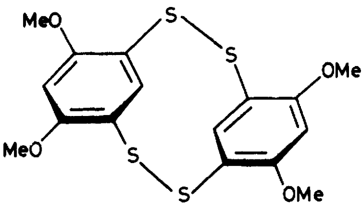
Figure 6. Two possible conformations of 1,2,9,10,17,18-hexathia-[2.2.2]metacyclophane (3)

the significant upfield shift of H_a ($\Delta\delta + 0.19$ p.p.m., computed by difference of its absorptions at +30 and −50 °C), and by the magnetic equivalence of H_b within the temperature range investigated. In contrast to our findings, the parent hydrocarbon[2.1.1]metacyclophane analogue has been shown to be quite able to undergo conformational changes down to −100 °C.[15]

As far as the stereochemistry of pentathia[2.1.1.1]metacyclophane (2) in solution is concerned, by analogy with previous studies on related tetrathia[1.1.1.1]-,[16] hexathia-[2.1.2.1]-,[5] and octathia[2.2.2.2]-metacyclophanes,[2,3] three possible conformations, *i.e.* basket, crown, and saddle, can be considered for (2). However, the significant upfield shift observed for all intra-annular aryl protons in (2), compared with the corresponding protons in open-chain models (6)—(10) (Table and Figure 1), is suggestive of the saddle-shape conformation (2a), depicted in Figure 5, the ring current shielding effect from two adjacent phenyl rings being ineffective in the basket as well as in the crown conformation. Further support for conformation (2a) was provided by the fairly comparable chemical shift of two equivalent intra-annular aryl protons in (2) {$\delta(CDCl_3)$ 6.55 and $\delta([^2H_6]DMSO)$ 6.27} with that of the shielded H_a in (5) {$\delta(CDCl_3)$ 6.44 and $\delta([^2H_6]DMSO)$ 6.03}.

The conformational preference of hexathia[2.2.2]metacyclophane (3) could be deduced by a comparison of its ^1H n.m.r. spectra with those of cyclic models (1) and (4). Molecular models show that the 15-membered macrocycle (3) can adopt several conformations which never result in magnetic equivalence of both internal and external aryl protons, because in each conformation considered only two of the three aromatic rings are related by symmetry. By assuming that the torsion angles around the S–S bonds are close to the generally observed value of 90°,[14] and that two of the three phenyl rings approach a stepped orientation, two possible conformations become apparent, according to whether the intra-annular H_b of the third ring is pointing into (3a) or out (3b) of the cavity of the macrocycle (Figure 6).

It is interesting to note that the intra-annular H_a of the two phenyl rings in a stepped arrangement are expected to be strongly shielded only in conformation (3b), since they would be in turn projected onto the π-cloud of the other phenyl ring. However, the actual ^1H n.m.r. data of (3) do not fit these requirements, and rather suggest the propeller-like conformation (3a). This conclusion is supported by the quite comparable chemical shift of H_a of the stepped portion of the molecule {$\delta(CDCl_3)$ 7.39 and $\delta([^2H_0]DMSO)$ 7.22} with that of the corresponding protons in model (1) {$\delta(CDCl_3)$ 7.23 and $\delta[^2H_6]DMSO)$ 6.98}, and by the striking chemical-shift coincidence of H_b with the corresponding proton in model (4) {$\delta(CDCl_3)$ 7.85 and $\delta([^2H_6]DMSO)$ 7.75}.



(4a)

Figure 7. The *anti*-conformation of 1,2,9,10-tetrathia[2.2]metacyclophane (4)

Finally, Mitchell and co-workers.[17] recently questioned the *anti*-conformation of (4) (Figure 7) earlier assigned by us,[10] and stated that (4) ' most likely exists as the *syn*-conformer '. We think that the *syn*-conformation for (4) is energetically disfavoured by the strong interactions of the unshared electrons of the adjacent sulphur atom, resulting from S–S torsion angles close to 0°; furthermore, this geometry is not corroborated at all by a concomitant upfield shift of the external aryl protons, which would be expected for a ' face to face ' arrangement of the two phenyl rings. Although an *X*-ray investigation on (4) is desirable to settle this controversy, we still believe that (4) adopts the stepped *anti*-conformation (4a), predicted also by other authors on the basis of a relationship between the length of the polysulphide bridges and the geometrical parameters in a series of *syn*- and *anti*-polysulphur-bridged metacyclophanes.[18]

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