Tetrahedron. Vol. 27, pp. 2737 to 2755. Pergamon Press 1971. Printed in Great Britain

MEDIUM-SIZED CYCLOPHANES—XII

SYNTHESES, VARIABLE TEMPERATURE PMR SPECTRA, AND CONFORMATIONAL ASPECTS OF [*m.n*]METACYCLOPHANE SULFUR ANALOGS—THE EFFECT OF RING SIZE AND SUBSTITUTION ON THE CONFORMATION AND CONFORMATIONAL CHANGES[1]

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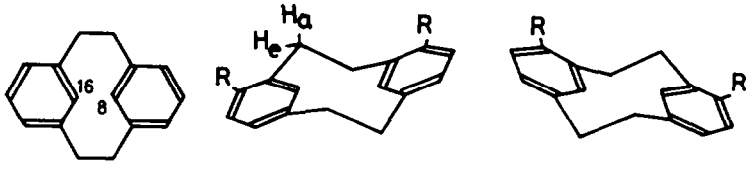
(*Received in Japan* 23 *January* 1971; *Received in the UK for publication* 25 *March* 1971)

Abstract—The preparation of [*m.n*]metacyclophane sulfur analogs with ring size up to 14 are described. They include 11- and 12-membered sulfides, sulfoxides, and sulfones as well as 12- and 14-membered rings having disulfide linkages. Through PMR spectral studies, including variable temperature spectroscopy, their conformation and conformational mobility are examined in relation to structural variation. While the parent compound of this series, [2,2]metacyclophane, has rigid system ($\Delta G^{\ddagger} > 27$ kcal/mol), an increase in ring size lowers the energy barrier, $\Delta G^{\ddagger}$'s found for 2-thia[3.2]- and 2,11-dithia[3.3]metacyclophanes are 13 and less than 9 kcal/mol, respectively. With the [3.2] system an increase in $\Delta G^{\ddagger}$ is observed in the sequence as going from sulfide to sulfoxide and then sulfone. A large effect of Me substitution in an aromatic ring on $\Delta G^{\ddagger}$ in the [3.3] system is attributable to buttressing effect, from which inversion mechanism is deduced. A highly substituted [3.3] system is found to exist in a stable cisoid geometry as well as transoid one. The UV spectrum of a series of compounds is examined to detect possible transannular interactions between the two benzene rings.

CONFORMATIONAL changes in [2.2]metacyclophane (I),[2] the lowest member of metacyclophanes having two benzene rings, is sufficiently slow as is exemplified by the isolation of stable optical antipodes (e.g. Ia, b) through the resolution of suitably substituted derivatives.[3]



I Ia Ib

The rigidity of otherwise quite mobile 10-membered ring system is the result of annelation by two benzene rings which bring benzyl methylene groups attached to them in a coplanar arrangement. Even with considerable angle deformation in both the aryl and aliphatic bonds the distance between C_8 and C_{16} is as short as *ca* 2·7 Å in a crystalline state,[4] and H atoms on these carbons experience severe compression upon ring inversion.

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The conformational aspect was also investigated by variable temperature PMR spectroscopy,[5] which showed that an A_2B_2 type absorption due to ethylene bridge protons were unaltered over a wide range of temperatures, −80 to 190°.[3] Similar studies on the heterocyclic analogs of I also indicated the presence of considerable energy barrier upon inversion.[6,7]

The rate of ring inversion may be dependent on the structural variation, such as substitution, incorporation of hetero atoms, or ring size. Of these, the latter is expected to be a dominant factor. Griffin *et al.*[8] carried out kinetic studies on the next higher homologs, [3.2]metacyclophane derivatives, and observed considerable lowering in the energy barrier compared with I and also noticed minor changes due to substituents. In a previous paper we have reported[9] the energy barrier to inversion in sulfur analogs of 11- and 12-membered metacyclophane compounds and discussed them in relation to the ring size and substitution on the bridge. Comparing with the carbocyclic analogs,[8] these heterophanes offered certain advantages to syntheses and PMR studies, namely, an incorporated S atom not only simplified methylene signals to an AB-type by elminating complex spin-spin couplings but also shifted them to a sufficiently lower field than ethylene proton signals permitting them to be observable as separate patterns.

In this paper we wish to describe the synthesis and spectral studies of [m.n]metacyclophane sulfur analogs with ring size up to 14, and discuss the effects of ring size and substitution in relation to conformation, conformational mobility, and inversion mechanism.

The syntheses. Model compounds subjected to spectral studies include 11- and 12-membered sulfides, sulfoxides, and sulfones (III–X) and 12- and 14-membered rings having disulfide linkages (XI, XII). The physical properties of these compounds are shown in Table 1. PMR data are summarized in Tables 2 and 3. UV spectral data compiled in Table 4 are discussed in a later section.

TABLE 1. PHYSICAL PROPERTIES OF METACYCLOPHANE SULFUR ANALOGS

Compd	Mp. °C	Formula	Carbon, %		Hydrogen, %	
			Calcd	Found	Calcd	Found
III	94–95	$C_{16}H_{16}S$	79·95	80·03	6·71	6·47
IV	130–131	$C_{16}H_{16}SO$	74·95	74·52	6·29	6·34
V	168–169	$C_{16}H_{16}SO_2$	70·55	70·44	5·92	5·80
VI	120–120·5	$C_{16}H_{16}S_2$	70·57	70·33	5·92	5·85
VIIa	232–234[a]	$C_{16}H_{16}S_2O_2$[b]				
VIIb	248–250[a]	$C_{16}H_{16}S_2O_2$[b]				
VIII	> 260	$C_{16}H_{16}S_2O_4$	57·13	56·50	4·79	4·78
IX	231–232	$C_{20}H_{24}S_2$[c]	73·12	73·48	7·36	7·35
Xa	260–261	$C_{22}H_{28}S_2$[d]	74·10	73·95	7·92	7·95
Xb	229–230	$C_{22}H_{28}S_2$	74·10	73·79	7·92	7·80
XI	165·5–167[a]	$C_{16}H_{16}S_2$	70·57	70·45	5·92	5·90
XII	168–170	$C_{16}H_{16}S_4$	57·10	56·87	4·79	4·82

[a] Recorded by using a heating block.
[b] Determined by mass spectroscopy.
[c] Anal. Sulfur: Calcd; 19·52, Found; 19·64.
[d] Anal. Sulfur: Calcd; 17·98, Found; 18·01.

The treatment of 3,3'-bis(bromomethyl)bibenzyl (IId),[8,9] which was prepared by a sequence of reactions IIa → IIb → IIc → IId, with sodium sulfide in methanol under high-dilution conditions produced 2-thia[3.2]metacyclophane (III), m.p. 94–95°, in 29·6% yield. Oxidation of III with hydrogen peroxide produced, depending on the reaction conditions, corresponding sulfoxide IV, m.p. 130–131°, or sulfone V, m.p. 168–169°. 2,11-Dithia[3.3]metacyclophane (VI) m.p. 120–120·5°, was prepared in 11·5% yield by the reaction of 1,3-bisbromomethyl benzene and sodium sulfide as described above. Later, this compound was also prepared by Vögtle[10] and Boekelheide.[11] Oxidation of VI under controlled conditions produced a mixture of bis-sulfoxides, which was separated by column chromatography on silica gel. Eluted first, which was designated VIIa, had m.p. 232–234° and the other VIIb had m.p. 248–250°. Sulfone VIII was prepared by the oxidation of VI with excess hydrogen peroxide, m.p. > 260°.

5,7,14,16-Tetramethyl-2,11-dithia[3.3]metacyclophane (IX) was prepared by the reaction of 4,6-bischloromethyl-*m*-xylene and sodium sulfide in dioxane–water. The use of methanolic solution as in the preparation of VI, for which bromide was used, resulted in the formation of methoxylation rather than condensation products. It was obtained in 21·1% yield, m.p. 231–232°.

5,7,9,14,16,18-Hexamethyl-2,11-dithia[3.3]metacyclophane (X) was obtained from 1,3-bischloromethylmesitylene following the same procedure as above. There were isolated two compounds, both of which have expected mol wt by mass spectra measurements. The least soluble compound which was assigned trans structure Xa based on the spectral data was obtained as colorless plates, m.p. 260–261°, in 6·1% yield. Cis compound Xb was isolated in 18·6% yield by column chromatography on alumina as colorless needles, m.p. 229–230°.

The oxidation of Bunte salt solution formed from IId with iodine in hot aqueous ethanol produced 2,3-dithia[4.2]metacyclophane (XI), m.p. 165·5–167°. By the same procedure 2,3,12,13-tetrathia[4.4]metacyclophane (XII), m.p. 168–170° was also prepared.

An attempted cyclization reaction to make 2,3-dithia[4.1]metacyclophane failed but produced dimer XIII.

PMR *spectra*. The PMR spectral data, recorded on a Varian Associates HA-100 spectrometer equipped with a variable temperature controller, are summarized in Table 2. The chemical shift listed are those obtained at the lowest temperatures studied. For compounds which showed temperature-dependent spectra, coalescence temperatures and energy barriers to ring inversion are recorded in Table 3.

The formation of the transoid cyclophane structures was most readily monitored by the PMR spectral measurement. With lower members an inner aryl proton signal appeared unusually at a high field due to diamagnetic ring current effect of the opposite benzene ring. In case of I, the resonance signal appeared at δ 4·25 with an upfield shift of almost 3 ppm,[3b,12–14] indicating that protons at $C_{8,16}$ were extended into a strong shielding region as expected from the stepped conformation with a C_{2h} symmetry (Ia, b: R=H).[4] Parallel with the prediction[15] and also with finding on [2.n]metacyclophanes,[16] the upfield shift became less prominent with increase in ring size. Thus III and V showed the signal at δ 5·13 and VI at δ 6·63. Even with larger rings (> 12-membered rings) the inner aryl signal is clearly separated from the rest of the aryl protons in most cases, although the shielding effect exerted by *o,o'*-dialkyl

TABLE 2. PMR PARAMETERS OF METACYCLOPHANE SULFUR ANALOGS[a]

Compd	out.—ArH	in.—ArH	Ethylene	Methylene	J_{AB}	out.—CH_3	in.—CH_3	T°	Solvent
III	7·20	5·13	3·08 (A$_2$B$_2$) 2·22	3·84 (AB) 3·45	13·4			−54·0	$CDCl_3$
IV	7·23	4·99 4·91	3·09 (ABCD) 2·30	4·06 (AB) 3·69	14·4			−35·0	$CDCl_3$
				4·65 (AB) 3·30	12·7				
V	7·43	5·13	3·13 (A$_2$B$_2$) 2·32	4·35 (AB) 3·98	17·0			6·5	$CDBr_3$
VI	6·98	6·82		3·11 (s)	15·0			−90·0	Toluene-d_8
	6·90	6·63		3·62 (s)				rt	$CDCl_3$
VIIa	7·06	6·67		4·22 (AB) 4·08	15·0			rt	$CDCl_3$
VIIb	7·02	6·96		4·41 (AB) 4·19	13·0			rt	$CDCl_3$
VIII	7·36	7·36		4·67 (s)				0	CF_3CO_2H

IX	6·50	6·58		3·65 3·51	(AB)	13·9	2·12		−55·5	Toluene-d_8
Xa	6·65			3·60 3·46	(AB)	13·9	2·35	1·11	rt	Toluene-d_8
	6·65			3·64 3·50	(AB)	13·9	2·37	1·14	rt	Benzene-d_6
	6·66			3·65 3·51	(AB)	13·9	2·38	1·11	rt	CS_2
Xb	6·67			3·58	(s)		2·24	2·24	rt	Benzene-d_6
	6·58			3·55	(s)		2·26	2·05	rt	CS_2
	6·87			3·72	(s)		2·33	2·17	rt	$CDCl_3$
XI	7·15	6·95	2·96 (s)	3·38	(s)				rt	$CDCl_3$
XII	7·23	6·63		3·79	(s)				rt	$CDCl_3$
XIII	7·10	6·83	3·23 (s)	3·89	(s)				rt	$CDCl_3$

[a] Spectra were recorded on a Varian HA-100 and Hitachi-R20B spectrometers.

Chemical shifts (δ, ppm) listed are those obtained at the lowest temperatures (T°). using a variable temperature controller. For compound XI partial spectrum was determined in thiophene at lower temperatures.

groups must be taken into account. The signal appeared as a characteristic triplet with $J = 1{\cdot}8$ wherever meta coupling is possible.

An inner methyl resonance in X occurring at δ 1·14 is also the results of the ring current effect. The magnitude of the upfield shift is again less than that of the lower members, namely, 8,16-dimethyl[2.2]metacyclophane showed the signal at δ 0·48–0·75.[17,18] Thus the inner aryl or Me proton signal serves not only for diagnostic purpose but also as a measure of ring size and conformation.

TABLE 3. PMR SPECTRA AND RATE PARAMETERS

Compd	Temp. range, °C (Solvent)	Proton type	δ, ppm		ν, cps	Tc, °C	$\Delta G^{\ddagger}$ (Kcal/mol)
III	−54·0–55·0	$A_2B_2(CH_2CH_2)$	2·22	3·08	86·5	0·5	13·1
	($CDCl_3$)	$AB(SCH_2)$	3·45	3·84	38·9	−8·0	13·1
IV	−35·0 ~ 64·5	$ABCD(CH_2CH_2)$	2·30	3·09	79·7	45·5	15·4
	($CDBr_3$)	$2AB(CH_2SOCH_2)$	3·30	4·65	135·4	*ca* 40	14·8
			3·69	4·06	37·3		15·6
		in.—ArH	4·91	4·99	7·8	11·5	
V	6·5 ~ 117·5	$A_2B_2(CH_2CH_2)$	2·32	3·13	81·8	57·5	16·5
	($CDCl_3$)	$AB(SO_2CH_2)$	3·98	4·35	36·9	41·5	16·2
VI	−90·0 ~ rt.	Singlet	3·62			< −90	< 9·3[b]
	(Toluene-d_8)						
VIII	0–rt.	Singlet	4·67			< 0[a]	
	(CF_3CO_2H)						
IX	−55·5 ~ rt.	$AB(SCH_2)$	3·60	3·56	14·0	−41	11·9
	(Toluene-d_8)						
Xa	rt. ~ 180·0	$AB(SCH_2)$	3·64	3·50	14·0	> 180	> 23·8
	(Toluene-d_8)						

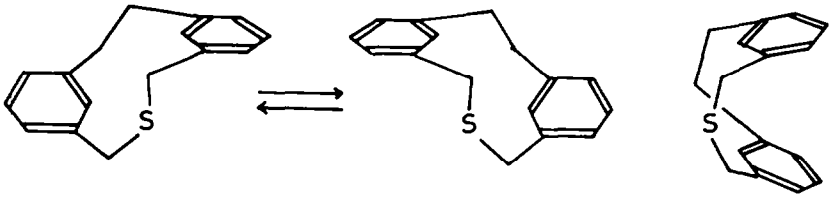
[a] Due to limited solubility of the material in CF_3CO_2H, spectra were not recorded below 0°.
[b] The chemical shift difference, $\Delta\nu$, was assumed to be 14·0 Hz, taking the value found for IX and Xa.

To learn more about these problems we have studied PMR spectra of these compounds using such techniques as variable temperature spectroscopy, H–D exchange, double resonance, and nuclear Overhauser effects (NOE's). The results will be described according to the ring size.

10- *and* 11-*Membered rings.* Axial (Ha) and equatorial protons (He) in I (R=H) appearing as an A_2B_2 type absorption with $\Delta\nu_{ae}$ = *ca* 1 ppm[14] was kept unchanged over a wide range of temperatures.[3] On this basis, activation energy required for interconversion between Ia and Ib (R=H) was calculated to be more than 27 Kcal/mol.[6a,8b] Incorporation of S atoms as a bridge member lowered the energy barrier, thus 24 Kcal/mol was found for 1,10-dithia[2.2]metacyclophane.[7a] Apparently this is attributed to the absence of a part of hydrogen atoms on the bridge and elongation of the bond length caused by replacing carbon atoms by sulfur, combination of which may contribute to lower the activation energy leading to the transition state. Partial hydrogenation of I was also shown to contribute to ease conformational changes.[19]

The conformation of the next higher homologs, 11-membered sulfide III, is depicted as IIIa. Both sulfide and sulfone (III and V) have a C_2 symmetry. The transoid, stepped conformation is favored not only by the appearance of a high-field

inner aryl proton signal but by considering unfavorable nonbonded interaction involved in the alternative cisoid structure, IIIc (C_s symmetry). At lower temperature III and V possessed A_2B_2- and AB-type absorptions (Table 2). As the temperature is raised, these signals gradually broaden, coalesce, and eventually give two sharp singlets. The transition corresponds to ring inversion between IIIa and IIIb. The



IIIa C_2 IIIb IIIc C_S

spectral changes are shown by the case of sulfone V (Fig 1). Observed coalescence temperatures for AB patterns of III and V were −8·0° and 41·5°, respectively, from which the energy barrier was estimated to be 13·1 and 16·2 kcal/mol, respectively.*

Griffin and Coburn[8] found the energy barriers in 2-substituted [3.2]metacyclophane lie between 15·8 and 19·1 kcal/mol depending on the substituents. That the sulfur

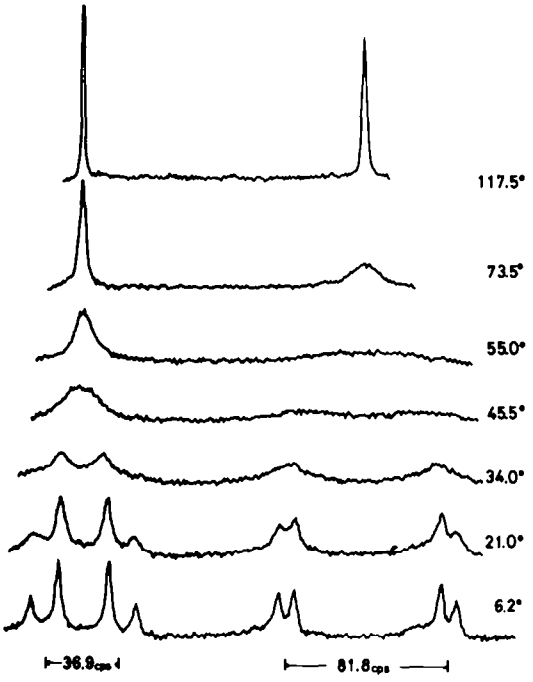


FIG 1. PMR spectra of 2-thia[3.2]metacyclophane 2,2-dioxide (V) at different temperatures ($CDBr_3$).

* Arrhenius plots of ln k vs 1/T was based on the Gutowsky–Holm equation using A_2B_2 part of the spectra gave a good linear correlation. Activation energy Ea was calculated to be 8·32 Kcal/mol (III) and 13·7 Kcal/mol (V).

analog III undergo conformational change with more ease compared with these carbocyclic analogs may be explained by the same reason found for I and its analog,[7a] namely. enlarged 11-membered ring and absence of 2-substituent. Comparison of III and V reveals that the effect of sulfonyl oxygen is reflected on the ring inversion possibly raising enthalpy at the transition state by their bulk. It is then to be expected that sulfoxide IV possess the energy barrier intermediate between those of III and V. This was proved to be the case, and $\Delta G^{\ddagger}$ for IV was found to be *ca* 15 kcal/mol (AB-pattern, Tc *ca* 40°).

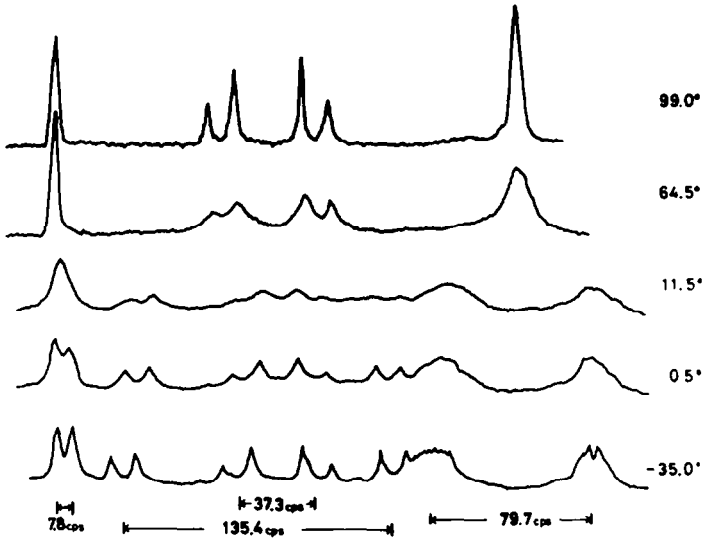
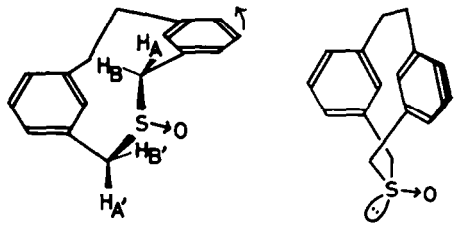


FIG 2. PMR spectra of 2-thia[3.2]metacyclophane 2-oxide (IV) at different temperatures ($CDCl_3$).

The sulfoxide IV exhibited remarkable temperature-dependent spectra in that not only ethylene and S-methylene proton signals but also inner aryl proton signal experience a series of transition. Thus an ABCD-pattern due to ethylene is transformed into a singlet at higher temperatures, similarly two AB-patterns due to S-methylene into an AB-type, and two peaks due to inner aryl protons into a singlet. Even with maximum span of signals recorded at the lowest temperatures of −35°, each of resonance patterns clearly recognized (Fig 2). It is noticed that sulfinyl methylene protons appear as an AB-quartet even in an averaged spectrum determined at 99° since they are non-equivalent due to a rigid pyramidal structure of sulfoxide group. Inner aryl protons become non-equivalent either due to the dissymmetric environment and possibly enhanced by slight deformation of the stepped conformation. Flipping of the aryl ring as indicated by the arrow (IVa) brings the sulfoxide group into favorable axial arrangement (IVb).[21]

Methylene protons α to sulfoxide group appear as two sets of AB-type absorption, $\Delta\nu$ = 135·4 Hz, J = 12·7 Hz and $\Delta\nu$ = 37·3 Hz, J = 14·4 Hz. These are arising from two sets of methylene groups designated as H_A and H_B, and $H_{A'}$ $H_{B'}$ (IVa). By ring inversion averaging between $H_{B'}$ and H_A, and also H_B and $H_{A'}$ occurs as illustrated schematically in Fig 3. Since sulfinyl methylene protons are known to be kinetically

non-equivalent as revealed by H–D exchange experiments carried on benzylmethyl sulfoxide,[22] the H–D exchange reaction of IV was carried out in D_2O-dioxane containing sodium deuteroxide at 40°. Removing aliquots at regular interval and



IVa IVb

stopping the reaction by the neutralization with dilute hydrogen chloride, the reaction was followed by PMR spectral measurements determined at 100°. Spectral change is shown in Fig 4.

Since H–D exchange occurs most readily in the conformation in which hydrogen bisect the projected angle between the lone pair and oxygen (hydrogen $H_{A'}$ in the Fig 3),[22] and since $\Delta\nu$ is expected to be larger with conformer B than with conformer

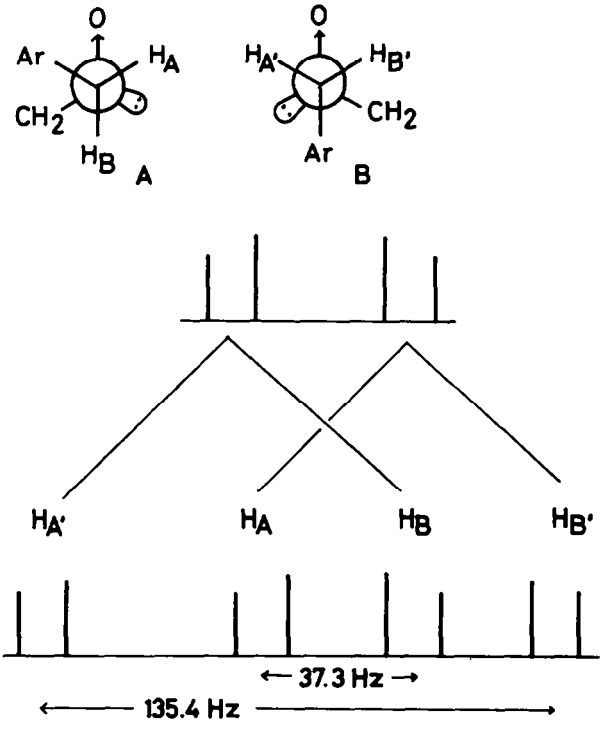


FIG 3. Assignment of sulfinyl methylene proton signals and the Newman projection of IV. Spectral changes are schematically shown (bottom, frozen spectrum: top, averaged spectrum).

A,[22,23] the assignment of the respective proton signals become apparent as indicated in the Fig 3. From these results it was found that the higher-field protons exchanged 40 times faster than the lower ones.

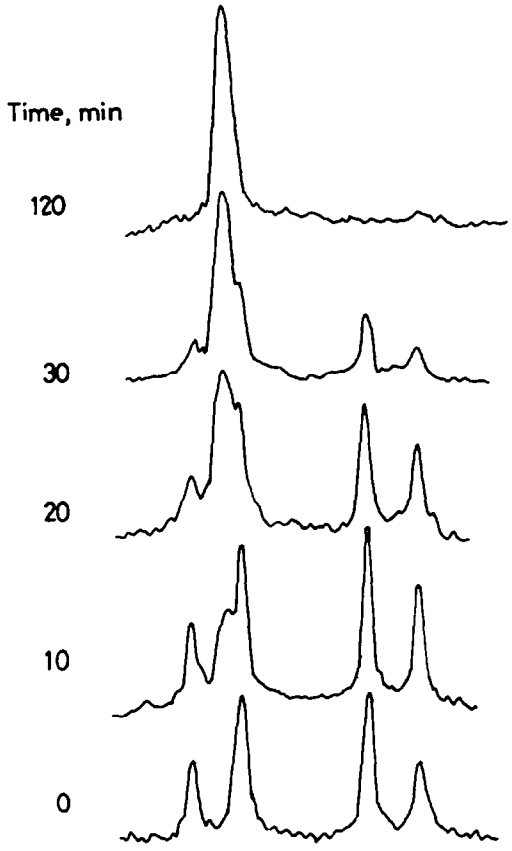


FIG 4. Hydrogen–deuterium exchange of sulfinyl methylene group in IV. Reaction carried out in NaOD-D_2O-dioxane at 40°. Spectra determined at 100° in $CDBr_3$.

12-*Membered rings.* Bis-sulfide VI, a model compound with ring size of 12, showed a methylene proton signal as a sharp singlet at δ 3·11 at room temperature, which remained unresolved even at −90°, indicating that the energy barrier to ring inversion was quite low. It appears that the compound undergoes a facile conformational motion which averages among various conformers (see below).

Bis-sulfoxide of VI may exist in *cis* and *trans* forms with respect to the sulfoxide groups. In fact two compounds having expected physical properties were obtained by the hydrogen peroxide oxidation of VI, which were separated by column chromatography.

PMR spectra of these compounds determined at room temperature are indicative of flexible nature of the systems by showing only one AB-pattern due to the methylene

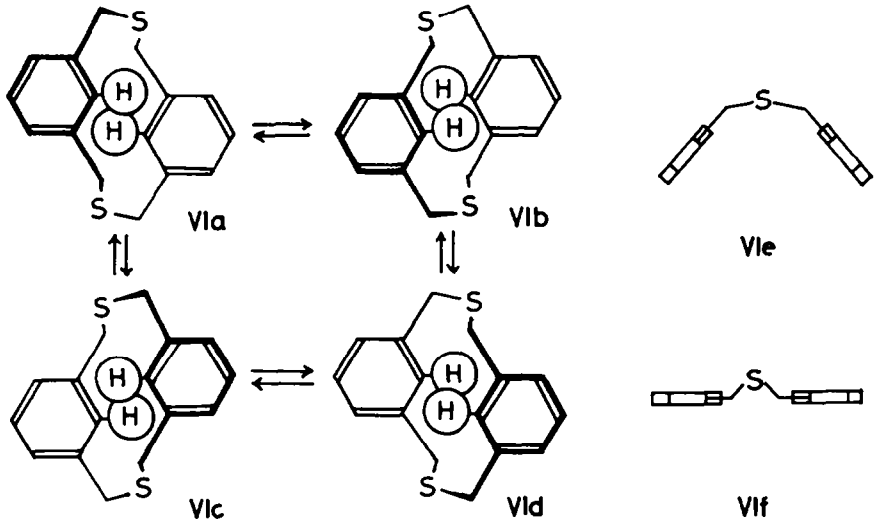
protons. They showed, however, distinctive differences in the chemical shift and coupling constants as shown in Table 2. Sulfinyl methylene and inner aryl proton signals for the low melting isomer VIIa appeared at δ 4·15 (J = 15) and 6·67, while those for VIIb occurring at 4·30 (J = 13) and 6·96. With trans isomer sulfoxide groups may exist in a diaxial arrangement and with *cis* isomer axial-equatorial, but no distinction was made on these compounds from the available data. Monosulfoxide showed absorptions at δ 3·80 (s, —CH_2S—), 4·17 (dd, J = 13·5, —CH_2SO—), 6·81 (inner aryl), and 6·99 (outer aryl).

Bis-sulfone VIII, m.p. > 260°, showed a sharp singlet at δ 4·67 in a trifluoroacetic acid solution. Essentially no change in the spectrum occurred at 0° again suggesting flexible nature of the system. Owing to unfavorable solubility in common solvents no satisfactory PMR spectra were recorded at lower temperatures.

For comparison with VI on the basis on different combination of bridge members, 12-membered disulfide XI was then subjected to variable temperature PMR studies. Additional interest in this compound is possible restricted rotation of a disulfide linkage.[24] Spectra were determined down to −42° in thiophene at which no change in methylene signals occurred. Owing to limited solubility of the material no spectra were measured at lower temperatures. Thus 12-membered rings VI and XI appear to have greater flexibility compared with lower members.

We then examined the effect of substituent on the ring inversion on VI. Tetramethyl derivatives IX showed a singlet at δ 3·58 (—CH_2S—) which began to broaden on lowering the temperature and finally appeared as an AB-quartet at −55·5°. From the observed Tc, −41°, $\Delta G^{\ddagger}$ was calculated to be 11·9 kcal/mol.* Since VI requires only less than 9·3 kcal/mol* for inversion, the effect of Me groups on the energy barrier may be attributed to buttressing effects, which raise the energy barrier leading to the transition state by more than 2·6 kcal/mol.

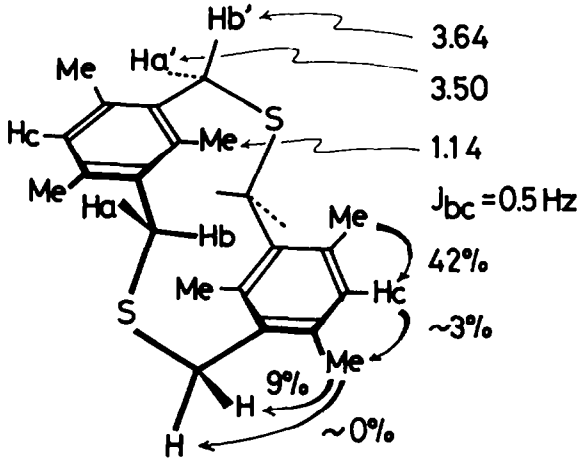
The mode of inversion in the 12-membered rings is shown in figures by the case of VI. Conformational changes VIa ⇄ VIc involves only C—S bond rotation without



* For the calculation $\Delta\nu$ was assumed to the same with Xa.

benzene ring inversion. On the other hand the processes VIa ⇄ VIb and VIc ⇄ VId are achieved by benzene ring flipping. Interconversions VIa ⇄ VId and VIb ⇄ VIc contain both motions. The largest energy may be required in the ring inversion processes. Of the inversion mechanisms the one which assumes a cisoid intermediate VIe may not subject to severe buttressing effects since the one-ring inversion leading to the cisoid structure is rather strain free. A large effect of methyl substitution as found in IX suggests that the inversion occurs in a concerted manner via nearly flat intermediate VIf.[25]

The reaction of 1,3-bischloromethylmesitylene with sodium sulfide produced *trans* and *cis* compounds (Xa and Xb) in 6·1% and 18·6% yield, respectively. Recently

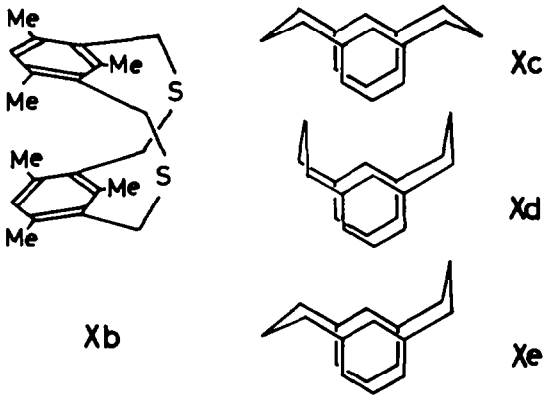


Xa

Boekelheide *et al.*[11] have isolated *cis* and *trans* isomers of 9,18-dimethyl-2,11-dithia[3.3]metacyclophane in the ratio 1:9, which is varied depending on the conditions. The assignment of the structures was mainly based on the PMR spectral consideration. The trans compound in toluene-d_8 showed two singlets each corresponding to the inner and outer Me groups at δ 1·11 and 2·37 in the ratio of 1:2. The high-field signal indicates the transoid stepped conformation Xa. On the other hand, the *cis* compound showed an inner Me proton signal at the normal position of δ 2·05 (CS_2). In an aromatic solvent Xb showed only a single peak for Me protons (Table 2).

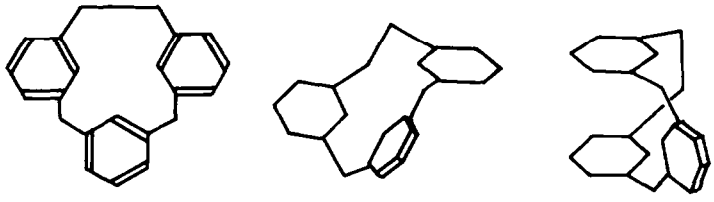
Methylene protons of Xa were observed as an AB quartet at δ 3·55 which was unaltered even at 180° indicating that the transoid geometry was fixed. The conformation was also supported from consideration of nuclear Overhauser effects,[26] data of which were indicated in the structural formula Xa. When outer Me groups at δ 2·37 was irradiated high field methylene proton signals (δ 3·50) showed 9% increase whereas the low field one (δ 3·64) remained unchanged. The results made possible to assign Ha and Ha' were nearer to the Me groups and hence the higher field one. A rather significant *m*-benzyl coupling, 0·5 Hz, was observed between Hb and Hc.

Usually *o*- and *p*-benzyl coupling was explained by π-mechanism.[27] Should *m*-coupling occur by the same mechanism, equal coupling of Hc with Ha and Hb might be expected unlike the experimental results. *m*-Benzyl coupling of the present case thus occurs by through δ-framework. On the other hand, *cis* compound Xb, which showed an aryl Me proton signal at δ 2·05–2·33 and methylene proton signal as a singlet at δ 3·72 ($CDCl_3$). seems to be conformationally fixed as far as two benzene nuclei are concerned. The low temperature spectrum determined at −80° exhibited only slight broadening of methylene signals, indicating that the compound is still undergoing conformational equilibration among Xc, Xd and Xe (only frameworks are shown). The chemical shift between two methylene protons were incidentaly the same probably due to folded molecular geometry.



Larger rings. Only a few [m.n]metacyclophanes with ring size larger than 12 have been synthesized. Griffin *et al.*[28] have obtained 2,3-dimethyl[4.2]metacyclophane-1-ene, a 12-membered compound, by the ring expansion of a [3.2]metacyclophane derivative. Compound showed sharp bridging methylene proton signals which remained invarient over the temperature range −52–70°. Bis-disulfide XII showed a sharp singlet at δ 3·79. 22-Membered compound XIII had sharp singlets at δ 3·23 (—CH_2CH_2—) and 3·89 (—CH_2S—). 2,4-Dioxa[5.2]metacyclophane, a 13-membered cyclic acetal,[29] showed only three singlets at δ 2·91 (—CH_2CH_2—), 4·54 (—CH_2O—) and 4·77 (—OCH_2O—). These cyclophanes seem to be quite flexible molecules as judged from the PMR spectral data and molecular model consideration.

Extra fixation may be expected by the ring fusion as in [2.1.1]metacyclophane (XIV).[1] The compound showed singlets at δ 2·78 (—CH_2CH_2—) and 3·60 (—CH_2—)



and three groups of absorption for the aryl protons at δ 6·27 (2H), 6·49 (1H) and 6·90 (9H). The upfield shift of two-proton and one-proton aryl signals which are assignable to $C_{8,22}$ and C_{15} protons, respectively, suggests a stepped conformation XIVa (C_2 symmetry) over a folded one (C_s symmetry) XIVb.

UV *absorption spectra.* Comparison of UV spectrum of [2.2]metacyclophane (I), λ_{max} 270 mμ (ε 570), with open-chain model compounds, such as *m*-xylene[16c,17] or 3,3'-dimethylbibenzyl.[30] has revealed anomalous nature of the cyclic system.[30] Characteristic to a bent benzene[2] fine structure of the benzenoid band was lost and the band maximum shifted to a longer wave length with decrease in intensity. Also in accord with the prediction from a simple MO calculation[30] transanular interaction between two benzene rings was recognized.

In Fig 5 absorption curves for 11- and 12-membered sulfides determined in n-hexane are recorded together with those of I and open chain models, *m*-xylene and XV.

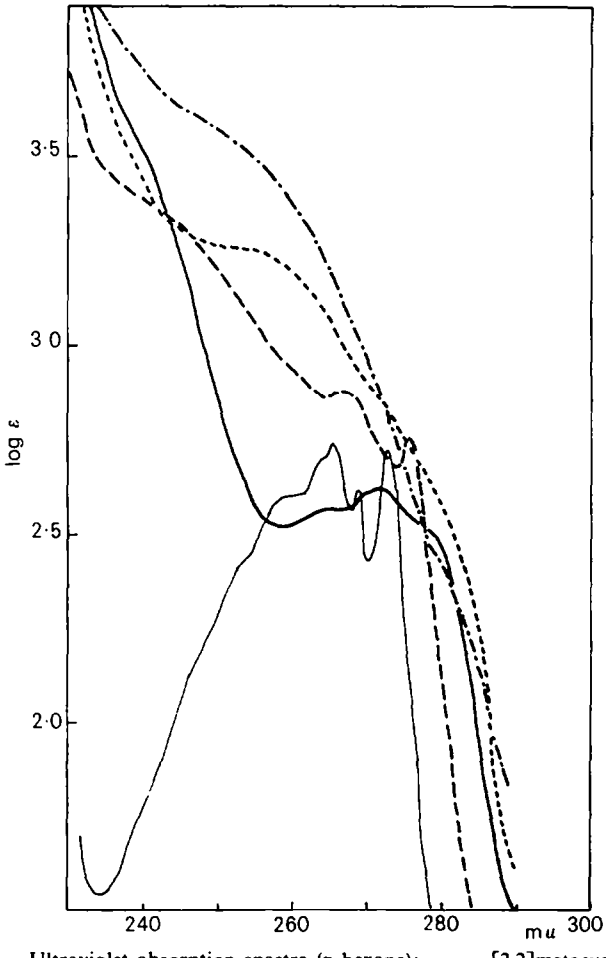
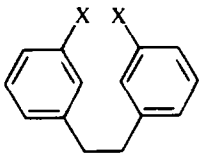


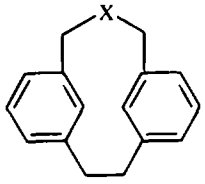
FIG 5. ——— Ultraviolet absorption spectra (n-hexane): ———[2.2]metacyclophane (I), ——— m-xylene (×2), – – – – – 3,3'-dimethybibenzylsulfide (XV), ····· 2-thia[3.2]metacyclophane (III), –·–·– 2-thia[3.3]metacyclphane (VI)

Owing to the interaction between sulfur lone pair and aryl electrons these benzylic sulfides showed only poorly resolved curves. Both III and VI did not show any absorption maxima in 270–280 mμ region, and instead, had absorptions at 252 mμ for 11-membered ring, and 250 mμ for 12-membered ring. This band is present in model compound XV and arises from through conjugation between aryl group and S atom.[31] A similar situation is seen with sulfoxides VII and XVI. For these compounds not much information was obtained with regard to transannular interaction between aryl groups.

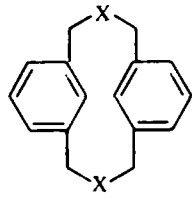


II

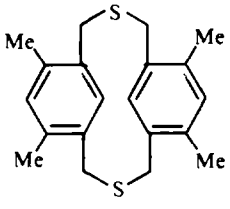
X
a: CN
b: COOMe
c: CH_2OH
d: CH_2Br



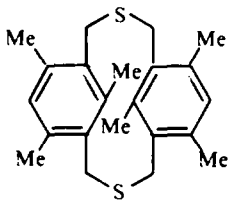
X
III: S
IV: SO
V: SO_2



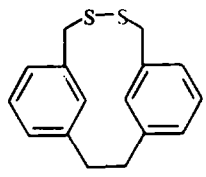
X
VI: S
VII: SO
VIII: SO_2



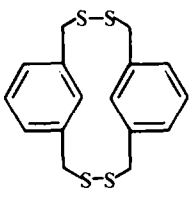
IX



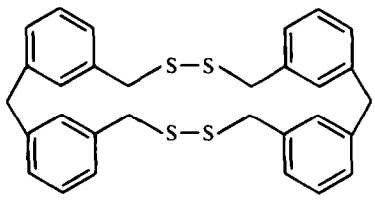
X



XI



XII



XIII

A progressive bathochromic shift is recognized in the end absorption by methyl substitution as going from VI to IX and then to Xa. The isomeric cisoid from Xb exhibited absorption similar to IX. Although distinction between Xa and Xb from the absorption spectrum is rather difficult, their TCNE complexes showed much difference, the longest band maxima being 555 for Xa and 520 mμ for Xb.*

* Charge-transfer absorption data were kindly supplied by Mr. S. Hayashi of Nihon University. The data seem to indicate more overlap of two benzene rings in a *transoid* conformer rather than *cis*. Band for Xb is quite similar to that of pentamethylbenzene (520 mμ).[32]

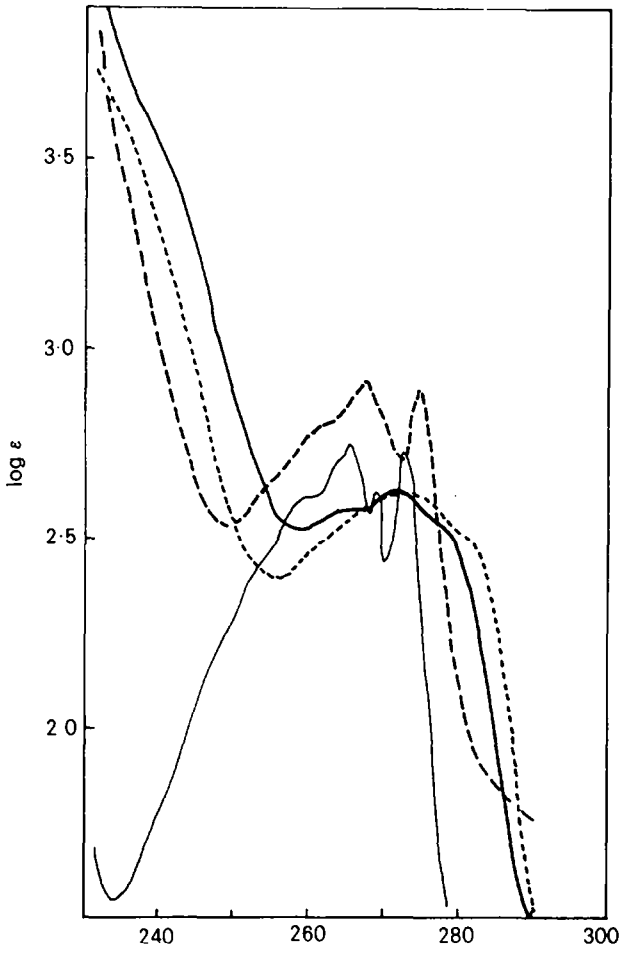


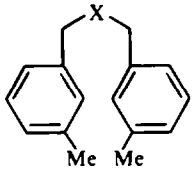
FIG 6. ——— Ultraviolet absorption spectra (n-hexane): ———[2.2]metacyclophane (I), ——— m-xylene (×2). ---------- 3.3′-dimethylbibenzylsulfone (XVII). ····· 2-thia[3.2] metacyclophane 2.2-dioxide

TABLE 4. UV ABSORPTION SPECTRA OF METACYCLOPHANE SULFUR ANALOGS[a]

Compd	max, mμ	ε	max, mμ	ε	max, mμ	ε
III	252	1,834	272[c]	714	280[c]	383
IV	248	6,569	273[c]	772	282[c]	297
V			274	412	282	308
VI	250	3,760	272[c]	740	280[c]	259
IX	256[c]	5,380	276	785	286	343
Xa	262[c]	3,104			294[c]	220
Xb	261	2,054	275	723	286	323
XV	244	2,160	266·5	765	275·5	573
XVI			269	775	276·5	653
XVII			268	810	275	790
m-Xylene			265·5	554[b]	273	533[b]
			269	413[b]		

[a] Spectra were recorded on a Hitachi EPS-3T spectrometer, using n-hexane solutions.
[b] Extinction coefficient is doubled.
[c] denotes inflection.

With cyclic sulfone, where electronic interaction between sulfur and aryl moiety is minimal, the deviation of absorption curve of cyclic form V from the open chain



X
XV: S
XVI: SO
XVII: SO_2

model XVII and *m*-xylene are quite clear and may indicate possible interaction between two benzene rings (Fig 6). The absorption curve of V is surprisingly similar to that of I. All pertinent UV data summarized in Table 4.

Acknowledgement—The authors wish to thank Miss Junko Horii for her assistance in carrying out a part of the experiments.

EXPERIMENTAL

*3,3'-*Biscyanobibenzyl* (IIa). A mixture of 46 g (0·26 mol) *m*-cyanobenzylbromide in 300 ml MeOH and activated Raney Ni prepared from 32 g of 50% Raney alloy was boiled under reflux for 17 hr. After decantation the MeOH soln was concentrated and diluted with water. From benzene extract there was obtained 7 g (23%) of colorless crystal. m.p. 160·5–161°, after recrystallization from benzene; IR (KBr) 2210 cm^{-1}. (Found: C, 82·65; H, 5·33; N, 11·94. Calcd for $C_{16}H_{12}N_2$: C, 82·73; H, 5·21; N, 12·06%).

2-*Thia*[3.2]*metacyclophane* (III). To a boiling mixture of 1 g (1·3 mmol) anhyd Na_2S in 1 ml water and 30 ml MeOH, 500 mg (1·4 mmol) of IId was added in small portions. During the addition. (18 hr) good stirring was maintained. After the mixture was boiled under reflux for an additional 20 hr. part of the solvent was removed under reduced pressure. The benzene extract contained an oily residue, which was subjected to column chromatography on alumina. Elution with *n*-hexane gave 93·5 mg (29·6%) white needles, m.p. 94–95° (91–92°), after recrystallization from *n*-hexane; *m/e* 240.

2-*Thia*[3.2]*metacyclophane* 2-*oxide* (IV). To a soln of 40 mg (0·17 mmol) of III in 10 ml acetone, 4 ml (0·2 mmol) 30% H_2O_2 diluted by 200 portions of acetone was added and the mixture kept in an icebox for 24 hr. It was then allowed to stand at room temp for 100 hr. The chloroform extract was washed with a small amount of water and dried. Concentration of the chloroform soln gave 25 mg (58·6%) colorless plates, m.p. 130–131° (132–133°), after recrystallization from chloroform–*n*-hexane; *m/e* 256, IR (KBr) 1030 cm^{-1}.

2-*Thia*[3.2]*metacyclophane* 2,2-*dioxide* (V). A mixture of 20 mg (0·08 mmol) of III, 4 drops 30% H_2O_2 and 1·5 ml glacial AcOH was warmed at 60° for 30 min. After it was kept at 90° for 1·5 hr, the soln was cooled and kept overnight. Then the mixture was poured onto ice and the ppt was collected and washed with water. Recrystallization from EtOH gave 15 mg (66%) colorless plates, m.p. 168–169° (169–170°); *m/e* 272, IR (KBr) 1315, 1300, 1120 cm^{-1}.

2,11-*Dithia*[3.3]*metacyclophane* (VI). With good stirring to a boiling soln of 25 g $Na_2S.9H_2O$ in 60 ml MeOH containing 5 ml water, a MeOH soln of 17 g (64 mmol) 1,3-bisbromomethyl benzene was added in the course of 72 hr. During the reaction a further 10 g $Na_2S.9H_2O$ was added in two portions. After the mixture had been worked up as described, the crude product was chromatographed on alumina using n-hexane–benzene as eluent. From the eluate yielded 1·0 g (11·5%) colorless needles, m.p. 120–120·5°, recrystallization from n-hexane; *m/e* 272.

2,11-*Dithia*[3.3]*metacyclophane* 2,11-*dioxides* (VIIa *and* VIIb). To a soln of 272 mg (1 mmol) of VI in 50 ml acetone, 220 mg of 30% H_2O_2 (2·2 mmol) was added and the mixture was kept in a refrigerator for 24 hr. Acetone was evaporated and the residue was taken up in chloroform. Chromatography on neutral alumina using chloroform–MeOH (300:1) as an eluent furnished mono-sulfoxide, (m.p. 187–188°), and bis-sulfoxide VIIa, (m.p. 232–234°), as colorless plates followed by bis-sulfoxide VIIb, (m.p. 248–250°), as colorless plates. Both VIIa and VIIb had *m/e* 304. Absorption due to the sulfoxide group for VIIa and VIIb appeared between 1030 and 1040 cm^{-1} ($CHCl_3$).

* All melting points are uncorrected. Determination was carried out using liquid bath and a heating block, and the latter cases are indicated by parentheses.

2,11-*Dithia*[3.3]*metacyclophane* 2,2,11,11-*tetraoxides* (VIII). A mixture of 94·5 mg (0·4 mmol) of VI, 0·5 ml of 30% H_2O_2 and 20 ml glacial AcOH was heated at 95° for 5 hr. A further 0·2 ml H_2O_2 was added during the reaction. After standing overnight at room temp, the mixture was poured into water and the ppt was collected and washed with water. The product, m.p. > 260°, after recrystallization from EtOH, was obtained in 78·8% yield; *m/e* 336, IR (KBr) 1303, 1254, 1170, 1100 cm^{-1}.

5,7,14,16-*Tetramethyl*-2,11-*dithia*[3.3]*metacyclophane* (IX). To a stirred soln of 12 g $Na_2S.9H_2O$, 10 ml water and 100 ml dioxane, 10 g (0·05 mol) 4,6-bischloromethyl-*m*-xylene was added dropwise during 50 hr under reflux, during which time 12 g $Na_2S.9H_2O$ was added in two portions. Then a part of the dioxane was removed under reduced pressure and residue was poured into water and the crystals separated. From the mother liquor a further 130 mg of IX was obtained by chromatography on alumina using benzene–n-hexane as eluent; total yield was 21·1%. recrystallization from benzene–n-hexane gave colorless plates, m.p. 231–232°; *m/e* 328.

5,7,9,14,16,18-*Hexamethyl*-2,11-*dithia*[3.3]*metacyclophane* (Xa *and* Xb). To a stirred, refluxing soln of 12 g $Na_2S.9H_2O$ and 10 ml water in 300 ml dioxane, 10·8 g (0·05 mol) 1,3-bischloromethylmesitylene in 200 ml dioxane was added dropwise in the course of 27 hr. During the reaction an additional amount of $Na_2S.9H_2O$ (12 g) was added. After the reaction was complete the mixture was worked up in the usual manner. On concentration of the benzene soln crystalline material which proved to be *trans* Xa was obtained from ethanol (370 mg) as colorless plates, m.p. 260–261°. By chromatographic separation of the mother liquor on neutral alumina benzene–n-hexane (1:1) eluted in addition to 170 mg of Xa, 1655 mg (18·6%) of *cis* Xb as colorless needles, m.p. 229–230°, which recrystallized benzene–EtOH. The total yield of *trans* compound was 6·1%. Both compounds had *m/e* 356.

To examine possible interchange between these two isomers *cis* Xb was heated in diethylene glycol at 230–240° for 4 hr. By NMR spectra the product was proved to be largely the starting material and no indication of isomerization into *trans* compound was obtained.

2,3-*Dithia*[4.2]*metacyclophane* (XI). The cyclization of IId to XI was achieved by using the Bunte salt method.[33] To a stirred soln of 370 mg (1·4 mmol) of IId in 12 ml $EtOH_2$ 365 mg (1·47 mmol) sodium thiosulfate heptahydrate was added dropwise in 9 ml water. The mixture was warmed at 85° until the soln was homogeneous. After the soln was diluted with 10 ml EtOH and 10 ml water, a soln of 400 mg (1·58 mmol) I_2 in 50 ml EtOH was added dropwisely during 10 hr. Worked up in the usual manner gave an oily solid, which was purified by chromatography on alumina to yield 7% colorless plates, (m.p. 166·5–167°) after recrystallization from benzene–n-hexane; *m/e* 272.

2,3,12,13-*Tetrathia*[4.4]*metacyclophane* (XII). This was prepared by the method employed for the preparation of XI in 6·7% yield by the reaction of 1,3-bisbromomethylbenzene and sodium thiosulfate followed by iodine oxidation, m.p. 168–170° (165–167°). It recrystallized from EtOH; *m/e* 336.

An attempted synthesis of 2,3-*dithia*[4.1]*metacyclophane*. Treatment of 3,3'-bisbromomethyl diphenylmethane as in the preparation of XI and XII did not produce the expected compound, but resulted in the formation of 22-membered ring XIII; m.p. 185–186°, *m/e* 516.

3,3'-*Dimethyldibenzylsulfide* (XV), -*sulfoxide* (XVI) *and* -*sulfone* (XVII). The sulfide XV was prepared by the reaction of *m*-bromomethyltoluene and sodium sulfide, m.p. 22–23°. (Found: C, 78·99; H, 7·39. Calcd for $C_{16}H_{18}S$: C, 79·31; H, 7·49%).

The sulfoxide XVI was obtained by controlled oxidation of XV with H_2O_2 in acetone, colorless needles, m.p. 103–104°, after recrystallization from n-hexane–chloroform; IR (KBr) 1020 cm^{-1}. (Found: C, 73·97; H, 6·86. Calcd for $C_{16}H_{18}SO$: C, 74·39; H, 7·02%).

The sulfone XVII was obtained by the oxidation of XV with HO_2 at 95°, colorless plates, m.p. 117–118°, recrystallization from EtOH; IR (KBr) 1306, 1282, 1207 and 1107 cm^{-1}. (Found: C, 69·92; H, 6·85. Calcd for $C_{16}H_{18}SO_2$: C, 70·05; H, 6·61%).

The H-D *exchange reaction of* IV. IV (15 mg) was dissolved in 2 ml of 0·05 M NaOH in deuterium oxide–dioxane (1:1) and was kept at 40°. To the aliquots removed at 10, 20, 30, 40, and 120 min after the start of the reaction were added 2·5% HCl in order to stop the reaction. NMR spectra were recorded on each of the chloroform extracts at 100°. The figure shown in Fig 4 was obtained by mean values after 12 scans. Based on the decrease in area due to proton signals psuedo first order rate constants were calculated to be $k_2 = 56 \times 10^{-4}\ 1M^{-1}\,sec^{-1}$ for high field protons and $k_2 = 1\,54 \times 10^{-4}\ 1M^{-1}\,sec^{-1}$ for low field protons.

Spectral measurements. 100 MHz spectra were measured on a Varian Associates HA-100 spectrometer using the frequency-swept and TMS-looked modes. Chemical shifts were measured by a equipped digital counter. Two Hewlett–Packard 200-ABR oscillators were used for the multiple resonance experiments including the NOE studies. Low temp spectra were recorded in combination with a variable temp controller.

Insufficient solubilities of the samples forced us to measure on the rather dilute soln less than a few mg/0·4 ml.

The NOE values were obtained by the usual integration method using degassed solns.[26] The deviations from at least 5 traces of integration were within 2%.

A part of the spectra were measured at 60 MHz on a Hitachi R-20B spectrometer.

UV spectra were recorded on a Hitachi EPS-3T spectrometer in n-hexane. IR spectra were recorded on a Hitachi grating infrared spectrophotometer EPI-G2.

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