Synthesis of Cyclophanes with Intra-Annular Functionality and Cage Structure

Arunachalam Kannan,[†] Perumal Rajakumar,*[,†,‡] V. Kabaleeswaran,[§] and S. S. Rajan[§,||]

Departments of Organic Chemistry and Crystallography and Biophysics, University of Madras, Guindy Campus, Guindy, Madras 600 025, India

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Cyclophanes of the type **1** and **2**, with large cavity sizes, have been synthesized from the corresponding dichloride **8** or **8a** and *o*-xylene-α,α′-dithiol (**9**), *p*-xylene-α,α′-dithiol (**10**), or *m*-terphenyldithiol (**11**). Similarly, cyclophanes of the type **3** with intra-annular functionality have been obtained by the coupling of the corresponding dithiol **15** or **19** and *m*-terphenyl dibromide **5**, **5a**, **5b**, or **5c**. With the aim of introducing multifunctionality, cyclophanes of the type **21** and **23** were prepared from 3,5-bis(mercaptomethyl)anisole or 3,5-bis(mercaptomethyl)phenol and the corresponding substituted *m*-terphenyl dibromide **5b** or **5c**. Cyclophanes **24**, **24a**, **24b**, and **32**, with a new type of cage structure, have been obtained by the coupling of the corresponding tetrathiol **29** with 2 equiv of the dibromides **5c**, **5a**, and **5b** or 1 equiv of the tetrabromide **31**, respectively. Further, the sodium salts of the cyclophanes **3c**, **21**, and **24b** were completely characterized by ^{1}H NMR spectroscopy. XRD analysis of the cyclophane **21** revealed the presence of an ethanol molecule inside the cavity, indicating the facile formation of a host−guest complex.

Introduction

Molecules with large cavities, and supramolecular chemistry in general, are of great current interest.[1] Though the synthesis of unstable *syn*-[2,2]metacyclophane was reported in 1985,[2] the modified cyclophanes called cuppedophanes and cappedophanes were only reported recently.[3] Thiacyclophanes have proved to be remarkably useful precursors to a number of novel compounds.[4] For example, Mitchell has recently reported the synthesis of novel aromatic systems via thiacyclophane.[5] Examples of the synthesis of dithiacyclophanes containing large molecular cavities have been reported by our laboratory.[6] The synthesis of functionalized cyclophanes has been an active research area recently with particular focus on hydrophilic cavities.[7]

We wish to report the synthesis of cyclophanes with large cavities that contain varied functionality. This permits a comparison of functional group chemistry within the outside a specifically designed microenvironment. Further, we report the synthesis of a new class of cyclophanes which contain a cage structure. We also discuss the formation of the sodium salt as well as the host−guest complex of some of the cyclophanes.

Cyclophanes in general can be used as host molecules for complexation of either metal ions or small guest molecules. The cyclophanes reported here have different molecular cavity size and therefore can be used for specific complexation. The aromatic units present in these cyclophanes ensure the necessary rigidity[8] and prevent the possible collapse of conformation which would reduce the cavity size.

Results and Discussion

Cyclophanes with Macrocyclic Cavities. Cyclophanes **1**−**3** are based on a *m*-terphenyl framework that can be obtained by the known tandem aryne sequence.[9] The angular nature of the *m*-terphenyl present in compounds **1**−**3** prompted us to use substituted *m*-terphenyl as the basic building block. Addition of 3 equiv of *p*-tolylmagnesium bromide to 2,6-dichloroiodobenzene followed by quenching with dilute HCl, Br_2, or CO_2 resulted in the formation of 4,4″-dimethyl-1,1′:3′,1″-terphenyl (**4**), 2′-bromo-4,4″-dimethyl-1,1′:3′,1″-terphenyl (**4a**), or 4,4″-dimethyl-1,1′:3′,1″-terphenyl-2′-carboxylic acid (**4b**) in excellent yield. The bromide **4a** can also be prepared by treating the reaction mixture of aryl Grignard and dichloroiodobenzene with CBr_4. Treatment of the carboxylic acid **4b** with CH_2N_2 in THF gave methyl ester **4c**, which can also be prepared by refluxing the acid chloride of **4b** with MeOH. Twofold radical bromination of **4**, **4a**, **4b**, and **4c** with NBS in CCl_4 gave 4,4″-bis(bromomethyl)-1,1′:3′,1″-terphenyl (**5**), 2′-bromo-4,4″-bis(bromomethyl)-1,1′:3′,1″-terphenyl (**5a**), 4,4″-bis(bromomethyl)-1,1′:3′,1″-terphenyl-2′-carboxylic acid (**5b**), and methyl 4,4″-bis(bromomethyl)-1,1′:3′,1″-terphenyl-2′-carboxylate (**5c**) in 80, 75, 65, and 60% yields, respectively. Bisalkylation of the dibromides **5** and **5a** with methyl *p*-hydroxybenzoate in the presence of K_2CO_3 in DMF afforded the diesters **6** and **6a** in 85 & 75% yields respectively. LAH reduction of the diesters **6** and **6a** followed by treatment with $SOCl_2$ in the presence of

[†] Department of Organic Chemistry.
[‡] Present Address: Department of Chemistry, Indian Institute of Technology, Madras 600 036, India.
[§] Department of Crystallography and Biophysics.
[||] To whom inquiries regarding X-ray structures should be directed.
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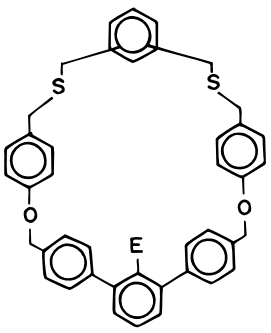

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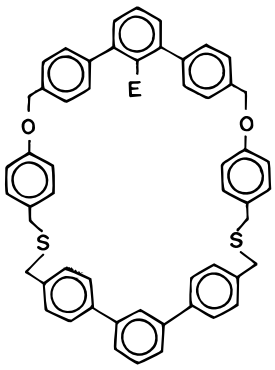
1



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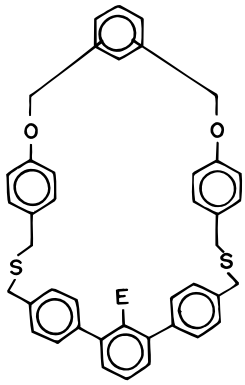

E = H, Br, COOH, $COOCH_3$

3

pyridine in CH_2Cl_2 resulted in the dichlorides **8** and **8a** in 82 and 77% yields, respectively (Scheme 1).

Coupling of the dichlorides **8** and **8a** with *o*-xylene-α,α′-dithiol (**9**) in benzene under high dilution in the presence of KOH in ethanol afforded the cyclophanes **1a** and **1b** in 70 & 60% yields, respectively (Scheme 2).

The ^{1}H NMR spectrum of **1a** showed three singlets each of four protons at δ 3.60, 3.65, and 5.25 for CH_2S, SCH_2, and OCH_2, respectively, in addition to the aromatic protons. The C_2H of the *m*-terphenyl frame appeared as a one-proton triplet at δ 7.67. The fact that the chemical shift of the C_2H of the *m*-terphenyl unit is not affected suggests that this hydrogen is not in the π-cloud of the *o*-xylylene unit. The ^{1}H NMR spectrum of **1b** showed the absence of a C_2H proton. Structures **1a** and **1b** were further supported by their ^{13}C NMR and mass spectra. XRD[10] studies on **1a** also confirmed the structure. The Ortep, unit cell packing, and CPK space-filling diagrams of cyclophane **1a** are shown in Figures 1, 2, and 3, respectively.

Similar coupling of the dichlorides **8** and **8a** with *p*-xylene-α,α′-dithiol (**10**) under identical conditions gave the cyclophanes **1c** and **1d** in 60 and 55% yields, respectively. The ^{1}H NMR spectrum of **1c** displayed three singlets of four protons each at δ 3.49, 3.55, and 5.25 for the CH_2S, SCH_2, and OCH_2 protons. In the ^{1}H NMR spectrum, the *p*-xylylene protons of **1d** appeared as a singlet at δ 7.16 indicating free rotation and a lack of shielding of these protons by the bromine atom at the $C_{2'}$ position. The bromo compounds **1b** and **1d** when treated with 1 equiv of *n*-BuLi at −78 °C followed by quenching with dilute HCl afforded, quantitatively, the cyclophanes **1a** and **1c**, respectively, indicating the generation of the lithium salt and demonstrating that the reaction permits the introduction of various functionalities at the $C_{2'}$ position of the *m*-terphenyl framework.

With the intent of further increasing the cavity size, the dichlorides **8** and **8a** were coupled with 4,4″-bis(mercaptomethyl)-1,1′:3′,1″-terphenyl (**11**) obtained from the dibromide **5** by application of the known standard procedure using KOH.[9] The coupling, after usual workup, afforded the cyclophanes **2a** and **2b** in 30 and 25% yields (Scheme 2), respectively, as supported by the spectral data and satisfactory elemental analysis.

Our attention was then focused on changing the positions of the S and O atoms to result in the formation of cyclophanes of the type **3**. Bisalkylation of *o*-xylene α,α′-dibromide with methyl *p*-hydroxybenzoate in K_2CO_3/DMF afforded the diester **12** in 90% yield. The dithiol **15** was obtained in an overall yield of 51% from the diester **12** by the conventional route.[11] Similarly, the dithiol **19** was obtained by the hydrolysis of the isothiouronium salt derived from the corresponding diester **16** (Scheme 3).

Coupling of the dithiol **15** with 1 equiv of the dibromide **5** in benzene under high dilution in the presence of KOH in ethanol afforded the cyclophane **3a** in 70% yield (Scheme 4). The ^{1}H NMR spectrum of **3a** showed three singlets of four protons each at δ 3.60, 3.65, and 5.25 for the CH_2S, SCH_2, and OCH_2 protons, respectively, in addition to the aromatic protons. The *o*-xylylenyl protons in **3a** each appeared as a two-proton multiplet at δ 7.09−7.19 and 7.17−7.21, respectively. Similarly, coupling of the dithiol **19** with 1 equiv of the dibromide **5** gave the cyclophane **3e** (65%) as evidenced by the ^{1}H NMR and ^{13}C NMR spectra.

Cyclophanes with Functionalized Microenvironment. The introduction of functional groups into the microenvironment of the cyclophane cavity comprised the next phase of this project.

The synthetic strategy was directed toward cyclophanes with intra-annular functionality. The dithiol **15** (Scheme 3) in benzene when coupled with the dibromide **5a** under high-dilution technique in the presence of KOH in ethanol afforded the cyclophane **3b**. Similarly, cyclophane **3f** was obtained from the dithiol **19** and the dibromide **5a** (Scheme 4). Coupling of the dithiol **15** with the dibromide **5b** in the presence of 3 equiv of KOH, followed by acidification of the reaction mixture before the usual workup, yielded the cyclophane **3c**. Similarly, cyclophane **3g** was obtained from the dithiol **19** and the dibromide **5b**. In **3c** and **3g** the carboxylic acid group is in the microenvironment of the cyclophane. Cyclophanes **3c** and **3g** were also obtained from the cyclophanes **3b** and **3f** using *n*-BuLi and CO_2. The lithium salt of cyclophanes **3b** and **3f** upon bubbling with dry CO_2 for 3 h followed by acidification gave the cyclophanes **3c** and **3g** in good yield. Acidification of the lithium salt from **3b** and **3f** with dilute HCl afforded the cyclophanes **3a** and **3e** in excellent yield. Coupling of the dithiol **15** or **19** with the dibromide **5c** in benzene using KOH in ethanol afforded the cyclophanes **3d** and **3h** with a COOMe group in the microenvironment. Cyclophanes **3d** and **3h** were also obtained from **3c** and **4c**, respec-

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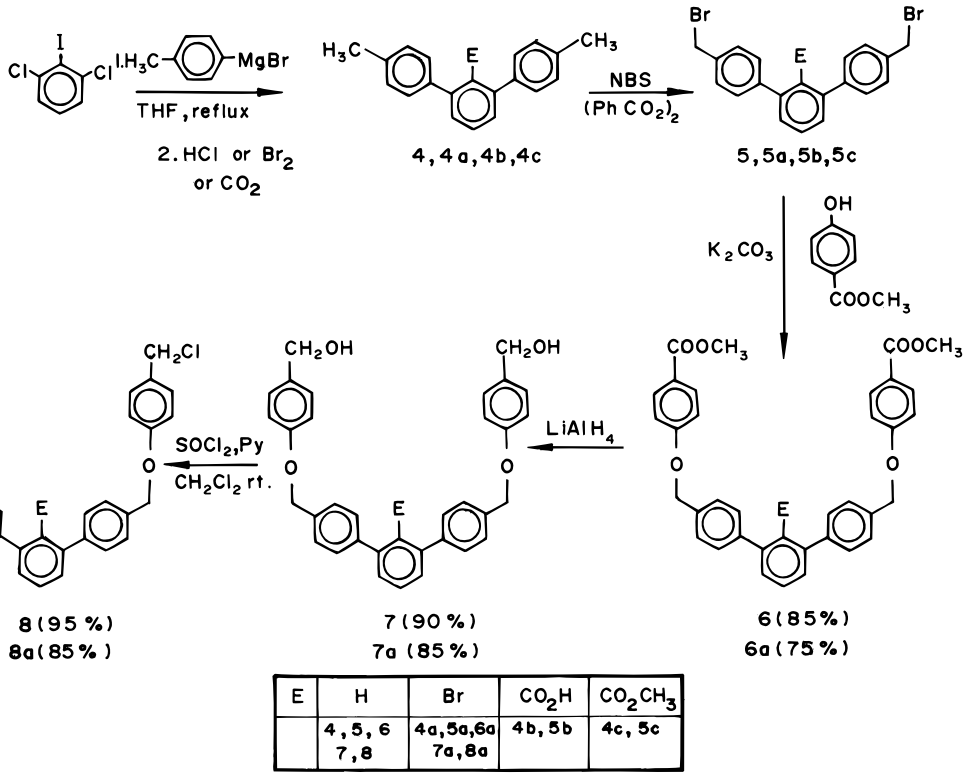
Scheme 1



E	H	Br	CO_2H	CO_2CH_3
	4, 5, 6 7, 8	4a, 5a, 6a 7a, 8a	4b, 5b	4c, 5c

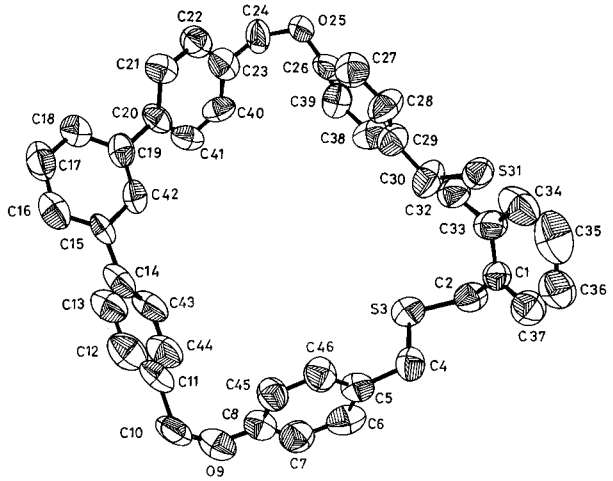


Figure 1. Ortep diagram of the cyclophane **1a**.

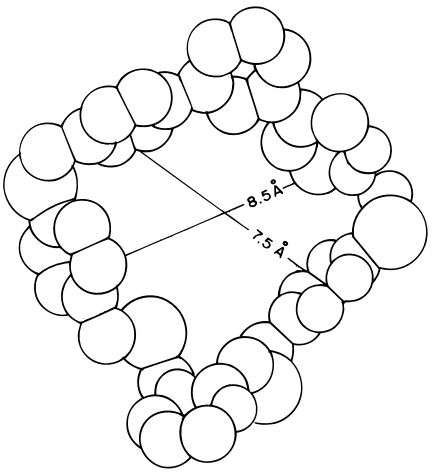


Figure 3. CPK space-filling model of cyclophane **1a**.

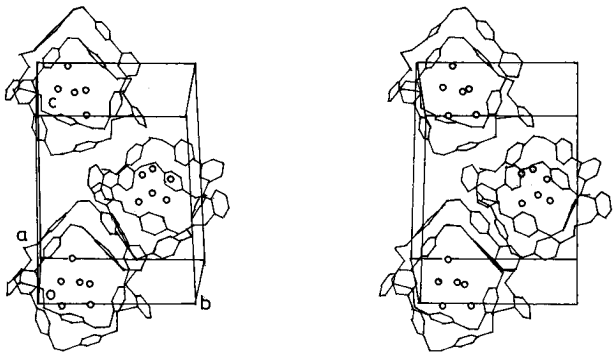


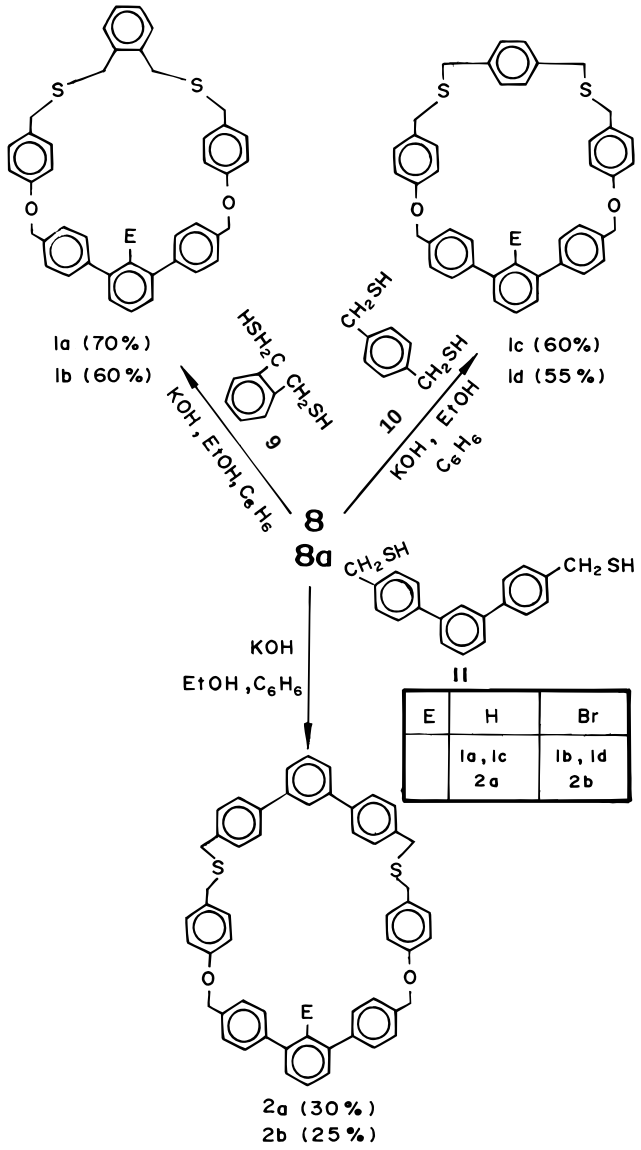
Figure 2. Unit cell packing of the cyclophane **1a**.

tively, by two different routes. Treatment of **3c** or **3g** with CH_2N_2 in THF afforded the cyclophane **3d** or **3h**. The alternate method is to convert the cyclophane carboxylic acids **3c** and **3g** into the acid chlorides using $SOCl_2$ in CH_2Cl_2 with few drops of pyridine and then to heat the reaction mixture in refluxing methanol. However, quantitative yields were obtained upon reaction with CH_2N_2.

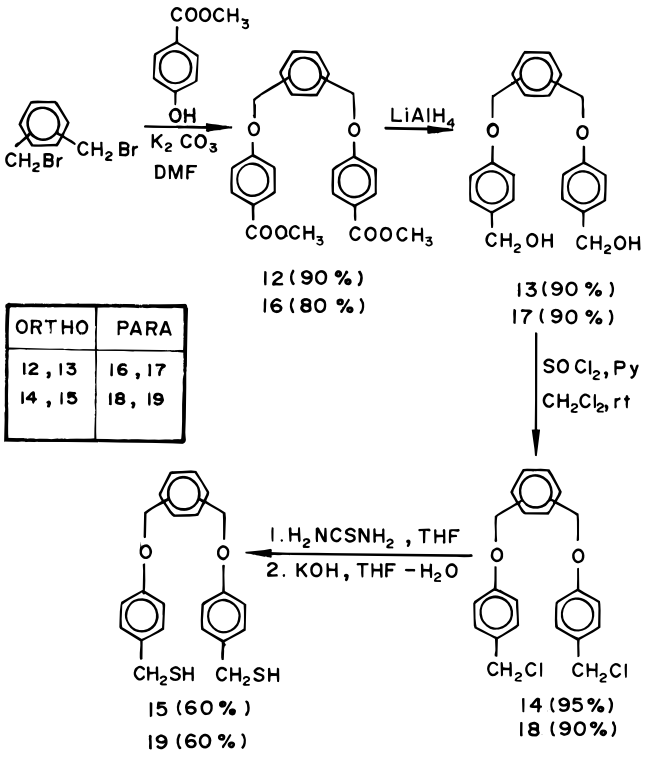
It is worth mentioning that the *p*-xylylenyl group in the cyclophanes **3e**, **3f**, **3g**, and **3h** showed free rotation, as revealed by the magnetically equivalent nature of all four of the xylylene protons in the ^1H NMR spectrum. Free rotation of the *p*-xylylenyl roof is possible because of the large cavity size of these cyclophanes.

Cyclophanes with Polyfunctional Microenvironment. Introduction of multifunctionality into the microenvironment of the cyclophane has several advantages. It enhances the solubility of the cyclophane, creates a hydrophilic cavity, and increases the complexing ability. We focused on the synthesis of cyclophanes **21**, **21a**, **23**, and **24**. Coupling of the dibromide **5b** with 3,5-bis(mercaptomethyl)anisole (**20**) gave the cyclophane **21** (40%) (Scheme 5).

Scheme 2



Scheme 3



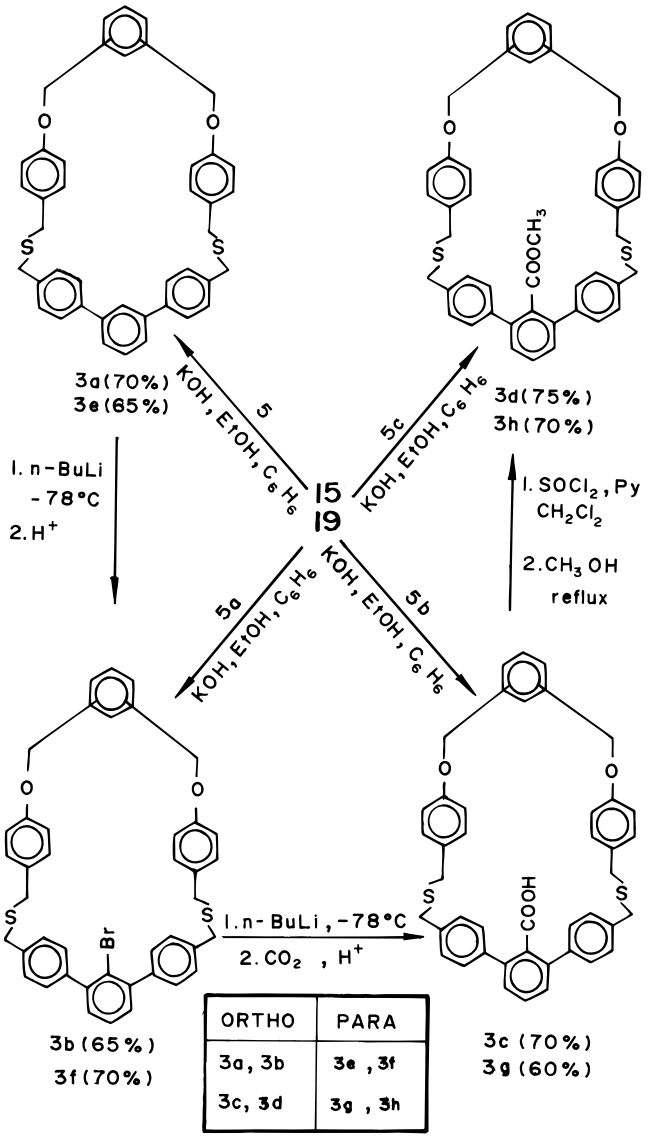
The high polarity and high melting point of **21** could be due to the presence of two carboxylic acid functionalities. The IR spectrum of **21** showed a carbonyl absorption at 1710 cm^{-1}. The ^1H NMR spectrum of **21** showed two singlets of eight protons at δ 3.58 and 3.62 for the SCH_2 and CH_2S protons, respectively, and a six-proton singlet at δ 3.69 for the methoxy protons. The ^1H NMR spectrum of cyclophane **21**, in addition to the aromatic protons, displayed broad singlets at δ 6.60 (H_A) of four protons and δ 6.76 of two protons (H_B) for the aromatic protons derived from the thiol unit. The shielding effect observed for the H_A and H_B protons of cyclophane **21** could be due to the electron-releasing effect of the methoxy group. In the ^{13}C NMR spectrum, the carboxyl carbon appeared at δ 159.51. In the mass spectrum, the molecular ion appeared at *m/e* 997. Although all of these data are consistent with a monomeric structure, the dimeric structure **21** received support from XRD studies.[12] The Ortep diagram, stereoview of the unit cell, and CPK space-filling model of cyclophane **21** are shown in Figures 4, 5, and 6, respectively.

Similarly, coupling of the dibromide **5c** with the dithiol **20** under identical conditions gave the cyclophane **21a**. The IR spectrum of **21a** showed the carbonyl absorption at 1715 cm^{-1}. The ^1H NMR and other spectral and analytical data supported the structure **21a**. Treatment of the cyclophane **21** with $SOCl_2$ in CH_2Cl_2 in the presence of pyridine afforded the acid chloride intermediate, which on refluxing with methanol gave the cyclophane **21a**. All attempts to demethylate **21** to the corresponding diphenolic cyclophane failed. The thio linkage in the cyclophane **21** was cleaved by reagents such as HI or BBr_3. Hence, our attention was diverted to the coupling reaction of the phenolic dithiol **22**[11] prepared from 3,5-bis(bromomethyl)anisole.[13] Coupling of dithiol **22** with dibromide **5c** in benzene and in the presence of KOH in ethanol afforded the cyclophane **23** in 40% yield. Hart et al.[11] have used the same thiol, and a similar report has been cited in the literature. The IR spectrum of cyclophane **23** showed a carbonyl absorption at 1720 cm^{-1} in addition to the hydroxyl absorption at 3500−3300 cm^{-1}. Spectral and analytical data also supported the proposed structure **23**. Our attempts to connect the OH groups in cyclophane **23** using *p*-xylylene α,α′-dibromide failed, and polymeric materials were obtained. However, coupling of the cyclophane **23** with 1 equiv of *o*-xylylene α,α′-dibromide in K_2CO_3/DMF under high dilution afforded the cyclophane **24** (50%), which has a cage structure. The ^1H NMR spectrum of **24** showed four singlets of eight protons each at δ 3.20 and 3.70 and a four-proton singlet at δ 5.00, in addition to the aromatic protons. Another independent method had been developed for the cyclophane **24** using the dibromide **5c** and tetrathiol **31**.

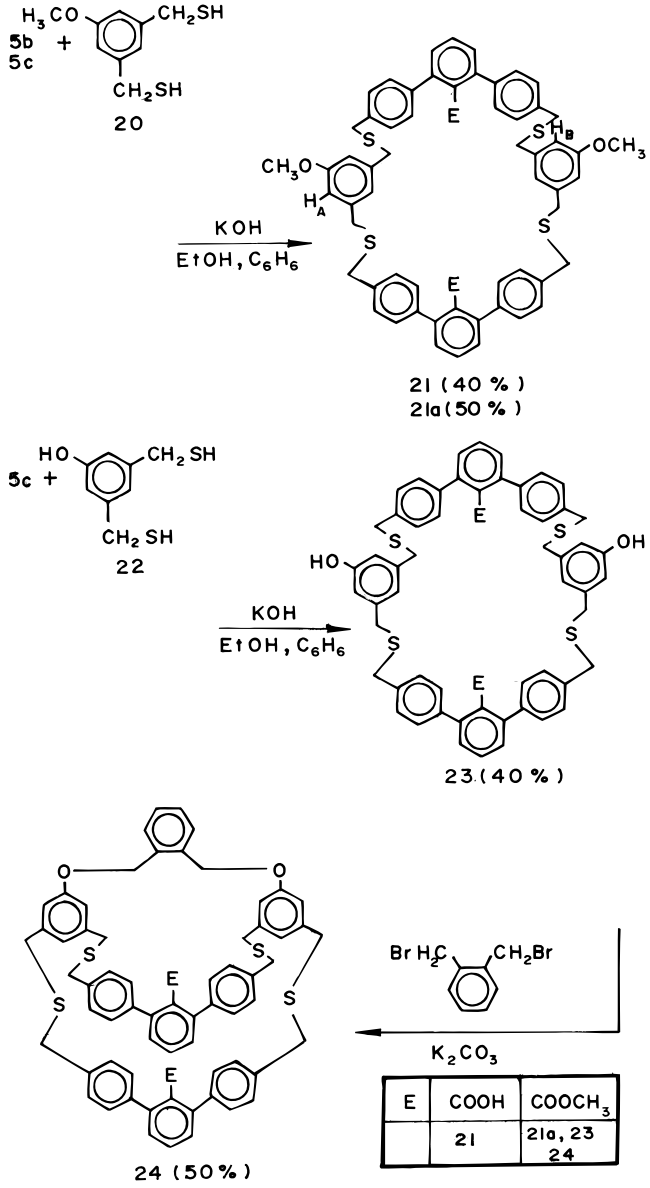
(12) The authors have deposited atomic coordinates for the cyclophanes **1a** and **21** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, U.K.

(13) Boekelheide, V.; Griffin, R. W., Jr. *J. Org. Chem.* **1969**, *34*, 1960.

Scheme 4



Scheme 5



Cyclophanes with a Cage Structure. The cyclophanes with a cage structure[14] may imitate some of the naturally occurring haemocyanin systems.[15] The copper atoms in haemocyanins are separated by a distance of 3.55A. We next studied the synthesis of cyclophanes with a cage structure and with a cavity size of about 4 Å bearing polar functional groups able to bind metal ions such as Cu^{2+}. Such cyclophanes can accommodate two Cu atoms and should support electron transfer reactions inside the microenvironment. Toward the synthesis of caged cyclophanes, the tetrathiol **29** was prepared from *o*-xylylene α,α′-dibromide. Reaction of *o*-xylylene α,α′-dibromide with 2 equiv of ethyl 5-hydroxyisophthalate (**25**) in the presence of K_2CO_3 in DMF gave the tetraester **26** in 80% yield. Reduction of **26** with LAH followed by treatment with $SOCl_2$ gave the dichloride **28**, which was converted into tetrathiol **29** in 70% yield by the conventional route[11] (Scheme 6). The ^{1}H NMR spectrum of **29** displayed a four-proton triplet at δ 1.70 for the SH protons, an eight-proton doublet at δ 3.50 for the CH_2S protons, and broad singlets at δ 4.95 and 6.60 of four and six protons, respectively. The *o*-xylylenyl protons appeared as a multiplet at δ 7.00−7.25.

Coupling of the tetrathiol **29** with 2 equiv of dibromide **5a** in benzene in the presence of KOH in ethanol afforded the cyclophane **24a** in 35% yield. Similarly, coupling of tetrathiol **29** under identical condition with 2 equiv of dibromide **5b** gave the cyclophane dicarboxylic acid **24b** in 40% yield (Scheme 7). In the IR spectrum, cyclophane **24b** displayed a carbonyl absorption at 1720 cm^{-1}. In the ^{1}H NMR spectrum, two singlets of eight protons each for SCH_2 and CH_2S were observed at δ 3.31 and 3.70 and the OCH_2 protons appeared as a singlet at δ 5.01. Further, in the aromatic region, H_A protons appeared at δ 6.93 as a singlet of two protons and another singlet of four protons (H_B) appeared at δ 6.30. The protons meta and para to the COOH group in the *m*-terphenyl unit appeared as a doublet at δ 7.37 (H_m) and as a triplet (H_p) at δ 7.52, respectively. The carboxylic acid proton appeared as a broad singlet at δ 12.6. In the ^{13}C NMR spectrum, the carbonyl carbon appeared at δ 170.343. The structure **24b** received further support from its mass spectrum and elemental analysis. Coupling of **29** with 2 equiv of **5c** afforded the cyclophane **24** in 35% yield, as evidenced by the spectral and analytical data. However, the coupling of **29** with **5** afforded colorless material insoluble in most of the usual solvents, which prevented

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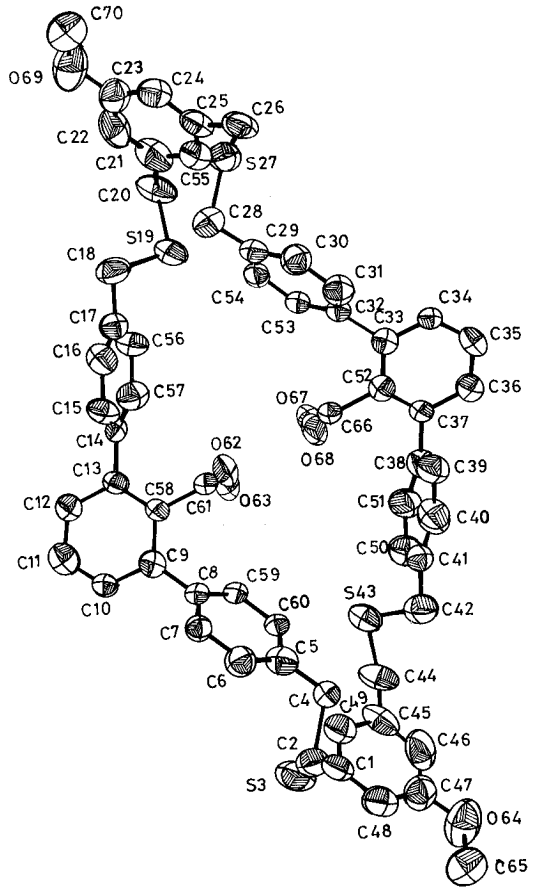


Figure 4. Ortep diagram of the cyclophane **2I**.

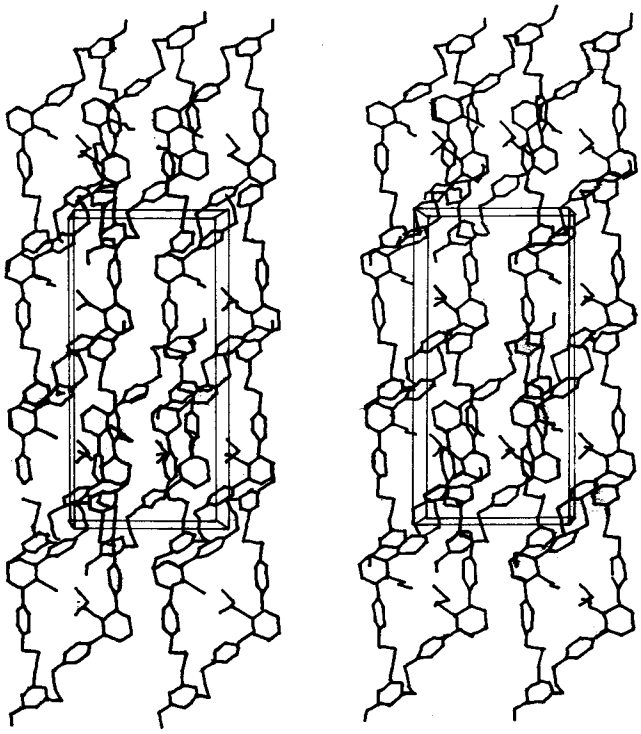


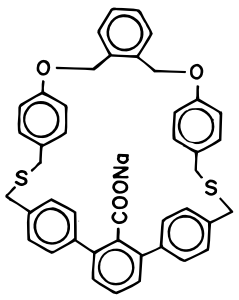
Figure 5. Stereoview of the unit cell of cyclophane **2I**.

its characterization by physical methods. Cyclophane **24** has also been obtained from **24b** by treatment with $SOCl_2$ in CH_2Cl_2 in the presence of pyridine followed by refluxing in methanol. Similarly, treatment of cyclophane **24a** with *n*-BuLi at −78 °C followed by bubbling with CO_2 resulted in the formation of **24b**.

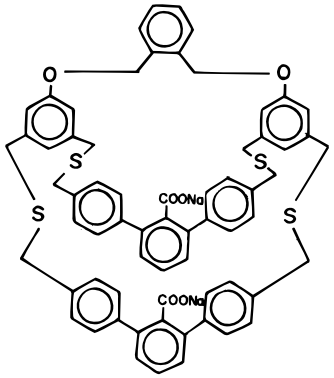
Treatment of 2 equiv of NaH with ethylene glycol in DMF gave the disodium salt. Reaction of the salt with the acid chloride, derived from *m*-terphenyl carboxylic acid **4b** and $SOCl_2$, gave ethylene 1,2-bis(4,4″-dimethyl-1,1′:3′,1″-terphenyl-2′-carboxylate) (**30**) in 35% yield. The diester **30** can be purified to a colorless crystalline solid on a silica gel column. Treatment of **30** with 4 equiv of NBS in CCl_4 in the presence of benzoyl peroxide afforded the tetrabromide **31** in 60% yield (Scheme 8).

The tetrabromide **31** can be purified only by crystallization because it decomposes on silica gel. Coupling of **31** with 1 equiv of **29** under the usual conditions afforded cyclophane **32** in 35% yield (Scheme 7). Cyclophane **32**, in its IR spectrum, showed an ester carbonyl at 1725 cm^{-1}, and in its ^1H NMR spectrum, four two-proton AB quartets were observed at δ 3.66, 3.77 and at δ 3.85, 3.96 for the SCH_2 and CH_2S protons. The OCH_2 protons appeared as a singlet at δ 3.72. The H_A and H_B protons of **32** appeared as singlets of two protons and four protons, respectively, at 6.95 and 6.60. The H_p protons appeared at δ 7.52 as a triplet and the H_m protons appeared at δ 7.35 as a doublet. In the ^{13}C NMR spectrum, the carbonyl carbon appeared at δ 169.78. The proposed structure **32** received further support from mass spectral and elemental analyses. However, coupling of α,α′-bis[3,5-bis(mercaptomethyl)phenoxyl-*p*-xylene with the dibromide **5a**, **5b**, or **5c** gave only polymeric products.

Formation of the Sodium Salt of Cyclophanes 3c, 21, and 24b. Encouraged by the synthesis of novel cyclophanes via a simple route, our attention turned to the formation of sodium salts of some of the cyclophane carboxylic acids as well as host−guest complexes.



Sodium salt of the Cyclophane 3c



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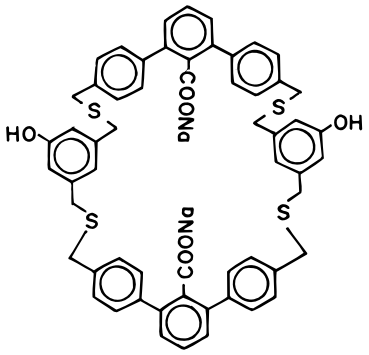
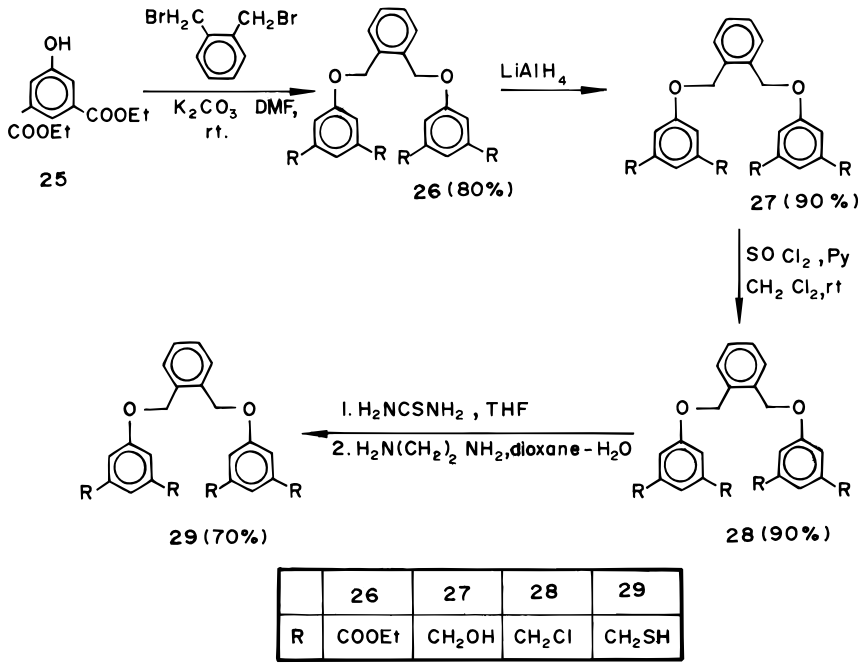


Disodium salt of the Cyclophane 21

Scheme 6



	26	27	28	29
R	COOEt	CH_2OH	CH_2Cl	CH_2SH

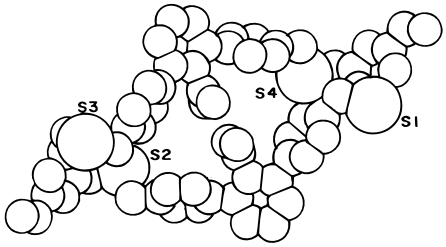


Figure 6. CPK space filling model of cyclophane **21**.

(a) Sodium Salt of Cyclophane 3c. Cyclophane carboxylic acid **3c** was treated with dry NaOMe in anhydrous DMSO-d_6. The ^{1}H NMR spectrum showed remarkable differences in the chemical shifts of some of the protons. Although no distinct change was seen with respect to the SCH_2 and CH_2S protons, the OCH_2 protons showed a significant shift. In cyclophane **3c**, the OCH_2 protons appeared at δ 5.20, while in the sodium salt they appeared as a singlet at δ 4.60. This suggests that the OCH_2 protons are proximate to the COOH group. Another remarkable change in the aromatic region is the appearance of the H_p and H_m protons at δ 6.87 as a triplet and at δ 6.47 as a doublet. However, in cyclophane **3c** these protons appeared as multiplets at δ 7.40−7.42 (H_m) and as a broad singlet at δ 7.44−7.48 (H_p). These changes suggest the formation of the sodium salt.

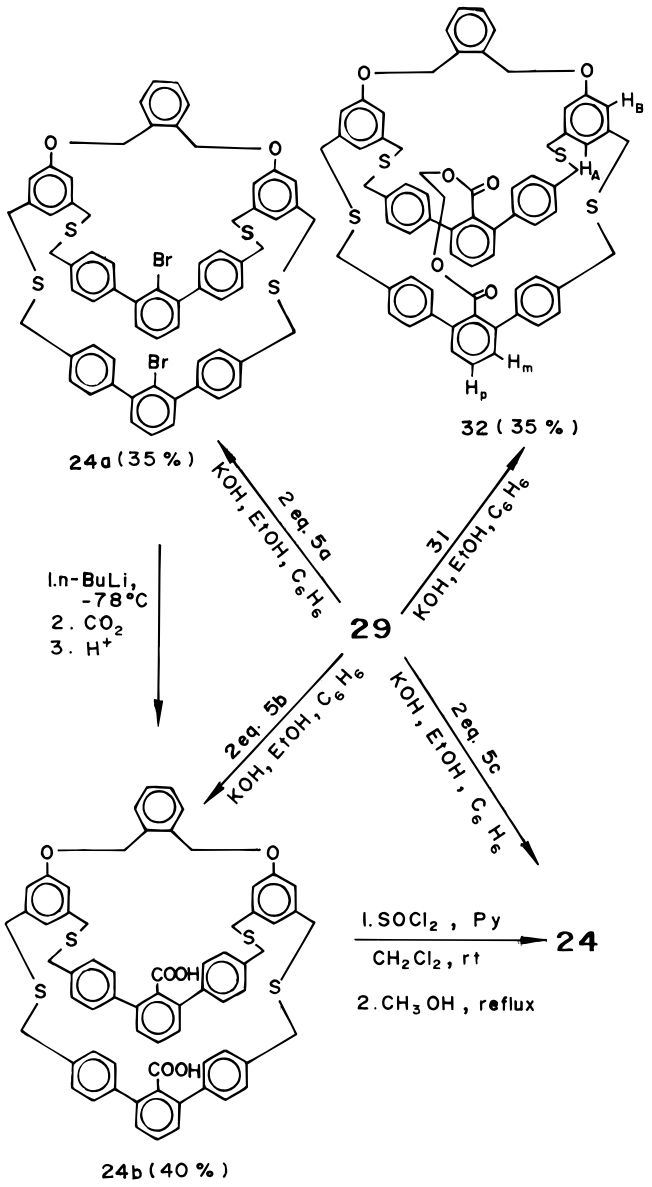
(b) Disodium Salt of the Cyclophane 24b. The disodium salt of cyclophane **24b** could be even more interesting. The cyclophane carboxylic acid **24b** reacts with NaOMe in DMSO-d_6, showing remarkable changes in the ^{1}H NMR spectrum. The SCH_2 and CH_2S protons of the disodium salt appeared at δ 3.30 and 3.70 as singlets. However, the OCH_2 protons appeared at δ 4.60 for the sodium salt instead of at δ 5.00. Possibly, the COO^- anion has a long-range shielding effect on the OCH_2 protons. The H_A protons of **24b** were not affected by the formation of the sodium salt which indicates that these protons are farther from the COOH group. However, the H_p and H_m protons underwent dramatic changes. In cyclophane **24b**, these appeared at δ 7.52 and 7.37 as a triplet and doublet, but in the disodium salt, they appeared at δ 6.87 and 6.47 as triplet and doublet, respectively. The shielding effect clearly indicates the formation of the COO^- anion. Furthermore, the solubility of the cyclophane carboxylic acid **24b** improved after the formation of the disodium salt.

(c) Disodium Salt of the Cyclophane 21. XRD analysis of the cyclophane **21** revealed that the cyclophane has an elliptical shape with the two carboxylic acid groups facing each other. X-ray analysis indicated the presence of hydrogen bonding between the two COOH groups and that the OCH_3 groups were farther apart. Treatment of dicarboxylic acid **21** with NaOMe in DMSO-d_6 showed remarkable changes in the ^{1}H NMR spectrum. The SCH_2 and CH_2S proton signals appeared at δ 3.58 and 3.62 in both the cyclophane **21** and its disodium salt. The H_p and H_m protons of the *m*-terphenyl system appeared at δ 6.88 and 6.45 as a triplet and a doublet for the sodium salt of the cyclophane **21**. However, the ^{1}H NMR spectrum of cyclophane **21** displayed a triplet at δ 7.37 for the H_p protons and the H_m protons merged in the aromatic region (δ 7.16−7.25). Upon formation of the disodium salt, the chemical shifts of H_p and H_m are shielded and show a clear triplet and doublet pattern for H_p and H_m, respectively. The OCH_3 protons appeared in the same region (δ 3.69) in both the cyclophane **21** and its disodium salt.

Formation of Host−Guest Complex of the Cyclophane 21. The ethanol complex of cyclophane **21** upon X-ray analysis, was found to have one ethanol molecule in the cavity. The ethanol complex of cyclophane **21** was also found to be thermally stable. The ethanol molecule remained as a guest in the host **21** even after heating over a water bath under vacuum for many hours. Apparently, cyclophane **21** trapped the ethanol molecule during its formation (ethanol is used as the solvent for the coupling reaction). Ethanol binds to the COOH groups present in the cyclophane **21**. Further host−guest complexation studies of other cyclophanes and metal ion chelation with the cyclophanes are under investigation.

X-ray Crystallography Study of Cyclophane 1a. Crystals from chloroform belong to orthorhombic space

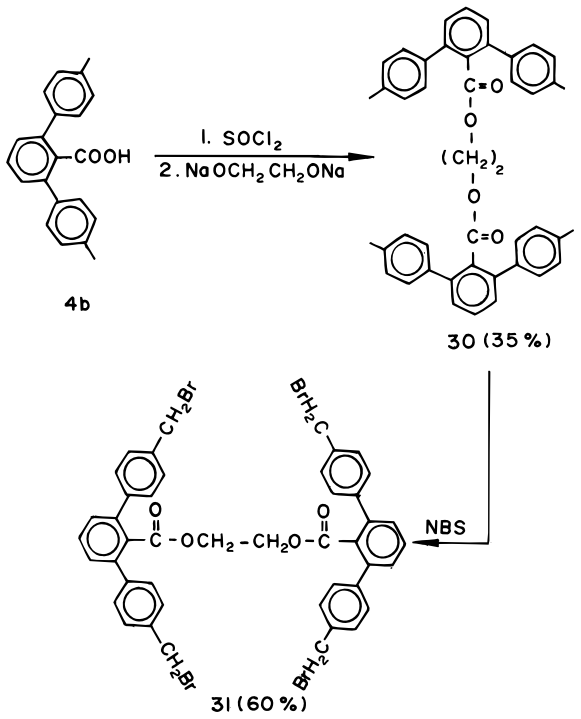
Scheme 7



group $Pna2_1$ with $a = 11.721(3)$, $b = 15.778(2)$, and $c = 20.879(4)$ Å, $V = 3861(4)$ Å^3, $Z = 4$, $D_C = 1.19$ g/cm^3, Cu Kα ($\lambda = 1.5418$ Å) radiation (graphite monochromated), $\mu = 1.54$ mm^{-1}, and $F(000) = 1480$. The structure was refined to a final $R = 0.070$, $R_w = 0.077$ for 2172 reflection, $I > 3\sigma(I)$. Three water molecules are caught inside the cavity, and they form hydrogen bonds with each other, forming a triangular plane. The molecule possesses a noncollapsible rigid cavity of size approximately 7.5 × 8.5 Å^2 measured between opposite arms of the molecule. The molecules are packed in the unit cell by van der Waals interactions.

X-ray Crystallographic Study of Cyclophane 21. Crystals from chloroform belong to monoclinic space group $A2/a$ with $a = 26.868(3)$, $b = 16.373(2)$, and $c = 13.025(3)$ Å, $\beta = 90.38(2)°$, $V = 5730(2)$ Å^3, $Z = 4$, $D_C = 1.20$ g/cm^3, Cu Kα ($\lambda = 1.5418$ Å) radiation (graphite monochromated), $\mu = 1.91$ mm^{-1}, and $F(000) = 2248$. The structure was refined to $R = 0.072$, $R_w = 0.079$ for 2246 reflections $I > 3\sigma(I)$. The molecule contains ethanol as the solvent of crystallization. The hydroxyl proton of the solvent molecule forms a hydrogen bond with one of the carbonyl oxygen atoms. The whole molecule has a center of inversion, and the oxygen atoms of the two carboxylic groups form parallel hydrogen bonds. The molecules are held in the lattice by van der Waals interactions.

Scheme 8



Conclusions

This paper describes the synthesis of cyclophanes with macrocyclic cavities and with functionalized microenvironments. Moreover, the synthesis of cyclophanes with polyfunctional microenvironments is described. Introduction of such functionality creates a hydrophilic cavity and improves the solubility of the cyclophanes. It also increases the complexing ability and chelating capacity of the cyclophanes. Finally, the synthesis of cyclophanes with a cage structure is described. Such cyclophanes are new, and our current work entails the modification of the synthesis of cyclophanes with a cage structure to make those that can bind two Cu(I) ions. We have also reported the formation of the sodium salt of some of these cyclophanes, one of which has been used for host−guest complexation. We are further investigating metal ion chelation and host−guest complexation with these reported cyclophanes.

Experimental Section

General Procedures. All melting points are uncorrected. ^{1}H NMR spectra were recorded at 400 and 90 MHz. ^{13}C NMR spectra were recorded at 100.6 MHz. *J* values are reported in hertz. Tetrahydrofuran was distilled from Na/benzophenone ketyl before use, DMF was distilled over calcium hydride, ethylenediamine and pyridine were distilled over sodium hydroxide, and thionyl chloride was freshly distilled prior to use. *n*-Butyllithium (15% solution in *n*-hexane) purchased from MERCK-Schuchardt was used. Mass spectra were measured at 25 or 70 eV. FAB mass spectra were obtained at the Michigan State University mass spectrometry facility. Column chromatography was carried out with SiO_2 (silica gel, ACME, 100−200 mesh). The organic extracts of crude products were dried over anhydrous magnesium sulfate.

4,4″-Dimethyl-1,1′:3′,1″-terphenyl (4). To a Grignard reagent, prepared by refluxing a mixture of 4-bromotoluene (14.0 g, 82.5 mmol) and Mg (2.2 g, 90 mmol) in dry THF (250

mL) under nitrogen, was added dropwise a solution of 2,6-dichloroiodobenzene (7.5 g, 27.5 mmol) in THF (50 mL), and the mixture was refluxed for 3 h. After removal of THF under reduced pressure, the reaction mixture was treated with dilute HCl (10% v/v, 75 mL) and extracted with ether. The extracts were washed successively with water and aqueous $NaHCO_3$, dried ($MgSO_4$), and concentrated in vacuo. The crude product was chromatographed on silica gel eluting with *n*-hexane to give crystalline **4** (5.7 g, 80%): mp 112 °C; ^{1}H NMR (CCl_4, 90 MHz) δ 2.30 (s, 6 H, CH_3), 7.00 (m, 12 H, ArH); ^{13}C NMR ($CDCl_3$, 25 MHz) δ 20.90, 125.80, 125.90, 127.16, 127.24, 129.30, 129.70, 137.30, 141.90; MS, *m/e* (relative intensity) 258 (M^+, 100).

2′-Bromo-4,4″-dimethyl-1,1′:3′,1″-terphenyl (4a). The same procedure used for **4** was followed except that prior to aqueous quench bromine (0.88 g, 5.5 mmol in 50 mL in CCl_4) was added dropwise to the reaction mixture and stirred for 30 min. The workup was as above except for sodium bisulfite wash (2 × 50 mL) to remove excess bromine gave **4a** (70%): mp 118 °C; ^{1}H NMR (CCl_4, 90 MHz) δ 2.30 (s, 6 H, CH_3), 7.00−7.25 (m, 11 H); MS, *m/e* (relative intensity) 338 (M^+, 100), 336 (M^+, 100), 257 (80), 242 (80), 226 (20).

4,4″-Dimethyl-1,1′:3′,1″-terphenyl-2′-carboxylic Acid (4b). A procedure similar to that for **4** was followed, the reaction was quenched with CO_2 (dry CO_2 was bubbled into the solution continuously for 10 h), and the resulting solution was treated with cold HCl (10% v/v, 40 mL). Usual workup followed by chromatographic separation on silica gel using CH_2Cl_2−hexane (3:2) gave **4b** (70%): mp 174 °C; IR (KBr) 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 2.30 (s, 6 H, CH_3), 7.00−7.25 (m, 11 H); MS, *m/e* (relative intensity) 302 (M^+, 100), 285 (60), 269 (10), 242 (20).

Methyl 4,4″-Dimethyl-1,1′:3′,1″-terphenyl-2′-carboxylate (4c). To a stirred suspension of acid **4b** (3.0 g, 10 mmol) in CH_2Cl_2 (120 mL) containing pyridine (0.80 g, 10 mmol) was added a solution of thionyl chloride (1.69 g, 10 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred at room temperature for 12 h and evaporated to dryness to give a pale yellow residue. Methanol (50 mL) was added to the residue, and then the solution was refluxed for 4 h. The reaction mixture was evaporated to dryness, extracted with CH_2Cl_2 (2 × 150 mL), and dried ($MgSO_4$). The crude product obtained after the removal of the solvent was chromatographed on silica gel eluting with CH_2Cl_2−hexane (1:3) to give **4c** (80%): mp 109 °C; IR (KBr) 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 2.35 (s, 6 H, CH_3), 3.35 (s, 3 H, CO_2CH_3), 7.15−7.50 (m, 11 H); MS, *m/e* (relative intensity) 316 (M^+, 50), 285 (100), 242 (25), 165 (10), 58 (50).

Alternate Procedure for 4c. To a stirred solution of the acid **4b** (1.5 g, 5 mmol) in THF (10 mL) was added an ethereal solution of diazomethane [generated from diazald (2.14 g, 10 mmol), water (5 mL), ether (30 mL), and aqueous NaOH (5 N, 6 mL)]. The reaction mixture was stirred at room temperature for 30 min, and the solvent was allowed to evaporate. The crude product was chromatographed on silica gel eluting with CH_2Cl_2−hexane (1:3) to give ester **4c** quantitatively.

General Procedure A. NBS Bromination of the *m*-Terphenyls. Freshly recrystallized NBS (92 mmol) was added in five−six equal portions 6 h apart to a solution of compound (44 mmol) in CCl_4 (350 mL) heated at reflux; each addition was immediately followed by the addition of a few milligrams of benzoyl peroxide. After 40 h of total reaction time at reflux, the mixture was cooled and the precipitated succinimide was removed by filtration. The solvent was removed, and the residue was chromatographed (SiO_2) and recrystallized from a CH_2Cl_2−hexane mixture.

4,4″-Bis(bromomethyl)-1,1′:3′,1″-terphenyl (5). According to the general procedure A, dimethylterphenyl **4** was converted to the corresponding dibromide **5** (80%): mp 108 °C; ^{1}H NMR (CCl_4, 90 MHz) δ 4.30 (s, 4 H, CH_2Br), 7.00−7.25 (m, 12 H); ^{13}C NMR ($CDCl_3$, 25 MHz) δ 33.10, 126.20, 126.50, 127.60, 127.80, 129.50, 129.90, 137.20, 141.30. Anal. Calcd for $C_{20}H_{16}Br_2$: C, 57.72; H, 3.88. Found: C, 57.66; H, 3.98.

2′-Bromo-4,4″-bis(bromomethyl)-1,1′:3′,1″-terphenyl (5a). According to the general procedure A, dimethylterphenyl **4** was converted to the corresponding dibromide **5a** (75%): mp 110 °C; ^{1}H NMR (CCl_4, 90 MHz) δ 4.30 (s, 4 H, CH_2Br), 7.00−7.25 (m, 11 H).

4,4″-Bis(bromomethyl)-1,1′:3′,1″-terphenyl-2′-carboxylic Acid (5b). According to the general procedure A, dimethylterphenyl **4** was converted to the corresponding dibromide **5b** (65%): mp 165 °C; IR (KBr) 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 4.35 (s, 4 H, CH_2Br), 7.00−7.25 (m, 11 H).

Methyl 4,4″-Bis(bromomethyl)-1,1′:3′,1″-terphenyl-2′-carboxylate (5c). According to the general procedure A, dimethylterphenyl **4** was converted to the corresponding dibromide **5c** (60%): mp 110 °C; IR (KBr) 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 3.35 (s, 3 H, CO_2CH_3), 4.50 (s, 4 H, CH_2Br), 7.20−7.55 (m, 11 H).

General Procedure B. Preparation of the Diesters 6, 6a, 12, and 16. A mixture of methyl *p*-hydroxybenzoate (63 mmol), the dibromide (27.7 mmol), and potassium carbonate (15 g) in anhydrous DMF (60 mL) was stirred under nitrogen for 48 h at 60 °C. The reaction mixture was poured into water (250 mL) and stirred. The resulting precipitate was filtered, washed with water, and dissolved in CH_2Cl_2 (350 mL). The organic layer was washed with NaOH solution (5% w/v, 2 × 50 mL), dried ($MgSO_4$), and evaporated to yield the corresponding diester.

Diester 6. According to the general procedure B, diester **6** (85%) was prepared from the dibromide **5**: mp 184 °C; IR (KBr) 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 3.70 (s, 6 H, CO_2Me), 4.90 (s, 4 H, OCH_2), 6.70 and 7.70 (ABq, J = 9, 8 H), 7.20−7.50 (m, 12 H). Anal. Calcd for $C_{36}H_{30}O_6$: C, 77.41; H, 5.41. Found: C, 77.32; H, 5.29.

Diester 6a. According to the general procedure B, diester **6a** (75%) was prepared from the dibromide **5a**: mp 185 °C; IR (KBr) 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 3.70 (s, 6 H, CO_2Me), 4.90 (s, 4 H, OCH_2), 6.80 and 7.75 (ABq, J = 9, 8 H), 7.20−7.50 (m, 11 H). Anal. Calcd for $C_{36}H_{29}BrO_6$: C, 67.83; H, 4.58. Found: C, 67.93; H, 4.69.

Diester 12. According to the general procedure B, diester **12** (90%) was prepared from *o*-xylylene α,α′-dibromide: mp 142 °C; IR (KBr) 1715 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 3.85 (s, 6 H, CO_2Me), 5.20 (s, 4 H, OCH_2), 7.00 and 8.05 (ABq, J = 9, 8 H), 7.35−7.50 (m, 4 H); MS, *m/e* (relative intensity) 406 (M^+, 100).

Diester 16. According to the general procedure B, the diester **16** (80%) was prepared from *p*-xylylene α,α′-dibromide: mp 128 °C; IR (KBr) 1715 cm^{-1}; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 3.85 (s, 6 H, CO_2CH_3), 5.20 (s, 4 H, OCH_2), 7.00 and 8.05 (ABq, J = 9, 8 H), 7.20 (s, 4 H); MS, *m/e* (relative intensity) 406 (M^+, 100).

General Procedure C. Reduction of the Diesters 6, 6a, 12, and 16. To a solution of the diester (13.8 mmol) in dry THF (300 mL) was added in portions LAH (0.59 g, 17.3 mmol) at room temperature. The reaction mixture was stirred at reflux for 6 h, poured into $Na_2SO_4 \cdot 10H_2O$ (10 g), and stirred. It was then digested on a steam bath (20 min) and filtered. The inorganic residue was further extracted (Soxhlet) with THF (200 mL). The combined THF fractions upon evaporation gave the alcohol, purified by recrystallization from a minimum volume of THF−MeOH (3:1).

Diol 7. According to the general procedure C, diol **7** (90%) was obtained from the diester **6**. For **7**: mp 208 °C; IR (KBr) 3500−3300 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.50 (d, J = 6.5, 4 H, CH_2OH), 5.10 (t, J = 6.5, 2 H, OH, exchanges with D_2O), 5.20 (s, 4 H, OCH_2), 7.04 and 7.29 (ABq, J = 8, 8 H), 7.60 and 7.84 (ABq, J = 8, 8 H), 7.71 (d, J = 3.6, 2 H), 7.73 (m, 1 H), 7.97 (m, 1 H); MS, *m/e* 485 ($M^+ - H_2O$). Anal. Calcd for $C_{34}H_{30}O_4$: C, 81.26; H, 6.01. Found: C, 81.35; H, 6.14.

Diol 7a. According to the general procedure C, diol **7a** (85%) was obtained from the diester **6a**. For **7a**: mp 210 °C; IR (KBr) 3500−3300 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 4.50 (d, J = 6.5, 4 H, CH_2OH), 5.10 (t, J = 6.5, 2 H, OH, exchanges with D_2O), 5.20 (s, 4 H, OCH_2), 7.31 and 7.60 (ABq, J = 8, 8 H), 7.62 and 7.86 (ABq, J = 8, 8 H), 7.73 (m, 2 H), 7.75 (m, 1 H); MS, *m/e* (relative intensity) 565 ($MH^+ - H_2O$, 100). Anal. Calcd for $C_{34}H_{29}BrO_4$: C, 70.23; H, 5.02. Found: C, 70.37; H, 5.18.

Diol 13a. According to the general procedure C, diol **13a** (90%) was obtained from the diester **12**. For **13a**: mp 187 °C; IR (KBr) 3500−3300 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 4.50 (s, 4 H, CH_2OH), 5.16 (bs, 1 H, OH), 5.20 (s, 4 H, OCH_2), 6.90−7.10 (m, 4 H), 7.20−7.35 (m, 8 H).

Diol 17. According to the general procedure C, diol **17** (90%) was obtained from the diester **16**. For **17**: mp 165 °C; IR (KBr) 3500−3300 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 4.50 (s, 4 H, CH_2OH), 5.10 (bs, 1 H, OH), 5.20 (s, 4 H, OCH_2), 7.15−7.45 (m, 12 H).

General Procedure D. Conversion of the Diol into the Dichloride. To a stirred suspension of the diol (9.76 mmol) in CH_2Cl_2 (120 mL) containing pyridine (1.54 g, 19.5 mmol) was added a solution of thionyl chloride [2.3 g, 19.5 mmol in CH_2Cl_2 (20 mL)]. The mixture was stirred at rt for 12 h and then washed with water (3 × 100 mL). The organic layer was dried ($MgSO_4$), and upon evaporation, a pale yellow solid was obtained. Recrystallization of the solid from CH_2Cl_2−hexane afforded the corresponding pure dichloride.

Dichloride 8. According to the general procedure D, dichloride **8** (95%) was obtained from the diol **7**. For **8**: mp 164 °C; ^1H NMR (CCl_4, 90 MHz) δ 4.40 (s, 4 H, CH_2Cl), 4.90 (s, 4 H, OCH_2), 6.70−6.80 (m, 4 H), 7.00−7.50 (m, 16 H). Anal. Calcd for $C_{34}H_{28}Cl_2O_2$: C, 75.69; H, 5.22. Found: C, 75.92; H, 5.33.

Dichloride 8a. According to the general procedure D, dichloride **8a** (85%) was obtained from the diol **7a**. For **8a**: mp 166 °C; ^1H NMR ($CDCl_3$, 90 MHz) δ 4.40 (s, 4 H, CH_2Cl), 4.90 (s, 4 H, OCH_2), 6.80−7.00 (m, 4 H), 7.10−7.60 (m, 15 H).

Dichloride 14. According to the general procedure D, dichloride **14** (95%) was obtained from the diol **13**. For **14**: mp 98 °C; ^1H NMR ($CDCl_3$, 90 MHz) δ 4.50 (s, 4 H, CH_2Cl), 5.10 (s, 4 H, OCH_2), 6.80−7.00 (m, 4 H), 7.20−7.40 (m, 8 H).

Dichloride 18. According to the general procedure D, dichloride **18** (90%) was obtained from the diol **17**. For **18**: mp 92 °C; ^1H NMR ($CDCl_3$, 90 MHz) δ 4.50 (s, 4 H, CH_2Cl), 5.15 (s, 4 H, OCH_2), 6.95−7.30 (m, 12 H).

General Procedure E. Synthesis of Dithiols 11, 15, 19, and 20. A stirred solution of dihalide (6.2 mmol) and thiourea (0.95 g, 12.4 mmol) in THF (60 mL) was heated at reflux for 12 h. The mixture was cooled, and the precipitated isothiouronium salt was filtered and dried. The salt was dissolved in H_2O−THF (1:2 v/v, 180 mL) under nitrogen, and to this solution was added KOH (0.52 g, 9.4 mmol). The mixture was heated under nitrogen at reflux for 12 h, and then cooled, and the resulting solution was carefully quenched with minimum amount of dilute HCl (2 N). The solvent was removed under vacuum, and the crude product was chromatographed (SiO_2) to give the corresponding dithiol.

4,4″-Bis(mercaptomethyl)-1,1′:3′,1″-terphenyl (11). According to the general procedure E, dithiol **11** (60%, SiO_2, CH_2Cl_2−hexane, 1:3) was obtained from the dibromide **5**. For **11**: mp 112 °C; ^1H NMR ($CDCl_3$, 90 MHz) δ 1.60 (t, J = 7.5, 2 H, SH), 3.60 (d, J = 7.5, 4 H, CH_2SH), 6.90−7.35 (m, 12 H); MS, *m/e* (relative intensity) 323 (M^+, 20), 306 (90), 289 (100).

Dithiol 15. According to the general procedure E, dithiol **15** (60%, SiO_2, CH_2Cl_2−hexane, 1:2) was obtained from the dichloride **14**. For **15**: mp 56 °C; ^1H NMR ($CDCl_3$, 90 MHz) δ 1.60 (t, J = 7.5, 2 H, SH), 3.60 (d, J = 7.5, 4 H, CH_2SH), 5.10 (s, 4 H, OCH_2), 6.80−7.00 (m, 4 H), 7.20−7.40 (m, 8 H).

Dithiol 19. According to the general procedure E, dithiol **19** (60%, SiO_2, CH_2Cl_2−hexane, 1:2) was obtained from the dichloride **18**. For **19**: mp 54 °C; ^1H NMR ($CDCl_3$, 90 MHz) δ 1.60 (t, J = 7.5, 2 H, SH), 3.55 (d, J = 7.5, 4 H, CH_2SH), 5.20 (s, 4 H, OCH_2), 6.90−7.30 (m, 12 H).

3,5-Bis(mercaptomethyl)anisole (20). According to the general procedure E, dithiol **20** (60%, SiO_2, CH_2Cl_2−hexane, 1:2) was obtained from 3,5-bis(bromomethyl)anisole. For **20**: ^1H NMR ($CDCl_3$, 90 MHz) δ 1.75 (t, J = 7.7, 2 H), 3.65 (d, J = 7.7, 4 H, CH_2SH), 3.70 (s, 3 H, OCH_3), 6.70 (bs, 2 H), 6.85 (bs, 1 H).

General Procedure F. Assembling Cyclophanes 1a−d, 2a,b, 3a−h, 21, 21a, and 23. A solution containing equimolar amounts (1 mmol) of the appropriate dibromide and the dithiol in nitrogen-degassed benzene (100 mL) was added dropwise over 8−10 h to a well-stirred solution of KOH (0.14 g, 2.5 mmol) in ethanol (95%, 800 mL). After addition was complete, the mixture was stirred for an additional 8 h and then evaporated to dryness. The crude product was chromatographed to give the corresponding cyclophane.

Cyclophane 1a. Coupling of the dichloride **8** with *o*-xylene-α,α′-dithiol[16] (**9**) (general procedure F) and purification on silica gel with CH_2Cl_2−hexane (1:1) as the eluent afforded the cyclophane **1a** (70%): mp 206 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.60 (s, 4 H, SCH_2), 3.65 (s, 4 H, CH_2S), 5.25 (s, 4 H, OCH_2), 6.80 and 7.15 (ABq, J = 8, 8 H), 7.09−7.13 (m, 2 H), 7.17−7.21 (m, 2 H), 7.40 and 7.55 (ABq, J = 8, 8 H), 7.56−7.59 (m, 3 H), 7.67 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 33.19 (SCH_2), 35.93 (CH_2S), 69.01 (OCH_2), 115.64, 125.52, 126.92, 127.01, 127.74, 128.16, 128.95, 129.67, 129.80, 130.35, 136.35, 136.74, 140.70, 141.67, 156.59 (15 Ar carbons). Anal. Calcd for $C_{42}H_{36}O_2S_2$: C, 72.21; H, 5.69. Found: C, 79.16; H, 5.76.

Cyclophane 1b. Coupling of dichloride **8a** with dithiol **9** (general procedure F) and purification on silica gel with CH_2Cl_2−hexane (1:1) as the eluent afforded the cyclophane **1b** (60%): mp 202 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.60 (s, 4 H, SCH_2), 3.65 (s, 4 H, CH_2S), 5.25 (s, 4 H, OCH_2), 6.73 and 7.08 (ABq, J = 8, 8 H), 7.02−7.06 (m, 2 H), 7.10−7.14 (m, 2 H), 7.33 and 7.48 (ABq, J = 8, 8 H), 7.49−7.52 (m, 3 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 33.25 (SCH_2), 36.00 (CH_2S), 69.09 (OCH_2), 115.71, 125.59, 126.98, 127.07, 127.82, 128.23, 129.00, 129.72, 129.87, 130.41, 136.39, 136.79, 140.78, 141.74, 156.65 (15 Ar carbons); MS (FAB) (*m*-nitrobenzyl alcohol matrix), *m/e* 716 (MH^+). Anal. Calcd for $C_{42}H_{35}BrO_2S_2$: C, 70.48; H, 4.92. Found: C, 70.61; H, 4.99.

Cyclophane 1c. Coupling of the dichloride **8** with *p*-xylene-α,α′-dithiol[17] (**10**) (general procedure F) followed by purification on silica gel with CH_2Cl_2−hexane (1:1) as the eluent afforded the cyclophane **1c** (60%): mp 155 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.49 (s, 4 H, SCH_2), 3.55 (s, 4 H, CH_2S), 5.25 (s, 4 H, OCH_2), 6.75 and 7.05 (ABq, J = 8, 8 H), 7.16 (s, 4 H), 7.38 and 7.55 (ABq, J = 8, 8 H), 7.46−7.53 (m, 3 H), 7.61 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 35.10 (SCH_2), 35.39 (CH_2S), 69.63 (OCH_2), 115.78, 125.74, 127.07, 127.39, 127.66, 129.03, 129.09, 29.79, 129.97, 136.42, 136.73, 140.67, 141.57, 156.96 (14 Ar carbons). Anal. Calcd for $C_{42}H_{36}O_2S_2$: C, 79.21; H, 5.69. Found: C, 79.34; H, 5.74.

Cyclophane 1d. Coupling of the dichloride **8a** with dithiol **10** (general procedure F) and purification on silica gel with CH_2Cl_2−hexane (1:1) as the eluent afforded the cyclophane **1d** (55%): mp 153 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.50 (s, 4 H, SCH_2), 3.55 (s, 4 H, CH_2S), 5.25 (s, 4 H, OCH_2), 6.75 and 7.05 (ABq, J = 8, 8 H), 7.16 (s, 4 H), 7.38 and 7.53 (ABq, J = 8, 8 H), 7.43−7.51 (m, 3 H), MS (FAB) (*m*-nitrobenzyl alcohol matrix), *m/e* 716 (MH^+). Anal. Calcd for $C_{42}H_{35}BrO_2S_2$: C, 70.48; H, 4.92. Found: C, 70.59; H, 4.99.

Cyclophane 2a. Coupling of the dichloride **8** with dithiol **11** (general procedure F) followed by purification on silica gel with CH_2Cl_2−hexane (3:2) as the eluent afforded the cyclophane **2a** (30%): mp 175 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.55 (s, 4 H, SCH_2), 3.58 (s, 4 H, CH_2S), 5.20 (s, 4 H, OCH_2), 6.74 and 7.04 (ABq, J = 8, 8 H), 7.15 (d, J = 8, 6 H), 7.24−7.27 (m, 4 H), 7.40−7.55 (m, 12 H), 7.64 (m, 1 H), 7.66 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 34.55 (SCH_2), 35.60 (CH_2S), 69.79 (OCH_2), 115.78, 125.57, 125.77, 126.01, 126.57, 126.87, 127.01, 127.41, 127.63, 129.18, 129.41, 129.71, 129.89, 130.77, 136.82, 136.98, 140.06, 140.90, 141.70, 157.22 (20 Ar carbons); MS (FAB) (*m*-nitrobenzyl alcohol matrix), *m/e* 788 (MH^+). Anal. Calcd for $C_{54}H_{44}O_2S_2$: C, 82.20; H, 5.62. Found: C, 82.33; H, 5.69.

Cyclophane 2b. Coupling of the dichloride **8a** with dithiol **11** (general procedure F) followed by purification on silica gel with CH_2Cl_2−hexane (3:2) as the eluent gave the cyclophane **2b** (25%): mp 177 °C; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.55 (s, 4 H, SCH_2), 3.58 (s, 4 H, CH_2S), 5.20 (s, 4 H, OCH_2), 6.78 and 7.08 (ABq, J = 8, 8 H), 7.19 (d, J = 8, 6 H), 7.28 (m, 4 H), 7.45−7.59 (m, 12 H), 7.68 (m, 1 H); MS (FAB) (*m*-nitrobenzyl

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alcohol matrix), *m/e* 867 (MH^+). Anal. Calcd for $C_{54}H_{43}BrO_2S_2$: C, 74.73; H, 4.99. Found: C, 74.87; H, 5.07.

Cyclophane 3a. Coupling of the dibromide **5** with the dithiol **15** (general procedure F) followed by purification on silica gel with CH_2Cl_2−hexane (1:1) as the eluent yielded the cyclophane **3a** (70%): mp 206 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.60 (s, 4 H, SCH_2), 3.65 (s, 4 H, CH_2S), 5.20 (s, 4 H, OCH_2), 6.81 and 7.15 (ABq, J = 8, 8 H), 7.09−7.13 (m, 2 H), 7.17−7.21 (m, 2 H), 7.40 and 7.50 (ABq, J = 8, 8 H), 7.55−7.58 (m, 3 H), 7.65 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 33.19 (SCH_2), 35.93 (CH_2S), 69.01 (OCH_2), 115.64, 125.52, 126.92, 127.01, 127.74, 128.16, 128.95, 129.67, 129.80, 130.35, 136.33, 136.74, 140.70, 141.67, 156.59 (15 Ar carbons). Anal. Calcd for $C_{42}H_{36}O_2S_2$: C, 79.21; H, 5.69. Found: C, 79.37; H, 5.78.

Cyclophane 3b. Coupling of the dibromide **5a** with the dithiol **15** (general procedure F) afforded the cyclophane **3b** (65%, SiO_2, CH_2Cl_2−hexane, 1:1): mp 203 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.60 (s, 4 H, SCH_2), 3.65 (s, 4 H, CH_2S), 5.25 (s, 4 H, OCH_2), 6.73 and 7.08 (ABq, J = 8, 8 H), 7.02−7.06 (m, 2 H), 7.10−7.14 (m, 2 H), 7.33 and 7.48 (ABq, J = 8, 8 H), 7.49−7.52 (m, 3 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 33.25 (SCH_2), 36.00 (CH_2S), 69.09 (OCH_2), 115.71, 125.59, 126.98, 127.07, 127.92, 128.23, 129.00, 129.72, 129.87, 130.41, 136.39, 136.79, 140.78, 141.74, 156.64 (15 Ar carbons). Anal. Calcd for $C_{42}H_{35}BrO_2S_2$: C, 70.48; H, 4.92. Found: C, 70.59; H, 4.97.

Cyclophane 3c. Coupling of the dibromide **5b** with the dithiol **15** (general procedure F) afforded the cyclophane **3c** (70%, SiO_2 CH_2Cl_2−hexane, 7:3): mp 201 °C; IR (KBr) 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.60 (s, 4 H, SCH_2), 3.65 (s, 4 H, CH_2S), 5.20 (s, 4 H, OCH_2), 6.81 and 6.86 (ABq, J = 8.7, 8 H), 7.00 and 7.20 (ABq, J = 8, 8 H), 7.30−7.33 (m, 4 H), 7.40−7.42 (m, 2 H), 7.44−7.48 (m, 1 H), 12.60 (bs, 1 H, CO_2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 35.22 (SCH_2), 35.65 (CH_2S), 67.84 (OCH_2), 115.16, 128.29, 128.35, 128.42, 128.66, 128.98, 129.09, 130.40, 131.02, 133.02, 134.65, 137.71, 138.46, 139.50, 156.17 (15 Ar carbons), 169.69 (CO_2H).

Cyclophane 3d. Coupling of the dibromide **5c** with the dithiol **15** (general procedure F) followed by purification on silica gel with CH_2Cl_2−hexane (1:1) as the eluent afforded the cyclophane **3d** (75%): mp 208 °C; IR (KBr) 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.10 (s, 3 H, CO_2CH_3), 3.43 (s, 4 H, SCH_2), 3.72 (s, 4 H, CH_2S), 5.03 (s, 4 H, OCH_2), 6.82 and 6.94 (ABq, J = 8, 8 H), 7.28−7.40 (m, 12 H), 7.49−7.53 (m, 3 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 34.11 (SCH_2), 36.44 (CH_2S), 51.81 (CO_2CH_3), 68.10 (OCH_2), 114.82, 128.38, 128.53, 128.86, 129.42, 129.54, 130.30, 130.79, 134.26, 135.04, 138.14, 139.30, 140.12, 157.78 (14 Ar carbons), 169.87 (CO_2CH_3); MS (FAB) (*m*-nitrobenzyl alcohol matrix), *m/e* 695 (MH^+). Anal. Calcd $C_{44}H_{38}O_4S_2$: C, 76.05; H, 5.51. Found: C, 76.19; H, 5.67.

Cyclophane 3e. Coupling of the dibromide **5** with the dithiol **19** (general procedure F) followed by purification on silica gel with CH_2Cl_2−hexane (1:1) as the eluent afforded the cyclophane **3e** (65%): mp 198 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.49 (s, 4 H, SCH_2), 3.55 (s, 4 H, CH_2S), 5.25 (s, 4 H, OCH_2), 6.75 and 7.05 (ABq, J = 8, 8 H), 7.16 (s, 4 H), 7.38 and 7.55 (ABq, J = 8, 8 H), 7.46−7.56 (m, 3 H), 7.61 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 35.10 (SCH_2), 35.39 (CH_2S), 69.63 (OCH_2), 115.78, 125.74, 127.07, 127.39, 127.66, 129.03, 129.09, 129.79, 129.97, 136.42, 136.73, 140.67, 141.57, 156.96 (14 Ar carbons). Anal. Calcd for $C_{42}H_{36}O_2S_2$: C, 79.21; H, 5.69. Found: C, 79.37; H, 5.68.

Cyclophane 3f. Coupling of the dibromide **5a** with the dithiol **19** (general procedure F) followed by purification on silica gel with CH_2Cl_2−hexane (1:1) as the eluent afforded the cyclophane **3f** (70%): mp 195 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.50 (s, 4 H, SCH_2), 3.55 (s, 4 H, CH_2S), 5.25 (s, 4 H, OCH_2), 6.75 and 7.05 (ABq, J = 8, 8 H), 7.16 (s, 4 H), 7.38 and 7.53 (ABq, J = 8, 8 H), 7.43−7.51 (m, 3 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 35.12 (SCH_2), 35.40 (CH_2S), 69.69 (OCH_2), 115.79, 125.74, 127.09, 127.41, 127.66, 129.03, 129.11, 129.80, 129.99, 136.44, 136.74, 140.67, 141.57, 156.99 (14 Ar carbons). Anal. Calcd for $C_{42}H_{35}BrO_2S_2$: C, 70.48; H, 4.92. Found: C, 70.57; H, 4.99.

Cyclophane 3g. Coupling of the dibromide **5b** with the dithiol **19** (general procedure F) followed by purification on silica gel with CH_2Cl_2−hexane (7:3) as the eluent gave the cyclophane **3g** (60%): mp 200 °C; IR (KBr) 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.60 (s, 4 H, SCH_2), 3.65 (s, 4 H, CH_2S), 5.20 (s, 4 H, OCH_2), 6.80 and 6.85 (ABq, J = 8.7, 8 H), 7.00 and 7.20 (ABq, J = 8, 8 H), 7.16 (s, 4 H), 7.40−7.42 (m, 2 H), 7.44−7.46 (m, 1 H), 12.60 (bs, 1 H, CO_2H).

Cyclophane 3h. Coupling of the dibromide **5c** with the dithiol **19** (general procedure F) followed by purification on silica gel with CH_2Cl_2−hexane (1:1) as the eluent gave the cyclophane **3h** (70%): mp 205 °C; IR (KBr) 1720 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.10 (s, 3 H, CO_2CH_3), 3.43 (s, 4 H, SCH_2), 3.72 (s, 4 H, CH_2S), 5.00 (s, 4 H, OCH_2), 6.80 and 6.90 (ABq, J = 8, 8 H), 7.25−7.35 (m, 12 H), 7.50−7.53 (m, 3 H). Anal. Calcd for $C_{44}H_{38}O_4S_2$: C, 76.05; H, 5.51. Found: C, 76.23; H, 5.61.

Conversion of Cyclophanes 1b, 1d, 2b, 3b, or 3f to 1a, 1c, 2a, 3a, or 3e. To a solution of cyclophane **1b**, **1d**, **2b**, **3b**, or **3f** (0.2 mmol) in dry THF (10 mL) was added *n*-butyllithium (1.6 M, 0.27 mL) at −78 °C under nitrogen. After the reaction mixtured was stirred for 3 h at −78 °C, the reaction was quenched with cold HCl (10% v/v, 3 mL), and the resulting solution was extracted with CH_2Cl_2 (2 × 20 mL) and dried ($MgSO_4$). The reaction mixture after usual workup afforded the cyclophanes **1a**, **1c**, **2a**, **3a**, or **3e** in 80, 85, 80, 70, and 80% yields, respectively.

Conversion of Cyclophanes 3b or 3f to 3c or 3g. To a solution of cyclophane **3b** or **3f** (0.2 mmol) in dry THF (10 mL) was added *n*-butylithium (1.6 M, 0.20 mL) at −78 °C under nitrogen. The mixture was stirred under nitrogen at that temperature for 3 h, and the reaction was quenched with CO_2 (bubbling dry CO_2 gas into the solution for 3 h). After usual workup and column chromatographic separation, the compound was found to be **3c** or **3g** (70%, 60%), respectively.

Conversion of Cyclophanes 3c or 3g to 3d or 3h. To a stirred suspension of cyclophane **3c** or **3g** (0.2 mmol) in CH_2Cl_2 (120 mL) containing pyridine (0.01 g, 0.1 mmol) was added a solution of thionyl chloride (0.01 g, 1 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred at room temperature for 3 h and then evaporated to dryness. Methanol (10 mL) was added to the residue, and then the solution was refluxed for 4 h. The reaction mixture was extracted with CH_2Cl_2 (2 × 20 mL) after the removal of methanol, washed with water (20 mL), and dried ($MgSO_4$). The crude product after purification was found to be identical with the cyclophane **3d** or **3h** (85 or 80%), respectively.

Alternate Procedure for the Conversion of the Cyclophanes 3c or 3g to 3d or 3h. To a stirred solution of cyclophane **3c** or **3g** (0.3 mmol) in THF (5 mL) was added an ethereal solution of diazomethane [generated from diazald (0.12 g, 1 mmol), water (0.5 mL), ether (3 mL), and aqueous NaOH (5 N, 0.6 mL)]. After usual workup of the reaction mixture, followed by chromatographic separation, the cyclophane **3d** or **3h** was afforded in quantitative yield.

Cyclophane 21. Coupling of the dibromide **5b** with the dithiol **20** followed by purification on silica gel with 5 drops of MeOH in 50 mL of CH_2Cl_2 as the eluent afforded cyclophane **21** (40%): mp 252 °C; Ir (KBr) 1710 cm^{-1}; ^{1}H NMR (DMSO-d_6, 400 MHz) δ 3.58 (s, 8 H, SCH_2), 3.62 (s, 8 H, CH_2S), 3.69 (s, 6 H, OCH_3), 6.60 (s, 2 H), 6.76 (s, 4 H), 7.16−7.25 (m, 20 H), 7.37 (t, J = 8.34, 2 H), 12.62 (bs, 2 H); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ 34.87 (SCH_2), 35.25 (CH_2S), 55.05 (OCH_3), 112.93, 122.65, 127.65, 128.40, 128.63, 128.70, 128.90, 130.05, 137.10, 137.45, 137.85, 139.68 (12 Ar carbons), 159.50 (CO_2H); MS (FAB) (*m*-nitrobenzyl alcohol matrix), *m/e* 997 (MH^+).

Cyclophane 21a. Coupling of the dibromide **5c** with the dithiol **20** followed by purification on silica gel with CH_2Cl_2−hexane (1:1) as the eluent gave the cyclophane **21a** (50%): mp 261 °C; IR (KBr) 1715 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.58 (s, 8 H, SCH_2), 3.62 (s, 8 H, CH_2S), 3.69 (s, 6 H, OCH_3), 3.72 (s, 6 H, CO_2CH_3), 6.60 (s, 2 H), 6.76 (s, 4 H), 7.16−7.25 (m, 20 H), 7.37 (t, J = 8.14, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 34.87 (SCH_2), 35.25 (CH_2S), 55.05 (OCH_3), 68.01 (CO_2CH_3), 112.93, 122.65, 127.65, 128.40, 128.63, 128.70, 128.90, 130.05, 137.10, 137.45, 137.85, 139.68, (12 Ar carbons), 161.05 (CO_2Me); MS (FAB) (*m*-nitrobenzyl alcohol matrix), *m/e* 1025 (MH^+). Anal. Calcd for $C_{62}H_{56}O_6S_4$: C, 72.63; H, 5.50. Found: C, 72.51; H, 5.48.

Conversion of Cyclophane 21 to 21a. To a stirred suspension of cyclophane **21** (0.1 g, 0.1 mmol) in CH_2Cl_2 (120 mL) containing pyridine (0.02 g, 0.2 mmol) was added a solution of thionyl chloride (0.024 g, 0.2 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred at room temperature for 4 h and then evaporated to dryness. Methanol (10 mL) was added to the residue, and then the solution was refluxed for 4 h. The reaction mixture was evaporated to dryness, extracted with CH_2Cl_2 (2 × 20 mL), washed with water (2 × 20 mL), and dried ($MgSO_4$). Evaporation of CH_2Cl_2 gave the crude product which, after purification on silica gel, was found to be cyclophane **21a** (0.065 g, 65%).

Cyclophane 23. Coupling of the dibromide **5c** with 3,5-bis(mercaptomethyl)phenol (**22**)[11] followed by purification on silica gel with 5% MeOH in CH_2Cl_2 as the eluent afforded the cyclophane **23** (40%): mp 272 °C; IR (KBr) 3500−3300, 1720 cm^{-1}; ^1H NMR [$CDCl_3/CD_3OD$ (4:1), 400 MHz] δ 3.60 (s, 8 H, SCH_2), 3.64 (s, 8 H, CH_2S), 3.68 (s, 6 H, CO_2CH_3), 6.71 (s, 2 H), 6.87 (s, 4 H), 7.19−7.20 (m, 20 H), 7.39 (t, J = 7.95, 2 H).

α,α′-Bis[3,5-bis(dicarbethoxy)phenoxy]-*o*-xylene (26). A mixture of diethyl 5-hydroxyisophthalate[18] (**25**), *o*-xylylene α,α′-dibromide (7.31 g, 27.7 mmol), and potassium carbonate (15 g) in anhydrous DMF (60 mL) was stirred under nitrogen for 60 h at room temperature. The mixture was poured into water (250 mL) and stirred. The colorless solid obtained was filtered, washed with water (3 × 50 mL), and dissolved in CH_2Cl_2 (350 mL). This solution was washed with aqueous NaOH (5% w/v, 2 × 50 mL), dried ($MgSO_4$), and evaporated to give a residue which, upon purification by column chromatography (SiO_2) with hexane−CH_2Cl_2 (2:3) as the eluent, afforded tetraester **26** (16.09 g, 80%): mp 82 °C; Ir (KBr) 1710 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 1.25 (t, J = 7.1, 12 H, CH_3), 4.30 (q, J = 7.1, 8 H, CO_2CH_2), 5.20 (s, 4 H, OCH_2), 7.30−7.50 (m, 4 H), 7.75 (bs, 4 H), 8.25 (bs, 2 H). Anal. Calcd for $C_{32}H_{34}O_{10}$: C, 66.43; H, 5.92. Found: C, 66.29; H, 5.89.

α,α′-Bis[3,5-bis(hydroxymethyl)phenoxy]-*o*-xylene (27). To a solution of tetraester **26** (8.0 g, 13.8 mmol) in dry THF (300 mL) was added in portions at room temperature LAH (1.18 g, 34.6 mmol) suspended in THF (30 mL). The mixture was stirred at reflux for 6 h. The reaction mixture was then poured into $Na_2SO_4 \cdot 10H_2O$ (10g) and stirred. It was then digested on a steam bath (30 min) and filtered. The inorganic residue was extracted (Soxhlet) with THF (200 mL). The combined THF fractions upon evaporation gave the tetra-alcohol **27** (4.55 g, 90%), which was purified by recrystallization from a minimum volume of THF−MeOH (3:1): mp 130 °C; IR (KBr) 3540, 3340−3320 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 4.50 (s, 8 H, CH_2OH), 5.15 (bs, 8 H, OCH_2 and OH), 6.90 (bs, 4 H), 6.92 (bs, 2 H), 7.40−7.43 (m, 2 H), 7.56−7.59 (m, 2 H); MS, *m/e* (relative intensity) 374 ($M^+ - 2\ H_2O$, 1), 257 (3), 239 (49), 209 (45), 105 (82), 104 (100). Anal. Calcd for $C_{24}H_{26}O_6$: C, 70.23; H, 6.38. Found: C, 70.21; H, 6.45.

α,α′-Bis[3,5-bis(chloromethyl)phenoxy]-*o*-xylene (28). To a stirred suspension of the tetraalcohol **27** (4.0 g, 9.76 mmol) in CH_2Cl_2 (120 mL) containing pyridine (3.08 g, 39 mmol) was added a solution of thionyl chloride (4.6 g, 39.0 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred at room temperature for 12 h and then washed with water (3 × 100 mL). The organic layer was dried ($MgSO_4$) and evaporated to yield the tetrachloride **28** (4.30 g, 90%): mp 85 °C; ^1H NMR ($CDCl_3$, 90 MHz) δ 4.40 (s, 8 H, CH_2Cl), 4.90 (s, 4 H, OCH_2), 6.85 (bs, 6 H), 7.40−7.45 (m, 2 H), 7.50−7.65 (m, 2 H); MS, *m/e* (relative intensity) 484 (M^+, 19), 482 (12), 332 (16), 330 (26), 328 (27), 310 (18), 308 (27), 295 (100), 294 (24), 293 (92). Anal. Calcd for $C_{24}H_{22}ClO_4$: C, 59.53; H, 4.58. Found: C, 59.65; H, 4.39.

α,α′-Bis[3,5-bis(mercaptomethyl)phenoxy]-*o*-xylene (29). A stirred solution of the tetrachloride **28** (3.0 g, 6.2 mmol) and thiourea (1.89 g, 24.8 mmol) in THF (60 mL) was heated at reflux for 12 h. The mixture was cooled, and the precipitated isothiouronium salt was filtered and dried (6.15 g, 76%). This salt was dissolved in H_2O−dioxane (1:2 v/v, 180 mL) under nitrogen, and to this solution was added ethylenediamine (1.13 g, 18.8 mmol). The mixture was heated under nitrogen at reflux for 12 h and then cooled, and the reaction was carefully quenched with a minimum amount of dilute HCl (2 N, 20 mL). The solvent was removed under vacuum, and the crude product was chromatographed [SiO_2, CH_2Cl_2−hexane (1:1)] to give **29** (1.82 g, 70%) as colorless solid: mp 58 °C; ^1H NMR ($CDCl_3$, 90 MHz) δ 1.70 (t, J = 7.6, 4 H, SH), 3.50 (d, J = 7.6, 8 H, CH_2SH), 4.95 (s, 4 H, OCH_2), 6.60 (bs, 6 H), 7.00−7.25 (m, 4 H); MS, *m/e* (relative intensity) 474 (M^+, 1.8), 438 (1), 407 (1), 290 (13), 289 (42), 288 (43), 257 (12), 256 (17), 255 (72), 105 (100). Anal. Calcd for $C_{24}H_{26}O_2S_4$: C, 60.72; H, 5.52. Found: C, 60.83; H, 5.49.

General Procedure G. Coupling of Tetrathiol with Tetrabromide or 2 Equiv of Dibromide. A solution containing tetrathiol **29** (0.235 g, 0.5 mmol) and the appropriate dibromide (1 mmol) or tetrabromide (0.5 mmol) in nitrogen-degassed benzene (100 mL) was added dropwise over 8−10 h to a well-stirred solution of KOH (140 mg, 2.5 mmol) in aqueous ethanol (95%, 800 mL). After addition was complete, the mixture was stirred for an additional 8 h and then evaporated to dryness. The crude product obtained after usual workup was purified by column chromatography.

Cyclophane 24. The coupling of 2 equiv of **5c** with 1 equiv of **29** (general procedure G) afforded the cyclophane **24** (35%) after purification on silica gel with CH_2Cl_2−hexane (1:1) as the eluent. For **24**: mp 285 °C (dec); IR (KBr) 1725 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.20 (s, 8 H, SCH_2), 3.70 (s, 14 H, CO_2CH_3 and CH_2S), 5.00 (s, 4 H, OCH_2), 6.35 (s, 4 H), 7.00 (s, 2 H), 7.20−7.50 (m, 26 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 34.39 (SCH_2), 35.74 (CH_2S), 51.70 (CO_2CH_3), 67.80 (OCH_2), 114.60, 121.90, 128.05, 128.26, 128.47, 128.99, 129.03, 129.26, 133.77, 135.13, 137.56, 139.01, 139.55, 139.79, 158.59 (15 Ar carbons), 169.52 (CO_2CH_3); MS (FAB) (*m*-nitrobenzyl alcohol), *m/e* 1099 (MH^+). Anal. Calcd for $C_{68}H_{58}O_6S_4$: C, 74.29; H, 5.23. Found: C, 74.23; H, 5.37.

Cyclophane 24a. The coupling of 2 equiv of **5a** with 1 equiv of **29** (general procedure G) afforded the cyclophane **24a** (35%) after purification on silica gel with CH_2Cl_2−hexane (1:1) as the eluent. For **24a**: mp 260 °C (dec); ^1H NMR ($CDCl_3$, 400 MHz) δ 3.40 (s, 8 H, SCH_2), 3.70 (s, 8 H, CH_2S), 5.00 (s, 4 H, OCH_2), 6.20 (s, 4 H), 7.10 (s, 2 H), 7.10−7.40 (m, 26 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 35.04 (SCH_2), 35.88 (CH_2S), 66.76 (OCH_2), 114.32, 121.62, 126.84, 127.51, 127.74, 128.56, 129.27, 129.65, 130.27, 134.75, 137.44, 139.59, 140.49, 143.42, 158.31 (15 Ar carbons); MS (FAB) (*m*-nitrobenzyl alcohol matrix), *m/e* 1141 (MH^+).

Cyclophane 24b. The coupling of 2 equiv of **5b** with 1 equiv of **29** (general procedure G) afforded the cyclophane **24b** (40%) after purification on silica gel with 10 drops of MeOH in CH_2Cl_2 (250 mL) as the eluent. For **24b**: mp 232 °C; IR (KBr) 1720 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 3.30 (s, 8 H, SCH_2), 3.70 (s, 8 H, CH_2S), 5.00 (s, 4 H, OCH_2), 6.30 (s, 4 H), 6.93 (s, 2 H), 7.15 and 7.26 (ABq, J = 8.8, 16 H), 7.31−7.33 (m, 4 H), 7.37 (d, J = 8, 4 H), 7.52 (t, J = 8.8, 2 H), 12.6 (bs, 2 H, COOH); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ 34.40 (SCH_2), 35.23 (CH_2S), 67.80 (OCH_2), 114.48, 121.90, 128.23, 128.52, 128.56, 128.69, 129.19, 129.23, 135.01, 135.49, 138.08, 138.77, 138.86, 139.95, 158.41 (15 Ar carbons), 170.34 (CO_2H); MS (FAB) (*m*-nitrobenzyl alcohol matrix), *m/e* 1071 (MH^+). Anal. Calcd for $C_{66}H_{54}O_6S_4$: C, 73.99; H, 5.08. Found: C, 73.78; H, 5.05.

Conversion of Cyclophane 24a to 24b. To a stirred solution of cyclophane **24a** (0.12 g, 0.1 mmol) in dry THF (10 mL) was added *n*-BuLi (1.6 M, 0.2 mL) at −78 °C under nitrogen. The mixture was stirred under nitrogen at that temperature for 3 h and heated with CO_2 (bubbling dry CO_2 gas into the solution for 3 h), and the reaction was quenched with dilute HCl (2 N, 2 mL). The reaction mixture was extracted with CH_2Cl_2, washed with water, and dried ($MgSO_4$). The crude product after purification on silica gel column was found to be cyclophane **24b**.

Conversion of Cyclophane 24b to 24. To a stirred suspension of cyclophane **24b** (540 mg, 0.05 mmol) in CH_2Cl_2 (120 mL) containing pyridine (0.01 g, 0.1 mmol) was added a solution of thionyl chloride (0.012 g, 0.1 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred at rt for 5 h and then evaporated to give a pale yellow solid as a residue. Methanol

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(10 mL) was added to the residue and then refluxed for 4 h. The reaction mixture was evaporated to dryness, extracted with CH_2Cl_2, washed with water, and dried ($MgSO_4$). The residue obtained after evaporation of the solvent on purification using silica gel gave cyclophane **24**.

Conversion of Cyclophane 23 to 24. A solution of cyclophane **23** (100 mg, 0.1 mmol) and *o*-xylylene dibromide (27 mg, 0.1 mmol) in nitrogen-degassed dry DMF (30 mL) was added dropwise over a period of 4−5 h to a well-stirred suspension of K_2CO_3 (1.0 g) in dry DMF (50 mL). The reaction mixture was stirred for an additional hour and evaporated to dryness under reduced pressure. Purification of the residue on silica gel by chromatography afforded the cyclophane **24** in 50% yield.

Ethylene 1,2-Bis(4,4″-dimethyl-1,1′:3′,1″-terphenyl-2′-carboxylate) (30). To a stirred suspension of acid **4b** (3.0 g, 10 mmol) in CH_2Cl_2 (120 mL) containing pyridine (800 mg, 10 mmol) was added a solution of thionyl chloride (1.16 g, 10 mmol) in CH_2Cl_2 (20 mL). The mixture was stirred at rt for 12 h and then evaporated to dryness. The acid chloride thus obtained was added in five−six equal portions to a stirred solution of ethylene glycol (310 mg, 5 mmol) and NaH (60%, 400 mg, 10 mmol) in dry DMF (100 mL). The reaction mixture was then stirred for 12 h at 70 °C. DMF was removed under low pressure. To the residue was added crushed ice (200 g). Then the resulting solution was extracted with CH_2Cl_2, and the organic layer was washed with water, dried ($MgSO_4$), and evaporated in vacuo. The crude product was chromatographed on silica gel using CH_2Cl_2−hexane (1:2) as the eluent to give diester **30** (1.16g, 35%) as a colorless solid: mp 218 °C; IR (KBr) 1735 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 2.20 (s, 12 H, CH_3), 3.50 (s, 4 H, OCH_2), 6.75−7.15 (m, 22 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 21.11 (CH_3), 61.88 (OCH_2), 128.27, 128.58, 128.91, 129.34, 132.45, 137.14, 137.47, 140.33 (8 Ar carbons), 169.18 (CO); MS, *m/e* (relative intensity) 630 (M^+, 20), 329 (25), 285 (100), 269 (5). Anal. Calcd for $C_{44}H_{38}O_4$: C, 83.78; H, 6.07. Found: C, 83.69; H, 5.98.

Tetrabromide 31. Freshly prepared NBS (1.43 g, 8 mmol) was added in four equal portions 6 h apart to a solution of ester **30** (1.25 g, 2 mmol) in CCl_4 (100 mL) heated at reflux, each addition being followed by a few milligrams of benzoyl peroxide. The mixture was cooled and filtered to remove the succinimide. The solvent was evaporated from the filtrate, and the residue was recrystallized from CH_2Cl_2−hexane (2:3) to give the tetrabromide **31** (1.14 g, 60%): mp 202 °C; IR (KBr) 1735 cm^{-1}; ^1H NMR ($CDCl_3$, 90 MHz) δ 3.50 (s, 4 H, OCH_2), 4.40 (s, 8 H, CH_2Br), 7.00−7.50 (m, 22 H). Anal. Calcd for $C_{44}H_{34}Br_4O_4$: C, 55.84; H, 3.62. Found: C, 55.84; H, 3.68.

Cyclophane 32. Coupling of 1 equiv of **31** with 1 equiv of **29** afforded cyclophane **32** (35%) after purification on silica gel with CH_2Cl_2−hexane (1:1) as the eluent. For **32**: mp 295 °C (dec); IR (KBr) 1725 cm^{-1}; ^1H NMR (DMSO-d_8, 400 MHz) δ 3.16 and 3.77 (ABq, J = 10, 8 H, SCH_2), 3.72 (s, 4 H, OCH_2), 3.85 and 3.96 (ABq, J = 16, 8 H, CH_2S), 5.10 (s, 4 H, OCH_2), 6.60 (s, 4 H), 6.95 (s, 2 H), 7.05 and 7.17 (ABq, J = 8.8, 16 H), 7.20−7.25 (m, 4 H), 7.35 (d, J = 8, 4 H), 7.52 (t, J = 8.8, 2 H); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ 35.53 (SCH_2), 35.79 (CH_2S), 61.88 (OCH_2), 68.86 (OCH_2), 114.22, 121.99, 126.38, 126.62, 126.68, 128.02, 128.38, 128.59, 129.03, 129.55, 137.79, 138.99, 139.75, 139.96, 158.25 (15 Ar carbons), 169.77 (CO); MS (FAB) (*m*-nitrobenzyl alcohol matrix), *m/e* 1097 (MH^+). Anal. Calcd for $C_{68}H_{56}O_6S_4$: C, 74.42; H, 5.14. Found: C, 74.29; H, 5.12.

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