Structural Characterization of Thiocyclophanes That Promote Edge-to-Face Aromatic–Aromatic Geometries

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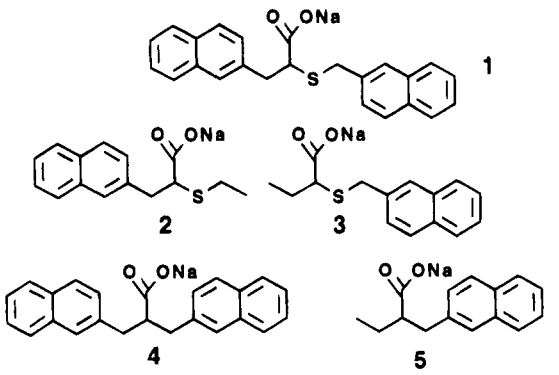
Several [4.4]thiocyclophanes have been examined in solution and the solid state. These molecules contain two aromatic units, phenyl and/or naphthyl, with linking chains attached meta or para on the phenyl groups, and 1,3 or 1,4 on the naphthyl groups. Most previous studies of cyclophanes containing two aromatic rings have focused on enforcing parallel alignment of those rings. The molecules discussed here, in contrast, were chosen to promote edge-to-face juxtapositions. Crystallographic data confirm that edge-to-face orientations between the linked aromatic groups are available for these cyclophanes, and ^{1}H NMR data indicate that conformations containing these orientations are populated in solution. These cyclophanes provide spectroscopic references for NMR-based studies of folding in more flexible diphenyl and dinaphthyl compounds.

Attractive interactions between aromatic groups have been proposed to stabilize protein folding patterns[1] and host–guest complexes.[2] The optimal orientation of the rings in hydrocarbon aromatic–aromatic pairs has been a subject of considerable discussion. In the crystalline states of benzene, naphthalene, and many other hydrocarbon aromatics, nearest neighbors are arranged in "herringbone" patterns, in which the edge of one molecule is oriented toward the face of another.[3] The benzene dimer in the gas phase also appears to have a nonparallel structure.[4] Molecular dynamics calculations predict that the benzene dimer in aqueous solution favors an edge-to-face geometry.[5] For the isolated benzene dimer, an energetic preference for the edge-to-face geometry relative to the parallel stacked geometry has been rationalized computationally in terms of Coulombic interactions,[6] quadrupole–quadrupole interactions,[7] and attractions between π-electrons and the σ-framework.[8] Elegant studies by Wilcox et al., however, have shown that any specific attraction between benzene rings in the edge-to-face orientation is quite small, and perhaps nonexistent, in organic solvents.[9] This conclusion is consistent with the observation that there is relatively little orientational preference among aromatic side chain pairs in folded proteins.[10]

In order to evaluate the contribution of aromatic–aromatic interactions to noncovalently controlled phenomena in solution, we have been studying model systems in which pairs of aromatic groups are connected to one another via flexible linkers.[11] In such compounds, ^{1}H NMR measurements allow the detection of intramolecular aromatic–aromatic proximity, because of the local magnetic anisotropy created by π-electron systems. Thus, for example, there are significant upfield ^{1}H NMR shifts of dinaphthyl carboxylate **1** in aqueous solution relative to reference compounds **2** and **3** ($\Delta\delta$ values up to 0.3 ppm).[11b] In contrast, no upfield ^{1}H NMR shifts are observed for dinaphthyl carboxylate **4** relative to reference compound **5** in aqueous solution.[11a] These observations indicate that there is intramolecular aromatic–aromatic proximity in **1**, but not in **4**. Simple computational modeling suggests that the three-atom linker of **4** allows only approximately parallel intramolecular orientations of the naphthyl groups, but that the four-atom linker of **1** is sufficiently long to allow both parallel and edge-to-face orientations of the tethered aryl groups. This structural difference suggests that the intramolecular aromatic–aromatic proximity detected in **1** may require an edge-to-face geometry. Unfortunately, it has been impossible to determine the aromatic–aromatic geometry in the folded form(s) of **1** (and related compounds), or the relative populations of unfolded and



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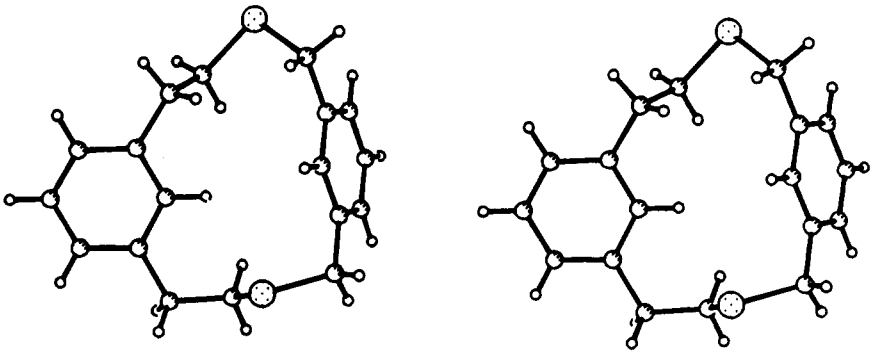


Figure 1. Crystal structure of cyclophane **6** (stereoview). The angle between the two aromatic planes is 62.3°.

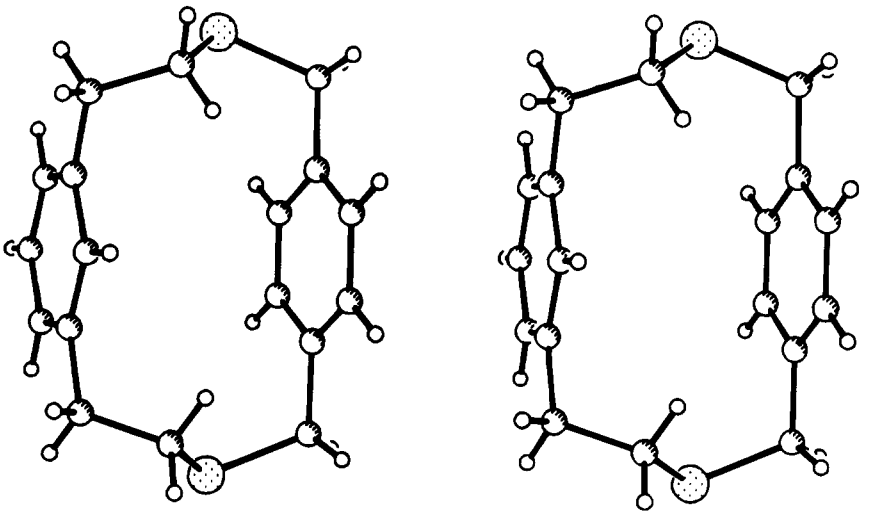


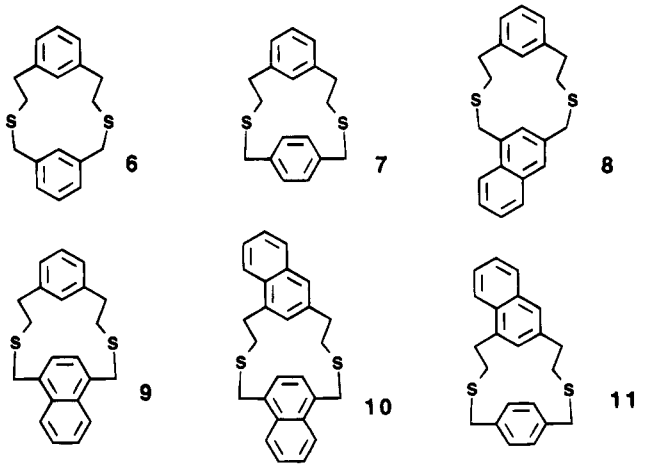
Figure 2. Crystal structure of cyclophane **7** (stereoview). The angle between the two aromatic planes is 3.6°.

folded forms, from ^{1}H NMR studies, because the conformational interconversions are rapid on the spectroscopic time scale, and the chemical shifts for the limiting folded states are unknown. Here, we describe analysis of several [4.4]thiocyclophanes that provide information on the upfield shifts to be expected in edge-to-face aromatic–aromatic pairs involving benzene and/or naphthalene units.

Many cyclophanes containing two aromatic moieties have been prepared,[12] but most of these molecules have been intended to induce the aromatic rings to lie in parallel planes. Among the reported cyclophanes that display aromatic–aromatic juxtapositions deviating significantly from planarity, internal strain makes it unlikely in most cases that the observed juxtaposition of the aromatic rings reflects the "natural" preference of those rings.[13] The linking segments are flexible in the cyclophanes described below, which should promote adoption of aromatic–aromatic geometries that are determined, at least in part, by any intrinsic aromatic–aromatic attraction.

Results and Discussion

Simple molecular mechanics calculations suggested that [4.4]thiocyclophanes containing two phenyl rings that were both meta-linked would be able to adopt conformations containing intramolecular edge-to-face arrangements. Such conformations appeared to be available also for [4.4]thiocyclophanes with one meta-linked and one para-linked phenyl ring. Cyclophane **6** has been previously prepared as a precursor to [3.3]metacyclophane;[14] we synthesized cyclophanes **7**–**11** by standard methods.



Crystals of cyclophanes **6**–**10** suitable for X-ray diffraction were obtained.[19] The solid state structures of these molecules are shown in Figures 1–5. The intramolecular angles between the aromatic planes in the crystal

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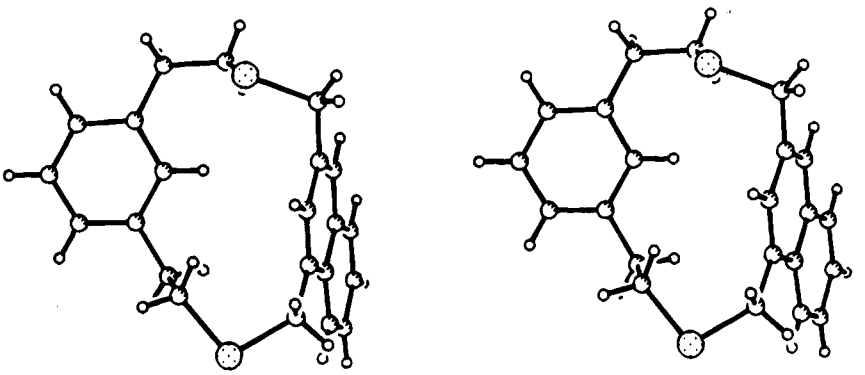

Figure 3. Crystal structure of cyclophane **8** (stereoview). The angle between the two aromatic planes is 68.9°.

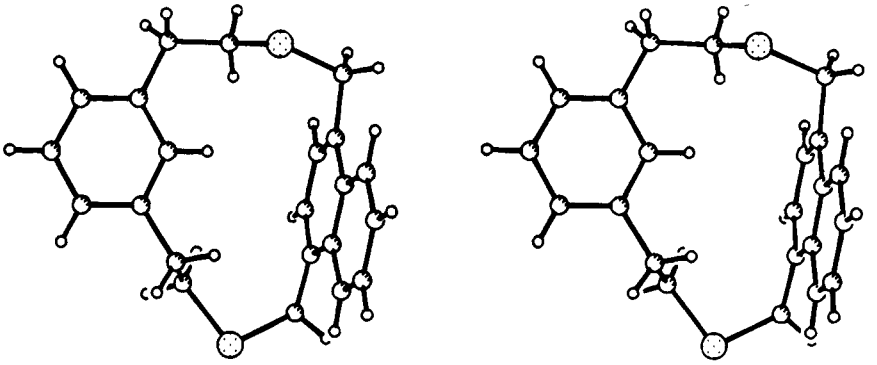

Figure 4. Crystal structure of cyclophane **9** (stereoview). The angle between the two aromatic planes is 89.8°.

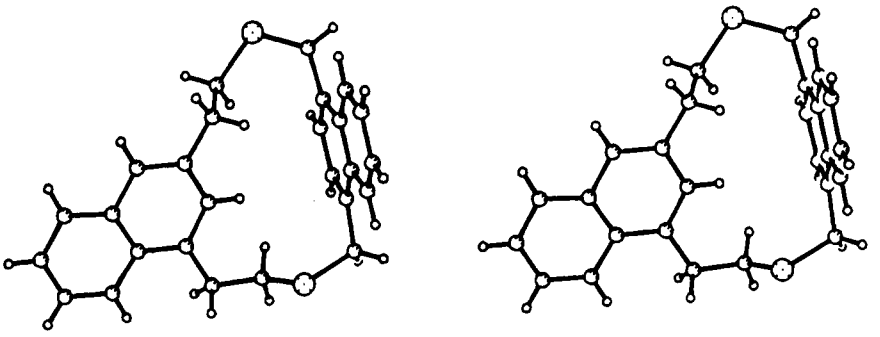

Figure 5. Crystal structure of cyclophane **10** (stereoview). The angle between the two aromatic planes is 85.9°.

structures are summarized in Table 1. Both cyclophanes containing two meta-linked rings, **6** and **8**, display intramolecular edge-to-face orientations in the solid state, with very similar aryl−aryl angles (62° and 69°). In contrast, considerable variation in aryl−aryl orientation is observed among the three cyclophanes with one meta-linked and one para-linked ring: **9** and **10** show perpendicular intramolecular edge-to-edge arrangements, but **7** displays a nearly parallel aromatic−aromatic arrangement. Molecular models indicate that **7**, **9**, and **10** are conformationally flexible; therefore, the variations in solid state structure probably originate at least in part from crystal packing forces.

Variable temperature ^{1}H NMR data provided evidence that the cyclophanes discussed here are conformationally mobile in solution. The ^{1}H NMR spectra of representative cyclophanes **7**−**9** at −78 °C were sharp and showed only one set of resonances, which suggests that these molecules are experiencing rapid conformational averaging on the NMR time scale at this temperature. This behavior contrasts with that of cyclophanes containing shorter linking segments (two or three atoms). [3.3]Metacyclophane, for example, shows significant broadening of one aromatic proton resonance at −20 °C, and decoalescence by −60 °C.[15] 2,2,13,13-Tetramethyl[4.4]metacyclophane also displays broadening of an aromatic proton resonance in this temperature range.[16]

^{1}H NMR comparisons of **6**−**11** with reference compounds **12** and **13** in CD_2Cl_2 provided information on the solution conformations of these cyclophanes. Table 1 summarizes $\Delta\delta$ values obtained at 22 °C by comparing resonances from the proton ortho to both 2-thioethyl substituents in **6**−**13**. In the crystal structures of **6**, **8**, **9**, and **10**, this proton is the "edge" that approaches most closely the face of the other aromatic ring in the cyclophane. (For the meta,para-linked cyclophanes, **7**, **9**, **10**, and **11**, this proton's resonance could be assigned by inspection of the one-dimensional ^{1}H NMR spectrum;

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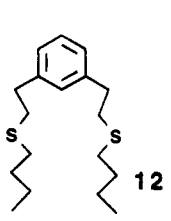
Table 1

cyclophane	interplanar angle,[a] deg	Δδ (+22 °C)[b]	Δδ (−78 °C)[c]
6	62.3	+0.46	–
7	3.6	+1.02	+1.25
8	68.9	+0.43	+0.84
9	89.8	+1.28	+1.60
10	85.9	+1.47	–
11	–	+1.19	–

[a] Angle between the mean planes of the linked aromatic moieties in the crystalline cyclophane. No value is provided for **11** because no crystal structure was obtained. [b] The difference between the cyclophane and the appropriate model compound, **12** or **13**, in the chemical shift of the aromatic proton ortho to the two thioethyl groups. (In all cases, the cyclophane resonance was upfield of the resonance from **12** or **13**.) [c] The difference between the cyclophane and model compound **12** in the chemical shift of the aromatic proton ortho to the two thioethyl groups (cyclophane and model compound resonances measured at −78 °C; only cyclophanes **7**−**9** were examined at low temperature). All NMR data were obtained in CD_2Cl_2.

however, for the meta,meta-linked cyclophanes **6** and **8**, assignment required NOESY data.)



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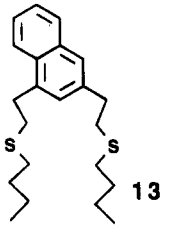

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Substantial Δδ values are observed for all six cyclophanes at 22 °C (Table 1), with the Δδ values for the four meta,para-linked cyclophanes (1.0−1.5 ppm) larger than those for the two meta,meta-linked cyclophanes (0.4−0.5 ppm). The consistently large Δδ values for the meta,para-linked cyclophanes suggest that these molecules have similar conformational preferences in solution, and that the structural variations observed among **7**, **9**, and **10** in the solid state result from crystal packing effects. For each of the four meta,para cyclophanes, the resonance of the proton ortho to both 2-thioethyl substituents is the furthest upfield of all the aromatic protons, and the only one that lies significantly outside the normal aromatic region (copies of the ^1H NMR spectra are provided in the supplementary material). This trend suggests that the unique upfield shift reflects population of conformers containing intramolecular edge-to-face aromatic−aromatic geometries, with the proton ortho to both 2-thioethyl substituents as the "edge". An alternative possibility, in which the upfield shift would result from conformers containing offset parallel aromatic rings, seems less likely, since such conformers would be expected to produce substantial upfield shifts of more than one aryl proton. The relatively small Δδ values for the meta,meta-linked cyclophanes suggest that edge-to-face conformations are populated to a lesser extent in these molecules than in the meta,para-linked cyclophanes.

For each of the three cyclophanes examined by variable temperature NMR, the Δδ value for the aryl proton ortho to the two 2-thioethyl substituents increased as temperature decreased. The Δδ values measured for **7**−**9** at −78 °C (relative to **12** at this temperature) are shown in Table 1. Variable concentration studies suggested that these increases in Δδ are due strictly to intramolecular effects; thus, for example, the absolute ^1H NMR chemical shifts for **8** at −78 °C were identical for 5 and 50 mM CD_2Cl_2 solutions. The consistent increase in the Δδ value at lower temperatures suggests that conformations containing edge-to-face aromatic−aromatic juxtapositions are increasingly populated at lower temperatures.

Fukazawa et al. have determined crystal structures and deduced solution structures for two meta,meta-linked [4.4]cyclophanes related to **6**, 2,2,12,12-tetramethyl[4.4]-metacyclophane[17] and, quite recently, 2,2,13,13-tetramethyl[4.4]metacyclophane.[16] These cyclophanes contain all-carbon linking segments. In the former crystal structure, the phenyl rings in each cyclophane molecule are well separated from one another, but in the latter there is an intramolecular edge-to-face arrangement. ^1H NMR data in solution show a large Δδ value for the "edge" proton in the latter cyclophane,[16] which indicates that conformations containing the edge-to-face arrangement are highly populated. Although the *gem*-dimethyl substituents in the linking segments of these two cyclophanes are expected to decrease conformational flexibility relative to our cyclophanes, the results of Fukazawa are qualitatively consistent with our findings.

Conclusions. Cyclophanes **6**−**11** readily adopt conformations in which the two aromatic moieties in the macrocycle are intramolecularly oriented in an edge-to-face manner. These cyclophanes appear to be conformationally flexible, and conformations that lack the intramolecular edge-to-face juxtaposition also appear to be populated in solution. The Δδ values given in Table 1 provide lower limits on the maximum upfield shifts to be expected for aryl protons when an aromatic−aromatic pair is arranged in edge-to-face fashion. These lower limits provide qualitative guidance on the interpretation of ^1H NMR data obtained with molecules containing two aromatic moieties more flexibly linked, e.g., **1** and **4**.[11] In particular, the cyclophane results suggest that there is not a single highly populated conformation of **1** containing an edge-to-face naphthyl−naphthyl juxtaposition, because the upfield aromatic proton shifts observed for **1** vs **2**+**3** are relatively modest (≤0.3 ppm).

Experimental Section

All melting points are uncorrected. THF was freshly distilled from sodium benzophenone ketyl under N_2. DMF was distilled from CaH_2 and stored over 4 Å sieves. CH_2Cl_2 was distilled from CaH_2 prior to use. All reagents were obtained from Aldrich Chemical Co. and used without purification. Column chromatography was carried out using low air pressure with 230−400 mesh silica gel 60 from EM Science.

1,3-Bis(cyanomethyl)naphthalene. To a solution of 5.0 g of (32 mmol) of 1,3-dimethylnaphthalene in 26 mL of CCl_4 was added ca. 3 mg of benzoyl peroxide followed by 6.26 g of (35.2 mmol) NBS. The solution was refluxed for 4 h and allowed to cool slightly, and the remaining 6.26 g (35.2 mmol) of NBS was added along with an additional 3 mg of benzoyl peroxide. The orange solution was then refluxed for an additional 16 h. The solution was then allowed to cool to rt, and 30 mL of CH_2Cl_2 was added. The precipitated succinimide was removed by filtration, and the solution was extracted twice with 100 mL portions of H_2O. The organic phase was dried over $MgSO_4$, and the solution was concentrated until only CCl_4 remained. As the CCl_4 solution cooled, a white solid crystallized. The solid was isolated by filtration and washed with hexanes to give 5.72 g (57% yield) of the desired dibromide: ^1H NMR ($CDCl_3$) δ 8.13 (d, J = 8.5 Hz, 1H), 7.83 (m, 2H), 7.58

(17) Fukazawa, Y.; Ogata, K.; Usui, S. *J. Am. Chem. Soc.* **1988**, *110*, 8692.

(m, 3H), 4.94 (s, 2H), 4.63 (s, 2H). This material was carried on without further purification.

To a well-stirred refluxing solution of 3.59 g (55.2 mmol) of KCN in 36 mL of EtOH/12 mL of H_2O was quickly added 3.77 g (12 mmol) of solid 1,3-bis(bromomethyl)naphthalene. The solution became dark brown almost immediately and was filtered through Celite to remove the black, amorphous, suspended material. The yellow filtrate was diluted with 35 mL of H_2O and extracted three times with 100 mL portions of ether. The combined extracts were dried over $MgSO_4$ and concentrated to give a yellow solid. The crude product was purified by SiO_2 column chromatography, eluting with 25% ethyl acetate in hexanes, to afford 1.24 g (50%) of the desired dinitrile as a light yellow, crystalline solid: mp 107–108 °C (recryst from ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.83–7.95 (m, 3H), 7.63 (m, 2H), 7.50 (s, 1H), 4.16 (s, 2H), 3.94 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 130.2, 129.1, 128.9, 128.2, 127.9, 127.8, 127.7, 127.6, 122.4, 117.4, 117.1, 23.7, 21.6; EI MS *m/z* obsd 206.0821, calcd for $C_{14}H_{10}N_2$ 206.0844. Anal. Calcd for $C_{14}H_{10}N_2$: C, 81.53; H, 4.89; N, 13.58. Found: C, 81.24; H, 4.97; N, 13.46.

Cyclophane 6. To a well-stirred suspension of 3.32 g (43.8 mmol) of $LiAlH_4$ in 250 mL of THF at 0 °C was slowly added a solution of 4.25 g (21.9 mmol) of 1,3-phenylenediacetic acid. When the addition was complete, the suspension was allowed to warm to rt. The suspension was then refluxed for 24 h, cooled to rt, and then stirred for an additional 24 h. The excess $LiAlH_4$ was quenched by addition of ca. 10 mL of freshly prepared, saturated Na_2SO_4 (aq). The precipitate was then removed by suction filtration, and the filtrate was concentrated. The resulted solid was dissolved in 50 mL of CH_2Cl_2, dried over $MgSO_4$, and concentrated, to afford 2.69 g (74% yield) of 1,3-bis(2-hydroxyethyl)benzene as a light yellow syrup: ^{1}H NMR (CD_3COCD_3) δ 7.12 (m, 4H), 3.71 (dt, J = 6.5 Hz, 6.5 Hz, 4H), 2.9 (s, 2H), 2.78 (t, J = 7.1 Hz, 4H). This material was carried on without further purification.

To a solution of 3.00 g (18.1 mmol) of 1,3-bis(2-hydroxyethyl)benzene and 14.32 g (181 mmol) pyridine in 50 mL CH_2Cl_2 at 0 °C was added 10.35 g of (54.3 mmol) TsCl. The mixture was stirred until the TsCl dissolved. The solution was then stored at 4 °C for 48 h. The solution was extracted three times with 200 mL portions of 2 M HCl (aq) at 0 °C. The solution was then extracted with 150 mL of brine, dried over $MgSO_4$, and concentrated. The crude product was purified by SiO_2 column chromatography, eluting with 25% ethyl acetate in hexanes to afford 6.36 g (74% yield) of the desired ditosylate as a white solid: mp 59–60 °C (recryst from ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.7 (d, J = 6.5 Hz, 4H), 7.30 (d, J = 6.5 Hz, 4H), 7.15 (t, J = 7 Hz, 1H), 6.97 (d, J = 7 Hz, 2H), 6.85 (s, 1H), 4.17 (t, J = 7 Hz, 4H), 2.88 (t, J = 7 Hz, 4H), 2.43 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 144.7, 136.6, 132.9, 130.0, 129.8, 128.8, 127.8, 127.4, 70.4, 35.2, 35.2, 21.6; IR (KBr pellet) 1356 (s), 1345 (s), 1177 (s) cm^{-1}; EI MS *m/z* obsd 475.1244, calcd for $C_{24}H_{26}O_6S_2$ (M^+ + H) 475.1204.

To a well-stirred suspension of 1.04 g (3.2 mmol) of Cs_2CO_3 in 88 mL of DMF under N_2 at 60 °C was added a solution of 0.227 g (1.6 mmol) of 1,3-bis(mercaptomethyl)benzene and 0.758 g of the ditosylate of 1,3-bis(2-hydroxyethyl)benzene in 12 mL of DMF, via syringe pump (0.2 mL/min). When the addition was complete, the solution was allowed to cool to rt and the solvent was concentrated. The residue was suspended in 25 mL of CH_2Cl_2 and extracted with brine. The organic layer was dried over $MgSO_4$ and concentrated. The crude product was purified by SiO_2 column chromatography eluting with 5% ethyl acetate in hexanes to afford 150 mg (37% yield) of cyclophane **6** as a white, crystalline solid: mp 103.5–104.5 °C (recryst from ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.22 (m, 1H), 7.19 (d, J = 1.5 Hz, 1H), 7.18 (t, J = 1.75 Hz, 1H), 7.13 (t, J = 7.5 Hz, 1H), 7.08 (s, 1H), 6.98 (dd, J = 7.5, 1.5 Hz, 2H), 6.67 (s, 1H), 3.66 (s, 4H), 2.73 (AA'BB', 8H); ^{13}C NMR ($CDCl_3$) δ 140.2, 138.6, 130.1, 128.1, 127.9, 127.7, 126.7, 36.0, 34.7, 30.7; EI MS *m/z* obsd 300.0985, calcd for $C_{18}H_{20}S_2$ 300.1006.

Cyclophane 7 was prepared from 1,4-bis(mercaptomethyl)benzene and the ditosylate of 1,3-bis(2-hydroxyethyl)benzene by an analogous procedure. The product was isolated by SiO_2 column chromatography, eluting with 3% ethyl acetate in hexanes to afford the desired cyclophane as a white, crystalline solid in 41% yield: mp 114.5–115.5 °C (recryst from 1,2-dichloroethane/hexanes), ^{1}H NMR ($CDCl_3$) δ 7.15 (s, 4H), 7.04 (t, J = 7.5 Hz, 1H), 6.84 (dd, J = 7.5, 1.5 Hz, 2H), 6.02 (s, 1H), 3.68 (s, 4H), 2.60 (s, 8H); ^{13}C NMR ($CDCl_3$) δ 140.2, 136.8, 129.5, 127.4, 127.0, 36.0, 35.0, 30.0; EI MS *m/z* obsd 300.0997, calcd for $C_{18}H_{20}S_2$ 300.1006.

Cyclophane 8. To a solution of 0.604 g (1.92 mmol) of 1,3-bis(bromomethyl)naphthalene in 20 mL of DMSO was added 0.351 g (4.61 mmol) of thiourea. The solution was stirred for 22 h and was then poured into 40 mL of a well-stirred 10% NaOH (aq) solution and allowed to stir for 1 h. The solution was then acidified to pH 2 and extracted three times with 50 mL portions of CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated to give ca. 6 g of a light yellow oil composed mostly of DMSO. The oil was chromatographed using SiO_2, eluting with 5% ethyl acetate in hexanes to afford 0.22 g of 1,3-bis(mercaptomethyl)naphthalene (52% yield) as a cloudy oil: ^{1}H NMR ($CDCl_3$) δ 8.03 (m, 1H), 7.81 (m, 1H), 7.65 (s, 1H), 7.52 (m, 2H), 7.44 (d, J = 1.5 Hz, 1H), 4.11 (d, J = 7.25 Hz, 2H), 3.80 (d, J = 7.75 Hz, 2H), 1.88 (t, J = 7.25 Hz, 1H), 1.79 (t, J = 7.75 Hz, 1H). This dithiol was carried on without further purification.

Cyclophane **8** was prepared from 1,3-bis(mercaptomethyl)-naphthalene and the ditosylate of 1,3-bis(2-hydroxyethyl)-benzene by a procedure analogous to that used to prepare the other cyclophanes. The product was isolated by SiO_2 column chromatography, eluting with 5% ethyl acetate in hexanes to afford the desired cyclophane as a white, crystalline solid in 15% yield: mp 144.5–145 °C (recryst from 1,2-dichloroethane/hexanes); ^{1}H NMR ($CDCl_3$) δ 8.18 (d, J = 8.5 Hz, 1H), 7.78 (dd, J = 8, 2 Hz, 1H), 7.58 (s, 1H), 7.48 (m, 2H), 7.22 (d, J = 2 Hz, 1H), 7.08 (t, J = 7.5 Hz, 1H), 6.96 (d, J = 8 Hz, 1H), 6.70 (s, 1H), 4.16 (s, 2H), 3.75 (s, 2H), 2.90 (s, 4H), 2.60 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 140.4, 139.4, 134.9, 133.8, 133.6, 130.7, 129.1, 128.5, 128.4, 127.9, 127.3, 126.8, 126.1, 126.0, 125.8, 124.0, 36.8, 33.9, 33.1, 32.2, 30.4; EI MS *m/z* obsd 350.1135, calcd for $C_{22}H_{22}S_2$ 350.1163.

Cyclophane 9 was prepared from 1,3-bis(mercaptoethyl)-benzene[14] and 1,4-bis(bromomethyl)naphthalene[18] by an analogous procedure. The product was isolated by SiO_2 column chromatography, eluting with 5% ethyl acetate in hexanes to afford the desired cyclophane as a white, crystalline solid in 10% yield: mp 159.5–161 °C (recryst from ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$) δ 8.2 (m, 2H), 7.52 (m, 2H), 7.16 (s, 2H), 6.71 (t, J = 7.5 Hz, 1H), 6.63 (d, J = 7.5 Hz, 2H), 5.79 (s, 1H), 4.16 (ABq, J = 13.5 Hz, 4H), 2.93 (m, 2H), 2.62 (m, 2H), 2.36 (m, 2H), 2.06 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 140.2, 139.7, 133.3, 131.9, 128.8, 128.7, 128.6, 127.3, 127.0, 126.6, 126.5, 126.1, 125.3, 35.6, 35.3, 34.6, 30.8, 29.7; EI MS *m/z* obsd 350.1139, calcd for $C_{22}H_{22}S_2$ 350.1163.

Cyclophane 10. To a solution of 0.927 g (4.5 mmol) of 1,3-bis(cyanomethyl)naphthalene and 5.25 mL (90 mmol) of absolute EtOH in 45 mL of 1,4-dioxane (at ca. 15 °C) was added gaseous HCl over a 45 min period. The flask was then sealed and stirred for 13 h. H_2O (20 mL) was then added, and the solution was extracted three times with 100 mL portions of $CHCl_3$. The combined organic extracts were dried over $MgSO_4$ and concentrated to give ca. 1.5 g of a yellow oil. The oil was dissolved in 15 mL of DMSO, and then 200 mL of 2 M HCl (aq) was added. The cloudy solution (which became clear upon heating) was refluxed for 14 h. The solution was allowed to cool and was then extracted three times with 200 mL portions of ether. The combined ether extracts were dried over $MgSO_4$ and concentrated to give 1.06 g (97% yield) of 1,3-bis(carboxymethyl)naphthalene as a white solid: mp 221–222 °C (dec, recryst from acetone/hexanes); ^{1}H NMR (CD_3COCD_3) δ 8.03 (m, 1H), 7.87 (m, 1H), 7.75 (s, 1H), 7.50 (m, 2H), 7.44 (d, J =

(18) Ried, W.; Bodem, H. *Chem. Ber.* **1958**, *91*, 1770.

(19) The author has deposited atomic coordinates for these structures 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, UK.

1 Hz, 1H), 4.09 (s, 1H), 3.78 (s, 1H); ^{13}C NMR ($CDCl_3/CD_3COCD_3$) δ 170.8, 132.9, 131.0, 130.5, 130.2, 128.7, 127.2, 126.6, 124.8, 122.9, 39.4, 37.2; EI Ms *m/z* obsd 244.0713, calcd for $C_{14}H_{12}O_4$ 244.0736.

1,3-Bis(2-hydroxyethyl)naphthalene was prepared from 1,3-bis(carboxymethyl)naphthalene via a procedure analogous to that used to prepare 1,3-bis(2-hydroxyethyl)benzene. The desired diol was isolated as a yellow oil in 85% yield: ^{1}H NMR ($CDCl_3$) δ 8.00 (m, 1H), 7.81 (m, 1H), 7.59 (s, 1H), 7.47 (m, 2H), 7.26 (s, 1H), 3.96 (t, J = 6.5 Hz, 2H), 3.93 (t, J = 6.4 Hz, 2H), 3.33 (t, J = 6.5 Hz, 2H), 2.99 (t, J = 6.4 Hz, 2H), 1.61 (s, 2H); ^{13}C NMR ($CDCl_3$) δ 135.6, 134.8, 134.1, 130.8, 128.8, 128.4, 126.8, 125.9, 125.6, 123.5, 63.4, 62.9, 39.1, 36.1; IR (KBr pellet): 3328 (vs) cm^{-1}; EI MS *m/z* obsd 216.1129, calcd for $C_{14}H_{16}O_2$ 216.1150.

The ditosylate of 1,3-bis(2-hydroxyethyl)naphthalene was prepared from 1,3-bis(2-hydroxyethyl)naphthalene in a procedure analogous to that used to prepare the ditosylate of 1,3-bis(2-hydroxyethyl)benzene. The product was isolated by SiO_2 column chromatography, eluting with 30% ethyl acetate in hexanes, to afford the desired ditosylate as a pale, yellow syrup in 74% yield: ^{1}H NMR ($CDCl_3$) δ 7.75 (m, 2H), 7.61 (d, J = 7.7 Hz, 4H), 7.44 (m, 2H), 7.21 (s, 1H), 7.14 (d, J = 8 Hz), 6.98 (d, J = 1.5 Hz, 1H), 4.29 (t, J = 7.3 Hz, 2H), 4.28 (t, J = 6.8 Hz, 2H), 3.35 (t, J = 7.3 Hz, 2H), 3.04 (t, J = 6.8 Hz, 2H), 2.39 (s, 3H), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 144.6, 133.9, 133.3, 132.8, 132.7, 132.4, 130.6, 129.9, 129.7, 128.5, 128.0, 127.7, 127.6, 127.3, 126.1, 126.0, 122.8, 70.3, 69.6, 35.2, 32.4, 21.6; IR (neat) 1357 (vs), 1189 (vs), 1173 (vs) cm^{-1}; EI MS *m/z* obsd 524.1320, calcd for $C_{28}H_{28}O_6S_2$ 524.1327.

1,4-Bis(mercaptomethyl)naphthalene was prepared from 1,4-bis(bromomethyl)naphthalene in a procedure analogous to that used to prepare 1,3-bis(mercaptomethyl)naphthalene. The desired mercaptan was isolated as a white solid in 79% yield: ^{1}H NMR ($CDCl_3$) δ 8.12 (m, 2H), 7.60 (m, 2H), 7.38 (s, 2H), 4.17 (d, J = 7.2 Hz, 4H), 1.89 (t, J = 7.2 Hz, 2H). This material was carried on without further purification.

Cyclophane **10** was prepared from 1,4-bis(mercaptomethyl)-napthalene and the ditosylate of 1,3-bis(2-hydroxyethyl)-naphthalene by a procedure analogous to that used to prepare the other cyclophanes. The product was isolated by SiO_2 column chromatography, eluting with 3% ethyl acetate in hexanes to afford the desired cyclophane as a white, crystalline solid in 24% yield: mp 187–189 °C (recryst from benzene/hexanes); ^{1}H NMR ($CDCl_3$) δ 8.31 (d, J = 8 Hz, 1H), 8.15 (d, J = 8 Hz, 1H), 7.76 (m, 1H), 7.55 (m, 2H), 7.52 (m, 1H), 7.31 (m, 2H), 7.24 (s, 2H), 7.16 (s, 1H), 5.83 (s, 1H), 4.30 (ABq, J = 13.3 Hz, 2H), 4.22 (ABq, J = 13.8 Hz, 2H), 3.15 (m, 2H), 2.70 (m, 4H), 2.38 (m, 1H), 1.95 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 137.2, 135.6, 133.9, 133.3, 132.9, 132.1, 131.7, 128.1, 127.2, 126.4, 126.3, 126.2, 125.9, 125.7, 125.3, 125.0, 124.9, 124.6, 124.5, 122.9, 36.9, 34.6, 34.4, 30.8, 30.5, 29.9; EI MS *m/z* obsd 400.1312, calcd for $C_{26}H_{24}S_2$ 400.1319.

Cyclophane 11 was prepared from 1,4-bis(mercaptomethyl)benzene and the ditosylate of 1,3-bis(2-hydroxyethyl)naphthalene by an analogous procedure. The product was isolated by SiO_2 column chromatography, eluting with 3% ethyl acetate in hexanes to afford the desired cyclophane as a white, crystalline solid in 14% yield: mp 129.5–130.0 °C (recryst from benzene/hexanes); ^{1}H NMR ($CDCl_3$) δ 7.85 (m, 1H), 7.68 (m, 1H), 7.37 (m, 2H), 7.32 (s, 1H), 7.25 (ABq, J = 7.75 Hz, 4H), 6.09 (s, 1H), 3.86 (s, 2H), 3.79 (s, 2H), 3.12 (t, J = 6.75 Hz, 2H), 2.89 (t, J = 6.75 Hz, 2H), 2.70 (t, J = 6.75 Hz), 2.56 (t, J = 6.75 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 137.4, 136.9, 136.2, 136.1, 133.4, 130.6, 130.0, 129.6, 129.0, 128.2, 125.5, 125.4, 125.3, 125.1, 123.1, 36.5, 36.1, 35.7, 30.9, 29.8, 28.9; EI MS *m/z* obsd 350.1166, calcd for $C_{22}H_{22}S_2$ 350.1163.

1,3-Bis[(butylthio)ethyl]benzene (12). To a degassed solution of ethoxide in ethanol (prepared by dissolving 92 mg (4 mmol) of Na in ethanol) was added 0.17 g (1.9 mmol) of butanethiol and a solution 0.474 g (1 mmol) of the ditosylate of 1,3-bis(hydroxyethyl)benzene in 5 mL of ethanol. The solution was allowed to stir for 42 h and acidified to pH 2 with 6 M HCl (aq), and 25 mL of H_2O was added. The cloudy, white solution was extracted 3 times with 50 mL portions of CH_2Cl_2. The combined extracts were dried over $MgSO_4$ and concentrated to give 0.41 g of a colorless oil. The crude product was purified by SiO_2 column chromatography, eluting with 1% ethyl acetate in hexanes to afford 0.14 g (45%) of the desired compound as a clear, colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.23 (m, 1H), 7.06 (dd, J = 7, 1.5 Hz, 2H), 7.05 (s, 1H), 2.8 (m, 8H), 2.54 (t, J = 7.4 Hz, 4 H), 1.5 (m, 8H), 0.91 (t, J = 7 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 140.7, 128.5, 128.4, 126.2, 33.5, 31.8, 31.6, 21.9, 13.6; EI MS *m/z* obsd 310.1777, calcd for $C_{18}H_{30}S_2$ 310.1789. Anal. Calcd for $C_{18}H_{30}S_2$: C, 69.61; H, 9.74. Found: C, 69.76; H, 9.83.

1,3-Bis[(butylthio)ethyl]naphthalene (13) was prepared in an analogous manner from the ditosylate of 1,3-bis(2-hydroxyethyl)naphthalene. Because of the insolubility of the ditosylate in ethanol, this compound was dissolved in 2.5 mL of DMF prior to addition. The crude product was purified by SiO_2 column chromatography, eluting with 1% ethyl acetate in hexanes to afford 50 mg (56% yield) of a clear, colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.97 (m, 1H), 7.80 (m, 2H), 7.54 (s, 1H), 7.46 (m, 2H), 7.22 (d, J = 1.8 Hz, 1H), 3.31 (t, J = 7.9 Hz, 2H), 3.01 (m, 2H), 2.85 (m, 4H), 2.57 (m, 4H), 1.45 (m, 8H), 0.91 (t, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 137.8, 136.9, 134.1, 130.3, 128.4, 127.6, 125.8, 125.7, 125.5, 123.3, 36.4, 33.7, 33.6, 33.5, 32.9, 32.0, 31.8, 31.7, 22.0, 13.7; EI MS *m/z* 360.1921, calcd for $C_{22}H_{32}S_2$ 360.1945. Anal. Calcd for $C_{22}H_{32}S_2$: C, 73.28; H, 8.94. Found: C, 73.00; H, 9.19.

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Supplementary Material Available: Copies ^{1}H NMR spectra for cyclophanes **6–11** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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