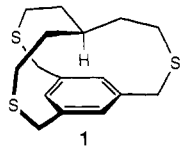
Small, Strained Cyclophanes with Methine Hydrogens Projected toward the Centers of Aromatic Rings

Robert A. Pascal, Jr.,* Charles G. Winans, and Donna Van Engen

Contribution from the Department of Chemistry, Princeton University, Princeton, New Jersey 08544. *Received September 8, 1988*

Abstract: The syntheses of 2,8,17-trithia-*in*-[3^{5,12}][9]metacyclophane, 2,7,16-trithia-*in*-[3^{5,11}][8]metacyclophane, and 2,6,15-trithia-*in*-[3^{4,10}][7]metacyclophane are described. Due to the extreme proximity of the apical methine hydrogen atoms and the centers of the aromatic rings, the compounds display very high field ^{1}H NMR resonances and very high frequency IR C-H stretching bands. X-ray crystallographic analyses of the latter two compounds reveal hydrogen-to-ring distances of only 1.81 and 1.69 Å, respectively. The experimentally determined geometries are contrasted with structures generated by molecular mechanics and semiempirical molecular orbital calculations.

We recently demonstrated that condensation of tris(2-bromoethyl)methane and 1,3,5-tris(mercaptomethyl)benzene yields the unusual macrocycle 2,8,17-trithia-*in*-[4^{5,12}][9]metacyclophane (**1**),[1]



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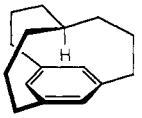

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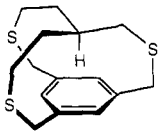

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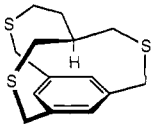

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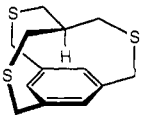

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and we unambiguously established the *in* geometry by X-ray crystallographic analysis of the corresponding trisulfone.[2] Thermal extrusion of sulfur dioxide from the latter material gives the exceptionally congested *in*-[3^{4,10}][7]metacyclophane (**2**), which exhibits a variety of unusual spectroscopic properties due to the extreme proximity of the *in*-methine hydrogen and the aromatic ring.[2] Unfortunately, we have been unable to obtain satisfactory crystals of compound **2** for structural work, and studies of the reactivity of **2** have been hampered by its rather tedious and low-yielding synthesis. We therefore sought to prepare a comparably congested cyclophane by a simpler method.

Molecular mechanics calculations [MM2(85)[3]] indicate that the steric energy of the *in* isomer of **1** is ca. 7 kcal/mol lower than that of the *out* isomer. Perhaps surprisingly, similar calculations indicate that *in* geometries should also be preferred for the increasingly strained macrocycles 2,8,17-trithia[3^{5,12}][9]metacyclophane (**3**), 2,7,16-trithia[3^{5,11}][8]metacyclophane (**4**), and 2,6,15-trithia[3^{4,10}][7]metacyclophane (**5**), in which one, two, and three methylene groups have beem removed, respectively, from **1**.

Compounds **3–5** are potentially preparable by condensation of 1,3,5-tris(mercaptomethyl)benzene with suitable trihaloalkanes, and it is important to note that the product stereochemistries are determined in the third and final ring closure, not before. To the extent that the *in* and *out* transition states for this step resemble the two possible product isomers, the calculated differences in steric energy between these isomers should be predictors of the product distribution—if macrocyclization occurs at all. In this paper we report the successful syntheses of cyclophanes **3–5**, their spectroscopic properties, the X-ray crystal structures of **4** and **5**, and a brief comparison of the experimentally determined structures with geometries obtained from molecular mechanics and semiempirical molecular orbital calculations.

Table I. Comparison of Selected Spectroscopic Data for Cyclophanes **1–5**

compd	UV λ_{max}, nm[a]	^{1}H NMR $\delta_{in\text{-}H}$[b]	IR $\nu_{in\text{-}CH}$, cm^{-1}[c]
1	256 (sh)	−1.68[d]	<3100
3	260 (sh)	−1.94	<3100
4	260	−2.43	3147
5	268	−2.84	3260
2	286[e]	−4.03[e]	3325[e]

[a] Recorded in *n*-heptane. [b] Recorded in $CDCl_3$ at 25 °C. [c] Recorded in KBr pellet (except for **2**, which was in CCl_4 solution). [d] Reference 1. [e] Reference 2.

Results and Discussion

Syntheses of Cyclophanes. The cyclophanes **3–5** were prepared by one-step cyclizations of 1,3,5-tris(mercaptomethyl)benzene with the appropriate tribromoalkanes. Mixtures (1:1) of the starting materials were used at high dilution (4–6 mM); the reactions were conducted in refluxing mixtures of ethanol and benzene, and potassium hydroxide was employed as the base. The yields were low and variable, ranging from 1% to 15%, but the isolation of pure products from the reaction mixtures was quite simple, since most of the byproducts of the reactions were polymeric. The reactions were not optimized, and even though essentially identical conditions were used for all of the cyclizations, there was no obvious correlation of yield with ring size: compounds **1** and **4** have been prepared in yields as high as 15%, but the yields for **3** and **5** did not exceed 4%.

We find it remarkable that these cyclophanes are so easily synthesized. The calculated steric energies for these compounds [MM2(85)] are as follows: **1**, 19.8 kcal/mol; **3**, 24.6; **4**, 28.6; **5**, 37.4. The strain rises significantly with each methylene group removed, but the macrocyclization reactions proceed without difficulty. The immediate synthetic precursors of compound **5**, tris(mercaptomethyl)benzene and tris(bromomethyl)methane, can each be prepared from commercially available starting materials (mesitylene and triethyl methanetricarboxylate) in two steps. Thus only five relatively simple synthetic operations are required to obtain even the singular cyclophane **5**.

Spurred on by these successes, we attempted to remove yet another carbon from one of the bridging chains. However, our attempts to condense 1,3,5-tris(mercaptomethyl)benzene with 1,2,3-tribromopropane yielded no products with very high field ^{1}H NMR resonances. The calculated steric energy for the desired product (an *in*-[2^{4,10}][7]metacyclophane) is 58.2 kcal/mol, much higher than the others in the series, so the failure of this reaction was not surprising. Furthermore, the calculated steric energy for the *out* isomer in this case is 58.8 kcal/mol, so it is by no means clear that the *in* isomer will be preferred. [In the case of compound **5**, the MM2(85) prediction that the *in* isomer is the more stable is a strong one—the steric energies for **5** and its *out* isomer are 37.4 and 48.2 kcal/mol, respectively.]

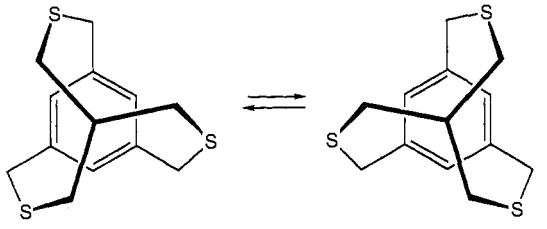
(1) Pascal, R. A., Jr.; Grossman, R. B. *J. Org. Chem.* **1987**, *52*, 4616.
(2) Pascal, R. A., Jr.; Grossman, R. B.; Van Engen, D. *J. Am. Chem. Soc.* **1987**, *109*, 6878–6880.
(3) Allinger, N. L. *QCPE* MM2(85), 1986.

0002-7863/89/1511-3007$01.50/0

Spectroscopic Properties. Table I lists selected spectroscopic data for cyclophanes **3–5** and compares these data with those reported previously for compounds **1** and **2**. As expected, all compounds show very high field ^{1}H NMR resonances due to the *in*-methine hydrogens, with the most extreme chemical shifts exhibited by the smallest cyclophanes. The proton resonance of the *in*-methine in **5** (δ −2.84) is 4.90 ppm upfield from the methine resonance in the acyclic model compound tris[(methylthio)-methyl]methane (δ 2.06). From Johnson and Bovey's table which estimates the magnitude of ring current effects on protons in various positions with respect to benzene rings,[4] the distance from the *in*-hydrogen to the center of the benzene ring was predicted to be approximately 1.96 Å. As will be seen, the hydrogen is actually much nearer to the ring.

Increasing bathochromic shifts in the UV spectra of these compounds are also noted, an effect believed to be associated with the bending of the aromatic rings, and which is widely observed in small meta- and paracyclophanes.[5] The absorption bands at 260–268 nm for compounds **3–5** are comparable to those observed in [8]- (266 nm)[6a] and [7]metacyclophane (273 nm),[6b] but they are not nearly as shifted as those of [6]- (280 nm)[6b] and [5]-metacyclophane (306.5 nm).[7] Most unusual, however, are the extremely large ν_{CH} frequency enhancements observed in the IR spectra of compounds **2**, **4**, and **5** due to severe steric compression of the *in*-methine groups. The hypsochromic shifts of 300–400 cm^{-1} (relative to the ν_{CH} of normal methines) seen in compounds **2** and **5** are by far the largest ever observed for aliphatic carbon–hydrogen bonds.[8]

One other spectroscopic characteristic deserves mention. The ^{1}H NMR of compound **5** at room temperature contains several broadened methylene resonances, a phenomenon which was previously also observed for compound **2**.[2] In solution, **5** should exist predominantly in a conformation with C_3 symmetry, and the broadened resonances are a reflection of the relatively slow enantiomerization of the molecule (illustrated below) on the NMR



time scale. At −68 °C, the rate of enantiomerization is greatly slowed and the broadened lines are resolved into two pairs of diastereotopic methylene resonances. In toluene-d_8, the diastereotopic protons of the methylenes adjacent to the apical methine are separated by 1.7 ppm. In a variable-temperature NMR experiment conducted on a 250-MHz spectrometer (see the Experimental Section), these resonances were observed to coalesce at 320 K; therefore, $\Delta G_c^{\ddagger}$ for the exchange process is approximately 14.4 kcal/mol, just slightly lower than the 14.8 kcal/mol barrier previously observed for the corresponding enantiomerization of cyclophane **2**.[2]

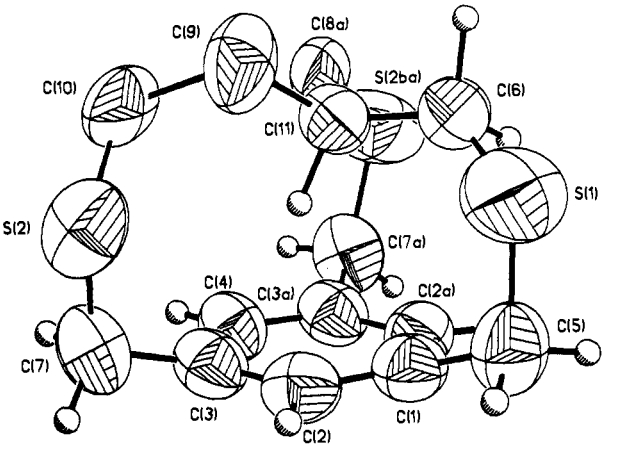


Figure 1. X-ray structure of compound **4**.

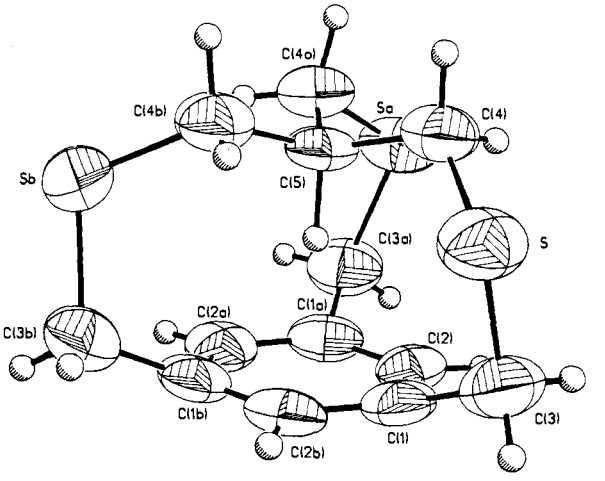


Figure 2. X-ray structure of compound **5**.

X-ray Crystal Structures of 2,7,16-Trithia[3^{5,11}][8]metacyclophane (4) and 2,6,15-Trithia[3^{4,10}][7]metacyclophane (5). The primary motivation for our syntheses of compounds **3–5** was to obtain detailed structural information for at least one example of a very strained *in*-cyclophane. Our past efforts to crystallize compound **2** were fruitless, but in the present work we were fortunate enough to obtain single crystals of cyclophanes **4** and **5** suitable for X-ray crystallographic analysis.

Compound **4** crystallized in the orthorhombic space group *Pnam* (standard: *Pnma*). The molecule resides on the mirror plane and is severely disordered across it (see the Experimental Section). The gross structure of the cyclophane is clearly established by the crystallographic data, and it is shown in Figure 1. However, due the high degree of disorder, not all of the hydrogens on the bridging arms were located and the accuracy of the most interesting structural parameters is limited. Fortunately, the *in*-methine hydrogen lies on the mirror plane and was located; it is only 1.81 Å from the mean plane of the aromatic ring (henceforth, this distance will be designated d_{ring-H}). The apical methine carbon is disordered across the mirror plane, and it is found to be 2.87 Å from the aromatic ring (d_{ring-C}). The d_{ring-H} observed in compound **4** is exceptionally small; prior to the solution of this structure, the closest crystallographically documented approach of a hydrogen to an aromatic ring was 2.16 Å in Boekelheide's [2,2]metaparacyclophane-1,9-diene[9a,b] and in one of the cappe-

(4) (a) Johnson, C. E.; Bovey, F. A. *J. Chem. Phys.* **1958**, *29*, 1012–1014. (b) Johnson and Bovey's "Table of Predicted Values of Shielding Contributions from Ring Currents in Aromatic Hydrocarbons" is contained in Appendix B of Emsley, J. W.; Feeney, J.; Sutcliffe, L. H. *High Resolution Nuclear Magnetic Resonance Spectroscopy*; Pergamon Press: New York, 1965.

(5) Rosenfeld, S. M.; Cho, K. A. *[n]Cyclophanes in Cyclophanes*; Keehn, P. M.; Rosenfeld, S. M., Eds.; Academic Press: New York, 1983; Vol. 1, p 339 and references cited therein.

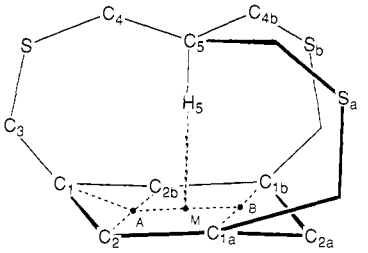
(6) (a) Hubert, A. J.; Dale, J. *J. Chem. Soc.* **1963**, 86–93. (b) Hirano, S.; Hara, H.; Hiyama, T.; Fujita, S.; Nozaki, H. *Tetrahedron* **1975**, *31*, 2219–2227.

(7) van Straten, J. W.; de Wolf, W. H.; Bickelhaupt, F. *Tetrahedron Lett.* **1977**, 4667–4670.

(8) Similar but smaller frequency enhancements have been observed for C–H stretches in many fused norbornane derivatives,[a–c] hexaisopropylbenzene,[d] and secododecahedrane.[e] (a) DeVries, L.; Ryason, P. R. *J. Org. Chem.* **1961**, *26*, 621–623. (b) Kivelson, D.; Winstein, S.; Bruck, P.; Hansen, R. L. *J. Am. Chem. Soc.* **1961**, *83*, 2338–2944. (c) Ermer, O.; Mason, S. A.; Anet, F. A. L.; Miura, S. S. *J. Am. Chem. Soc.* **1985**, *107*, 2330–2334. (d) Arnett, E. M.; Bollinger, J. M. *J. Am. Chem. Soc.* **1964**, *86*, 4729–4731. (e) Paquette, L. A.; Ternansky, R. J.; Balogh, D. W.; Kentgen, G. *J. Am. Chem. Soc.* **1983**, *105*, 5446–5450.

(9) (a) Boekelheide, V.; Anderson, P. H.; Hylton, T. A. *J. Am. Chem. Soc.* **1974**, *96*, 1558–1564. (b) Hanson, A. W. *Acta Crystallogr., Sect. B* **1971**, *B27*, 197–202. (c) Vinod, T. K.; Hart, H. *J. Am. Chem. Soc.* **1988**, *110*, 6574–6575.

Table II. Comparison of the Experimentally Determined Geometry of Compound **5** with Structures Calculated by Various Methods



parameter	X-ray data	MMPI	MM2(85)	MNDO
H_5-M (Å)[a]	1.69	1.937	1.815	1.911
C_5-M (Å)[a]	2.78	3.005	2.894	3.011
C_4-C_5-H_5 (deg)	105.4	101.0	102.4	103.2
C_4-C_5-C_{4b} (deg)	113.2	116.5	115.5	114.9
S-C_4-C_5 (deg)	116.1	116.2	114.5	116.4
C_3-S-C_4 (deg)	106.3	104.9	105.6	115.8
C_1-C_3-S (deg)	110.2	112.0	109.8	111.7
C_3-C_1-A (deg)[b]	160.2	163.1	163.1	163.3
C_1-A-B (deg)[b]	175.6	166.5	170.8	167.4

[a] Point M is the centroid of the six aromatic ring carbons. [b] Points A and B are the centroids of carbons 2 and 2b and carbons 1a and 1b, respectively.

dophanes recently prepared by Vinod and Hart.[9c] Furthermore, both d_{ring-H} and d_{ring-C} are significantly shorter than the corresponding distances in the structure predicted for **4** by using MM2(85)—1.98 Å and 3.02 Å, respectively. Even allowing for possible inaccuracies in the crystal structure of **4**, the *in*-hydrogen must be considerably closer to the aromatic ring than calculated by the molecular mechanics program.

Cyclophane **5** crystallized in the trigonal space group *R3c*, and the X-ray analysis yielded an excellent structure, which is illustrated in Figure 2. The molecule has crystallographic C_3 symmetry, and no disorder was observed. The critical distances d_{ring-H} and d_{ring-C} were found to be only 1.69 and 2.78 Å. A number of bond angle distortions are evident in this structure. The apical methine group is significantly "flattened" from an ideal tetrahedral geometry: the angle C_4-C_5-C_{4b} is expanded to 113.2° from the normal value of 109.5°, while C_4-C_5-H_5 is contracted to 105.4°. Two of the bond angles in the bridging arms are substantially enlarged as well: angles S-C_4-C_5 and C_3-S-C_4 are 116.1° and 106.3°, respectively, much higher than the usual 109° and 96°. In addition, the aromatic ring adopts a shallow chair conformation, but the bond angles in the aromatic ring of 121.5° (C_2-C_1-C_{2b}) and 118.4° (C_1-C_2-C_{1a}) are not far from the standard value. However, perhaps the most striking aspect of the structure is how *ordinary* the molecule appears on casual inspection. Given that the *in*-hydrogen is fully 0.47 Å closer to the aromatic ring than ever observed previously and the IR spectrum of the compound exhibits a ν_{CH} of 3260 cm^{-1} (suggesting extreme steric compression), the observed angular distortions must be considered relatively modest.

Comparison of Experimental and Computationally Derived Structures of Cyclophane 5. The experimentally determined structure of compound **5** is substantially different from structures obtained by use of commonly employed types of molecular mechanics calculations and semiempirical molecular orbital calculations. We calculated the geometry of compound **5** by using the programs MMPI,[10] MM2(85),[3] and MNDO.[11] The salient features of the X-ray structure and the computationally derived structures are summarized in Table II and the attendant drawing. Meaningful comparison of the various geometrical parameters is simplified by the fact that all of the structures have C_3 symmetry. The various computer programs invariably overestimate (a) d_{ring-H} and d_{ring-C} (the Table II distances H_5-M and C_5-M), (b) the degree of distortion of the apical methine group from an ideal tetrahedral geometry (as judged by angles C_4-C_5-C_{4b} and C_4-C_5-H_5), and (c) the degree of deformation of the aromatic ring from planarity into a chair conformation (as judged by the angle C_1-A-B). The experimental bond angles in the bridging arms are fairly well reproduced by the calculations, but interestingly, all of the programs slightly underestimate the amount out-of-plane bending at the points of attachment of the bridging arms (as judged by angle C_3-C_1-A). In most respects the MM2(85) structure is superior to the others, and perhaps a slight softening of the parameters which determine the hydrogen–carbon nonbonded repulsive force would yield an even better structure.

Conclusion

The results described herein are testimony to the utility of molecular mechanics calculations. It is not possible to build CPK models of cyclophanes **3–5**, and most chemists (in our experience) do not ordinarily consider the possibility that *in* geometries would be preferred in such compounds. However, MM2(85) clearly predicted that *in* geometries should be favored over *out* and that the degree of strain in these molecules should not be inordinately high. With cyclophanes **3–5** now easily prepared in reasonable quantities, the study of the reactivity of these unusual, crowded molecules and their derivatives may begin.

Experimental Section

1,3,5-Tris(mercaptomethyl)benzene,[12] 3-(bromomethyl)-1,5-dibromopentane,[13] 2-(hydroxymethyl)-1,4-butanediol,[14] and tris(hydroxymethyl)methane[15] were prepared as described previously.

2,8,17-Trithia[3^{5,12}][9]metacyclophane (3). 3-(Bromomethyl)-1,5-dibromopentane (2.82 g, 8.74 mmol) and 1,3,5-tris(mercaptomethyl)benzene (1.87 g, 8.66 mmol) were dissolved in benzene (125 mL). Potassium hydroxide (2.28 g, 40.71 mmol) was dissolved in ethanol (125 mL). The two solutions were saturated with argon and simultaneously added dropwise (~1 drop/s) to refluxing ethanol (1200 mL) which had been previously saturated with argon. The solution was refluxed overnight under an argon atmosphere. When heat was removed from the product solution in preparation for solvent removal, a white solid immediately began to precipitate on the walls of the reaction flask. The solvent was evaporated under reduced pressure, precipitating a yellow and white solid. Carbon tetrachloride (250 mL) was added and heated over a Bunsen burner flame until slight reflux occurred with swirling in order to dissolve selectively any monomeric cyclophane products present. The hot solution was filtered through glass wool to remove insoluble particles of unidentified, presumably polymeric solid. This extraction procedure was conducted several times. The extracts were combined, and the solvent was evaporated under reduced pressure to yield a brown residue (1.17 g). The crude product mixture was purified by passage through a short column of silica gel (eluting solvent: toluene) to remove any soluble, polymeric byproducts. The first product-containing fraction was concentrated under reduced pressure to yield **3** as a pale yellow solid (0.040 g, 0.166 mmol, 1.9% yield): mp 218–222 °C (rapid heating); ^{1}H NMR ($CDCl_3$, 300 MHz) δ −1.94 (m, 1 H, *in*-methine), 1.05 (m, 2 H, long bridge CH_2), 1.32 (m, 2 H, long bridge CH_2), 2.16 (d, 2 H, J = 7.5 Hz, short bridge aliphatic CH_2S), 2.40 (dd, 2 H, J = 14 Hz, 10.5 Hz, long bridge aliphatic CH_2S), 2.53 (dd, 2 H, J = 14 Hz, 6.0 Hz, long bridge aliphatic CH_2S), 3.61 (d, 2 H, J = 13.5 Hz, long bridge benzylic CH_2), 3.70 (d, 2 H, J = 13.5 Hz, long bridge benzylic CH_2), 3.75 (s, 2 H, short bridge benzylic CH_2), 7.18 (s, 2 H, aryl H), 7.24 (s, 1 H, aryl H); IR (KBr) ν_{max} 3060, 3019, 3002, 2920, 2889, 2852, 2829, 1591, 1450, 1426, 1413, 1282, 1220, 1158, 898, 867, 723 cm^{-1}; UV (heptane) λ_{max} 206, 222 (sh), 260 (sh) nm; MS m/z 296 (M^+, 100), 263 (M − SH, 15), 162 (14), 151 (16), 150 (67), 149 (23), 148 (26), 147 (36), 119 (48), 118 (72), 117 (59), 115 (59), 113 (23), 111 (19), 103 (14), 91 (26); exact mass 296.0735, calcd for $C_{15}H_{20}S_3$ 296.0727.

2-(Bromomethyl)-1,4-dibromobutane. Sulfuric acid (27 mL), 48% HBr (100 mL), and 2-(hydroxymethyl)-1,4-butanediol (8.54 g, 71.2 mmol) were mixed together, and the solution was refluxed overnight. The black reaction mixture was extracted with hexanes, and the extract was washed several times with water. After drying over anhydrous

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(11) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899–4907 and 4907–4917.
(12) Nakazaki, M.; Yamamoto, K.; Miura, Y. *J. Org. Chem.* **1978**, *43*, 1041–1044.
(13) Prelog, V.; Cerkovnikov, E. *Justus Liebigs Ann. Chem.* **1936**, *525*, 292–296.
(14) Harnden, M. R.; Jarvest, R. L. *Tetrahedron Lett.* **1985**, *26*, 4265–4268.
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$MgSO_4$, the solution was concentrated to yield 2-(bromomethyl)-1,4-dibromobutane (8.54 g, 27.6 mmol, 39% yield): ^1H NMR ($CDCl_3$, 300 MHz) δ 2.03 (q, 2 H, J = 7 Hz, 3-CH_2), 2.34 (m, 1 H, methine), 3.47 (t, 2 H, J = 7 Hz, 4-CH_2Br), 3.50 (dd, 2 H, J = 11, 6.5 Hz, 1,1'-CH_2Br), 3.63 (dd, 2 H, J = 11, 3.5 Hz, 1,1'-CH_2Br); MS m/z 229 (M - Br [$C_5H_9{}^{79}Br^{81}Br^+$], 57), 147 (M - Br - HBr, 100); exact mass (M - Br ion) 228.9057, calcd for $C_5H_9{}^{79}Br^{81}Br$ 228.9051.

2,7,16-Trithia[3^{5,11}][8]metacyclophane (4). 2-(Bromomethyl)-1,4-dibromobutane (1.79 g, 5.80 mmol) and 1,3,5-tris(mercaptomethyl)benzene (1.26 g, 5.80 mmol) were dissolved in benzene (100 mL). Potassium hydroxide (1.46 g, 26 mmol) was dissolved in ethanol (100 mL). These two solutions were saturated with argon and simultaneously added dropwise (~1 drop/s) to refluxing ethanol (700 mL) which had previously been saturated with argon. The solution was refluxed overnight under an argon atmosphere. The solvent was then evaporated under reduced pressure leaving a light yellow precipitate. Carbon tetrachloride (250 mL) was added and heated with swirling over a Bunsen burner flame until slight reflux began in order to dissolve selectively any desired, monomeric cyclophane products present. The hot solution was filtered through glass wool to remove insoluble particles of unidentified, presumably polymeric byproducts. This extraction was conducted several times. The extracts were then combined, and the solvent was evaporated under reduced pressure to yield a brown residue. Additional byproducts were removed by passing the crude product through a short column of silica gel (eluting solvent: toluene). The solvent from the first product-containing fraction was evaporated under reduced pressure to yield white crystals of **4** (0.24 g, 0.851 mmol, 14.7% yield). Single crystals for X-ray analysis were obtained from a methylene chloride–methanol solution; mp >400 °C (but darkens above 250 °C). **4**: ^1H NMR ($CDCl_3$, 250 MHz) δ -2.43 (m, 1 H, *in*-methine), 1.17 (m, 2 H, long bridge CH_2), 2.27 (dd, 2 H, J = 15 Hz, 8 Hz, short bridge aliphatic CH_2S), 2.35 (dd, 2 H, J = 15 Hz, 7.5 Hz, short bridge aliphatic CH_2S), 2.58 (m, 2 H, long bridge aliphatic CH_2S), 3.59 (s, 2 H, long bridge benzylic CH_2), 3.72 (d, 2 H, J = 12.5 Hz, short bridge benzylic CH_2), 3.82 (d, 2 H, J = 12.5 Hz, short bridge benzylic CH_2), 7.12 (s, 2 H, aryl H), 7.33 (s, 1 H, aryl H); IR (KBr) ν_{max} 3147, 3083, 3060, 3026, 3002, 2920, 2851, 1597, 1498, 1458, 1432, 1420, 1286, 1226, 1164, 882, 869, 761, 722, 704 cm^{-1}; UV (heptane) λ_{max} 210, 260 nm; MS m/z 282 (M^+, 100), 236 (M - CH_2S, 17), 162 (15), 148 (13), 147 (12), 119 (33), 118 (48), 117 (32), 115 (28), 99 (17), 91 (14); exact mass 282.0573, calcd for $C_{14}H_{18}S_3$ 282.0571.

X-ray Crystallographic Analysis of Cyclophane 4. A single crystal of **4** measuring 0.28 mm × 0.42 mm × 0.50 mm was used for X-ray measurements. Crystal data: $C_{14}H_{18}S_3$; orthorhombic, space group *Pnam*; a = 8.304 (3) Å, b = 12.603 (4) Å, and c = 13.299 (4) Å, V = 1391.9 (8) Å^3, Z = 4, D_{calcd} = 1.35 g/cm^3. Intensity measurements were made with $3° \le 2\theta \le 114°$ by using graphite monochromated Cu Kα radiation (λ = 1.541 78 Å) at room temperature on a Nicolet R3m diffractometer. A total of 982 unique reflections were measured, and after Lorentz, polarization, and empirical absorption corrections were applied, 898 were considered to be observed [$|F_o| > 3\sigma(F_o)$]. The structure was solved by direct methods in space group *Pna*2 using the SHELXTL software. It became apparent in preliminary refinement that the molecule was severely disordered. It was determined that the correct space group was *Pnam*, and all further refinement was conducted in this group. The C(1) and C(4) atoms of the phenyl ring (see Figure 1) are located on the mirror plane as are C(5) and S(1)—two atoms of one of the three-atom bridges. The third atom C(6) of this bridge is disordered across the mirror plane. The other three-atom bridge [C(7)-S(2)-C(8)] and the four-atom bridge [C(7)-S(2)-C(10)-C(9)] are completely disordered across the mirror plane. Two positions were identified for S(2) and C(10) of the four-atom bridge. Refinement converged (shift/error ≤ 0.15) at R = 0.084, R_w = 0.119.

Tris(bromomethyl)methane. Sulfuric acid (20 mL), 48% HBr (75 mL), and tris(hydroxymethyl)methane (3.50 g, 33 mmol) were mixed together, and the solution was refluxed overnight. The black reaction mixture was extracted with hexanes, and the extract was washed several times with water. After drying over anhydrous $MgSO_4$, the solution was concentrated to yield tris(bromomethyl)methane (2.50 g, 8.48 mmol, 26% yield): ^1H NMR ($CDCl_3$, 250 MHz) δ 2.42 (septet, J = 6 Hz, 1 H, methine), 3.58 (d, J = 6 Hz, 6 H, CH_2Br); MS m/z 296 (M^+ [$^{79}Br^{81}Br_2$], 8), 215 (M - Br, 100), 133 (M - Br - HBr, 46); exact mass 295.8058, calcd for $C_4H_7{}^{79}Br^{81}Br_2$ 295.8057.

2,6,15-Trithia[3^{4,10}][7]metacyclophane (5). Tris(bromomethyl)methane (2.05 g, 6.95 mmol) and 1,3,5-tris(mercaptomethyl)benzene (1.43 g, 6.64 mmol) were dissolved in benzene (100 mL). Potassium hydroxide (1.67 g, 30 mmol) was dissolved in ethanol (100 mL). The two solutions were saturated with argon and simultaneously added dropwise (~1 drop/s) into refluxing ethanol (1500 mL) which had been previously saturated with argon. The solution was refluxed overnight under an argon atmosphere. The solvent was then evaporated under reduced pressure. Carbon tetrachloride (250 mL) was added to the resulting precipitate and heated over a Bunsen burner until slight reflux commenced in order to dissolve selectively any monomeric cyclophane products. The hot carbon tetrachloride solution was filtered through glass wool to remove insoluble particles of unidentified, presumably polymeric byproducts. This extraction procedure was conducted three times. The extracts were combined, and the solvent was evaporated under reduced pressure to yield a dark orange residue and a white solid (1.27 g). These were dissolved in a minimal amount of hexanes and passed through a short column of silica gel in order to remove any remaining soluble byproducts. The polarity of the eluting solvent was progressively increased by successive 100 mL elutions with 100:0, 75:25, 50:50, 25:75, 0:100 hexanes–toluene solutions. The solvent was evaporated under reduced pressure from the first product-containing fraction to yield **5** as a white solid (0.050 g, 0.187 mmol, 2.8% yield). Single crystals for X-ray analysis were obtained from a methylene chloride–methanol solution; mp >400 °C (but darkens above 250 °C). **5**: ^1H NMR ($CDCl_3$, 250 MHz, 25 °C) δ -2.84 (septet, 1 H, J = 7.5 Hz, *in*-methine), 1.7 (br, 3 H, aliphatic CH_2), 3.1 (br, 3 H, aliphatic CH_2), 3.77 (s, 6 H, benzylic CH_2), 7.18 (s, 3 H, aryl); ^1H NMR (toluene-d_8, 250 MHz, -68 °C) δ -3.15 (m, 1 H), 1.20 (dd, J = 14, 12 Hz, 3 H), 2.90 (dd, J = 14, 2 Hz, 3 H), 3.21 (d, J = 12 Hz, 3 H), 3.27 (d, J = 12 Hz, 3 H), 6.72 (s, 3 H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 67.9 MHz) δ 27.3 (*in*-methine), 33.0 (aliphatic CH_2), 39.1 (benzylic CH_2), 134.7 (aromatic methine), 143.7 (aromatic bridgehead); IR (KBr) ν_{max} 3260, 3086, 3062, 3027, 3005, 2920, 2852, 1635, 1602, 1493, 1453, 1407, 1235, 1158, 869. 756, 716, 698 cm^{-1}; UV (heptane) λ_{max} 215, 268 nm; MS m/z 268 (M^+, 100), 235 (M - SH, 5), 222 (M - CH_2S, 5), 203 (5), 180 (8), 161 (14), 150 (11), 148 (13), 147 (12), 118 (53), 117 (35), 115 (21), 91 (16); exact mass 268.0409, calcd for $C_{13}H_{16}S_3$ 268.0414.

Variable-Temperature NMR Measurements on Cyclophane 5. Compound **5** was dissolved in toluene-d_8 and 250-MHz ^1H NMR spectra were recorded at a variety of temperatures from 205 to 375 K. Temperatures were measured by means of a thermocouple mounted in the NMR spectrometer probe, and the sample was allowed to equilibrate at each of the chosen temperatures for 15 min prior to the recording of the spectrum. Coalescence of the diastereotopic methylene resonances of compound **5** was observed at approximately 320 K. The value of k_c (947 s^{-1}) was calculated by using the equation appropriate for a coupled AB system ($\Delta\nu_{AB}$ = 426 Hz, J_{AB} = 14 Hz) with equal populations,[16] and a transmission coefficient of 1 was assumed for the Eyring equation. Thus, $\Delta G_c^{\ddagger}$ for the exchange process is 14.4 kcal/mol.

X-ray Crystallographic Analysis of Cyclophane 5. A single crystal of **5** measuring 0.18 mm × 0.20 mm × 0.32 mm was used for X-ray measurements. Crystal data: $C_{13}H_{16}S_3$; trigonal, space group $R3c$; $a = b$ = 12.558 (3) Å, c = 14.141 (6) Å, V = 1931 (1) Å^3, Z = 4, D_{calcd} = 1.38 g/cm^3. Intensity measurements were made with $3° \le 2\theta \le 114°$ by using graphite-monochromated Cu Kα radiation (λ = 1.541 78 Å) at room temperature on a Nicolet R3m diffractometer. A total of 306 unique reflections were measured, and after Lorentz, polarization, and empirical absorption corrections were applied, 303 were considered to be observed [$|F_o| > 3\sigma(F_o)$]. The structure was solved by direct methods with the SHELXTL software. Refinement converged (shift/error ≤ 0.10) of R = 0.026, R_w = 0.031.

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Supplementary Material Available: Crystallographic data and processing descriptions, final atomic coordinates, bond lengths and angles, anisotropic thermal parameters, and additional drawings for compounds **4** and **5** (15 pages). Ordering information is given on any current masthead page.

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