Synthesis of a Symmetric Octathio Bis(calix[4]arene) Cage Molecule

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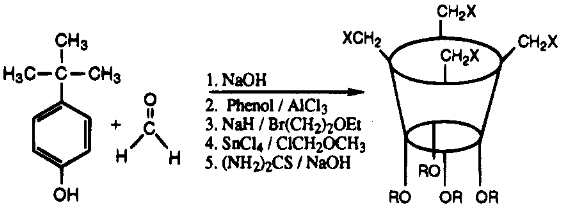
Calixarenes are semimobile cyclic oligimers of para-substituted phenols that may contain four to eight aromatic units. Even though many other sizes of calixarenes can be formed, they are not synthetically viable starting materials due to their isolation in low yields. The rigidified "cone" conformation of calix[4]arenes represents a readily available building block from which a myriad of interesting cage molecules may be constructed. When the upper rims of two calix[4]arene molecules are tethered together, a hollow, hydrophobic, superstructure is formed whose interior dimensions are large enough to encapsulate small- to medium-sized neutral guest molecules. The entrances and exits to and from the interior are defined by the linker groups. Furthermore, the steric nature of the linker groups provide the properties of shape and size selectivity to the host's recognition process. Bohmer et al.[1] and Shinkai et al.[2] have reported the syntheses and characterizations of bis(calix[4]arene) and bis(calix[6]arene) cage molecules, respectively, although in very low yields. Recently, however, Shinkai has published an improved synthesis of a bis(calix[4]arene) which resulted from the joining of two slightly different bowl-shaped precursors via four molecules of ethylene glycol.[3] These compounds are reminiscent of the carcerands and hemicarcerands reported by Cram and co-workers[4] which are based on resorcinol-derived calixarenes, yet may be further functionalized at their opposite lower rims more readily. This is an important difference, since one anticipated goal is the construction of water-soluble cages which will function as unimolecular micelles.

Herein, we wish to report the synthesis, characterization, and preliminary binding properties of a symmetric, octathiobis(calix[4]arene) cage molecule **1**. It is noteworthy that our synthesis differs from the Shinkai method in that the latter produces an unsymmetrical cage while the former results in a highly symmetrical structure possessing D_{4h} symmetry. In the ultimate shell closure reaction, wherein eight covalent C−S bonds are formed, the isolated yield was routinely 25−30%.

Synthesis of the Cone Precursor. The host molecule was obtained by joining two thiomethylated calixarene molecules via a single carbon spacer unit. The tetrathiol **5** was obtained in five steps starting from *para-tert*-butylphenol and formaldehyde using literature procedures (Scheme 1).[5] The initial unprotected, alkylated product obtained from the base-catalyzed condensation was dealkylated using phenol and aluminum trichloride.[6] The four phenolic oxygen atoms on the lower rim of the calixarene were then protected with ethoxyethyl groups to ensure that through the annulus rotation would not occur, thus locking the structure into the cone conformation.[7] Subsequently, the upper rim of the cone was functionalized by reacting the material with chloromethyl ethyl ether in the presence of tin tetrachloride.[2] The chloromethylated compound **4** was then converted to the tetrathiol **5** by reacting it with thiourea followed by basic hydrolysis of the isothiouronium salt.[2]

Scheme 1



Cone Conformation
R = $-CH_2CH_2OCH_2CH_3$

4: X = Cl
5: X = SH

Inter- vs Intramolecular Substitution. When a 50-mL solution that was 0.022 M in **5** and 0.089 M in methylene iodide was added dropwise over a 6-h period to a reaction vessel containing 700 mL of *N,N*-dimethylacetamide (DMA) and 7 g of Cs_2CO_3, the only product obtained after chromatography on silica gel proved to be the bis(calixarene) host **1** resulting from an intermolecular reaction (Scheme 2). Initial attempts using *N,N*-dimethylformamide as the solvent and K_2CO_3 as the base resulted in a mixture of products that was tenuous to separate. However, when the solvent was changed to DMA and the base to cesium carbonate, the crude reaction product was remarkably clean; only one spot was present in the thin layer chromatograph. Also surprising was the fact that none of the "basket handle" calixarene was formed as the result of an intramolecular substitution in which adjacent sulfur atoms within a single calixarene molecule had become bonded together. To test the general applicability of the high dilution method, an analog of the octathio bis(calixarene) cage was synthesized from the tetrabenzyl chloride **4** and 1,2-ethanedithiol in the presence of Cs_2CO_3.[8] Even with this longer linker the host **2** was isolated in 20% yield. It should be noted, however, that this reaction was not as clean as when the methylene linker was employed, as minor amounts of other products were formed. Furthermore, when **5** was reacted with α,α-dibromo-*o*-xylene *only* the basket handle **3** compound was formed.[9] Apparently, when the linker is greater than four or five atoms, the intramolecular pathway predominates over the intermolecular one.

Results and Discussion

As mentioned, the octathiobis(calixarene) cage **1** was isolated in good yield by the high-dilution method.

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(1) Bohmer, V.; Goldman, W.; Vogt, J.; Vicens, J.; Asfari, Z. *Tetrahedron Lett.* **1989**, *30*, 1391.

(2) Arimura, T.; Matsumoto, S.; Teshima, O.; Nagasaki, T.; Shinkai, S. *Tetrahedron Lett.* **1991**, *32*, 5111.

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(4) Bryant, J. A.; Blanda, M. T.; Vincenti, M.; Cram, D. J. *J. Am. Chem. Soc.* **1991**, *113*, 2167. Sherman, J. C.; Knobler, C. B.; Cram, D. J. *Ibid.* **1991**, *113*, 2194. Quan, M. L. C.; Cram, D. J. *Ibid.* **1991**, *113*, 2754.

(5) Gutsche, C. D.; Iqbal, M.; Stewart, D. *J. Org. Chem.* **1986**, *51*, 742.

(6) Gutsche, C. D.; Lin, L.-G. *Tetrahedron* **1986**, *42*, 1633.

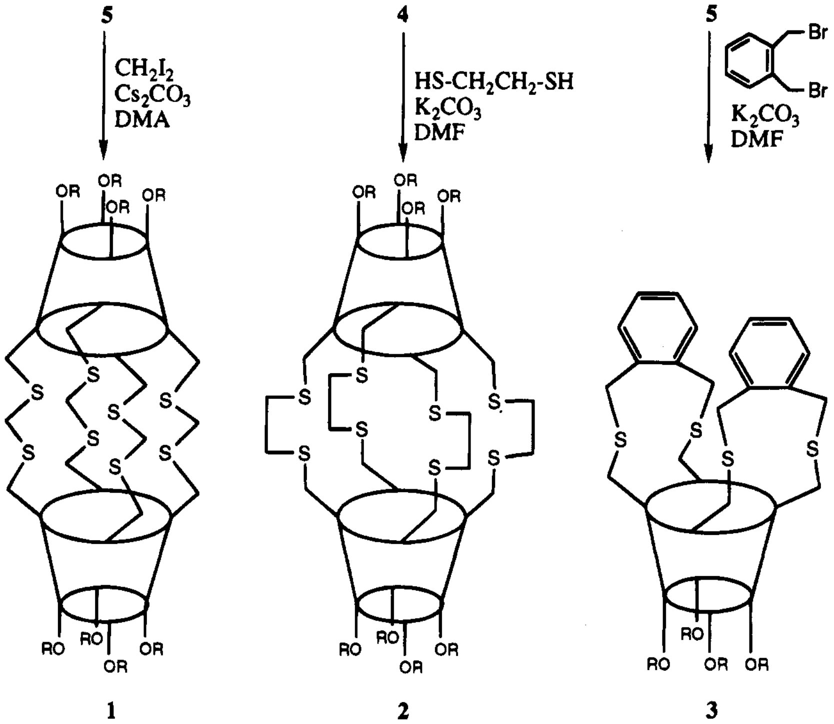
(7) Arduini, A.; Manfredi, G.; Pochini, A.; Sicuri, A. R.; Ungaro, R. *J. Chem. Soc., Chem. Commun.* **1991**, 936.

(8) Blanda, M. T.; Griswold, K. E. Unpublished results.

(9) Blanda, M. T.; Griswold, K. E. Unpublished results.

0022-3263/94/1959-4313$04.50/0

Scheme 2



Furthermore, 1 was found to be in its uncomplexed form, suggesting that if a molecule of solvent (DMA) acted as a templating guest during shell closure, it escaped through the portals formed by the —CSCSC— bridging units. The uncomplexed nature of the host was implicated by the absence of DMA protons in the ^{1}H-NMR spectrum of the host. This notion was further reinforced by the desorptive chemical ionization mass spectrum, which contained a parent ion of $M^+ = 1842$, as well as the C, H, and S elemental analysis; both of which correlated with uncomplexed **1**.

When rotations through the annulus are prevented, the ^{1}H-NMR spectra for symmetrically 1,7,13,19-tetrasubstituted calix[4]arenes are characterized by a distinct pair of doublets for the geminally coupled pseudoaxial and pseudoequatorial hydrogens on methylene carbon atoms 4, 10, 16, and 20.[10] For example, in the ^{1}H-NMR spectrum of **5** the pseudoequatorial and pseudoaxial hydrogens appeared as cleanly resolved doublets with chemical shifts centered at 4.45 and 3.08 ppm, respectively (J = 13.6 Hz). However, this was not the case in the room-temperature ^{1}H-NMR spectrum of **1** wherein an eight-line pattern was observed instead of the anticipated four-line pattern. The doublet of doublets for the equatorial hydrogens was centered at $\delta = 4.48$ and 4.29 while the pair of doublets for the axial hydrogens was located at $\delta = 3.29$ and 3.01. In fact, all the proton resonances were doubled which suggests that the top and bottom of the cage structure are not magnetically equivalent. However, as the sample was heated from room temperature to 85 °C, the eight-line pattern was observed to collapse to a four-line pattern which would be anticipated based on the structure shown in the scheme above. We believe this temperature-dependent process to be associated with conformational changes in the host's structure, since the four $-CH_2SCH_2SCH_2-$ bridging units could permit considerable structural flexibility at the higher temperatures.

Preliminary Binding Studies. The basic binding characteristics of the cage compound were investigated by preparing complexes with a series of substituted aromatic compounds in order to probe the dimensions of the portals and the interior space of the cage. The complexes were prepared by heating approximately 25 mg of the pure empty host in 20 mL of neat solvents which included toluene, ethylbenzene, *p*-xylene, *p*-chlorotoluene, *p*-diethylbenzene, and *p*-methylanisole. In all cases, the solvent volume was reduced under vacuum and methanol was added to precipitate the complex.

The effects of the host on the chemical shifts of the encapsulated guests were most dramatically illustrated in the case of *p*-xylene where the signal for the methyl groups appeared at $\delta = 1.64$ which is 0.76 ppm upfield from their normal position. Unfortunately, identifying the shifted guest signals in the proton spectra of the other complexes was not so unambiguous due to the resolution power of the low-field spectrometer. Nonetheless, complexation of the guests by the host was inferred by performing decomplexation experiments. In these studies the complexes were dissolved in tetrachloroethane-d_2 and heated in an NMR tube at 100 °C for 24 h. When the spectrum was reacquired the presence of the guest was confirmed by the observation of protons signals for uncomplexed guests in their normal positions. Currently, we are investigating in closer detail the rates of decomplexation of the guests at different temperatures in order to calculate the activation barriers for decomplexation.

Experimental Section

Tetrathiol **5** (1 g, 1.12 mmol) and CH_2I_2 (0.36 mL, 4.48 mmol) were dissolved in 50 mL of dry, degassed $(CH_3)_2NCOCH_3$. This solution was drawn into a large syringe and added dropwise over 6 h to a reaction vessel containing 700 mL of $(CH_3)_2NCOCH_3$ and 7 g of Cs_2CO_3 heated to 80 °C. After 24 h, another 50 mL of solution containing 4.5 mmol of CH_2I_2 was added and the

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[10] Gutsche, C. D. The Calixarenes. In *Host Guest Complex Chemistry*; Vogtle, F., Weber, E., Eds.; Springer-Verlag: New York, 1985; p 375.

mixture was stirred for 24 h, making the total reaction time 48 h. The $(CH_3)_2NCOCH_3$ was removed under reduced pressure, and the residue was redissolved in 500 mL of $CHCl_3$ and filtered through a Celite plug. The filtrate was concentrated to a minimal volume and chromatographed on a silica gel column using 20% $CH_3CO_2CH_2CH_3$ and 80% C_6H_{14} as the eluent. All pure fractions containing the bis(calixarene) cage molecule **1** (R_f = 0.37) were collected and concentrated under vacuum to yield 308 mg (30%) of pure **1**. Mp: 205–207 °C (uncorrected). Anal. Calcd for $C_{100}H_{128}O_{16}S_8$: C, 65.24, found 65.78; H, 7.00, found 7.20; S, 13.92, found 13.65. DCI-MS (positive ion mode, isobutane matrix) m/e: 1842 (M^+, 35), 1796 (M^+ –OEt, 100%). ^1H-NMR (80 MHz, $C_2D_2Cl_4$) δ: 1.24 (t, 24H); 3.29, 3.01 (d of d, 8H); 3.46–4.17 (five overlapping signals, 72H); 4.48, 4.29 (d of d, 8H); 6.72 (s, 8H); 7.30 (s, 8H).

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