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Molecular Design and Synthesis of a Biscalix[4]arene-Based Cage Molecule

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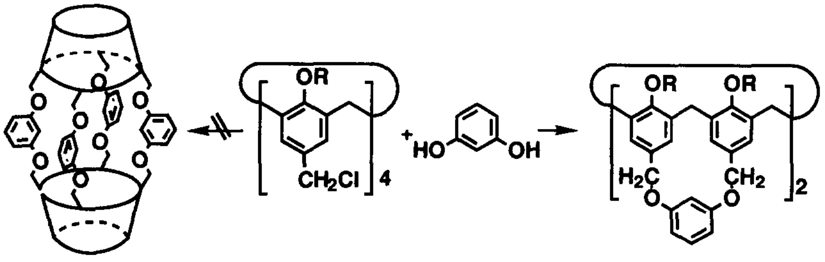
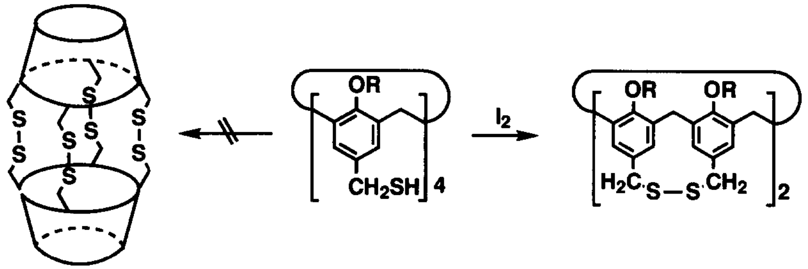
Summary: The biscalixarene-based cage molecule, the synthesis of which is precedented but only in "very low yield", was designed on the basis of the careful assessment of the reaction route and molecular models and synthesized for the first time in reasonable yield.

Calixarenes are $[1_n]$metacylophanes with a half-bowl-shaped architecture. This architecture tempted us to design a mid-air capsule from two calixarenes by the binding of two upper rims with "adhesive" functional groups. The similar idea has been reported by Cram *et al.*: they used cyclic resorcinol tetramers as half-bowl building-blocks for the synthesis of "carcerands".[1-3] Calixarenes have the isomeric spectrum from tetramer to octamer. This suggests the synthetic possibility of new cage molecules with a different mid-air size which cannot be achieved by the use of cyclic resorcinol tetramers. Böhmer *et al.*[4] succeeded in the synthesis of a biscalix[4]arene-based cage molecule by cyclization of 1,10-bis(4-hydroxyphenyl)-decane and 1,10-bis[3,5-bis(bromomethyl)-4-hydroxy-phenyl)decane. We also isolated a cage molecule composed of two calix[6]arenes.[5] In both systems, unfortunately, the yields were so low that the detailed characterization of their inclusion properties could not be conducted. Is there any new, general methods which lead to the improvement of the yield? In the synthesis of "carcerands" from resorcinol tetramers, the products were obtained in *ca.* 30%.[1-3] We thus applied the methods used therein to the calixarene system. We learned, however, that in a calixarene system the intramolecular cross-link occurs predominantly in preference to the intermolecular dimerization.[6-8] For example,



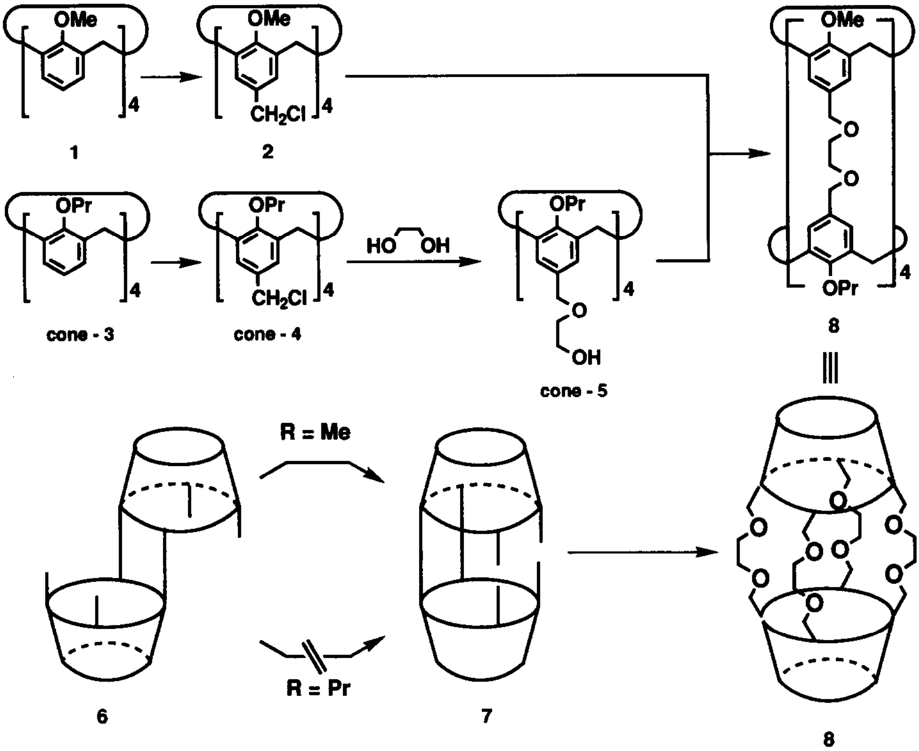


These lines of failure consistently teach us that in resorcinol tetramers the intramolecular cross-link is more or less suppressed because of the limited molecular motion whereas in calixarenes it is allowed because of the increased molecular motion. We thus reached a conclusion that "adhesive" functional groups on the upper rim should be different between two calixarenes so that they cannot react intramolecularly.

On the basis of the foregoing lines of information, we contemplated the following reaction route for the synthesis of a biscalix[4]arene-based cage molecule. Preparations of **2** and cone-**4** were described previously.[9] To suppress the intramolecular cross-link, the preparation of cone-**5** was conducted in ethylene glycol as solvent (note that 1,3-phenylenediamine and resorcinol cannot be used in great excess as solvent): mp 131-132 °C, yield 55%, identified by IR, ^1H NMR and elemental analysis. It is known that in calix[4]arenes the methoxy group can rotate through the annulus whereas the propyl group is bulky enough to suppress the rotation.[10] If the conformationally-immobile tetra-O-propylated analogue of **2** is used instead of **2**, one must take the "mis-stitching" (as in **6**) into consideration. On the other hand, conformationally-mobile **2** can rotate to **7** and the "mis-stitching" is eventually compensated to afford the desired cage molecule (**8**).

Compound **8** was prepared from **2** and cone-**5** under the high-dilution conditions in THF in the presence of NaH: yield 12%, mp (decomp.) 290 °C; Mass (SIMS) $[M+Na]^+$ 1439. The ^1H NMR spectrum is shown in Fig. 1. A pair of doublets for the $ArCH_2Ar$ methylene protons supports the view that the calix[4]arene moiety from **2** is also immobilized to a cone conformation. We observed the serious line-broadening for the ^1H NMR spectrum of our previous cage molecule in which two calix[6]arenes are linked by $-CH_2SCH_2-$ spacers.[5] In contrast, the peaks in Fig. 1 are relatively sharp, indicating that the cage obtained here is rather flexible. As expected, the yield of the molecular capsule was very low (less than 1.0%) when a tetrapropyl counterpart of **2** was used instead of **2**.[12]

To the best of our knowledge, this is the first example for the synthesis of a biscalixarene-based cage molecule in the reasonable yield. We are now investigating the inclusion properties of **8**. The preliminary ^1H NMR measurements indicate that **8** can include several organic guest molecules (particularly, $RNMe_3^+$ with the aid of cation-π interactions[11]) and the exo-cage-endo-cage exchange rate is slower than



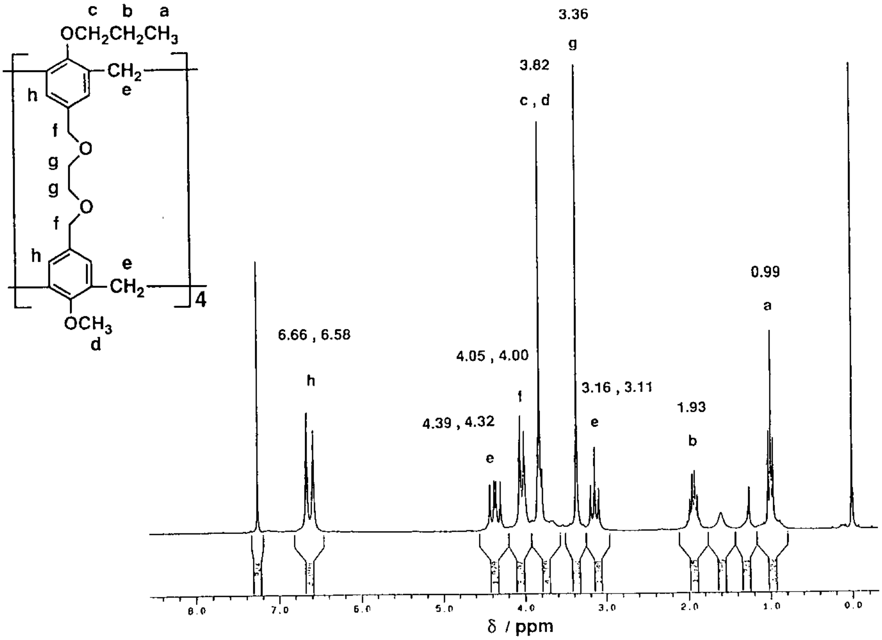


Fig. 1. ${}^{1}H$ NMR spectrum of **8** ($CDCl_3$, 250 MHz, room temperature).

that of the NMR time-scale and guest-shape-dependent.

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