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Regioselective Intramolecular-Bridging of Calix[8]arenes: Unexpected Isolation of a Doubly-Bridged Unimolecular Capsule-like Compound

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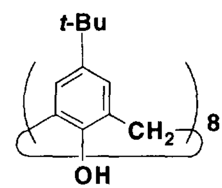
Abstract: We report new methods for the synthesis of intramolecularly-bridged calix[8]arenes by bis(bromomethyl) reagents. We could isolate not only singly-bridged compounds but also a doubly-bridged compound. The doubly-bridged compound has a unique capsule-like structure, the cavity of which consists of eight phenolic oxygens.

Calix[n]arenes which are n-meric cyclic oligomers have very useful cavities for designing molecular receptors. In particular, the cavities of calix[8]arenes are large enough to capture various organic compounds. It is known, in fact, that calix[8]arenes can include ammonium ions,[1] fullerenes (C_{60}),[2] etc. In the molecular design processes, however, we frequently meet the difficulties such as the regioselective synthesis of *O*-alkylation products and the immobilization of the conformational freedom. In the last few years, several articles have been devoted to regioselective *O*-alkylation and conformation-immobilization of calix[8]arenes.[3,4] Neri et al.[3] reported that the reactions of *p-tert*-butylcalix[8]arene **1** with bis(bromomethyl) reagents, which are useful as a protecting group for calix[6]arenes,[5] afford only polymeric materials even under high-dilution conditions. Here, we report new methods by which intramolecularly-bridged calix[8]arenes are provided in high yields without using high-dilution conditions. Furthermore, we unexpectedly isolated a doubly-bridged unimolecular capsule-like compound in the high yield.



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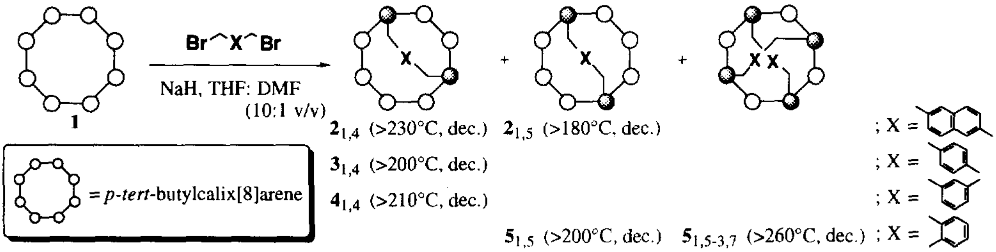
When **1** was refluxed with NaH (8 equiv.) and each bis(bromomethyl) reagent (1 equiv.) in dry THF/DMF (10:1 v/v), **2** - **5** were obtained as major products (Scheme 1 and Table 1). These products were isolated by column chromatography or TLC (silica gel). When **1** and 2,6-bis(bromomethyl)naphthalene were mixed at one time, $\mathbf{2}_{1,4}$[6] resulted as a major product (34% yield). On the other hand, when 2,6-bis(bromomethyl)naphthalene was added dropwise to the solution of **1**, not only $\mathbf{2}_{1,4}$ (12% yield) but also $\mathbf{2}_{1,5}$ (12% yield) was produced. In contrast, 1,2- and 1,3-bridged compounds could not be found in the reaction mixture. When 1,2-bis(bromomethyl)benzene was used, a doubly-bridged compound $\mathbf{5}_{1,5\text{-}3,7}$ was successfully isolated.[7]

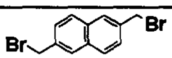
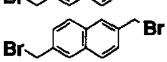
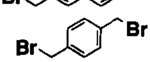
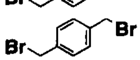
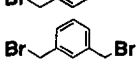
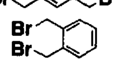
In ^{1}H-NMR spectroscopy $\mathbf{3}_{1,4}$ gave five singlets for the $ArCH_2Ar$ methylene protons (δ 4.08, 3.91, 3.90, 3.86 and 3.81 in 4H:4H:4H:2H:2H), four singlets for the *tert*-butyl protons (δ 1.32, 1.29, 1.26 and 1.22 in 18H:18H:18H:18H) and one singlet for the $ArCH_2O$ methylene protons (δ 4.88 in 4H) in $CDCl_2CDCl_2$ at



Scheme 1 The structure of products (The values in the parentheses indicate the melting points.)

100 °C. This splitting pattern can be ascribed either to a 1,2-singly-bridged calix[8]arene or to a 1,4-singly-bridged one. As described in Reference 8 (method 1), this compound was finally assigned to $\mathbf{3}_{1,4}$ by further derivatization and 2D-NOESY. The splitting patterns of $\mathbf{2}_{1,4}$ and $\mathbf{4}_{1,4}$ are similar to that of $\mathbf{3}_{1,4}$ in respect to the signals for the $ArCH_2Ar$ methylene protons and *tert*-butyl protons. These results support that these compounds are also 1,4-singly-bridged calix[8]arenes. As described in Reference 8 (method 2), these compounds were finally assigned to $\mathbf{2}_{1,4}$ and $\mathbf{4}_{1,4}$ by further derivatization, respectively. On the other hand, $\mathbf{2}_{1,5}$ gave two singlets for the $ArCH_2Ar$ methylene protons (δ 4.06 and 3.90 in 8H:8H), three singlets for the *tert*-butyl protons (δ 1.32, 1.26 and 1.23 in 18H:36H:18H) and one singlet for the $ArCH_2O$ methylene protons (δ 4.92 in 4H) in $CDCl_3$ at 50 °C. This splitting pattern is commensurate only with a 1,5-singly-bridged calix[8]arene (i.e., $\mathbf{2}_{1,5}$). For $\mathbf{5}_{1,5}$ the $ArCH_2Ar$ methylene protons gave two pairs of doublets in a 1:1 integral intensity ratio in $CDCl_3$ at 50 °C (δ 3.94 (J = 14 Hz), 3.83 (J = 15 Hz) ,3.65 (J = 16 Hz) and 3.61 (J = 15 Hz)). At higher temperature region (at 130 °C), however, these signals became two singlets (δ 3.80 and 3.75) in $CDCl_2CDCl_2$. The results imply that the rate of calix[8]arene ring inversion is slower than the NMR time-scale at room temperature. The three singlets (δ 1.26, 1.24 and 1.19 in 18H:36H:18H) and one singlet (δ 5.45 in 4H) can be assigned to the *tert*-butyl protons and the $ArCH_2O$ methylene protons, respectively. The simple splitting pattern for $\mathbf{5}_{1,5}$ is similar to that for $\mathbf{2}_{1,5}$ and the similarity indicates that $\mathbf{5}_{1,5}$ also adopts a 1,5-singly-bridged structure. The MS spectral datum supports that $\mathbf{5}_{1,5}$ is a singly-bridged compound (SIMS; m/z 1398 (M^+ =

Table 1 Bridging Reactions of **1** with Bis(bromomethyl) Reagents

Bis(bromomethyl) reagent	Addition of bis-(bromomethyl) reagent	Bis(bromomethyl) reagent/1	Yield (%) of isolated products[a]		
			1,4-Bridged compound	1,5-Bridged compound	1,5-3,7-Bridged compound
	i[b]	1	34	0	0
	d[b]	0.5	12	12	0
	i	1	64	0	0
	d	0.5	94[c]	0	0
	i	1	20	0	0
	i	1	0	13	19

a) All of these yields are referred to the bis(bromomethyl) reagents.
b) d shows that the THF solution of the bis(bromomethyl) reagent was added "dropwise" to the reaction mixture and i shows that bis(bromomethyl) reagent was added "immediately".
c) This percentage was determined by HPLC.

1399)). For $5_{1,5\text{-}3,7}$ the $ArCH_2Ar$ methylene protons gave only one pair of doublets (δ 4.12 (J = 14 Hz) and 3.24 (J = 14 Hz)) in $CDCl_2CDCl_2$ at 130°C. This splitting pattern is similar to that of cone-calix[4]arenes. In other words, $5_{1,5\text{-}3,7}$ adopts a cone-like conformation with four OH groups directed toward the molecular center. The integral intensity ratio of the $ArCH_2O$ methylene protons and the MS spectral datum (SIMS; m/z 1501 (M^+ = 1501)) indicate that $5_{1,5\text{-}3,7}$ is a doubly-bridged compound with a novel globular structure. The *tert*-butyl protons gave two singlets (δ 1.26 and 1.11 in 36H:36H) in $CDCl_2CDCl_2$ at 130°C. It is obvious that $5_{1,5\text{-}3,7}$ is a 1,5-3,7-doubly-bridged compound, because the simple splitting pattern in the ^{1}H-NMR spectrum is in agreement with the theoretical splitting pattern of the highly-symmetrical 1,5-3,7-doubly-bridged compound and only $5_{1,5}$ can act as a precursor to result in this globular molecule. The structure proposed for $5_{1,5\text{-}3,7}$ is illustrated in Fig. 1.

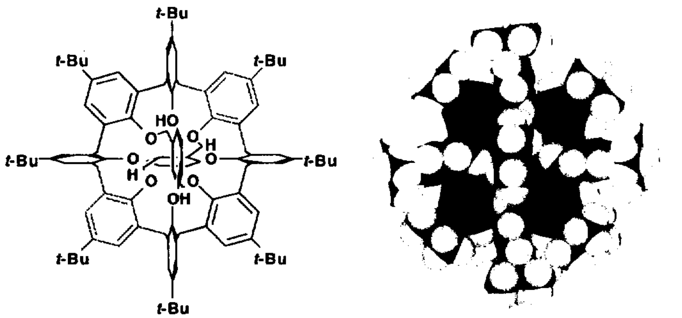


Fig.1 Schematic structure of $5_{1,5\text{-}3,7}$ and its energy-minimized structure.[9]

In $5_{1,5\text{-}3,7}$ the central cavity is composed of eight phenolic oxygens (Fig. 1). This structure is basically classified into D_{2d}-symmetry. Although the $ArCH_2Ar$ methylene protons and the $ArCH_2O$ methylene protons appear as one pair of doublets and one singlet, respectively, in

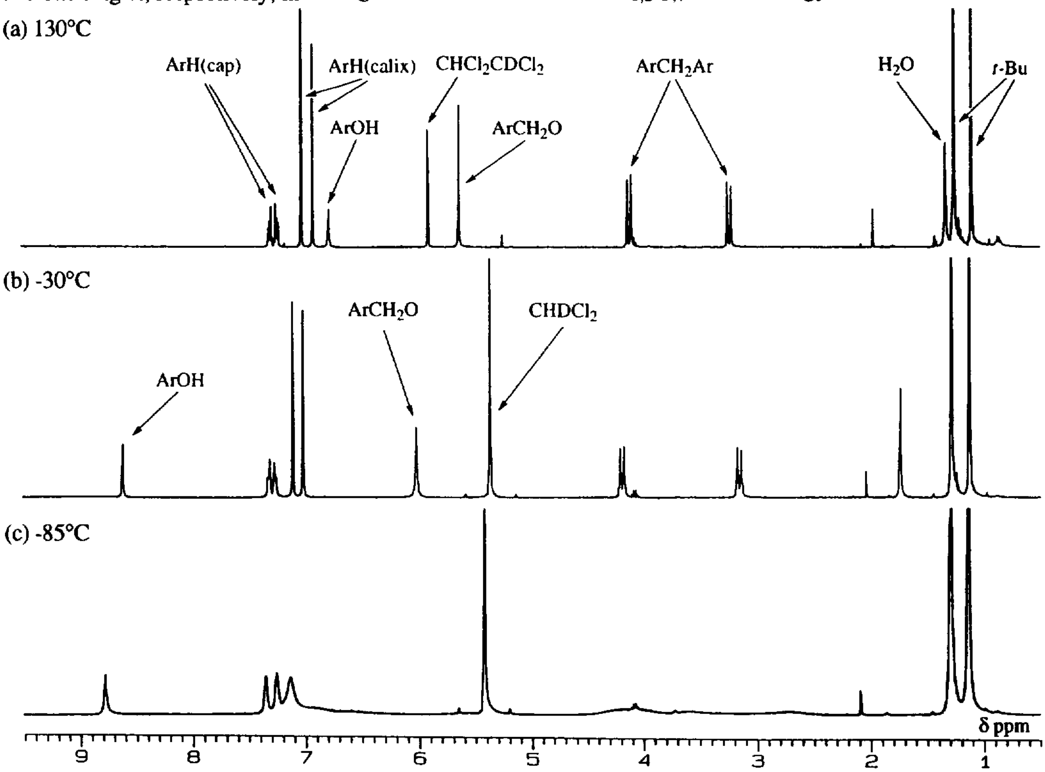


Fig. 2 Partial ^{1}H-NMR spectra for $5_{1,5\text{-}3,7}$ (a) in $CDCl_2CDCl_2$ (b), (c) in CD_2Cl_2 (400MHz)

high-temperature region (between 30 °C and 130 °C), these peaks are broadened at around -85 °C (the solvent used was $CDCl_2CDCl_2$ above -30 °C and CD_2Cl_2 below -30 °C). The results imply that the structure of $\mathbf{5}_{1,5\text{-}3,7}$ is somewhat inclined from D_{2d}-symmetry in solution. It was shown by MM3(92) that the energy-minimized structure[9] of $\mathbf{5}_{1,5\text{-}3,7}$ has two twisted bridged groups (Fig. 1). This molecular deformation from D_{2d}-symmetry is in line with the ^{1}H-NMR data obtained in solution.

In this paper we reported the synthesis of the singly-bridged compounds by using bis(bromomethyl) reagents. Contrary to our expectation that calix[8]arenes should be linked at the phenyl units which have the distance similar to the bis(bromomethyl) reagents, the 1,4-bridged compound was obtained by using the long bridging reagents whereas the 1,5-bridged compound was obtained by using the short bridging reagent. Furthermore, the doubly-bridged compound was unexpectedly obtained by one step. This compound has an interesting cavity composed of eight phenolic oxygens, suggesting its high potentials in host-guest chemistry.

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6. The subscript indicates the bridged positions. For example, 1,4 and 1,5-3,7 indicate a 1,4-singly-bridged compound and a 1,5-3,7-doubly-bridged compound, respectively .
7. Similar 1,5-3,7-doubly-bridged calix[8]arenes were synthesized by Neri et al. from tetrabenzylated calix[8]arene: Geraci, C.; Piattelli, M.; Neri, P., *Tetrahedron Lett.*, **1995**, *36*, 5429-5432.
8. **Method 1**; $\mathbf{3}_{1,4}$ was hexamethylated. Using this product, we could confirm that the bridging occurs at the 1,4 positions by means of 2D-NOESY experiment. The details will be described in our full paper. **Method 2**; For hexamethylated products of $\mathbf{2}_{1,4}$ and $\mathbf{4}_{1,4}$ we could not determine the bridged positions by the same method. Thus, we removed the bridges by reduction with Pd/C and compared the products with that obtained from hexamethylated $\mathbf{3}_{1,4}$. These compounds are all identical, 5,11,17,23,29,35,41,47-octa-*tert*-butyl-49,50,51,52,54,55-hexamethoxycalix[8]arene-53,56-diol.
9. To evaluate the stable structure of this compounds, we carried out a molecular mechanics calculation MM3(92).[10] Input structure for this calculation was established by the combination of the standard bond lengths[11] followed by a small modification using a molecular modeling system, MOLGRAPH.[12] This molecular structure was optimized with MM3(92)[10] by a block diagonal monomozation method.
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12. MOLGRAPH™ is a molecular design support system from DAIKIN Ind. Ltd.

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