

X-ray Structure and Alkyl Ammonium Recognition of Quadruply Bridged Calix[6]arene: A Selective Inclusion of Primary Alkyl Ammonium with Calix[6]arene

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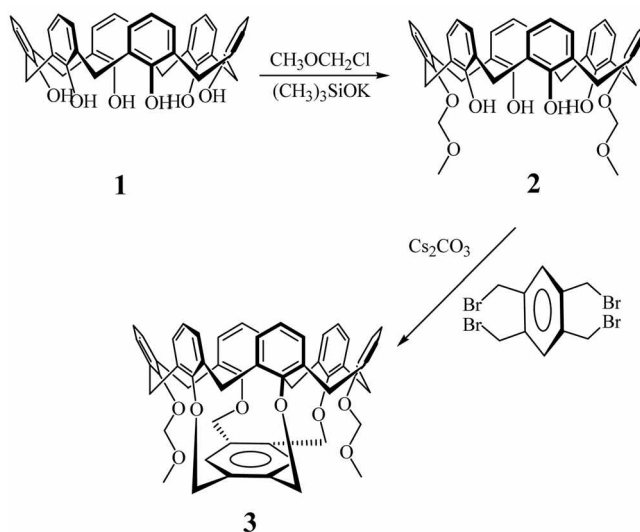
Numerous attempts have been made to design new host systems which can selectively interact the target guest and perform intriguing molecular recognition processes.¹⁻³ The selective recognition of many important biogenic amines is one of the fundamental research interests in the field of the biomimetic chemistry.^{4,5} Particularly, selective binding of organic ammonium guests attracts an important research interest due to the application of biological systems, which results in developing of many sophisticated host systems.⁶

Calixarenes present attractive possibilities in the host-guest chemistry as molecular frameworks for the preparation of conformationally preorganized polyfunctional derivatives, whose convergent ligating groups can act cooperatively to selectively bind ions or neutral molecules.^{7,8} Especially, the architecture of calixarenes is such that they also possess hydrophobic cavities generated by the aromatic walls of phenol residues, which are potentially useful for the inclusion of alkyl ammonium ions.⁹ Whereas the calix[4]arene cavity in the cone conformation is too narrow to accommodate even small amine salts, that of calix[6]arene is large enough to include small to medium-sized ammonium ions. The parent calix[6]arenes, however, are conformationally mobile. The most effective approach to make them immobile is to build a bridge at the lower or upper rim. Ever since Gutsche created the lower rim-bridged calix[6]arene in 1993, several lower rim-multibridged calix[6]arenes have been reported.^{10-12,14} Also the calix[6](aza)cryptand which has a tripodal poly-aza cap on the lower rim as a efficient host for small ammonium was reported by U. Darbost *et al.*¹³

The quadruply bridged calix[6]arene derivatives, which had been reported by our group, are also known for having a well-defined cavity capable of incorporating various cations.^{15,16} Here we report the X-ray structure of quadruply bridged calix[6]arene (**3**) and the binding properties for various alkylammonium picrates by the ¹H NMR analysis. Binding properties also were analyzed from the X-ray structure and the NOE study.

Results and Discussion

The quadruply bridged calix[6]arene (**3**) was prepared by the two step reaction from calix[6]arene as shown in Scheme



Scheme 1. Synthesis of quadruply bridged calix[6]arene.

1.¹⁵ When a quadruple bridge was made at the lower rim of calix[6]arene, a much more rigid calix[6]arene was expected. The ¹H NMR spectrum of **3** shows two pair of doublets at δ 4.96, 4.56, 3.61 and 3.47 for the bridging methylene protons at the ratio of 2 : 1. A pair of doublets as δ 5.21 and 4.60 with a coupling constant of 11.3 Hz, which should correspond to eight diastereotopic protons of four -OCH₂-groups. Also, calixarene aromatic protons attaching alkyl group appeared as a doublet at δ 6.26 ppm, a triplet at δ 6.00

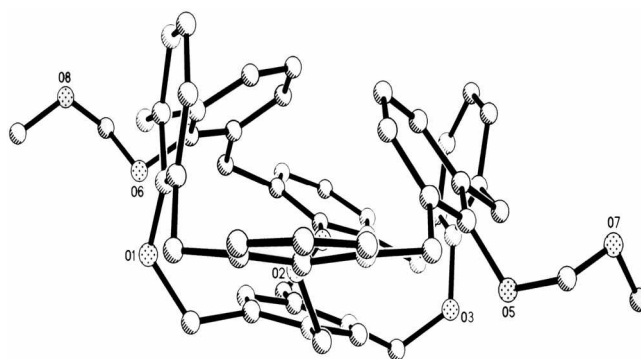


Figure 1. X-ray crystallography of Compound **3**.

Table 1. Crystal data and structure refinement for **3**

| | |
|-----------------------------------|--|
| Empirical formula | C ₅₆ H ₅₀ O ₈ |
| Formula weight | 850.96 |
| Temperature | 298(2) K |
| Wavelength | 0.71073 Å |
| Crystal system | Triclinic |
| Space group | P-1 |
| Unit cell dimensions | a = 12.681(2) Å α = 103.943(3)° b = 13.284(2) Å β = 111.352(3)° c = 14.696(3) Å γ = 99.495(3)° |
| Volume | 2148.5(6) Å ³ |
| Z | 2 |
| Density (calculated) | 1.315 Mg/m ³ |
| Absorption coefficient | 0.087 mm ⁻¹ |
| F(000) | 900 |
| Crystal size | 0.2 × 0.2 × 0.3 mm ³ |
| Theta range for data collection | 1.57 to 28.35° |
| Index ranges | -9 ≤ h ≤ 16, -17 ≤ k ≤ 17, -19 ≤ l ≤ 18 |
| Reflections collected | 14005 |
| Independent reflections | 9690 [R(int) = 0.0585] |
| Completeness to theta = 28.35° | 90.3% |
| Absorption correction | None |
| Refinement method | Full-matrix least-squares on F ² |
| Data / restraints / parameters | 9690 / 8 / 577 |
| Goodness-of-fit on F ² | 1.050 |
| Final R indices [I > 2sigma(I)] | R1 = 0.0829, wR2 = 0.2273 |
| R indices (all data) | R1 = 0.1554, wR2 = 0.2683 |
| Largest diff. peak and hole | 1.851 and -0.561 e.Å ⁻³ |

ppm. A high temperature ¹H NMR spectrum was studied and showed no change of spectrum up to 100 °C, indicating that **3** is considerably rigid.

Figure 1 shows the X-ray structure of **3**. The all six aromatic rings were placed at the upper side of bridge methylene carbons, providing an overall cone conformation. But the two aromatic rings with alkyl substituents were tilted inward to fill the empty calixarene cavity. The detail crystal data for X-ray structure for **3** are shown in Table 1.

Binding properties of various ammonium picrates with host **3** were investigated by the ¹H NMR analysis. Figure 2 displays the representative spectrum showing the chemically induced shifts (CIS) by addition of alkylammonium picrate. The considerable upfield shift of proton resonances of the butyl group in *n*-butylammonium guest was observed when complexed with **3**. Each of them shifted 0.4 ppm for methyl, 0.55 ppm and 0.3 ppm for methylenes of β,γ -position, and 0.59 ppm for α -position of nitrogen atom in upfield direction, which indicates that the guest is under the influence of the aromatic cavity of calixarene, thus forming *endo*-type complex. The relatively large upfield shifts can tell that the so-called CH- π interaction¹⁷ comes into play in forming the *endo*-type complex by the ring current of phenyl groups. Also, ethylammonium picrate and propylammonium picrate shifted upfield highly confirming *endo*-complex with host **3**. It was found that the complexation of ethylammonium with

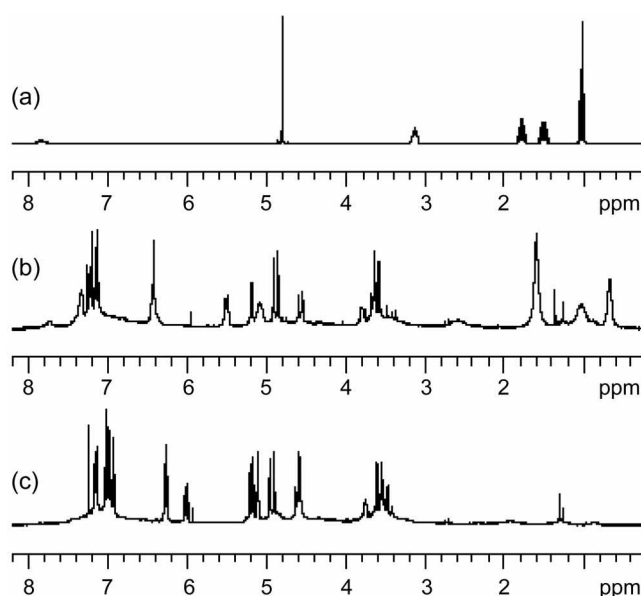


Figure 2. ¹H NMR spectrum of (a) *n*-butylammonium picrate (solvent: CD₃OD), (b) 3-*n*-butyl-ammonium picrate (solvent: CDCl₃ : CD₃OD = 98 : 2) and (c) host **3** (solvent: CDCl₃)

host **3** is slightly more favorable among three alkylammonium ions by the NMR chemically induced upfield shifts (CIS).

On the contrary, in the case of secondary, tertiary and quaternary ammonium picrates such as *t*-butyl ammonium, piperidinium, trimethyl ammonium and tetrabutyl ammonium, none of ammonium picrates show a meaningful change of chemical shift, indicating that they are not able to form a complex with **3**, presumably due to their bulky sizes.

To obtain further insights of the ammonium binding mode, the chemical shift change of host **3** was investigated. The chemical shift difference between **3** and the 3-*n*-butylammonium complex is summarized in Figure 3. A most significant down field shift was observed for the durenyl ArH (H₆, $\Delta\delta = +0.81$) and a moderate shift for ArH protons (H₄) and two -OCH₂- protons (H_e and H_f) ($\Delta\delta = +0.42$,

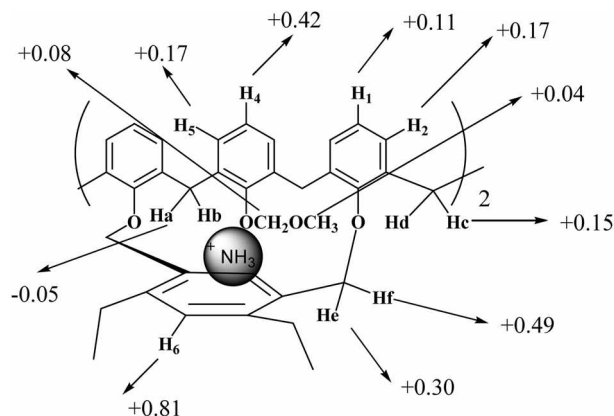


Figure 3. Chemical shift difference between free **3** and the 3-*n*-butylammonium complex. A plus sign (+) denotes a shift to lower magnetic field and a minus sign (-) denotes a shift to higher magnetic field.

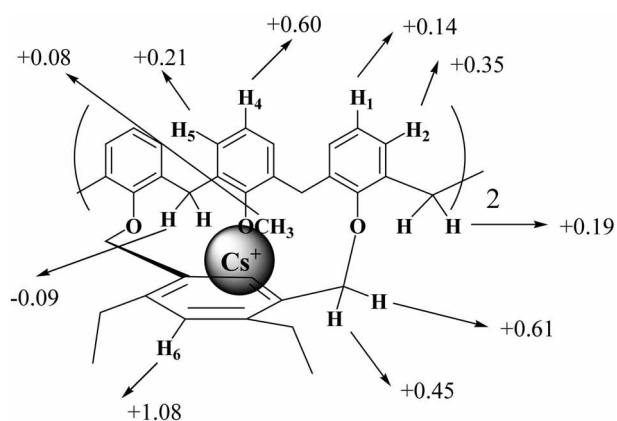


Figure 4. Chemical shift difference between free **3** and the **3**·Cs⁺ complex. A plus sign (+) denotes a shift to lower magnetic field and a minus sign (−) denotes a shift to higher magnetic field.¹⁹

+0.49 and +0.3 ppm, respectively). But the methoxy methylene protons were least affected ($\Delta\delta = +0.08$ and +0.04). It is well known that the cation- π interaction operates in the ammonium binding and that the chemical shifts of ArH protons in such complexes mostly move to lower magnetic field.¹⁶

The observed chemical shift difference showed a similar result when **3** was complexed with cesium ions¹⁹ as shown in Figure 3 and 4. The remarkably similar downfield shifts suggest that binding sites of ammonium and cesium within a host **3** are the virtually same.

Two phase solvent extraction of alkylammonium cations with picrate anion into chloroform was performed by the standard method.²⁰ An aqueous solution of picrate salts was stirred with an equimolar solution of host **3** in chloroform. Then the percentage extraction was deduced from the absorbance at 355 nm in the UV spectra of the aqueous layer. Each of them was 2.4%, 3.7%, 2.7%, and 2.8% on ammonium picrate, ethylammonium picrate, *n*-propyl ammonium picrate, and *n*-butylammonium picrate, respectively. Though the extraction ability was not so high, the tendency that ethylammonium ion binds well with host **3** was consistent with the result of NMR work.

From the 2D NOESY, the correlation peak between quadruply bridged calixarene (**3**) and *n*-butylammonium was not found. It is suggested that *n*-butylammonium could enter the calixarene cavity through the side space generated by the tilted aromatic rings with methoxymethyl substituents from the X-ray structure and non-correlation peak in NOESY.

Experimentals

Nuclear magnetic resonance (NMR) spectra were recorded on 300 MHz Varian UnityPlus300 and 500 MHz Varian Inova spectrometers. Chemical shifts were reported as δ values in parts per million relative to tetramethylsilane (TMS) as an internal standard. X-ray structure analysis was determined from data collection on a Bruker SMART CCD

diffractometer.

All the experiments were performed at 27 °C, using the Varian variable temperature controller. The 2D-NOESY spectra were measured in the phase-sensitive mode with mixing time and relaxation delay, respectively, of 200 ms and 2.0 sec at 27 °C. The bridging of the calix[6]arene was accomplished by first converting it to a 1,4-dialkyl ether, which was then treated with 1,2,4,5-tetrakis(bromomethyl) benzene in the presence of Cs₂CO₃ in dilute solution as reported.¹⁴ Selective 1,4-dialkylation of calix[6]arene was carried out by treating calix[6]arene(**1**) with the corresponding alkyl halides in the presence of (CH₃)₃SiOK and a pure compound was obtained in high yield without a further additional purification procedure.

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