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Self-assembled octameric cage constructed by the potassium salt of *p-tert*-butylcalix[6]arene *p*-bromophenylalanine derivative in the solid state†

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Received (in Cambridge, UK) 19th April 2006, Accepted 12th July 2006
First published as an Advance Article on the web 26th July 2006
DOI: 10.1039/b605555a

Potassium salts of *p-tert*-butylcalix[6]arene *p*-bromophenylalanine derivative formed sizable octameric cages in the solid state that were revealed by X-ray crystallographic analysis.

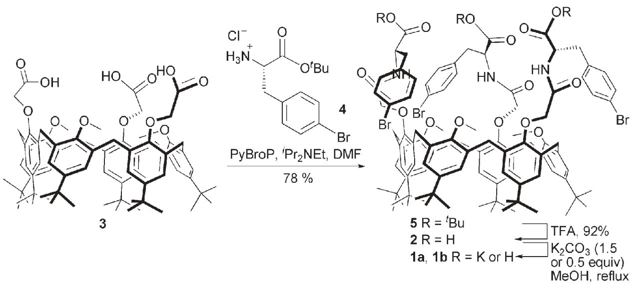
Investigation of self-assembled molecular capsules and molecular cages has attracted much interest in supramolecular chemistry.[1] They can serve as molecular containers for inclusion of guest molecules, and have been applied to isolation of unstable intermediates,[2] selective recognition of guest molecules,[3] promotion of chemical reactions,[4] and regio- and stereoselective reactions.[5] In the self-assembly process, hydrogen bonding and metal coordination play an important role in building unique cage structures, which have a larger size than single molecules can create.[1a,6] Many self-assembled cage structures have been reported so far.[1–6] However, more progress is required to elaborate their functions and to enable them to accommodate a wide variety of guest molecules.

Calixarenes have been extensively studied as excellent host molecules in host–guest chemistry.[7] Calixarenes and their congeners are known to form molecular capsules and molecular cages by self-assembly. In particular, there are many examples of dimeric molecular capsules, *e.g.*, calixresorcinarene derivatives,[8a] ureidocalixarenes,[8b,c] and calixarenes connected with amino acids or peptides.[9,10] However, there are few examples for further polymerization. Chiral calix[4]arene dimelamines form an asymmetric trimer box with barbiturates,[11] and *C*-methylcalix[4]resorcinarenes form a hexameric cage.[12]

Here, we show that the potassium salts of *p-tert*-butylcalix[6]arene *p*-bromophenylalanine derivative construct novel octameric cage structures in the solid state that were revealed by X-ray crystallographic analysis using synchrotron radiation. To investigate the structural difference due to variation of the amount of potassium ions, two kinds of potassium salts, **1a** and **1b**, were prepared by neutralization of the calix[6]arene derivative **2** with 1.5 and 0.5 equiv. of potassium carbonate, respectively. We found that they formed very similar octamers regardless of the amount of potassium ions. However, the mode of their self-assembly was different. In the crystal of **1a** rich in potassium ions, the driving force of the self-organization was the coordinate bonds and the ionic bonds between the amino acid moieties and the potassium ions. In the crystal of **1b** containing fewer potassium ions, the hydrogen bonding between the carboxyl groups of the amino acids compensated for the lack of ions. While the inner spaces of the preceding molecular capsules were hydrophobic,[1,6] the insides of the cages of **1a** and **1b** were hydrophilic since the carboxyl groups of the amino acids were directed inside. To the best of our knowledge, this is the first report describing X-ray structures of a calix[6]arene amino acid derivative as well as those of rare octamers.

p-tert-Butylcalix[6]arene *p*-bromophenylalanine derivative **2** was synthesized in good yield from the known tricarboxylic acid **3**[13] (Scheme 1). Potassium salts **1a** and **1b** were prepared by treatment of **2** with 1.5 and 0.5 equiv. of potassium carbonate, respectively. In the mass spectral data of **1a**, molecular ion peaks corresponding to the mono-, di-, and tripotassium salts were observed. For **1b**, the peaks corresponding to the monopotassium salt and the free acid **2** were observed. These results suggest that compounds **1a** and **1b** are an equilibrium mixture of these molecules.‡

Crystals of **1a** and **1b** were obtained from aqueous methanol. Because their total molecular weights were large and the collected data with the X-ray source in a laboratory were low resolution due to containing many disordered solvent molecules in the structure, direct methods for phase calculations were unsuccessful in the X-ray crystallographic analysis. Thus, the X-ray diffraction data sets were measured by synchrotron radiation at four wavelengths, and the phases were calculated with the multiwavelength anomalous diffraction method,[14] using the anomalous scattering



Scheme 1 Synthesis of **1a** and **1b**. PyBroP® = bromotripyrrolidinophosphonium hexafluorophosphate.

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† Electronic supplementary information (ESI) available: Crystallographic data, experimental section for synthesis, Fig. S1, Table S1 and Table S2. See DOI: 10.1039/b605555a

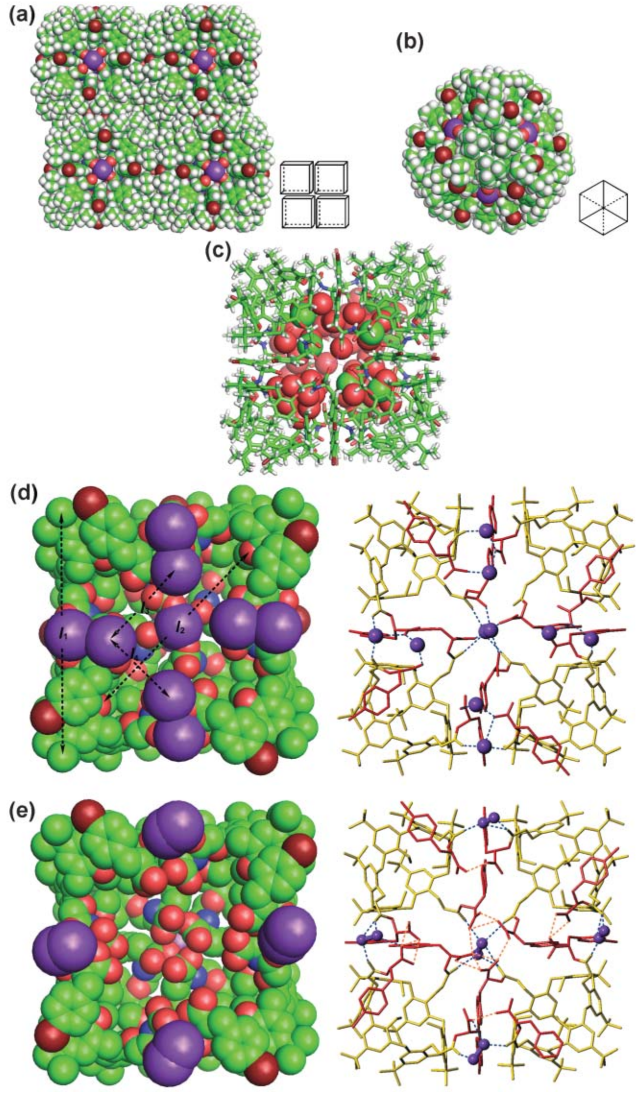

Fig. 1 (a) Crystal packing of **1a** (green: carbons; white: hydrogens; red: oxygens; blue: nitrogens; purple: potassiums). The four cube-like octamers are displayed and solvents are omitted for clarity. (b) The octameric cage of **1a** viewed along the *c* crystal axis. (c) Solvent molecules inside the octameric cage of **1a** shown by space-filling model. (d) Inside of the octameric cage **1a**. Four calixarenes and two potassium ions of the octamer have been omitted for clarity. Hydrogens and solvents are also omitted. The selected interatomic distances in the left space-filling model are as follows. l_1 (between the ^{t}Bu groups) = 25.5 Å, l_2 (between the oxygens of the methoxy groups) = 23.5 Å, l_3 = 10.1 Å, l_4 = 8.2 Å. The right stick model displays coordination and ionic bonds by blue dotted lines. (e) Inside of the octameric cage **1b**. Each potassium ion is disordered and occupies two positions. In the right stick model, hydrogen bonds are represented by orange dotted lines.

effect of bromines.§ The obtained crystal structures are shown in Fig. 1.

The crystals of the potassium salts **1a** and **1b** formed a cube-like supramolecular cage consisting of eight *p*-*tert*-butylcalix[6]arene *p*-bromophenylalanine molecules. Each calixarene moiety was located at a corner of the cube, and the hydrophilic carboxyl groups of the *p*-bromophenylalanine residues were directed to the inside of the octameric cage. The inner hydrophilic area in the cage was filled with methanol and water molecules, although some were not assigned because of their great disorder. Inside the cage of **1a**, fifteen methanol molecules and forty-two water molecules were assigned (Fig. 1c). In the cage of **1b**, only twenty-four waters and six methanols were assigned because of their severer disorder than **1a**. The volumes of the solvent regions inside the cages are 890 Å^3 and 1160 Å^3 in **1a** and **1b**, respectively.[15] *p*-Bromophenyl groups were inserted between adjoining calixarene moieties, though there was no stacking among the *p*-bromophenyl groups and aromatic rings of the calixarenes. Near the center of all the cube surfaces, four *p*-bromophenylalanine residues were aggregated around two potassium ions in **1a** and one potassium ion in **1b**. The space group of both crystals was *R*3. The octamers of **1a** and **1b** were constructed with two complete C_3 symmetric molecules and six pseudo C_3 symmetric molecules (see Fig. S1 in ESI†).

In each octamer, there were two modes of potassium ion uptake, which is crystallographically asymmetric. Fig. 2a shows two kinds of aggregation sites of the amino acid moieties in the crystal of **1a**. These structures resembled each other. In both sites, two potassium ions were included by ionic or coordinate bonds with the carboxyl groups and the amide carbonyl groups in the *p*-bromophenylalanine residues. The upper potassium ion was bound to the four carboxyl groups and water molecule(s). Two carboxyls, three amide carbonyls, and water(s) interacted with the lower potassium ion.

In contrast, only one potassium ion existed in the aggregation sites of **1b** (Fig. 2b). The highly disordered potassium ion was apart from the carboxyl anion and occupied almost the same position as the lower potassium ion in **1a**. The carboxyl groups of the *p*-bromophenylalanine residues formed hydrogen bonds with each other. That is, the hydrogen bonding between the carboxyl groups compensated for the lack of potassium ion.

In conclusion, we have elucidated the X-ray structure of the *p*-*tert*-butylcalix[6]arene *p*-bromophenylalanine derivatives **1a** and **1b**. In the crystal **1a** with high ion content, eight calixarenes were assembled by the aid of twelve potassium ions, thereby making up into a unique cube-like cage structure. The octameric cage has a hydrophilic hole at each center of the six surfaces and two potassium ions were included in each hole. It is noteworthy that a

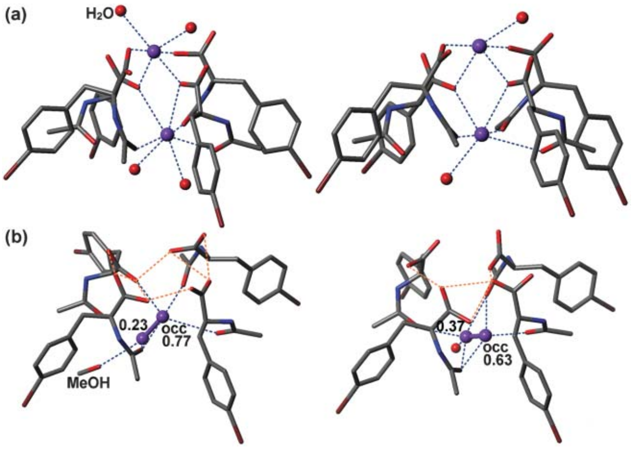

Fig. 2 Two kinds of the aggregation sites of **1a** (a) and **1b** (b). Only *p*-bromophenylalanine moieties, potassium ions, and solvents without hydrogens are shown for clarity. Occupancies of the disordered potassium ions in **1b** are indicated.

similar cube-like octameric structure was constructed even in the crystal **1b** with lower ion content. In sharp contrast to **1a**, the hydrogen bond network between the carboxyl groups compensated for the loss of interaction with the potassium ion in the crystal **1b**. These results show that coordination of amides to potassium ion is preferred over that of carboxylic acids despite the attractive ion–ion interaction. The self-assembled *nano-cages* stimulate our imagination for the design of new supramolecules as well as their application. Further study is in progress.

The synchrotron radiation experiments were performed at the BL38B1 in the SPring-8 with the approval of the Japan Synchrotron Radiation Research Institute (JASRI) (Proposal No. 2005A0258-NL1-np).

Notes and references

‡ Preparation of **1a** and **1b**: potassium carbonate (2.2 mg, 16.1 μmol) was added to a solution of **2** (20 mg, 10.7 μmol) in MeOH (5 mL). After the solution was refluxed for 40 min, the solvent was evaporated to give **1a** as a colorless powder. **1b** was also prepared using **2** (30 mg, 16.1 μmol) and 0.5 equiv. of potassium carbonate (1.1 mg, 8.0 μmol) by the same procedure as that described for **1a**. Crystals for X-ray analysis were obtained from aqueous MeOH. The mass spectroscopic data showed that **1a** exists as a mixture of monopotassium (**A**), dipotassium (**B**), and tripotassium (**C**) salts: MS (FAB): *m*/*z* 1907 ([**A** + H]$^+$, calcd 1907), 1944 ([**B** + H]$^+$, calcd 1945), 1983 ([**C** + H]$^+$, calcd 1983). **1b** also exists as a mixture of the neutral molecule (**2**) and the monopotassium salt: MS (FAB): *m*/*z* 1891 ([**2** + Na]$^+$, calcd 1891), 1907 ([**A** + H]$^+$, calcd 1907).

§ X-Ray crystallographic analysis of **1a** and **1b**: diffraction data sets of the crystal of **1a** were collected on a beamline BL38B1 at SPring-8 (Hyogo, Japan), and those of **1b** were collected on a beamline BL-6A at the Photon Factory (Tsukuba, Japan) using a Quantum 4R CCD X-ray detector (Area Detector Systems Corporation, California, USA). The crystals were cryoprotected with glycerol in a nitrogen stream at 95 K. Four X-ray wavelengths—peak (a peak of the K edge of bromine), inflection (an inflection point of the K edge), low-energy remote (a remote point from the K edge to the low-energy wavelength side), and high-energy remote (a remote point from the K edge to the high-energy wavelength side)—were determined by the X-ray absorption spectrum of bromine atoms. X-Ray diffraction data were collected at the four wavelengths (X-ray diffraction statistics are included in Table S1 and S2 of the ESI†). Diffraction data were processed and scaled using the HKL2000 package[16] and the CCP4 program package.[17] Phasing with the multiwavelength anomalous diffraction (MAD) method was carried out using SHELXD[18] and SHELXE.[19] The structural models were built and viewed using TURBO FRODO[20] and PyMOL.[21] The structures were refined by full matrix least squares on F^2 using SHELXL-97[22] with the diffraction data; for these data, X-ray wavelengths were 0.7000 Å in **1a** and 0.9220 Å in **1b**. The positions of hydrogen atoms, excepting those of the carboxyl groups and all solvent molecules, were calculated and refined using the riding model. Non-hydrogen atoms without solvents were refined by the anisotropic temperature factor, and hydrogens and solvents were isotropic. Crystal data of **1a**: $8C_{102}H_{118.5}Br_3N_3O_{15}\cdot12K\cdot33CH_3OH\cdot66H_2O$, M_r = 17645.6, rhombohedral, a = 43.05(4), c = 44.17(4) Å, V = 70897(123) Å^3, space group $R3$, Z = 3, μ = 1.145 mm^{-1}, 60089 reflections measured, 20981 unique which were used in all calculations (Friedel pairs were not merged), 3205 parameters, 4522 restraints. The final R_1 ($I > 2\sigma(I)$) = 0.1347, wR_2 = 0.3053 for all data. CCDC 290779. Crystal data of **1b**: $8C_{102}H_{119.25}Br_3N_3O_{15}\cdot6K\cdot21CH_3OH\cdot27H_2O$, M_r = 16330.0, rhombohedral, a = 43.22(4), c = 43.40(4) Å, V = 70187(121) Å^3, space group $R3$, Z = 3, μ = 0.532 mm^{-1}, 97012 reflections measured, 36570 unique which were used in all calculations (Friedel pairs were not merged), 3123 parameters, 4280 restraints. The final R_1 ($I > 2\sigma(I)$) = 0.1437, and wR_2 = 0.4079 for all data. CCDC 268806.

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