Synthesis, conformational and host–guest properties of water-soluble pillar[5]arene†

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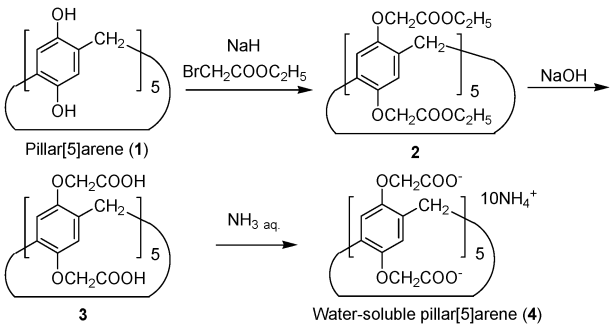
Water-soluble pillar[5]arene was synthesized by the introduction of carboxylate anions at both upper and lower rims. When cationic viologen salt was mixed with the water-soluble pillar[5]-arene in aqueous media, a very stable 1 : 1 host–guest complex was formed.

Macrocycles such as cyclodextrins,[1] calixarenes[2] and cucurbiturils[3] continue to be the focus of considerable research activity because of their interesting conformational and host–guest properties. We synthesized a new type of macrocycle for the first time and named it "pillar[5]arene" (**1**, Scheme 1).[4–7] The composition of pillar[5]arene is analogous to those of typical calixarenes. However, because its repeating units are connected by methylene bridges at the *para*-position, pillar[5]-arene forms a unique symmetrical pillar architecture, which is different from the basket-shaped structure of *meta*-bridged calixarenes. Pillar[5]arene exhibits very interesting host–guest properties in organic media. This is in sharp contrast to cyclodextrins and cucurbiturils, which can form a variety of host–guest complexes in aqueous media. The difference results from the poor solubility of pillar[5]arene in aqueous media. Consequently, in this communication, we report the synthesis of a new water-soluble pillar[5]arene. Pillar[5]arene (**1**) has reactive OH groups at both rims. Therefore, by modification of the OH groups, we prepared water-soluble pillar[5]arene (**4**, Scheme 1). In this study, the conformational characteristics and host–guest properties of **4** were investigated.

The synthesis of **4** is outlined in Scheme 1. By etherification of pillar[5]arene, ethoxycarbonylmethoxy groups-substituted pillar[5]arene (**2**) was synthesized. In pillar[5]arene (**1**), the constituent phenolic units freely rotate around the methylene bridge as the axis.[5] The rotational motion is fast on the NMR time scale at 25 °C, consequently, the proton signals of **1** are observed as equivalent at that temperature. On the other hand, after etherification the proton peaks were complex split peaks at 25 °C (ESI†), suggesting formation of a mixture of various conformers. The modification of the substituents at both rims inhibits the rotation of the phenolic units and immobilizes the



Scheme 1 Synthesis of water-soluble pillar[5]arene (**4**).

conformation. This fact is consistent with the conformational characteristics of non-symmetric pillar[5]arene.[6] The rotation of the ethoxy–methoxy-substituted non-symmetric pillar[5]-arene, which has short alkyl substituents compared with **1**, did not occur or was slow on the NMR time scale even at elevated temperature. By silica gel chromatography and recrystallization, we successfully isolated a single conformer of **2**. From the ^{1}H NMR spectrum of **2** (Fig. 1a), proton signals from the phenyl moieties (peak A), methylenes at both rims (peak B) and methylene bridge (peak C) were observed as singlets (blue rectangles), indicating that the structure of the isolated product was highly symmetric and stereoregular. Considering possible conformers by immobilization of the conformation, all of the substituents at both rims should have the same orientation (Fig. 2a). To examine the conformation characteristics of **2**, variable-temperature ^{1}H NMR measurements in DMF-d_7 were carried out (ESI†). Proton signals were not split even at −50 °C, strongly suggesting that the constituent units do not rotate but retain the conformational freedom of the cavity.

The hydrolysis of **2** under basic conditions afforded the carboxylic acid-substituted pillar[5]arene (**3**). **3** was soluble in DMSO and DMF but insoluble in chloroform and water. Unlike **2**, the methylene protons at both rims were split into two sets of peaks in a 1 : 1 integration at 25 °C (Fig. 1b, peak B, pink circle). Due to the *intra*-molecular hydrogen bond between the carboxylic acid moieties, mobility of the methylene protons at both rims was suppressed and slow on the NMR time scale at 25 °C. The interior of the cavity is an electron-rich space, thus the methylene protons located in the inner and outer spaces were shielded and deshielded, respectively. Consequently, the split should reflect the low conformational freedom of the cavity. At 76 °C (Fig. 1c), the peaks coalesced, and the proton signal from the carboxylic acid moieties disappeared. On heating, exchange of the protons from carboxylic acid moieties occurred and weakened the *intra*-molecular

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† Electronic supplementary information (ESI) available: Experimental procedures and full spectroscopic data, ^{1}H NMR spectrum of the product after etherification, variable-temperature ^{1}H NMR spectra of **2** and **3** in DMF-d_7, variable-temperature ^{1}H NMR spectra of the mixture of **4** and **DMeBpy**, determination of the association constant for **4-DMeBpy** complex from fluorescence measurements. See DOI: 10.1039/c0cc00348d

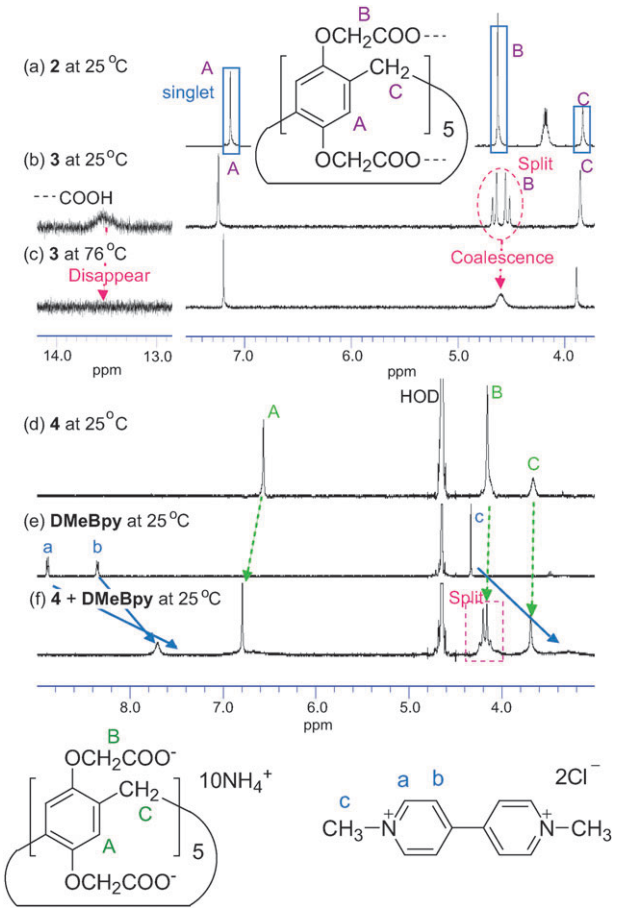

Fig. 1 Partial ^{1}H NMR spectra of (a) **2** and (b) **3** at 25 °C and (c) **3** at 76 °C in DMF-d_7. ^{1}H NMR spectra of (d) **4**, (e) **DMeBpy** and (f) the mixture of **4** and **DMeBpy** in 2.0 mM in D_2O at 25 °C.

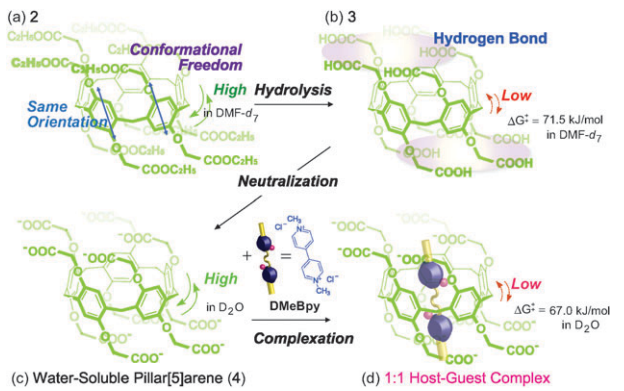

Fig. 2 Conformational characteristics of pillar[5]arene derivatives by hydrolysis, neutralization and complexation with **DMeBpy**.

hydrogen bond. From the coalescence temperature, the free energy barrier for the mobility of the methylene protons was 71.5 kJ mol^{-1} (Fig. 2b).[8]

Neutralization to the ammonium salt by treatment with aqueous ammonia solution afforded pillar[5]arene salt (**4**). **4** was soluble in aqueous solution but insoluble in organic solvents. Fig. 1d shows the ^{1}H NMR spectrum of **4** in D_2O. Proton signals from the phenyl (peak A), methylene (peak B) and methylene bridge (peak C) were observed as equivalent, indicating the highly symmetrical structure of **4**. Unlike **3**, the methylene protons at both rims were not split at room temperature. Due to the lack of the *intra*-molecular hydrogen bond by neutralization, the cavity of **4** has high conformational freedom (Fig. 2c).

Since **4** comprises electron donor dialkoxybenzene moieties and has carboxylate anions at both rims, the cationic electron acceptor of dimethyl viologen salt (**DMeBpy**) was used as a guest molecule. Formation of a host–guest complex between **4** and **DMeBpy** was examined by UV-Vis measurements (Fig. 3a). The broad absorption band that was observed from 700 nm increased in intensity with increase in the concentration of **DMeBpy**. The band is ascribed to a charge-transfer complex between **DMeBpy** and **4**. From the intensity of the charge-transfer band, the stoichiometry of the host–guest complex was determined by Job plots (Fig. 3b). The peak

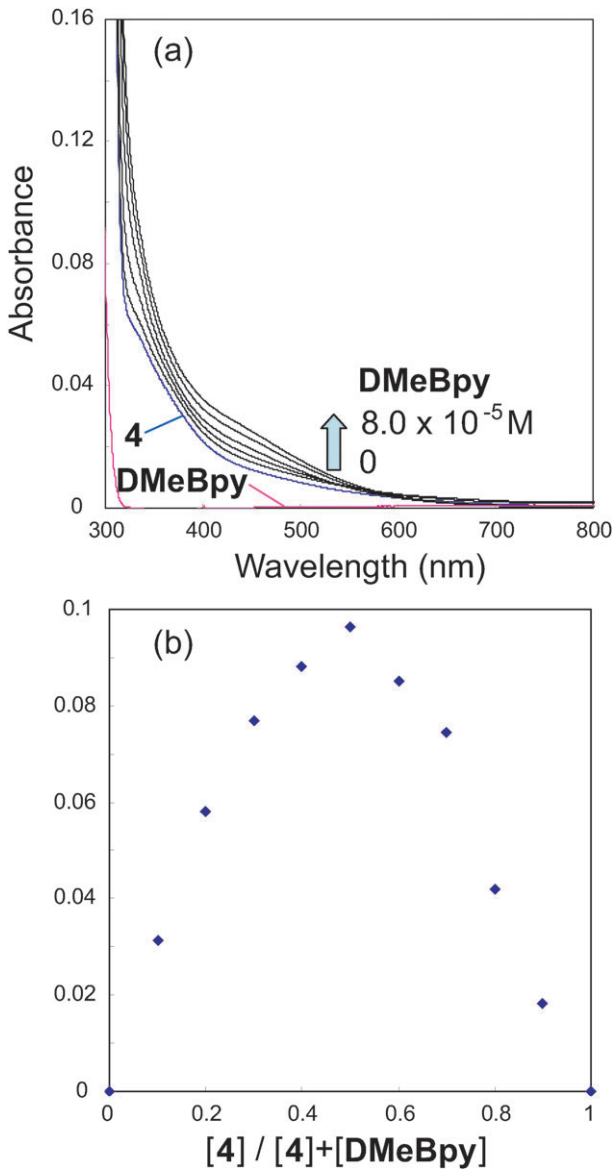

Fig. 3 (a) UV-Vis spectra of **4** (4.0×10^{-5} M) upon addition of **DMeBpy** in aqueous solution. (b) Job's plot of **4** and **DMeBpy**, where the absorbance at 330 nm was plotted against the molar fraction of **4** at an invariant total concentration of 0.10 mM in aqueous solution.

top was observed at the molar fraction $X_{guest} = 0.50$, indicating that the stoichiometry of **DMeBpy–4** complex is 1 : 1. When **4** was added to **DMeBpy** in D_2O, the proton peaks of **DMeBpy** shifted upfield (Fig. 1f). The observation indicates the formation of the host–guest complex. At the same time, the proton peaks of the methylene moieties at both rims were split into two set of peaks in a 1 : 1 integration (pink rectangle), which is the same phenomenon as for **3** in DMF-d_7. The inclusion of **DMeBpy** in the cavity of **4** restricted the swinging of the constituent units (Fig. 2d). From the coalescence temperature (51 °C), the free energy barrier for movement of the methylene at both rims was determined as 67.0 kJ mol^{-1}.[8] To determine the association constant for the **DMeBpy–4** complex, steady-state fluorescence spectra of **4** at varying **DMeBpy** concentrations were recorded (ESI†). The association constant was determined as $8.2 \pm 1.7 \times 10^4$ M^{-1} for the complex. Compared with pillar[5]arene (**1**),[4] **4** is able to strongly capture viologen salt. This should be due to synergetic effects. Multiple interactions such as electrostatic, charge-transfer, and hydrophobic–hydrophilic interactions should stabilize the host–guest complexation.

In conclusion, we successfully synthesized the new stereoregular water-soluble pillar[5]arene (**4**) for the first time. **4** formed very stable inclusion complex with **DMeBpy** in aqueous media and complexation with **DMeBpy** lowered the conformational freedom of the cavity. The inclusion of the viologen guest in the cavity of **4** in aqueous media will enlarge host–guest chemistry of pillar[5]arene. Combinations of water-soluble pillar[5]arene with hetero-macrocyclic water-soluble receptors such as cyclodextrins and cucurbiturils will open new directions of supramolecular chemistry, because multiple interactions between two or more complex molecules give insights into molecular recognition and self-assembly processes.

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