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Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

A Cucurbit[5]uril Analogue From Dimethylpropanediurea-Formaldehyde Condensation

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

A new host $\text{Me}_{10}\text{TD}[5]$ was prepared for the first time from propanediurea-formaldehyde condensation. $\text{Me}_{10}\text{TD}[5]$ is soluble in both water and common organic solvents, and binds protonated amines in a 1:2 stoichiometry in H_2O with the K_1 and K_2 values on the order of 10^3 M^{-1} . The self-assembling of $\text{Me}_{10}\text{TD}[5]$ with 1,4-xylylene diamine dihydrochloride results in the formation of a linear supramolecular polymer.

Cucurbit[n]urils (CBs) are pumpkin-like rigid molecules obtained from the glycoluril-formaldehyde condensation. They can bind with noble gases, alkanes, alkenes, alcohols, carboxylic acids, amines and positive charged guests because of their characteristic hydrophobic cavities and polar carbonyl groups surrounding the portals,¹ and were widely used to construct different kinds of supramolecular systems, such as molecular switches,² drug carriers,³ and supramolecular polymers.⁴

Poor solubility in common solvents and inability to be functionalized are the early inconvenience of CBs.^{5, 6} So many efforts have been made to overcome these disadvantages by 1) direct oxidizing of CBs by $\text{K}_2\text{S}_2\text{O}_8$ to introduce hydroxyl groups at the "equators";⁷ 2) using substituted glycolurils or aldehydes in the cucurbituril-forming reactions to obtain cucurbituril homologues, such as $\text{Me}_{10}\text{CB}[5]$,⁸ $\text{Cy}_5\text{CB}[5]$,⁹ $\text{Cy}_6\text{CB}[6]$,⁹ $\text{Me}_{12}\text{CB}[6]$,¹⁰ $\text{Cp}_5\text{CB}[5]$,¹¹ $\text{Cp}_6\text{CB}[6]$,¹¹ $\text{Cp}_7\text{CB}[7]$,¹¹ $\text{Ph}_2\text{CB}[6]$,¹² $\text{mPheCB}[6]$,¹³ $\text{Me}_6\text{CB}[6]$,¹⁴ $\text{Me}_4\text{CB}[6]$,¹⁵ $\text{Cy}_2\text{CB}[6]$,¹⁶ $(\text{Me}_2\text{CyP})_n\text{CB}[6]$,¹⁰ and $\text{Cy}_n\text{CB}[6]$ ($n=1-6$);¹⁷ and 3) condensing glycoluril hexamer with glycoluril bis(cyclic ethers) to achieve the useful mono-functionalized $\text{CB}[7]$.¹⁸

9,9-Dimethyl-2,4,6,8-tetraazabicyclo[3.3.1]nonane-3,7-dione (Me_2TD), which is also known as dimethylpropanediurea, has been used to create varieties of molecular clips.¹⁹ The fact that Me_2TD has a similar structure of glycoluril makes us believe that its condensation with formaldehyde would give cucurbituril-like hosts, which are expected to be soluble in common solvents because of plenty of methyl groups staying on the equators, and thus would pave the way to further applications. Herein, we report for the first time the synthesis of a new $\text{CB}[5]$ analogue, which was prepared from the condensation of Me_2TD with formaldehyde (Fig. 1).

After several unsuccessful attempts, the condensation of Me_2TD with paraformaldehyde was carried out in the presence of

conc. HCl at 95°C for 24 hrs, after the mixture was cooled to room temperature, a white precipitate could be obtained. At this time we were able to separate one pure substance from the white precipitate by recrystallizing from H_2O , the yield of which was 5%.

The ^1H NMR spectra of the pure solid in D_2O shows four groups of proton resonances with 1:1:1:3 intensity, two doublet peaks at $\delta = 4.2$ ($J = 14.9$ Hz) and 6.5 ppm ($J = 14.9$ Hz), and two singlet ones at 1.3 and 4.9 ppm (Fig.S1, ESI[†]). Furthermore, the corresponding ^{13}C NMR spectra in D_2O shows five peaks at $\delta = 154.2, 77.5, 62.0, 29.5$ and 20.1 ppm, respectively (Fig.S2, ESI[†]). These results indicate that this substance might be a typical symmetrical $\text{CB}[n]$ analogue. Further MALDI-TOF mass spectrometric experiment (Fig.S7, ESI[†]) gives two intense peaks at m/z 1041 and 1059, which suggests that the structure of the product might contain five Me_2TD units doubly bridged by methylene linkers, because in this way, the m/z 1041 and 1059 correspond to the $[\text{M}+\text{H}]^+$ and $[\text{M}+\text{H}_2\text{O}+\text{H}]^+$, respectively.

The single crystal of this compound was then prepared in dilute CaCl_2 aqueous solution and the X-ray crystallography confirms the CB-like structure, as can be seen in Fig.1. The obtained product is a $\text{CB}[5]$ analogue ($\text{Me}_{10}\text{TD}[5]$), with the ten methyl groups decorated on the ring equator. The cavity, portal and outskirts diameters are accordingly determined as 4.7 Å, 2.5 Å and 7.0 Å, respectively, and the height is 5.4 Å.

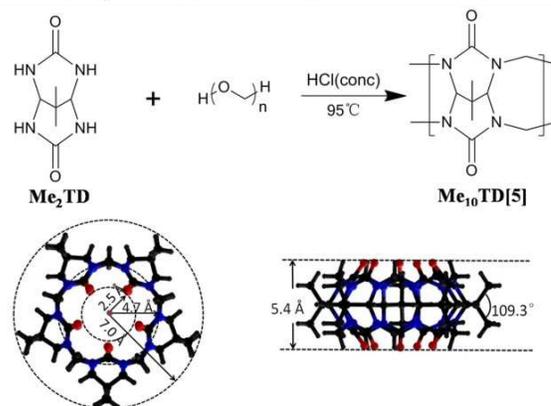


Fig. 1. The formation of $\text{Me}_{10}\text{TD}[5]$ and its single crystal structure (the Ca^{2+} , Cl^- and H_2O are omitted for clarity).

The solubility of $\text{Me}_{10}\text{TD}[5]$ was measured at room temperature in water (11.5 mmol/L), methanol (5.6 mmol/L),

DMSO (9.6 mmol/L), DMF (2.2 mmol/L), CH₃CN (<0.1 mmol/L), acetone (< 0.1 mmol/L), CH₂Cl₂(<0.1 mmol/L). It is surprising that **Me₁₀TD[5]** is more soluble in water than in organic solvents despite of the presence of the ten CH₃ groups.

The binding behaviors between **Me₁₀TD[5]** and aniline hydrochloride were then investigated in D₂O using ¹H NMR spectroscopy, which is a useful technique for the binding mode identification of CB-based inclusion complexes. On one hand, the stoichiometric ratio between the host and guest is determined as 1:2 by constructing the corresponding NMR Job plot (Fig.2 & Fig.S8). On the other hand, the aniline hydrochloride shows distinct downfield shift of *m*-protons by ca. 0.4ppm, and the scarcely affected *o*- and *p*-proton signals after complexation (Fig.S8). In most cases, the guest protons inside the hydrophobic cavity undergo shielding effects and their ¹H NMR signals upfield shift; on the contrary, the outside ones have downfield-shifted signals, whereas those protons sitting around the carbonyl portals are nearly unaffected.²⁰ These results indicate that the complexation of **Me₁₀TD[5]** with aniline hydrochloride is an outside portal binding mode,²¹ with the amine group shallowly included in the portal, leaving the *o*-protons staying near the portal, the *p*-proton standing on the axle and far away from the portal, and the *m*-protons residing among the strong deshielding area, as shown in Fig.2.

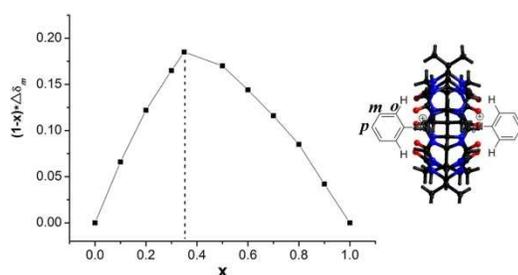


Fig. 2. Job plot for the complexation of aniline hydrochloride and **Me₁₀TD[5]** (the total concentration is 4.0 mM). The maximum value of vertical axle corresponds to 0.33 at horizontal axle, and the stoichiometry of **Me₁₀TD[5]** and aniline hydrochloride is 1:2.

Basing on the fact that each portal of **Me₁₀TD[5]** would bind to a protonized amino, linear supramolecular polymers would be expected to form when diamine molecules are mixed with **Me₁₀TD[5]**. Phenylenediamine dihydrochloride (**G₁**), which is rigid diamine molecule, was firstly used to construct the polymer. When the two aqueous solutions, both at 0.2 mM, were mixed in an equivalent molar ratio, needle like crystals with the length of several hundred nanometers can be observed in the transmission electron microscopy (TEM) image (Fig.3a). The Dynamic light scattering (DLS) measurement also gave a center of the peak at 190 nm (Fig.S9). The TEM and DLS of the macrocycle at 0.2 mM in H₂O without any guest were also recorded as controls (Fig.S10), and no obvious aggregation could be observed. These observations indicate that supramolecular complexation indeed occurs when they are mixed.²² However, many efforts had been made to obtain the single crystal of the complex but failed, and the NMR measurements of the product were also unsuccessful because of the poor solubility.

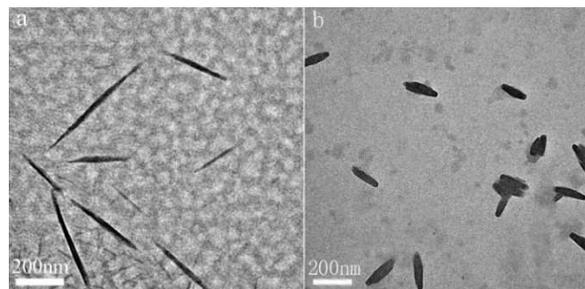


Fig. 3. TEM images of a) **Me₁₀TD[5]**+**G₁** and b) **Me₁₀TD[5]**+**G₂** (both 1 : 1, 0.2mM).

Then we turned to the second diamine, namely 1,4-xylylene diamine dihydrochloride (**G₂**), whose mixing with **Me₁₀TD[5]** in D₂O gave the distinct ¹H NMR signals (Fig.S11). Compared with the free **G₂**, the *p*-xylylene protons show downfield-shifted signals ($\Delta\delta_{H_{Me}} = +0.061$, $\Delta\delta_{H_{Ph}} = +0.059$) after mixing. These results are coincident with the suggested outside portal complexation, where the *p*-xylylene locates outside the cavity and experiences shielding effects. Rod-like crystals with the length of several hundred nanometers can be observed from the TEM image (Fig.3b) when the two aqueous solutions (both at 0.2mM) were mixed. The DLS measurements also show that the size of the crystals grows with the increasing concentrations of the binding pair from 0.05 to 0.2 mM (Fig.S9). These phenomena again prove the formation of the supramolecular polymer, which is confirmed by the subsequent X-ray crystallography. As can be seen in Fig.4, the single crystal structure clearly shows the 1:1 binding behaviour between **Me₁₀TD[5]** and **G₂**. The *p*-xylylene groups stay in the middle outside of two **Me₁₀TD[5]** macrocycles and every ammonium group binds to one carbonyl portal, leaving **Me₁₀TD[5]** and **G₂** linking end to end to form a linear supramolecular polymer.

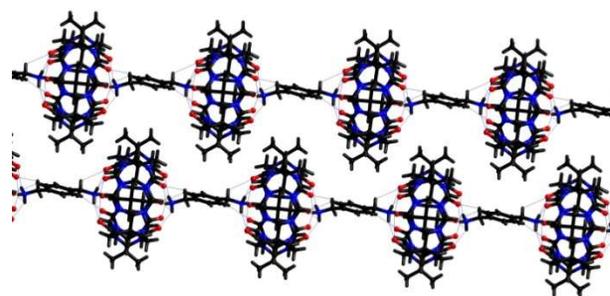


Fig. 4. The single crystal structure of the supramolecular polymer formed between **Me₁₀TD[5]** and **G₂**.

In order to estimate the binding affinities of **Me₁₀TD[5]** with aromatic ammonium and benzyl ammonium units, isothermal titration calorimetry (ITC) measurements were carried out using phenyl amine hydrochloride and benzyl amine hydrochloride as the guests of **Me₁₀TD[5]** in aqueous solution at 25°C. As illustrated in Fig.S12, the obtained K_1 and K_2 for phenyl amine hydrochloride are $(3.7\pm 1.1)\times 10^3 \text{ M}^{-1}$ and $(4.9\pm 1.2)\times 10^3 \text{ M}^{-1}$, and those for benzyl amine hydrochloride are $(8.8\pm 2.4)\times 10^3 \text{ M}^{-1}$ and $(5.9\pm 1.2)\times 10^3 \text{ M}^{-1}$, respectively. These results indicate that the binding abilities of the two portals are almost equal during the complexation.

In summary, a new CB[5]-like macrocycle **Me₁₀TD[5]** was firstly prepared and characterized. **Me₁₀TD[5]** shows special properties, such as good solubility in water and some organic solvents, as well as strong affinity with ammonium salts. Although it may not have large portal size and cavity volume as the CB analogue, but we think that the discovery of **Me₁₀TD[5]** would lead to a series of soluble CB analogues and thus push the progress of this kind of hosts. More chemistry of **Me₁₀TD[5]** is currently underway.

This work was financially supported by the National Basic Research 973 Program of China (2011CB808400), the Science Fund for Creative Research Groups (21421004), and the NSFC/China (21372076, 21190033). Q. Wang gratefully acknowledges Dr. Xin Li for the crystallography computations.

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