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The smallest cucurbituril analogue with high affinity for Ag^+

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A new host Me_8TD[4] was prepared for the first time from propanediurea-formaldehyde condensation in the presence of $CaCl_2$ as template and it is the smallest cucurbituril analogues reported so far. Thermodynamic quantities (logK, ΔH, and ΔS values) measurements of the interactions of Me_8TD[4] with a series of cations by isothermal titration calorimetry indicated that Me_8TD[4] binds selectively towards Ag^+ with a high binding constant K~$1.3\times10^6 M^{-1}$.

Cucurbit[n]uril (CB[n]) are cyclic oligomers that consist of n glycoluril units doubly linked by 2n methylene bridges.[1-4] These hosts display remarkable affinity towards positively charged species for their polar uredio carbonyl groups on both portals and the hydrophobic cavities.[5] The interaction of CB[n] with various metal ions established the CB[n]-based coordination chemistry as an increasingly important area in CB[n] chemistry.[6,7] Novel poly-dimensional CB[n]-metal ions coordination polymers exhibit important application potentials in areas such as ionic/molecular transport[8], heterogeneous catalysis[9] and gas absorption/separation[10]. It is easy to understand that CB[n] are of various portal sizes and consequently bind selectively towards metal ions[11]. For example, Me_{10}CB[5], the smallest analogue, shows a high selectivity for Pb^{2+}.[12] It is obvious that the smaller n value would result in smaller portal size, and thus might lead to selectivity towards special ions. Interestingly, the repeated number n that a cucurbituril (or an analogue)[13,14] possesses has not been lower than 5, mainly due to the high strain energy upon the cyclization of glycoluril with aldehyde (a calculated value of 23.03 Kal/mol for CB[4][15]).

We[16] have firstly reported the preparation of a CB[5]-like macrocycle **Me_{10}TD[5]** using the acid-catalyzed condensation of 9,9-Dimethyl-2,4,6,8-tetraazabicyclo[3.3.1]nonane-3,7-dione (**Me_2TD** in Scheme 1) with formaldehyde (Sindelar's group[17] reported independently the same macrocycle nearly at the same time, and named it as Me_{10}prCB[5]). It is interesting that only **Me_{10}TD[5]** was separated during our previous preparation, unlike CB[5] would form during common CB[6] synthesis[2b], which led us to think about the possibility of synthesizing a smaller homologue. Herein we report a new member of cucurbituril analogue, **Me_8TD[4]** (Figure 1), which is of smaller cavity than ever and binds selectively to Ag^+, and the value of n in cucurbit family is reduced to 4 for the first time.

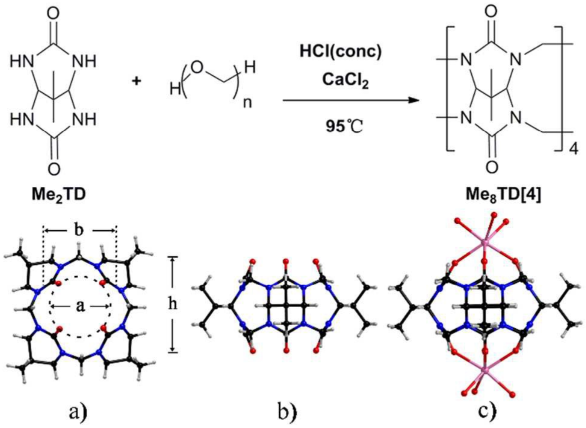

Figure.1 The formation of **Me_8TD[4]** and its single crystal structure in the absence (a, b) and presence (c) of calcium (H_2O are omitted for clarity. Hydrogen: gray, Carbon: black, nitrogen: blue, oxygen: red, Calcium: purple).

Numerous attempts for synthesizing **Me_8TD[4]** had been carried out under template-free conditions (e.g., verifying the reaction temperature, acid types and concentrations, and equivalents of formaldehyde), **Me_{10}TD[5]** had always been the sole product obtained and no **Me_8TD[4]** was found. Then we turned to the template-directed synthesis. The use of templates in the synthesis and purification of cucurbiturils is an interesting part of cucurbituril chemistry. For example, *p*-xylylenediammonium template was used to originate glycoluril

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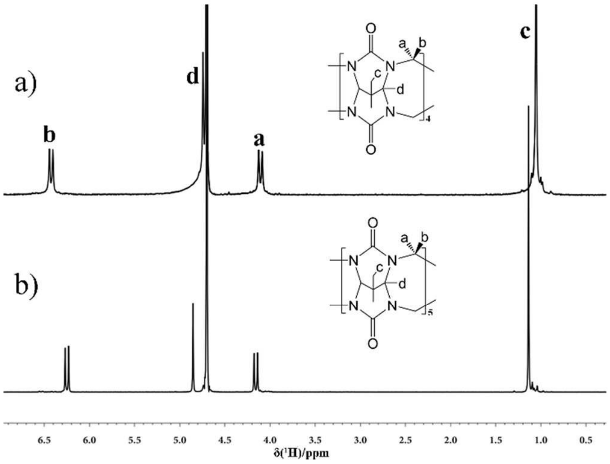

Figure 2. The ^{1}H NMR spectra (400 MHz, 25 °C, D_2O) of a) **Me_8TD[4]** and b) **Me_{10}TD[5]**, all in the presence of $CaCl_2$.

Table 1 Cavity dimensions of **Me_8TD[4]** and CB[5]

	Portal diameter (Å) (a) [a]	Cavity width (Å) (b) [a]	Height (Å) (h) [a]
Me_8TD[4]•$2Ca^{2+}$	1.2	3.4	8.6
Me_8TD[4]	1.5	3.4	8.8
CB[5]	2.4	4.4	9.1

[a] The values quoted for a, b, and h take into account the van der Waals radii of the relevant atoms.

Table 2 The solubility and thermostability of **Me_8TD[4]**

	S_{H_2O} [mM]	S_{CH_3OH} [mM]	S_{DMSO} [mM]	Stability[℃]
Me_8TD[4]•$2Ca^{2+}$	48.5	11.3	2.5	560
Me_8TD[4]	4.5	1.8	< 0.1	495

Table 3 Log K, ΔG ($kJ \cdot mol^{-1}$), ΔH ($kJ \cdot mol^{-1}$), and TΔS ($kJ \cdot mol^{-1}$) values for interactions of **Me_8TD[4]** with metal ions determined calorimetrically at 25.0 °C in deionized water.

cation	Ionic radius	Log K	ΔG	ΔH	TΔS	anion
Li^+	0.59Å	a				Cl^-
Na^+	0.97Å	3.54±0.05	-17.2±0.8	-4.8±0.8	12.4	Cl^-
K^+	1.33Å	3.38±0.05	-18.8±0.1	-1.6±0.1	17.2	Cl^-
Ag^+	1.15Å	6.11±0.03	-43.0±0.2	-62.5±0.2	-19.5	NO_3^-
Cs^+	1.67Å	a				Cl^-
Mg^{2+}	0.72Å	a				Cl^-
Co^{2+}	0.75Å	a				Cl^-
Cu^{2+}	0.73Å	a				Cl^-
Zn^{2+}	0.75Å	a				Cl^-
Ca^{2+}	0.99Å	4.85±0.04	-27.7±0.2	-21.0±0.2	6.7	Cl^-
Sr^{2+}	1.13Å	4.66±0.04	-25.7±0.2	-19.3±0.2	6.4	Cl^-
Ba^{2+}	1.35Å	4.88±0.03	-34.7±0.4	-27.5±0.4	7.2	Cl^-
Pb^{2+}	1.19Å	4.79±0.04	-27.4±0.2	-11.3±0.2	16.1	NO_3^-

a No measurable heat during the isothermal titration calorimetry experiments.

hexamer and the preparation of monofunctionalized CB[6][18], and the addition of K^+ produced a high proportion of CB[5], which gave a convenient method for isolating CB[5][19].

Positive results were thus expected to be achieved during the **Me_8TD[4]** forming reaction by using suitable templates, for their structural similarities to cucurbituril. It was indeed surprising when calcium chloride was added to the reaction of **Me_2TD** with formaldehyde. The ^{1}H NMR spectra of the precipitated solid (Figure 2a) shows four groups of proton resonances with 1 : 1 : 1 : 3 intensity, indicating a typical symmetrical CB[n] analogue. The chemical shifts of the two ethylene protons move from 6.26 & 4.19ppm to 6.44 & 4.11ppm, respectively, when compared with **Me_{10}TD[5]**+$CaCl_2$, possibly indicating the formation of a new homologue. Further MALDI-TOF measurement (Fig. S4) gave the expected result—an intense peak at m/z= 855.3736, which corresponds to the $[M+Na]^+$ (calcd. 855.3739) of **Me_8TD[4]**. The X-ray crystallography (Figure 1) demonstrated the tetrameric structure of four **Me_2TD** units doubly bridged by 8 methylene linkers.

The products of **Me_8TD[4]** at this stage was the complex with $CaCl_2$ in a ratio of 1:2, which was confirmed by X-ray crystallography (Fig. S19) and Atomic Absorption Spectroscopy (Fig. S20). The calcium ion was finally removed from **Me_8TD[4]** after several unsuccessful attempts (for example, column chromatography on ion-exchange resin and repetitive recrystallization from dilute HCl), using ethylenediaminetetraacetic acid (EDTA, a calcium chelator) and $(CH_3)_4N^+OH^-$ (the yield of **Me_8TD[4].2Ca^{2+}** was 5%, and the final yield of **Me_8TD[4]** was 2%, see supporting information).

The Ca^{2+}-free **Me_8TD[4]** was also characterized by single-crystal X-ray diffraction, as can be seen in Figure 1. The structural dimensions of **Me_8TD[4]** and its calcium complex obtained from the crystallographic computations are listed in Table 1. The cavity dimensions *a*, *b* and *h* of **Me_8TD[4]** are greatly reduced to 1.2 Å, 3.4Å and 8.6Å respectively, which are significantly smaller than those of the smallest cucurbit family CB[5] (*a*=2.4Å, *b*=4.4Å, and *h*=9.1Å). The cavity volume of the **Me_8TD[4]** is accordingly estimated as 38 Å^3, making it the smallest cucurbituril-like cavity size so far to the best of our knowledge. It should be noted that the portal size of **Me_8TD[4]** decreases by 0.3Å and the height decreases by 0.2Å when binds with calcium cation.

The solubility of **Me_8TD[4]** in common solvents at room temperature was also determined by ^{1}H NMR spectroscopy with an internal standard[13a] (see Supporting Information), as illustrated in Table 2. It can be seen that **Me_8TD[4]** shows somewhat solubility in water and methanol (4.5mM and 1.8mM, respectively) and almost no solubility in DMSO. In comparison , the Ca^{2+}-complexed **Me_8TD[4]** show remarkable increased solubility in these solvents—48.5mM in water, 11.3mM in methanol and 2.5mM in DMSO.

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Thermal gravimetric analysis (TGA) of **Me_8TD[4]** was carried out in nitrogen atmosphere to 600℃ to evaluate their thermal stability. We did not detect mass loss related to the decomposition of **Me_8TD[4]** or its calcium complex up to 490 ℃ (Table 2 & Fig. S5), indicating that the macrocycle possesses excellent thermal stability which is comparable with cucurbiturils (exceed 370℃) [20].

The relatively good solubility of free **Me_8TD[4]** allows us to investigate the host-guest chemistry of **Me_8TD[4]** with metal ions in neutral water. Log K, ΔG, ΔH, and TΔS values for the interactions of the metal ions with **Me_8TD[4]** in H_2O are listed in table 3. Those metal ions with small radius—Li^+(0.59Å), Mg^{2+}(0.72Å), Co^{2+}(0.75Å), Cu^{2+}(0.73Å) and Zn^{2+}(0.75Å)[5b]—show no measurable heat during the titration (see Supporting Information), suggesting none or tiny complexation with **Me_8TD[4]**, and Cs^+, which is of tremendous radius(1.67Å), also shows no complexation. By contrast, those metal ions, whether they are one monovalent or bivalent, with moderate ionic radius—Na^+ (0.97Å), Ca^{2+} (0.99Å), Sr^{2+}(1.13Å), Ag^+(1.15Å), Pb^{2+} (1.19Å), K^+(1.33Å) and Ba^{2+} (1.35Å)—display considerable affinities with **Me_8TD[4]**. For those monovalent ions, it seems that there has an optimal radius during the combination, because Ag^+ has the maximum K value of $1.3\times10^6M^{-1}$, Na^+ (smaller radius than Ag^+ with smaller $K{\sim}3.5\times10^3M^{-1}$) and K^+ (bigger radius with smaller $K{\sim}2.4\times10^3M^{-1}$) come second, while Li^+ (smallest radius) and Cs^+ (biggest radius) rate final (no combinations). While for those bivalent ions, no optimal ionic radius can be found because the ions whose radius ranging from 0.99Å to 1.35Å are of similar K values ($Ca^{2+}{\sim}7.1\times10^4$, $Sr^{2+}{\sim}4.7\times10^4$, $Ba^{2+}{\sim}7.6\times10^4$, and $Pb^{2+}{\sim}6.2\times10^4M^{-1}$, respectively). Nevertheless, the none-combination to **Me_8TD[4]** of the bivalent ions (Mg^{2+}, Co^{2+}, Cu^{2+} and Zn^{2+}) with small radius is the same situation as that of the monovalent ion. It should be pointed out that **Me_8TD[4]** bind selectively to Ag^+ with a K value of more than two orders of magnitude larger than other ions.

The isothermal titration calorimetry results also indicate that Ag^+, Pb^{2+} and Ba^{2+} form 1:1 complexes, while the other cations form 2:1 ones with **Me_8TD[4]**. These phenomenons should be attributed to the fact that the two cucurbituril portals, on one hand, could bind respectively with two ions to form a capsule-like molecule; and on the other hand, could binds to one ion end to end, generating a linear supramolecular polymer. These two binding behaviors have been confirmed in Tao's report[21], where pentacyclopentanocucurbit[5]uril binds 1:2 with Ca^{2+} and Sr^{2+}, and 1:1 with Ba^{2+}.

In conclusion, we have synthesized a new cucurbituril-like macrocycle, **Me_8TD[4]**, by acid-catalyzed condensation of dimethylpropanediurea and formaldehyde in the presence of $CaCl_2$ template. **Me_8TD[4]** is the smallest cucurbituril analogues reported so far with four repeated bi-uredio units, having smaller portal diameter, cavity width, and lower height when compared with other cucurbituril species, and exhibits excellent thermal stability. It should be emphasized that **Me_8TD[4]** shows an outstanding binding selectivity toward silver ion over a series of other metal ions.

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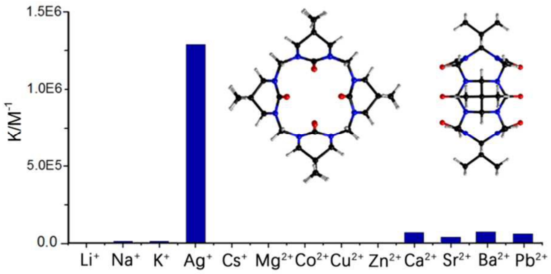

A smallest cucurbituril analogue with four repeated bi-uredio units was firstly synthesized and it binds selectively towards Ag$^+$.