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Helianthus-like Cucurbit[4]uril and Cucurbit[5]uril analogues

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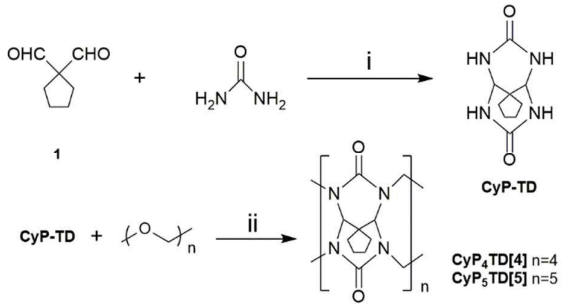
A new glycoluril-like molecule, cyclopentanopropanediurea (CyP-TD), was prepared from malonic ester synthesis. Its condensation with paraformaldehyde resulted in two Helianthus-like cucurbituril analogues, $CyP_4TD[4]$ and $CyP_5TD[5]$, with cyclopentano groups evenly decorated on the equators. The structures of the two macrocycles were confirmed by by ^1H NMR, HRMS-ES and single crystal X-ray diffraction. $CyP_4TD[4]$ and $CyP_5TD[5]$ both exhibits excellent thermal stability, and $CyP_5TD[5]$ has better solubility in water and organic solvents while $CyP_4TD[4]$ could hardly dissolve.

Cucurbit[n]urils (CB[n]), macrocyclic hosts obtained from glycoluril-formaldehyde condensation,[1] are of high binding affinity and selectivity towards charged guest species[2], and have been widely used in the fields of such as molecular machines,[3] drug carriers,[4] supramolecular polymers[5] and sensing ensembles.[6] The exploration of new cucurbituril homologues and analogues has been being the hot topic in the area of cucurbituril chemistry.[7] These new hosts have greatly enlarged the cucurbituril family and aroused further interest on their modification, so as to endow them aditional functions[8-11] or to improve their solubility.[12,13] However, glycoluril derivatives with too large substituents stretching away on both sides of the glycoluril at the waist methine bridge positions would be unfavourable to the cyclization upon the condensation with formaldehyde, and as a result, few glycolurils, except dimethyl,[14] cyclopentano[15] and cyclohexano[16] glycoluril have been reported to produce cucurbiturils. In comparison, when substituents are introduced on the central methylene position of a propanediurea (2,4,6,8-tetraazabicyclo[3.3.1]nonane-3,7-dione, **TD**), which possesses the similar structure characteristics of glycoluril, they might have less influence upon the cucurbituril-forming cyclization.



Scheme 1. The synthesis of CyP-TD[n]s. Reaction condition: (i) CH_3COOH, H_2SO_4, 90°C. (ii) concd HCl, 90°C. $CaCl_2$ was added in the case of $CyP_4TD[4]$.

For example, we has been able to use dimethylpropanediurea **Me_2-TD** to synthesize decamethyl-decorated cucurbit[5]uril analogue (**$Me_{10}TD[5]$**),[17] so does Sindelar's group[18]. More recently, we also reported the synthesis of the smallest cucurbituril analogue **$Me_8TD[4]$**, [19] which binds selectively towards Ag^+ with high K constant, basing on the same building block. With the above works done, we naturally expected to see 1) whether **TD** with larger substituents on the equator could conduct the cyclization reaction with formaldehyde, and 2) if the above cyclization undergoes, whether the formed

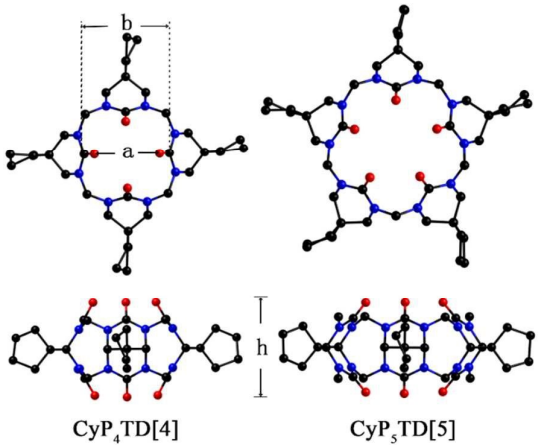


Figure.1 Top and side view of X-ray crystal structures of **$CyP_4TD[4]$** and **$CyP_5TD[5]$**. Color codes: carbon, black; nitrogen, blue; oxygen, red (the Ca^{2+}, Cl^- and H_2O are omitted for clarity).

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cucurbituril analogues could have better solubility.

Herein we report a facile strategy to obtain glycoluril-like cyclopentanopropanediurea (**CyP-TD**) and its condensation with formaldehyde to form two helianthus-like cucurbituril analogues, **CyP$_4$TD[4]** and **CyP$_5$TD[5]**, as shown in Scheme 1. Owning to the introduction of the five hydrophobic cyclopentano groups, **CyP$_5$TD[5]** has better solubility in organic solvents such as CH_3OH and DMSO, but poorer solubility in H_2O, when compared with **Me$_{10}$TD[5]**. But for **CyP$_4$TD[4]**, its solubility in these common solvents is extremely low instead of being improved.

The preparation of **CyP-TD** was started from the cyclic alkylation of malonic ester, followed by the reduction to diol using $LiAlH_4$, then the oxidation to 1,1-cyclopentanedicarbaldehyde (**1**) [20] (Scheme S1, supporting information), and the final condensation with urea. This strategy allows the preparation of other substituted **TD**s by simply changing the alkylating agent. The condensation of **CyP-TD** with formaldehyde was then carried out in concentrated HCl at 95°C for 24 h, the same procedure as used in the preparation of **Me$_{10}$TD[5]**. White precipitate appeared after cooling and was collected by filtration. After being washed with dilute HCl solution, a pure substance was obtained. The ^{1}H NMR spectra of this solid in D_2O shows 3 groups of proton resonances (Figure S4, supporting information), with the propanediurea CH proton signal covered by the solvent peak of D_2O. After the addition of $CaCl_2$, the CH proton signal moves out and the ^{1}H NMR spectra (Figure 2a) shows four groups of proton resonances with the integration ratio of 1: 1: 1: 4. The NMR result indicates a structure of typical symmetrical CB[n] analogue. The HRMS-ES measurement (Figure S7) revealed the formation of the cyclic pentamer **CyP$_5$TD[5]**, giving an intense peak at m/z 1193.5486 that corresponds to $[M+Na]^+$ (calcd. 1193.5481). The final structural confirmation was conducted by X-ray crystallography, as shown in Figure 1. **CyP$_5$TD[5]** consists of five **CyP-TD** units linked by 10 methylene bridges, bearing a hydrophobic cavity and two identical carbonyl portals, and shows the same structural characteristic as cucurbituril, and the top view of which looks like a sunflower.

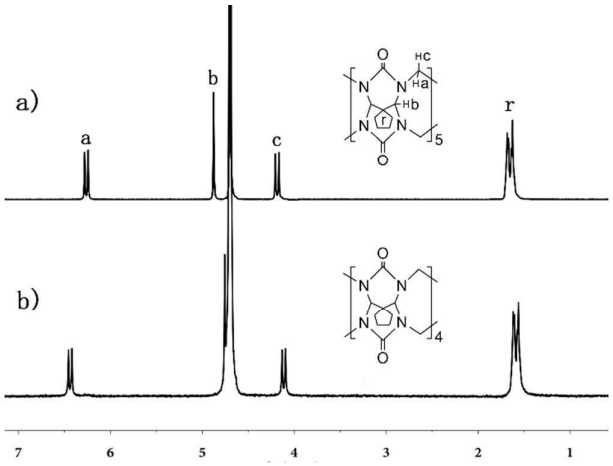

Figure 2. The ^{1}H NMR spectra (400 MHz, 25 °C, D_2O) of a) **CyP$_5$TD[5]** and b) **CyP$_4$TD[4]**, both in the presence of $CaCl_2$.

The yield of **CyP$_5$TD[5]** was 8%.

When calcium chloride was added to the reaction of **CyP-TD** with formaldehyde, the same template-directed strategy as used in the preparation of **Me$_8$TD[4]**, the ^{1}H NMR spectra of the precipitated solid gave one set of peaks, as shown in Figure 2b. The chemical shifts of the two ethylene protons move from 6.26 & 4.19ppm to 6.44 & 4.11ppm, respectively, when compared with **CyP$_5$TD[5]**+$CaCl_2$. The NMR result again suggested the formation of a new symmetrical homologue. Further MALDI-TOF measurement (Figure S10) gave an intense peak at m/z=959.4362, which corresponds to the $[M+Na]^+$ (calcd. 959.4365) of **CyP$_4$TD[4]**. The X-ray crystallography (Figure 1 & Figure S12) confirmed the tetrameric structure of four propanediurea units doubly bridged by 8 methylene linkers.

The X-ray crystallography and Atomic Absorption Spectroscopy (Figure S13) measurements indicated that the product at this stage was the complex of **CyP$_4$TD[4]** with $CaCl_2$ in a ratio of 1:2. The calcium was then removed by treating **CyP$_4$TD[4]•2CaCl$_2$** solution with EDTA and $(CH_3)_4N^+OH^-$ (see supporting information for details). The validity of this method was confirmed by elemental analysis (Figure S15). The yield of **CyP$_4$TD[4]•2CaCl$_2$** was 5% and the final yield of **CyP$_4$TD[4]** was 2%.

It can be seen that the yields of **CyP$_4$TD[4]** and **CyP$_5$TD[5]** were both low, so we turned to study the composition of the filtrates. Acetone was then added to filtrates respectively and the resulting precipitates were collected by filtration. The ^{1}H NMR spectrum of the solid from the **CyP$_4$TD[4]** filtrate (Figure S16) indicated that no **CyP$_5$TD[5]** formed during the Ca^{2+} template-directed **CyP$_4$TD[4]** synthesis, because the typical peak at 4.88 ppm (H_b of **CyP$_5$TD[5]** in the presence of Ca^{2+}) was not found. And the ^{1}H NMR spectrum of the solid from the **CyP$_5$TD[5]** filtrate (Figure S17) showed it might contain homologues or acyclic oligomers. However, further MS measurements (Figure S18) showed no sign of other homologues, such as **TD[6]** (*m/z* 1404.6701) or **TD[7]** (*m/z*

Table 1 Cavity dimensions of **CyP-TD[n]**[a]

	Portal diameter (Å) (a)[b]	Cavity width (Å) (b)[b]	height (Å) (h)[b]
CyP$_5$TD[5]	2.2	4.8	8.2
CyP$_4$TD[4]	1.2	3.4	8.6

[a] Based on X-ray crystal structures of CyP-TD[n]/Ca^{2+} complexes.
[b] 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 **CyP-TD[n]**

	S_{H_2O} [mM]	S_{CH_3OH} [mM]	S_{DMSO} [mM]	Stability[℃]
CyP$_5$TD[5]	6.3	10	14	490
CyP$_4$TD[4]	< 0.1	< 0.1	< 0.1	490
CyP$_4$TD[4][c]	24.2	12.5	2.1	560

[c] The solubility and stability in this case was measured in the form of Ca^{2+} complex at 25°C.

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1638.7817). Many efforts had been made to isolate any pure species from the above two filtrate, but all failed.

The structural dimensions of **CyP$_4$TD[4]** and **CyP$_5$TD[5]** basing on the X-ray crystal structures are listed in table 1. The portal size, cavity width, and the height of **CyP$_4$TD[4]** are 1.2Å, 3.4Å and 8.6Å, respectively, while those of **CyP$_5$TD[5]** are 2.2Å, 4.8Å and 8.2Å, respectively. The cavity volume of **CyP$_4$TD[4]** and **CyP$_5$TD[5]** were then calculated as 38Å^3 and 82Å^3 respectively. The structural dimensions of **CyP$_4$TD[4]** is essentially the same as those of **Me$_8$TD[4]**, just like the fact that the cavity of **CyP$_5$TD[5]** equals to that of **Me$_{10}$TD[5]**.

The solubility of **CyP$_4$TD[4]** and **CyP$_5$TD[5]** in water and organic solvents was determined by ^{1}H NMR spectroscopy with an internal standard[6a] at 25°C (see Supporting Information for details), as illustrated in Table 2. It can be seen that **CyP$_5$TD[5]** has better oil solubility (10mM in methanol and 14mM in DMSO), but poorer solubility in H_2O (6.3mM), when compared with **Me$_{10}$TD[5]** (5.6mM in methanol, 9.6mM in DMSO, and 11.5mM in H_2O), mainly due to the introduction of the five hydrophobic cyclopentano groups. In comparison, **CyP$_4$TD[4]** does not show the solubility enhancement as expected, it could hardly dissoveled among these solvents. However, it should be noted that **CyP$_4$TD[4]•2CaCl$_2$** shows remarkable solubility in water (24.2mM), moderate one in methanol (12.5mM), though relatively poor in DMSO (2.1mM).

Thermogravimetric analysis revealed that **CyP$_4$TD[4]** and **CyP$_5$TD[5]** have good thermal stability. We did not detect any mass loss connected with the decomposition of **CyP$_5$TD[5]** and **CyP$_4$TD[4]** samples under nitrogen atmosphere up to 490°C (Figure S11), which is comparable with cucurbituril homologues.

In summary, we have successfully prepared two new cucurbituril-like macrocycle, **CyP$_4$TD[4]** and **CyP$_5$TD[5]**, by acid-catalyzed condensation of cyclopentanopropanediurea and formaldehyde, in the presence and absence of $CaCl_2$ template, respectively. Compared to **CyP$_4$TD[4]** which has poor solubility in common solvents, **CyP$_5$TD[5]** has better solubility in organic solvents than **Me$_{10}$TD[5]** as expected. It should be emphasized that other substituted propanediurea could be conveniently obtained using the malonic ester synthetic strategy in this work, and other functionalized **TD[n]** might consequently be accessible.

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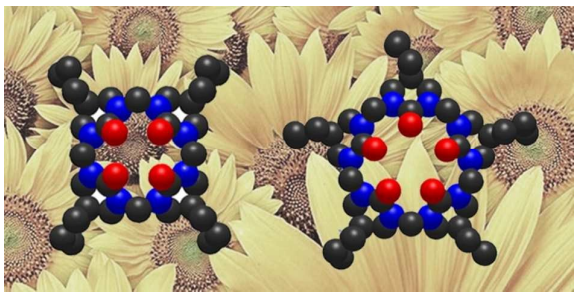

Two cucurbituril-like macrocycles were synthesized by condensing cyclopentano-subsituted propanediurea with formaldehyde in the presence or absence of Ca^{2+} respectively.