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A macrocycle-based "Russian doll": The smallest cucurbit[4]uril in cucurbit[10]uril

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ABSTRACT

Host-guest recognition-based macrocycle in macrocycle to form "Russian doll" assemblies remains an interesting topic in supramolecular chemistry. Herein, a macrocycle-in-macrocycle assembly was studied using cucurbit[10]uril (Q[10]) and the smallest cucurbituril-like macrocycle (TD[4]). X-ray crystal structure analysis revealed that TD[4] was encapsulated in the cavity of Q[10] to form a 1:1 complex. Importantly, competitive guest studies suggested that TD[4] had the highest binding constant with the Q[10] host among the guests used, including Q[5], Me_8TD[4], and amantadine molecules in water. Our results provided a new cucurbituril-based Russian-doll structure containing both the largest and smallest cavities of the cucurbiturils, which expanded the family of molecular Russian dolls.

Macrocycle-in-macrocycle assemblies, which are reminiscent of Russian dolls, have intrigued supramolecular chemists for over a decade due to their potential application in a variety of research areas [1,2]. Various molecular Russian dolls have been described in the literature based on a diverse range of supramolecular assemblies, such as fullerenes [3–6], cage-within-cage compounds [7], crown ether [2], metal clusters [8,9], cycloparaphenylenes [10], calixarene [11], porphyrin [12], ring-in-ring complexes [13], TPA Ligands [14], pillararene [15], and cucurbituril [16]. The host-guest recognition between two macrocycles to form hierarchical non-intertwined ring-in-ring or host-in-host assemblies remains a fascinating and challenging goal in noncovalent synthesis. Such complexes are promising precursors for the construction of Russian doll-like superstructures or higher order mechanically interlocked molecules, such as molecular Borromean rings [17]. However, few examples of cucurbituril-based molecular "Russian dolls" prepared *via* host-guest interactions.

Cucurbit[*n*]urils (Q[*n*]s or CB[*n*]s) [18–24], as classical macrocyclic hosts (Scheme 1), have attracted an increased research interest from supramolecular chemists given their novel hos-guest properties in catalysis [25–27], sensing [28], polymer materials [29,30], luminescent emissions [31,32], biomedical applications and so on [33–36]. In the early studies of Q[*n*]s, such as Q[8], can encapsulate macrocyclic guests, including cyclen and cyclam, allowing the formation of a "macrocycle within macrocycle" complex [16,37]. For example, a number of Russian doll-type metal-ion complexes have been successfully constructed by Kim *et al.* using Q[8] to encapsulate tetraaza macrocycles, which are modified with Cu(II) and Zn(II). Moreover, the larger cavity of Q[10] compared to Q[8] enables it to encapsulate larger macrocyclic guests. Liu [24] reported the inclusion complex of a "Russian doll" pseudorotaxane, which was assembled by threading a guest through the cavities of both the tetracationic cyclophane and Q[10]. In 2002, Day *et al.* [20] discovered that the first example of a small Q[5] contained within a large Q[10].

The formation of the 1:1 complex between Q[10] and Q[5] also led us to consider whether a smaller cucurbituril-like macrocycles would be encapsulated inside the cavity of Q[10]. TD[4] is a cucurbituril-like macrocycle synthesized from propanediurea (Scheme 1) and formaldehyde *via* an acid-catalyzed condensation reaction [38]. In this work, we have developed a "macrocycle within macrocycle" complex, in which cucurbituril-like macrocycle TD[4] and its metal complexes were encapsulated in Q[10]. By considering the capacity of this macrocycle to coordinate metal ions, the structural characteristics of TD[4] included in Q[10] were

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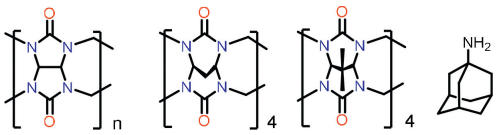

Scheme 1. Chemical structures of Q[*n*], TD[4], Me_8TD[4], and AD.

examined in the present study. This macrocycle complex is expected to have applications in several areas, such as drug delivery and ion and gas separation.

A detailed investigation on the binding of TD[4] was carried out using ^{1}H NMR spectroscopy in deuterium oxide at 295 K. The binding of a guest within the cavity of a cucurbit[*n*]uril is known to induce an upfield perturbation of the chemical shifts of its corresponding signals [39]. Fig. 1 shows the ^{1}H NMR spectra obtained for the TD[4] guest in D_2O, which was recorded in the absence and presence of different concentrations of Q[10]. The free TD[4] guest peaks were well-resolved when no Q[10] was added. Upon increasing the molar ratio of Q[10], significant ^{1}H NMR up-field shifts of the signals corresponding to TD[4] were observed. The upfield proton chemical shift was due to the shielding effect of the hydrophobic cavity of the Q[10] host. This indicated TD[4] was accommodated within the cavity of Q[10]. Moreover, after the addition of the Q[10] host to the guest solution, the resonance corresponding to the protons of TD[4] were observed to be split into two sets of signals. When adding 0.5 equiv. of Q[10], the spectrum was identical to that of the TD[4]@Q[10] complex with the addition of a second set of resonances corresponding to the free TD[4]. These spectra provided evidence that the kinetics of the exchange between the bound and unbound states was slow on the NMR time scale and thus, suggested a low dissociation rate and a high binding affinity.

We used diffusion-ordered NMR spectroscopy (DOSY) to characterize the interaction between TD[4] and Q[10] in D_2O. It is widely known that a decrease in the diffusion coefficient characterized by DOSY suggests the formation of inclusion complexes. It was found that TD[4] had a diffusion coefficient of 2.797×10^{-10} m^2/s at a concentration of 1.0 mol/L in D_2O. However, the solution comprised of a mixture of TD[4] and Q[10] (1:1) in D_2O displayed a diffusion coefficient of 1.656×10^{-10} m^2/s at the same concentration, which suggested the formation of supramolecular inclusion complexes (Fig. S1a in Supporting information). Similar to the results found with Q[5], a pronounced decrease in the DOSY values was observed upon binding Q[5] to Q[10] due to an increase in the molecular size (Fig. S1b in Supporting information). However, the difference between the values observed for the TD[4] and Q[5] complexes was very small.

Our competition studies were carried out using this system to ascertain whether there was a dominant guest in the macrocycle for Q[10]. The exchange phenomenon of the guest molecules can be observed using ^{1}H NMR spectroscopy. Herein, we monitored the spectra obtained for TD[4] combined with the Q[5]@Q[10] inclusion complex. The ^{1}H NMR titration spectra obtained for Q[5]@Q[10] recorded in the absence and presence of different equivalents of TD[4] in neutral D_2O are shown in Fig. 2. Clear upfield shifts of the signals of the Q[5] were observed when Q[10] was added. Notably, upon further addition of TD[4] to the Q[5]@Q[10] complex, the chemical shift corresponding to the signal of Q[5] returned to those observed for free Q[5], whereas all of the signals corresponding to TD[4] moved upfield. This result indicated that TD[4] competitively displaced Q[5] from the Q[10] cavity. In other words, TD[4] showed stronger binding towards Q[10] when compared to Q[5].

Subsequently, we conducted competition experiments using other guest molecules with TD[4] and Q[5], including amantadine (AD) and a methyl-substituted cucurbituril analogue (Me_8TD[4]) [40]. Amantadine is a drug that is effective in the prevention and treatment of various influenza A viruses [41] and has high binding affinities to the Q[7] host [42]. It is often used to purify Q[10] in cucurbital chemistry [43]. Considering the high binding of TD[4] to Q[10], we thought it may be possible to release amantadine from their complexes with Q[10] *via* the addition of TD[4]. AD was mixed with an equivalent of Q[10]. Upfield shift was observed for AD, indicating the formation of the AD@Q[10] complex (Fig. 3). After the addition of TD[4] to the solution, an downfield shift was observed for AD, returning the NMR signal to near that observed for the unbound chemical shift, indicating the release of AD. Similar to the results obtained for complex AD@Q[10], upon the dropwise addition of Me_8TD[4] and Me_8TD4@Q[10] with the addition of Q[5], both of the latter guests replaced the guest in the macrocycle (Figs. S2 and S3 in Supporting information). Competition experiments have allowed us to obtain the order of the binding strength of the guests with Q[10] as follows: TD[4] > Q[5] > Me_8TD[4] > AD.

Isothermal titration calorimetry (ITC) experiments were conducted at 298.15 K in a neutral aqueous solution in order to better understand the binding properties between Q[10] and the guests. ITC can also be employed to measure the thermodynamic contributions to the binding interactions between the hosts and guests. Table 1 and Figs. S4–S6 (Supporting information) show the thermodynamic parameters, which suggested that the host-guest

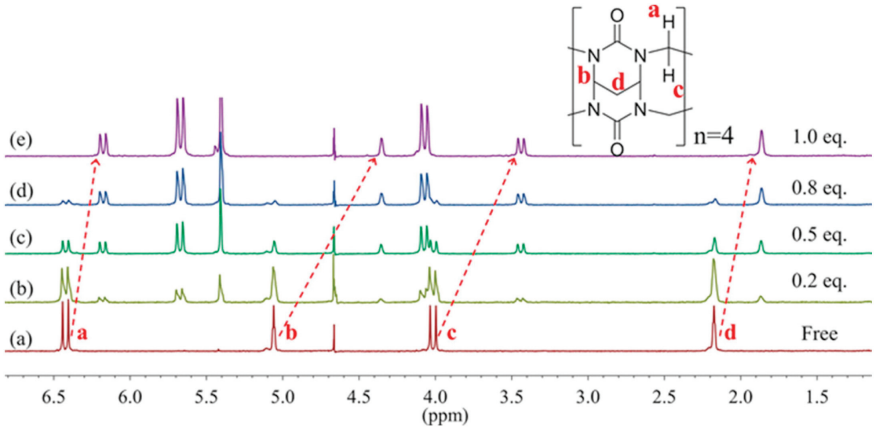

Fig. 1. Interaction of TD[4] and Q[10] (295 K): ^{1}H NMR titration spectra obtained for TD[4] in the absence (a) and presence of 0.2 equiv. (b), 0.5 equiv. (c), 0.8 equiv. (d), and 1.0 equiv. (e) of Q[10].

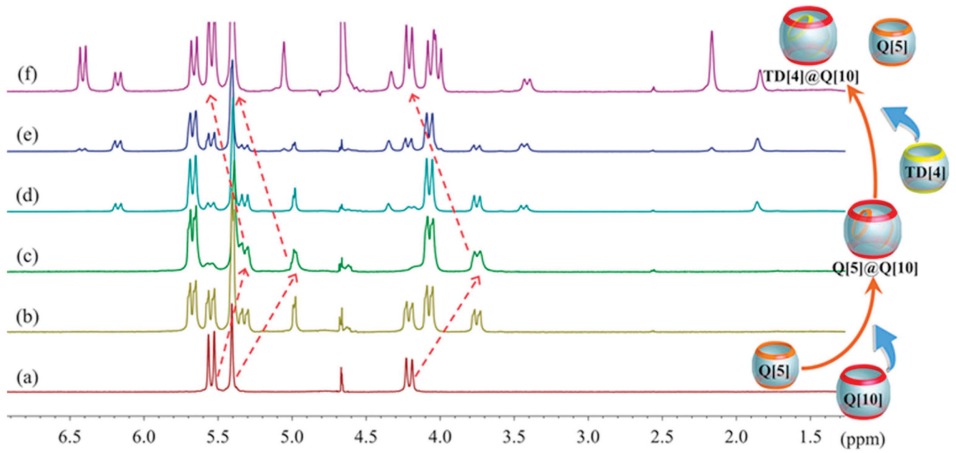

Fig. 2. ^{1}H NMR spectra obtained for Q[5] in the absence (a) and presence of 0.5 equiv. (b) and 1.0 equiv. (c) of Q[10], and the addition of 0.4 equiv. (d), 0.8 equiv. (e), and 1.2 equiv. (f) of TD[4] to the solution. Samples were prepared at a concentration of 1.0 mmol/L in deuterium oxide at 295 K.

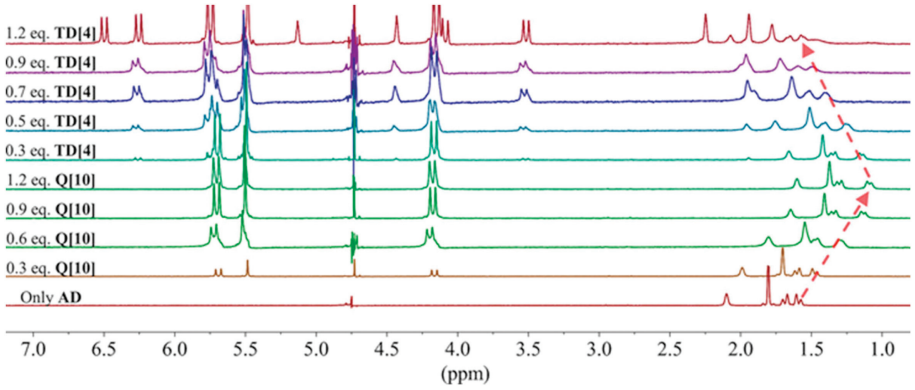

Fig. 3. ^{1}H NMR spectra obtained for AD in D_2O (1.0 mmol/L, 295 K) upon increasing the concentration of Q[10] and the addition of TD[4] to the solution.

Table 1
Binding constants (K_a) and relevant thermodynamic parameters obtained for TD[4]@Q[10], Q[5]@Q[10], and AD@Q[10].

Complex	K_a (L/mol)	ΔG (kJ/mol)	ΔH (kJ/mol)	ΔS (J mol^{-1} K^{-1})
TD[4]@Q[10]	3.96×10^6	−37.66	−53.07	−51.70
Q[5]@Q[10]	2.14×10^6	−36.14	−65.88	−99.77
AD@Q[10]	9.95×10^5	−34.23	−5.05	97.89

interactions of Q[10] with TD[4] and Q[5] were driven by enthalpy factors. Furthermore, the binding constants (K_a) of the complexations were found to be 3.96×10^6, 2.14×10^6, and 9.95×10^5 L/mol for TD[4]@Q[10], Q[5]@Q[10], and AD@Q[10], respectively. The ordering of the binding constants of these complexes from largest to smallest were in agreement with those observed in our competition experiments using ^{1}H NMR spectroscopy.

Consequently, we obtained the X-ray crystal structure of TD[4]@Q[10] complex in an effort to gain more detailed information on the host-guest interactions between Q[10] and TD[4]. In the presence of NaCl, the slow evaporation of an aqueous solution containing an equal mixture of the Q[10] host and TD[4] over two days at room temperature produced colorless crystals. Crystal structure analysis revealed that one TD[4] guest was included inside the cavity of the Q[10] host forming a 1:1 complex (Fig. 4).

The key feature of the crystalline structure of this "Russian doll" was the concentric location of TD[4] inside Q[10] with the molecular axis of TD[4] inclined 45.19° to the axis of Q[10]. Notably, other than the inclusion angle between the two macrocycle planes, the inclusion also resulted in the deformation of the host rings. It can

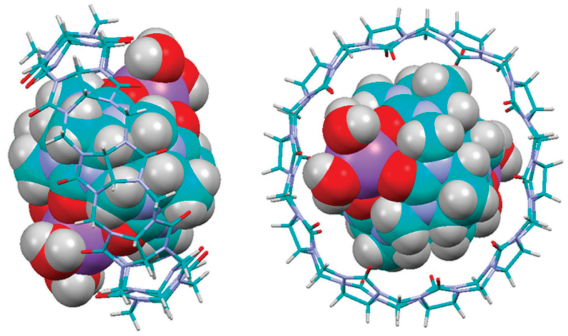

Fig. 4. Side- and top-views of the X-ray crystal structure of TD[4]@Q[10].

be seen that after inclusion, the Q[10] changed from a round cycle with a portal diameter of 13 Å to an ellipse with major and minor axes of 13.5 Å and 12.5 Å, respectively. The inner macrocycle was located in the center of the host cavity. Meanwhile, there was a sodium ion with two water molecules bound over each of the two carbonyl portals of TD[4]. Each of the sodium ions capping the TD[4] portals were also well inside Q[10]. The Na^+ with water molecules on the portals of the guest acted as two "arms" holding tightly the portals of the host. The deformation of the outer ring and stability of the complex were attributed to multiple noncovalent interactions, including hydrogen bonding between the portal carbonyl groups of Q[10] with the protons on the water molecules, which interact with the sodium ions (C=O···H–O; distances 2.774–2.818 Å) and the coordination interactions between the portal

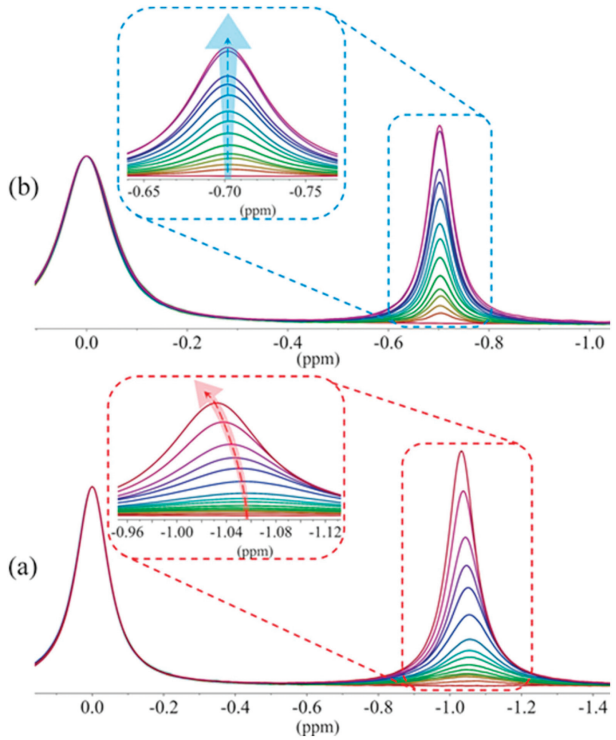

Fig. 5. ^{23}Na NMR spectra obtained for NaCl added dropwise to TD[4]@Q[10](a) and deuterated water (b), respectively.

carbonyl groups of TD[4] and the sodium ions (C=O···Na^+; distances 2.436 Å).

Similar to the structure reported by Liu [44], the macrocycle was encapsulated in the cavity of the larger Q[10] macrocycle, which resulted in the formation of a molecular Russian doll. The most salient feature of the title complex was the sodium ions, instead of potassium ions, bound over each of the two carbonyl portals of the inner macrocycle. In the reported literature of cucurbituril-based Russian doll structures, the metal ions are all simultaneously coordinated to the portals of inner macrocycle and Q[10] [44,45]. Here, however, the sodium ions were only coordinated to the portals of inner macrocycle and not to the Q[10] in the structure of the title complex. More importantly, the angle between the two macrocycle planes was ~45°, which is a relatively small inclination angle that has been reported with respect to macrocycles in similar macrocycle complexes. The angles between the two plane of Q[5]@Q[10] was ~64°. It was assumed that the larger size of the inner macrocycle forces it to adopt a larger inclination angle in the cavity of Q[10], which was similar to the presumption proposed by Kim *et al.* [16].

In the crystal structure, sodium ions play a key role in stabilizing the structure *via* coordination with the ports of the guest. The electron cloud density around the sodium ion was affected by the carbonyl-rimmed portal of TD[4], which can be characterized using ^{23}Na NMR spectroscopy. 1.0 mmol/L NaOH in deuterated water was sealed in a capillary tube as an internal standard in our ^{23}Na NMR tests. Fig. 5a shows the ^{23}Na NMR spectra obtained for TD[4]@Q[10] in D_2O, which were recorded in the absence and presence of different concentrations of NaCl. No significant signal was observed except for the peak of the internal standard (NaOH) when no NaCl was added. After the addition of NaCl to the solution, a new peak appeared at −1.06 ppm, which was ascribed to the sodium ions in the host-guest complex. Upon titration of excess NaCl into the solution, the resonances signal first increase and then exhibit a downfield shift. However, NaCl was dropwise added to deuterated water and the sodium signal was only enhanced without any significant chemical shift change, as shown in Fig. 5b. The results showed that the binding of sodium ions with the complexes led to a change in the chemical shift of sodium. We attributed this to the carbonyl oxygen of the TD[4] port, which increased the electron cloud density around the sodium ions.

Moreover, this interesting phenomenon described above was not only present in the title complex, but also in small homologous of cucurbituril. Fig. S7 (Supporting information) shows the sodium signal exhibited a significant downfield shift when NaCl was introduced dropwise to TD[4], Q[5], and Q[5]@Q[10], respectively. However, similar to deuterated water, adding sodium ions to a large polymerized cucurbituril, such as Q[10], the sodium signal was only enhanced without any significant chemical shift. Furthermore, we clearly saw that the smaller portal of cucurbituril corresponded to the more obvious shift in the sodium signal. We presumed that the smaller degree of cucurbituril polymerization led to a greater concentration of portal carbonyl oxygen atoms, which had a stronger effect on the sodium ions.

In summary, we constructed a cucurbit-based macrocycle-in-macrocycle assembly, TD[4]@Q[10], which was characterized using ^{1}H NMR spectroscopy, ITC, and X-ray crystallography. Our results showed that the Q[10] host included TD[4] to form a 1:1 complex. In particular, TD[4] showed strong binding towards Q[10] when compared to Q[5], which likely resulted from the multiple cooperation of the hydrogen binding interactions and coordination interactions between the host and guest. More detailed host-guest chemistry and coordination chemistry of TD[4]@Q[10] and its functions are currently underway in our laboratory.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cclet.2024.109782.

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