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# **Russian-Doll-Like Molecular Cubes**

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**ABSTRACT:** Nanosized cage-within-cage compounds represent a synergistic molecular self-assembling form of three-dimensional architecture that has received particular research focus. Building multilayered ultralarge cages to simulate complicated virus capsids is believed to be a tough synthetic challenge. Here, we synthesize two large double-shell supramolecular cages by facile self-assembly of presynthesized metal—organic hexatopic terpyridine ligands with metal ions. Differing from the mixture of prisms formed from the inner tritopic ligand, the redesigned metal—organic hexatopic ligands bearing high geometric constraints that led to the exclusive formation of discrete double-shell structures. These two unique nested cages are composed of inner cubes (5.1 nm) and outer huge



truncated cubes (12.0 and 13.2 nm) with six large bowl-shape subcages distributed on six faces. The results with molecular weights of 75 232 and 77 667 Da were among the largest synthetic cage-in-cage supramolecules reported to date. The composition, size and shape were unambiguously characterized by a combination of <sup>1</sup>H NMR, DOSY, ESI-MS, TWIM-MS, TEM, AFM, and SAXS. This work provides an interesting model for functional recognition, delivery, and detection of various guest molecules in the field of supramolecular materials.

## INTRODUCTION

Artificial synthetic cages are inspiring species, which could provide biomimetic microenvironments to study the weak interactions within a cavity.<sup>1</sup> Just like the ubiquitous, elegant, and functional self-assemblies in living organisms, the resulting cage complexes have precise spatial structures and, more important, consequent powerful functionalities, such as guest recognition,<sup>2</sup> chemical separations,<sup>3</sup> catalysis,<sup>4</sup> and so on.<sup>5</sup> Although the ultralarge three-dimensional molecular architectures are prevalent in biological systems such as various spherical virus capsids,<sup>6</sup> it is full of challenges to artificially obtain the nanoscale ones with accurate size and geometry using the chemical synthetic method, especially for very large self-assembled structures.' In comparing with the single-shell nanosized containers, the double-shell ones, such as cagewithin-cage structures, are attractive but rarer in nonbiological chemistry.

Coordination-driven supramolecular self-assembly is an appropriate strategy to synthesize the desired supramolecules due to its high directionality and moderate bonding strength.<sup>9</sup> Indeed, multitudinous 3D polyhedral and cage-like architectures have been expediently generated via coordination reaction of the ligands and metal ions,<sup>10</sup> represented by the prominent work of Fujita,<sup>11</sup> Stang,<sup>12</sup> Nitschke,<sup>13</sup> Raymond,<sup>14</sup> Clever,<sup>15</sup> and others.<sup>16</sup> Among these excellent works, many efforts have been dedicated to construct complex and giant 3D supramolecular structures by means of precisely designing the

ligands and rationally controlling the self-assembly process. The typical and perfect work was the giant polyhedral cage  $[M_{48}L_{96}]$  obtained by subtle control over the bent angle and geometry of bipyridine ligands from Fujita's group.<sup>7b,17</sup> In addition, the multicomponent heteroleptical coordination-driven self-assembly is an alternative strategy to construct the desired intricate and huge 3D architectures.<sup>18</sup> Another strategy to construct well-defined megastructures is using the hierarchical stepwise coordination reaction, which could avoid the unwanted self-sorting or oligomers in a multiligands system and to finally generate the predefined structures via thermodynamically driven assembly.<sup>19</sup>

Even though these sophisticated and giant synthetic metallosupramolecular cages have been well-established, before mimicking the functionality of biological systems, it remains necessary to construct supramolecular architectures with comparable size to biological molecules. For example, most virus capsids vary in diameter from tens to hundreds of nanometers and the smallest animal viruses are about 20 nm, notably the artificially synthesized well-defined supramolecules

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larger than 10 nm in diameter are rare.<sup>7b,20</sup> It is worth mentioning that the synthesis of multilayered 3D structures is of importance to further understanding of the interaction behaviors and potential applications in the field of supramolecular materials. However, only a few examples about complex-in-complex cages were reported so far. The first artificial sphere-in-sphere architecture was obtained by Fujita and co-workers by employing two tethered ligands.<sup>21</sup> The groups of Li and Mukherjee developed the square planar coordination self-assembly through tetramonodentate ligands with  $M^{2+}$  ions (M = Pd and Pt).<sup>22</sup> Different types of double-shell supramolecules and nanoclusters were also demonstrated by Schmitt,<sup>23</sup> Wang,<sup>24</sup> Sun,<sup>25</sup> and others very recently.<sup>26</sup> Terpyridine-based supramolecular double-shell structures, however, have not been reported to the best of our knowledge.

In this paper, two huge double-shell Russian-doll-like cubes were rationally designed and synthesized by the self-assembly of preorganized metal—organic multitopic terpyridine ligands and metal ions. As shown in Figure 1, the nonplanar tritopic



Figure 1. Cartoon representation of a mixture formed from tritopic ligand and a giant double-decker Russian-doll-like cube from the branched ligand with increasing coordination numbers.

ligand was assembled to form a mixture of octamer, decamer, dodecamer, and other oligomers instead of single species. Most interestingly, by introducing the affiliated outer layer through a rigid  $\langle Tpy-Ru^{2+}-Tpy \rangle$  connection to increase coordination numbers, the redesigned hexatopic units (L1 and L2) could be accurately assembled to generate the discrete double-shell architectures (L1<sub>8</sub>Zn<sub>24</sub> and L2<sub>8</sub>Zn<sub>24</sub>) due to the high geometric constraints. These two unique nested cages are composed of inner cubes and outer huge truncated cubes. Viewed from another perspective, six large bowl-shape subcages were distributed on six faces, which may provide a new type of functional supramolecular hosts for shape-, size-, and charge-selective guests.<sup>27</sup>

## RESULTS AND DISCUSSION

One Step, Self-Assembly of a Tripodal Organic Ligand with  $Zn^{2+}$ . Initially, the tripodal ligand 3 was synthesized by Suzuki Coupling reaction of bromo-substituted compound 1 and 4'-(4-boronatophenyl)[2,2':6',2"]terpyridine with Pd catalyst (Scheme S1). As shown in Figure 2, the self-



**Figure 2.** (A) Schematic illustration of self-assembly of tripodal organic ligand **3** into a mixture of octamer, decamer, and dodecamer; (B) DOSY NMR spectra (500 MHz, 298 K) of the mixtures in CD<sub>3</sub>CN/DMF- $d_{7i}$  (C) ESI-MS of multiple resultant products. Multimer complexes are named  $M_n^{x+}$ , where *n* designates the number of repeat ligands and *x* is the number of charges.

assembly of ligand 3 with  $Zn^{2+}$  ions was performed by precisely mixing two components with 2/3 ratio in CHCl<sub>3</sub>/CH<sub>3</sub>CN/ CH<sub>3</sub>OH. With the fact that ligand 3 possess the rigid ridge 1,1,1-triphenylethane core and the bent angle of tpy moieties is ca. 109°, which is similar to the adjacent edge angle  $(108^\circ)$  of dodecahedron, we expected that the 3 could form the desired single cage-like dodecahedrons. Unfortunately, both <sup>1</sup>H NMR and 2D Diffusion-ordered spectroscopy (DOSY) NMR spectra indicate the forming of mixed assemblies. As shown in Figure 2, the <sup>1</sup>H NMR spectrum of resultant products showed characteristic signals shift of terpyridine ligands after complexing, the expected upfield shift of the tpyH<sup>6,6</sup>" proton from 8.75 to 7.91 ppm was observed. Besides, there are several obvious overlapped peaks corresponding to the same proton, for example, two discernible singlets around 9.18 ppm contributed to tpyH<sup>3',5'</sup> proton (see Figure S40). Furthermore, the DOSY spectrum displayed three signal bands with log D (D is diffusion coefficient) = -10.30, -10.39, and -10.46, respectively (Figure 2B), demonstrating the formation of a mixture in  $CD_3CN/DMF-d_7$ . Further, the components of the resultant mixture were characterized by the electrospray ionization mass spectrometry (ESI-MS), in which a series of sequential charged peaks assigned to octamer, decamer, dodecamer, and others were clearly observed (Figure 2C).

Synthesis of Metal–Organic Hexatopic Ligands and Assembly of Russian-Doll-Like Cubes. Above results indicate that the tripodal ligands have a flexible structure, which could bend to form compact geometry. In order to obtain more complicated discrete assemblies, the new metal– organic ligands were synthesized by stepwise method using the

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Scheme 1. (A) Synthesis of Metallo-Organic Ligands L1 and L2 and (B) Energy-Minimized Structure of Russian-Doll-Like Cube C2



<sup>*a*</sup>Reagents and conditions: (i) *N*-ethyl morpholine, CH<sub>3</sub>OH:CHCl<sub>3</sub> (1:1, v:v), reflux, 1 d; (ii) *N*-ethyl morpholine, CH<sub>3</sub>OH:CHCl<sub>3</sub> (1:1, v:v), reflux, 1 d; (iii) Pd(PPh<sub>3</sub>)<sub>4</sub>, K<sub>2</sub>CO<sub>3</sub>, CH<sub>3</sub>CN:CH<sub>3</sub>OH (5:1, v:v), reflux, 6 d.



Figure 3. <sup>1</sup>H NMR spectra (500 MHz, CD<sub>3</sub>CN, 298 K) of (A) Metallo-organic ligand L2 and (B) Russian-doll-like cube C2; (C and D) DOSY NMR spectra (500 MHz, 298 K) of C1 and C2 in CD<sub>3</sub>CN, which showed narrow single bonds, confirming that only one species exists in the solution.

irreversible  $\langle Tpy-Ru^{2+}-Tpy \rangle$  units as connections. As shown in Scheme 1, bromo-substituted complex 13 was generated by stepwise coordination reactions, in which tetrapodal terpyridine compound 5 was first reacted with  $RuCl_3$  adducts 8 to produce mononuclear complex 9 and then when complexed

with adducts 12 to afford the desired products. The final multitopic terpyridine ligand L1 was obtained by a six simultaneous Suzuki couplings of complex 13 with 4'-(4-boronatophenyl)[2,2':6',2"]terpyridine catalyzed by [Pd-(PPh<sub>3</sub>)<sub>4</sub>] and purification by column chromatography

(Al<sub>2</sub>O<sub>3</sub>) and subsequent recrystallization. With similar process, the larger metal-organic ligand L2 was also successfully synthesized. The structures of L1 and L2 were undoubtedly characterized by NMR spectra and ESI-MS (the detailed analyses are available in the Supporting Information). As observed from Figure 3, the <sup>1</sup>H NMR of L2 showed four singlets around 9.13 ppm assigned to the tpyH<sup>3',5'</sup> protons for  $\langle$ Tpy-Ru<sup>2+</sup>-Tpy $\rangle$  moieties and two singlets at 8.88 and 8.85 ppm with 1:1 integrated ratio attributed to the tpyH<sup>3',5'</sup> of free terpyridyl fragments, and all of signal assignments were performed by 2D COSY and 2D-NOESY NMR spectra (Figure S32). As well, the ESI-MS spectrum of complex L2 showed the clear and sequential peaks at 838.83(7+), 1025.28(6+), 1286.31(5+), and 1677.85(4+), supporting the desired structure (Figure S38).

The self-assembly of Russian-Doll-Like Cubes C1 (or C2) was performed by precisely mixing ligand L1 (or L2; 1 equiv) and Zn(NO<sub>3</sub>)<sub>2</sub>·6H<sub>2</sub>O (3 equiv) in CH<sub>3</sub>CN at 85 °C for 24 h, giving a translucent red solution. After cooling to room temperature, excess lithium *bis*(trifluoromethylsulfonyl)imide  $(LiNTf_2)$  solution was added to generate a precipitate, which was washed with plenty of  $H_2O$  to give complexes C1 (or C2). The <sup>1</sup>H NMR spectrum of cubes C1 and C2 was showed in Figures S49 and 3, respectively, in which a broad signal pattern was observed due to the slow tumbling motion resulting from the formation of giant complexes.<sup>28</sup> However, both <sup>1</sup>H NMR results were similar to those for corresponding ligands L1 and L2, indicating that the resultant products are highly symmetrical. Moreover, all protons signals could be completely assigned via the 2D-COSY and NOESY NMR spectra (The detailed analyses are available in the Supporting Information).

In comparison of metal-organic ligand L2, the obvious resonance peak change for complex C2 was easily found, including obvious downfield shifts from 8.9 to 9.1 ppm for the signals of tpyH<sup>3',5'</sup> and tpyH<sup>3',3"</sup> of free terpyridine segments, owing to the tangential electron-withdrawing effects upon coordination and a dramatic upfield shift ( $\delta = 0.9$  ppm) for  $tpyH^{6',6''}$  protons due to the electron shielding effect (Figure 3B).<sup>29</sup> Similar signals shift were also observed for complex C1 (Figure S49). Such characteristic change of the tpy moieties demonstrates that the assembled complex was designedly produced. Single and discrete self-assembled structures of C1 and C2 were further supported by diffusion-ordered NMR spectroscopy (DOSY) spectrum (Figure 3C), in which all of resonance signals for the complex were on a narrow band with  $\log D = -10.03$  (C1) and -10.12 (C2), respectively, supporting the respective formation of one discrete species in CD<sub>3</sub>CN. In addition, the experimental hydrodynamic radius (rH) of C1 and C2 which derived from the Stokes-Einstein equation was ca. 6.2 and 7.4 nm, respectively.

The composition and structure of Russian-doll-like cubes C1 and C2 were fully characterized by ESI mass spectrum and traveling-wave ion mobility-mass spectrometry (TWIM-MS). As displayed in Figure 4A,C, a series of sequential peaks with charge states varying from 24<sup>+</sup> to 46<sup>+</sup> for complex C1 and 31<sup>+</sup> to 51<sup>+</sup> for complex C2 were detected, respectively. These continuous signals matched well with the simulated m/z from the theoretical molecular formula of  $(Zn_{24}Ru_{32}C_{2680}H_{1760}N_{336}O_{24})^{112+}\cdot112(NTf_2^{-})$  with the molecular weight 75232.41 Da for complex C1 and  $(Zn_{24}Ru_{32}C_{2872}H_{1888}N_{336}O_{24})^{112+}\cdot112(NTf_2^{-})$  with the molecular weight 77667.55 Da for complex C2, demonstrating the formation of desired octameric Russian-doll-like supramolec-



**Figure 4.** (A) ESI-MS and (B) 2D ESI TWIM-MS plot (m/z vs drift time) of complex C1 and (C) ESI-MS and (D) 2D ESI TWIM-MS plot (m/z vs drift time) of complex C2. The charge states of intact assemblies are marked.

ular cubes. Unfortunately, the experimental isotope pattern of each charge state for both C1 and C2 were indistinct possibly due to resolution limits by high molecular weight and/or the large cavity encapsulating the solvent molecules. Alternatively, the ESI-TWIM-MS experiments afforded additional structural evidence, in which one dominant series of continuous charge signal distributions ranging from 30<sup>+</sup> to 39<sup>+</sup> derived from complex C1 and 31<sup>+</sup> to 44<sup>+</sup> for complex C2 with a narrow drift time were discernible, and no signal peaks of other oligomer were found, which indicated that the formation here was discrete and rigid structures, as well no other isomers or structural conformers exist (Figure 4B,D).

Size Characterization by Transmission Electron Microscopy (TEM), Atomic Force Microscopy (AFM), and Small-Angle X-ray Scattering (SAXS). Many attempts to grow X-ray single crystals for Russian-doll-like cubes C1 and C2 were unsuccessful to date probably because the huge molecular frameworks and solvent molecules or counterions in the cavity. To provide more structural evidence, the TEM and AFM measurements were performed by drop-casting dilute solutions of C1 and C2 in MeCN at a concentration of  $\sim 10^{-6}$ M onto superthin carbon film-coated Cu grid or freshly cleaved mica sheet. As depicted in Figure 5C,D, TEM images displayed

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Figure 5. (A and B) Representative energy-minimized structures from molecular modeling of C1 and C2; (C and D) TEM images of C1 and C2, (E and F) AFM images of C1 and C2, and (G) SAXS profiles of the C1 and C2.

mounts of uniform dots with an average diameter of  $12.0 \pm 0.1$  nm for complex C1 and  $13.2 \pm 0.2$  nm for complex C2, which were consistent with the size simulated from molecular modeling (see also Figure S56). As well, the AFM images (Figures 5E,F, S57, and S58) showed a series of dots with average height of 8.2 and 9.5 nm, which were in accordance with the calculated height from model structure of 8.6 and 9.8 nm for C1 and C2, respectively. Furthermore, Dynamic light scattering experiments (DLS) have been also employed to measure the molecular sizes of the supramolecular complexes (Figure S59), confirmed the size distribution correlates well with the size of optimized molecular models (12.0 and 13.2 nm).

With the above structural composition and size information in mind, small-angle X-ray scattering (SAXS) measurement were further performed for C1 and C2, respectively, in solutions to access more structural information and the SAXS datum were summarized in Figure 5G. Theoretical SAXS plots were afforded using the Crysol software on the basis of the optimized structure models of C1 and C2, generated from the Material Studio platform. The experimental SAXS curves fitted quite well with the simulated data, especially the oscillation features and local minimum, suggesting that the overall morphology of the two samples in solutions are consistent well with the theoretical models. In addition, the discrepancy between the theoretical plots of a small cubic structures and experimental scattering data of C1 and C2 excludes the possibility of the formation of small nanocages (Figure S60). The less-resolved peaks with low amplitude may be due to the existence of large void areas in the framework structures, which verifies the incompact structures of Russian-doll-like cubes C1 and C2.

# CONCLUSIONS

In conclusion, we herein report a synthetic approach to Russian-doll-like cubes whose molecular weight and size were among the largest cage-within-cage supramolecules. The inner cubic shell and the outer huge truncated cube were bridged through eight  $\langle Tpy-Ru^{2+}-Tpy \rangle$  connectivities. This successful result shows that mutil-topic ligands with high geometric constraints are important for the generation of single species. The cage-within-cage structures were confirmed by a series of experiments including <sup>1</sup>H NMR, DOSY, ESI-MS, TWIM-MS, TEM, AFM, and SAXS, suggesting that the designed double-shell cages have a molecular weight up to 77 667 Da and possess a size up to 13.2 nm. This strategy used in this study will pave a new avenue toward precisely constructing more giant supramolecules. In addition, the large bowl-shape

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subcages within the assemblies that may provide a new type of functional supramolecular hosts for shape-, size-, and chargeselective guests. Such exquisite and huge self-assembled architectures will also arouse more interest and further research on exactly where is the end for the size of well-defined artificial synthetic assemblies.

## ASSOCIATED CONTENT

## **Supporting Information**

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.0c11703.

Experimental procedures and characterization data, including <sup>1</sup>H, <sup>13</sup>C, COSY, NOESY, and DOSY spectra of the new compounds and ESI-MS spectra, TEM, and AFM images of related compounds (PDF)

Movie of the Russian-doll-like cube C1 (MOV)

Movie of the Russian-doll-like cube C2 (MOV)

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#### **Author Contributions**

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#### Notes

The authors declare no competing financial interest.

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## NOTE ADDED AFTER ASAP PUBLICATION

This paper published ASAP on December 30, 2020 with an error in Figure 5. The figure was replaced and the revised paper reposted on January 5, 2021.