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Assembling Pentatopic Terpyridine Ligands with Three Types of Coordination Moieties into a Giant Supramolecular Hexagonal Prism: Synthesis, Self-Assembly, Characterization, and Antimicrobial Study

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Abstract

Three dimensional (3D) supramolecules with giant cavities are attractive due to their wide range of applications. Herein, we used pentatopic terpyridine ligands with three types of coordination moieties to assemble two giant supramolecular hexagonal prisms with a molecular weight up to 42 608 and 43 569 Da, respectively. Within the prisms, two double-rimmed Kandinsky Circles serve as the base surfaces as well as the templates for assisting the self-sorting during the self-assembly. Additionally, hierarchical self-assembly of these supramolecular prisms into tubular-like nanostructures was fully studied by scanning tunneling microscopy (STM) and small-angle X-ray scattering (SAXS). Finally, these supramolecular prisms show good antimicrobial activities against

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Supporting Information

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Synthetic details, molecular modeling, ligand and complex characterization, including ¹H NMR, ¹³C NMR, 2D COSY, 2D NOESY, 2D DOSY, ESI-MS, UV-vis, emission spectra and additional STM images (PDF)

The authors declare no competing financial interest.

Gram-positive pathogen methicillin-resistant *Staphylococcus aureus* (MRSA) and *Bacillus subtilis* (*B. subtilis*).

Graphical Abstract

INTRODUCTION

Self-assembly as an “order-out-of-chaos” strategy is widely utilized by nature to efficiently assemble biological structures with sophisticated functionalities.¹ In the supramolecular chemistry field, coordination-driven self-assembly plays an important role in the construction of a wide variety of metallo-supramolecules in a well-controlled manner.² Particularly, three-dimensional (3D) supramolecules³ with cavities are very attractive due to their applications in catalysis,⁴ stabilization of (air/water)-sensitive molecules,⁵ drug delivery,⁶ and artificial transmembrane channels.⁷ Among these 3D structures, supramolecular prisms have been assembled mainly through the following four strategies: (i) two-component self-assembly with multitopic subunits at the lateral/base faces hinged by ditopic motifs as the vertices or pillars;^{8,9} (ii) multicomponent self-assembly with lateral face motifs, base building blocks, and metal vertices;^{5b,c,10,11} (iii) multicomponent self-assembly with the assistance of template molecules;¹² (iv) subcomponent self-assembly with linear ligands as the edges of both base and lateral face.^{7a,13} However, most of the ligands were designed with high symmetry to afford all the metal binding sites with the same chemical environment. It remains a challenge to introduce different coordination environments into the same ligand to further enhance the complexity of prisms.

In supramolecular chemistry, pyridinium salts have been extensively utilized as building blocks to assemble cages with good solubility in water and tunable host–guest interactions on the basis of their multiple positive charges.¹⁴ Consequently, a wide range of 3D structures, such as triangular prism,¹⁵ molecular dice,¹⁶ bowl shape cage,¹⁷ and octahedron,¹⁸ have been constructed with pyridinium moieties. In most of these cases, pyridinium groups were introduced into the backbone via pendent linkers. Without sufficient rigidity and directionality, the so-formed pyridinium ligands, however, were unable to assemble large 3D supramolecules with higher complexity through a directional bonding approach.^{2b} Pyrylium salt–aryl primary amine condensation is an alternative synthetic approach to introduce a pyridinium group into supramolecular architectures with rigid backbones.¹⁹ Benefiting from the efficient condensation reaction as well as the modularized synthetic strategy, a series of giant 2D Kandinsky Circles (**KCs**) with concentric hexagon rings was obtained in our previous study, in which pyridinium groups were acting as bridges connecting different rims.²⁰ In addition, these 2D **KCs** showed potent antimicrobial activity against Gram-positive pathogen methicillin-resistant *Staphylococcus aureus* (MRSA) through the formation of transmembrane channels.^{20a}

Beyond 2D concentric hexagons, we herein designed and assembled hexagonal prisms based on pyrylium salts and pyridinium salts chemistry. We prepared two pentatopic 2,2':6',2''-terpyridine (TPY) ligands, in which the metal-TPY coordinations are settled in three different environments (Scheme 1, TPY^{a-c}). After assembly, giant and discrete 3D supramolecular hexagonal prisms, were constructed with two **KCs** as the bases and the tail-anchored <TPY–Cd–TPY> linkages as the lateral edges, respectively. The obtained hexagonal prisms have a high tendency to further hierarchically assemble into 1D nanostructures by base-to-base stacking in solution. In addition, these hexagonal prisms display antimicrobial activity against Gram-positive bacteria, including MRSA and *Bacillus subtilis* (*B. subtilis*).

RESULTS AND DISCUSSION

Synthesis of the Ligands and Self-Assembly of the Complexes.

To incorporate 2D **KCs** into 3D hexagonal prisms, an additional TPY group is necessary to serve as the lateral edges, which act in a distinct structural role compared to the base edges. As such, the 1,3-substituted phenyl group was introduced to the ligand as a spacer, providing the anchored TPY a freely rotating axle as well as the rigid backbone with a proper intrinsic angle for adapting a vertical conformation to the hexagonal base surface during the self-assembly. Accordingly, a new pentatopic TPY ligand, **L1**, was designed as shown in Scheme 1 and efficiently synthesized by utilizing the pyrylium–pyridinium salts chemistry.²⁰ During the synthesis, the key precursor diketone **5** was prepared via a 3-fold Suzuki coupling reaction based on the tribromo-pyrylium salt **3**. Note that the reaction time (6 h) was one of the most crucial parameters to achieve a good yield (65%), owing to the instability of **5** under basic condition. Another ligand, **L2**, with a longer alkyl chain was prepared via the similar procedure.

With the ligands in hand, another crucial requirement of forming the desired prism is a precise narcissistic self-sorting of the three distinct types of TPY groups to form <TPY^a–Cd(II)–TPY^a>, <TPY^b–Cd(II)–TPY^b>, and <TPY^c–Cd(II)–TPY^c> coordination sites during the self-assembly. Without fully excluding the possibilities of undesired coordination, polymeric complex instead of discrete structure could be formed during the assembly. To address the above concerns, self-assembly of the pentatopic ligands with Cd(II) ion was performed because of its higher reversibility.^{20a} The self-assembly was performed in DMSO (10 mg/mL of **L1** or **L2**) at 80 °C for 12 h with the stoichiometric ratio of ligand/metal = 2/5 (Figure 1a).

Characterization of Supramolecules.

Electrospray ionization-mass spectrometry (ESI-MS) was first utilized to characterize the obtained complexes (the anions were exchanged to PF₆[–]), as shown in Figure 2. Figure 2a (**HP1**) shows one dominant set of peaks with continuous charge states ranging from 16+ to 32+, due to successive loss of the counterions, PF₆[–]. A very similar spectrum of **HP2** is observed (Figure 2c) with slight shifts of the peaks toward higher *m/z* region. After deconvolution, the average molar masses of **HP1** and **HP2** are 42 608 and 43 569 Da, respectively, matching well with their expected chemical compositions

$[(C_{164}H_{139}N_{16}O_4)_{12}Cd_{30}(PF_6)_{72}]$ (**HP1**) and $[(C_{170}H_{151}N_{16}O_4)_{12}Cd_{30}(PF_6)_{72}]$ (**HP2**), ruling out the possibilities of forming other undesired complexes. These two supramolecules are among the largest metallo-supramolecules ever reported.²¹ The traveling wave ion mobility-mass spectrum (TWIM-MS)^{20a,22} of **HP1** (Figure 2b) displays a series of bands with narrowly distributed drifting time at each charge state, indicating no other isomers or conformers exist. **HP2** also displays similar TWIM-MS spectrum shown in Figure 2d.

NMR spectroscopy was further employed to identify the structural information on the complexes by comparing with their corresponding ligands. Figure 3 displays the 1H NMR spectra of **HP1** and **L1**. **L1** exhibits three different sets of TPY protons with an integration ratio of 1/2/2 (Figure 3a), corresponding to the TPY groups in the tail (TPY^a), the outer rim (TPY^b), and the inner rim (TPY^c) of the ligand, respectively. After coordination, characteristic upfield shifts of all TPY-H_{6,6''} signals are observed with $\delta = 0.8$ –1.0 ppm (Figure 3b), which is attributed to the electron shielding effect of the <TPY–Cd(II)–TPY> coordination environments.²³ Also, much broader spectrum is displayed after coordination, due to the lower tumbling motion of the protons in the large complex.²¹ Notably, four sets of distinct TPY-H^{3',5'} signals were clearly observed in the spectrum of **HP1** instead of three sets in the case of **L1**. The additional set of signals is caused by the splitting of TPY-H^{a3',5'} after the formation of the <TPY–Cd(II)–TPY> lateral edges. One possible reason for the splitting is probably ascribed to the steric hindrance of the lateral faces, which blocks the free rotation of the TPY group and further slows down the tumbling motion of TPY-H^{a3',5'}. As a result, much broader TPY-H^{a3',5'} signals are observed, compared with TPY-H^{b,c3',5'} signals. 1H NMR spectrum of **HP2** shows exactly the same set of signals in the aromatic region (Figure S41).

A 2D diffusion-ordered NMR spectroscopy (2D DOSY) analysis of **HP1** in d_6 -DMSO reveals a single band at $\log D \approx -10.5$ (Figure S47); **HP2** also displays one dominant signal band with the same $\log D$ value (Figure S48). After conducting calculations by using the modified Stocks–Einstein equation based on the column model (detailed calculating procedure is summarized in the Supporting Information),²⁴ the experimental diameter of the base is found to be 7.0 nm, and the height of the prism is 2.5 nm. Such sizes are comparable to the predicted results (8.0 nm in base diameter, and 2.7 nm in height) from the molecular modeling of these hexagonal prisms (Figure 1b,c). The other NMR spectroscopic results are summarized in Figures S1–28 and 35–46, including 2D COSY, 2D NOESY, and ^{13}C NMR spectra (see Supporting Information).

To obtain more shape and size information, atomic force microscopy (AFM) and transmission electron microscopy (TEM) were applied to image individual hexagonal prisms. AFM images were first collected on a fresh mica surface by drop casting a diluted DMF solution (3.5×10^{-6} mol/L) of **HP1** for a short time (1 min) and then washing and drying the surface, to avoid aggregation. Particles with ring-like structures were observed under AFM with uniform diameters (Figure 4a,b, Figure S49) by utilizing an ultrasharp cantilever tip (1–2 nm) to reduce the broadening effect. Detailed analysis of the size and shape of one selected particle (Figure 4c) reveals a hexagonal ring with an outer rim diameter at *ca.* 9 nm and an inner rim diameter at 4.7 nm, comparable to the modeling size (Figure 1b,c). The average height of these particles is around 2.5 nm, corresponding to the

height of one prism molecule. In addition, individual dots with uniform diameters were also observed under TEM, as shown in Figure 4d. The zoomed-in TEM image (Figure 4d inset) shows a ring-like structure, which can also be assigned to the base of **HP1** with a comparable size (*ca.* 8 nm in diameter).

Investigation of the Hierarchical Self-Assembly Behavior.

In our previous report, we found that **KCs** were able to hierarchically self-assemble into tubular-like nanostructures through the face-to-face packing.^{20a} With the similar **KCs** structure acting as the bases, we speculated **HP1** could similarly pack into nanostructures through base-to-base packing, which might provide us additional structural information on the prism. Gels were obtained by slow diffusion of ethyl acetate (the poor solvent) into the DMSO solution of **HP1**, then investigated by TEM (Figures S50). Worm-like nanostructures with uniform diameters at *ca.* 8 nm were observed, and most of them further interacted with each other to form bigger aggregation without well-defined pattern.

To obtain more detailed information on the nanostructures, scanning tunneling microscopy (STM) was utilized to image the samples on a highly oriented pyrolytic graphite (HOPG) surface. Acetonitrile instead of ethyl acetate was used as the aggregation solvent, due to its better solubility of the supramolecules, in order to get well-dispersed nanostructures on the surface (the detailed sample preparation procedure was summarized in the Supporting Information). A tubular-like nanostructure was observed as shown in Figure 5a with a uniform diameter around 8 nm, corresponding to the diameter of the **KC** base surface. Breakages on the nanowire were observed owing to the spacing between prisms. The periodic distribution of the bright areas and the gaps observed on the nanowires suggested the base-to-base packing of the prisms in the 1D nanostructure. The measured thickness of each repeating substructure in the nanostructure (marked distance in Figure 5b) was around 2.5 nm, which was well consistent with the predicted height of each supramolecular prism (Figure 1b). (More STM images of the nanostructures were included in Figure S51.)

One dimensional small angle X-ray scattering (1D-SAXS) was further used to study **HP1** and its aggregates in acetonitrile solution (2.5×10^{-4} mol/L), and the results are summarized in Figure 5d. As expected, a q^{-1} decay was observed stemming from the low- q region beyond the probing range (Figure 5d, region I), suggesting the existence of long cylindrical objects with the average length over 1000 Å, consistent with the nanostructures observed in the STM images. Apparently, the **HP1** aggregates in acetonitrile with the base-to-base configuration prior to the incubation process on the HOPG surface for STM imaging. Apart from the tubular-like structure, scattering signals corresponding to individual **HP1** unimers were also observed at a higher q region (Figure 5d, region II) with three quasi-Bragg peaks located between 0.15 and 0.5 Å⁻¹ corresponding to the high order harmonics (q^* , $2q^*$, and $3q^*$), likely originating from the well-defined repeat spacing, d of the hexagonal prisms in the cylindrical aggregate. As a result, the best fitting model contains the contributions from discoidal shells, hollow cylinders, and three Gaussian peaks (Figure 5c). As shown in Figure 5d, the best fit agrees well with the experimental data, and the fitting parameters are listed in Table S1. The best fits for the prism height, outer rim, and inner rim diameters are (2.5 ± 0.2), (6.8 ± 1.1), and (4.0 ± 0.5) nm, respectively, which are consistent with the molecular

modeling results (Figure 1b,c). Moreover, the cylindrical aggregates share the same inner rim and outer rim diameter with those of the unimer, except for an ultralong length. The uniform d derived from q^* as $d = \frac{2\pi}{q^*} \approx 4.2$ nm is also consistent with the STM result (Figure 5b).

Study of the Self-Assembly Mechanism.

After characterization of the desired supramolecular hexagonal prisms, we further studied the self-assembly mechanism of these prism structures. Briefly, the self-assembly of **L1** with Cd(II) (molar ratio: 2/5) was performed under a milder condition (i.e., 2 mg/mL of **L1** in DMSO, 50 °C for 3 h) in order to determine the intermediate state of the assembling procedure. The ESI-MS spectrum (the anions were transferred to PF₆[−]) shows two dominant sets of sharp peaks (Figure 6a), located at the lower m/z (700–1500 Da) and higher m/z (1500–2300 Da) regions, respectively. After deconvolution, the averaged molar mass of the signals at the lower m/z region was 20 094 Da, which exactly fits the chemical composition of [(**L1**)₆Cd₁₂(PF₆)₃₀]. In addition, the isotope pattern of each charge state (12+ to 22+) agrees well with the corresponding simulated one (Figure 6 inset and Figure S52). Such a chemical composition is assigned to a double-rimmed **KC** with six tail-anchored metal-free TPY groups (Scheme 2). It can be viewed as an intermediate prior to the formation of our desired prism structure (**HP1**). The peaks at a higher m/z region are assigned to **HP1** with 18+ to 23+ charge. The coexistence of **KC** intermediates with **HP1** was further confirmed by the TWIM-MS spectrum (Figure 6b) with two sets of signals. The signal bands at the lower m/z region with relative shorter drifting time are attributed to the intermediates, while the well split signal bands at higher m/z region correspond to the hexagonal prism structure with longer drift time. Between [(**L1**)₆Cd₁₂(PF₆)₃₀] and **HP1**, other intermediates such as [(**L1**)₆Cd₁₃(PF₆)₃₀(OH)₂] and [(**L1**)₆Cd₁₄(PF₆)₃₀(OH)₄] (Scheme 2) were also detected by isotope analysis of mass spectra (Figures S53–S54). Every two of these **KC** intermediates together with a proper amount of Cd(II) finally formed **HP1** by forming the lateral edges as the scaffold of the 3D structure. Such a stepwise assembly mechanism leads to precise self-sorting of the three types of TPY groups into three distinct coordination environments (Scheme 2). As a result, the **KC** rings play dual roles during the formation of the supramolecular hexagonal prisms by acting as the structural base surface and the template to guide the formation of the lateral edges.

Antimicrobial Activity.

It is expected that these 3D prisms might show antimicrobial activity against Gram-positive bacteria for the following reasons: (i) the high density of positive charges on these supramolecules provides high affinity with the negatively charged cell envelope of the Gram-positive bacteria;²⁵ (ii) pyridinium containing molecules are widely applied as antimicrobial agents;²⁶ (iii) the prisms may act as transmembrane channels to disrupt the bacterial membrane.^{20a} As a result, the antibacterial activities of **HP1/2** were evaluated with two Gram-positive bacteria, MRSA and *B. subtilis*, (Table 1)

Both **HP1/2** showed antimicrobial activity on MRSA with IC₅₀s as 1 μg/mL (*ca.* 22 nmol/L), which was lower than the IC₅₀s of the corresponding ligands (3 μg/mL, 1200

nmol/L) and the control group, $\text{Cd}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$, ($\text{IC}_{50} > 25 \mu\text{g/mL}$, $8.1 \times 10^5 \text{ nmol/L}$). Compared with the previous reported 2D KCs,^{20a} **HP1/2** displayed lower antibacterial activity, probably due to their low solubilities and high aggregation tendency proven by TEM/STM/SAXS studies. These features caused the precipitation or aggregation of **HP1/2** in contact with the growth medium before their effective interaction with MRSA cells. As a result, supramolecular prisms with better water-solubility are expected to possess enhanced antimicrobial activity.

In addition, to expand the antimicrobial spectrum of this type of supramolecule, *B. subtilis* was used to evaluate the new agents. **HP1/2** showed obvious antimicrobial activity against *B. subtilis*, while **L1/2** did not exhibit potent activity (Table 1). Note that the weight-based IC_{50} value of $\text{Cd}(\text{II})$ control was comparable to the values of **HP1/2**. However, considering the much lower weight percentage of $\text{Cd}(\text{II})$ in **HP1** (8.0%) and **HP2** (7.8%) than in $\text{Cd}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$ (37%), as well as the strong chelation of $\text{Cd}(\text{II})$ with the pentatopic TPY ligands in **HP1/2**, the antibacterial potency of the supramolecules should be mainly derived from the ensembles rather than individual component.

The red-blood-cell hemolysis studies of **HP1/2** show negligible hemolytic toxicity (HC_{50} higher than $250 \mu\text{g/mL}$), leading to their good antimicrobial selectivity toward MRSA and *B. subtilis*. We speculated that such a good selectivity should be based on the stronger electrostatic interaction of cationic **HP1/2** with the negative charged surfaces of the Gram-positive bacteria,²⁵ than with the zwitterionic surfaces of the mammalian cells.²⁷

3D deconvolution fluorescence microscopy, a combination of optical and computational techniques to maximize the observed resolution and signal from a biological specimen,²⁸ was further employed to monitor the location of **HP1/2** during the growth inhibition in *S. aureus* and *B. subtilis*. Benefiting from the strong fluorescence (FL) nature of these two supramolecules (the FL spectra of **HP1/2** are recorded in Figures S55–S56), no external dye is needed to visualize the cell membrane. As shown in Figure 7, strong fluorescence was observed on the surface of both *S. aureus* and *B. subtilis* after being treated with **HP1/2**. In addition, in both cases, significant fluorescence signal was absent outside of the cells. These results indicate the high selectivity and binding affinity of the antimicrobial materials for the Gram-positive bacteria, and then inhibit the growth of MASA and *B. subtilis*.

CONCLUSIONS

We were able to construct giant metallo-supramolecular hexagonal prisms with pentatopic terpyridine ligands, which displayed three different coordination environments during the self-assembly. Such a design fully takes advantage of the rigid scaffold of the pyridinium-aryl group and its facile synthesis. In addition, the detailed study of the self-assembly process reveals that the double-rimmed KCs are the key intermediates required to form a hexagonal prism architecture. The assembled supramolecular hexagonal prisms had a strong tendency to form a tubular-like nanostructure in solution as evidenced by STM imaging and SAXS study. Furthermore, the pyridinium salt containing supramolecular prisms showed potent antimicrobial activities against two Gram-positive bacteria, possibly due to their high binding affinity on the membrane of these bacteria. Overall, through deep understanding of

the design and self-assembly process, this study may shed more light on designing more sophisticated 3D supramolecular architectures with desired functions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

(a) Self-assembly of hexagonal prisms **HP1** and **HP2**; (b) side view and (c) top view of the representative energy-minimized structures from molecular modeling of **HP1/2**; alkyl chains were omitted for clarity.

Figure 2.
(a, c) ESI-MS and (b, d) TWIM-MS plots (m/z vs drift time) of **HP1** and **HP2**, respectively.

Figure 3.

^1H NMR spectra (600 MHz, 300 K) of (a) **L1** in CDCl_3 (the asterisk (*) represents the solvent residue of CHCl_3) and (b) **HP1** in d_6 -DMSO.

Figure 4.

AFM images of (a) individual **HP1** on mica surface, (b) a selected single **HP1** molecule and its 3D image (right bottom inset), (c) cross-section of the molecule shown in image b, (d) TEM images of individual **HP1**, zoomed-in image in inset.

Figure 5.

(a) STM images of tubular-like nanostructure on a HOPG surface; (b) cross-section of the line marked on the nanostructure shown in panel a. (c) The hollow cylinder model of the aggregated tubular-like nanostructure is hierarchically self-assembled by a hexagonal prism unimer. (d) 1-D SAXS of **HP1** in acetonitrile solution (2.5×10^{-4} mol/L): ($\square$) experimental data. The solid black line represents the best fit result.

Figure 6. (a) ESI-MS and (b) TWIM-MS (m/z vs drift time) of the self-assembly of **L1** with Cd(II) under a milder condition. Both intermediates (A series of signals) and **HP1** (B series of signals) were observed; (right inset of a) theoretical and experimental isotope patterns of A19+.

Figure 7.
3D deconvolution fluorescence microscopy images of bacteria cells with and without treatment of **HP1/HP2** (4 $\mu\text{mol/L}$, DMSO as the control agent). Scale bar: 1 μm .

Scheme 1. Synthesis of Ligands L1 and L2^a

^aConditions: (i) BF₃·Et₂O, 100 °C, 2 h; (ii) Pd(PPh₃)₄, NaHCO₃, H₂O, toluene, *tert*-butanol, 80 °C, 6 h; (iii) HBF₄ (35% aqueous solution), MeOH, CHCl₃, 12 h; (iv) 4 Å molecular sieve, DMSO, 120 °C, 24 h.

Scheme 2.

Proposed Self-Assembly Mechanism of L1 Coordinating with Cd(II) to form HP1

Table 1.

Antimicrobial Activity and Selectivity of the Ligands and Supramolecules

	HP1	HP2	L1	L2	Cd(NO ₃) ₂
MRSA (IC ₅₀ , µg/mL)	1	1	3	3	>25
<i>B. subtilis</i> (IC ₅₀ , µg/mL)	3	2	None	None	3
hemolysis (HC ₅₀ , µg/mL)	>250	>250	>250	>250	>250
selectivity HC ₅₀ /IC ₅₀ (MASA)	>250	>250	>80	>80	>10
selectivity HC ₅₀ /IC ₅₀ (<i>B. subtilis</i>)	>80	>120	N/A	N/A	>80