

Communication

# Virus-like Cage Hybrid: Covalent Organic Cages Attached to Metal Organic Cage

Zhuoqian Lv <sup>1</sup>, Chenjuan Yu <sup>2</sup>, Xinyuan Zhu <sup>1</sup> and Youfu Wang <sup>1,\*</sup>

<sup>1</sup> School of Chemistry and Chemical Engineering, Frontiers Science Center for Transformative Molecules, Shanghai Jiao Tong University, Shanghai 200240, China

<sup>2</sup> School of Materials Engineering, Shanghai University of Engineering Science, Shanghai 201620, China

\* Correspondence: wyfown@sjtu.edu.cn

**Abstract:** A well-defined virus-like cage hybrid (VCH) with 24 covalent organic cages (COCs) attached to one metal organic cage (MOC) is presented here. The quantitative assembly of VCH was completed through coordination between soluble anisotropic COC bearing one bipyridine moiety and Pd(II) ions. The obtained VCH exhibited discrete, uniform and stable structures with good solubility and was well characterized by NMR, FT-IR, TEM, AFM, DLS, TGA, and so on. This designable cage hybrid promotes a new strategy to expand the structural and functional complexities of porous molecular cages.

**Keywords:** cage hybrid; covalent organic cage; metal organic cage; virus-like structure; precise nanoobject



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## 1. Introduction

For billions of years, the evolution of nature has given birth to huge amounts of precise objects with various structures and functions, ranging from atoms, molecules, biomacromolecules, bacteria, viruses, cells, organs, to lives [1]. Inspired by these precise objects that nature has brought to perfection, the last few decades have also seen an upsurge in research related to well-defined nanoobjects, based on nanoscience and nanotechnology. Moreover, this leads to deeper insight into biological evolution, as well as the exploration of practical functionality and applicability.

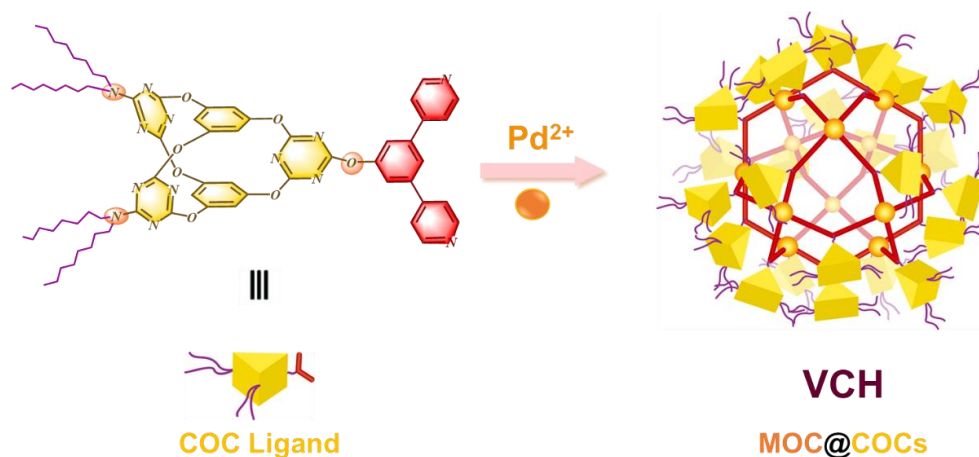
The typical well-defined nanoobjects include nanocarbons [2–4], dendrimers [5,6], metal nanoclusters [7,8], and porous molecular cages (PMCs) [9–11]. By virtue of their high specific surface area, tunable porosity and excellent chemical stability, PMCs are gaining more and more recent attention [10]. A growing number of PMCs are developed by linking various building blocks with different bending angles and decoration of functional groups through metal coordinative or strong covalent bonds [12,13]. Based on the interaction modes between building blocks, PMCs are mainly divided into two categories: covalent organic cages (COCs) and metal organic cages (MOCs). Different from insoluble extended porous frameworks, these cages have good solubility, which allows processing options. The permanent intrinsic cavities inside a rigid structure and windows as the passages make the binding of guests possible. Therefore, this relatively new type of porous material has proven to be a versatile functional material platform in catalysis, controlled drug release, gas adsorption and compound separation. Recent work in this area encompasses a wide range of sophisticated architectures, such as interlocked cages [14], cage oligomers [15,16], porous polymers [17,18], and so on. However, compared to their natural paradigms, the complexity of PMCs is still at the infancy stage [19]. With these structures limited to single kinds of PMCs, it is encouraging to realize the hybridization of different cage species, because this undoubtedly gives full play to their respective advantages.

The main challenge to effectively construct cage hybrids is that most of the PMCs are structurally isotropic with high symmetries, and tend to form infinite frameworks instead of discrete cage hybrids. Until recently, we achieved the combination of two types

of cages for the first time by designing anisotropic COCs bearing one isophthalate moiety, which coordinate with Cu(II) ions, with or without the help of extra dicarboxylic ligands, to generate different topological MOCs [20]. We obtained discrete and uniform planet-satellite cage hybrids with excellent solubility in common solvents and with film-forming properties.

Among a series of giant MOCs with the general formula  $\text{Pd}_n\text{L}_{2n}$ , developed by the Fujita group, the highly-stable  $\text{Pd}_{12}\text{L}_{24}$  complexes self-assembled from 12 Pd(II) ions and 24 bipyridine ligands have been mostly studied [21,22]. An attractive aspect of this system is the capability of exohedral or endohedral cage functionalization via introducing side chains, which makes them highly attractive for areas like molecular recognition processes [23,24] and bioimaging [25]. What is more, being in possession of a rigid skeleton, both with a large cavity and many apertures that are permeable to small molecules, the  $\text{Pd}_{12}\text{L}_{24}$  nanospheres can also be effectively employed for drug delivery [26–29] and as catalyst carriers [30].

Herein, in a continuation of our earlier work, we designed a soluble anisotropic COC ligand tethered with one bipyridine moiety. Through its coordination with naked Pd(II) ions, a well-defined virus-like cage hybrid (VCH) with 24 COCs attached symmetrically to the surface of Pd-based MOC were formed quantitatively. They resemble the spike-like surface protein and capsid of a virus, respectively (Scheme 1).



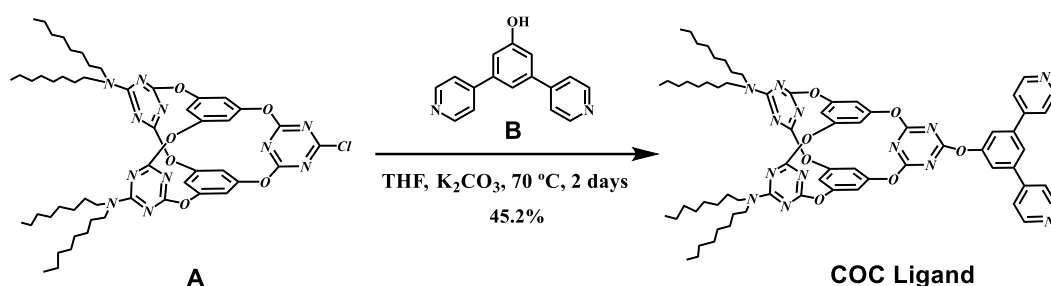
**Scheme 1.** The construction of the VCH with 24 COCs attached to one MOC through coordination between anisotropic COC ligand bearing one bipyridine moiety and Pd(II) ions.

## 2. Materials and Methods

All the reagents and solvents were purchased from commercial sources and used as received without further purification. All glassware were cleaned with aqua regia and rinsed several times with water prior to use.

### 2.1. Synthesis of COC Ligand

The COC ligand was synthesized through a substitution reaction according to the Scheme 2. Functional cage, compound **A**, was synthesized according to our previously reported method [16]. Compound **A** (0.22 g, 0.22 mmol, 1.0 eq.), Compound **B** (60.35 mg, 0.243 mmol, 1.1 eq.) and  $\text{K}_2\text{CO}_3$  (39.47 mg, 0.286 mmol, 1.3 eq.) were added in tetrahydrofuran (THF, 150 mL) and the mixture was refluxed at 70 °C for 48 h. Then, the solvent was removed under reduced pressure. The residue was subjected to column chromatography with  $\text{CH}_2\text{Cl}_2:\text{CH}_3\text{OH}$  (100:1, *v/v*) as eluent to afford the COC ligand as a white solid (0.12 g, yield 45.2%).  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.66 (d, *J* = 3.8 Hz, 4H), 8.03 (s, 1H), 7.75 (d, *J* = 4.8 Hz, 4H), 7.69 (s, 2H), 6.60 (s, 2H), 6.59 (s, 4H), 3.50 (t, *J* = 7.4 Hz, 8H), 1.57 (br, 8H), 1.27–1.23 (m, 40H), 0.83 (t, *J* = 2.66 Hz, 12H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  174.28, 174.16, 172.12, 167.49, 153.55, 152.77, 152.44, 150.51, 146.84, 141.12, 123.88, 121.79, 120.82, 116.14, 114.62, 47.66, 31.83, 29.43, 29.29, 27.61, 26.89, 22.68, 14.12. MS (MALDI TOF): Calculated for  $\text{C}_{69}\text{H}_{85}\text{N}_{13}\text{O}_7$ ,  $[\text{M}+\text{H}]^+$  1208.6695, found 1208.6726.



**Scheme 2.** The synthetic route of the anisotropic COC ligand.

## 2.2. Synthesis of VCH

The COC ligand (24.2 mg, 0.02 mmol, 2.0 eq) in  $\text{CDCl}_3$  (1.5 mL) and  $\text{Pd}(\text{NO}_3)_2$  (2.3 mg, 0.01 mmol, 1.0 eq) in  $\text{DMSO-d}_6$  (1.5 mL) were mixed and stirred at  $50^\circ\text{C}$  for 12 h. After NMR analysis, the solution was evaporated to remove  $\text{CDCl}_3$  and, then, freeze-dried for two days to remove  $\text{DMSO-d}_6$ , allowing the isolation of the product as a pale-yellow solid.

## 2.3. Characterization

$^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker AVANCE III HD 400 at 400 and 100 MHz, respectively, using an internal deuterium lock for the residual protons in  $\text{CDCl}_3$  and  $\text{DMSO-d}_6$  at ambient probe temperature. Two-dimensional diffusion ordered spectroscopy (DOSY) and correlation spectroscopy (COSY) were recorded on Bruker AVANCE III HD 500 at 500 MHz. Chemical shift values ( $\delta$ ) are reported in ppm relative to the proton residual of the deuterated solvents, and coupling constants ( $J$ ) are reported in Hertz (Hz).

The precise molecular weights of the synthesized compounds were recorded through mass spectra. Matrix-assisted laser desorption ionization time of flight (MALDI-TOF) mass spectra were performed on a Bruker Speed MALDI-TOF 7090 (Bruker, Germany). The sample was dissolved in  $\text{CDCl}_3$  at a concentration of 4 mg/mL, and, then, mixed with DCTB solution (10 mg/mL, in  $\text{CHCl}_3$ ) at a volume ratio of 1/5. Before testing the sample drop, we needed to make sure its solvent had volatilized.

Fourier transform infrared (FT-IR) spectra were recorded on a Bruker Tensor 27 FT-IR using ATR measurements for solids as neat samples. KBr was used as a diluting agent. The frequency range was  $400\text{ cm}^{-1}$  to  $4000\text{ cm}^{-1}$ .

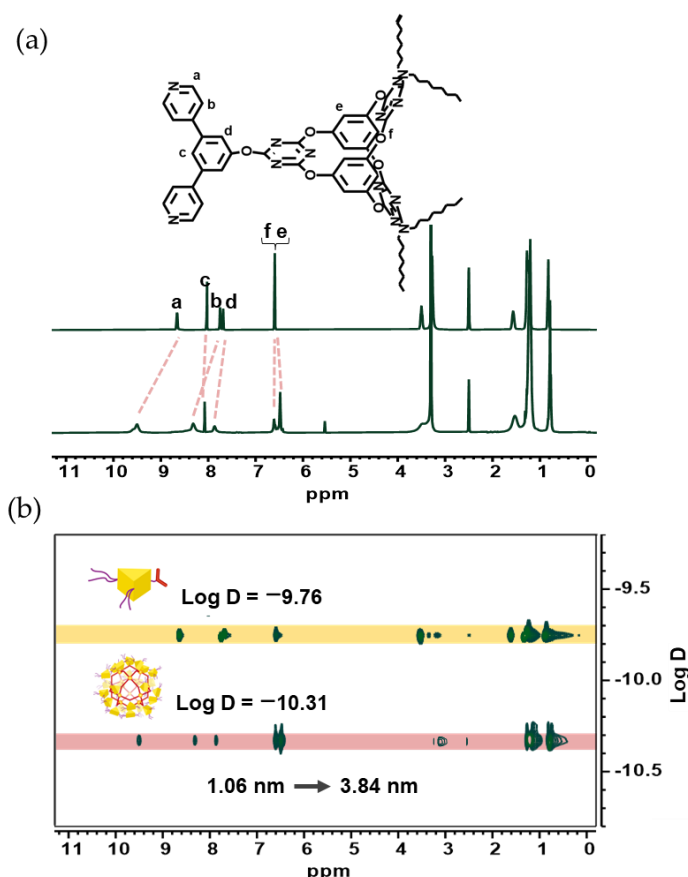
The morphologies and sizes of VCH were estimated by transmission electron microscopy (TEM) on Talos L120C G2 (Waltham, MA, USA) operated at an acceleration voltage of 120 kV. Carbon film supported by a standard copper grid was chosen as the sample carrier. Atomic force microscopy (AFM) images were obtained on MFP-3D (Oxford) by spin-casting a highly diluted THF solution of VCH (10 ng/mL) on freshly cleaved mica substrate. The sizes of the cage hybrids were recorded through dynamic light scattering (DLS) performed with a size and zeta potential analyzer (Malvern, UK).

UV-Vis measurements were performed on a UV-1800 (Kyoto, Japan) spectrophotometer with a 1 cm path length cuvette at 298 K. To investigate the thermal stability of VCH, we performed thermal gravimetric analysis (TGA) using a TG 209 F1 Libra thermogravimetric analyzer in flowing air atmosphere.

## 3. Results and Discussion

The initial COC that we used was a conformationally rigid bis(tetraoxacalix[2]arene[2]-triazine) cage with  $D_{3h}$  symmetry and electron-deficient V-shaped clefts [16,31,32]. Of their three evenly distributed reactive sites, we modified two of them with alkyl chains to improve their solubility in organic solvents and the other one was coupled with a bipyridine moiety to construct Pd-based cuboctahedral MOC. The structure of the anisotropic COC ligand was well confirmed by NMR and MS (see Supplementary materials Figures S1 and S2). The external COCs did not interfere with the Pd-pyridine coordination bond, so the formation of  $\text{Pd}_{12}\text{L}_{24}$  cage was not disrupted during the self-assembly process.

After the dissolution of COC ligand in  $\text{CDCl}_3$  and  $\text{Pd}(\text{NO}_3)_2$  in  $\text{DMSO-d}_6$ , respectively, the two solutions were mixed at  $50^\circ\text{C}$  for 12 h, from which the quantitative self-assembly of a single product was detected by  $^1\text{H-NMR}$  spectroscopy (see Supplementary Materials Figures S3 and S4). As shown in Figure 1a, only one set of ligand signals was observed, indicating a discrete and highly-symmetric structure of VCH. The characteristic broadened resonance signals also confirmed giant species formation, the motion of which was dynamically slow on the NMR time scale. Besides, some signals from protons adjacent to the pyridyl nitrogen atom exhibited distinct downfield shift ( $\Delta\delta = 0.85\text{--}0.035\text{ ppm}$  for  $\text{H}_a$ ,  $\text{H}_b$ ,  $\text{H}_c$ ,  $\text{H}_d$ ), indicative of the coordination with metal ions.



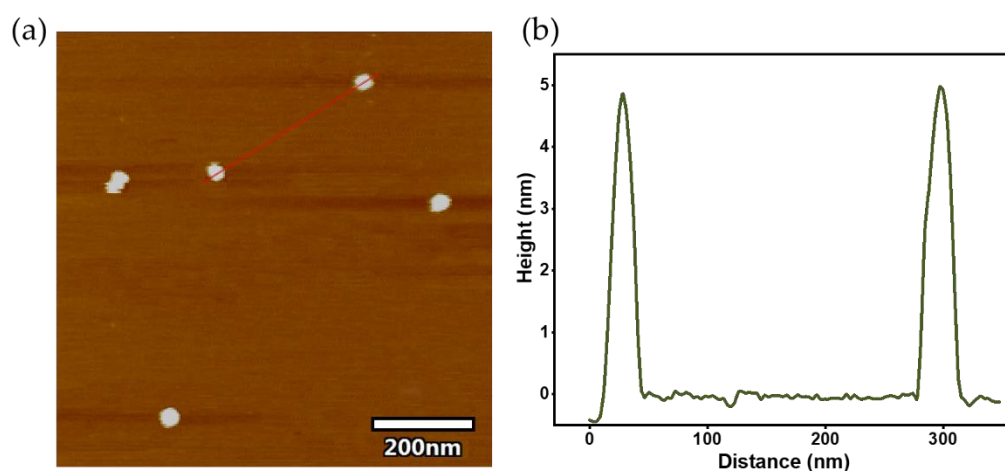
**Figure 1.** (a)  $^1\text{H-NMR}$  (400 MHz,  $\text{DMSO-d}_6$ :  $\text{CDCl}_3 = 1:1$ , 298 K) spectra of COC ligand and VCH. (b) DOSY (500 MHz,  $\text{DMSO-d}_6$ :  $\text{CDCl}_3 = 1:1$ , 298 K) spectra of COC ligand and VCH.

The graph from DOSY showed a clear single band after the assembly at 298 K, indicating the formation of a sole product. As shown in Figure 1b, the diffusion coefficient ( $D$ ) of VCH ( $\log D = -10.33$ ) was apparently lower than that of COC ligand ( $\log D = -9.77$ ), which further proved that a giant species was formed from the coordination procession. According to the Stokes–Einstein equation ( $D = k_B T / 6\pi\eta r$ , where  $D$  is the Diffusion Coefficient,  $k_B$  is the Boltzmann constant,  $T$  is the temperature,  $\eta$  is the viscosity coefficient of solvents,  $r$  is the hydrodynamic radius.), the dynamic diameters of the COC ligand and VCH were calculated to be 1.06 and 3.84 nm. COSY proved the correlation between  $\text{H}_a$  and  $\text{H}_b$ , which were coupled to each other in the NMR spectrum (see Supplementary Materials Figure S5).

We obtained the FT-IR spectra of the structure of COC ligand and VCH (see Supplementary Materials Figure S6). There was little difference before and after the assembly. However, the characteristic peak at  $1593\text{ cm}^{-1}$ , assigned to the vibration of  $\text{C}=\text{N}$  of the pyridine ring, was shifted to  $1629\text{ cm}^{-1}$ , and the signal peak ( $1567\text{ cm}^{-1}$ ), corresponding to the stretching vibration of  $\text{C}=\text{C}$  on the benzene ring, also moved to a higher wave number ( $1589\text{ cm}^{-1}$ ), both of which changes were caused by the coordination of  $\text{Pd}(\text{II})$  ions [33].

Tests showed that VCH could be easily dissolved in common solvents, like THF, DMSO, and DMF, which was very favourable to further experiments and practical application.

To detect the morphology and size of the obtained VCH, we performed a transmission electron microscopy (TEM) experiment by placing a drop of VCH solution in THF (about 0.2 mg/mL) on a copper grid. It was shown that the VCH were discretely and compactly spherical nanoobjects with a uniform diameter of about 4.0 nm (see Supplementary materials Figure S7). The result was consistent with the value calculated from the Stokes–Einstein equation. An AFM image was obtained by spin-casting a highly diluted THF solution of VCH (10 ng/mL) on freshly cleaved mica substrate. A clear AFM image was obtained showing discrete spherical-shaped particles with a uniform height of 4.9 nm above the surface, as shown in Figure 2. This also revealed the stability of the complex under AFM conditions. However, because of the unavoidable tip broadening effect [34], the measured widths of the dots were slightly larger than that from TEM measurement.



**Figure 2.** The (a) AFM image and (b) height analysis of VCH.

In dynamic light scattering (DLS) experiments, the hydrodynamic diameters of the COC ligand and VCH were measured to be 0.6 nm and 3.6 nm with a small polydispersity index (PDI) of 0.21 (see Supplementary materials Figure S8). This was consistent with the sizes estimated from DOSY measurement. Therefore, all the experimental results validated the formation of VCH.

We also performed TGA experiments to explore the thermal stability of VCH (see Supplementary materials Figure S9). The system remained thermally stable before 300 °C, only gradually losing solvent molecules. Alkyl chain decomposition occurred between 300 °C and 450 °C. As the temperature rose, the skeleton of the MOCs and COCs rapidly collapsed. The final stabilized mass residual was supposed to be PdO.

#### 4. Conclusions

In summary, we demonstrated a novel virus-like cage hybrid with 24 COCs uniformly attached to one Pd-based MOC. The anisotropic COC ligand modified with one bipyridine moiety could coordinate with naked Pd(II) ions in a quantitative manner to form a supramolecular structure. The formed cage hybrid exhibited discrete, uniform and stable structures with good solubility. Climbing further up the ladder of constructing atomically-precise nanoobjects, the covalent attachment of COCs on the surface of MOC opens up new strategies to expand the complexity and functionality of PMCs. We envisage that the cooperation will package their relative properties and applications, thereby constituting promising multifunctional self-assembled nanoobjects in the future.



**Supplementary Materials:** The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/chemistry4030062/s1>, Figure S1: The  $^1\text{H}$ -NMR and  $^{13}\text{C}$ -NMR spectra of the COC ligand in  $\text{CDCl}_3$ . Figure S2: The MALDI-TOF mass spectrum of COC ligand. Figure S3: The  $^1\text{H}$ -NMR spectrum of COC ligand in  $\text{CDCl}_3$  and  $\text{DMSO-d}_6$ . Figure S4: The  $^1\text{H}$ -NMR spectrum of VCH in  $\text{CDCl}_3$  and  $\text{DMSO-d}_6$ . Figure S5: The  $^1\text{H}$ - $^1\text{H}$  COSY spectrum of VCH in  $\text{CDCl}_3$  and  $\text{DMSO-d}_6$ . Figure S6: The FT-IR spectra of COC ligand and VCH. Figure S7: The TEM images of VCH. Figure S8: The DLS plots of COC ligand and VCH in THF. Figure S9: The TGA plots of VCH under air. Figure S10: The UV-Vis curve spectra of COC ligand and VCH.

**Author Contributions:** Conceptualization, Y.W.; methodology, Z.L.; software, Z.L.; validation, Z.L. and C.Y.; formal analysis, Z.L.; investigation, Z.L.; resources, Y.W.; data curation, Z.L.; writing—original draft preparation, Z.L.; writing—review and editing, Y.W.; visualization, Y.W.; supervision, Y.W.; project administration, X.Z.; funding acquisition, Y.W. All authors have read and agreed to the published version of the manuscript.

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