Water-Soluble Self-Assembled Molecular Cage and Two-Dimensional Framework through Flexibility Adjustment of the Precursors

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ABSTRACT: The diversified self-assembly in water is a versatile and significant phenomenon with far-reaching implications in materials science, medicine, biotechnology, and various other fields. Through subtle tailoring in the amphipathic molecular structures, two completely different self-assembly behaviors in water were obtained. The precursors **M1-X** (X= I or Cl⁻) with rigid and shorter bridges between the hydrophobic core and the hydrophilic edge form 2D framework structures, while precursor **M2-I** molecule with flexible vinyl bridges gives 3D cube-like supramolecular cages. Notably, all the single crystals of the assemblies were obtained. The single-crystal X-ray diffraction analysis provided unambiguous evidence of the 2D framework and cube-like structures.

Supramolecular self-assembly refers to the spontaneous formation of highly ordered complex structures through non-covalent interactions such as hydrogen bonding,¹⁻⁶ π - π stacking,7-9 host-guest interactions,10-13 hydrophobic/hydrophilic interactions,¹⁴⁻¹⁷ and so on.¹⁸⁻²⁰ The self-assembly process can give rise to different supramolecular structures, including supramolecular macrocycles,²¹⁻²⁴ cages,²³⁻³¹ frameworks,³²⁻³⁷ et al. The determinants of the formation of various self-assembled structures are influenced by various factors, including molecular design,³⁸⁻³⁹ the driving forces (diversified non-covalent interactions).⁴⁰⁻⁴² solvent effects,43-44 external conditions (concentration, temperature, pH, et al.),45-46 and so on.47-48 Among all the self-assembly processes, the study of aqueous self-assembly holds significant importance due to its relevance to biology and potential biomedical applications. Many biological processes, such as protein folding, enzyme activity, and cell signaling, occur in aqueous environments.⁴⁹⁻⁵¹ By studying aqueous self-assembly, we can gain insights into the fundamental principles underlying biological self-assembly and mimic biological processes for biomedical applications.⁵² However, the study of self-assembly in water presents several challenges due to the unique characteristics of the aqueous environment. For example, micelles and vesicles can be readily induced by conventional amphiphiles bearing a hydrophilic head and hydrophobic tail in aqueous media. However, achieving precise control over these self-assembly structures proves challenging due to the inherently random self-assembly process in water.53-56 Nature's well-defined cavities or channels often assume a central role in biochemical processes. The establishment of meticulously self-assembled nanostructures in aqueous environments holds significant promise within the realms of biology and medicine.57-58 Controlling the hydrophobicity/hydrophilicity properties and interactions of molecules is crucial for constructing supramolecular structures with specific functions.59-60

Herein, we intend to introduce both hydrophilic and hydrophobic moieties into a molecular structure simultaneously. By tuning the linkages between hydrophilic and hydrophobic parts, the self-assembly behaviors and structural morphologies can be controlled. Two structurally similar precursors containing hydrophobic hexaphenylbenzene core and hexa-substituted hydrophilic methylpyridine as edges were designed and synthesized. The only difference

in the structures of these two precursors is the flexible double bond or the rigid single bond as bridges (Figure 1). Two completely different self-assembly structures were observed in water under the same conditions. Compound M1-**X** ($X = I^{-}$ or CI^{-}) was self-assembled into a two-dimensional framework with well-defined channels, while a supramolecular cage was obtained through the self-assembly of M2-I. The single-crystal X-ray diffraction (SCXRD) provided unequivocal evidence of the 2D framework from M1-X (X = I⁻ or Cl⁻) and the cube-like structure assembled from M2-I. These diversified self-assemblies in water open up new possibilities for designing and synthesizing advanced materials and nanoscale structures. By subtle tailoring of the molecular structure and controlling the interactions between different components, a diverse array of materials with unique properties can be constructed.

The structures of the precursors **M1-X** (X = I⁻ or Cl⁻) and **M2-X** (X = I⁻ or Cl⁻) are shown in Figure 1. The synthesis details are given in the Supplementary Materials. Both **M1-X** (X = I⁻ or Cl⁻) and **M2-X** (X = I⁻ or Cl⁻) adopt hexaphenylbenzene as the hydrophobic cores and methylpyridine as the hydrophilic edges. Compared to the rigid **M1-X** (X = I⁻ or Cl⁻), a vinyl linkage was introduced between the hydrophobic core and the hydrophilic edges of **M2-X** (X = I⁻ or Cl⁻). This slight difference in the structure leads to a totally different self-assembly behavior in water. Various counter anions, such as iodide and chloride, can be exchanged to give **M1-I**, **M1-CI**, **M2-I**, and **M2-CI**. Both **M1-X** (X = I⁻ or Cl⁻) and **M2-X** (X = I⁻ or Cl⁻) have acceptable solubilities in water. However,



Figure 1. The structures of M1-X (X = I^{\cdot} or Cl^{\cdot}) and M2-X (X = I^{\cdot} or Cl^{\cdot}).



Figure 2. Single-crystal structure of **M1-I** (a) and **M1-Cl** (d). View along the *c*-axis of the crystal-packing diagram of **M1-I** (b) and **M1-Cl** (e). View along the *a*-axis of the crystal-packing diagram of **M1-I** (c) and **M1-Cl** (f). The distribution of I⁻ in the single crystal of **M1-I** (g, h) and **M1-Cl** (i, j).

the ¹H NMR spectra of **M1-I** and **M2-I** indicate different selfassembly behaviors. As shown in Figure S1, the ¹H NMR spectrum of **M2-I** in the D₂O exhibits a very complicated pattern. In contrast, the ¹H NMR spectrum of **M1-I** is very clear and matches well with the structure. The aggregation behavior of **M2-I** is further validated by concentration-dependent experiments. No obvious difference in ¹H NMR spectra of **M2-I** at different concentrations is observed, demonstrating the self-assembly of **M2-I** in water is concentration-in-dependent (Figure S2). The ¹H NMR spectrum study suggested different self-assembly behaviors of **M1-X** (X = I⁻ or Cl⁻) and **M2-X** (X = I⁻ or Cl⁻) in water.

We then studied the photophysical properties of these two molecules in water. Generally, the photophysical properties are usually associated with molecular structures and self-assembly behavior.⁶¹ As shown in Figure S3a, **M1-I** exhibits the main UV absorption peak at 315 nm, whereas M2-I shifts towards the longer wavelength at 353 nm. The fluorescence emission peak of M1-I is located at 476 nm, and M2-I exhibits a redshift at 500 nm. This is understandable since the introduction of the vinyl linkage extends the π -conjugation and thus leads to the redshift in the UV absorption and fluorescence spectra. Similar absorption and emission properties were observed when the counter anion was exchanged to chloride (Figure S3c and S3d). Notably, M1-X (X = I^{-} or Cl^{-}) exhibits more than ten times stronger fluorescent intensity than M2-X (X = I^{-} or Cl^{-}) (Figure S3b and S3d). M1-X (X = I⁻ or Cl⁻) is composed of rigid bonds between the benzene rings, which effectively increase the conformational rigidity and reduce the loss of energy via vibration motions, thus will produce strong fluorescence.⁶² M2-X (X = I or Cl⁻) with flexible vinyl bridges



Figure 3. (a) Single-crystal structure of the **M2-I**. (b) A picture of the "Luban" lock. Crystal-packing diagram of **M2-I** in a capped stick style (c) and spacefill style (d). The hydrogen atoms, H_2O molecules, and the counter anions are omitted due to clarity in all the Figures.

makes the structure lack rigidity and thus produce weak fluorescence.⁶³ In the meanwhile, the two precursors, **M1-X** (X = I⁻ or Cl⁻) and **M2-X** (X = I⁻ or Cl⁻), with counter anions chloride, show stronger emitting fluorescence and less brightness than counter anions iodide under 365 nm light irradiation (Figure S3b, S3d, S3e and S3f). This is due to the fluorescence quenching and chromogenic effects of iodide ions.⁶⁴

To gain further insights into the self-assembly process, single crystals of **M1-I**, **M1-Cl** and **M2-I** were acquired through a carefully controlled, gradual cooling process of recrystallization. For the details, see the Supplementary Materials. As shown in Figure S4, the single crystals of **M1-I**, **M1-Cl** and **M2-I** all have regular polygon morphology, and the sizes are larger than 100 microns to fully meet the requirements of SCXRD. The colors of the **M1-I** and **M2-I** single crystals are yellow, while the **M1-Cl** single crystals are colorless. Then, the SCXRD analysis provided the accurate structure information of **M1-I**, **M1-Cl** and **M2-I** and clarified the precise self-assembled modes of **M1** and **M2**.

As shown in Figure 2a, **M1-I** was deliberately crafted with a central hexaphenylbenzene core and six protruding methylpyridine arms. These six arms were meticulously aligned in a head-to-tail manner, resulting in a captivating triangular plane tiling arrangement. The distance between the two neighboring methylpyridine planes is 3.61 Å. A clearly 2D layered structure was observed from the *a* or *b*axis direction, which adopted an eclipsed (AA) stacking mode (Figure 2b and 2c). A clear channel structure formed, which can be seen from the *c*-axis direction. The distance between each layer is 8.40 Å. The counter anions I⁻ exist inside the triangle pores and between the layers (Figure 2g and 2h). For **M1-CI**, the self-assembly mode in each layer is exactly the same as **M1-I**. The distance between the two neighboring methylpyridine planes is 3.36 Å (Figure 2d). However, the stacking mode of **M1-Cl** is completely different. An obvious staggered shift was observed. A regular ABC stacking mode is adopted, and the distance between the layers is 8.60 Å (Figure 2d, 2e and 2f). The counter anions Cl⁻ exist inside the triangle pores in each layer and intervals between the layers (Figure 2i and 2j). The types of counter anions affect the self-assembly modes along the *c*-axis due to the changes in the hydrogen bond formation between the counter anions and the hydrogen in the monomers. While the self-assembly modes are the same in the 2D plane of *a* or *b*-axis directions due to the stronger hydrophilic and hydrophobic interactions.

For M2-I, a completely different self-assembly mode was adopted. As shown in Figure 3a, six arms from each M2-I molecule engage with other arms from other M2-I molecules to form a perfect three-dimensional (3D) cubelike structure. Each M2-I molecule takes on the role of one of the square faces within the cubic assembly, reminiscent of the classic "Luban" lock depicted in Figure 3b. Notably, the methylpyridine units on each arm of M2-I, functioning as hydrophilic ends, exhibit a propensity to aggregate, thus constituting the hydrophilic periphery of the resulting cube. Simultaneously, the iodide ions, serving as counter anions, arrange themselves along the external surface of the cube. The as-formed 3D cubes are then arranged along the *a*, *b*, and *c*-axis to form even bigger 3D cube-like self-assembled structures (Figure 3c and 3d). As we know, the specific supramolecular self-assembly process depends on several factors, including the internal structure of the monomers and the external environment.⁶⁵ The self-assembly of both M1 and M2 takes place within a water environment under similar external conditions. Consequently, the inherent structures of the monomers play a pivotal role in governing the self-assembly process. The vinyl linkage in M2 results in different intermolecular interactions and thus affects their self-assembly behavior. The extended vinyl linkages provide M2 with certain rotational freedom and flexibility, thus causing the relatively flexible orientations of the six arms in M2 during the self-assembly process. Each arm from one M2 molecule meshes with another two arms from the other M2 molecules like gear to form the cube. The hydrophilic effect provides a main driving force for the formation of a hollow supramolecular cage. The methylpyridine groups as hydrophilic ends tend to stay together to realize the meshing process of the hydrophilic arms. An inner hydrophobic cavity was formed. Thus, the exposure of the hydrophobic core surface areas to the water was then minimized. M1 consisted of a series of short and rigid benzene rings, which limited the freedom of movement. An obvious π - π interaction between the headto-tail methylpyridine rings from adjacent M1 molecules was observed, leading to the 2D framework structures. This head-to-tail orientation can effectively minimize the Coulombic repulsive interactions between the methylpyridine cations. Notably, a large portion of counter anions was found to locate between the interlayer and the triangular pores. A large number of hydrogen bonds between the counter anions and the hydrogen of M1 formed, especially for the counter anions located between the interlayer. Therefore, the exchange of the counter anions from I to Cl induced the change of the stacking mode along

the *c*-axis. The complementarity and synergy of the π - π interactions and the multiple hydrogen bonds lead to the 2D framework structure with diversified stacking.

In summary, two series of six-armed amphipathic molecules were designed for the study of the different self-assembly behaviors in water. The slight difference in the flexibility and the length of the linkages leads to completely different self-assembly behaviors. Under similar external conditions, two distinct self-assembly outcomes were observed: the formation of 2D framework structures through the selfassembly of M1 molecules characterized by a rigid and short bridge connecting the hydrophobic core to the hydrophilic edges; alternatively, a 3D cube-like supramolecular cage emerged through the coordinated interaction of six M2 molecules. These M2 molecules were adorned with six hydrophilic and flexible vinyl pyridyl groups, affixed to a hydrophobic hexaphenyl benzene core, facilitated by hydrophobic forces within the aqueous milieu. It was also observed that the various counter anions located in the interlayer of the 2D frameworks play a key role in adjusting the stacking modes relying on a large number of hydrogen bonds between the counter anions and the hydrogen of M1. The SCXRD gave unambiguous evidence of the 2D framework and the 3D cube-like structures. The preparation of well-defined discrete self-assembled structures in water holds immense significance in exploring the fundamental principles of supramolecular chemistry and advancing the understanding of biological systems. In addition, the advantage of designing structurally diverse monomers allows for the fine-tuning of the self-assembled structure and the physical, chemical, and mechanical properties of the resulting supramolecular assemblies.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Supporting methods and experimental section, Tables and Figures, Single-crystal X-ray Diffraction Data of M1-I, M1-Cl and M2-I, CCDC numbers: 2280568, 2280576 and 2280826 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data request/cif, or by emailing data request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

H. F. performed all the experiments and wrote the draft. H. L. guided the synthesis and single crystals growth. H. W. did the SCXRD, W. Q, X. J., and X. Z. did the synthesis of M1 and M2. R. S. and Y. Z. directed the whole process in this work. H.L and Y.Z supervised and wrote the manuscript. Notes

There are no conflicts to declare.

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A subtle tailoring in the amphipathic molecular structures leads to two totally different self-assembly patterns in water. The rigid and shorter bridges between the hydrophobic core and the hydrophilic edge form 2D framework structures, while flexible vinyl bridges give 3D cube-like supramolecular cages.

