

#### Article

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Zhongwei Sun, Pan Li, Shijun Xu, Zi-Ying Li, Yoshiaki Nomura, Zimu Li, Xiaoyun Liu, and Shaodong Zhang J. Am. Chem. Soc., Just Accepted Manuscript • DOI: 10.1021/jacs.0c03330 • Publication Date (Web): 20 May 2020 Downloaded from pubs.acs.org on May 20, 2020

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# **Controlled Hierarchical Self-Assembly of Catenated Cages**

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**ABSTRACT**: Constructing hierarchical superstructures to achieve comparable complexity and functions to proteins with four-level hierarchy is challenging, which relies on the elaboration of novel building blocks with complex structures. We present a series of catenated cages with unique structural complexity and tailorablity. The rational design was realized as such: CSC-1 with all rigid imine panels was converted to CDC-1 with two exterior flexible amine panels, and CDC-5 was tailored from CDC-1 by introducing an additional methyl group on each blade to increase lateral hindrance. CDC-1s with the most irregular and flexible configuration form supramolecular dimers, which self-organize into 3D continuous wave-like plank with three-level hierarchy, precedently undiscovered by conventional building blocks. Drastically different 3D triclinic crystalline phase with four-level hierarchy and trigonal phase with three-level hierarchy were constructed by distorted CSC-1s and the most symmetric CDC-5s, respectively. The wavelike plank exhibits the lowest order, and the triclinic phase has a lower order than the trigonal phase with the highest order. It correlates with the configuration of the primary structures, namely the most disordered shape of CDC-1, low-order configuration of CSC-1, and the most ordered geometry of CDC-5. The catenated cages with subtle structural differences therefore provide a promising platform for the search of emerging hierarchical superstructures that might be applied to proton conductivity, ferroelectricity, and catalysis.

# **INTRODUCTION**

First proposed by Linderstrøm-Lang,<sup>1</sup> hierarchical structures of proteins with four levels, namely primary, secondary, tertiary and quaternary structures, have been well-documented to play a pivotal role in biological functions of living systems.<sup>2</sup> Inspired by the wisdom of nature, synthetic hierarchical structures have been developed with a large variety of building blocks and applied to biomimetics,<sup>3</sup> electronics,<sup>4</sup> and catalysis.<sup>5</sup> Synthetic systems, however, were still unable to reach the parallel structural sophistication and functions as proteins. This challenge can be addressed by increasing the complexity of existing building blocks<sup>6</sup> or searching for novel candidates.<sup>7</sup> Considering the 3D topological diversity of cage- or capsule-like compounds,<sup>8</sup> they could be one type of promising building blocks. For more than two decades, research focus has been mainly dedicated to the design, synthesis and applications.<sup>9</sup> Awareness of their potential as powerful synthons for hierarchical superstructures has been raised only very recently.<sup>10</sup> Among these cagelike molecules, catenated (or interlocked) cages composed of two or more monomeric cages,<sup>11</sup> particularly covalent catenated cages pioneered by Cooper, Mastalerz, Zhang, Sessler and Li,<sup>12</sup> have attracted increasing interest due to their aesthetic structures and potential applications. On the basis of the unique threedimensional and complex topology, self-assembly of catenated cages might provide a powerful toolbox for the discovery of hierarchical superstructures that are inaccessible by conventional molecules and cages, but it remains underexplored.13

We herein present a series of catenated cages, which were rationally designed with unique structural complexity and tailorability. Starting from a catenane composed of two symmetric cages, denoted CSC-1, we converted it to the corresponding catenane composed of two dissymmetric cages, CDC-1 (Figure 1). As CDC-1 exhibits two exterior amine panels (in red), more structural flexiblity is implanted with respect to CSC-1 with four rigid imine panels (in blue). We also tailored CDC-1 by introducing an additional methyl group on each dithiane moiety, yielding CDC-5 with more steric hindrance on its periphery. More

importantly, we demonstrate that these catenated cage with subtle structural differences can self-assemble in a controlled hierarchical manner, leading to dramatically different superstructures. These hierarchical superstructures include: an unprecedented 3D continuous wave-like plank with three-level hierarchy, which was previously inaccessible by conventional building blocks; a 3D triclinic crystalline with four clearly defined levels of structure, which is close to the four-level hierarchy of proteins; a 3D trigonal crystalline with three-level hierarchy, which exhibits the highest order compared to other two superstructures. As such, a small structural modification of the catenated cages alters dramatically their topological configurations, which in turn results in substantially different hierarchical superstructures. The structural effect of catenated cages on their configurations and hierarchical self-assembly behaviors in crystal state is also elaborated in this work.



**Figure 1**. Rational design of catenated cages for hierarchical self-assembly. Compared to **CSC-1** with four relatively rigid imine panels, **CDC-1** with two exterior amine panels exhibits higher configurational flexibility. With one extra methyl group (highlighted in green) on each dithiane moiety, **CDC-5** has higher lateral hindrance than **CDC-1**. The amine panels are shown in red, and imine panels in blue.

#### **RESULTS AND DISSCUSSION**

Synthesis and Characterization of Catenated Cages. We previously developed a synthetic strategy to construct catenane with two dissymmetric cages (denoted CDC).<sup>14</sup> We started from the catenane composed of two symmetric cages, namely CSC-1. As the inner cavity of CSC-1 is inaccessible by voluminous NaBH(OAc)<sub>3</sub>, it allowed us to selectively reduce all imines on its exterior panels, leading to the formation of CDC-1. Similarly, CDC-5 was produced by a two-step procedure. [4+6] cycloimination of four TFB panels and six (4*R*)-2-(3,5-di(3-aminophenyl)phenyl)-4-methyl-1,3-dithiane (DAPMD)

linkers first yielded **CSC-5**. The subsequent selective reduction of the exterior imines of **CSC-5** by bulky reductant NaBH(OAc)<sub>3</sub> led to the formation of **CDC-5** (44% two-step overall yield, see Supporting Information for details). Its chemical structure was confirmed by MALDI-TOF and NMR spectroscopies, respectively (Figures S8-S12). The MALDI-TOF spectrum of **CDC-5** shows an ion peak at m/z 2799.936 ([M+H]<sup>+</sup> calcd for 2799.927), and its <sup>1</sup>H NMR spectrum exhibits the resonances related to the exterior amine bonds (protons H<sub>b</sub><sup>,</sup> and H<sub>n</sub><sup>,</sup>), the interior imine bonds (proton H<sub>s</sub><sup>,</sup>), **TFB** (protons H<sub>a</sub><sup>,</sup> and H<sub>r</sub><sup>,</sup>), and two sets of **DAPMD** (typically protons H<sub>c</sub><sup>,</sup>-H<sub>f</sub><sup>,</sup> vs. protons H<sub>j</sub><sup>,</sup>-H<sub>m</sub><sup>,</sup>), respectively.



**Figure 2**. Molecular structures of catenated cages **CSC-1**, **CDC-1** and **CDC-5**. (a, c, e) Top view in spacefilling and (b, d, f) side view in stick modes of the catenated cages, respectively. They are dissected into two monomeric cages for easy inspection of their configurations, including their rotation and twisting. The exterior amine panels are shown in red, interior imine panels in blue, lateral linkers in light/dark grey to differentiate the two interlocked partner cages. Methyl groups in **CDC-5** are highlighted in green. Curved arrows show the rotating direction of the blades, and straight arrows indicate the swaying direction of dithiane rings. Solvent molecules and hydrogen atoms are omitted for clarity.

Molecular Configurations of Catenated Cages in Crystalline State. Single crystals suitable for Xray crystallography were obtained by slow vapor diffusion of diethyl ether into concentrated THF solution of CSC-1,<sup>14</sup> slow evaporation from the saturated solutions of CDC-1 in THF and CDC-5 in CH<sub>3</sub>CN/THF = 2:5 v/v at 35 °C, respectively. CSC-1 crystallized into triclinic space group  $P\overline{1}$ , CDC-1 into monoclinic space group C2/c, and CDC-5 into trigonal space group R32. Their molecular configurations were unambiguously inspected by dissecting them into two partner cages (Figure 2).

**CSC-1** exhibits a fairly irregular propeller-like configuration. Its top view shows the three *m*-terphenyl blades of each partner cage exhibit different rotating directions (Figure 2a). Its side view reveals its four relatively rigid imine panels (in blue) are aligned nearly parallel to each other (Figure 2b). Their parallel packing with close distances (3.6, 3.7 and 3.6 Å) ensures efficient intramolecular  $\pi$ - $\pi$  stacking, which provides, to some extent, ridigity of CSC-1 during crystallization. Besides, all the dithiane rings are swaying in different directions. CDC-1 with two flexible amine panels (in red) adopts a very disordered shape without any element of symmetry. Its top view shows three *m*-terphenyl blades of one partner cage (in dark grey) simultaneously rotate clockwise, while the three blades of another cage (in light grey) are irregularly twisted (Figure 2c). This highly disordered geometry is also apparent from its side view (Figure 2d). The exterior amine panel (in red) of each partner cage is notably distorted. This leads to uneven distribution of centroid distances between four panels, *i.e.*, 4.1, 3.8, and 3.8 Å. It therefore precludes efficient intramolecular  $\pi$ - $\pi$  stacking between the exterior amine panels (in red) and the adjacent interior imine panels (in blue) of CDC-1. Similar to CSC-1, all dithiane rings of CDC-1 exhibit different swaying fashion. CDC-5 with one additional methyl group on each blade exhibits a highly symmetric configuration with one  $C_3$ -symmetric axis and three perpendicular  $C_2$ -symmetric axes. Its top view reveals all three blades of each partner cage rotating in the same direction (Figure 2e), and the side view shows its four panels are aligned parallel to each other (Figure 2f). Their close distances (3.8, 3.6 and 3.8 Å) and parallel packing

also ensure efficient intramolecular  $\pi$ - $\pi$  stacking, which favors the ordered interlocking of the two partner cages.

Comparison of these catenated cages therefore clearly shows their subtle structural changes, namely **CSC-1** with more rigid imine panels vs. **CDC-1** with two flexible amine panels, and **CDC-5** with flexible amine panels but laterally bulkier vs. **CDC-1**, dramatically alters their topological configurations in crystalline state. It leads to the most disordered and flexible configuration for **CDC-1**, fairly irregular shape for **CSC-1**, and highly symmetrical geometry for **CDC-5** in crystalline state. It is noteworthing the structural tailoring can also be realized with the homologous simple cages, but imine-to-amine conversion often leads to the collapse of their crystal structures.<sup>15</sup> This structure-to-configuration correlation therefore demonstrates the unique structural feature of our catenated cages.

**3D** Hhierarchical Structures Self-Assembled by Catenated Cages. It is worth noting that all these three catenated cages adopt highly symmetrical geometries in solution, as revealed by their <sup>1</sup>H NMR splitting patterns determined in CDCl<sub>3</sub> (Figure S8).<sup>14</sup> The irregular configurations of CSC-1 and CDC-1 in crystal state seemly result from their dense packing during crystallization, which requires considerable distortion so that the void in crystals is minimized. As the configuration of a molecule and its self-assembly behavior, *i.e.*, molecular packing, are interdependent during crystallization,<sup>16</sup> it prompted us to investigate the self-assembly of CSC-1, CDC-1 and CDC-5 in crystalline state, respectively.

**CSC-1** exhibits a fairly irregular propeller-like shape with all blades twisting differently, but with four imine panels (in blue) aligned in parallel (Figures 2a, 2b, and 3b). As revealed by a combination of structural and retrostructural analysis (Figures 3),<sup>17</sup> **CSC-1** molecules self-assemble into triclinic crystalline phase via controlled hierarchy with well-defined primary, secondary, tertiary, and quaternary structures. This is reminiscent of the hierarchical self-assembly of polypeptides into proteins.<sup>2a</sup>



**Figure 3**. Controlled hierarchical self-assembly of **CSC-1**s into 3D triclinic crystalline phase with welldefined primary, secondary, tertiary, and quaternary structures. (a) Stick mode of primary structure **CSC-1**. (b) Supramolecular dimer (secondary structure) self-assembled by **CSC-1**s. Dashed arrows through **CSC-1**s indicate their opposite orientations. (c) Staggered helical column (tertiary structure) formed by supramolecular dimers. The simplified cartoon model (right) of four **CSC-1**s (two dimers) showing their intermolecular arrangement with detailed packing parameters. Two neighbouring **CSC-1**s with opposite orientation are arranged off the columnar axis (in yellow), around which each **CSC-1** rotates by 180° with respect to another. (d) Quaternary structures self-organized by supramolecular columns, viewed along crystallographic *a*- (left) and *c*-axis (right), respectively. The imine panels are in blue. Light/dark grey on lateral linkers and cartoon model of each **CSC-1** is to differentiate the two interlocked monomeric cages. Solvent molecules and hydrogen atoms are omitted for clarity.

Two **CSC-1**s (primary structures) aggregate into a supramolecular dimer within a unit cell, in which one **CSC-1** molecule adopts the opposite orientation with respect to another, as illustrated by the dashed arrows placed through **CSC-1**s (Figure 3b). Besides, these two **CSC-1**s are offset by 9.6 Å. This packing therefore impedes intermolecular  $\pi$ - $\pi$  stacking between the imine panels (in blue) of adjacent **CSC-1**s. The parallel alignment of the four panels of a **CSC-1** is therefore maintained only by intramolecular  $\pi$ - $\pi$  stacking (vide supra). These dimers (secondary structures) are packed to form a staggered helical column (tertiary structure, Figure 3c). The simplified cartoon model of the column clearly illustrates their intermolecular arrangement (right panel in Figure 3c). Two neighbouring **CSC-1**s with opposite orientation are arranged off the columnar axis (in yellow), around which each **CSC-1** rotates by 180° with respect to another. Such arrangement leads to the formation of a  $2_1$ -helix with a pitch of 29.0 Å. Besides, every two adjacent molecules are offset by 3.4 Å along the columnar axis. These supramolecular columns self-organize into 3D quaternary supramolecular structure, with a center-to-center distance of 18.3 Å (Figure 3d).



**Figure 4**. Controlled hierarchical self-assembly of **CDC-1**s into 3D continuous wave-like plank with welldefined primary, secondary, and tertiary structures. (a) Stick mode of primary structure **CDC-1**. (b) Supramolecular dimer (secondary structure) self-assembled by **CDC-1**s. Dashed arrows through **CDC-1** indicate their opposite orientations. (c) Tertiary structure self-organized by supramolecular dimers (upper panel). This packing is illustrated with a simplified model of tiling of bricks in a zig-zag fashion (bottom panel). Each supramolecular dimer "brick" is labeled in blue or orange to distinguish dimers with different orientation, and deep and light colors tell different layers of "bricks". The exterior amine panels are shown in red, interior imine panels in blue. Lateral linkers are in light/dark grey to differentiate the two interlocked monomeric cages. Solvent molecules and hydrogen atoms are omitted for clarity.

**CDC-1** molecules with the most disordered and flexible configuration crystallize into the hierarchical superstructure of monoclinic crystalline phase with well-defined primary, secondary, and tertiary structures (Figures 4). The primary structures, *i.e.*, **CDC-1**s also self-assemble into a supramolecular dimer. Similar to the case of **CSC-1**s, within the dimer the two **CDC-1** molecules adopt opposite orientation with respect to each other, as illustrated by the dashed arrows placed through **CDC-1**s (Figure 4b). Besides, the two **CDC-1**s are offset by 9.4 Å. This packing also precludes intermolecular  $\pi$ - $\pi$  stacking between the amine

panels (in red) of adjacent **CDC-1**s. Along with the absence of efficient intramolecular  $\pi$ - $\pi$  stacking (*vide supra*), it leads to the distortion of the exterior amine panels of **CDC-1**s (Figures 4b). These dimers, serving as secondary building blocks, self-organize into a strikingly special superstructure in a wave-like manner, which we refer to as 3D continuous wave-like plank (Figure 4c). This unique packing is reminiscent of tiling of bricks, which is illustrated and self-explanatory with two representative layers of planks, assembled with the "bricks" (simplified model for supramolecular dimers) in a zig-zag fashion (bottom panel in Figure 4c). Each supramolecular "brick" is labeled in blue or orange, respectively, to distinguish dimers with different orientations. Besides, two layers of "bricks" with an offset of 6.8 Å are differentiated with deep and light colors. As illustrated by Figure S16, the seemingly energetically unfavourable zig-zag is stablized by both edge-to-face packing (along crystallographic *c*-axis) and face-to-face packing (along *b*-axis) of the adjcent dimer "bricks", leading to a tight packing of **CDC-1** molecules in the crystalline phase.

To the best of knowledge, this novel hierarchical superstructure has not been discovered by conventional self-assembling building blocks. The highly irregular and adaptable geometry of **CDC-1**s (with flexible exterior amine panels and with less steric hindrance on the periphery, Figure 4a) seemly plays a key role in such unusual and inefficient packing. This structure-to-superstructure correlation might provide a guideline for the design of similar building blocks for the search of novel supramolecular structures in the future.

**CDC-5** is a tailored version of **CDC-1**, with one extra methyl group on each blade, and its self-assembly is dramatically altered (Figure 5). Highly symmetrical **CDC-5** molecules with a radius of 14.3 Å aggregate into the trigonal crystalline phase (Figure 5a). The structural and retrostructural analysis of this supramolecular structure reveals that **CDC-5** self-assemble in a controlled hierarchical manner as well.



**Figure 5.** Controlled hierarchical self-assembly of **CDC-5** into 3D trigonal crystalline phase with welldefined primary, secondary, and tertiary structures. (a) Stick mode of primary structure **CDC-5**. (b) Supramolecular column (secondary structure) self-assembled by **CDC-5**s. The red dashed circle highlights alignment of dithiane rings, and the enlarged image shows distance between two **CDC-5**s. (c) Tertiary structure with columnar crystalline hexagonal lattice self-organized by supramolecular columns, with colors distinguishing different columns. Upper panel shows three representative columns viewed along crystallographic *b*-axis, with the inset showing detailed packing parameters. Bottom panel shows the packing of columns viewed along *c*-axis, with the enlarged image revealing the dithiane rings are interwoven with each other (yellow dashed rectangle) between neighbouring **CDC-5**s. Solvent molecules and hydrogen atoms are omitted for clarity.

**CDC-5**s, serving as primary structures, are packed into supramolecular columns (Figure 5b). In each column **CDC-5**s are perfectly superimposed with each other, with an intermolecular distance of 3.8 Å (side view in Figure 5b). This packing facilitates effective intermolecular  $\pi$ - $\pi$  stacking between the exterior amine panels (in red) of adjacent **CDC-5**s. Along with the intramolecular  $\pi$ - $\pi$  stacking (*vide supra*), it favors the ordered alignment of all panels of a **CDC-5**, and ensures its symmetric configuration during crystallization. Besides, every dithiane ring is tilted and aligned with its homologues of other **CDC-5**s along the column axis, as highlighted by red dashed circle (tilt view in Figure 5b). These columns (secondary structures),

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self-organize into tertiary 3D supramolecular structure (Figure 5c). They are labelled with different colors for easy analysis. Along crystallographic *b*-axis, three representative columns are aligned in parallel with a center-to-center distance of 19.5 Å and an average vertical offset of 4.9 Å (upper panel in Figure 5c). The dithiane rings are staggered evenly with distance of 4.0 Å. When viewed along *c*-axis, each column is packed with six columns, forming a columnar hexagonal lattice (bottom panel in Figure 5c). As the diameter of each CDC-5 is 28.6 Å (Figure 5a), which is larger than the center-to-center distance of 19.5 Å of two columns, the dithiane rings are therefore interwoven with each other between the neighbouring CDC-5s, as highlighted by yellow dashed rectangles. Along with the vertical offset mentioned above, CDC-5s adopt such packing pattern where these erstwhile bulky dithiane moieties are hosted within the intercolumnar channels, so as to avoid their steric hindrance yet ensure tight packing of CDC-5 molecules. This packing also seemly facilitates the maintenance of the highly symmetric configuration of CDC-5 during crystal formation. It is also worth noting that CDC-5s exhibit the most regular configuration among the three catenate cages in the current study, which aggregate to form the 3D superstructure with the highest order.

Structural Effect on Topological Configuration and Self-Assembly Behaviour of Catenated Cages. As mentioned above, the structural tailoring of these catenated cages was realized as follows: CSC-1 with all rigid imine panels vs. CDC-1 with two flexible amine panels, and CDC-5 with flexible exterior amine panels but laterally bulkier vs. CDC-1. CSC-1 adopts a fairly irregular propeller-like shape, but the relatively rigid imine bonds help to maintain the parallel alignment of its four panels. They self-assemble into supramolecular dimers, and the dimers form low-order helical columns, which self-organize into the 3D triclinic crystalline with four clearly defined levels of structure. Two flexible exterior amine panels and less hindered periphery of CDC-1 favor the highly irregular distortion. It facilitates the self-assembly of CDC-1s into brick-like supramolecular dimers, which self-organize into the unusual 3D wave-like plank in a zig-zag fashion (the lowest order). Compared to CDC-1s, extra methyl groups on the periphery of

**CDC-5**s urge the interweaving of their dithiane rings during the self-assembly, which is beneficial to maintain their most symmetric propeller-like geometry. They self-assemble into perfect supramolecular columns, which self-organize into the 3D trigonal crystalline with the highest order. The order of the triclinic crystalline phase is lower than that of the trigonal crystalline phase, which results from the difference between the low-order configuration of **CSC-1** and the high-order geometry of **CDC-5**. It therefore demonstrates that subtle structural change of catenated cages alters dramatically their topological configurations, which in turn leads to their different hierarchical self-assembly behaviors. Although the symmetric molecules are generally believed to form the most thermodynamically favored polymorphs during self-assembly, the influence of solvent cannot be overlooked. The complexation of these catenated cages with various solvents during crystallization is currently under investigation in our laboratories.

#### CONCLUSIONS

In conclusion, we prepared various 3D superstructures by self-assembly of a series of catenated cages in a controlled hierarchical manner. Our study reveals that catenated cages provide a promising molecular platform, which allows us to seek hierarchical superstructures that are inaccessible for conventional self-assembling building blocks and simple cages, such as 3D wave-like plank self-assembled by **CDC-1** presented in this work. This unusual packing pattern is attributed to the highly distorted topology and configurational flexibility of **CDC-1**. Three different hierarchical superstructures were achieved with subtle structural modification of our catenated cages, and it therefore highlights the advantage of their tailorablity.

These superstructures could be used for the discovery of emerging materials with unusual properties. For example, the Connolly surface analyses of these superstructures (Figure S13) reveal that potential porous channels can be constructed by the controlled hierarchical self-assembly of our catenated cages to form various types of extrinsic voids. Along with the strategy of our selective post-modification—not limited to the reduction—of the external panels of an symmetric catenated cage, it will open up new

opportunities for exploring chirality manipulation, proton conductivity, ferroelectricity, catalysis, and so on, which are the ongoing endeavours within our laboratories.

# **ASSOCIATED CONTENT**

#### Supporting Information

The Supporting Information is available free of charge at on the ACS Publications website.

Characterization methods, experimental details and characterization of compounds (PDF)

Crystal structure for CSC-1 (CIF)

Crystal structure for CDC-1 (CIF)

Crystal structure for CDC-5 (CIF)

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#### Notes

The authors declare no competing interests.

## ACKNOWLEDGMENTS

This work was supported by National Natural Science Foundation of China (key program 21890733), and the Shanghai Natural Science Foundation (18ZR1420800). We thank Dr. Hang Wang (MALDI-TOF MS) and Wanping Lu (Supercritical Fluid Chromatography) at the Instrumental Analysis Centre of SJTU, and Rongrong Yu for his assistance in chiral HPLC characterization. We thank Dr. Shan Jiang from ShanghaiTech University for constructive discussion and suggestions.

### ABBREVIATIONS

CSC, Catenane of symmetric cages; CDC, Catenane of dissymmetric cages.

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