Stacking Cyclophanes into Chiral Microvessels

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Abstract: Engineering novel micro-/nanoscale systems and devices based on supramolecular assembly has tremendous potential from diverse applications perspective. However, controlling the size, shape, spatial arrangements, and hierarchical transcription by a dimensional organizing principle (1D–3D arrangement) without the help of templates remains a challenging task. In this vein, a recent study by Oki and colleagues reporting the stacking of chiral cyclophanes via intermolecular non-covalent interactions for crafting synchronous microcrystalline 3D chiral vessels with controlled conformational arrangements represents a truly remarkable illustration of molecular engineering. The microvessels bear stereocontrolled skeletal morphology, recognize stereoisomers and serve as containers to accommodate microcrystals, polymer particles, and fluorescent dyes. The full application scope of this fascinating research is far beyond non-covalent interactions, supramolecular self-assembly, and crystal engineering.

Nature has developed a remarkable level of control over the multiple-hierarchical organization and assembly at the molecular level, thus ultimately transforming inanimate matter into complex living matter such as DNA and proteins with specific features and functions.[1] DNA and protein biopolymers rely on certain non-covalent interactions (e.g., hydrogen bonds and π–π stacking) and covalent forces (such as peptide bonds).[2] Although no synthetic material exists to outperform Nature's spectacular levels of multi-functionalities, by mimicking nature and biological pronciples as a model, materials engineering with controlled arrangements at the microscopic, nanoscopic, and molecular levels has arguably been one of the most important and long-standing objectives in fields ranging from nanotechnology to materials and interfacial science.[3]

Building synthetic molecules and studying their properties is a broad area of research; however, when transforming small molecular components into useful functional systems or devices, various challenges and opportunities arise depending on the system's dimensionality (1D–3D arrangement).[4,5] In particular, a challenging task in engineering supramolecular materials via non-covalent intermolecular interactions is to control spatial arrangements and hierarchical transcription at different length scales, without the aid of templates.[6] Integrating intrinsic molecular features into molecular assemblies, for instance, chirality, responsiveness, and other functions that operate under specific physical/chemical environments have tremendous potential from applications perspectives.[7,8] In this context, Oki and colleagues report an innovative synthesis strategy to craft unprecedented crystalline chiral microvessels in a highly-controlled, uniaxial manner by stacking chemically-programmed chiral [2.2]paracyclophane (PCP) scaffolds via supramolecular interactions (Figure 1).[9] This strategy exploits a simple drop-casting approach on a quartz substrate to construct chiral 3D microvessels within only a few seconds. The microvessels grow outward with an average side length and height of 0.8 and 0.3 μm, respectively, forming a 0.5 μm thick hexagonal pyramidal void. The single crystal X-ray diffraction analysis shows multiple intermolecular non-covalent interactions of C–H···π, C–H···O, and π–π interactions holding PCP molecular tectons together in a counter-clockwise rotation of 60° along a crystallographic six-fold screw axis. In the crystal, (S_p)-PCP molecules are arranged symmetrically. The (S_p)-PCPs form complementary π–π and C–H···O interactions side by side within the sheet. The interlayers of the sheets stack on each other via multiple C–H···π and C–H···O interactions. Synchronous assembly of the (R_p)-PCPs is likewise accomplished, showing a mirror-image molecular arrangement. S_p and R_p describe the planar chirality of PCP.[10]

The ingenious design of the chemically programmed PCP tectons in enantiopure form is of utmost relevance, brings the innate stereochemical features (planar chirality) and facilitates vital noncovalent interactions to direct conformational arrangements, which eventually lead to the stereocontrolled skeletal morphology. The researchers then studied the growth kinetics, morphological and hierarchical transition processes by varying the constituent feed PCP-concentration. It was observed that the chiral microvessels built with (S_p)-PCP molecules recognize S_p stereoisomers in the successive secondary growth process (Figure 2). However, this was not operative when (R_p)-PCPs and racemic mixture as feed were applied to the (S_p)-PCP-based microvessels upon assembly.

This research on 3D microvessels has been of fundamental interest and understanding, predominantly spanning molecular design and assembly pathways. However, because of the ease of their synthesis, and considering the innate

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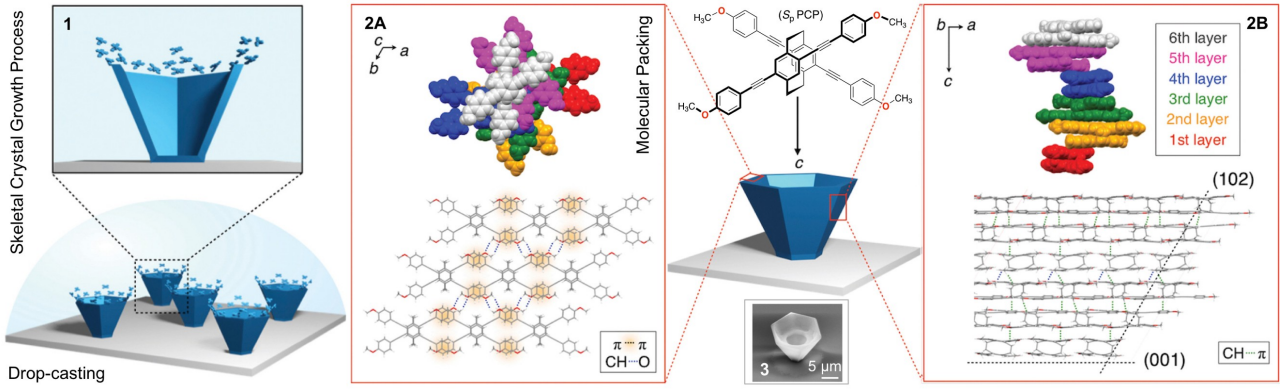

Figure 1. Morphological representation of the vessel-shaped skeletal chiral microcrystals (**1**); Molecular packing arrangement of the (S_p)-PCPs in microvessel viewed from the *c*-axis (left) and *b*-axis (right) directions (**2**); The intermolecular interactions are visualized with orange circles (π–π), blue (C H···O) and green (C H···π) dashed lines. PCP molecules in each stack (layer) are colored red, orange, green, blue, magenta, and gray in order. SEM image of the microcrystalline vessel (**3**). Scale bar: 5 μm. Reproduced with permission.[9] Copyright **2022**, Science, American Association for the Advancement of Science (AAAS).

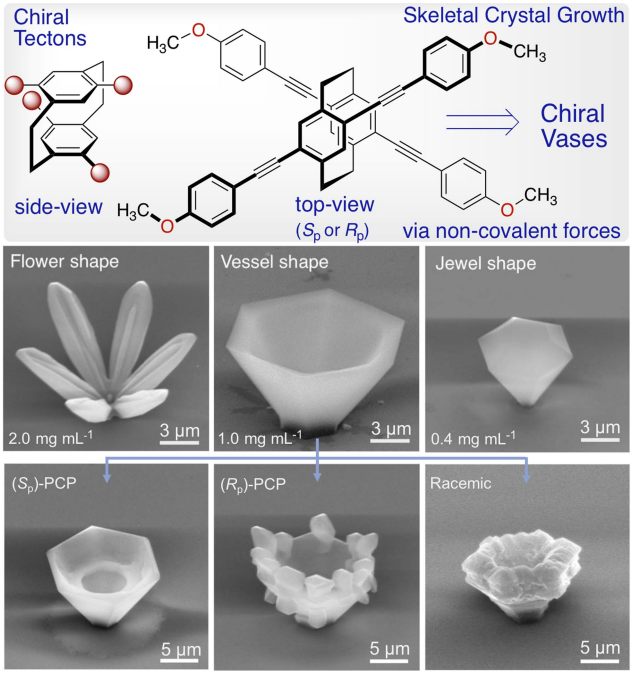

Figure 2. Morphology control and hierarchical crystal growth: Bespoke planar chiral tectons (top); SEM images of the resultant microcrystals formed by varying concentrations of the constituent (S_p)-PCP (middle); and stereoselective crystal growth with successive S_p-, R_p- and racemic PCPs as feed (bottom). Reproduced with permission.[9] Copyright **2022**, Science, AAAS.

electronic and chiroptical properties of the PCP tectons, this research may evolve from being a synthetic curiosity to having practical applications for developing technologically useful micro-devices. Sketching out possible future research, we would also like to highlight a few points: For further translational potential, addressing the mechanical stability of the microvessels would also be crucial as noncovalent skeletal assemblies built with weak intermolecular interactions could be fragile, and their distinct molecular arrangement sequence may deform under mechanical stress, temperature, or exposure to solvents vapors. Advanced fabrication methods like automated spraying techniques could be optimized for scaling up (with the same level of organization). Microvessels could be grown on other functionalized substrates (e.g., glass, mica, and gold wafer) that direct the nucleation site, orientation, and structure of the deposited crystals as known for other materials.[11]

In a proof-of-principle study, the 3D microvessels are described to serve as "containers" that can accommodate azo-functionalized crystals, polymer particles, and fluorescent dyes. It would be exciting to explore if such vessels allowed guest molecules to go in and out without significantly changing their structures. Specific methods such as small-angle XRD techniques could be helpful to provide more insights into pore size, if analyses on this microvessel scale could be possible.

Beyond the prototypical double-layered PCP, it remains to be explored whether this approach might be compatible with even larger molecular tectons.[12] For instance, co-facially stacked PCP-based multi-layered molecules, ring-fused or bridge-extended cyclophane homologue systems could lead to new structural and functional attributes by constructing large, intricate, and highly ordered skeletally novel structures. In this respect, computer-aided in silico methods and design approaches can assist in selecting superior-performing molecular components to engineer function-inspired nano- and micro-assemblies.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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