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Self-Assembly

Self-Dissociating Tubules from Helical Stacking of Noncovalent Macrocycles**

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The construction of tubular structures by molecular self-assembly is a topic of great current interest because of the potential applications of such assemblies in the fields of biotechnology and materials science.[1] Inspired by natural tubules created in biological systems,[2] diverse synthetic tubular structures have been developed through self-assembly of designed molecular modules including lipid molecules,[1a] aromatic amphiphiles,[3] and helical polymers.[4] The organization of shape-persistent macrocycles into supramolecular structures is an alternative way to construct tubular structures.[5] The macrocyclic segments with conformational rigidity stack on top of each other through π–π stacking interactions to create a hollow tubular interior that is separated from the exterior. The shape-persistent macrocyclic structures can also be constructed by non-covalent interactions such as hydrogen-bonding interactions of nucleotide mimic base pairs[6] and metal-coordination bonding of bent-shaped ligands.[7] Although this strategy is well established, the construction of the shape-persistent macrocycles through non-specific interactions has been rarely reported.[8]

Noncovalent macrocyclic structures may be constructed by self-assembly of laterally grafted bent-shaped rigid segments with an internal angle of 120° through a combination of shape complementarity and phase separation of dissimilar blocks. The resulting noncovalent macrocycles are expected to stack on top of each other to form tubular structures. In addition to noncovalent synthesis of 1D structures, another attractive aspect regarding these 1D structures is their possibility to dynamically respond to external stimuli, including stimuli-responsive sol–gel interconversion,[9] thermo-responsive supramolecular chirality,[10] and fluorescence switching.[11] Accordingly, we synthesized the laterally grafted bent-rod amphiphile **1**, which consists of a *meta*-linked aromatic segment and an oligoether dendron side-group.

Herein we present the formation of hexameric macrocycles from the self-assembly of small block molecules based on an *m*-linked aromatic segment. The macrocycles stack on top of each other to form an elongated tubular structure (Figure 1). Notably, the resulting tubules dissociate into discrete toroidal stacks in response to addition of a silver salt. The rigid-flexible block molecules described here were prepared in a stepwise fashion according to previously reported similar procedures.[8,12]

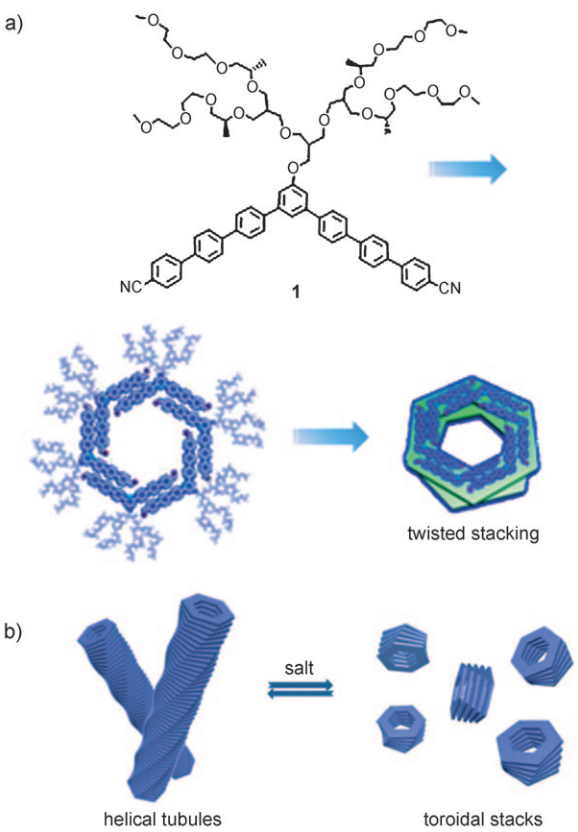

Figure 1. Schematic representation of a) helical stacking of hexameric macrocycles and b) dissociation into toroidal stacks.

The aggregation behavior of the molecules was investigated in aqueous solution by using optical spectroscopy, dynamic light scattering (DLS), TEM, AFM, and small-angle X-ray scattering (SAXS) experiments. The emission maximum of **1** in aqueous solution is red-shifted by approximately 10 nm with respect to that observed in chloroform and the fluorescence intensity is significantly quenched, which is

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indicative of aggregation of the bent-shaped aromatic segments (Figure 2a). Circular dichroism (CD) spectra of the aqueous solutions of **1** show a significant Cotton effect above certain concentrations (0.005 wt%) in the spectral region of the aromatic units, thus indicating the formation of one-handed helical structures (Figure 2b).

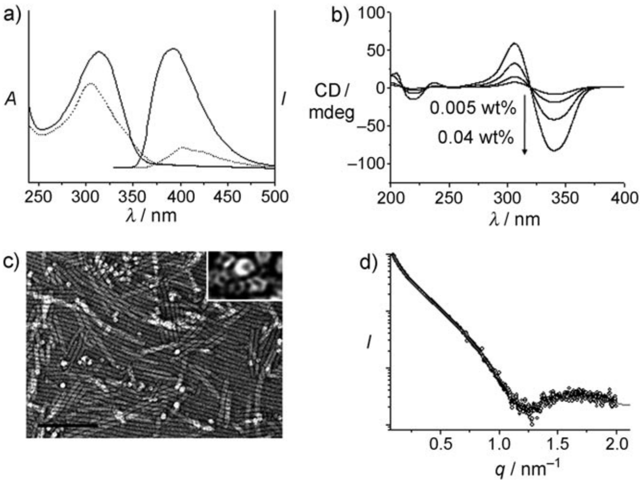

Figure 2. a) Absorption and emission spectra of **1** (0.02 wt%) in $CHCl_3$ (solid line) and aqueous solution (dashed line); $\lambda_{ex} = 330$ nm. b) CD spectra of **1** in aqueous solution at various concentrations. c) TEM image of **1** from 0.005 wt% aqueous solution (stained with uranyl acetate, scale bar = 100 nm). The inset image shows the top view of helical tubules. d) SAXS profile of **1** (0.5 wt% aqueous solution) plotted against the scattering vector $q = 4\pi \sin\theta/\lambda$.

The formation of the cylindrical aggregates was further confirmed by TEM experiments performed on samples from aqueous solutions (0.005 wt%). When the sample was cast from solution and then negatively stained with uranyl acetate, the image shows elongated cylindrical objects with a uniform diameter of 6.5 nm and lengths of at least several micrometers. The top-view image (Figure 2c, inset) shows that the cylinders have a hollow interior with a diameter of 3 nm. SAXS measurements were performed with an aqueous solution (0.5 wt%) to confirm the formation of the cylindrical objects in the bulk solution (Figure 2d).[13] The scattering profile can be best fitted by using the form factor of an elongated cylindrical model with a thickness of 6.3 nm, which is consistent with the TEM images.

To gain insight into the packing arrangement of the bent-shaped aromatic segments, we have performed molecular dynamics (MD) simulations using GROMACS 4 (Figure 3).[14] Energy minimization of the suprastructure revealed that the six bent-shaped aromatic segments are arranged in a single slice and the terminal nitrile groups are located at the bay position of the adjacent molecule to form a hexameric macrocycle. In addition, the calculations showed that complementary electrostatic interactions between electron-withdrawing nitrile groups and electron-donating phenoxy groups enhance the stability of the hexameric cycles.[15] The macrocycles stack on top of each other with mutual rotations at an angle of 16.5° in the same direction to give rise to helical tubules. The hollow helical structure was found to be stable in aqueous solution and sustained its initial structure for up to 5 ns of MD simulations. The size of the internal cavity is 2.7 nm in diameter and the external diameter is 6.5 nm, which is in excellent agreement with the dimensions obtained from TEM and SAXS.

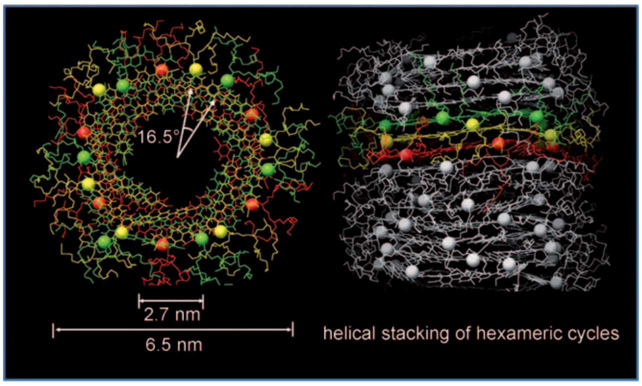

Figure 3. Top view (left) and side view (right) of a helical tubule obtained by molecular modeling of **1**. The inner and outer diameters are calculated to be 2.7 and 6.5 nm, respectively. The balls represent phenoxy oxygen atoms.

On the basis of these results, we propose that **1** self-assembles into hexameric macrocycles with an internal diameter of approximately 3 nm through π–π stacking and electrostatic interactions between the aromatic segments. The resulting macrocycles stack on top of each other with mutual rotation at an angle of 16.5° in the same direction to form a tubular structure with an external diameter of 6.5 nm. Consequently, this helically staggered stacking of the hexameric macrocycles would lead to a tubular structure with supramolecular chirality that consists of an aromatic wall surrounded by hydrophilic oligoether dendritic chains that are exposed to the aqueous environment (Figure 1).

The hydrophobic internal surfaces of the tubules are functionalized by nitrile groups. Therefore, it can be hypothesized that the internal cavities can encapsulate a hydrophobic silver salt through hydrophobic interactions together with silver–nitrile interactions in aqueous solution. Remarkably, addition of up to 10 equivalents of silver dodecylsulfate (AgDS) as a hydrophobic guest triggers the aggregates to significantly decrease in hydrodynamic diameter from 65 nm to 8 nm, as confirmed by DLS experiments (Figure 4a). The TEM images also reveal that the long fibers decrease in length upon addition of AgDS (Figure 4b). When 10 equivalents of AgDS with respect to **1** are added to the fibers, the tubules transform into discrete nanostructures with a highly uniform size of an average diameter of 8 nm (Figure 5), which is consistent with the DLS result.[16] The images (negatively stained with uranyl acetate) show the formation of discrete nanostructures with a light exterior and a dark interior, hence indicating that the discrete objects consist of a defined interior of approximately 3 nm in diameter, similar to that of the intact tubules. To further confirm the formation of the toroids, we performed AFM measurements on the samples prepared by drop casting of an aqueous solution (0.001 wt%)

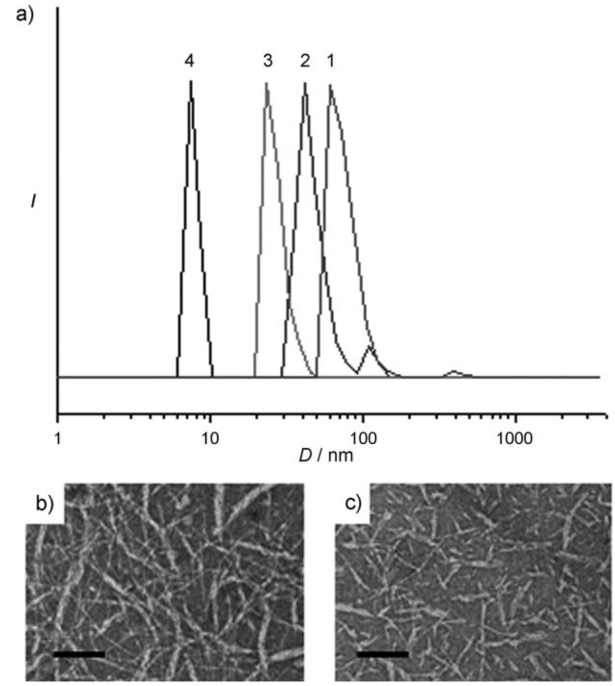

Figure 4. a) Size distribution graphs from DLS measurements of aqueous solutions (0.02 wt%) of **1** with 1) 0, 2) 3, 3) 5, 4) 10 equiv AgDS added. b), c) TEM micrographs of **1** with varying amounts of AgDS added (Scale bars = 200 nm; b) 0.6 equiv, c) 5 equiv. The TEM images show that the length of the cylindrical tubules decreases gradually upon addition of AgDS.

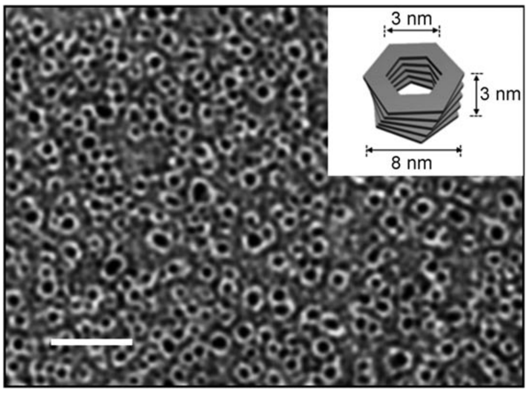

Figure 5. TEM image of **1** after addition of 10 equiv of AgDS (Scale bar = 50 nm).

on hydrophilic high grade mica as a substrate (Figure 6a). The AFM investigations reveal exclusively toroid-shaped nanostructures; the height of the toroids was observed to be about 1.3 nm, which is less than the value determined by TEM. This difference could in part arise from deformation of the toroids on the mica surface.[17]

To investigate whether AgDS influences the packing arrangements of the bent-shaped aromatic segments in the tubular walls, spectroscopic studies have been performed with solutions that contain different amounts of AgDS (Figure 6b and c). Upon addition of AgDS, the UV absorption and emission spectra remain nearly unchanged. Furthermore, CD spectra show that the Cotton effect of **1** is maintained even after addition of up to 10 equivalents of AgDS (Figure 6c). All these observations suggest that the addition of guest molecules does not influence the packing arrangement of the aromatic segments of the tubular structure. On the basis of these results, it can be concluded that the discrete objects consist of helical stacks of several hexameric macrocycles that result in a toroidal structure with a height of approximately 3 nm (Figure 5, inset). Preservation of the hexameric macrocyclic building block even after dissociation is also reflected in the external and internal dimensions of the suprastructure, which were essentially unaltered compared to those of the intact tubules. Considering the height of approximately 3 nm together with 4.4 Å π–π stacking distance determined from the molecular simulations, each toroid is estimated to consist of seven stacks of the hexameric macrocycles.

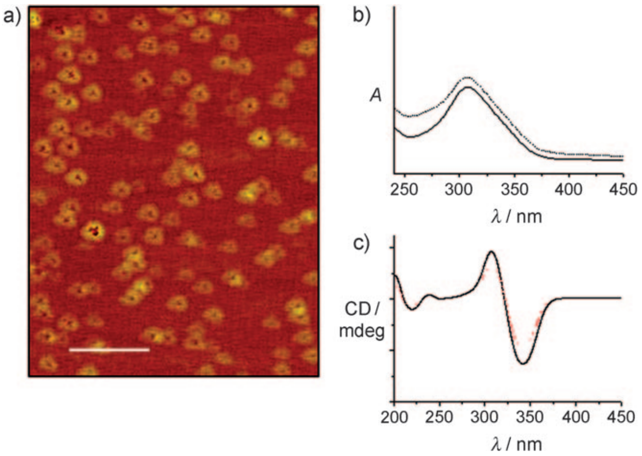

Figure 6. a) AFM image of **1** after addition of 10 equiv of AgDS drop-cast from aqueous solution (0.001 wt%) on mica (scale bar = 200 nm). b) Absorption and c) CD spectra of **1** (solid line) and **1** with 10 equiv of AgDS (dashed red line) in aqueous solution (0.02 wt%).

These results demonstrate that the elongated tubules dissociate into segmented tubules triggered by salt addition while maintaining the helical order of the aromatic segments (Figure 1). This dissociation into toroids upon addition of AgDS might be understood by considering the space-filling requirements of the tubular cavity. Upon addition of AgDS, a part of the hydrophobic guest molecules is able to fill the tubular cavity through hydrophobic interactions and metal–nitrile coordination bonds.[18] This coordination interaction is reflected in the downfield shift of the aromatic protons at the *ortho*-positions of the nitrile group in the ^{1}H NMR spectrum (Figure S4 in the Supporting Information).[19,20] As the AgDS content increases, the internal cavity requires more space to efficiently encapsulate the guest molecules. The elongated tubules break up into shorter objects and eventually transform into toroidal stacks with helical order to give more room to the guest molecules without sacrificing π–π stacking interactions. Detailed investigations to clarify this proposed mechanism are currently underway.

The most notable feature of the rigid-flexible block molecule investigated here is its ability to self-assemble into hexameric macrocycles through nonspecific interactions, which are the combination of shape complementarity and aromatic stacking interactions. This driving force for self-assembly is in contrast to that of previous supramolecular macrocycles, which is dominated by specific attractive interactions such as hydrogen-bonding and coordination-bonding interactions.[6,7,21] The hexameric macrocycles stack together with mutual rotation in the same direction to form helical tubules. More importantly, these helical tubules are segmented into sliced tubules while maintaining helical order in these discrete nanostructures upon addition of a silver salt. The preservation of the shape-persistent hexameric macrocycles during this transition is responsible for the retention of supramolecular chirality. Transition from chiral columns into discrete nanostructures while maintaining the supramolecular chirality is reported for thermotropic liquid crystals of dendritic molecules.[22] There is, however, no precedent of such a transition for well-defined nanoscale synthetic assemblies in aqueous solution. The results described herein represent a significant example of dynamic helical fibers that are able to respond to external triggers by segmentation into discrete nanostructures with preservation of their supramolecular chirality. Furthermore, this transition should provide an insight into the dynamic control of the regular dissociation of 1D chiral structures.

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