

Pulsating (脈動する) Tubules from Noncovalent Macrocycles

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1. Introduction

- Self-assembly of small molecular modules into tubules with hollow cavities is a key structural feature of living systems (e.g. tobacco mosaic virus and cytoplasmic micro tubules).
- Numerous self-assembled molecules that can form such hollow nanostructures through orchestrated interplay of various non-covalent interaction are known (e. g. vesicles, nanotubes etc.).¹
- One of the ultimate challenges would be to develop artificial analogs of cardiac (心臓の) muscle cell that pulsate autonomously.

Problem: Integration of dynamic response characteristics into synthetic systems.

- Chemical reactions incompatible with dynamic motion are usually required for one-dimensional (1-D) fixation into tubules. (cross-linking etc). Therefore external triggers can lead to the collapse of their hollow structure due to poor aggregation stability.

This work: thermally responsive nanotubules induced by pyridine unit

- Pyridine-unit-introduced amphiphiles **1** self-assembled into thermoresponsive tubules (Fig. 1).
- The hydration of pyridine derivatives have been experimentally studied by high pressure mass spectrometry (HPMS) and by calculation (Fig. 2).²
- Pyridine units would exhibit thermoresponsive behavior, because the pyridine units undergo thermally regulated dehydration upon heating.²

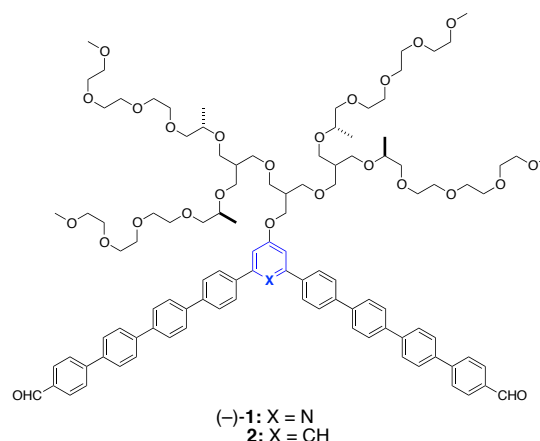


Figure 1. Structure of amphiphile (–)-**1** and **2**

2. Results and Discussion

2.1 Self-assembly of pyridine-introduced amphiphile **1**

- The transmission electron microscopy (TEM) image of the aggregates showed toroidal objects with a uniform diameter of 11 nm and an internal cavity of 4 nm in a diameter (Fig. 3a). (aggregates of **2**: diameter 7 nm, cavity 3 nm)

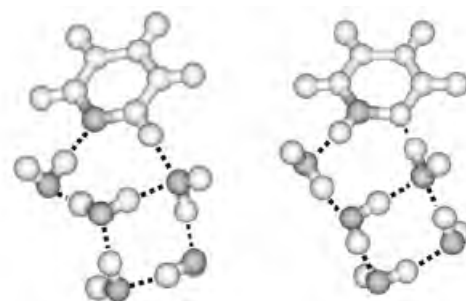


Figure 2. Structure for pyridine-water complexes

- The expansion of the hexameric macrocycles could be determined at the B3LYP/cc-p VDZ level.² explained by the formation of water clusters at the pyridine moieties of **1**.

- The water clusters induced adjacent molecules to slide into a loose packing arrangement.
 - The expanded macrocycles undergo supramolecular polymerization with increasing concentration by stacking on the top of each other to form elongated helical tubule.
 - Assemblies derived from (+)-**1** (enantiomer of (-)-**1**) display opposite circular dichroism (CD) signals with a mirror image relationship (Fig. 3c).³
- ➔ Molecular chirality is transferred to the self-assembled structure.

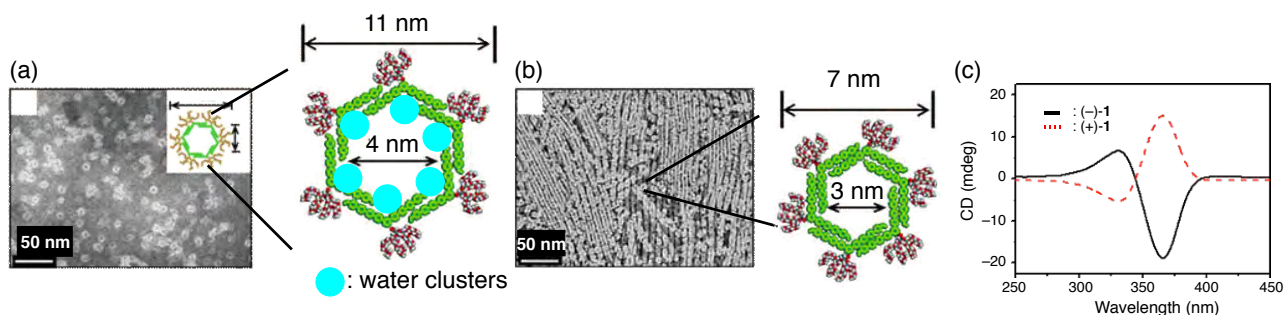


Figure 3. (a) TEM image of **1** from 0.002 wt% aqueous solution and the schematic magnified image. (b) TEM image of **2** from 0.01 wt% aqueous solution and the schematic magnified image. (c) Comparable CD spectra of (-)-**1** and (+)-**1** in aqueous solution (0.006 wt%) at 25 °C.

2.2. Expansion-contraction process

- On heating to 60 °C, significant size decrease was observed (external diameters: 11 to 7 nm, 47% reduction) (Fig. 4a, b).
- The size change is fully reversible on cooling and subsequent heating cycles.
- Dehydration of pyridine units could induce sliding of the aromatic segments from slipped arrangement into the fully overlapped motif.
- Up-field shift of pyridine peak and broadening of ethylene oxide peaks were observed in ¹H NMR spectrum of model compound **3**, indicating the loss of hydrogen bonding (Fig. 5).

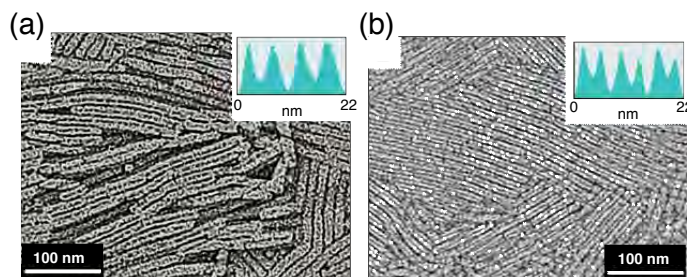


Figure 4. (a) TEM image of **1** (0.02 wt%). (b) TEM image of **1** (0.01 wt%) prepared at 60 °C (negatively stained with uranyl acetate). Inset image is contrast intensity of cross-section.

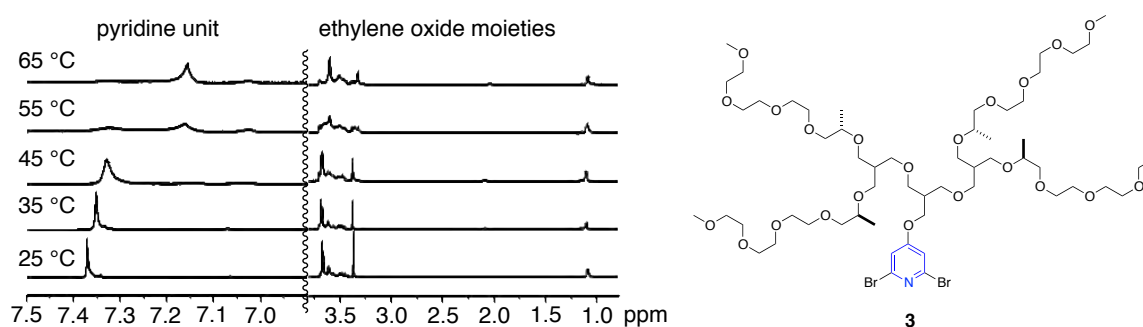


Figure 5. ¹H NMR spectra of **3** in D₂O (0.5 wt%) with temperature variation.

2.3. Chirality inversion

• Notably, the expansion-contraction motion of the tubules is accompanied with chirality inversion (Fig. 6a, b). Upon heating, the CD signal was inverted from the negative minimum to a strong Cotton effect, indicating that helical sense switched to opposite-handedness.⁴

• Atomic force microscopy (AFM) experiment with (-)-**1** and (+)-**1** on highly oriented pyrolytic graphite (HOPG) showed rod-like aggregates with a diameter of 7 nm, corresponding to the contracted tubules (dehydrated state) (Fig. 6c, d). The magnified image of tubules comprising of (-)-**1** revealed a

right-handed helical structure, which is the mirror image of the tubules comprising of (+)-**1**.

• In contrast with contracted tubules on HOPG, elongated objects with a diameter of 11 to 12 nm probably corresponding to the expanded state were observed on hydrophilic mica (Fig. 6e, f).

2.4. Molecular dynamics simulation

• In the expanded state, there are marginal spaces outside of the aromatic rings that dendrimers occupy, resulting in steric repulsion between bulky dendric segments on left side of each vertex. To relieve the steric repulsions without sacrificing π -stacking interactions, the upper-layerd macrocycles rotate clockwise

→ **left-handed** (Fig. 7A, C)

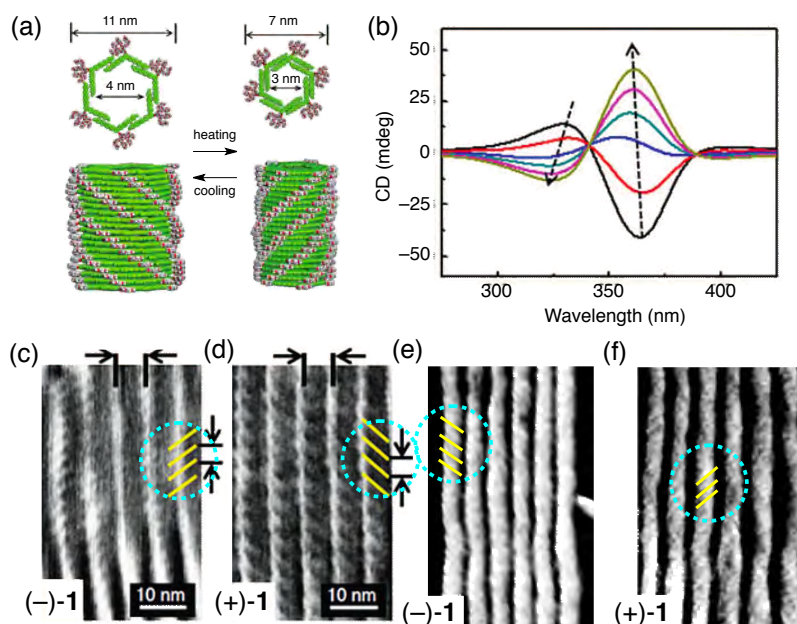


Figure 6. (a) Schematic image of reversible switching of the tubules between expanded and contracted state with chirality inversion. (b) Temperature-dependent CD spectra of **1** (0.01 wt%) with temperature variation from 25 to 60 °C. AFM phase image of self-assembled **1** and tubules comprising of (-)-**1** revealed a *ent*-**1** (c, d) on HOPG and on mica (e, f) respectively.

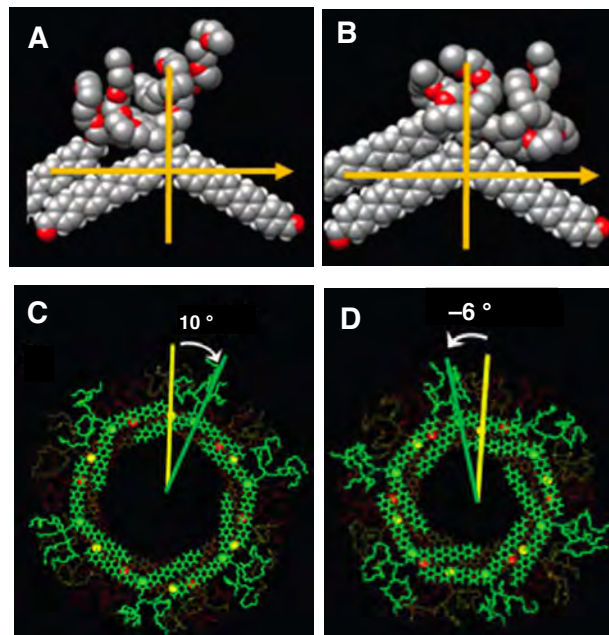


Figure 7. Molecular dynamics simulation. The macrocyclic plane of the expanded state (A), and the contracted state (B) Expanded (C) and contracted (D) forms of helical tubules.

- In the contracted motif, the closely-packed macrocycles crowd out the dendrimers from marginal space leading to steric crowding on the right side. This spacial requirement induces the upper-layered macrocycles to rotate counter clockwise.

➔ **right-handed** (Fig. 7B, D)

2.5. Application of thermoresponsive nanotubules

- This dynamic motion of the tubules can be accompanied by encapsulating and releasing hydrophobic guest molecules. The tubules with aromatic cavities can take up C_{60} through hydrophobic interaction during assembly (Fig. 8).

- Using thermal trigger, C_{60} - C_{60} interaction can be regulated through the pulsating motion.

- After cooling of the tubules from 65 °C, considerably reduced absorbance at 452 nm was observed.

➔ C_{60} - C_{60} interactions are diminished due to expansion of the internal volume.

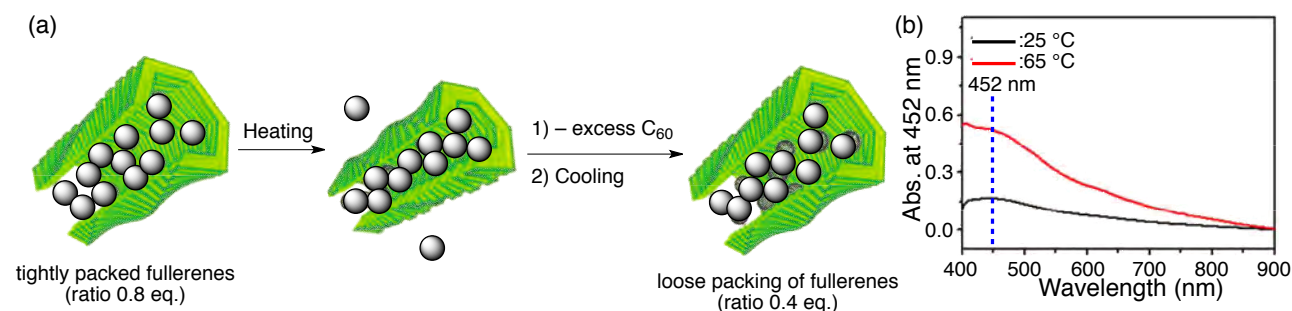


Figure 8. (a) Schematic image of regulation of C_{60} - C_{60} interaction within the tubular cavities when the tubule contains 0.4 eq. of C_{60} in aqueous solution. (b) UV-vis spectra of **1** with C_{60} (0.4 eq.).

3. Conclusion

- The pyridine unit and ethylene oxide moieties enable the tubules to undergo drastic contraction accompanied with chirality change on helical sense upon heating.

- The tubules can encapsulate hydrophobic materials. Upon heating, the shrinking nanotube pushed out of some of its hydrophobic guests.

➔ **Pulsating motion was demonstrated by the synthetic tubules without the collapse of the systems.**

< References >

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