

Hierarchical chiral supramolecular nanoarchitectonics with molecular detection

Li, Heng; Han, Liang; Li, Qing; Lai, Hanjian; Fernandez-Trillo, Francisco; Tian, Leilei; He, Feng

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Hierarchical Chiral Supramolecular Nanoarchitectonics with Molecular Detection: Helical Structure Controls upon Self-Assembly and Co-Assembly

*Heng Li, Liang Han, Qing Li, Hanjian Lai, Paco Fernández-Trillo, Leilei Tian and Feng He**

H. Li, L. Han, H. J. Lai, Prof. F. He
Shenzhen Grubbs Institute and Department of Chemistry, Southern University of Science and Technology, Shenzhen, 518055 (China).
E-mail: hef@sustech.edu.cn

H. Li, P. Fernández-Trillo
School of Chemistry, University of Birmingham, B15 2TT, UK.

P. Fernández-Trillo
Departamento de Química, Facultade de Ciencias and Centro de Investigacións Científicas Avanzadas (CICA), Universidade da Coruña A Coruña, 15071 (Spain).

Prof. F. He
Guangdong Provincial Key Laboratory of Catalysis, Southern University of Science and Technology, Shenzhen, 518055 (China)

Q. Li, L. L. Tian
Department of Materials Science and Engineering, Southern University of Science and Technology, Shenzhen, 518055 (China).

Keywords: supramolecular self-assembly, chiral supramolecular, hierarchical self-assembly, molecular detection, functionalized supramolecule

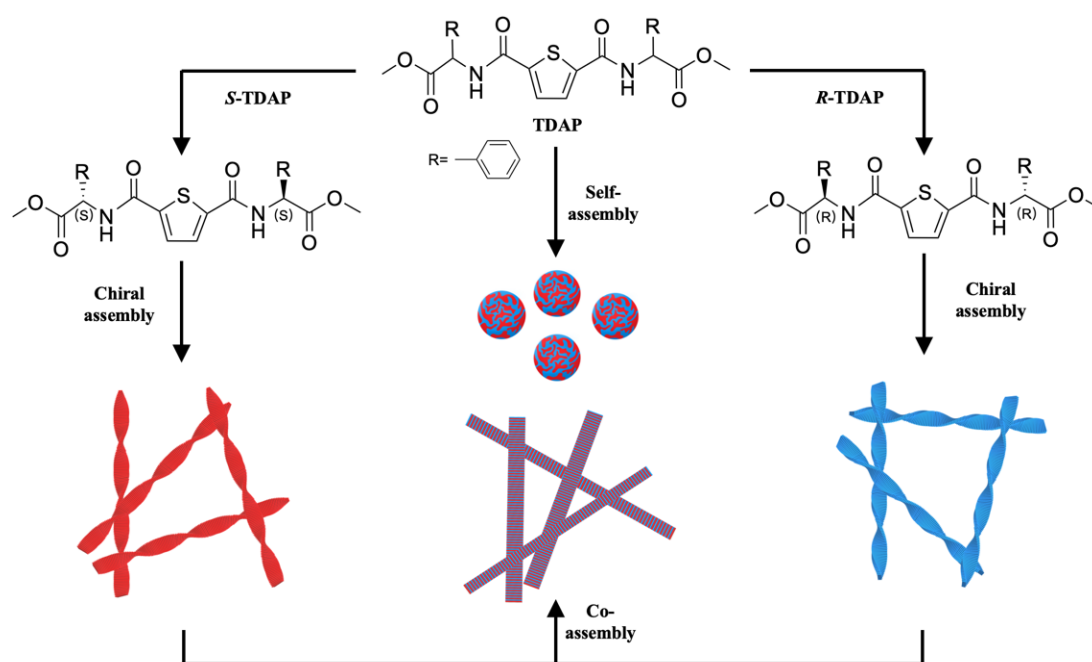
The morphological transformation from microspheres to helical supramolecular nanofibers with controllable handedness was achieved by the introduction of molecular chirality based on amino acid derivatives (TDAP), and the chirality of the supramolecular architectures that were achieved was nullified through the co-assembly of the equivalent TDAP enantiomers. The molecular detection of achiral melamine based on the *R*-TDAP-COOH supramolecular system was achieved by the appearance of helicity and inversion.

1. Introduction

Chiral compounds play a vital role in organisms and their chirality is strongly related to their biomolecular functions. This has continuously attracted interest in biology, physics, chemistry, and material sciences.^[1] Typical examples found in biological systems are sugars and amino acids which have L- and D-enantiomers. Recently, artificially chiral molecules have been designed and have displayed potential applications in chemistry,^[2,3] materials science,^[4] and biological systems.^[5] For well-defined chiral architectures, a general strategy has been established to design building blocks based on biologically relevant molecules (such as amino acids or DNA).^[6,7] Among these, supramolecular self-assembly,^[8] which is an important method in nature to construct chiral ordered structures, opens an efficient way by noncovalent interactions, such as hydrogen-bonding, hydrophobic interactions, and π - π stacking to design functional materials with tailored properties.^[9] Notably, chirality is also extended to the supramolecular level, and the stereochemical communication or chiral–chiral interaction between various chiral molecules becomes extremely important.^[10] Molecular chirality has been well explored but the importance of supramolecular chirality and its biofunction has not yet been fully recognized.^[11]

The self-assembly of chiral molecules into various architectures can be expressed across a broad range of structures, such as helices, Möbius strips, and gyroids.^[12-15] Among these, chiral helicity exhibits great sensitivity to external stimuli. Manipulation of the chirality of nano-architectures is a promising way to develop the biological functions of artificial materials. Hence, focusing on in-depth studies of supramolecular chirality is currently vigorously pursued.^[16] However, it is still challenging to fabricate desirable nano-structures that can mimic helical biomolecules through self-assembly from artificial molecules and utilize the sensitivity of helicity to explore the potential biological application of such helical biomolecules.^[16-17]

Herein, we report the synthesis of a thiophene-2,5-dicarboxamide with enantiomeric and racemic phenylalanine methyl ester branches (TDAP) (Scheme S1). Enantiopure *R*-TDAP, *S*-TDAP, and racemate TDAP were characterized by nuclear magnetic resonance (NMR) and liquid chromatography-mass (LC-MS) spectroscopy (Figure S1-S4). Uniform microspheres were self-assembled from TDAP, while right-handed (*P*-helicity) and left-handed (*M*-helicity) nanofibers were constructed by the introduction of chiral enantiomers into the supramolecular system (Scheme 1). In comparison, by co-assembly with *R*-TDAP and *S*-TDAP, only racemic micro sheets lacking chiral characteristics were produced. To explore the biological applications, the *R*-TDAP was modified as *R*-TDAP-COOH to take advantage of the helicity. Melamine (MA) can be detected by explicit morphology transformation including the appearance and inversion of helicity.



Scheme 1. Structure transition from microspheres (TDAP) to twisted fibers with different chirality (*S*-TDAP, *P*-helicity, and *R*-TDAP, *M*-helicity) and micro sheets without chirality (*R*+*S*-TDAP).

2. Results and discussions

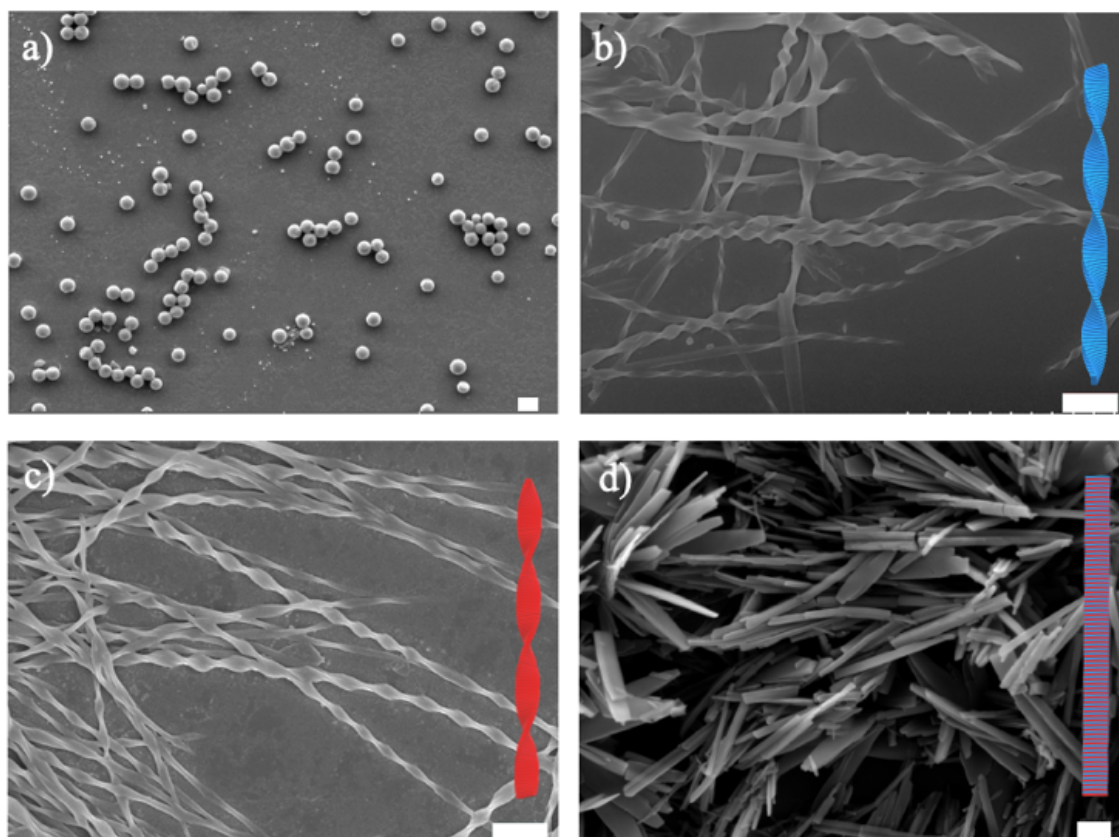


Figure 1. SEM images of (a) racemic, (b) *R*-, (c) *S*-, and (d) *R*+*S*-TDAP assembled architectures prepared in isopropanol/H₂O (1:1) mixtures. The schematic diagram of observed assemblies showed the structure characteristic, consisting of aggregation of many single molecular chains. Scale bars in the SEM images are 1 μm .

We investigated the self-assembled nanostructures of TDAP in different solvent systems including pure water and mixtures of methanol/H₂O (1:1), ethanol/H₂O (1:1), and isopropanol/H₂O (1:1) (Figures 1a, S6-S8). Among the aggregations that were to be obtained, the microspheres formed in a mixture of isopropanol and water (1:1), attracted our attention because of their uniformity and assembled potential (Figure 1a). For structural growth of *R*-TDAP and *S*-TDAP, the isopropanol/H₂O (1:1) is also the best solvent system like achiral TDAP, as a result of the suitable aggregating rates (Figure S9 and S10). The self-assembly of enantiopure *R*-TDAP was carried out and twisted nanofibers with left-handedness (M-type) were obtained (Figure 1b). As expected, *S*-

TDAP were organized into nanofiber with P-type helicity (Figure 1c). For the helical fiber architecture of *S*-TDAP, the helical pitch was in the range of 200–400 nm, while the left-handed helices formed from *R*-TDAP had helical pitch in the 300-500 nm range. Next, we mixed an equimolar ratio of *R*-TDAP and *S*-TDAP in the mixture of isopropanol and H₂O (1:1) at a concentration of 0.5 mg mL⁻¹ and followed by the same assembly approach. Interestingly, in contrast to the initial supramolecular structures, the co- assembled morphology, in this case, was the rectangular platelet without helicity, and the width was in the range of 500-800 nm. In all, the statistics of structural features based on every different morphology including helical pitch, diameter, length and width were calculated in Table S1. This indicated that the co-assembly of *R*- and *S*-compounds resulted in the nullification of chiral characteristics. These architectures obtained from co-assembly are also totally different from initial microspheres formed by racemic TDAP. As shown in Figure S11, racemic sphere objects are composed of molecules with three molecular configurations, while 2D platelet micelles are co-assembled with only two *R*-TDAP and *S*-TDAP components. In addition, we checked the morphological changes of *R*-, *R*+*S*-, and racemic-TDAP in the cooling assembly process at 80, 60, and 40 °C (Figure S12). The formation process of nanofibers, sheets, and spheres showed a significant morphological transformation from crystallization aggregation to fibred growth, quite different from those of sheets, and spheres. Therefore, this reveals that molecular structures whose symmetric chiral centers have the same chiral configuration play a key role in the process of the formation of supramolecular architectures as chiral nanofibers or platelet micelles rather than microspheres.

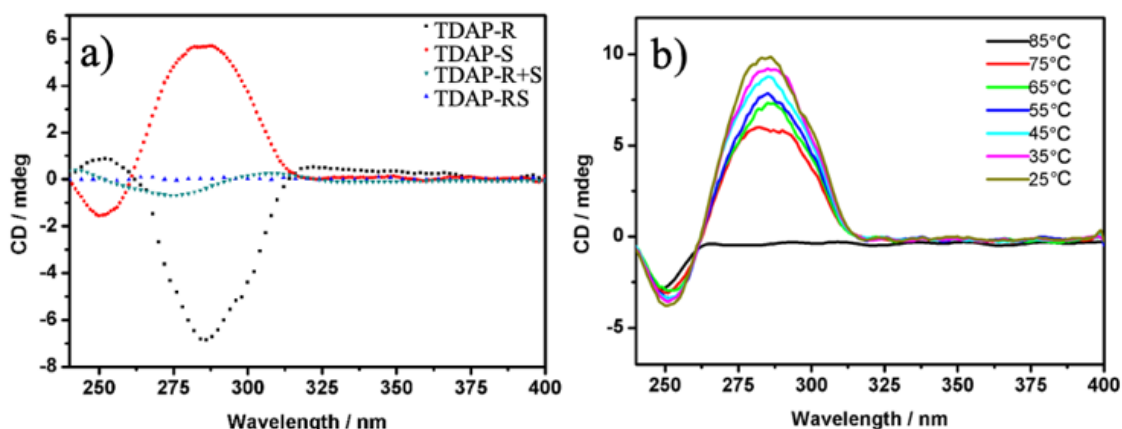


Figure 2. (a) CD spectra for *S*-, *R*-, racemic, and *R*+*S*-TDAP in the assembly state measured at 25.0 °C. (b) CD spectral changes of *S*-TDAP self-assemblies under different temperatures in the range of 25–85 °C with 10 °C intervals. These experiments were performed in the mixture of isopropanol/water (1:1) at 0.5 mg mL⁻¹.

CD spectroscopy was employed to examine the chiroptical properties. The CD spectrum of *S*-TDAP showed a significant Cotton effect with a strong positive (286 nm) and a weak negative CD signal (250 nm). The negative signal could be attributed to the intrinsic molecular chirality and the strong positive counterpart could be assigned to the chiral scattering of light caused by the interaction with the chiral supramolecular structure.^[5] These results indicated that aromatic rings in the helical fibers are in a highly asymmetric environment. *R*-TDAP showed a mirror image of the signal of *S*-TDAP (Figure 2). The racemate TDAP displayed a linear CD signal, confirmed the cancelation of the optical rotation in the microspheres. The CD spectrum of the co-assembly system of *S*-TDAP and *R*-TDAP failed to reveal any peak at 286 nm, thus showing that there was no chirality in the 2D platelet micelles because of the presence of opposing stereogenic centers. These results are further confirmation that molecular chirality and symmetric chiral configuration play key roles in the formation of supramolecular assembled architecture, which is consistent with SEM results.

To further confirm the existence of chirality in the supramolecular, variable-temperature CD (VT-CD) spectra were applied with the *S*-TDAP (Figure 2b). It is clear that the interactions in the assembled structures were broken due to the increase in the extent of molecular motion at high temperatures. When initially heating to 75 °C, the positive peak at 286 nm gradually decreased because of heating-induced disassociation of the twisted nanofibers. Upon further heating to 85 °C, the spectrum showed CD silence at around 286 nm, suggesting the *S*-TDAP molecules were completely in the freely moving state. However, *S*-TDAP still revealed negative CD absorption at around 250 nm originating from molecular intrinsic chirality. All in all, the supramolecular chirality was mainly evident below 70 °C, while the signal of molecular chirality was dominant over 60 °C.

In addition, single crystals of the enantiomers *S*-TDAP and *R*-TDAP were carried out (Figure 3 and Table S2). It was obvious that the molecular structures of the two TDAP isomers were symmetric as mirror images. In the case of the TDAP enantiomers, these molecules were arranged in a molecular chain and connected with each other by H-bonding interactions, which were formed between the carbonyl (C=O) and the secondary amine (N-H) groups with an interaction distance of 2.31 Å. It can be seen that the transfer directions of the H-bonding in the molecular chains are different as mirror images of each other. The different transfer directions of the H-bonding induce the different molecular arrangements and the packing of the molecular chains in different conformations. Aggregation of multiple molecular chains leads to the final helical morphologies with the different supramolecular chirality (Figure 3e and 3f). For the *R*+*S*-TDAP co-assembly system, it could be inferred that the H-bonding interactions would be disordered and the dominant orientation of the molecular arrangement would disappear, and this kind of multiple molecular chain aggregations might lead to the 2D tape-like architectures lacking helicity (Figure 3g).

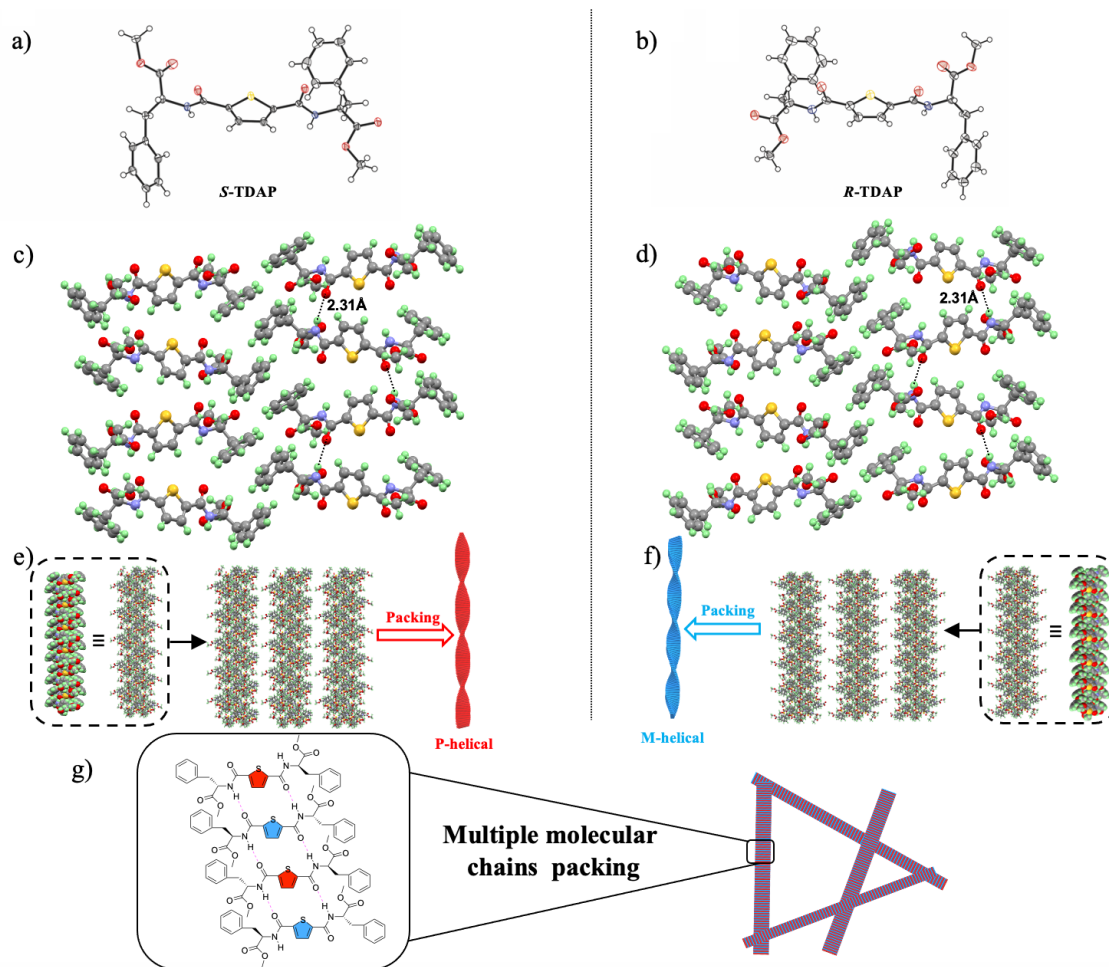


Figure 3. Single-crystal structures of *S*-TDAP and *R*-TDAP: (a-b) Molecular structures of thermal ellipsoids; (c-d) Intermolecular H-bond interactions; (e-f) Three-dimensional packing structures. Different molecular arrangements result in different handedness. In these figures, the molecular chains were observed as spacefilling models and the stacking modes were observed as ball and stick models. (g) The possible co-assembly mechanism of *R*+*S*-TDAP architecture (*R*-TDAP and *S*-TDAP are shown in blue and red, respectively.).

Among the supramolecular interactions in the assembly systems, the stacking of the hydrophobic phenyl core of the phenylalanine-based supramolecular system and the hydrogen bonding based on carboxylic acid moieties may provide an approach for efficient co-assembly with achiral structural analogues.^[7] So we synthesized the *R*-TDAP-COOH to explore biological applications (Scheme S2, and Figure S5). Then we tested its self-assembly in the H₂O, which stimulates the biological assembled situation

without organic solvents. The achieved morphology was a nanofiber with no twist or chirality (Figure 4b). Due to the appearance of carboxylic acid moieties after functionalization, the new H-bonding was formed between carboxylic acid (O-H) and the original amide group. This interaction hindered the initial intermolecular H-bonding resulting in the disappearance of helicity and destruction of the consistency of chirality. We tried to co-assemble *R*-TDAP-COOH with MA (1:1) by the heating-cooling process in H₂O. The achieved morphology was long twisted fiber with mainly P helicity (Figure 4a). In addition, we also tried to utilize *R*-TDAP-COOH to recognize MA structural analogue, Cyanuric acid (CA). There was no helicity in the co-assembly system (Figure 4c), which proved the specificity of TDAP recognition system for MA. SEM images were also recorded by varying the ratios of MA/ *R*-TDAP-COOH. SEM images showed helical fibers with a gradual increase in pitch and diameter as the proportion of melamine analogues increases (Figure 5 and S14-S15).

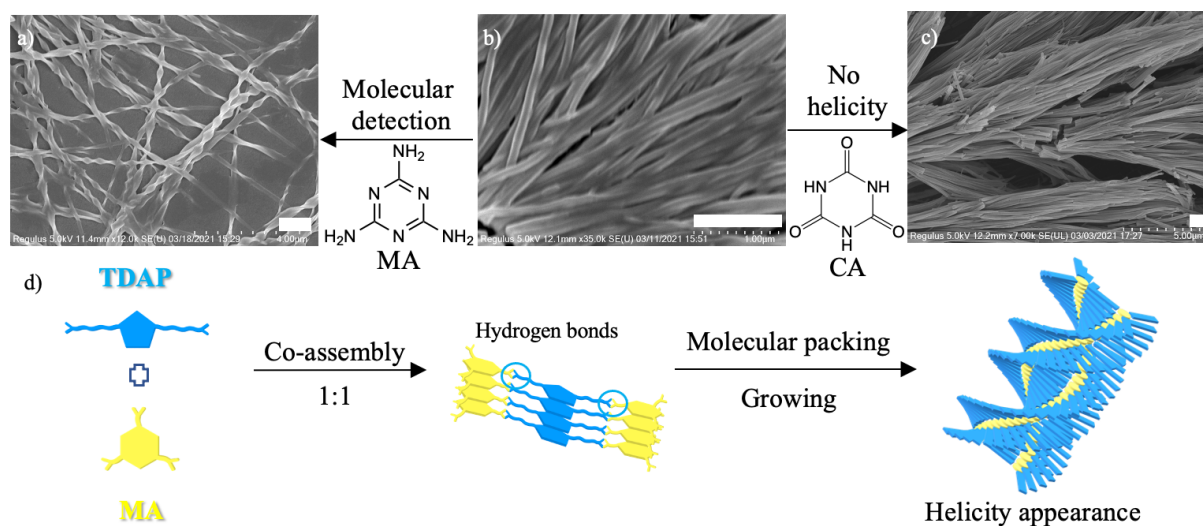


Figure 4. SEM images of (a) MA/*R*-TDAP-COOH (b) *R*-TDAP-COOH and (c) CA/ *R*-TDAP-COOH assembled architectures. Scale bars in the SEM images are 1 μ m. (d) Schematic representation for the molecular detecting process in MA/TDAP co-assembly system.

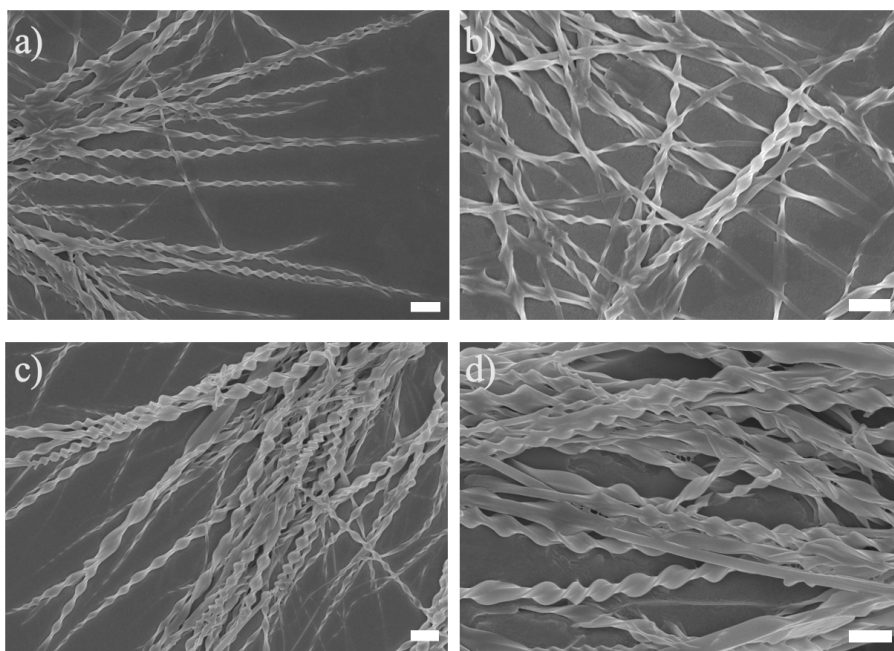


Figure 5. SEM images of TDAP/MA at molar ratios of (a) 1: 0.5, (b) 1:1, (c) 1:2, and (d) 1:3 co-assembled architectures. The concentration of *R*-TDAP-COOH in all samples was 0.5 mg mL⁻¹. Scale bars in the SEM images are 1 μm.

We tried to test limit of recognition of MA (0.5 mg mL⁻¹, 0.25 mg mL⁻¹, 0.1 mg mL⁻¹, 0.05 mg mL⁻¹ and 0.01 mg mL⁻¹) (Figure S13). These results showed that molecular recognition by helicity appearance can be realized even at 0.05 mg mL⁻¹. It indicated that molecular recognition by the TDAP system can be realized even at very low concentrations. Then variable-temperature ¹H NMR spectra were also measured (Figure S16). The results showed that the proton signals of the amine in MA at around 5.9 ppm shifted upfield, broadened and decreased in the intensity^[18] as the temperatures increased, suggesting the formation of carboxylic acid-amine hydrogen bonds within assemblies. As the temperature increased, the upfield shift of the protons of the amide group in TDAP-COOH at around 8.7 ppm implied the presence of similar H-bonding with *R*-TDAP nanofibers. These characteristics can be interpreted as an indication of restricted freedom of motion of the proton due to the H-bonding between the amide of MA and the carboxylic acid groups of TDAP molecules at RT. In the detection system,

the H-bonding based on carboxylic acid moieties could be restrained by the addition of MA leading to the reconstruction of helicity. Meanwhile, the new H-bonding between the amine of MA and the carboxylic acid groups of TDAP was formed, which contributed to the construction of new helicity. (Figure 4d) Thus multiple H-bonding sites of melamine and self-aggregation of TDAP, play dominant roles in regulating the molecular arrangement, so MA is considered to be a stimulus in detecting process. In all, these SEM, TEM, and NMR results suggest that molecular detection of MA by TDAP system can be achieved by the supramolecular assembly.

3. Conclusions

In summary, the morphology transformation from microspheres to nanofibers with controllable handedness was achieved. The molecular chirality is transmitted into the supramolecular level through the hydrogen bond which has been confirmed as a driving force. In addition, we explored the biological application of *R*-TDAP-COOH by utilizing co-assembly with MA through supramolecular interactions. Helicity appearance and inversion were observed for the TDAP-MA system, which was used to provide a detection method for melamine.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

Acknowledgements

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Morphology transformation from achiral microspheres to chiral supramolecular structures as helical nanofibers with controllable handedness is achieved through the introduction of molecular chirality, and further to achiral 2D micro sheets by hierarchical supramolecular assembly using the enantiomers. In addition, *R*-TDAP-COOH was synthesized to explore the biological applications through supramolecular interactions. Helicity appearance and inversion were observed for the TDAP-MA supramolecular system, which provided a molecular detection method for melamine.

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