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ABSTRACT

One dimensional (1D) nanotubes and three dimensional (3D) flowerlike supernanostructures were transformed reversibly, which was controlled by the oxidation and reduction cycle of aromatic diamide-derived thiol **1** and disulfide **2**, as evidenced by SEM study. Their self-assembling patterns were investigated by UV-vis, ¹H NMR, X-ray crystallographic, and powder X-ray diffraction experiments. © 2012 Elsevier Ltd. All rights reserved.

Materials that can respond to external input have aroused considerable interest in the past decades due to their crucial role in fundamental understanding of the stimuli-responsive phenomena of biomolecules as well as practical application in fabricating the socalled 'smart materials', which can adapt themselves to the change of surroundings.¹ In this context, molecular self-assembly, a process that individual molecules are drawn together by noncovalent interactions to form well-ordered aggregates, was regarded as an ideal tool for the fabrication of such dynamically tunable materials because the reversibility and weak binding strength of noncovalent bonds usually enable self-assembled structures readily responsive to the change of the environmental conditions. Up to date, a range of stimuli, including changes in pH,² temperature,³ concentration,⁴ polarity of medium,⁵ the formation of charge-transfer complex,⁶ or even the application of external forces, such as shear, sonication or agitation,⁷ have been employed to achieve efficient transformation between assembled entities of distinctly different morphologies. The examples above are mainly based on aggregates assembled from identical building blocks and concerned on changes of noncovalent interactions. We envisioned that the stimuli-responsive transformation should also be accessed for the entities assembled from different building blocks, as long as the blocks themselves can interconvert when exposed to external stimuli. For this requirement, the 'dynamic covalent bond' such as S-S should work well due to its feature of reversible formation and cleavage upon

oxidation/reduction.⁸ By exploiting this advantage, Yang and coworkers reported the fabrication of hydrogels in a homogeneous and controllable way by reductive cleavage of the disulfide bond which connects a hydrogelator and a hydrophilic molecule.⁹ Nilsson and Bowerman demonstrated that the transformation of conformationally constrained cyclic peptides to unconstrained β-strand linear peptides via reduction of disulfide led to the formation of hydrogels.¹⁰ However, the strategy employed in these examples just made use of unidirectional process, this is, the reductive cleavage of disulfide bond. To further exploit the potential of the dynamic character of disulfide bond for the construction of responsive materials, we became interested in developing the bidirectional process of both reductive cleavage and oxidative formation of disulfide bond. through which transformation between two well-defined structures with distinctly different morphologies could be controlled reversibly. We herein report that the reversible transformation between 1D nanotubes and 3D flowerlike supernanostructures can be regulated via oxidation/reduction of thiol and disulfide, which represents a promising approach to controlling transformation between two distinct nanostructures.

The structures used in this study are shown in Scheme 1. We previously found 5-(benyloxy or isobutyloxy) substituted isophthalamide could self-assemble into fine nanotubes in methanol.¹¹ In the present study, the 5-position of the parent isophthalamide was substituted with (4-mercapto-butyloxy) to give thiol **1** (see ESI for the synthesis and characterizations), and thiol **1** could be further oxidated to generate disulfide **2**.¹²

Initially, the self-assembly of thiol **1** and disulfide **2** in methanol was investigated. Scanning electron microscopy (SEM) was



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Scheme 1. Chemical structures of compounds 1 and 2.

employed to characterize the morphology of the assembled structures. The samples were prepared by drop-casting of their methanol solution onto freshly cleaved mica surface. The respective images are illustrated in Figure 1. SEM images showed that compound 1 self-assembled into 1D nanotubes with hundreds of nanometers in width and tens of microns in length. Their hollow nature was readily evidenced by their open-ended features (Fig. 1a-b) and was further confirmed by high-resolution TEM, which exhibited a clear contrast between their inner and outside areas (Fig. 1d). However, under similar conditions, disulfide 2 gave rise to 3D flowershaped supernanostructures. As shown in Figure 1c, the 'flower' is constituted by multiple petals of hundreds of nanometers in width, and the size of the whole 'flowers' is larger than 5 microns ('microflowers'). The different shape and dimension of the aggregates fabricated from the thiol and disulfide thus create a favorable platform on which the transformation of nanostructures with distinctly different morphologies could be processed. The influence of conditions for self-assembly on the formation of nanostructures was also investigated. It was found that changing concentration or PH did not have significant impact on the morphologies of the selfassembled aggregates (ESI, Fig. S1-2).

Compounds **1** and **2** can be interconverted reversibly via oxidation and reduction.¹³ Thus, we further investigated if this interconversion could cause in situ reversible transformation between different nanoscale architectures. In order to test this possibility, 0.5 equiv of iodine was added into a solution of thiol **1** to oxidize thiol to disulfide (step 1). After stirring at room temperature for 0.5 h, the aggregates formed in solution was then subjected to SEM observation, which revealed that the nanotubes totally disappeared, while flowerlike supernanostructures were observed (Fig. 2a), which should be generated from the self-assembly of disulfide 2 in methanol. The as-prepared solution above was then mixed with 60 equiv of dithiothreitol (DTT) (step 2), a strong reducing reagent that can reduce disulfide to thiol. The morphology of the assembled entities after reduction was characterized by SEM again, which showed that tubular structures came back while 'microflowers' totally disappeared (Fig. 2b). The above solution could be oxidized again with 50 equiv of iodine (step 3). For the resulting solution, 'microflowers' were observed again and tubular structures could not be found with SEM (Fig. 2c). These results clearly demonstrated that well-controlled morphology transformation of the two different nanostructures could be realized on the basis of simple oxidation/reduction of thiol and disulfide. Because the accumulation of the oxidant and reductant had an interference on the SEM observation, no further oxidation/ reduction cycle was performed after step 3.

In order to get insight to the assembling mechanism, ¹H NMR and UV–vis spectroscopies were used to probe the packing model of the molecules in the aggregates. Compared to that in chloro-form, in which aromatic stacking is reported to be weak,¹⁴ blue shift and remarkable hypochromism effect were observed for both **1** and **2** in methanol (ESI, Fig. S3). This result provided evidence for



Figure 1. SEM images of samples fabricated from (a) and (b) thiol 1 (2.0 mM), and (c) disulfide 2 (2.0 mM) in methanol, and (d) TEM image of sample obtained from thiol 1 (0.2 mM) in methanol.



Figure 2. SEM images of samples fabricated from (a) thiol 1 after oxidized by iodine, (b) further reduced by DTT, and (c) oxidized again by iodine, and (d) illustration of the transformation process (**■** represents nanotubes, and • represents 'microflowers').

the π - π stacking of their aromatic cores and suggested H-type aggregation (face-to-face stacking) arrangement of the molecules.¹⁵ ¹H NMR dilution experiments for both compounds in chloroform- d_1 showed that the signals of the amides shifted downfield while the protons of aromatic ring shifted upfield with the increase of the concentration (ESI, Fig. S4 and S5), suggesting the amide protons were involved in the formation of intermolecular hydrogen bonds and aromatic stacking existed. Furthermore, the IR spectra

of the nanotubes and 'microflowers', upon removal of the solvent under the reduced pressure, exhibited the N–H stretching vibrations around 3259 cm⁻¹ (for nanotubes) and 3269 cm⁻¹ (for 'microflowers'), also indicating that the NH units were hydrogenbonded (ESI, Fig. S6 and S7). Attempts to grow single crystals from 1 and 2 suitable for the X-ray crystallography were not successful. However, single crystals of compound **3** (Fig. 3), an analog of thiol 1, was grown by slow evaporation of its solution in methanol.¹⁶



Figure 3. The chemical structure of compound **3** and its packing structure in the single crystal: (a) viewing along a axis, and (b) viewing along b axis, highlighting the stacking of molecules stabilized by hydrogen bonds and π-stacking.

The crystallographic study on **3** revealed that the neighboring molecules were packed with each other in oppositely alternate manner, which was stabilized by two pairs of hydrogen bonds: one formed between oxygen of carbonyl and proton of amide with the O…H distance being 2.11 Å, while another formed between oxygen of ethyloxyl and proton of amide with longer O···H distance, being 2.42 Å (Fig. 3a-b). The crystal structure also revealed that the aromatic units stacked in face-to-face manner with an average distance of 3.44 Å, which is typical for the columnar stacking of aromatic amides.¹⁷ The observation of hydrogen-bonding and face-to-face stacking of benzene rings in the solid state of 3 is also consistent with the above ¹H NMR and UV-vis results of **1** and 2 in solution, suggesting that the aggregates of 1 and 2 in solution should adopt similar molecular arrangement as that in the crystal state of **3**. On the basis of these results, we proposed that the self-assembly of compounds **1** and **2** should be driven by their self-assembling units, this is, the aromatic ring and the hydrogenbonding units, and the arrangement of their self-stacking of the molecules might dictate a 1D growing process which firstly leads to the formation of 1D ribbons and eventually evolves into nanotubes (Fig. 4).¹⁸ However, **2** bears two self-assembling units which is connected by S-S bond. According to the reported crystal structures of several disulfides,¹⁹ the two substituents connected with S–S bond adopt a roughly perpendicular conformation. We thus proposed that the aromatic amide units of **2** adopted 1D stacking at both ends of its disulfide, which resulted in a radial arrangement of the molecules, leading to the formation of the flowerlike supernanostructures which can be regarded as radial arrangement of 1D structures (Fig. 4). This assumption was supported by the powder X-ray diffraction (XRD) analysis of 1 and 2 (Fig. 5). The as-prepared nanotubes and 'microflower' displayed sharp diffraction peaks, suggesting crystalline features of their aggregates. Diffraction

peaks near d-spacing of 3.4 Å were observed for both nanotubes and 'microflowers', which are corresponding to the π - π stacking. The broad peak of the latter might reveal a less packed stacking of aromatic units in the 'microflowers'. Furthermore, both the nanotubes and 'microflowers' also displayed diffraction peaks at 12.0 and 4.6 Å, further suggesting similar packing model for their self-assembling units. Extra peaks at 6.0 and 4.9 Å were observed for the 'microflowers' generated from 2, which might be corresponding to some periodic arrangements deriving from its branched packing (Fig. 4). Therefore, the transformation between the two nanostructures is a result of the transformation between the supramolecular building blocks, this is, thiol 1 and disulfide 2 under redox. Once thiol **1** is oxidized to disulfide **2**, it adopts the self-assembly behavior of disulfide to form 'microflowers'. On the other hand, the self-assembly property of thiol will be followed to generate nanotubes after disulfide **2** is reduced to thiol **1**.

In conclusion, by exploiting the advantage of the dynamic feature of disulfide bond, the in situ reversible transformation between 1D and 3D nanostructures that respond to oxidation/reduction has been realized. This strategy, different from those reported before, is built on the interconversion of supramolecular building blocks in which the formation and cleavage of covalent bond are involved. As demonstrated in this letter, the thiol-disulfide interconversion can be exploited as a potential switch on which redox-responsive system can be constructed. Although the example shown here just concerns morphology transformation, reversible interconversion between two functionalized systems constructed on the basis of this strategy should also be expected. In this context, supramolecular building blocks based on thiol and disulfide should be very promising to fabricate redox-responsive materials. Once well-defined self-assembling systems with certain functions from derivatives of thiol and disulfide can be established



Figure 4. Schematic representation of the formation of nanotubes and 'microflowers'.



Figure 5. Powder XRD patterns of the nanotubes formed from thiol 1 (top) and the 'microflowers' from disulfide 2 (bottom).

individually, the reversible transformation between the assembled entities is readily accessed through oxidation and reduction cycle.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.06. 063.

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- 12. Nelson, J. C.; Saven, J. G.; Moore, J. S.; Wolynes, P. G. Science 1997, 277, 1793. 13 Procedure for the oxidative conversion of thiol 1 to disulfide 2: To a solution of compound $1\ (110\ \text{mg},\ 0.29\ \text{mmol})$ in methanol (10 mL), $\text{Et}_3\text{N}\ (1.0\ \text{mL})$ and iodine (76 mg, 0.3 mmol) were added. The mixture was stirred at room temperature until compound 1 was consumed. After removal of the solvent, the resulting residue was dissolved in methylenechloride (30 mL), and then washed with water (2 \times 10 mL), and saturated aqueous Na_2SO_3 (2 \times 10 mL) and the organic phase was dried over anhydrous sodium sulfate. After removal of the solvent with a rotavapor, the crude product was subjected to column chromatography (methylenechloride/ethyl acetate, 20:1), to give compound 2 as a white solid (105 mg, 95%). ¹H NMR (300 MHz, $CDCl_3$): 1.45 (s, 36 H), 1.83– (n, 8 H), 2.76 (s(br), 4 H), 4.01 (s(br), 4 H), 6.20 (s, 4 H), 7.27 (s, 4 H), 7.53 (s, 2 H).
 (n, 8 H), 2.76 (s(br), 4 H), 4.01 (s(br), 4 H), 6.20 (s, 4 H), 7.27 (s, 4 H), 7.53 (s, 2 H). 116.8, 137.4, 159.0, 166.0. MS (ESI): 759.0 [M+H]⁺, 780.9 [M+Na]⁺, HRMS (ESI): Calcd for C40H62N4NaO6S2: 781.40030. Found: 781.39973
- 14. Procedure for the reductive conversion of disulfide 2 to thiol 1: A mixture of compound 2 (30 mg, 0.04 mmol), dithiothreitol (731 mg, 4.7 mmol) and NEt₃ (0.12 mL) in methanol (10 mL) was stirred under argon atmosphere until compound 2 disappeared. The solvent was removed under reduced pressure and the resulting residue was dissolved in chloroform (50 mL). The organic phase was washed with water $(2 \times 10 \text{ mL})$ and brine (10 mL) and then dried over anhydrous sodium sulfate. After removal of the solvent with a rotavapor, crude product was subjected to column the chromatography (methylenechloride/ethylacetate, 30:1) to give compound 1 as a white solid (27 mg, 90%).
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