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Communication

Redox-responsive diphenylalanine aggregate mediated by cyclodextrin

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ABSTRACT

The molecular assembling properties can be dramatically improved using redox-responsive nanoplatforms, which can bring quite different aggregation modes and binding behaviors in the redox states. In this work, we fabricated a redox-responsive system based on the host–guest complexation of β-cyclodextrin (β-CD) with ferrocene-modified diphenylalanine (Fc-FF). The morphological conversion of Fc-FF can be easily achieved from nanofibers to nanospheres in the presence of β-CD, and the supramolecular nanospheres can be reversibly assembled and disassembled by the chemical redox of ferrocenyl groups in the Fc-FF⊂β-CD nanoassemblies. These results demonstrate that the incorporation of stimuli-switchable components with macrocyclic receptors may become a promising approach to the construction of smart peptide-involved supramolecular assemblies.

Supramolecular assemblies involved with macrocyclic receptors offer a bottom-up strategy to construct biomimetic architectures with the desired stimuli-responsivity and unique structural diversity [1–4]. On one hand, among the numerous macrocyclic molecules that are available for the host–guest complexation, cyclodextrins (CDs), biocompatible cyclic oligosaccharides composed of six to eight D-glucopyranose units, have been intensively studied during the past decades, due to the immense advantages to form intermolecular complexes with their intrinsic hydrophobic cavities [5–7]. In this respect, there is an unquestioned fact that photochromic azobenzenes and electroactive ferrocenes are two main frequently used guest molecules in the fabrication of CD-based stimuli-responsive supramolecular systems, because they exhibit strikingly distinctive binding affinities with α- and β-CDs in the reversible *E* (*trans*)/*Z*(*cis*) photoisomerization and single-electron oxidation/reduction processes, respectively [8–11]. Subsequently, considerable endeavors have been devoted to exploring functional nanoarchitectures using α-CD/azobenzene and β-CD/ferrocene supramolecular couples.

On the other hand, among the non-macrocyclic building blocks, linear oligopeptides have been recognized as a promising candidate for developing bioactive self-assembled nanostructures [12–15]. In particular, diphenylalanine (L-Phe-L-Phe, FF), a much simpler amphiphilic aromatic dipeptide, has shown potent capabilities in fabricating a wide range of well-defined molecular assemblies [16–18]. For example, by introducing ferrocenyl group into the FF backbone, Qi *et al.* reported the hierarchically self-assembling behaviors of such redox-responsive dipeptide in the formation of topologically different nanostructures, thus making it appealing for chiral sensing and amplification [19]. More, recently, Li and his co-workers demonstrated a light-controlled phase transition between gel and solution of FF-based supramolecular assemblies by a long-lived photoacid generator [20].

In line with these fascinating results, one can believe that the synergetic integration of oligopeptides and macrocycles into a single supramolecular assembled entity will be a powerful strategy to construct more advanced functional biomaterials [21,22]. Thus, our group has developed some diphenylalanine–macrocycle conjugated nanosystems with controlled morphological conversion using FF derivatives bearing bispyridinium [23], azophenyl [24], and adamantyl moieties [25]. One representative example is that, the topological aggregates of bispyridinium-modified FF can be well tuned by simple complexation of bispyridinium terminal with cucurbituril, pillararene, and tetrasulfonated crown ether, respectively [23]. Herein, inspired by the smart morphological conversion of dipeptide derivatives and functional redox center of ferrocene, we would like to report a morphological conversion from nanofibers to nanoparticles based on ferrocene-modified diphenylalanine (Fc-FF) and β-cyclodextrin (β-CD), in which the formation of binary Fc-FF⊂β-CD nanoparticles could be reversibly

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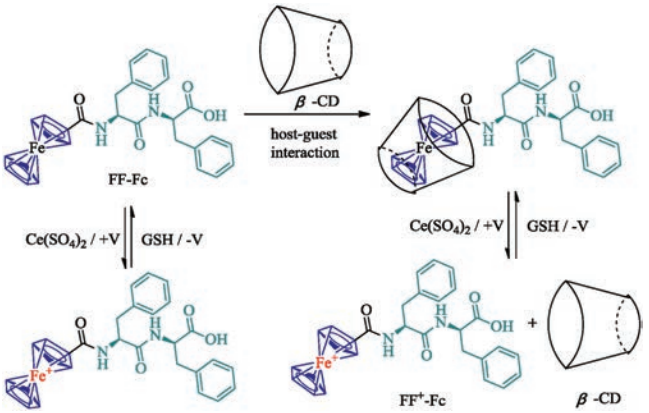

Scheme 1. Self-assembling and disassembling processes of redox-responsive Fc-FF in the presence of β-CD.

generated *via* the chemically redox control (Scheme 1). The present study can make a good supplement to the existing peptide–macrocycle supramolecular systems.

The guest Fc-FF was synthesized according to the literature with slight modification [26]. Next, Job plot was performed to determine the binding stoichiometry between Fc-FF and β-CD. As shown in Fig. S1 in Supporting information, a maximum peak at the molar ratio of 0.5 was clearly observed, indicative of a 1:1 host–guest binding stoichiometry. The direct evidence on the formation of Fc-FF⊂β-CD complex was obtained from electrospray ionization–mass spectrometry (ESI-MS); that is, the m/z peak at 1659.5097 could be clearly assigned to $[Fc\text{-}FF + \beta\text{-}CD + H]^+$ (Fig. S2 in Supporting information). Next, the noncovalent complexation of Fc-FF with β-CD was further verified by ^1H NMR experiments. That is, the proton signals at 4.46 and 4.63 ppm assigned to the ferrocene in Fc-FF underwent an obvious complex-induced downfield shift upon continuous addition of β-CD in D_2O (Fig. S3 in Supporting information).

Meanwhile, NOESY (nuclear Overhauser effect spectroscopy) spectrum of equimolar Fc-FF and β-CD was conducted to investigate the molecular binding mode. It can be seen that clear NOE (nuclear Overhauser enhancement) correlations were observed between ferrocenyl protons in Fc-FF and β-CD's inner protons, here again corroborating that ferrocenyl moiety was included in β-CD's cavity to form binary host–guest complex (Fig. 1). In contrast, after addition of $Ce(SO_4)_2$ as oxidant, no NOE cross-peak was found in the Fc^+-FF with β-CD, indicating that the oxidized Fc (Fc^+) could not be included in the cavity anymore (Fig. S4 in Supporting information). In addition, isothermal titration calorimetric (ITC) experiments were performed to measure the association constant in Fc-FF⊂β-CD complexation as *ca.* 5.1×10^2 L/mol in water (Fig. S5 in Supporting information).

The electrochemical behaviors of Fc-FF in the absence and presence of β-CD were also investigated by cyclic voltammetry. The typical cyclic voltammetry (CV) curves for Fc-FF before and after complexation with β-CD are depicted in Fig. 2. The addition of equimolar β-CD into Fc-FF solution could cause a positive shift of half-wave potential and a decrease in the peak current. These phenomena demonstrate that Fc-FF becomes more difficult to be oxidized, reflecting the stabilization effect originated from the protection of β-CD toward ferrocene in aqueous media.

Considering the diphenylalanine peptide possesses many interesting physicochemical properties, we next explore the morphological conversion of Fc-FF upon complexation with β-CD, which was investigated by transmission electron microscopic (TEM) and scanning electron microscopic (SEM) experiments. As can be seen in Fig. 3, Fc-FF alone could self-assemble to bunch of nanofibers with several micrometers in length, as a result of the chirality of phenylalanine moieties and π–π stacked adjacent phenyl rings (Figs. 3a and b). After addition of β-CD, a series of ordered nanospheres was observed, and this morphology was quite different from the unbound Fc-FF molecules (Figs. 3c and d). Furthermore, when the ferrocenyl group of Fc-FF in Fc-FF⊂β-CD complex was oxidized to the corresponding cationic form (Fc^+-FF) by $Ce(SO_4)_2$ as oxidizing agent, only amorphous aggregates were found in the TEM and SEM images. In this case, the ferrocenyl group could be completely expelled from the cavity of β-CD upon formation of Fc^+-FF in the presence of $Ce(SO_4)_2$, thus resulting in the unfavorable electrostatic repulsion among the positively charged Fc^+-FF (Figs. 3e and f). In contrast, when Fc^+ moieties were further reduced by glutathione (GSH), the neutral Fc-FF⊂β-CD complex was regenerated, accompanied by the recovery of supramolecular nanoparticles (Figs. 3g and h). More microscopic images can be found in Figs. S6–S9 (Supporting information). Thus, by utilizing the chemical redox of Fc-FF, the morphological conversion could be reversibly regulated between amorphous aggregates and uniform nanospheres.

In conclusion, the molecular binding behaviors between Fc-FF and β-CD were investigated in this work and the morphological conversion from nanofibers to nanospheres was successfully regulated by the host–guest complexation of Fc-FF and β-CD. It is also found that the resultant binary nanoparticles could be dissipated to amorphous aggregates by the oxidation of ferrocenyl group in Fc-FF⊂β-CD complex, while the nanoparticulate morphology could be recovered under reduction condition. Thus, we

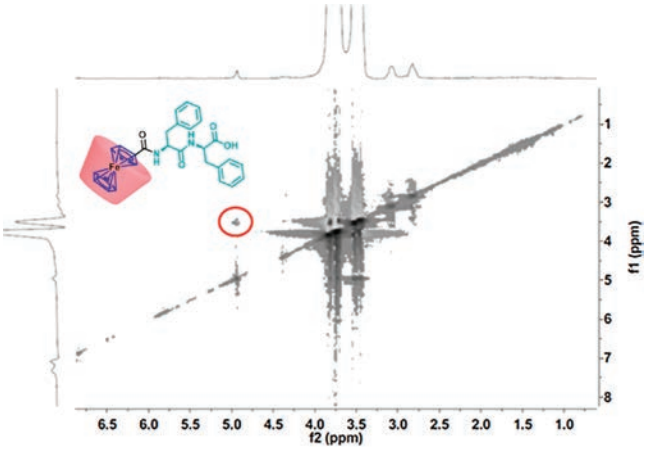

Fig. 1. 2D NOESY spectrum of Fc-FF⊂β-CD complex (D_2O, 400 MHz, 25 °C, [Fc-FF] = [β-CD] = 1.0 mmol/L). The red circle indicates the NOE cross-peaks between ferrocenyl moiety and β-CD's cavity.

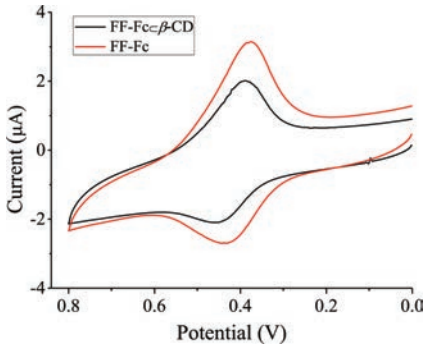

Fig. 2. CV curves of Fc-FF in the absence and presence of β-CD (0.5 mmol/L in 5 mL 0.1 mol/L NH_4PF_6 solution and the scan rate is 50 mV/s).

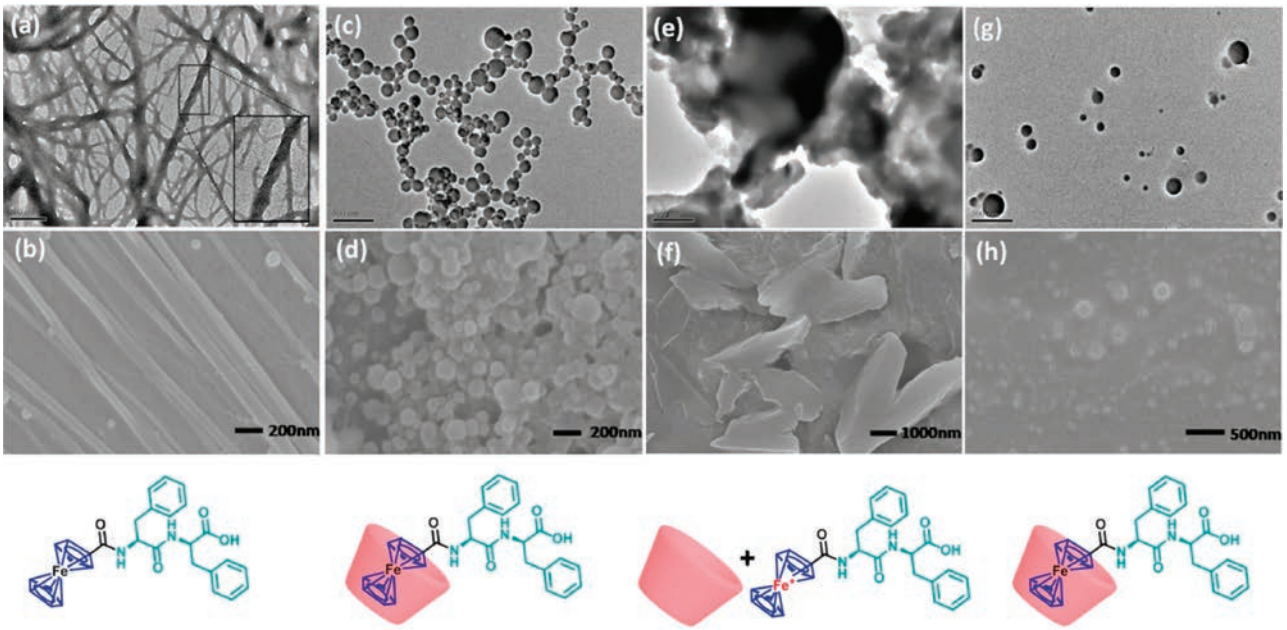

Fig. 3. TEM and SEM images of (a, b) nanofibers formed by Fc-FF self-assembly; (c, d) nanospheres formed by Fc-FF⊂β-CD complex; (e, f) amorphous aggregates formed by Fc^{+}-FF and β-CD after oxidation by $Ce(SO_4)_2$; (g, h) recovery of nanospheres after reduction by GSH ([Fc-FF] = [β-CD] = [$Ce(SO_4)_2$] = [GSH] = 4.0 mmol/L).

can envisage that the obtained Fc-FF⊂β-CD nanoassemblies with redox-controlled morphological changes may provide us with a convenient avenue for deeply understanding the dynamic and stimuli-responsive biological events in many peptide-based molecular assembling processes.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.cclet.2018.04.028.

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