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Electrochemical redox responsive polymeric micelles formed from amphiphilic supramolecular brushes[†]

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The end-decorated homopolymer poly(ε -caprolactone)-ferrocene threaded onto a β -cyclodextrin-functionalized main-chain polymer can form a class of amphiphilic noncovalent graft copolymers based on the host-guest interactions of the terminal groups on the side chains. These new supramolecular polymer brushes can further self-assemble into micellar aggregates that exhibit reversible assembly and disassembly behavior under an electrochemical redox trigger, which opens up a new route to building dynamic block copolymer topologies.

Stimuli-responsive polymers have gained much attention in recent years due to their prospective applications in biomedicine, nanotherapeutics, and gene transportation.¹ As a type of intelligent polymer, they can undergo reversible physiochemical changes to adjust their aggregated structures in response to environmental stimuli such as pH,² temperature,³ light,⁴ and gas.⁵ Here we turn our sights to an emerging stimulation mode, electrochemical redox, which plays a crucial role in controlling the biological membrane activities in cells. Furthermore, an electrochemical stimulus can avoid artificially causing redox agent accumulation. In view of this, developing new electrochemical-responsive polymers holds great promise for mimicking electro-mediated cytomembrane systems.⁶

Supramolecular block copolymers, dynamic polymer arrays differing from traditional copolymers, are formed from noncovalent connections between two or more homopolymer chains based on supramolecular interactions (*e.g.* H-bonding, metal–ligand bonds, π – π stacking, and host–guest interactions) located at specific sites.⁷ So far, a variety of polymer topologies including linear,⁸ star-shaped,⁹ and hyperbranched¹⁰ have been successfully synthesized. Besides these, brush-like block copolymers, regarded as orderly one-dimensional branched architectures, have drawn growing interest in polymer science.¹¹ However, to the best of our knowledge, building supramolecular polymer brushes owing electrochemical redox responsiveness still remains a challenge.

Herein, we attempted to incorporate electrochemical redox responsiveness into a new supramolecular polymer brush, so as to realize the voltage-controlled dynamic association and dissociation of the polymer chain. To this end, we have designed and synthesized two kinds of polymers, poly(ethylene glycol)-block-poly(glycidyl methacrylate) decorated with β-CD pendants (GA-CD) and poly(caprolactone) containing end-capping ferrocene (Fc) moieties (L-Fc). On the basis of host-guest interactions between the β-CD and Fc moieties, GA-CD and L-Fc can form a quasi-brush-like macromolecular adduct through noncovalent connections between the side groups. Normally, uncharged Fc species can bind to the cavity of β-CD, forming a β-CD-Fc inclusion complex. On the contrary, when applying an electrochemical oxidative stimulus, the charged Fc⁺ species are rapidly excluded from the cavity.¹² This reversible process can be accomplished by an opposite reductive voltage. Hence, it is anticipated that our supramolecular polymer brushes linked by these responsive and dynamic linkers could reversibly undergo an association and dissociation effect, further driving the electrochemical redox-modulated self-assembly and disassembly behavior of the supramolecular polymer assemblies, as shown in Scheme 1.

Typically, the two polymeric components, GA-CD and L-Fc, were prepared, respectively, *via* reversible addition-fragmentation chain transfer (RAFT) and ring-opening polymerization (ROP), affording well-defined and monodispersive structures (ESI†). In particular, the entire biodegradable segments endow the polymer with favourable biocompatibility, offering us the chance to apply it in biomedical fields.

We first aimed to confirm that the two polymers are able to form a supramolecular brush through host-guest pairs. After mixing GA-CD and L-Fc into a common solvent (THF, 1.0 mg mL⁻¹, keeping a CD/Fc 1:1 molar ratio) and using an ultrasound method to ensure the solid completely dissolved, a homogenous and transparent

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Scheme 1 Schematic illustration of the formation of electrochemical redox responsive micelles from brush-like supramolecular block copolymers and their controlled assembly and disassembly.

binary solution was obtained. To elucidate the formation of the host–guest complex, UV/Vis spectroscopy and 2D nuclear Overhauser enhancement spectroscopy (NOESY) were employed. Initially, single L-Fc displayed a characteristic Fc absorption at 270 nm in the UV/vis spectrum. Increasing the amount of the GA-CD host in the L-Fc solution resulted in nearly doubling the intensity of the Fc absorption (Fig. 1a), implying the formation of inclusion complexes between β -CD and Fc. Furthermore, as shown in Fig. 1b, the presence of a series of 2D NOESY cross peaks between H-3 and H-5 of β -CD and H-a, H-b and H-c of Fc indicates that the Fc species can be orthogonally threaded into the cavity of β -CD.¹³ These results demonstrate that a brush-like pseudocopolymer can be formed by GA-CD and L-Fc through their CD–Fc complementary pairs.

Since the β-CD-Fc connection determines the electro-sensitivity, we then focused on whether the GA-CD-L-Fc aggregates possess similar electrochemical redox responsiveness. Slowly injecting a specific amount of the pseudocopolymer in THF into the water enables self-assembly, as suggested by the translucent colloidal solution formation. The critical aggregation concentration (CAC) is ca. 0.20 mg mL $^{-1}$, as measured by a Nile Red fluorescent probe (Fig. S2, ESI[†]). It is worth noting that the CAC of these brush-like supramolecular copolymers ($\sim 0.20 \text{ mg mL}^{-1}$) is much lower than that of most linear supramolecular copolymers (>0.50 mg mL⁻¹), indicating that such brush-like supramolecular copolymers may be more inclined to assemble in aqueous solution owing to their relatively large molecular weights. To further visualize the morphology of GA-CD-L-Fc in aqueous media, transmission electron microscopy (TEM) was used to characterize the selfassembled nanostructure. As shown in Fig. 2a, without any stimulus, the supramolecular polymers can self-assemble into typical spherical micelles with an average diameter of 220 nm, which corresponds to the hydrodynamic radius of ~ 105 nm monitored by dynamic light scattering (DLS) experiments (Fig. S3, ESI⁺). The slight and negligible aggregated size deviation between the TEM and DLS results is due to



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Fig. 1 (a) UV/Vis spectra of L-Fc before and after adding GA-CD, (b) 2D-NOESY spectrum of the complex of L-Fc with GA-CD in DMSO- d_6 .



Fig. 2 TEM images of the reversible assembly and disassembly of the electrochemical redox responsive micelles with an electric stimulus: (a) no external voltage, (b) +1.0 V (after 2 h), (c) +1.0 V (after 8 h), and (d) -1.0 V (after 8 h).

the dry state results obtained by TEM, but the DLS measurements are of the real state in solution.

When we applied an electrochemical redox trigger to the micellar solution, interestingly, a series of assembly changes occurred. Relative electrochemical analysis was carried out by a three-electrode system (reference electrode: Ag/AgCl, working

electrode: platinum plate, counter electrode: platinum plate) in a supporting electrolyte (0.2 M KNO₃), and TEM traced all of the morphological changes in response to the redox potential. When we applied an oxidative potential (+1.0 V) to the copolymer solution for 2 h, parts of the spheres were disrupted and they could not retain their shapes (Fig. 2b). It is believed that, triggered by a short positive voltage, some of the Fc species converts to the charged Fc^+ form, which is removed from the β -CD hosts, resulting in partial dissociation of the supramolecular polymer brushes and further destroying the hydrophilic-hydrophobic balance in the polymer micellar system. However, owing to the relatively large micellar sizes and the low liquidity, there are still a small number of micelles not disrupted. After prolonging the electrochemical oxidative time to 8 h, most of the micelles disappeared and no available aggregates could be observed (Fig. 2c), indicating that the micelles completely disaggregated into small fragments because all of the L-Fc "brushing" chains were excluded from the GA-CD backbone. Reversibly, in the presence of an opposite reductive potential stimulus (-1.0 V) for 8 h, the spherical micelles reassembled with similar shapes and sizes (Fig. 2d), which is ascribed to Fc^+ gaining one electron and associating with β -CD again. Nevertheless, since this electrochemical conversion (Fc⁺ + e⁻ \leftrightarrow Fc) is incomplete, the number of the reverted micelles decreases. By applying an alternating electric field to this supramolecular micellar system, the reversible procedure could be repeated over three times (Fig. S3, ESI⁺). After multiple oxidation-reduction loops, the micelles could maintain a constant size of ~ 200 nm as monitored by DLS (Fig. S3, ESI⁺). It is proven that the supramolecular micelles determine the electrochemical redox-tunable assembly and disassembly behaviour. It is worth noting that these kinds of micellar assemblies were quite stable for at least one month in the absence of a stimulus. In addition, the electrochemical redox potential stimulus mode avoids introducing redox agent accumulation, thus making it favourable to be applied in industry and biological systems.

In conclusion, we have developed a new kind of brush-like supramolecular copolymer topology based on the side chain host-guest interactions between β -CD and Fc. Due to the dynamic and responsive connections, the supramolecular brush can further self-assemble into a micellar structure and exhibit voltage-triggered reversible self-degradable and self-repairable behaviour. We envisage that this mobile polymeric model could open up a new route to smart nanocapsules for electrochemical applications.

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Notes and references

(a) X. Yan, F. Wang, B. Zheng and F. Huang, *Chem. Soc. Rev.*, 2012,
41, 6042–6065; (b) Y. Zhao, F. Sakai, L. Su, Y. Liu, K. Wei, G. Chen and M. Jiang, *Adv. Mater.*, 2013, 5215–5256; (c) S. Mura, J. Nicolas and P. Couvreur, *Nat. Mater.*, 2013, 12, 991–1003; (d) Q. Zhang, N. R. Ko and J. K. Oh, *Chem. Commun.*, 2012, 48, 7542–7552; (e) J. Wang, Y. P. Chen, K. Yao, P. A. Wilbon, W. Zhang, L. Ren,

- J. Zhou, M. Nagarkatti, C. Wang, F. Chu, X. He, A. W. Decho and C. Tang, *Chem. Commun.*, 2012, **48**, 916–918.
- 2 (a) S. Y. Liu and S. P. Armes, Angew. Chem., Int. Ed., 2002, 41, 1413–1416; (b) J. Rodriguez-Hernandez and S. Lecommandoux, J. Am. Chem. Soc., 2005, 127, 2026–2027; (c) X. Yan, P. Wei, Z. Li, B. Zheng, S. Dong, F. Huang and Q. Zhou, Chem. Commun., 2013, 49, 2512–2514; (d) W. Chen and J. Du, Sci. Rep., 2013, 3, 2162.
- (a) X. Zhang, W. Li, X. Zhao and A. Zhang, *Macromol. Rapid Commun.*, 2013, 34, 1701–1707; (b) Y. Ding, Z. Wang and X. Zhang, *Chem. Commun.*, 2013, 49, 5580; (c) Q. Yan, J. Yuan, Y. Kang, Z. Cai, L. Zhou and Y. Yin, *Chem. Commun.*, 2010, 46, 2781–2783; (d) C. D. Sorrell, M. C. D. Carter and M. J. Serpe, *Adv. Funct. Mater.*, 2011, 21, 425–433; (e) A. O. Moughton and R. K. O'Reilly, *Chem. Commun.*, 2010, 46, 1091–1093.
- 4 (a) Q. Yan, J. Hu, R. Zhou, Y. Ju, Y. Yin and J. Yuan, *Chem. Commun.*, 2012, 48, 1913–1915; (b) H. J. Zhang, Y. Xin, Q. Yan, L. L. Zhou, L. Peng and J. Y. Yuan, *Macromol. Rapid Commun.*, 2012, 33, 1952–1957; (c) H. i. Lee, W. Wu, J. K. Oh, L. Mueller, G. Sherwood, L. Peteanu, T. Kowalewski and K. Matyjaszewski, *Angew. Chem., Int. Ed.*, 2007, 46, 2453–2457.
- 5 (a) Q. Yan, J. Wang, Y. Yin and J. Yuan, Angew. Chem., Int. Ed., 2013, 52, 5070–5073; (b) Q. Yan and Y. Zhao, Angew. Chem., Int. Ed., 2013, 52, 9948–9951; (c) Q. Yan, R. Zhou, C. Fu, H. Zhang, Y. Yin and J. Yuan, Angew. Chem., Int. Ed., 2011, 50, 4923–4927; (d) S. Kumar, X. Tong, Y. L. Dory, M. Lepage and Y. Zhao, Chem. Commun., 2013, 49, 90–92; (e) A. Feng, Q. Yan and J. Yuan, Prog. Chem., 2012, 24, 1995–2003.
- 6 (a) Q. Yan, J. Yuan, Z. Cai, Y. Xin, Y. Kang and Y. Yin, J. Am. Chem. Soc., 2010, 132, 9268–9270; (b) Q. Yan, A. Feng, H. Zhang, Y. Yin and J. Yuan, Polym. Chem., 2013, 4, 1216–1220; (c) H. Kim, S. M. Jeong and J. W. Park, J. Am. Chem. Soc., 2011, 133, 5206–5209; (d) P. Du, J. Liu, G. Chen and M. Jiang, Langmuir, 2011, 27, 9602–9608; (e) L. Peng, A. Feng, H. Zhang, H. Wang, C. Jian, B. Liu, W. Gao and J. Yuan, Polym. Chem., 2014, 5, 1751–1759; (f) L. Peng, A. Feng, H. Wang, H. Zhang and J. Yuan, Prog. Chem., 2013, 25, 1942–1950.
- 7 (a) A. Harada, Y. Takashima and H. Yamaguchi, *Chem. Soc. Rev.*, 2009, 38, 875–882; (b) F. Wang, J. Zhang, X. Ding, S. Dong, M. Liu, B. Zheng, S. Li, L. Wu, Y. Yu, H. W. Gibson and F. Huang, *Angew. Chem., Int. Ed.*, 2010, 49, 1090–1094; (c) G. R. Whittell, M. D. Hager, U. S. Schubert and I. Manners, *Nat. Mater.*, 2011, 10, 176–188; (d) R. J. Wojtecki, M. A. Meador and S. J. Rowan, *Nat. Mater.*, 2011, 10, 14–27; (e) J. M. Pollino and M. Weck, *Chem. Soc. Rev.*, 2005, 34, 193–207.
- 8 (a) Q. Yan, Y. Xin, R. Zhou, Y. Yin and J. Yuan, Chem. Commun., 2011, 47, 9594–9596; (b) G. Wang, C. Wang, Z. Wang and X. Zhang, Langmuir, 2011, 27, 12375–12380; (c) H. Liu, Y. Zhang, J. Hu, C. Li and S. Liu, Macromol. Chem. Phys., 2009, 210, 2125–2137.
- 9 (a) L. Chen, X. Zhu, D. Yan, Y. Chen, Q. Chen and Y. Yao, Angew. Chem., Int. Ed., 2005, 45, 87–90; (b) F. Huang, D. S. Nagvekar, C. Slebodnick and H. W. Gibson, J. Am. Chem. Soc., 2005, 127, 484–485; (c) R. Hoogenboom, B. C. Moore and U. S. Schubert, Chem. Commun., 2006, 4010–4012.
- 10 (a) R. Fang, Y. Liu, Z. Wang and X. Zhang, *Polym. Chem.*, 2013, 4, 900–903; (b) X. Yan, S. Li, J. B. Pollock, T. R. Cook, J. Chen, Y. Zhang, X. Ji, Y. Yu, F. Huang and P. J. Stang, *Proc. Natl. Acad. Sci. U. S. A.*, 2013, 110, 15585–15590; (c) Z. Ge, H. Liu, Y. Zhang and S. Liu, *Macromol. Rapid Commun.*, 2011, 32, 68–73; (d) X. Zhu, L. Chen, D. Yan, Q. Chen, Y. Yao, Y. Xiao, J. Hou and J. Li, *Langmuir*, 2004, 20, 484–490.
- (a) W. Lin, Y. Zheng, J. Zhang and X. Wan, Macromolecules, 2011, 44, 5146–5154; (b) D. Han, X. Tong and Y. Zhao, Macromolecules, 2011, 44, 5531–5536; (c) W. Shao, K. Miao, H. Liu, C. Ye, J. Du and Y. Zhao, Polym. Chem., 2013, 4, 3398–3410; (d) Y. Chen, P. A. Wilbon, Y. P. Chen, J. Zhou, M. Nagarkatti, C. Wang, F. Chu, A. W. Decho and C. Tang, RSC Adv., 2012, 2, 10275–10282; (e) L. Gu, Z. Shen, C. Feng, Y. Li, G. Lu and X. Huang, J. Polym. Sci., Part A: Polym. Chem., 2008, 46, 4056–4069; (f) L. Gu, C. Feng, D. Yang, Y. Li, J. Hu, G. Lu and X. Huang, J. Polym. Sci., Part A: Polym. 3142–3153; (g) S. Zhai, X. Song, C. Feng, X. Jiang, Y. Li, G. Lu and X. Huang, Polym. Chem., 2013, 4, 4134–4144.
- (a) C. Feng, G. Lu, Y. Li and X. Huang, Langmuir, 2013, 29, 10922–10931; (b) S. Zhai, J. Shang, D. Yang, S. Wang, J. Hu, G. Lu and X. Huang, J. Polym. Sci., Part A: Polym. Chem., 2012, 50, 811–820; (c) C. Feng, Z. Shen, D. Yang, Y. Li, J. Hu, G. Lu and X. Huang, J. Polym. Sci., Part A: Polym. Chem., 2009, 47, 4346–4357.
- 13 (a) M. Nakahata, Y. Takashima, H. Yamaguchi and A. Harada, Nat. Commun., 2011, 2, 511; (b) Y. Kang, J. Yuan, Q. Yan, L. Zheng and L. Zhou, Polym. Adv. Technol., 2012, 23, 255–261.