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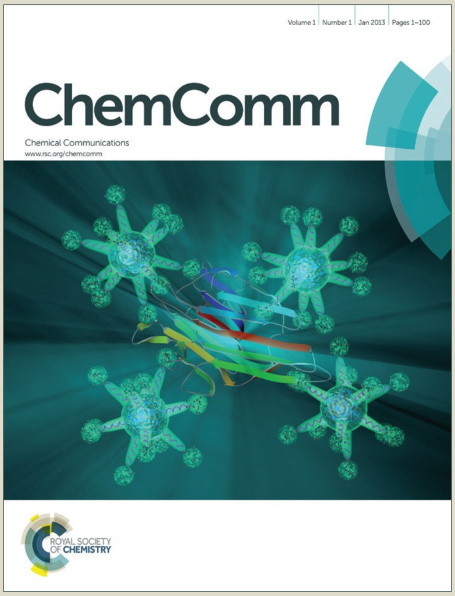

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Voltage-responsive single-chain polymer nanoparticles via host-guest interaction

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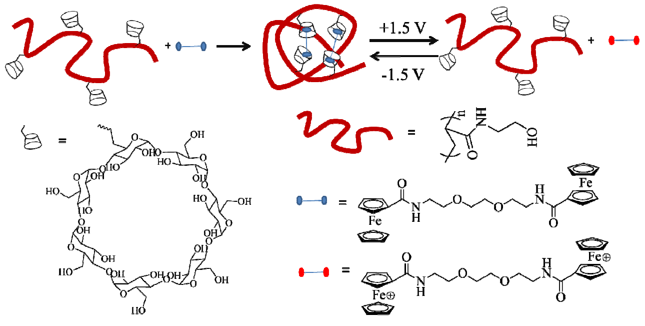
Poly(N-(2-hydroxyethyl)acrylamide) with pendant β-cyclodextrin was synthesized and intramolecularly crosslinked with bridged bis(ferrocene). This supramolecular nanoparticle can be changed reversibly between a coil and a nanoparticle upon external voltage stimuli.

The fabrication and application of polymer nanoparticles have attracted wide attention in recent years.[1] To obtain polymer nanoparticles via intramolecular folding and collapsing of single polymer chain containing reactive and crosslinkable groups is a relatively new strategy for the formation of the nanoparticles below 20 nm.[2] For the established and up-and-coming applications in the field of nanomedicine,[3] catalysis,[4] sensing,[5] as well as mimicry of biomacromolecules,[6] there is an urgent drive to fabricate new types of single-chain polymer nanoparticles (SCNPs) which possess the virtues of stimuli-responsiveness, where the nanoparticles can respond to the external stimuli (such as pH,[7] light,[8] redox,[9] temperature,[10] and so forth) and change their structure and morphology. Alternatively, the electrochemical redox reaction can be a useful method for the well-defined intramolecular crosslinking of the polymers, which has not been reported yet. Furthermore, controlled folding and unfolding of SCNPs via external stimuli is still challenging and not widely studied. Thus, it is extremely attractive to exploit the method via voltage stimuli to achieve the transformation between a particle and a random coil without adding external substance, which may lead in contamination.

β-Cyclodextrin (β-CD) can form 1:1 inclusion complex with uncharged ferrocene (Fc) and show weak inclusion ability toward charged Fc^+. This process can be controlled through external voltage stimuli,[11] which are considered to be significantly attractive and can achieve the redox reaction of the system with easy operation and no contamination to the system. In present study, β-CD was tethered to poly(N-(2-hydroxyethyl)acrylamide) (PHEAm), and 1,8-diamino-3,6-dioxaoctane bridged bis(ferrocene) (BisFc) (as the crosslinker) was synthesized. Thus the single-chain polymer nanoparticles were prepared via the supramolecular interaction between BisFc and β-CD on PHEAm in diluted solution. The structure of the polymers can be changed between the nanoparticles and the random coils upon external voltage stimuli (Scheme 1).



Scheme 1 Schematic representation of formation of SCNPs via intramolecular host-guest interaction and the voltage responsiveness of SCNPs

PHEAm was synthesized via reversible addition fragmentation chain transfer (RAFT) polymerization. PHEAm with pendant β-CD (PHEAm-β-CD) was prepared via the reaction between mono-6-deoxy-6-(p-tolylsulfonyl)-β-cyclodextrin (β-CD-OTs) and the hydroxyl groups on PHEAm. Gel permeation chromatography (GPC) curves of PHEAm and the corresponding PHEAm-β-CD are shown in Fig. 1a. The longer retention time of PHEAm-β-CD demonstrates the successful grafting of β-CD onto PHEAm. Proton nuclear magnetic resonance (^1H NMR) spectra of PHEAm and PHEAm-β-CD in d_6-DMSO are shown in Fig. 1b. The chemical shifts at 5.87-5.58 ppm, 4.82-4.13 ppm, and 3.74-3.43 ppm in the spectrum of PHEAm-β-CD, which belong to the protons of β-CD, also demonstrate the incorporation of β-CD onto PHEAm. The integration of the resonances at 5.87-5.58 ppm and 7.90-7.30 ppm allow the level of incorporated groups to be calculated: y= $(A_{5.87\text{-}5.58}/14)/A_{7.90\text{-}7.30}$, where the chemical shift from 7.90 ppm to 7.30 ppm belongs to -CONH- on PHEAm and the chemical shift from 5.87-5.58 ppm belongs to -OH in the cavity of β-CD. Compared with that of β-CD, Fourier Transform

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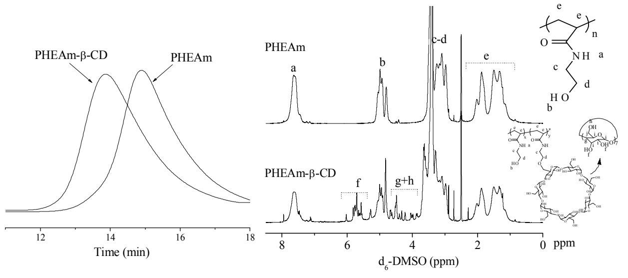
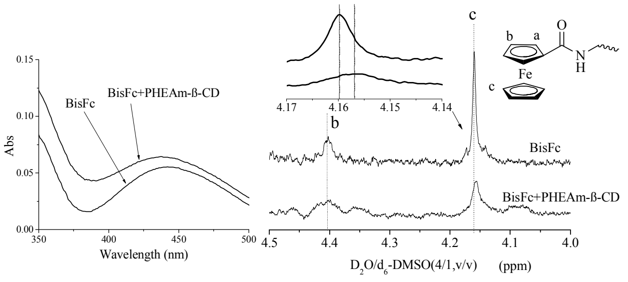


(a) (b)

Fig. 1 (a) GPC curves of PHEAm 2 and the corresponding PHEAm -β-CD (P2); (b) ^{1}H NMR of PHEAm and PHEAm-β-CD (P2) in d$_6$-DMSO.



(a) (b)

Fig. 3 (a) UV-Vis absorption spectra of BisFc (c=0.067 mg/mL) and BisFc in the presence of PHEAm-β-CD, solvent (EtOH/H$_2$O, v/v, 1/4); (b) ^{1}H NMR spectra of BisFc (c=0.067 mg/mL) and BisFc in the presence of PHEAm-β-CD.

Infrared (FTIR) spectra of PHEAm and PHEAm-β-CD (Fig. S1, ESI†) further confirm the grafting of β-CD onto PHEAm. The crosslinker, 1,8-diamino-3,6-dioxaoctane bridged bis(ferrocene), which has two ferrocene groups and can achieve the eventually intramolecular collapsing, was synthesized via amidation between 1,8-diamino-3,6-dioxaoctane and ferrocenecarboxylic acid. The structure is confirmed via ^{1}H NMR, ^{13}C NMR, FTIR, and ESI-MS (Fig. S2, ESI†).

Single-chain polymer nanoparticles were prepared by drop-wise addition of the crosslinker (EtOH solution) to PHEAm-β-CD diluted solution. Dynamic light scattering (DLS) was used to detect the formation from linear polymer to single-chain folded nanoparticle. After drop-wise addition of the crosslinker to the polymer solution, an obvious decrease in the hydrodynamic diameter between linear polymer precursors and the corresponding nanoparticles can be observed, which indicates that intramolecular crosslinking happens and the linear polymer transfers from a coil to a particle (Fig. 2).

To confirm the supramolecular crosslinking assisted by 1,8-diamino-3,6-dioxaoctane bridged bis(ferrocene), ^{1}H NMR and UV/Vis measurements are taken directly to compare 1,8-diamino-3,6-dioxaoctane bridged bis(ferrocene) and the analogous nanoparticles. As shown in Fig. 3a, the absorption peak assigned to Fc exhibits blue shift from 442 nm (A=0.055) to 437 nm (A=0.064) upon the addition of PHEAm-β-CD. The high electron density in the cavity of β-CD may induce the electron shift of the guest molecules, which is consistent with the literature.[12] Furthermore, clear differences in chemical shift can be observed when comparing the ^{1}H NMR spectra of BisFc and the analogous nanoparticles (Fig. 3b). The up-field shift, weakening, and broadening corresponding to cyclopentadiene protons also indicate the complexation of β-CD and ferrocene groups. To further determine the binding affinity of β-CD with ferrocene groups in H$_2$O/EtOH (4/1, v/v), β-CD and 1,8-diamino-3,6-dioxaoctane bridged bis(ferrocene) were used as model molecules. The association constant Kt calculated by Hidebrand-Benesi equation is 3.36×10^4 M^{-1} in UV/Vis spectra (Fig. S4, ESI†), which is consistent with the literature.[12b]

Atomic force microscopy (AFM) can be helpful for imaging nanostructure of the nanoparticles in the solid state, which were collapsed from individual macromolecules. The solution of the nanoparticles (NP1) was filtered with a Teflon filter (0.45 μm) to reduce the amount of large dust particles and atmospheric contaminants and then 10 μL solution (c=10 μg/mL) was dropped onto freshly cleaved silica wafer and then dried under room temperature. A scanned area of 2×2 μm^2 is depicted in Fig. 4 (A and D). The particles on silica show an average diameter about 36.0 nm in the top view and an average height about 3.0 nm in the 3D image. Thus, on silica surface the nanoparticles adopt a pancake-like shape. This phenomenon has been reported in the literature.[13] Thus, following Meijer's methods,[7a] taking the shape of the particles as a half ellipsoid, the nanoparticles possess a calculated diameter about 15.6 nm in globule state when in solution. Furthermore, the AFM observation could lead to an enhanced width of the nanoparticles due to the broadness of the AFM tip. So, the nanoparticles observed via AFM should have a diameter less than 15.6 nm in solution. This result agrees well

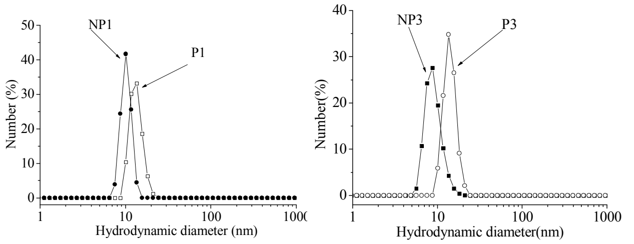


Fig. 2 DLS results of linear polymer (P1 and P3) and the corresponding nanoparticles (NP1 and NP3).

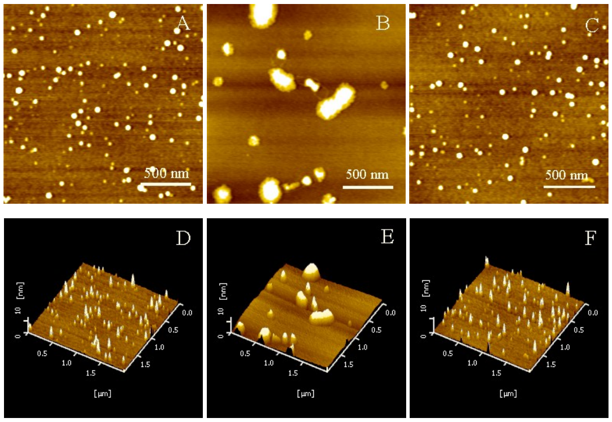


Fig. 4 AFM images of the reversible collapsing and discollapsing of the voltage-responsive single-chain nanoparticles upon electric stimuli: A and D, no external stimuli; B and E, +1.5 V, 3 h; C and F, -1.5 V, 3 h.

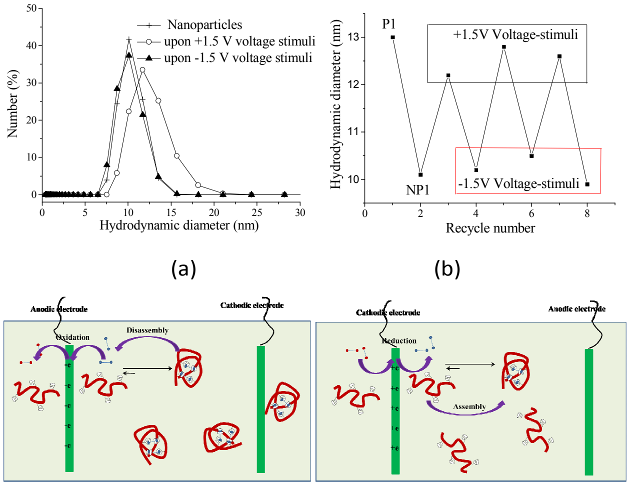
Table 1 Comparison of DLS data of PHEAm-β-CD and the corresponding nanoparticles

	PHEAm-β-CD					Nanoparticles	
	β-CD(%)^a	Mn^b	D^b	Dh(nm)^c	PDI^c	Dh(nm)^c	PDI^c
P1-NP1	3.6%	58800	1.21	13.0	0.29	10.1	0.32
P2-NP2	4.0%	42100	1.30	11.8	0.30	9.4	0.36
P3-NP3	6.7%	66400	1.36	13.8	0.26	8.7	0.31

a Mole contents of β-CD units as measured by ^{1}H NMR spectroscopy in d_6-DMSO.
b Determined by GPC, using H_2O (containing 0.8 wt% $NaNO_3$) as eluent.
c Hydrodynamic diameter (Dh) is measured by dynamic light scattering (DLS) in H_2O/EtOH (v/v, 4/1) at a concentration of 1.0 mg/mL.

with the hydrodynamic diameter (Dh) measured by DLS (Table 1). Furthermore, the clear difference can be seen between linear PHEAm-β-CD and the corresponding nanoparticles in AFM phase images, which may be resulted from the different states of linear polymers and collapsing nanoparticles (Fig. S7, ESI†). When taking these reasons into consideration, the size characterized by AFM is reasonable for the nanoparticles via single-chain folding. Transmission electron microscopy (TEM) images of nanoparticles (NP1) on carbon coated copper grids are shown in Fig. S6-A (ESI†). The mean diameter of the nanoparticles in Fig. S6-A (ESI†) is about 24.0 nm, which is larger compared with DLS results (about 10.1 nm). The possible reason is that the nanoparticles via non-covalent bond crosslinking are soft and less dense. The nanoparticles adopt a flattened structure on carbon film when cast onto a plane.

To investigate the reversibility of the nanoparticles, two electrodes were utilized to conduct the voltage stimuli with a potentiostat. Upon +1.5 V voltage stimuli for 3 h, the hydrodynamic diameter of the nanoparticles (Fig. 5a) increases from 10.1 nm to 12.2 nm, which indicates that the intramolecular host-guest interaction is partially destroyed and the charged Fc$^+$ species dissociate from the cavity of β-CD. Downfield of protons assigned to Fc groups in ^{1}H NMR spectra further confirm dissociation of the inclusion complex (Fig. S9, ESI†). The corresponding AFM image and TEM are shown in Fig. 4-B and Fig. S6-B (ESI†) respectively. Upon -1.5 V voltage stimuli for 3 h, surprisingly, the hydrodynamic diameter of the nanoparticles decreases from 12.2 nm to 10.1 nm, which indicates that Fc$^+$ gets one electron and the intramolecular host-guest interaction happens again. Upfield of protons assigned to Fc groups in ^{1}H NMR spectra further confirm the inclusion complex formation (Fig. S9, ESI†). The nanoparticles observed via AFM and TEM (Fig. 4-C and Fig. S6-C, ESI†) also show a similar diameter to the nanoparticles before voltage stimuli. This process was conducted for another three times and the hydrodynamic diameter of the nanoparticles shows similar rules (Fig. 5(b) and Fig. S8 in ESI†). That is to say, the collapsing and discollapsing can be controlled via the external voltage stimuli reversibly.



(a) (b)

(c) (d)

Fig. 5 (a) DLS results of the reversible assembly and disassembly of the voltage-responsive SCNPs upon electric stimuli; (b) DLS results of intramolecular assembly and disassembly of supramolecular nanoparticles (NP1) via voltage-stimuli; (c) Schematic illustration of electrochemical oxidation mechanism of SCNPs; (d) Schematic illustration of electrochemical reduction of single-chain folding.

Herein, a new fabricating approach for voltage-responsive polymer nanoparticles is described. The reversible transformation between a random coil and a particle can be achieved via external voltage stimuli. This method paves the way towards stimuli-responsive single-chain polymer nanoparticles for the established and up-and-coming applications in the field of nanomedicine, catalysis, sensing, and a simple mimicry of biomacromolecules.

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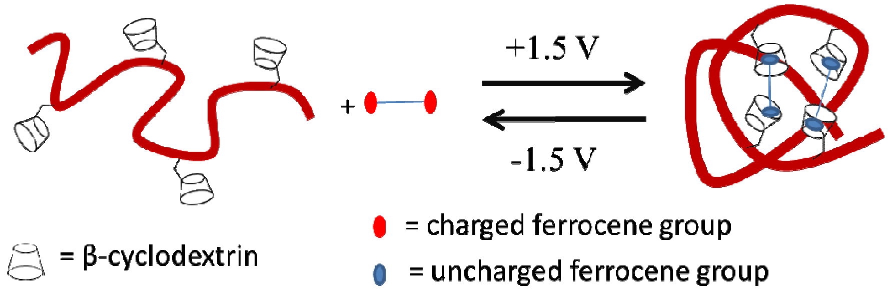
Graphic Abstract



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