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COMMUNICATION

A pH-responsive Amphiphilic Supramolecular Graft Copolymer Constructed by Crown Ether Based Molecular Recognition†

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Graft polymers always play a significant role in polymer chemistry as they are preferred materials for a large variety of applications, such as drug/gene delivery systems, hybrid and biomedical materials, soft rubbers, and opto-electronic materials. Compared with traditional graft copolymers, supramolecular graft copolymers whose main chains and side chains are connected by non-covalent forces, (e.g. hydrogen bonding, metal-coordination, host−guest interactions, etc), could be easily obatained in a facile and dynamic manner instead of tedious and time-consuming synthesis. Herein, based on the BMP32C10/paraquat molecular recognition in water, we have successfully prepared an amphiphilic supramolecular graft copolymer by synthesizing poly(styrene-*co*-paraquat) **1** as the hydrophobic main chain and modified poly(ethylene oxide) **2** as the hydrophilic side chains. The self-assembly behaviour of the amphiphilic supramolecular graft copolymer in water was investigated by DLS, TEM and SEM. As confirmed, it could self-assemble into bilayer vesicles in water, which would be destroyed with the treatment of HCl. Therefore, the vesicles were further used in the pH controlled release of water-soluble molecules.

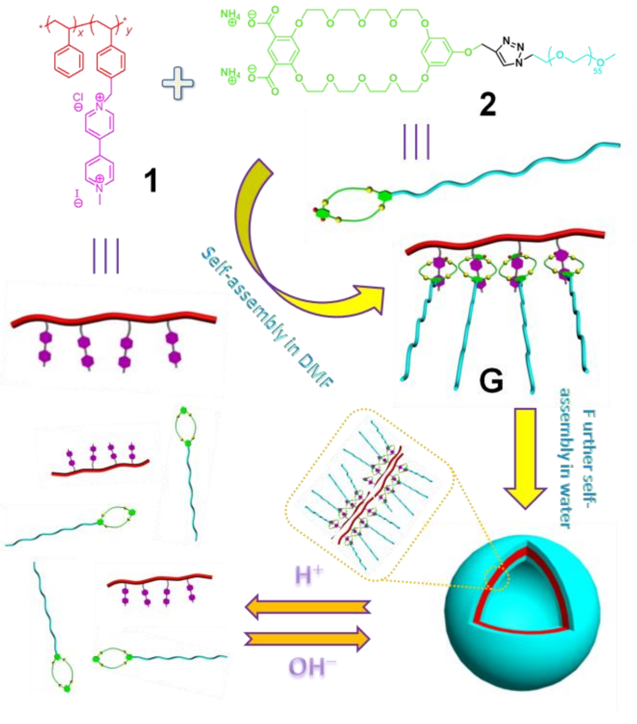
Introduction

Graft polymers always play a significant role in polymer chemistry as they are preferred materials for a large variety of applications, such as drug/gene delivery systems,[1] hybrid and biomedical materials,[2] soft rubbers,[3] and opto-electronic materials.[4] Supramolecular graft copolymers refer to a kind of graft polymers whose main chains and side chains are connected by non-covalent forces.[5] Compared with traditional graft copolymers, supramolecular graft copolymers could be easily obtained in a facile and dynamic manner instead of tedious and time-consuming synthesis due to the dynamic and reversible natures of noncovalent interactions. Recently, amphiphilic supramolecular graft copolymers (ASGCs) have been fabricated by non-covalently grafting hydrophilic/hydrophobic side chains to the hydrophobic/hydrophilic main chain.[6] With the combination of non-covalent forces and amphiphilicity, ASGCs can self-assemble into well-defined aggregates in water which could be disrupted by the destruction of non-covalent forces, implying the potential applications in controlled drug delivery. Among all the non-covalent forces, such as hydrogen bonding, metal-coordination, and host–guest interactions, host–guest interactions have always gained much attention due to their abundant stimuli-responsiveness (e.g. redox-responsive cyclodextrin/ferrocene recognition motif).[6f] To date, most ASGCs were fabricated by cyclodextrin-based host–guest recognition,[6b-g] ASGCs constructed by other macrocycle-based (such as calixarenes[7], cucurbiturils[8] and pillar[*n*]arenes[9]) host–guest recognition motifs have rarely been reported. Crown ethers,[10,11] the first generation of macrocyclic hosts, have been extensively employed to construct functional supramolecular materials (such as supramolecular polymers and gels[12]) in organic solvents due to their rich host-guest chemistry. Consequently, it is of great importance to employ crown ether-based molecular recognition to fabricate ASGCs. However, to the best of our knowledge, crown ethers have never been utilized in the ASGC systems.

In our recent work, we have successfully prepared some supramolecular systems driven by bis(*m*-phenylene)-32-crown-10 (BMP32C10)/paraquat (*N*,*N*′dimethyl-4,4′-bipyridinium)-based molecular recognition in aqueous media.[13] The enhanced crown ether-based molecular recognition in aqueous media is due to the introduction of electrostatic attractions between the COO^- groups on the crown ether host moiety and the cationic groups of the viologen guest unit, which was also demonstrated by other research groups for other crown ether-based host−guest systems.[14] In this work, the enhanced BMP32C10/paraquat molecular recognition motif in water was utilized to fabricate an ASGC. As shown in Scheme 1, Poly(styrene-co-paraquat) **1** and polymer **2** (poly(ethylene oxide) PEO terminated with a BMP32C10 host containing two COO^- groups) were used as hydrophobic and hydrophilic segments, respectively, to prepare this ASGC. It can self-assemble into bilayer vesicles in water, which would be destroyed with the treatment of HCl. Therefore, the vesicles were further used in the pH controlled release of water-soluble molecules.

Results and Discusion

There were about 9.0 paraquat moieties per single polymer chain for **1** as calculated based on proton NMR spectra (Fig. S3 and S5, ESI†). Polymer **2** was synthesized according to previous literature.[13b] It has been demonstrated that the BMP32C10 containing two COO^{-} groups is able to form [2]pseudorotaxanes with paraquat salts in water,[13] thus an anphiphilic supramolecular graft copolymer formed by mixing **1** and **2** in DMF. The modified PEG **2** acted as the hydrophilic side chains and polymer **1** served as the hydrophobic main chain.



Scheme 1. Chemical structures of polymer **1** and **2** and the cartoon representation of the vesicle formed by the self-assembly of the amphiphilic supramolecular graft copolymer in water.

Due to the poor solubility in water, the main chain polymer **1** was first dissolved in N,N-dimethylformamide (DMF, 1.00 mL) with a concentration of 5.00 mM. The side chain polymer **2** was also dissolved in the above solution with a concentration of 45.0 mM, thus a mixture of the ASGC **G** was obtained in DMF with the solution concentration 5.00 mM. The grafting process was firstly invesgated in DMF by ^{1}H NMR. As shown in Fig. S6, the protons on the paraquat moities of polymer **1** shifted upfield after mixing with **2**, indicating the formation of the ASGC **G**. To investigate the self-assembly of **G** in water, 0.10 mL of **G** DMF solution was dropped into 0.90 mL of H_2O, and DMF was then removed by dialysis.

The self-assembly behaviour of **G** in water was investigated by dynamic light scattering (DLS), scanning electron microscopy (SEM) and transmission electron microscopy (TEM) experiments. First of all, the self-assembly behaviour of the main chain polymer **1** was investigated by TEM. Fig. 1a showed that the aggregates formed by **1** alone were irregular assemblies. However, the aqueous solution of **G** was relatively transparent, indicating that the self-assembly behaviour of **G** was not the same as that of **1**. Moreover, Tyndall effect was observed for the solution of **G**, indicating that the assemblies were more than 100 nm in diameter (Fig. 1b).[15] The DLS result (Fig. 1c) showed that the aggregates of **G** have an average diameter of about 300 nm with a narrow size distribution, implying that some spherical regular assemblies formed. SEM and TEM experiments were further performed to confirm the DLS result in the visualization of the nanostructures self-assembled from **G**. As confirmed by a SEM image (Fig. 1d), some spherical assemblies about 300 nm in diameter were observed. Moreover, the TEM image (Fig. 1e) demonstrated that the spherical assemblies were hollow spheres, strongly proving the formation of vesicles rather than micelles. The enlarged picture (Fig. 1f) of the vesicles showed that the wall thickness was measured to be about 40 nm, almost twice of the length of the side chain polymer **2**, indicating that the vesicles have a bilayer wall where the hydrophilic side chains reside on the wall surface and the hydrophobic main chains stay in the middle.

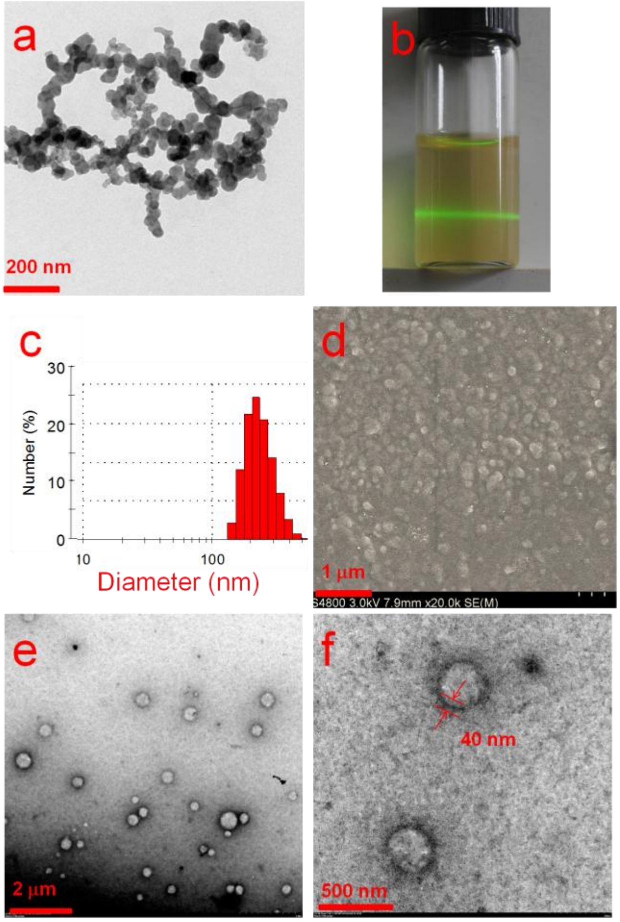


Fig. 1 (a) TEM image of the main chain polymer **1** (5.00×10^{-4} M) in water; (b) Tyndall effect of **G** (5.00×10^{-4} M) in water; (c) DLS result of **G** (5.00×10^{-4} M) in water; (d) SEM image of the ASGC **G** (5.00×10^{-4} M) in water; (e) TEM image of **G** (5.00×10^{-4} M) in water; (f) Enlarged picture of e.

Depending on the fact that the COO^{-} groups can be converted into the neutral carboxylic acid groups by adding acid, the complexation between the BMP32C10 unit and the viologen moiety would be weakened in water and the double-layered vesicles could be destroyed. The reversible transition between assembled and disassembled structures can be achieved by changing the solution pH. TEM and DLS experiments were utilized to investigate the effect of pH on the aggregation behavior. After adding a small drop of HCl (pH = 3.0), the transparent **G** solution became a little turbid, indicating that the vesicles was destroyed. The DLS result (Fig. 2a) exhibited a wide range of the aggregate size from 100 nm to over 1000 nm, which was quite different from that obtained before the addition of HCl. Moreover, the TEM image directly confirmed the damage of the vesicles formed by **G** in water. As shown in Fig. 2b, the spherical vesicles were gone instead of some irregular assemblies with different sizes by adjusting the solution pH to 3.0. One reason why these irregular assemblies appeared might be that the ASGC **G** was destroyed and the main chain polymer tended to precipitate in water, while the side chain polymers still remained water-soluble even though the hydrophilic COO^- groups were changed to hydrophobic COOH groups upon acidification. Interestingly, upon adding NaOH to adjust the solution pH to 10.0, the DLS result (Fig. 2c) showed a relatively narrow distrubution compared to 2a, from 150 nm to 350 nm, which was almost the same as that of **G**. The TEM image (Fig. 2d) showed that the vesicles formed again, suggesting that the reassembly of **G** led to the reformation of vesicles.

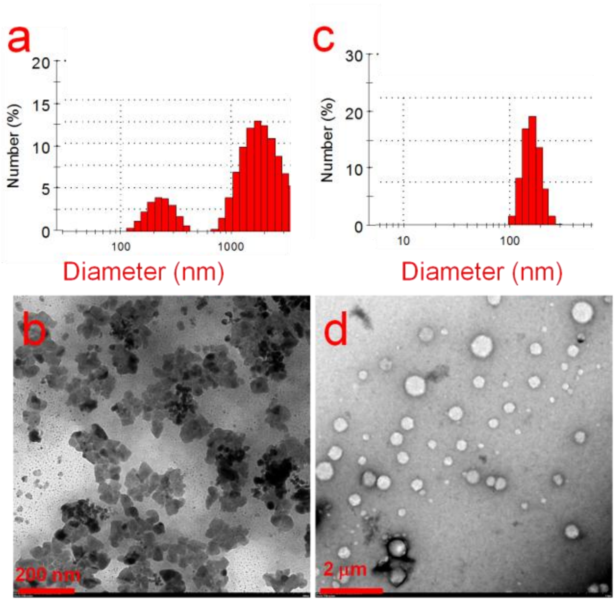


Fig. 2 (a) DLS result of **G** (5.00×10^{-4} M) in water after adding HCl to adjust the solution pH to 3.0; (b) TEM image of **G** (5.00×10^{-4} M) in water after adding HCl to adjust the solution pH to 3.0; (c) DLS result of **G** (5.00×10^{-4} M) in water after adding NaOH to adjust the solution pH to 10.0; (d) TEM image of **G** (5.00×10^{-4} M) in water after adding NaOH to adjust the solution pH to 10.0.

Based on the pH-responsiveness of the crown ether-based molecular recognition, the release of the encapsulated hydrophilic molecules from the interior of the vesicles could be realized upon the addition of HCl. It is well-known that calcein as a hydrophilic fluorescent guest could be encapsulated in the interior of the vesicles. In order to remove the calcein molecules outside the vesicles, dialysis experiment was performed for 2 days until few calcein molecules were outside the vesicles before we measured the fluorescence change. As shown in Fig. 3, no obvious fluorescence intensity corresponding to the characteristic absorbance of calcein could be observed, indicating that the calcein molecules were stably located in the interior of the vesicles. Upon the addtion of HCl to the solution, the vesicles were collapsed, resulting in the release of calcein molecules from the interior of vesicles accompanied by an increase in the fluorescence intensity. Moreover, after adjusting the solution pH to 10.0 by adding NaOH, the fluorescence intensity was decreased by almost 2 times, indicating that partial of the calcein was located in the reformed vesicles.

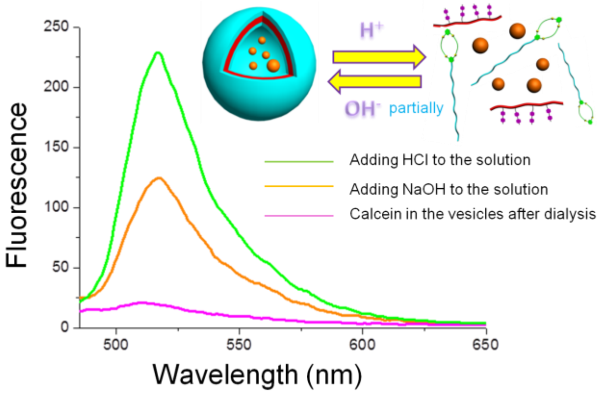


Fig. 3 Fluorescence change of calcein before/after adding HCl and after adding NaOH to the calcein-loaded vesicle solution and its corresponding cartoon representation.

Conclusions

In summary, based on the BMP32C10/paraquat molecular recognition in water, we have successfully prepared an amphiphilic supramolecular graft copolymer by the combination of modified hydrophilic PEO and hydrophobic PS. This amphiphilic supramolecular graft copolymer can self-assemble into bilayer vesicles in water, which would be destroyed with the treatment of HCl. Therefore, the vesicles were further used in the pH controlled release of calcein. Furthermore, they have potential applications in controlled drug delivery and biotherapeutics. This novel amphiphilic supramolecular graft copolymer contributes to the development of supramolecular chemistry in aqueous medium and offers a new method to combine polymer science with supramolecular chemistry to construct functional materials.

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† Electronic Supplementary Information (ESI) available: Characterizations, ^{1}H NMR data and other materials. See DOI: 10.1039/b000000x/

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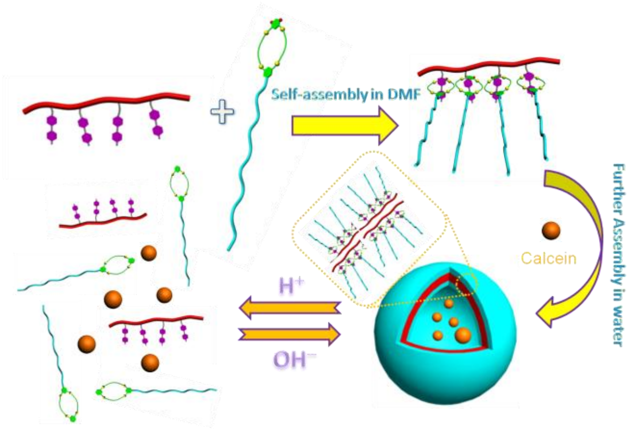
ToC Graphic



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