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COMMUNICATION

Amphiphilic diselenide-containing supramolecular polymers

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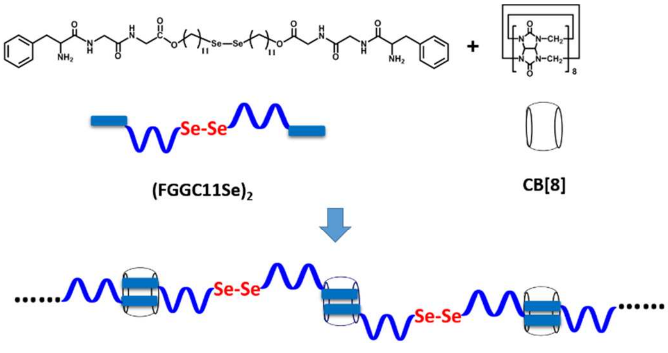
This communication describes the fabrication of diselenide-containing supramolecular polymers. The diselenide-containing supramolecular polymers were fabricated by equimolarly mixing (FGGC11Se)$_2$ and CB[8] in aqueous solution driven by host-guest interactions between cucurbit[8]uril (CB[8]) and Phe-Gly-Gly. The amphiphilic diselenide-containing supramolecular polymers could further form aggregates for loading hydrophobic small molecules such as Nile Red and releasing them upon addition of oxidants or reductants. This line of research not only expands the library of selenium-containing polymers, but also offers a new strategy to develop functional supramolecular polymers for drug delivery.

Supramolecular polymers are formed by monomers through noncovalent interactions[1-8]. The noncovalent interactions can be multiple hydrogen bonding[8-10], metal coordination[11-16] and host-guest interaction[16-29]. Owing to the dynamic nature of noncovalent interactions, supramolecular polymers can be a type of promising materials with reversible, stimuli-responsive, degradable and self-healing characteristics[30-34]. In recent years, we have developed a series of cucurbit[8]uril(CB[8])[35]-based supramolecular polymers through supramolecular polymerization of small monomers or covalent polymerization of supramonomers[19-25]. Although the field of supramolecular polymers has progressed rapidly[36-42], it is still highly demanded to establish new methods to prepare functional supramolecular polymers.

Selenium-containing polymers are a new kind of stimuli-responsive polymers which are sensitive to either oxidants or reductants[43]. The redox responsiveness of selenium-containing polymers is faster and more sensitive compared to that of sulfur-containing polymers. We have developed a series of amphiphilic selenium-containing polymers, which can self-assemble to form micellar structures for drug-delivery vehicles[43-46]. We are wondering if we can combine selenium chemistry and supramolecular polymeric chemistry to fabricate selenium-containing supramolecular polymers. With the aim to develop a new type of functional supramolecular polymers, the diselenide bond with high sensitivity to redox stimuli has been chosen to be introduced to the supramolecular polymeric system.

To this end, we designed and synthesized diselenide-containing bifunctional monomer, (FGGC11Se)$_2$, which was confirmed by ^{1}H NMR, ^{13}C NMR, ^{77}Se NMR and ESI-MS. As shown in Scheme 1, the bifunctional monomer beared a diselenide bond in the core linking to two undecyl chains



Scheme 1 Molecular building blocks for fabricating diselenide-containing supramolecular polymers.

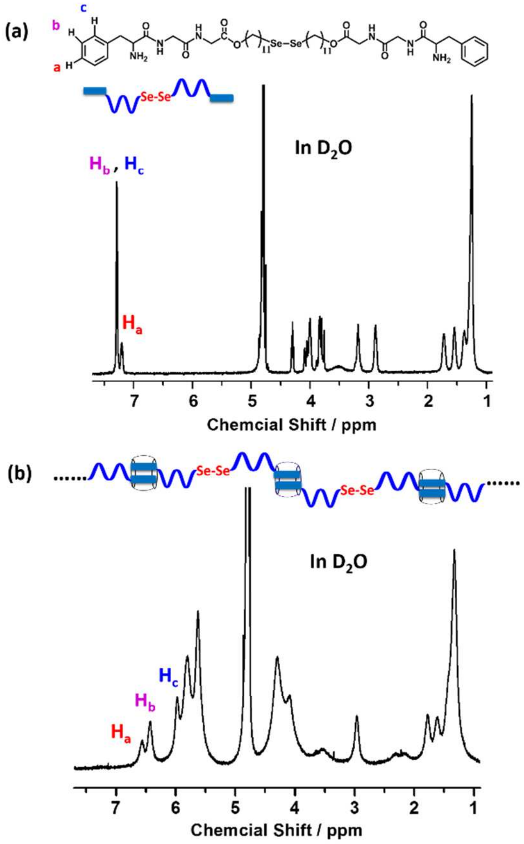


Figure 1 (a) ^{1}H NMR spectra of the bifunctional monomer (FGGC11Se)$_2$, and (b) the supramolecular polymers formed by mixing (FGGC11Se)$_2$

with CB[8] in D_2O at 25 °C.

franked by two tripeptides of Phe-Gly-Gly (FGG) as end groups. The binding constant of the strong and specific host-guest interaction between CB[8] and FGG can be as high as 10^{11}, [47] and the interaction was employed to drive the supramolecular polymerization by equimolarly mixing CB[8] and $(FGGC11Se)_2$ in aqueous solution. Considering it contains both hydrophilic and hydrophobic segments, the diselenide-containing supramolecular polymers may form aggregates for controlled loading and releasing of hydrophobic species.

The formation of the diselenide-containing supramolecular polymers is clearly suggested by the ^1H NMR spectra shown in Figure 1. As shown in Figure 1(a), the chemical shift of the protons in the aromatic area of $(FGGC11Se)_2$ were around between 7.0 and 7.5 before supramolecular polymerization. As shown in Figure 1(b), the protons in the aromatic area of $(FGGC11Se)_2$ displayed significant upfield shifts after mixing with CB[8] in a molar ratio of 1:1, indicating that the supramolecular complexation of these two building blocks indeed happened. Moreover, the broadening and fusion of the peaks in the ^1H NMR spectra of the $(FGGC11Se)_2$-CB[8] complex suggest the formation of supramolecular polymers.

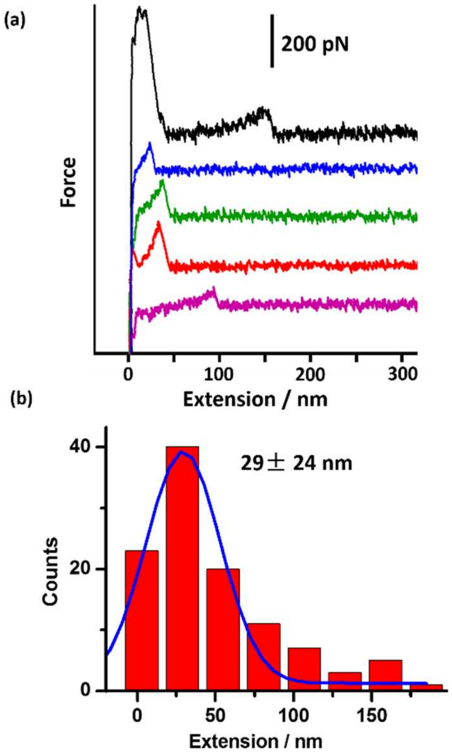


Figure 2 (a) Typical force-extension curves of the supramolecular polymers consisting of $(FGGC11Se)_2$ and CB[8] in a molar radio of 1:1. (b) Histogram of the lengths of the force peaks; the most probable length was determined to be 29±24 nm by Gaussian fitting.

The formation of the supramolecular polymers fabricated by the $(FGGC11Se)_2$-CB[8] complex is supported by AFM-based single-molecule force spectroscopy (SMFS, detailed in the ESI†)[48-50]. Representative force-extension curves of the supramolecular polymers consisting of $(FGGC11Se)_2$ and CB[8] in a molar ratio of 1:1 are displayed in Figure 2a. The forces increased with the extension of the supramolecular polymers and then dropped to zero with the rupture of the polymer bridges, suggesting the existence of linear-polymer-like substances in the system. The lengths of the force peaks in all the force curves were statistically analysed, as shown in Figure 2b. The Gaussian fitting gave the most probable length of 29±24 nm, corresponding to 10 ~ 15 units. As a control experiment, no force curves were obtained in a solution containing only $(FGGC11Se)_2$. Therefore, the formation of the supramolecular polymers formed by $(FGGC11Se)_2$-CB[8] complex is further supported by SMFS as well.

The formation of the diselenide-containing supramolecular polymers is further corroborated by asymmetric flow field flow fractionation (AsF-FFF)[23-25]. The absence of a stationary phase makes AsF-FFF a very mild technique that can significantly reduce the possibility of supramolecular polymer degradation. The typical elution curve of supramolecular polymers (1.0 mM $(FGGC11Se)_2$-CB[8]) obtained with a UV detector is shown in Figure 3. The molecular weight of the supramolecular polymers is calculated to be 1.2×10^5 $g\cdot mol^{-1}$ with the polydispersity of about 2.5.

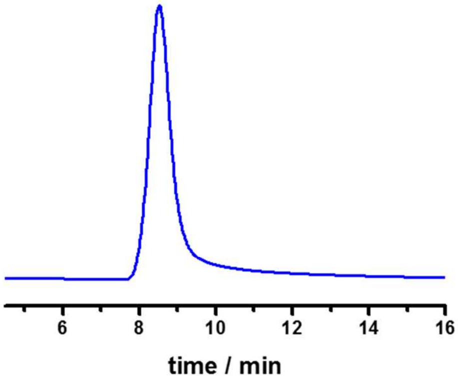


Figure 3 The typical AsF-FFF elution curve of $(FGGC11Se)_2$-CB[8] obtained by the UV detector.

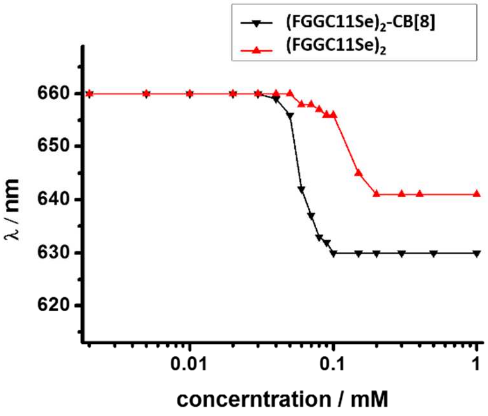


Figure 4 The CAC measurements of $(FGGC11Se)_2$ and $(FGGC11Se)_2$-CB[8] complex using the NR probe at 25 °C.

To study if the supramolecular polymers consisting of $(FGGC11Se)_2$ and CB[8] are amphiphlic and able to aggregate in an aqueous environment, we used the fluorescent method with Nile Red (NR) as the probe to measure the critical aggregate concentration (CAC). The fluorescence wavelength of NR depends on the polarity of the environment[51]. As shown in Figure 4, in the $(FGGC11Se)_2$-CB[8] complex solution, the fluorescence of NR exhibits a significant blue shift with the increase of concentration in the area from 0.04 mM to 0.1 mM, while in the $(FGGC11Se)_2$ solution, the blue shift area is from 0.06 mM to 0.2 mM. The CAC values of $(FGGC11Se)_2$-CB[8] complex and $(FGGC11Se)_2$ are about 0.04 mM and 0.06 mM, respectively. This fact suggests that the supramolecular polymers can further form aggregates for loading small molecules. It should be noted that the fluorescence wavelength of NR in the $(FGGC11Se)_2$-CB[8] complex solution can shift to 630 nm while that in the $(FGGC11Se)_2$ solution can only shift to 641 nm. This fact indicates that the internal microenvironment formed by supramolecular polymers of $(FGGC11Se)_2$-CB[8] complex is much more hydrophobic than that formed by $(FGGC11Se)_2$

Considering that the diselenide-containing supramolecular polymers are redox responsive, we wonder whether the small molecules (e.g. hydrophobic NR) incorporated into the aggregates can be released upon addition of oxidants or reductants. NR was used as a model compound in the controlled release experiments. The amount of NR loaded in hydrophobic cavities in 0.2 mM $(FGGC11Se)_2$-CB[8] complex solution is estimated to be about 1.0 μmol by drawing a fluorescence intensity−NR concentration standard curve in $V_{THF}/V_{water} = 4:1$ solution. As shown in Figure 5(a), under a mild oxidizing environment of 0.01% H_2O_2, the intensity of NR decreases gradually, corresponding to the release of NR. As shown in Figure 5(b), after about 6 h, almost all of the NR was released. It should be noted that the release of NR was much faster in 0.1% H_2O_2 than in 0.01%, and almost all of the NR was released in 1 h. However, in the absence of H_2O_2, there were only a little release of NR, even after 3 days, and there still remained about 85% NR, as shown in Figure S8. Therefore, there is a sensitive oxidation controlled release indeed.

Besides oxidation controlled release, the NR can also be released in the presence of reductants. As shown in Figure 5(c), after adding tris(2-carboxyethyl)phosphine (TCEP), almost all of the NR was released in 5 min. All of these results indicate that specific small molecules can be effectively incorporated into the aggregates of the amphiphilic diselenide-containing supramolecular polymers, kept stably for a relatively long time, and released under a certain condition. Moreover, the release rate of small molecules is tunable, from a slow release to a burst release, by adding oxidant (H_2O_2) or reductant (TCEP) with different concentration.

Conclusions

In summary, we have employed the host-guest interactions between cucurbit[8]uril and tripeptide of Phe-Gly-Gly to fabricate amphiphilic diselenide-containing supramolecular polymers. Hydrophobic molecules such as Nile Red can be loaded and retained in the aggregates of amphiphilic diselenide-containing supramolecular polymers, and then be released upon addition of oxidants or reductants. The good performance of loading and controlled-release properties makes this type of supramolecular polymers to be potential drug delivery vehicles. Furthermore, because of the biocompatible nature of the

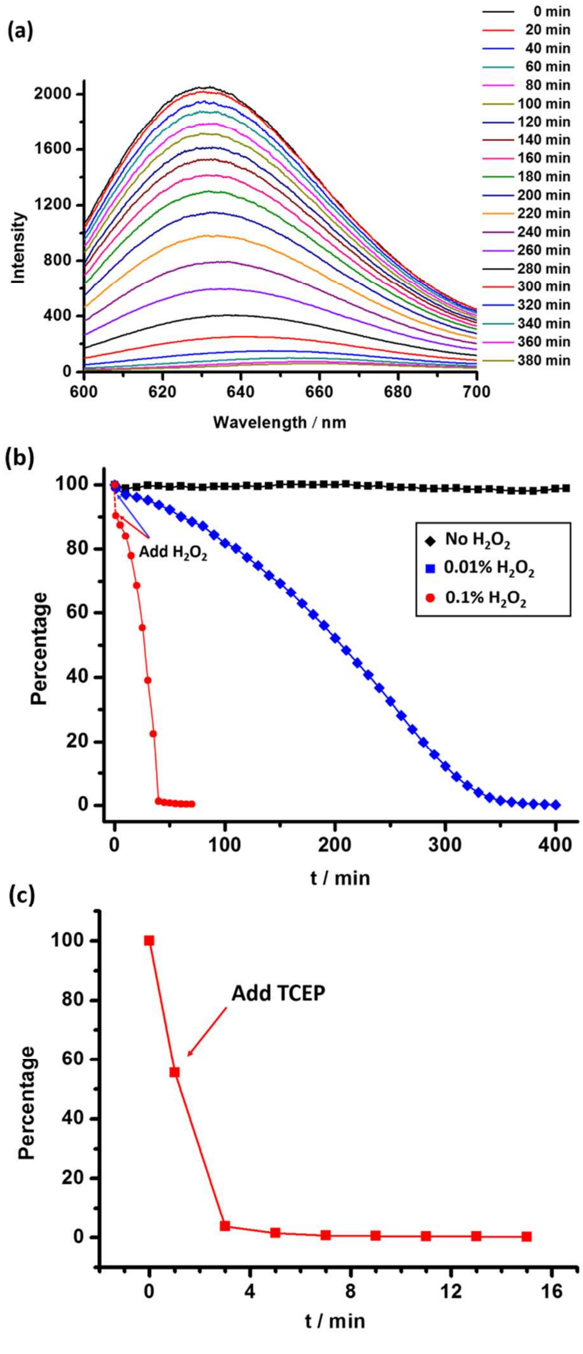


Figure 5 (a) Fluorescence spectra of NR loaded in aggregates of 0.2 mM $(FGGC11Se)_2$-CB[8] complex under treatment of 0.01% H_2O_2. (b) The release behavior of NR in H_2O_2 and control experiment. (c) The release behavior of NR in 0.5 mM TCEP.

building blocks, selenium-containing supramolecular polymers are expected to be environmentally friendly and biocompatible materials.[48] Therefore, the construction of amphiphilic selenium-containing supramolecular polymers not only expands the library of selenium-containing polymers, but also offers a new strategy to develop functional supramolecular polymers.

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Notes and references

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