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COMMUNICATION

Supramolecular polymers bearing disulfide bonds

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This work is aimed to report a new type of multiple stimuli-responsive supramolecular polymers through combining dynamic covalent bonds with cucurbit[8]uril (CB[8])-based host-guest interaction. Supramonomer (DSN) containing a disulfide bond can bind with CB[8] to fabricate supramolecular polymers by host-enhanced π - π interaction. Additionally, the dynamic nature of disulfide bond and host-guest chemistry endow these supramolecular polymers with redox and guest competitive responsiveness, respectively.

Introduction

Supramolecular polymers have their unique properties including dynamic, reversible and degradable characteristics on account of the nature of non-covalent interactions.¹⁻¹³ Different kinds of non-covalent interactions have been applied as driving forces to construct supramolecular polymers, including multiple hydrogen-bonding,¹⁴⁻¹⁷ metal-coordination,¹⁸⁻²⁵ and host-guest interaction.²⁶⁻⁴¹ Recently, our group has successfully employed cucurbit[8]uril (CB[8])-enhanced π - π or charge-transfer interaction to fabricate supramolecular polymers with high degree of polymerization in aqueous solution.³⁰⁻³⁹

Dynamic covalent bond is a kind of covalent bond but with dynamic and reversible properties, meaning that they can be broken and reformed quickly.⁴²⁻⁴⁷ Therefore, they can be applied for fabricating various stimuli-responsive or self-healing materials.⁴⁸⁻⁵³ Among various dynamic covalent bonds, disulfide bond is of great interest on account of its redox responsiveness in nature.⁵⁴⁻⁵⁸

Herein, we integrated redox and guest competitive responsiveness to one supramolecular polymer by combining disulfide bond and CB[8]-enhanced π - π interaction (Fig. 1). First, we designed a redox-responsive monomer 4,4'-disulfanediybis(1-(naphthalen-2-ylmethyl)pyridin-1-ium) bromide (DSN), which contains a dynamic disulfide bond in the middle and two naphthalene groups in the terminals (Scheme S1). Then, CB[8] can bind with two naphthalene groups in the supramonomer with a molar ratio of 1:2 to fabricate multiple stimuli-responsive supramolecular polymers through CB[8]-enhanced π - π interaction.

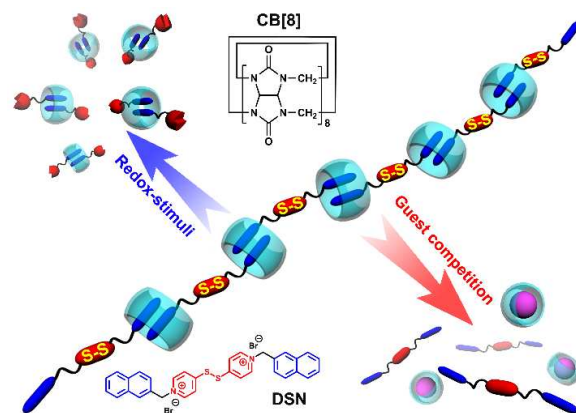


Fig. 1 Illustration of the fabrication of the multi-stimuli responsive supramolecular polymers.

Results and discussion

In order to demonstrate the host-guest interaction between DSN and CB[8], ¹H NMR spectra of DSN before and after addition of CB[8] were studied. After adding CB[8] into the solution of DSN, the proton peaks of naphthalene groups in the supramonomer broadened and shifted upfield from 7.5 to 6.5 ppm (Fig. 2). In contrast, the proton peaks of pyridine units shifted downfield from 8.0, 8.8 to 8.2, 9.0 ppm (Fig. 2), respectively. These data indicate that naphthalene groups of DSN located inside the cavity of CB[8] and the host-enhanced π - π interaction between CB[8] and DSN was formed indeed.

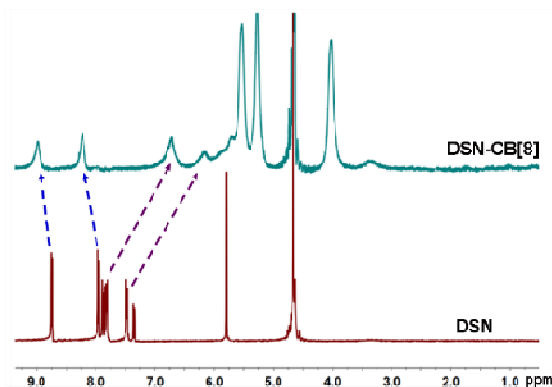


Fig. 2 ¹H NMR spectra of DSN (1 Mm, D₂O), DSN-CB[8] (the molar ratio of CB[8] to DSN is 1:1, 1 Mm, D₂O) at 25 °C.

To further confirm the stoichiometry and binding constant of DSN and CB[8], the isothermal titration calorimetry (ITC) experiment of CB[8] (0.1 mmol/L) titrated by DSN (1.0 mmol/L) was performed. As shown in Fig. 3, the top curve referred to a thermal titration curve recorded simultaneously when DSN was added dropwise into the solution of CB[8]. Additionally, an abrupt change in the titration curve appeared, indicating that the binding stoichiometry of naphthalene units to CB[8] is 2:1. Considering that DSN contains two naphthalene units, it indicates clearly a binding stoichiometry of 1:1 for CB[8] to DSN. Moreover, the binding constant between CB[8] and DSN is estimated to be $1.11 \times 10^6 \text{ M}^{-1}$, which is strong enough for the formation of supramolecular polymers. Therefore, both ^1H NMR and ITC data indicate that CB[8]-enhanced π - π interactions with DSN were successfully formed in the supramolecular polymers.

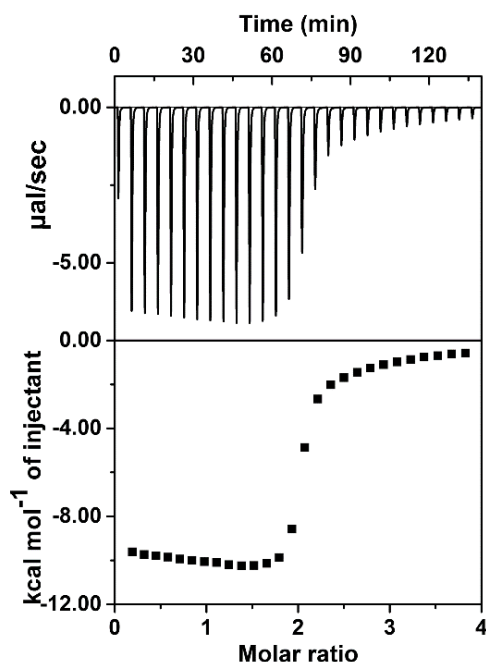


Fig. 3 ITC data for the titration of 0.1 mM CB[8] with 1.0 mM DSN in the buffered aqueous solution (pH=4.75) at 298 K. The molar ratio is defined as naphthalene units to CB[8].

Aimed to characterize the formation of supramolecular polymer, diffusion-ordered NMR spectroscopy (DOSY) was employed to determine the diffusion coefficients before and after supramolecular polymerization.⁶ Comparing with the average diffusion coefficients of CB[8] ($2.95 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$), the supramolecular polymers show an independent and relatively low diffusion coefficient with a value of $5.87 \times 10^{-11} \text{ m}^2 \text{ s}^{-1}$. The significant decrease of the diffusion coefficient implies that large polymeric species has formed. According to Stokes-Einstein equation, the average size of supramolecular polymers (DSN-CB[8]) is calculated to be about 50 times to the CB[8] macrocycles. Therefore, CB[8] can bind with DSN to form supramolecular polymers.

The formation of the supramolecular polymers can be further confirmed through the combination of asymmetric flow field flow fractionation (AsF-FFF), which is an efficient method to obtain the molecular weight and distribution of supramolecular polymers.^{39, 59} Typical elution curves of monomer and

supramolecular polymers were obtained with an ultraviolet detector (Fig. 4). It is noted that the ultraviolet signal of monomer alone was not observed, which indicates that monomer alone can not form large aggregates in the solution. In contrast, when the molar ratio of CB[8] to DSN is 1:1, the intensity of the ultraviolet signal increased, which indicates the formation of supramolecular polymers. The average molecular weight of the supramolecular polymers was calculated to be $5 \times 10^5 \text{ g mol}^{-1}$ with a polydispersity of 1.2. In addition, the average degree of supramolecular polymerization was calculated to be about 200. Therefore, we have successfully fabricated supramolecular polymers with high molecular weight through CB[8]-enhanced π - π interaction between CB[8] and DSN.

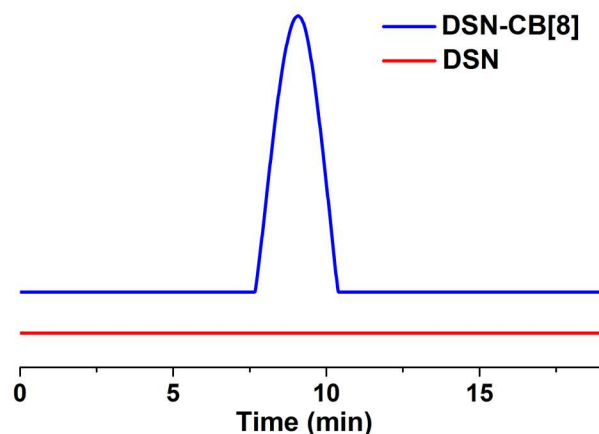


Fig. 4 AsF-FFF elution curves of DSN-CB[8] (0.5 mM) and DSN (0.5 mM) obtained by the ultraviolet detector.

To understand if this supramolecular polymerization can be controlled by adjusting the molar ratio of CB[8] to DSN, a series of DOSY experiments were carried out. As indicated in Fig. 5, increasing the molar ratio of CB[8] to DSN could decrease the diffusion coefficients of the complexes. When the molar ratio between CB[8] and DSN is 1:1, the diffusion coefficient reached the minimum value. Therefore, the supramolecular polymerization can be controlled by adjusting the molar ratio of CB[8] to DSN. Moreover, supramolecular polymers with the highest molecular weight can only be formed when the molar ratio of CB[8] to DSN is 1:1.

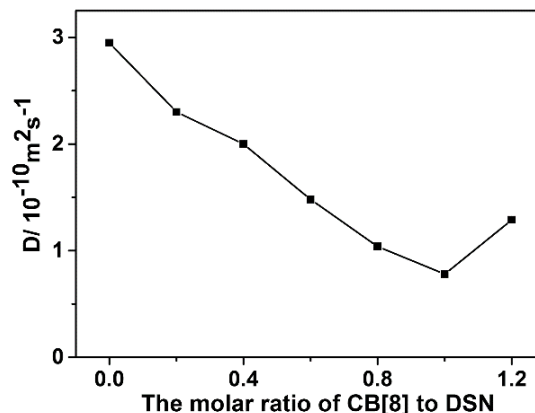


Fig. 5 The diffusion coefficient (D) of DSN (1 mM, D₂O) with different molar ratio of CB[8] at 25 °C.

The dynamic property of host-guest chemistry endows supramolecular polymers with guest competitive responsiveness. We chose 1-adamantanamine hydrochloride (ADA) to induce the depolymerization of supramolecular polymers, due to the high binding constant between CB[8] and ADA ($K_a = 8.19 \times 10^8 \text{ M}^{-1}$).³⁶ Upon adding ADA into the solution of supramolecular polymers, the diffusion coefficient of DSN increases from $5.87 \times 10^{-11} \text{ m}^2 \text{ s}^{-1}$ to $3.22 \times 10^{-10} \text{ m}^2 \text{ s}^{-1}$ (Fig. S1), indicating the decrease of the size of the polymeric species. In other words, it implies that ADA can induce the depolymerization of DSN-CB[8]. Therefore, supramolecular polymers have a guest competitive responsiveness.

The introduction of disulfide bonds into the supramonomers also endows supramolecular polymers with redox responsiveness. Here, L-glutathione (GSH) as a reductant was applied to reduce disulfide bonds in the supramolecular polymers, which may mimic the physiological condition of cell because it can protect the mercapto group in protein from oxidation and reduce the damage caused by free radical species. After adding 1.5 equiv GSH into DSN solution, UV-Vis absorbance of DSN at 275 nm, ascribed to the absorbance of disulfide bond, decreased with extending the reduction time of GSH to 120 min (Fig. S2 and Fig. 6), indicating the breakdown of disulfide bond in DSN. Meanwhile, UV-Vis absorbance at 313 nm increased, indicating the formation of C=S double bond in the reduced product of DSN. These data implied that disulfide bond in DSN was broken, and then a new product was formed after the reduction of GSH. Moreover, UV-Vis absorbance at 265 nm increased upon increasing the oxidation time of H_2O_2 (100 equiv) to 250 min (Fig. S3 and Fig. 7), indicating the formation of the oxidative product of DSN. Furthermore, upon increasing the reduction time of GSH or the oxidation time of H_2O_2 , UV-Vis spectra of supramolecular polymers (Fig. S4 and S5) had similar changes as that of DSN, which indicates the depolymerization of supramolecular polymers by adding GSH or H_2O_2 . Therefore, these supramolecular polymers have good redox responsiveness as designed.

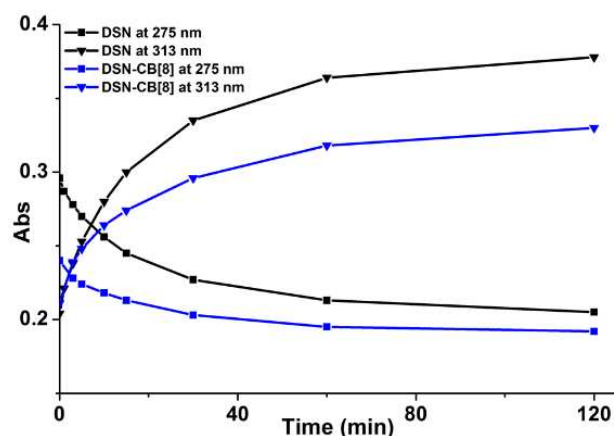


Fig. 6 UV-Vis absorbance at 275 and 313 nm of DSN (10 μM) and DSN-CB[8] (10 μM) upon adding GSH.

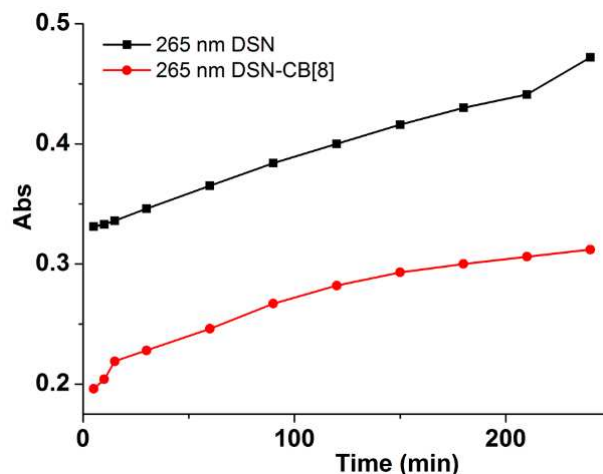


Fig. 7 UV-Vis absorbance at 265 nm of DSN (10 μM) and DSN-CB[8] (10 μM) upon adding H_2O_2 .

Conclusions

In summary, we have demonstrated a new strategy for fabricating supramolecular polymers with multiple stimuli-responsiveness through combining dynamic covalent bond with host-guest chemistry. Moreover, the disulfide bond in the supramonomer and CB[8]-based host-guest chemistry endow these supramolecular polymers with redox and guest competitive responsiveness, respectively. Considering that various disulfide bonds bearing supramolecular polymers can be fabricated with similar methodology, this work may enrich the field of functional supramolecular polymers, which have potential applications in the fields of biomaterials, drug release, to name a few.

Acknowledgements

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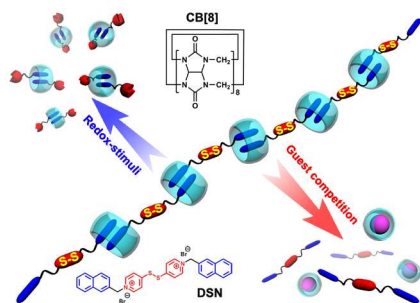
Notes and references

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Supramolecular polymers bearing disulfide bonds have successfully been fabricated through combining dynamic covalent bond with host-guest chemistry.

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