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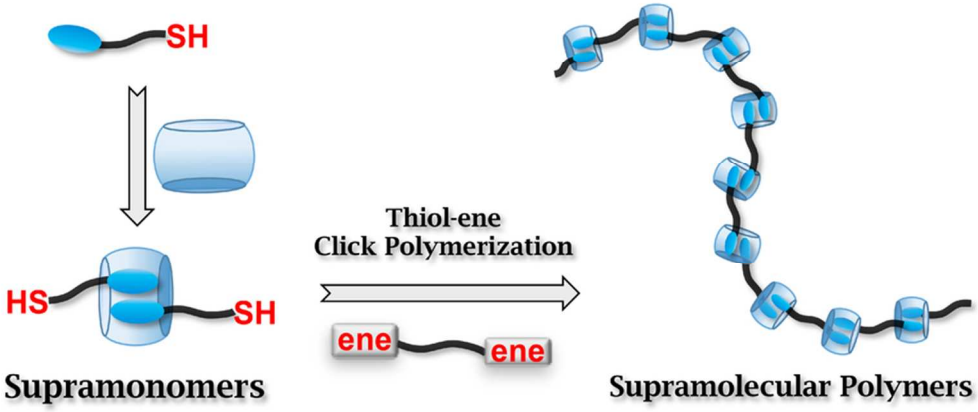


This communication describes supramolecular polymers fabricated by thiol-ene click polymerization from supramonomers
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# Supramolecular polymers synthesized by thiol-ene click polymerization from supramonomers

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Qiao Song, Fei Li, Liulin Yang, Zhiqiang Wang and Xi Zhang*

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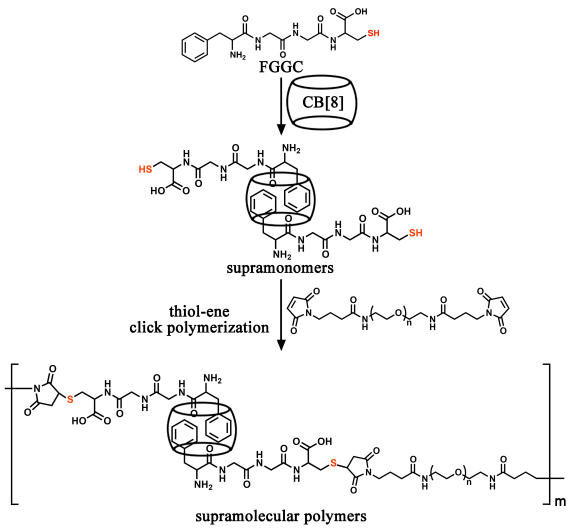
**This communication describes the fabrication of supramonomers based on supramolecular complexation between cucurbit[8]uril and the tetrapeptide Phe-Gly-Gly-Cys. The supramolecular polymers are obtained by thiol-ene click polymerization of the supramonomers with maleimide-terminated poly (ethylene glycol). Benefiting from the green and pH dependent nature of thiol-ene click reaction, it is expected that this line of research will enrich the methodology for fabricating supramolecular polymers with controlled compositions and structures**.

Supramolecular polymers refer to polymers whose monomers are connected through noncovalent interactions.[1-13] Conventional supramolecular polymers are constructed by noncovalent polymerization of covalent monomers. In this way, bifunctional monomers should first be covalently synthesized. Then supramolecular polymers are fabricated on the basis of various noncovalent driving forces, including hydrogen bonding, metal-coordination, π-π interaction, host-guest interaction and so on.[14-25] In contrast, we have proposed a method for fabricating supramolecular polymers by polymerization of supramonomers. Compared to typical monomers, supramonomers are monomers which are constructed by noncovalent synthesis, which are able to further polymerize through conventional polymerization process.[26-28] In this regard, we successfully convert the spontaneous process of supramolecular polymerization into easy-controllable covalent polymerization, which provides a new perspective on the fabrication of supramolecular polymers with controlled compositions and structures.

In this work, we designed supramonomers based on the specific host-guest supramolecular complexation of CB[8] and a tetrapeptide, Phe-Gly-Gly-Cys (FGGC), as shown in Scheme 1 (Supporting Information Fig. S1). It is reported that Phe-Gly-Gly group can bind strongly with CB[8] in a molar ratio of 2:1, which allows for the formation of supramonomers with well-defined compositions.[29-30] The resultant supramonomers bear one thiol function group on each end, which is ready for the subsequent thiol-ene polymerization with maleimide terminated poly (ethylene glycol) (Mal-PEG-Mal, $M_n$=2 kDa, Supporting Information Fig. S2-S3). It should be noted that the thiol-ene click reaction between thiol group and maleimide group is of high efficiency and widely utilized in the fields of bioconjugation and polymer synthesis for its mild reaction condition and controllable reaction rate,[31-40] thus allowing us to achieve controllable supramolecular polymerization through polymerization of supramonomers.




Scheme 1 Supramolecular polymers synthesized by thiol-ene click polymerization from supramonomers.

Supramonomers were fabricated by mixing FGGC and CB[8] in a molar ratio of 2:1 in aqueous solutions. The formation of supramonomers was confirmed by $^1$H NMR, electrospray ionization mass spectrometry (ESI-MS) and isothermal titration calorimetry (ITC). As shown in $^1$H NMR spectra (Fig. 1), peaks at 7.4 ppm and 7.2 ppm ascribable to benzene ring of FGGC shifted to higher field after the complexation of FGGC and CB[8], while no residual signals from free FGGC were detected, indicating that FGGC and CB[8] form a complex and the binding ratio should be 2:1. ESI-MS spectrum showed a molecular ion peak with mass/charge ratio of

1047.84, which is in good accordance with the calculated molecular weight of supramonomers with two positive charges (Supporting Information Fig. S4). Furthermore, as shown in the ITC results (Fig. 2), complexation induced a significant change in the titration curve when 2 equivalent of FGGC was added into the solution of CB[8]. Two sets of binding sites model was utilized to fit the isothermal titration curve, which gave a binding constant estimated to be $1.0\times10^{12}$ $M^{-2}$. All of these results confirm the supramonomers are successfully fabricated due to the strong specific host-guest complexation of FGGC and CB[8].

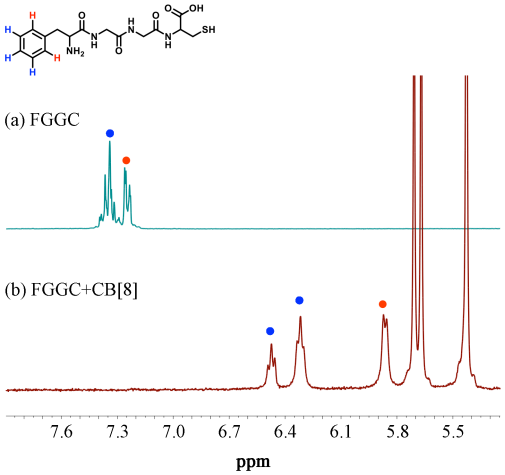



Fig. 1 $^1$H NMR spectra of (a) FGGC, (b) supramonomers ($D_2O$, 400 MHz).

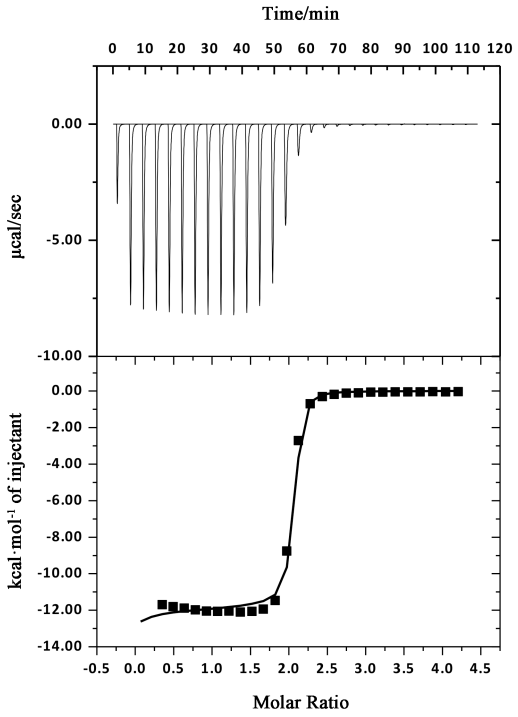



Fig. 2 ITC data for titration of CB[8] (0.1 mM) with FGGC (2.0 mM) in 50 mM sodium phosphate (pH = 7.0) at 25 °C. Fitting data using two sets of binding sites model gave a binding constant of $1.0\times10^{12}$ $M^{-2}$.

Supramolecular polymers were constructed by adding Mal-PEG-Mal into the aqueous solution of the supramonomers in an equivalent molar ratio. Thiol-ene reaction between supramonomers and Mal-PEG-Mal belongs to a class of catalyst-free click reactions, which is widely used in polymer synthesis. As indicated in the $^1$H NMR (Supporting Information Fig. S5), the maleimide peak at 6.8 ppm totally disappeared after 24 h reaction at 35 °C, while peak at 1.6 ppm belonging to the methyl group besides the thiol group shifted to 1.7 ppm, indicating the completion of the click polymerization.

Diffusion-ordered NMR spectroscopy (DOSY) was used to confirm the formation of the supramolecular polymers.[41-42] As shown in Fig. 3(a), the average diffusion coefficient of supramolecular polymers was estimated to be $6.6\times10^{-11}$ $m^2\bullet s^{-1}$, while the diffusion coefficient of supramonomers was $1.7\times10^{-10}$ $m^2\bullet s^{-1}$. Such a decrease in the diffusion coefficient supports the formation of supramolecular polymers. The molecular weight is estimated to be around $3.5\times10^4$ $g\bullet mol^{-1}$ on the basis of Stokes-Einstein equation.

The formation of supramolecular polymers was further confirmed by asymmetric flow field flow fractionation (AsF-FFF). Unlike gel-permeation chromatography, AsF-FFF, belonging to a family of field flow fractionation techniques, is a very mild technique and can significantly reduce the probability of the degradation of supramolecular polymers. Connecting in-line to ultraviolet, differential refraction and multi-angle light scattering detectors, the AsF-FFF has proved to be an efficient technique to determine the molecular weight and the polydispersity of supramolecular polymers.[23,43-44] As shown in Fig. 3(b), the elution curve of supramolecular polymers was obtained by detecting with a differential refraction detector. The molecular weight is calculated to be $2.1\times10^4$ $g\bullet mol^{-1}$, which is close to the DOSY data. In addition, the polydispersity is about 1.3. Therefore, the formation of supramolecular polymers is confirmed.

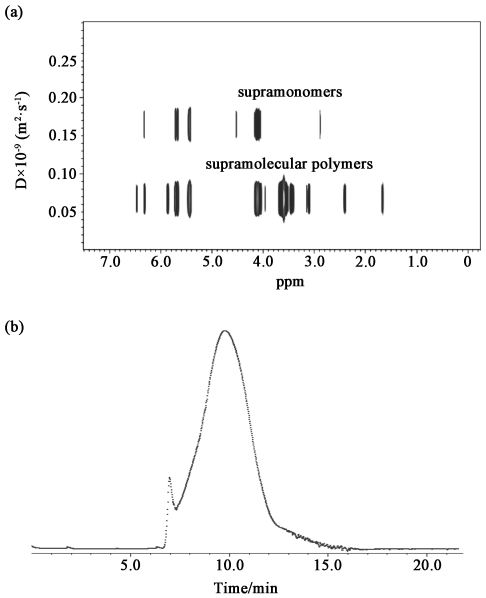



Fig. 3 (a) DOSY of supramolecular polymers and supramonomers. The average diffusion coefficient of supramolecular polymers is estimated to be $6.6\times10^{-11}$ $m^2\cdot s^{-1}$ while supramonomers is $1.7\times10^{-10}$ $m^2\cdot s^{-1}$. (b) AsF-FFF elution curve of supramolecular polymers obtained by differential refraction detector, giving molecular weight as $2.1\times10^4$ $g\bullet mol^{-1}$.

As mentioned above, the thiol-ene click reaction requires no catalyst. Moreover, the reaction rate relies seriously on the pH of the aqueous environment, which enables us to further control the polymerization rate during the formation of supramolecular polymers. Upon monitoring the peak at 6.8 ppm ascribable to maleimide group using in situ $^1$H NMR, we are able to measure and calculate the reaction rate at various pH (See Supporting Information). As shown in Fig. 4, the reaction rate increases rapidly as the increase of pH. The reaction rate constant can be $10^3$ times smaller at pH=0.73 ($9.30\times10^{-4}$ L•mol$^{-1}$•min$^{-1}$) than the rate constant at pH=4.34 (~1 L•mol$^{-1}$•min$^{-1}$), which allows us to control the polymerization rate in a wide range (Table 1). In doing so, we are able to convert the supramolecular polymerization process into easy-controllable thiol-ene click covalent polymerization through pH control. Thus, it is possible to take "snapshots" to investigate the intermediate state of this polymerization process by lowering down the pH to slow down the reaction rate far behind the measurement timescale, which is advantageous to the mechanism study of supramolecular polymerization.

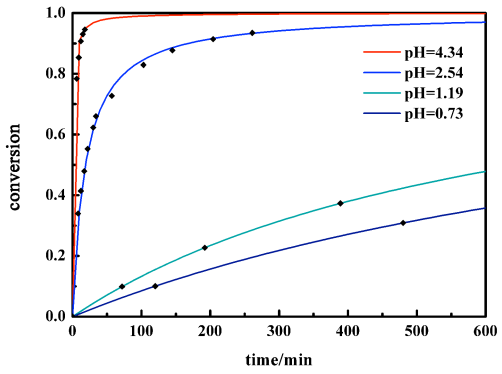



Fig. 4 Conversion of supramonomers and Mal-PEG-Mal at different pH as a function of time monitored by $^1$H NMR at 35 °C while concentration of supramonomers and Mal-PEG-Mal is 2 mM.

Table 1. Reaction rate between supramonomers and Mal-PEG-Mal at different pH.

| pH | 4.34 | 2.54 | 1.19 | 0.73 |
|---|---|---|---|---|
| k/(L·mol$^{-1}$·min$^{-1}$) | ~1 | $5.35\times10^{-2}$ | $1.53\times10^{-3}$ | $9.30\times10^{-4}$ |

## Conclusions

In conclusion, we have successfully fabricated supramolecular polymers through covalent polymerization of supramonomers based on thiol-ene click reaction. Benefiting from the concept of supramonomers, we are able to convert the supramolecular polymerization process into pH-controlled covalent polymerization process. It is anticipated that this concept of supramonomers will provide a new perspective on the fabrication of supramolecular polymers with controlled compositions and structures.

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## Notes and references

The Key Lab of Organic Optoelectronics & Molecular Engineering, Department of Chemistry, Tsinghua University, Beijing 100084, P. R. China.
E-mail: xi@mail.tsinghua.edu.cn
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