Fate of Host-Stabilized Charge Transfer Complexation Based on Cucurbit[8]uril: Inducing Cyclization of PNIPAM and Dissociation in Self-Assembly of the Cyclic Polymer

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Supporting Information

ABSTRACT: Host-stabilized charge transfer (HSCT) complex based on cucurbit[8]uril has been widely used in building novel supramolecular structures, which could further self-assemble into nano-objects. High stability of the HSCT interaction during the assembly process is always assumed or defaulted. However, the stability during self-assembly has never been well characterized in previous studies. In this work, we realized cyclization of linear PNIPAM by CB[8]-based HSCT interaction first. And then we found unexpectedly that during the heating-induced self-assembly of the cyclic PNIPAM, dissociation of the HSCT interaction took place. In this process, charged CB[8] complex was released from the aggregates of the cyclic polymer to solution, and it could be recaptured by newly added guest molecules. This HSCT dissociation was driven by the incompatibility of the hydrophobicity of the PNIPAM aggregates and the cationic nature of the HSCT complex. To the best of our knowledge, this assembly induced dissociation phenomenon has not been reported in literature.

In the past decade, in the studies on supramolecular chemistry, a family of highly symmetrical pumpkin-shaped host molecules of cucurbit[n]uril (CB[n]) has drawn increasing attention due to their variable-sized cavities accessible by certain guests driven by hydrophobic and ion-dipole interactions.1 In this family of host molecules, CB[8] became a newly emerged star molecule because of its unique character in incorporating two kinds of guests simultaneously.2 It was reported that the interaction between an electron-deficient guest such as viologen and an electron-rich guest such as naphthalene could be greatly enhanced when both of them remain in the cavity of CB[8], leading to the host-stabilized charge transfer (HSCT) complex.3 This interaction processed an extremely high association constant, that is, in complexation of 1:1:1 CB[8]/viologen/naphthalene, the constant reaches as high as 1010 M−1 in aqueous solution.4 Since Kim first reported HSCT, by which supramolecular oligomers from small molecules were constructed,5 it has been successfully employed as a driving force to build a plethora of supramolecular structures including cyclic dimer,6 glycolipid,7 block copolymer,8 graft copolymer,9 and supramolecular polymers.10 Besides, further self-assembly of such host–guest supramolecular structures into complex ordered aggregates has inspired great research interest. We noticed that in all the studies, high stability of such HSCT during both the supramolecular structure formation and their further self-assembly are assumed or defaulted. In fact, to the best of our knowledge, the stability of HSCT interactions after self-assembly has not been well characterized in all the previous studies.

Quite recently, we reported unimolecular cyclization of linear polyethylene glycol (PEG) by connecting its functional ends supramolecularly, that is, by CB[8]-stabilized π–π interaction, which was a new strategy in obtaining cyclic polymers characteristic of its reversibility.11 Cyclic polymers usually show distinctively unique characters due to the absence of chain ends, leading to their all repeating units physically and chemically equivalent.12 Typically, due to their more contracted chain structure, cyclic polymers exhibit higher retention time in gel permeation chromatography (GPC), lower intrinsic viscosity, and lower translational friction coefficient than their linear counterpart.13 Although the comparative studies on solution properties of cyclic polymers with their linear counterpart has been carried out extensively, self-assembly of the cyclic polymers responsive to environment has been rarely explored.14

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In this work, there are two points we are concerned with most. First, we employed HSCT to make cyclization of an environmental-responsive polymer. Second, that is even more importantly, we intend to see whether HSCT would keep its stability during the subsequent self-assembly of the cyclic polymers. Thus, for this propose, cyclic polymers from thermoresponsive poly(N-isopropylacrylamide) (PNIPAM) with naphthalene (Np) ends was obtained first by means of HSCT between host CB[8] and guests of viologen dimer (2) and the Np ends. During subsequent self-assembly of the resulted cyclic PNIPAM upon heating, quite unexpectedly, dissociation of the HSCT complex took place as a result of the change in the polarity of the surroundings of the complex. In this process, the Np ends escaped from the CB[8] cavity and free complex of 2 and CB[8] (2 ⊂ CB[8]) was released to solution. Furthermore, reversibility of this dissociation was achieved as the ternary complex and then the cyclic polymer was formed again during cooling.

To prepare a cyclic polymer via CB[8]-based host–guest interaction, Np-end functionalized PNIPAM (P1, M_{n, NMR} = 6370 g/mol, Figure S1) was prepared through RAFT (reversible addition–fragmentation chain transfer) polymerization by utilizing a previously reported CTA (chain transfer agent). GPC (gel permeation chromatography) showed a narrow molecular weight distribution (PDI = 1.12, Figure S2) of the product. Effective incorporation of Np groups at both chain ends of PNIPAM was assessed by $^1$H NMR, showing excellent accordance between the DP (degree of polymerization) calculated from $^1$H NMR (DP_{exp} = 50, relative integration of –NHCH(CH$_3$)$_2$ to the peak belonging to Np) and theoretical value (DP_{theory} = 50, M_{theory} = 6310 g/mol). Then the supramolecular cyclization of the Np-ended PNIPAM was realized by simply mixing P1, viologen dimer 2 and CB[8] together in a highly dilute solution, with the stoichiometry as 1:1:2, which is denoted as P1 + 2 ⊂ CB[8] in this paper (Scheme 1). The success of this procedure was proved in our previous study on cyclic PEG via CB[8]-based inclusion complexation. Successful HSCT inclusion complexation among Np ends of P1, 2, and CB[8] was visualized by the color change from light-yellow to wine-red after addition of equimolar CB[8] to the mixture of 2 and P1 (Figure S3).

The cyclic topology of P1 + 2 ⊂ CB[8] in dilute solution was first supported by its high LCST (lower critical solution temperature) determined by turbidity test (Figure S4). The LCST of P1 + 2 ⊂ CB[8] was measured as 24.4 °C at 0.2 mg/mL of P1, 2.8 °C higher than its linear counterpart, which was formed by P1, monotopic viologen 3, and CB[8], denoted as P1 + 3 ⊂ CB[8] (Scheme S1). This high LCST phenomenon was similar to covalently cyclized PNIPAM. More convincing result supporting cyclization came from the comparative viscometry of P1 + 2 ⊂ CB[8] and P1 + 3 ⊂ CB[8] measured at 15 °C. It is known that the intrinsic viscosity of cyclic polymer is significantly lower than the linear one under the same molecular weight. As shown in Figure 1a, at all examined concentrations (P1 < 0.1 mM), P1 + 2 ⊂ CB[8] provided a lower relative viscosity than that of P1 + 3 ⊂ CB[8]. Considering the high similarity between these two supramolecular systems, we deduced that the viscosity decrease of P1 + 2 ⊂ CB[8] in dilute concentrations was caused by the conformation transformation of PNIPAM from linear to cyclic. The calculated inherent viscosity ratio ([$\eta$]_{exp}/[$\eta$]_{theory}) of P1 + 2 ⊂ CB[8] to P1 + 3 ⊂ CB[8] (Figure 1b) was about 0.72 at concentrations below 0.5 mg/mL of P1, close to, but larger than, the theoretical value of 0.66, probably due to the reversible linkage composed of CB[8] and the guest species. The value increased to 0.76 at a higher concentration of 0.6 mg/mL of P1, indicating the appearance of a slight amount of oligomers. In short, this viscosity result was very similar to that of our previous cyclic PEG system, proving the successful cyclization of PNIPAM driven by CB[8]-based HSCT interaction.

The self-assembly of cyclic P1 + 2 ⊂ CB[8] and linear P1 + 3 ⊂ CB[8] during a slow heating process was then examined comparatively by laser light scattering (LLS) in detail. Temperature dependence of their dynamic radii (⟨R_h⟩) is shown in Figure 2a. This routine measurement was started at 25 °C for P1 + 2 ⊂ CB[8] and 22 °C for P1 + 3 ⊂ CB[8], as below this temperature, the scattered light intensity was too low to give a rational ⟨R_h⟩ (Figure S5). It was found that during heating, the two supramolecular systems exhibit a similar ⟨R_h⟩ tendency, both increasing gradually at early stage and reaching a constant plateau at a high temperature, while in the whole tested temperature range, the particle size of the cyclic polymer was always smaller than that of the linear one. Because P1 + 2

![Figure 1.](image1.png)

![Figure 2.](image2.png)
CB[8] has less extended conformation and less active chain ends compared to its linear counterpart, it is less likely to assemble intermolecularly, which always results in a higher LCST and smaller particle size. Moreover, similar tendency was observed in temperature dependence of average aggregation number \( \langle N_{agg} \rangle \), which was measured from static light scattering measurements, that is, the ratio of the weight-average molar masses of the resultant particles to those of individual polymer chains (Figure 2b). Guinier approximation (Figures S6 and S7) was employed here due to the large particle size. At 38 °C, \( \langle N_{agg} \rangle \) of \( P1 + 2 \subset CB[8] \) reached \( \sim 1.7 \times 10^8 \) g/mol, which was half of that of \( P1 + 3 \subset CB[8] \) (\( \sim 3.5 \times 10^8 \) g/mol) at the same temperature.

With the above data in hand, we tried to monitor evolution of the HSCT interaction during the heat-induced self-assembly of \( P1 + 2 \subset CB[8] \) by variable temperature-\(^1\)H NMR (VT-\(^1\)H NMR). As shown in Figure 3, the peaks belonging to the 2-naphthol was selected to replace CB[8] without Np group (denoted as \( CB[8] \)) at 25 °C, both of the peaks belonging to viologen and 2-naphthol kept constant, indicating the high stability of the HSCT interaction upon heating. This result was completely different from that of \( P1 + 2 \subset CB[8] \) at the same temperature range, clearly showing that the observed dissociation of HSCT interaction in the cyclic PNIPAM was not the direct consequence of temperature increase. In addition, the dissociation of HSCT interaction was found totally reversible, that is, as detected by VT-\(^1\)H NMR (Figure S8), the spectrum of \( P1 + 2 \subset CB[8] \) returned to its original state showing the characters of the HSCT ternary complex upon cooling from 36 to 20 °C.

To explore this unexpected dissociation of HSCT interaction further, VT-\(^1\)H NMR on the PNIPAM chain of \( P1 + 2 \subset CB[8] \) was investigated. Figure 4a showed the ratio of the peak intensity of -NHCH(CH\(_3\)) (\( \delta 3.8 \) ppm) of PNIPAM to that of its solvated state (\( I_{PNIPAM} \)) during heating. From 20 to 29 °C, \( I_{PNIPAM} \) was around 95%, indicating that PNIPAM kept full hydration in its single chain stage as well as in the loose aggregates formed in 25–29 °C. A sharp decrease of \( I_{PNIPAM} \) was observed from 29 to 36 °C, where gradual dissociation of the HSCT interaction was found (Figure 3) as well. This meant that the tight aggregation of polymer chains was accompanied by the dissociation of HSCT interaction. Furthermore, zeta potential was employed to track the positively charged viologen

**Figure 3.** \(^1\)H NMR of (a) 2; \( P1 + 2 \subset CB[8] \) at 0.4 mg/mL (calculated as \( P1 \)) at (b) 20, (c) 21, (d) 23, (e) 25, (f) 27, (g) 29, (h) 31, (i) 33, (j) 36 °C; (k) \( P1 + 2 \subset CB[8] \) at 25 °C; (l) \( P1 + 2 \subset CB[8] \) at 36 °C after subsequent addition of Np-PDMA in \( D_2O \). Triangle shows the peaks belonging to Np groups in \( P1 + 2 \subset CB[8] \).

**Figure 4.** (a) Relative peak intensity of -NHCH(CH\(_3\)) (\( \delta 3.8 \) ppm) of \( P1 \) in \( P1 + 2 \subset CB[8] \) ([\( P1 \) = 0.4 mg/mL) and (b) zeta potentials of \( P1 + 2 \subset CB[8] \) ([\( P1 \) = 0.1 mg/mL) during heating.
A complex of aggregates was more favorable and meanwhile, the charged CB[8] cavities as for which the hydrophobic PNIPAM HSCT interaction, that is, the Np end groups escaped from the hydrophilic to hydrophobic. This led to the dissociation of the change of the surroundings of the HSCT complex, that is, from compact particles via dehydration, which caused a dramatic PNIPAM chains further rearranged in close packing to form.

Thus, the whole process can be described and explained as follows (Scheme 2). During the initial aggregation of the cyclic PNIPAM (from 25 to 29 °C), the HSCT interaction was stable and was immersed in the interior of the early stage aggregates as which was still highly hydrated. Then from 29 to 36 °C, PNIPAM chains further rearranged in close packing to form compact particles via dehydration, which caused a dramatic change of the surroundings of the HSCT complex, that is, from hydrophilic to hydrophobic. This led to the dissociation of the HSCT interaction, that is, the Np end groups escaped from the CB[8] cavities as for which the hydrophobic PNIPAM aggregates was more favorable and meanwhile, the charged complex of 2⊂CB[8] were released. This interpretation could find strong supports as follows. From VT-1H NMR, no obvious chemical shift and narrowing of the low signals from Np groups were observed upon heating, indicating that when HSCT dissociated, Np existed in a confined hydrophobic environment. Furthermore, during dissociation of HSCT, a large amount of the free charged 2⊂CB[8] was released to the solution as small molecular complex. This was evidenced by an supplementary experiment: addition of Np-ended hydrophilic poly(methyl methacrylate) (Np-PDMA) into the mixture of P1, 2, and CB[8] at 36 °C resulted in obvious peak broadening and an intensity decrease of protons from Np and viologen in 1H NMR (Figure 3). This clearly indicated the formation of HSCT complex from the Np end group and 2⊂CB[8] existing in solution. Here Np-PDMA (Mn,NMR = 8000 g/mol, Figure S10) was deliberately chosen because its long soluble PDMA chain hardly penetrates into the aggregates and thus could only capture free 2⊂CB[8] in solution.

In conclusion, we demonstrated the successful preparation of dynamic cyclic PNIPAM via the CB[8]-stabilized charge transfer interaction. The cyclic topology exerted stringent restrictions on backbone conformation, leading to higher LCST and smaller aggregates during phase transition, compared to its linear counterpart. More importantly and unexpectedly, dissociation of the HSCT interaction during the self-assembly of the cyclic PNIPAM was observed, which has never been reported in literature. The result indicates that the newly formed hydrophobic environment during self-assembly disrupts the rather stable HSCT interaction, leading to the exclusion of hydrophilic viologen/CB[8] complex to aqueous solution and embedment of the hydrophobic Np moiety in the aggregate. Finally, the take-home message of this paper is that the assembly induced dissociation phenomenon cannot be ignored in future studies.

ASSOCIATED CONTENT

S Supporting Information
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Characterization of P1, including 1H NMR and GPC results, as well as a turbidity test (PDF).

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Notes
The authors declare no competing financial interest.

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