

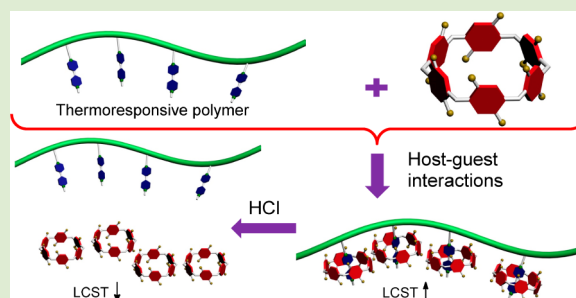
# pH-Responsive Supramolecular Control of Polymer Thermoresponsive Behavior by Pillararene-Based Host–Guest Interactions

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## Supporting Information

**ABSTRACT:** We demonstrate precise control of the lower critical solution temperature (LCST) behavior of a thermoresponsive polymer in water by pillararene-based host–guest interactions. The LCST value of the polymer increases upon the stepwise addition of either of the two pillararene hosts. On account of the pH-responsiveness of the pillararene-based host–guest interactions, the recovery of the LCST is achieved by treatment with acid, reflecting the pH-responsive supramolecular control of the LCST.



Thermoresponsive polymers,<sup>1</sup> materials that exhibit an inverse phase behavior in solution, have received much attention in the field of smart materials due to their practical applications, including controlled drug delivery,<sup>2</sup> smart surfaces,<sup>3</sup> biomaterials,<sup>4</sup> and molecular separation.<sup>5</sup> These materials are soluble in solution below a certain temperature, the lower critical solution temperature (LCST),<sup>6</sup> and undergo phase separation when the temperature exceeds the LCST. One explanation for this unique phase transition is the competition of two kinds of interactions: one is the hydrogen bonding interactions between the polymers and the surrounding water molecules, and the other is the intra- and intermolecular hydrogen bonding interactions between polymers.<sup>7</sup> At low temperature, the former interactions dominate. Upon heating, the intra/interpolymer interactions increase, and polymer aggregation occurs when the temperature reaches the LCST, resulting in phase transition.<sup>7</sup> Consequently, the LCST can be increased by incorporating hydrophilic components and reduced by merging hydrophobic components on the thermoresponsive polymer. However, intricate and tedious organic and/or polymer synthesis and purification processes were usually needed to introduce these components. In recent years, the use of supramolecular interactions to tune the LCSTs of thermoresponsive polymers is a new research hotspot because this method is facile and environmentally friendly, just by mixing thermoresponsive polymers with the corresponding supramolecular compounds in solution.<sup>8,9</sup> Environmental responsiveness is a very important feature for supramolecular complexes because it can create adaptive supramolecular materials by changing their structures and/or adjusting their arrays. However, environmental responsiveness of the supramolecular control of the LCST of thermoresponsive polymers has been rarely reported.<sup>8,9</sup>

Pillararenes,<sup>10</sup> a new generation of supramolecular macrocyclic hosts after crown ethers, cyclodextrins, calixarenes, cucurbiturils, and other macrocyclic hosts,<sup>11</sup> have developed vigorously thanks to their unique structures and high functionality, bringing along many applications in the fabrication of interesting and functional supramolecular systems.<sup>10</sup> In this communication, we demonstrate that we can realize pH-responsive control of the LCST behavior of a thermoresponsive polymer in water using pillararene-based host–guest interactions. This is the first time that pillararene-based host–guest interactions are used to control the LCST behavior of a thermoresponsive polymer.

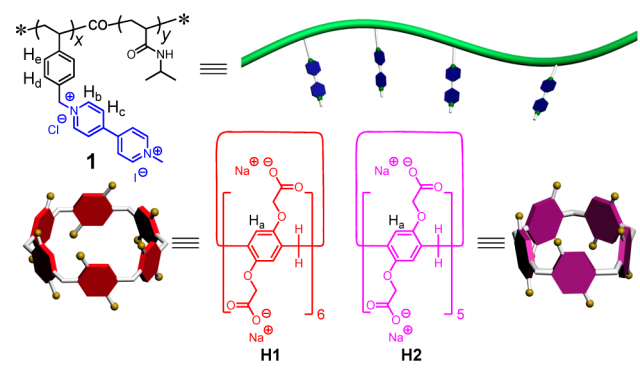
As shown in Scheme 1, polymer **1** is a random copolymer of NIPAAm and styrene with paraquat derivative (*N,N'*-dialkyl-4,4'-bipyridinium) pendants, and it shows phase separation in water as the temperature increases. As demonstrated before, paraquat can form 1:1 supramolecular complexes in water with water-soluble pillar[6]arene **H1** and pillar[5]arene **H2**.<sup>10a,e,f</sup> Therefore, side-chain polypseudorotaxanes<sup>11a,c</sup> will form after the addition of **H1** or **H2** to an aqueous solution of **1**, influencing the thermosensitive behavior of **1** and changing its LCST value. Due to the pH-responsiveness of these pillararene/paraquat host–guest interactions,<sup>10a,e,f</sup> the supramolecular hosts can be removed by adding acid to the solution, resulting in the recovery of the LCST value.

Polymer **1** was synthesized according to the synthetic route in the Supporting Information (SI, Scheme S1). The number-average molecular weight of copolymer **1** was determined to be  $M_n = 2.7 \times 10^4$ , using gel-permeation chromatography (GPC) with polystyrene standards. The ratio of the NIPAAm units to

Received: October 18, 2013

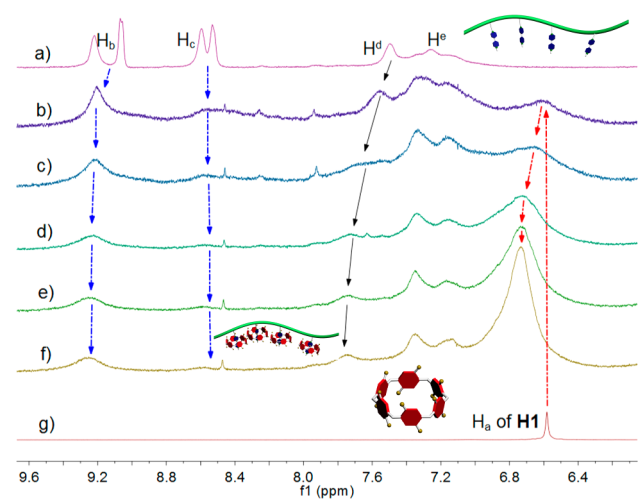
Accepted: January 2, 2014

Published: January 6, 2014

**Scheme 1. Cartoon Representation of Thermoresponsive Copolymer 1 and Water-Soluble Pillararene Hosts H1 and H2**


the paraquat derivative moieties was 13:1 as measured by  $^1\text{H}$  NMR (SI, Figure S2). Therefore, it can be calculated that there were about 17 paraquat derivative moieties per single polymer chain. To investigate the LCST behavior of **1** in water, turbidity measurements were carried out.<sup>8,9</sup> Figure S5 (SI) shows the change in transmittance of **1** with increasing temperature. A sudden change in transmittance was observed at 40.5 °C upon heating, and the optically clear aqueous solution became turbid. The fact that the turbidity point of copolymer **1** was higher than that of poly(NIPAAm) (around 32.0 °C) was due to the hydrophilic paraquat derivative because they not only enhance the solubility in water but also disrupt the intermolecular assemblies through their negative charges.<sup>1f,8</sup>

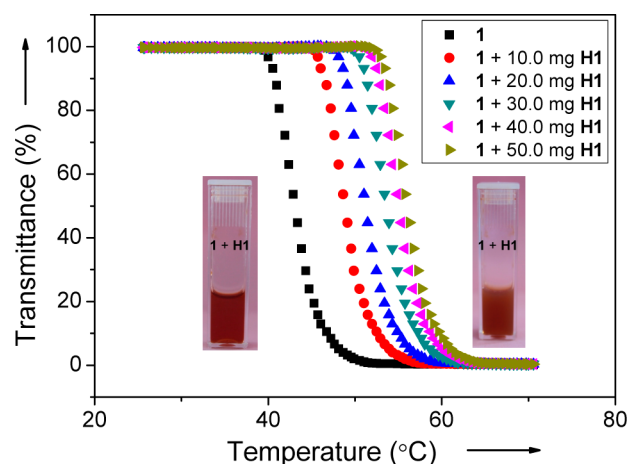
Here, we used two water-soluble pillararenes, **H1** and **H2**, with different cavity sizes to study the host size effect on the supramolecular control of the thermoresponsive behavior of copolymer **1**. First, **H1** whose cavity size was larger than that of **H2** was investigated. To confirm the complexation of **H1** with the paraquat derivative moieties pendent on copolymer **1**, proton  $^1\text{H}$  NMR titration of **H1** into a 1.11 mM solution of **1** in  $\text{D}_2\text{O}$  was performed. From Figure 1, we can see that the



**Figure 1.** Partial  $^1\text{H}$  NMR spectra ( $\text{D}_2\text{O}$ , 298 K, 400 MHz) of copolymer **1** at a concentration of 1.11 mM (30.0 mg/mL) with different concentrations of **H1**: (a) 0.00 mM; (b) 3.80 mM; (c) 7.60 mM; (d) 11.4 mM; (e) 15.2 mM; (f) 19.0 mM. (g) Partial  $^1\text{H}$  NMR spectrum ( $\text{D}_2\text{O}$ , 298 K, 400 MHz) of **H1** at a concentration of 1.11 mM.

signals of protons on both **H1** and paraquat moieties exhibited obvious changes with the increasing concentration of **H1**. Downfield chemical shift changes were found for aromatic protons  $\text{H}_a$  of **H1** (shifted from 6.582 to 6.734 ppm gradually,  $\Delta\delta = 0.152$  ppm) and protons  $\text{H}_d$  of copolymer **1** (shifted from 7.495 to 7.755 ppm gradually,  $\Delta\delta = 0.260$  ppm), which was coincident with a known pillar[6]arene/paraquat complexation system in water.<sup>10e</sup> Moreover, protons  $\text{H}_b$  and  $\text{H}_c$  on the viologen group of **1** not only changed from two peaks to one peak but also became broad after association with **H1**. These results proved the existence of **H1**/paraquat complexes in the mixture as a side-chain-type polypseudorotaxane.

Next the influence of **H1** on the thermoresponsive behavior of copolymer **1** was studied by turbidity measurements. As shown in Figure 2, the LCST of copolymer **1** was 40.5 °C in



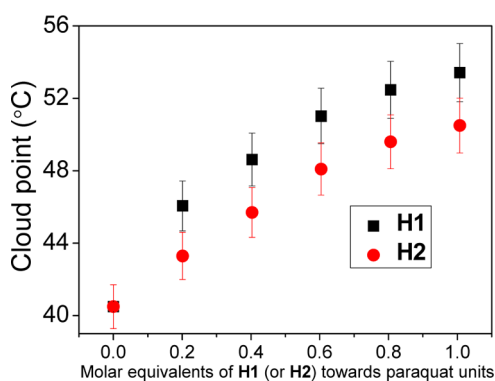
**Figure 2.** Transmittance changes (550 nm) of copolymer **1** (45.0 mg in 1.5 mL of  $\text{H}_2\text{O}$ , 1.11 mM) with the addition of different amounts of **H1** (from 3.80 to 7.60, 11.4, 15.2, and to 19.0 mM).

the absence of **H1**. By increasing the amount of **H1** added to the aqueous solution of copolymer **1**, the LCST rose continuously. The reason was that the formation of supramolecular complexes prevented the shrinking of the polymer chains in solution.<sup>1,6,7</sup> Since the **H1**/paraquat complexes owned more water-soluble groups and bigger volume compared to the paraquat moieties, the polypseudorotaxane had better solubility in water, and the increased electrostatic repulsion and steric hindrance inhibited intra/interpolymer aggregation. Moreover, from the inset photographs in Figure 2, a distinct change of solubility was also observed in the heating process.

Supramolecular host **H2** with a smaller cavity size was also used for comparison. Similarly,  $^1\text{H}$  NMR titration was carried out (SI, Figure S6). With increasing concentration of **H2**, both the aromatic protons  $\text{H}_a$  of **H2** and protons  $\text{H}_d$  of copolymer **1** shifted downfield, and protons  $\text{H}_b$  and  $\text{H}_c$  of **1** became broad, indicating the formation of host–guest complexes. However, the chemical shift change of protons  $\text{H}_a$  of **H2** ( $\Delta\delta = 0.101$  ppm) was smaller than that of **H1** ( $\Delta\delta = 0.152$  ppm), as were protons  $\text{H}_d$  ( $\Delta\delta = 0.097$  ppm). The fact that the association constant for the complexation between **H1** and paraquat in water was much higher than that of the complexation between **H2** and paraquat could account for this phenomenon.<sup>10a,e,f</sup>

Turbidity measurements were also used to investigate the effect of **H2** on the LCST value of copolymer **1** (SI, Figure S7). Upon adding **H2** to an aqueous solution of **1**, the LCST of **1** increased gradually, suggesting the same supramolecular effect

on the LCST behavior as **H1**. To compare the two supramolecular hosts in detail, we plotted the turbidity temperatures against the molar equivalents of **H1** (or **H2**) toward paraquat units in water (Figure 3).<sup>8</sup> A stepwise increase



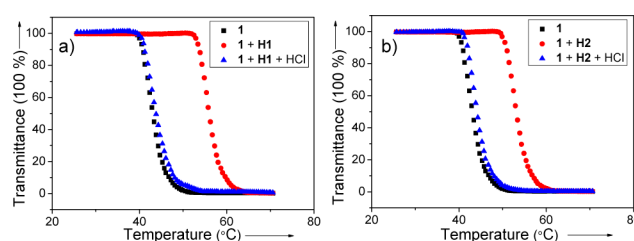
**Figure 3.** Turbidity temperatures plotted against the molar equivalents of **H1** (or **H2**) toward paraquat units in water.

of the molar equivalents from 0.201 to 1.01 led to a continuous increase of the turbidity temperature. The cloud point of the mixture of **1** and **H2** changed from 43.3 to 50.5 °C, while that of the mixture of **1** and **H1** changed to a wider extent, from 46.1 to 53.4 °C. This result was caused by the difference in the structures of the two supramolecular hosts. First, in contrast to **H2**, the cavity size of **H1** was bigger, bringing about stronger steric hindrance to inhibit the shrinking of polymer chains. Second, there were more negatively charged groups on **H1** compared to **H2**, enhancing the solubility of **H1** in water and increasing the electrostatic repulsion between polymers. On the basis of the above reasons, the supramolecular host **H1** had more influence on the LCST behavior of copolymer **1** than **H2**.

Transmission electron microscopy (TEM) and dynamic light scattering (DLS) measurements (SI, Figures S8 and S9) revealed the pillararene-based supramolecular effects on the aggregation of copolymer **1** in water at different temperatures. For copolymer **1**, its aggregates were nanoparticles with size about 50.8 nm at 30 °C (SI, Figures S8a and S9a), which was below its LCST. Heating the solution to 45 °C, above the LCST, led to the emergence of nanoparticles with an increased size, 255 nm on average (SI, Figures S8b and S9b). The increase in size was the result of polymer aggregation when the aqueous solution was heated above the LCST. When supramolecular host **H1** was added to an aqueous solution of copolymer **1** at 45 °C, forming a side-chain-type polypseudorotaxane and improving the solubility of the copolymer in water, nanoparticles with a relatively smaller size formed (SI, Figures S8c and S9c). This phenomenon indicated that the formation of **H1**/paraquat complexes had increased the LCST of copolymer **1**. Next, after the temperature was raised to 60 °C, exceeding the LCST of the polypseudorotaxane (Figure 2), the polypseudorotaxane gathered together and formed particles with a bigger size (SI, Figures S8d and S9d). Supramolecular host **H2** also improved the LCST of copolymer **1** (SI, Figures S8e and S9e) and had a similar effect on the aggregation of copolymer **1** (SI, Figures S8f and S9f).

On the other hand, because the carboxylic groups on the rims of **H1** and **H2** could be protonated to insoluble carboxylic acid groups,<sup>10a,e,f</sup> the molecular recognition between **H1** (**H2**) and paraquat was pH-responsive in water. Thus, the supramolecular hosts could be removed from copolymer **1** by adding

acid, recovering the previous LCST. <sup>1</sup>H NMR experiments provided convincing evidence for this process (SI, Figures S10 and S11). When enough aqueous HCl solution was added to a mixture of **H1** (**H2**) and **1** (pH = 6.0), the chemical shifts of protons H<sub>b</sub>, H<sub>c</sub>, and H<sub>d</sub> returned nearly to their original positions, and the signals for protons H<sub>a</sub> disappeared, demonstrating the disassociation of the supramolecular complexes. Furthermore, correspondingly, the turbidity temperature of **1** reduced almost to the initial value upon treatment with acid (Figure 4).



**Figure 4.** Transmittance changes (550 nm) of copolymer **1** (45.0 mg in 1.50 mL of H<sub>2</sub>O, 1.11 mM), copolymer **1** with the addition of (a) **H1** (19.0 mM) and the mixture of **H1** (19.0 mM) and HCl aqueous solution (42.0 μL), respectively, and copolymer **1** with the addition of (b) **H2** (19.0 mM) and the mixture of **H2** (19.0 mM) and HCl aqueous solution (36.0 μL), respectively.

In conclusion, we have demonstrated precise control of the LCST behavior of copolymer **1** in water by pillararene-based host–guest interactions. Since the supramolecular complexes made a considerable contribution to the solubility of copolymer **1** in water and the restraint of interpolymer aggregation, the LCST value of the polymer increased readily upon the stepwise addition of supramolecular host **H1** or **H2**. Because of the difference in cavity size and the amount of water-soluble groups, the two supramolecular hosts changed the LCST to different extents. More importantly, on account of the pH-responsiveness of the host–guest interactions, the recovery of the LCST was achieved by the treatment with acid, reflecting the pH-responsive supramolecular control of the LCST. As far as we know, the supramolecular control of polymer thermoresponsive behavior by pillararene-based molecular recognition has not been reported before. Therefore, this study can not only promote the development of supramolecular chemistry but also enrich thermosensitive systems. We are currently exploring temperature-sensitive hydrogels and temperature sensors with the use of water-soluble pillararene-based host–guest interactions.

## ■ ASSOCIATED CONTENT

### 📄 Supporting Information

Full experimental details and characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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### Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

This work was supported by National Basic Research Program (2013CB834502), the National Natural Science Foundation of China (21125417), the Fundamental Research Funds for the Central Universities, and the Key Laboratory of Supramolecular Structure and Materials.

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