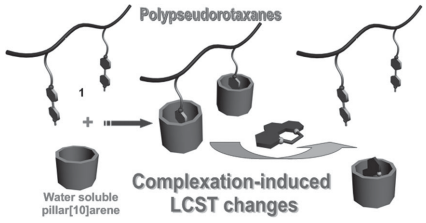
Pillar[10]arene-Based Size-Selective Host–Guest Complexation and Its Application in Tuning the LCST Behavior of a Thermoresponsive Polymer

Guocan Yu,* Jiong Zhou, Xiaodong Chi

A new molecular recognition motif between a water soluble pillar[10]arene (**WP10**) and 1,10-phenanthrolinium guest (**G**) in water is established. Mainly driven by the cooperativity of multiple electrostatic interactions, hydrophobic interactions, and π–π stacking interactions between **WP10** and **G**, this host–guest complex exhibits a high association constant in water, which is about 17 times higher than that between **WP10** and paraquat (**PQ**). Furthermore, this size selective host–guest complexation is employed to tune the lower critical solution temperature behavior of a random copolymer with **PQ** derivative pendants.



1. Introduction

Over the past decades, stimuli-responsive polymers, which can respond to environmental stimuli, such as pH change, temperature change, light, redox, and ionic strength, have attracted remarkable attention and shown great potential in various biomedical applications, including sophisticated drug/gene delivery, cell culture, tissue engineering, and biosensors.[1] Among them, water-soluble thermoresponsive polymers exhibiting lower critical solution temperature (LCST) behavior are one of the most appealing stimuli-responsive species due to their potential biomedical applications.[2] Examples of LCST polymers include poly(*N*-isopropylacrylamide) (PNIPAAM), poly(poly(ethylene glycol) methacrylate), and elastin-like proteins, of which PNIPAAM has been the most studied thermoresponsive polymer. When the temperature is below LCST, the polymer chains are in random coil conformation and totally soluble in water arising from the hydrogen-bonding interactions between the polymer and water molecules. However, the hydrogen bonds are weakened and the polymer chains collapse into globule conformation and precipitate from the solution as the temperature increases.[3]

Since the LCST is determined by the capability of the repeat units to form hydrogen bonds with water molecules, the LCST can be tuned both by the choice of the comonomers and by the change of the composition, according to the needs in the designated applications. By introducing hydrophilic or hydrophobic moieties into the polymer, the corresponding cloud-point temperature (T_{cp}) can be increased or decreased, respectively.[4] Unfortunately, each copolymer requires a new polymerization process, which needs intricate and tedious organic and/or polymer synthesis and time-consuming purification. Due to the dynamic and reversible nature of noncovalent interactions, such as electrostatic interactions, π–π stacking, hydrogen bonding, and hydrophobic interactions, supramolecular functionalizations exhibit huge advantages.[5] In sharp contrast to covalent modifications, the LCST can be reversibly regulated and precisely controlled by employing various noncovalent

G. Yu, J. Zhou, X. Chi
Department of Chemistry, Zhejiang University, Hangzhou 310027, China
E-mail: guocanyu@zju.edu.cn

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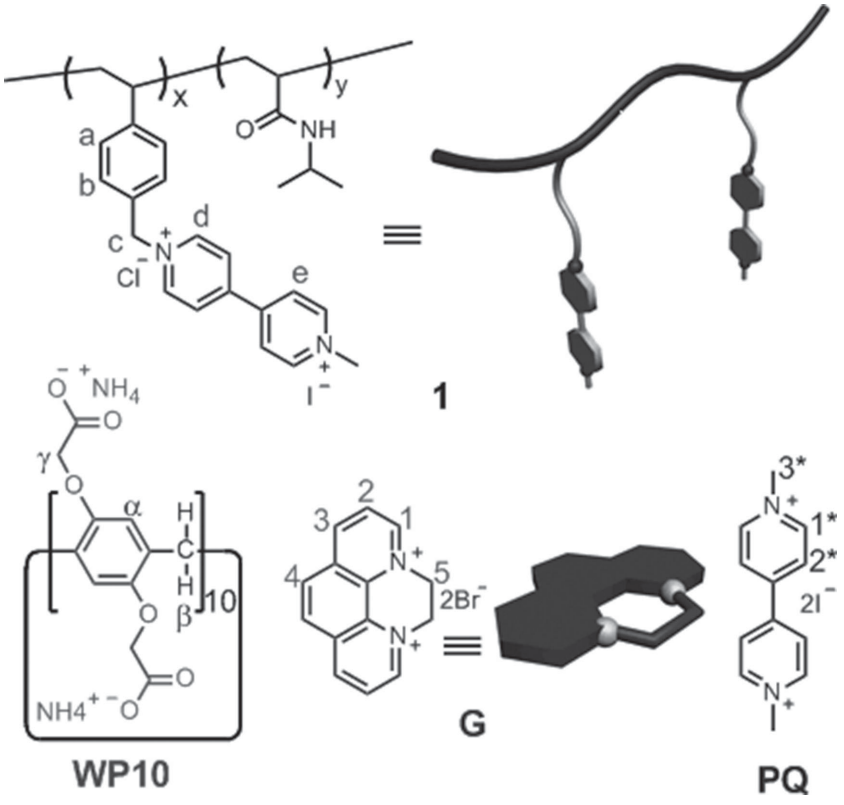
interactions, endowing the resultant supramolecular architectures with excellent stimuli responsiveness in the meantime.[6]

Pillar[*n*]arenes,[7,8] a new kind of macrocyclic hosts next to crown ethers,[9] cyclodextrins,[10] calixarenes,[11] and cucurbiturils,[12] have gained much interest as "smart" and advanced building blocks in the last few years. In comparison to the basket-shaped structure of *meta*-bridged calixarenes, pillar[*n*]arenes are linked by methylene (—CH_2—) bridges at *para*-positions of 2,5-dialkoxybenzene rings, resulting in the formation of a unique rigid pillar architecture. Pillar[*n*]arenes acting as useful platforms have been widely applied in the fabrication of various interesting supramolecular systems due to their unique symmetrical structure and easy functionalization, such as cyclic dimers, chemosensors, supramolecular polymers, drug delivery systems, transmembrane channels, and cell glue.[13] On account of the discrepancy in cavity size, pillar[*n*]arenes exhibited size selective complexation with different guests.[8f] Herein, we employed a water soluble pillar[10]arene (**WP10**) to tune the LCST behavior of a random copolymer of NIPAAM and styrene with paraquat (**PQ**) derivative (*N*,*N*′-dialkyl-4,4′-bipyridinium) pendants (**1**) by taking advantage of host–guest interactions between **WP10** and **PQ** (Scheme 1). 1,10-Phenanthrolinium cation (**G**) possessing a higher association constant with **WP10** was used as a competitive guest molecule to disassociate **WP10** from the host–guest complexes on the side-chains of **1** resulted from the size-selective complexation, which resulted in the recovery of the LCST.



Scheme 1. Chemical structures and cartoon representations of **1**, **WP10**, **G**, and **PQ**.

2. Experimental Section

2.1. Materials and Methods

All reagents were commercially available and used as supplied without further purification. Compounds **WP10**,[14] and **1**[15] were used as received. NMR spectra were recorded with a Bruker Avance DMX 500 spectrophotometer using the deuterated solvent as the lock and the residual solvent or TMS as the internal reference. UV–vis spectra were taken on a Shimadzu UV-2550 UV–vis spectrophotometer. The fluorescence experiments were conducted on a RF-5301 spectrofluorophotometer (Shimadzu Corporation, Japan). Transmission electron microscopy (TEM) investigations were carried out on a HT-7700 instrument. Dynamic light scattering (DLS) measurements were carried out using a 200 mW polarized laser source Nd:YAG (λ = 532 nm). The polarized scattered light was collected at 90° in a self-beating mode with a Hamamatsu R942/02 photomultiplier. The signals were sent to a Malvern 4700 submicrometer particle analyzer system.

3. Results and Discussion

Firstly, the host–guest interactions between **WP10** and **G** were studied by ^{1}H NMR investigations. In comparison to the spectrum of free **G** (Figure 1a), all of the resonance peaks corresponding to the protons on **G** shifted upfield in the presence of **WP10** (Figure 1b,c). For example, upfield shift changes were observed for the signals related to the protons H_1, H_2, H_3, H_4, and H_5 ($\Delta\delta$ = –0.78, –0.51, –0.67, –0.96 and –0.61 ppm for H_1, H_2, H_3, H_4, and H_5, respectively) upon addition of an equivalent amount of **WP10** (Figure 1c). The reason was that **G** threaded into the cavity of **WP10** to form a [2]pseudorotaxane-type host–guest complex, and these protons were shielded by the electron-rich macrocyclic structure.[7c] Moreover, the peaks of the protons on **WP10** also exhibited slight chemical shift changes in the presence of **G** arising from the interactions between **WP10** and **G** (Figure 1b,c). In order to investigate the relative positions of the components in host–guest inclusion complex,

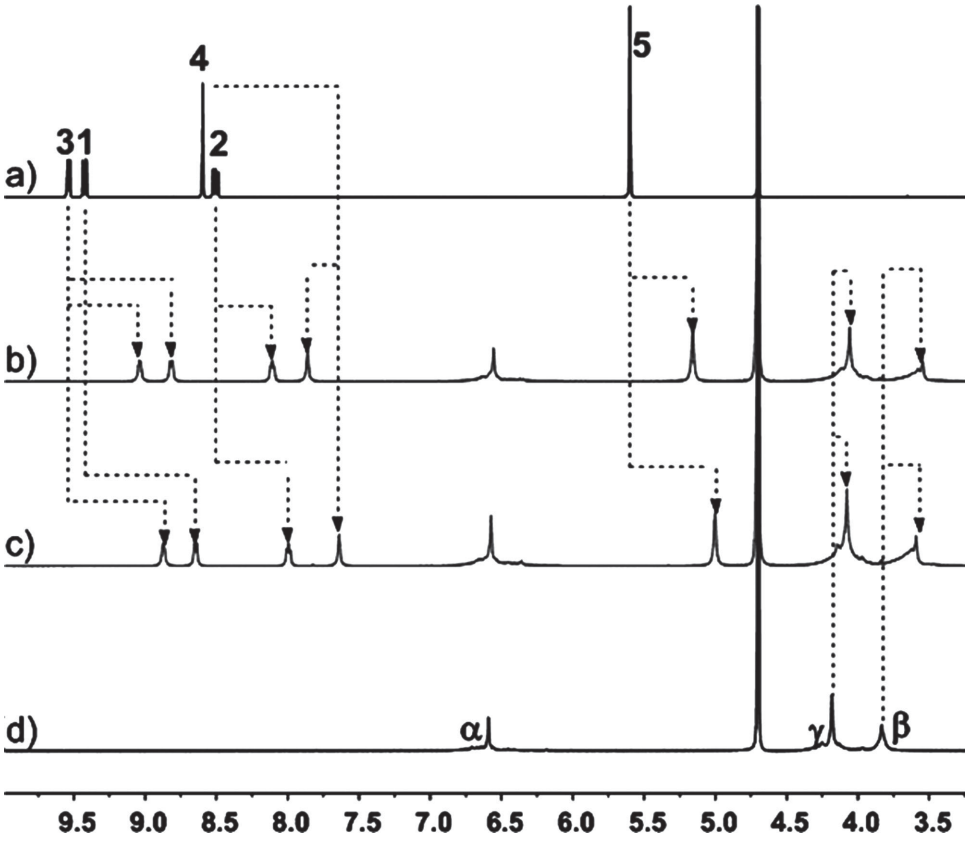


Figure 1. Partial ^{1}H NMR spectra (500 MHz, D_2O, 295 K): a) **G** (2.00 mM); b) **WP10** (2.00 mM) and **G** (6.00 mM); c) **WP10** (2.00 mM) and **G** (2.00 mM); and d) **WP10** (2.00 mM).

2D NOESY NMR spectroscopy was carried out. Nuclear Overhauser effect (NOE) correlations were observed between the signals related to protons H_1, H_2, H_3, H_4, and H_5 on **G** and protons H_α, H_β, and H_γ on **WP10** (Figure 2), indicating that **G** penetrated into the cavity of **WP10** deeply.[13b] Furthermore, evidence for the formation of a stable host–guest complex **WP10⊃G** was obtained from UV–vis absorption spectroscopy (Figure S1, Supporting Information). The spectrum of an aqueous solution containing **WP10** and **G** (molar ratio = 1:1) exhibited a broad absorption in the range of 400–600 nm, which corresponded to the characteristic absorption of the charge-transfer complex between electron-rich **WP10** and electron-deficient **G**.[8f] Furthermore, the resulting solution had a wine red color when **WP10** and **G** (molar ratio = 1:1) were mixed in water, indicating the formation of a typical charge-transfer complex (Figure S1, Supporting Information).[8f]

Fluorescence titrations were conducted at room temperature in water to measure the binding affinity for the complexation between **WP10** and **G**. As shown in Figure S2 (Supporting Information), the quenching of fluorescence intensity at 330 nm was found to be effective upon gradual addition of **G** due to the host–guest interactions.[8d] A mole ratio plot based on the fluorescence titration data confirmed that the complexation between **WP10** and **G** had a 1:1 stoichiometry (Figure S3, Supporting Information). The association constant (K_a) of the host–guest complex was calculated to be $(2.13 \pm 0.32) \times 10^8$ M^{-1} by using a nonlinear curve-fitting method (Figure S4, Supporting Information). The high binding affinity of **WP10⊃G** should be attributed to the cooperativity of multiple electrostatic interactions, hydrophobic interactions and π–π stacking interactions between the anionic **WP10** and dicationic **G**.[8f] From our previous work, we knew that the K_a value for the complexation between **WP10** and **PQ** was $(1.25 \pm 0.21) \times 10^7$ M^{-1}, which was much lower than that of **WP10⊃G**.[14] The reason was that the internal cavity of **WP10** was too large for **PQ**, thus resulting in the insufficient host–guest complexation between **WP10** and **PQ**. While the size of **G** was larger than that of **PQ**, and more efficient hydrophobic interactions and π–π stacking interactions could be achieved. As a consequence, **WP10⊃G** exhibited a higher association constant than that of **WP10⊃PQ**.

Next, we employed the host–guest complexation to tune the LCST behavior of a random copolymer (**1**, $M_n = 2.7 \times 10^4$) with the molar ratio between the NIPAAM units and the **PQ** derivative moieties of 13:1.[15] **WP10**

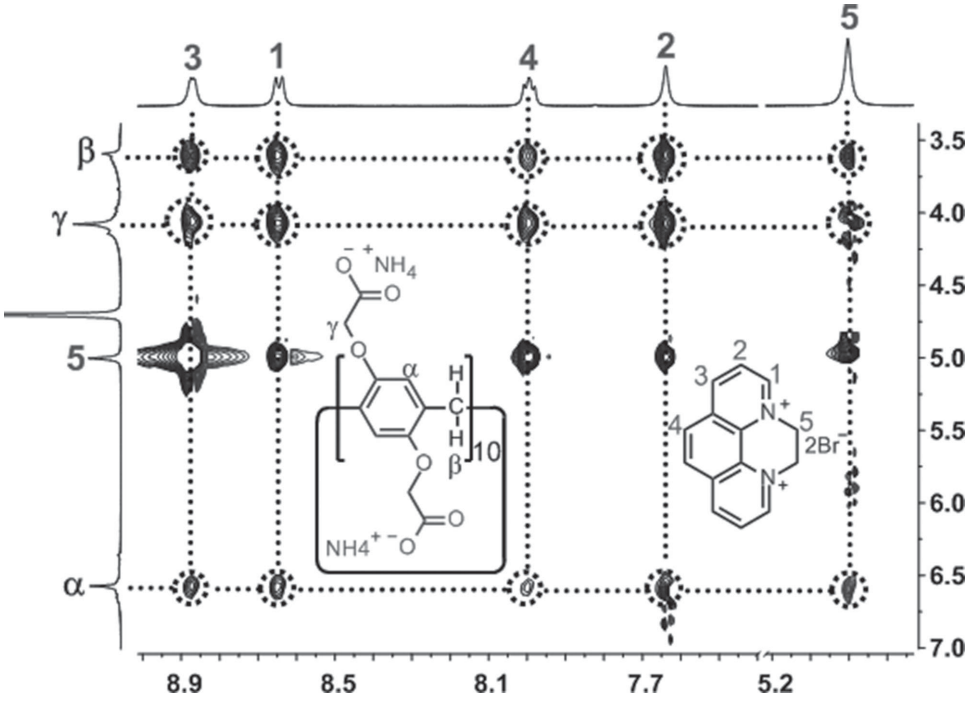


Figure 2. Partial 2D NOESY spectrum (500 MHz, D_2O, 295 K) of **WP10⊃G**. The concentrations of **WP10** and **G** were 10.0 mM.

could interact with the **PQ** groups pendent on copolymer **1** to form stable host–guest complexes. As shown in Figure 3, evident chemical shift changes could be observed for the signals of the protons on both **WP10** and **PQ** moieties upon gradual addition of **WP10**, which was caused by the host–guest interactions. The peaks of protons H_d and

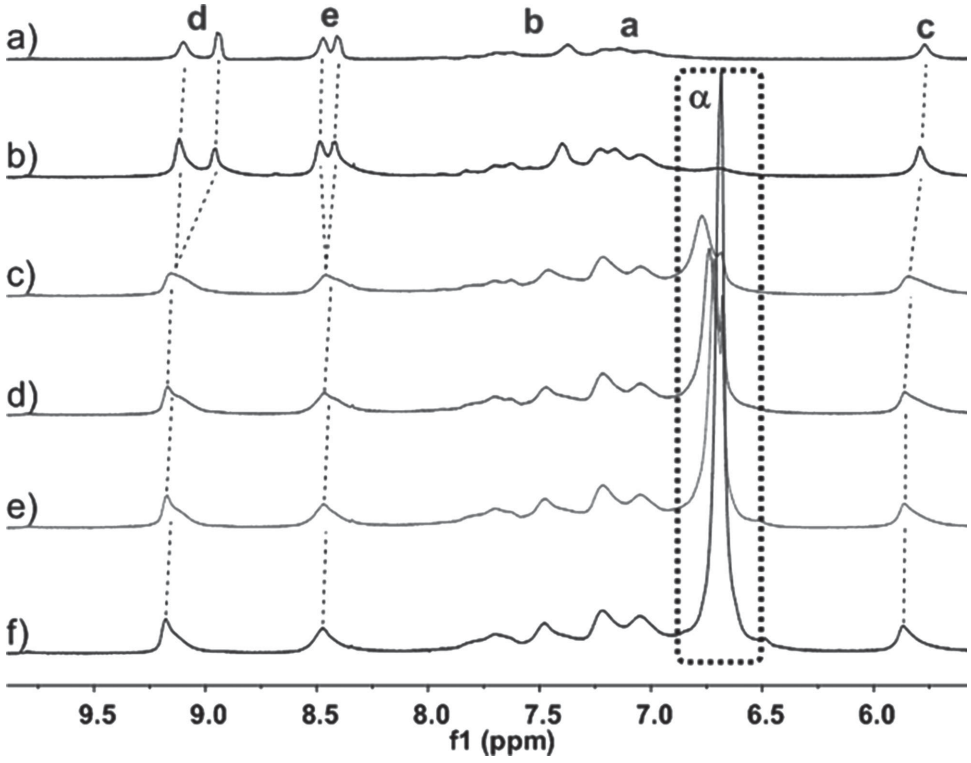


Figure 3. Partial ^1H NMR spectra (D_2O, 298 K, 500 MHz) of copolymer 1 at a concentration of 1.00 mM (27.0 mg mL^{-1}) with different concentrations of **WP10**: a) 0.00 mM; b) 5.00 mM; c) 7.50 mM; d) 10.0 mM; e) 15.0 mM; and f) 20.0 mM.

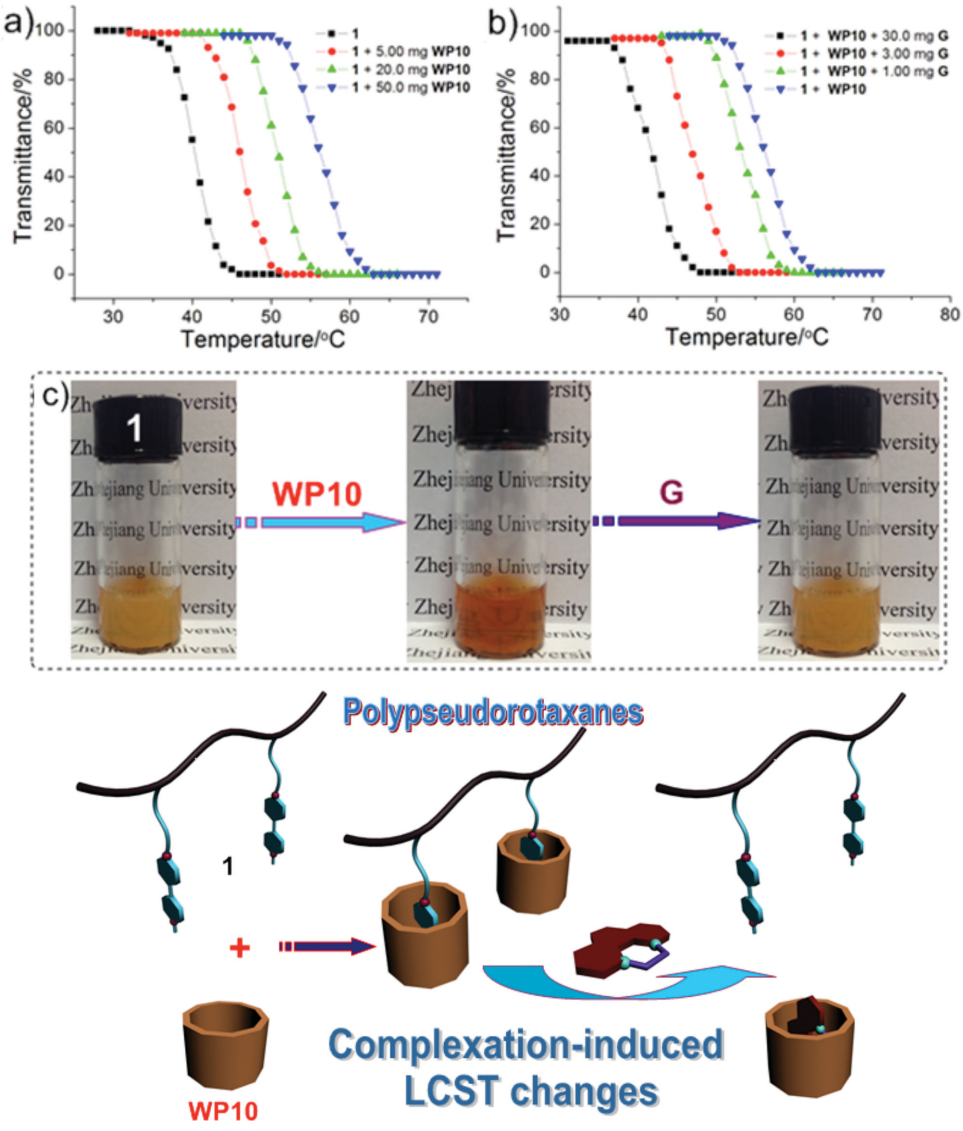


Figure 4. a) Transmittance changes of the solution containing copolymer **1** (30 mg, 1.5 mL) upon gradual addition of **WP10** (5.00, 20.0, 50.0 mg) using a heating rate of 1 °C min^{-1}. b) Transmittance changes of the solution containing copolymer **1** (30 mg, 1.5 mL) and **WP10** (50.0 mg, 1.5 mL) upon gradual addition of **G** (1.00, 3.00, 30.0 mg) using a heating rate of 1 °C min^{-1}. c) The solubility of **1**, **1** + **WP10**, and **1** + **WP10** + **G** at 45.0 °C. The concentrations of **1**, **WP10**, and **G** were 20.0, 33.3, and 20.0 mg mL^{-1}, respectively.

H_e on the **PQ** groups not only changed from two peaks to one peak but also shifted downfield after association with **WP10**. Additionally, extensive broadening effect occurred when the dicationic **PQ** groups interacted with **WP10** due to complexation dynamics.[8d] Charge-transfer interactions between **WP10** and **PQ** groups on **1** were also monitored by UV–vis absorption spectroscopy (Figures S5 and S6, Supporting Information). These phenomena provided convincing insight into the existence of **WP10**⊃**G** host–guest complexes in the mixture as the side-chains of the polypseudorotaxanes.

After the formation of side-chain polypseudorotaxanes, the thermosensitive behavior of **1** changed effectively. To investigate the LCST behavior of **1** in water, turbidity measurements were performed. As shown in Figure 4, the T_{cp} of copolymer **1** was 40.7 °C in the absence of **WP10**, which was higher than that of PNIPAAM (around 32.0 °C),[16] because the introduction of hydrophilic **PQ** derivative not only enhanced the solubility of **1** in water but also disrupted the intermolecular assemblies through electrostatic repulsion resulted from their positive charged feature. Figure 4a shows the transmittance of an aqueous solution of **1** in the absence and presence of different amounts of **G** as a function of temperature. Upon gradual addition of **WP10**, the LCST of copolymer **1** rose continuously. The corresponding T_{cp} values of the mixture increased from 40.7 °C to 45.9 °C, 50.8 °C, and 56.1 °C by adding 5.00, 20.0, and 50.0 mg of **WP10** into the

solution of **1**, respectively. The complexation-induced LCST improvement was caused by the increased electrostatic repulsion and steric hindrance arising from the introduction of **WP10**, which inhibited intra/interpolymer aggregations in solution more effectively. Furthermore, the hydrophilicity of **1** was enhanced dramatically when the **PQ** groups complexed with **WP10**, thus further improving the solubility of the polymer. From the photographs in Figure 4c, a distinct change of solubility was also observed after the addition of **WP10**.

TEM and DLS measurements (Figures S7–S11, Supporting Information) were further conducted to investigate the effects of host–guest complexation on the aggregation of **1** in water at different temperatures. The random copolymer **1** itself self-assembled into nanoparticles with a diameter of about 55 nm at 30 °C (Figure S7a, Supporting Information), which was below its LCST. However, the diameter of the nanoparticles increased significantly to about 300 nm by heating the solution to 45 °C (Figure S7b, Supporting Information), which caused by the aggregation of **1** when the solution temperature was above the LCST. For the mixture of **1** and **WP10** at 45 °C, the average size of the nanoparticles kept at 55 nm as well due to the formation of side-chain-type polypseudorotaxanes (Figure S7c, Supporting Information), which enhanced the LCST of the copolymer in water. By further increasing the solution temperature to 60 °C, exceeding the LCST of the polypseudorotaxane, the polypseudorotaxane aggregated to formed nanoparticles with a larger size (Figure S7d, Supporting Information). The diameter changes of the aggregates were monitored by DLS, which was in good agreement with the results obtained from TEM experiments (Figures S8–S11, Supporting Information). These phenomena also demonstrated that the host–guest complexation between **WP10** and the **PQ** groups on the side-chain of **1** could improve the LCST of **1**.

G possessing a higher binding affinity with **WP10** could be employed as a competitive guest to disassociate the polypseudorotaxanes to regulate the LCST behavior of **1**. As shown in Figure S12 (Supporting Information), the signals for the protons on **PQ** shifted downfield by adding **G** into a mixture of **WP10** and **PQ**, demonstrating the disassociation of the host–guest complex **WP10⊃PQ**. Upon gradual addition of 1.00, 3.00, and 30.0 mg of **G** into an aqueous solution of **1** (30 mg, 1.5 mL) and **WP10** (50.0 mg, 1.5 mL), the T_{cp} value of the mixture decreased to 53.8 °C, 46.7 °C, and 41.3 °C, respectively. The reason was that **WP10** was disassociated from the side-chains of the polypseudorotaxane in the presence of **G**, associated with the formation of the host–guest complexes **WP10⊃G**. It should be emphasized that the T_{cp} value of **1** could not recover to the original state ($\Delta T_{cp} = 0.6$ °C), although excess **G** was added. Due to the dynamic and reversible nature of the noncovalent interactions, there existed a dynamic equilibrium between the complexed and uncomplexed states of the **PQ** groups on **1**. Although excess **G** was added, trace amounts of **WP10** could interact with the **PQ** groups, in accord with the result obtained from ^{1}H NMR (Figure S12g, Supporting Information). On the other hand, the increased salt concentration might also influence the LCST behavior.

4. Conclusion

In conclusion, a novel molecular recognition motif between a water soluble **WP10** and a **G** in water was established. Due to the suitable size of **G**, **WP10** exhibited a much higher binding affinity with **G** than that with **PQ**, mainly driven by the cooperativity of multiple electrostatic interactions, hydrophobic interactions and π–π stacking interactions. This size-selective host–guest complexation could tune the LCST behavior of a random copolymer (**1**) with **PQ** derivative pendants. The host–guest interactions between **WP10** and the **PQ** groups made a remarkable contribution to the solubility of **1** in water and the restraint of intra/interpolymer aggregations, which resulted in the enhancement of the T_{cp} value of **1**. The T_{cp} value could be tuned back by adding **G**, since it acted as a competitive guest for the complexation between **WP10** and **1**. This supramolecular method to tune LCST can be potentially applied in many biorelevant fields, such as smart bioactive surfaces, enzyme recovery, protein purification, and tissue engineering.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

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