Polymeric Thermometers

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# Programmable Polymer-Based Supramolecular Temperature Sensor with a Memory Function**

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**Abstract:** *A new class of polymeric thermometers with a memory function is reported that is based on the supramolecular host–guest interactions of poly(N-isopropylacrylamide) (PNIPAM) with side-chain naphthalene guest moieties and the tetracationic macrocycle cyclobis(paraquat-p-phenylene) (CBPQT$^{4+}$) as the host. This supramolecular thermometer exhibits a memory function for the thermal history of the solution, which arises from the large hysteresis of the thermoresponsive LCST phase transition (LCST = lower critical solution temperature). This hysteresis is based on the formation of a metastable soluble state that consists of the PNIPAM–CBPQT$^{4+}$ host–guest complex. When heated above the transition temperature, the polymer collapses, and the host–guest interactions are disrupted, making the polymer more hydrophobic and less soluble in water. Aside from providing fundamental insights into the kinetic control of supramolecular assemblies, the developed thermometer with a memory function might find use in applications spanning the physical and biological sciences.*

Polymers that exhibit a lower critical solution temperature (LCST) have found a diverse range of applications spanning advanced “smart” materials, drug delivery, and catalysis.[1] The ability of such polymers to undergo an entropy-driven phase transition from a soluble coiled state at temperatures below the LCST to an insoluble aggregated globular state at temperatures above the LCST offers a convenient and tunable method to control their physicochemical properties. Poly(*N*-isopropylacrylamide) (PNIPAM) derivatives are the most widely studied polymers featuring LCST behavior,[2] which mainly results from their good biocompatibility, a robust phase transition (with regard to minor fluctuations in polymer chain length, pH, and ionic strength), tunable transition temperatures within normal physiological temperatures, and the ability to be synthesized using living anionic and controlled radical polymerization techniques.[3] In recent years, it has been demonstrated that host–guest interactions can be utilized to tune the LCST phase transition temperature of PNIPAM.[4]

The fundamental importance of temperature in a range of scientific disciplines has stimulated the development of molecular and polymeric thermometers that display a colorimetric and/or fluorometric response to a change in temperature.[5] Polymeric temperature sensors are especially interesting, as their intrinsic phase transitions, such as glass, melting, liquid crystalline, and solubility transitions, may be exploited for the development of temperature sensors with a memory function.[6] However, all of these recently reported examples exhibit a thermal memory that is based on glass and melting transitions in solid shape memory and liquid-crystalline polymeric materials. We are not aware of any previous examples of soluble polymeric sensors with a memory function that is based on a solubility phase transition; such sensors have a great potential for the in vivo thermography of living matter, as has already been demonstrated for polymeric thermometers without memory.[5b,e]

Herein, we report a supramolecular polymeric temperature sensor with a memory function that is based on kinetic control over the LCST phase transition of PNIPAM.[6] It was hypothesized that the reversible increase of the phase-transition temperature of PNIPAM with hydrophobic dialkoxynaphthalene moieties in the side chain (**1**) by host–guest interactions with the hydrophilic tetracationic macrocyclic host cyclobis(paraquat-*p*-phenylene) tetrachlor-

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ide (CBPQT$^{4+}$) could induce hysteresis for the LCST phase transition. This hysteresis was envisioned to result from the loss of the host–guest complexation when the polymer collapses at the LCST phase transition; this process is presumably driven by the decreased polarity of the polymer microenvironment lowering the association constant, which is largely driven by hydrophobic interactions. As such, the solubility of the polymer during heating will be different to that during cooling, which leads to a thermal memory window (Figure 1).

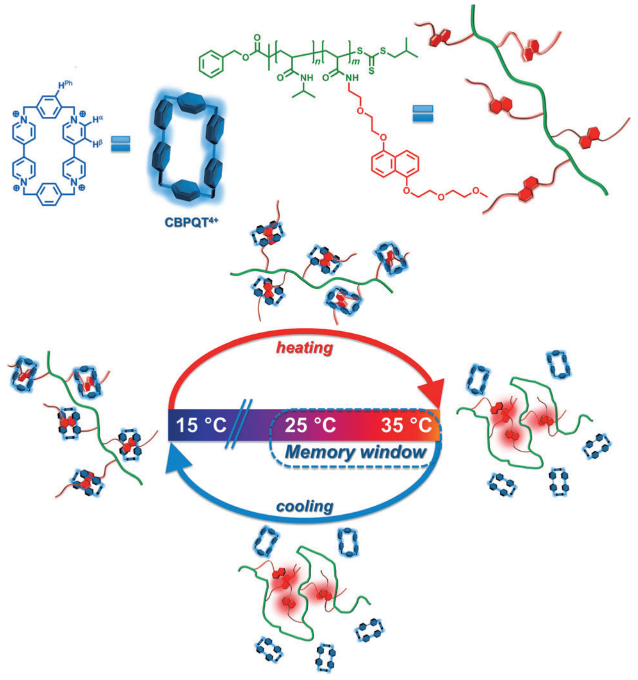

**Figure 1.** Top: Structures of the utilized CBPQT$^{4+}$ host and the dialkoxynaphthalene-functionalized PNIPAM. Bottom: Schematic representation of the thermal hysteresis of the supramolecular assembly of the dialkoxynaphthalene-functionalized polymer with CBPQT$^{4+}$, which results from decomplexation of the host–guest assembly during the LCST phase transition providing a thermal memory window.

To evaluate this proposed supramolecular temperature sensor with a memory function, copolymer **1** was prepared by statistical copolymerization of NIPAM and the naphthalene-based acrylamide monomer **M1** using reversible addition–fragmentation chain transfer (RAFT) polymerization (Figure 2).[7] The resulting copolymer **1** has a number-average molar mass ($M_n$) of 19.2 kDa and a dispersity (Đ) of 1.2, as determined by size-exclusion chromatography (SEC; see the Supporting Information, Figure S7). The molar ratio between NIPAM and monomer **M1** was estimated to be 195:5, based on the relative integration of the representative signals in the $^1$H NMR spectrum (Figure S8).

The ability of copolymer **1** to form supramolecular host–guest complexes with CBPQT$^{4+}$ in water was first evaluated by isothermal titration calorimetry, which revealed an association constant, $K_a$, of $1.8(\pm 0.1)\times 10^4\,\text{M}^{-1}$ and a binding stoichiometry, $N$, of 4.6 (± 0.1; Figure 2). These results clearly demonstrate that (nearly) all of the dialkoxynaphthalene moieties in copolymer **1** are available and accessible for the formation of host–guest complexes with CBPQT$^{4+}$.

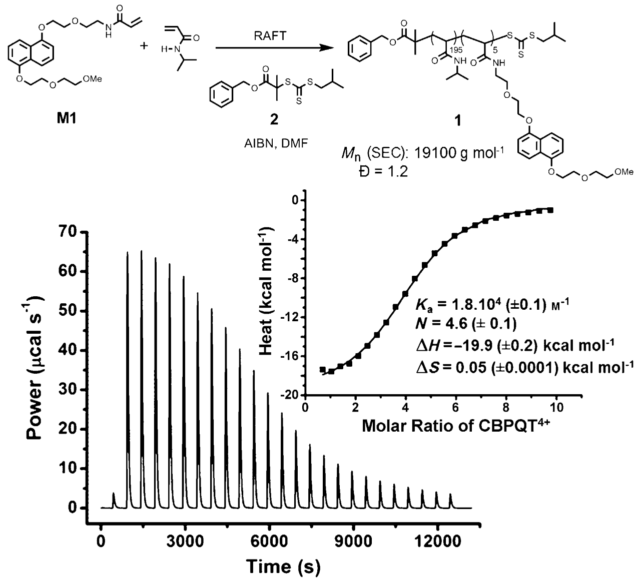

**Figure 2.** Top: Synthesis of copolymer **1** by RAFT copolymerization of NIPAM and dialkoxynaphthalene acrylamide **M1**. Bottom: Isothermal titration calorimetry data for the addition of aliquots of CBPQT$^{4+}$ (5.17 mM) to copolymer **1** (0.16 mM), recorded in $H_2O$ at 15 °C. AIBN = 2,2′-azobisisobutyronitrile.

The formation of host–guest complexes of copolymer **1** with CBPQT$^{4+}$ was also confirmed by $^1$H NMR spectroscopy (Figure S9 and S10) and UV/Vis spectroscopy (Figure S11). In brief, $^1$H NMR spectroscopy revealed significant broadening and characteristic shifts of the naphthalene proton resonances upon addition of CBPQT$^{4+}$ to an aqueous solution of copolymer **1** with $N \approx 5$ (Figure S9). 2D NOESY NMR spectroscopy of copolymer **1** in the presence of five equivalents of CBPQT$^{4+}$ clearly showed dipolar correlations between the $H_{2/6}$, $H_{3/7}$, and $H_{4/8}$ protons of the naphthalene units and the $H_{Ph}$ protons of CBPQT$^{4+}$. Furthermore, the addition of CBPQT$^{4+}$ to a colorless solution of copolymer **1** in water immediately resulted in the formation of a purple solution and the appearance of an absorption band at approximately 520 nm in the UV/Vis spectra, which is characteristic for naphthalene–CBPQT$^{4+}$ donor–acceptor inclusion complexes (Figure S11).[8]

After establishing that copolymer **1** is capable of forming host–guest complexes with CBPQT$^{4+}$, we turned our attention to its thermoresponsive behavior in aqueous solution. Because of the hydrophobic dialkoxynaphthalene side chains, the cloud-point temperature ($T_{cp}$) of copolymer **1** is 20.5 °C (Figure 3a), which is significantly lower than for unmodified PNIPAM having a $T_{cp}$ of 32 °C. Upon addition of CBPQT$^{4+}$, the $T_{cp}$ gradually increased up to 31 °C, which is due to an increase in the hydrophilicity of copolymer **1** upon the formation of host–guest complexes with CBPQT$^{4+}$ (Figure 3b). The $T_{cp}$ increased linearly during the addition of up to two equivalents of CBPQT$^{4+}$, after which the increase in $T_{cp}$ started to level off revealing that the formation of the first two host–guest complexes has a stronger effect on the overall hydrophilicity of copolymer **1** than the consecutive binding

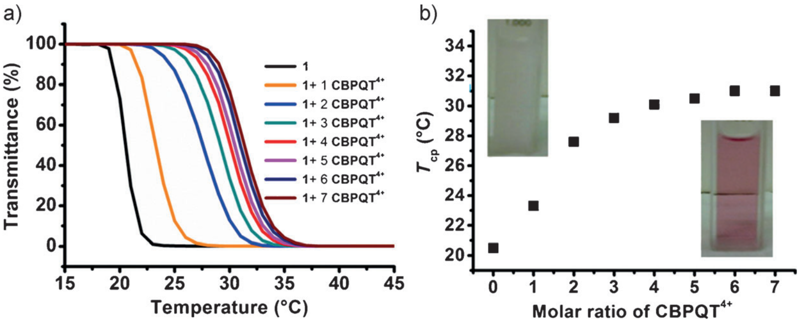

***Figure 3.*** Thermoresponsive properties of copolymer **1** and its complexes with $CBPQT^{4+}$. a) Transmittance (recorded at 800 nm and 1 °C $min^{-1}$) as a function of temperature for **1** (3 mm in $H_2O$) with various amounts of $CBPQT^{4+}$. b) Dependence of the cloud point temperature ($T_{cp}$) on the molar ratio of $CBPQT^{4+}$. The insets show pictures of a solution of copolymer **1** with five equivalents of $CBPQT^{4+}$ below (bottom; clear purple solution) and above (top; white opaque solution) the $T_{cp}$.

events. To confirm that the increase in $T_{cp}$ is due to the formation of host–guest complexes of copolymer **1**, $CBPQT^{4+}$ was also added to unmodified PNIPAM in a control experiment: No change in $T_{cp}$ was observed with five equivalents of $CBPQT^{4+}$ (Figure S12). Hence, the aforementioned data clearly demonstrate that the naphthalene-functionalized PNIPAM copolymer **1** and its supramolecular assemblies with $CBPQT^{4+}$ act as programmable thermometers with an associated visible readout.

Interestingly, turbidity experiments on copolymer **1** with $CBPQT^{4+}$ revealed that the LCST-mediated polymer phase transition of PNIPAM caused a complete disappearance of the purple color, suggesting complete disassembly of the donor–acceptor complexes and thereby providing a direct visual readout for the use of this system as a temperature sensor (Figure 3b, insets). This LCST-mediated decomplexation of the host–guest complexes was further confirmed through variable-temperature $^1H$ NMR spectroscopy (Figure 4). When a solution of copolymer **1** and three equivalents of $CBPQT^{4+}$ was heated to above the $T_{cp}$, all of the proton resonances that belong to copolymer **1** disappeared owing to its precipitation, while resonances that are characteristic of the free cyclophane units appeared in the spectrum. These observations provide further evidence for the disruption of the host–guest complexes during the polymer phase transition (Figure 4). Furthermore, the relative integrals of the $H_{2/6}$ protons of the naphthalene moiety were found to reversibly change when cycling the temperature between 15 °C and 40 °C during three consecutive cycles (Figure S13). A final confirmation of complete disassembly was obtained by isolating the aggregated copolymer **1** above the $T_{cp}$ by centrifugation. This recovered material had the same $T_{cp}$ when mixed with one equivalent of $CBPQT^{4+}$ as the fresh batch of copolymer **1** mixed with one equivalent of $CBPQT^{4+}$ (Figure S14). The recovery of uncomplexed copolymer **1** also enables the reprogramming of the supramolecular temperature sensor (for details, see Figure S14).

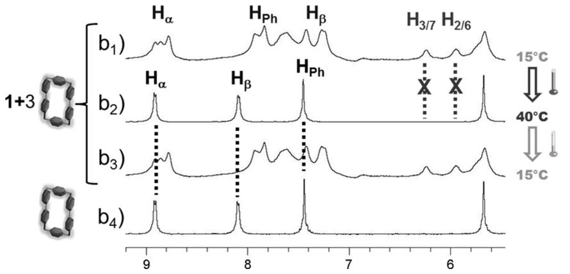

***Figure 4.*** Partial $^1H$ NMR spectra of a mixture of copolymer **1** (1 mm) with three equivalents of $CBPQT^{4+}$ in $D_2O$, which was subjected to the following sequence: 15 °C ($b_1$)→40 °C ($b_2$)→15 °C ($b_3$; the temperature was changed by the VT unit of the NMR spectrometer). The partial $^1H$ NMR spectrum of $CBPQT^{4+}\cdot 4Cl^-$ (in $D_2O$ at 40 °C) is shown for comparison ($b_4$).

The finding that the supramolecular complexation is lost during the temperature-induced phase transition of copolymer **1** inspired a more detailed evaluation of the reversibility of the thermoresponsive behavior, as the change in the supramolecularly assembled state may alter the physical behavior of the solution. Therefore, we recorded two heating–cooling cycles of the LCST phase transition of copolymer **1** in the presence of five equivalents of $CBPQT^{4+}$ (Figure 5a). Upon heating, the polymer phase transition occurred at 31 °C, as discussed previously, but during cooling, redissolution of the polymer

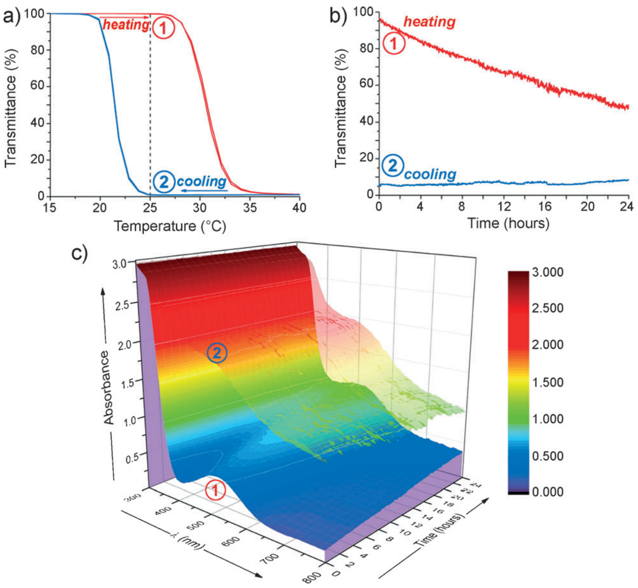

***Figure 5.*** UV/Vis measurements demonstrating memory stability. All of the memory-stability experiments were performed on aliquots from a solution containing copolymer **1** (5 mg $mL^{-1}$) and five equivalents of $CBPQT^{4+}$. a) Transmittance–temperature plot (two overlapping heating/cooling cycles). The memory-stability experiments were performed at 25 °C (•••••), within the limits of the hysteresis window. Heating rate: 1 °C $min^{-1}$, $\lambda = 700$ nm. b) Evolution of transmittance at 700 nm at 25 °C for a sample that was heated from 15 °C to 25 °C (1) and for a sample that was cooled from 45 °C to 25 °C (2). c) Full UV/Vis absorbance spectra of the solutions that correspond to the heated and cooled samples in (b) at 25 °C. The spectra were isothermally recorded over a period of 24 hours (1 scan/1.4 min.).

only occurred at 21 °C, which is similar to the $T_{cp}$ of copolymer **1** in the absence of CBPQT$^{4+}$. This unprecedentedly large hysteresis can be directly ascribed to the destruction of the host–guest complexes during precipitation: During heating, the solubility of the supramolecular assembly is determined by the ensemble of copolymer **1** and the more hydrophilic CBPQT$^{4+}$ host; during cooling, however, the solubility behavior of copolymer **1** prevails, as the host–guest complexes can apparently only be reformed when the copolymer goes back in solution. As such, the state of the polymer solution within the hysteresis window strongly depends on the thermal history, which provides a potential basis for a memory function. The dissolved state in between the $T_{cp}$ of the polymer without cyclophane and the $T_{cp}$ of copolymer **1** with five equivalents of CBPQT$^{4+}$ can be regarded as a kinetically trapped, metastable state (see the Movie in the Supporting Information).

For a robust memory function, the soluble and insoluble states within the hysteresis window of our system must be stable in time. Therefore, isothermal UV/Vis turbidity measurements were performed to quantify the extent to which the memory function is maintained during 24 hours. Hence, an aqueous solution of copolymer **1** (5 mg mL$^{-1}$) and five equivalents of CBPQT$^{4+}$ was heated beyond $T_{cp}$ (heating) to become a white opaque solution, which was followed by cooling back to 25 °C, which is within the hysteresis window. This sample was kept at 25 °C for 24 hours, revealing that the solution maintained its cloudy appearance (Figure 5 b), and no visible changes, such as redissolution or macroscopic precipitation of the collapsed polymeric globules, occurred. This clearly demonstrates that the system has a memory function, and that the solution "remembered" being heated above the $T_{cp}$ by remaining cloudy when cooled back to 25 °C.

Conversely, an aliquot of the same solution was cooled down below the $T_{cp}$ (cooling), which resulted in a purple transparent solution. This solution was subsequently heated to 25 °C, where the evolution of its transmittance was followed for 24 hours (Figure 5 b). In this case, a steady decrease of transmittance could be observed, as the naphthalene–CBPQT$^{4+}$ host–guest interactions of the kinetically trapped, metastable complex were progressively lost, and as a result, the polymer collapsed and aggregated. The disassembly of the naphthalene–CBPQT$^{4+}$ complex can also be followed by the progressive flattening of the absorbance band at approximately 520 nm ((1) in Figure 5 c; see also Figure S16). However, this transition from the kinetically trapped, soluble polymer to the thermodynamically stable, precipitated state was found to be very slow, and the solution still exhibited 70 % transmittance even after 10 hours at 25 °C. Furthermore, as seen in Figure 5 b, the solution still displayed 50 % transmittance after 24 hours, which is clearly distinguishable by eye from the opaque heated sample (Figure S15).

As such, this supramolecular polymer system represents the first reported soluble polymeric temperature sensor with a memory function. Moreover, the memory can simply be erased for re-use by cooling down the sensor to temperatures below the cooling $T_{cp}$ (see the Movie in the Supporting Information).

Next, the stability of the thermal memory function was tested against small temperature changes. Therefore, analogous spectrophotometric experiments were performed at 22.5 °C, which is closer to typical room temperature, but still in the hysteresis window. The behavior of the sample that was cooled and then heated to 22.5 °C was similar to that observed at 25 °C. However, the sample that was first heated to above the $T_{cp}$ and then cooled quickly lost 15 % of its opacity at 22.5 °C. Nonetheless, this transmittance remained stable at 15 % for 24 hours, confirming the robustness of the hysteresis window against small temperature variations (Figure S17).

In conclusion, we have developed a straightforward supramolecular strategy for the creation of the next generation of soluble polymeric thermometers with a thermal memory function, which are based on a relatively simple thermoresponsive copolymer that contains electron-rich pendant naphthalene guest units in the side chain and its host–guest complexes with an electron-deficient host molecule. This thermometer was found to be (re)programmable and had the capability to memorize the thermal history of the solution with an associated visible readout. To the best of our knowledge, the developed system constitutes the first reported (re)programmable temperature sensor with a memory function that does not rely on any energy input or electronics, but solely on specific supramolecular interactions.

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