Switching between Polymer Architectures with Distinct Thermoresponses

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Thermoresponsive linear polymers and their corresponding aggregates or nanogels typically show similar thermoresponsive profiles. In this study, the authors demonstrate reversible chemical switching between linear polymers and their cross-linked nanogels. The linear polymers exhibit sharp thermal transitions typical of common thermoresponsive polymers but the cross-linked nanogels exhibit “linear” thermal transitions over a relatively broad temperature range. The reversible switching between these two different polymer architectures with distinct thermoresponses represents a unique example of how the responsive properties of smart polymers can be significantly manipulated via polymer architecture engineering.

1. Introduction

Responsive polymeric materials that can change their physical properties and/or chemical structures in response to external stimuli, such as temperature, pH, and ionic strength, have attracted significant attention for their potential use in advanced technologies. Among them, thermoresponsive micro/nanoparticles are of particular interest due to their large surface area for bioconjugation, the ability to encapsulate biomolecules, and rapid response, and they have been intensively investigated in drug delivery, bio-imaging, catalysis, tissue engineering, and optical switching.

As reported in our previous work, we have developed thermoresponsive copolymers of poly(2-methoxyethyl acrylate-co-poly(ethylene glycol) methyl ether acrylate) (P(MEA-co-PEG)) with sharp thermal transitions in water. However, unexpectedly, the nanogels consisting of poly(N,N-dimethylacrylamide) (PDMA) shell and a cross-linked (CL) P(MEA-co-PEG) core, synthesized via aqueous dispersion copolymerization of MEA and PEGA, exhibit a linear thermoresponse, i.e., their nanogel diameter decreases almost in a linear fashion upon increasing the solution temperature over a broad temperature range (≈40 °C). More recently, we showed that microgels based on cross-linked P(MEA-co-PEG), synthesized via traditional radical dispersion polymerization, also display a similar linear response, suggesting that this interesting property may be extended to other forms of...
polymers. This unique linear thermoresponsive behavior has been investigated by Fourier transform infrared (FTIR) spectroscopy studies, which reveal at the molecular level that the thermal transition of these nanogels is accompanied by a gradual loss of water molecules from the P(MEA-co-PEGA) copolymers. Nevertheless, the exact cause, from a structural point of view, of the linear response of these nanogels remains unclear.

Cross-linked polymer nanoparticles could be obtained based on thiol-disulfide exchange. The reaction conditions are mild with no need for organic solvents, catalysts, or stabilizers. These redox-responsive nanogels can be easily cleaved by adding some reducing reagents, for example, 1,4-dithiothreitol (DTT) or glutathione, and distinct architectures between polymer chains and nanogels can be switched. Recently, reversibly cross-linked thermoand redox-responsive nanogels based on poly(vinyl alcohol)-b-poly(N-vinylcaprolactam) (PVOH-b-PNVCL) copolymers were prepared. These redox-responsive nanoparticles can be easily cleaved by adding some reducing reagents, for example, 1,4-dithiothreitol (DTT) or glutathione, and distinct architectures between polymer chains and nanogels can be switched. Recently, reversibly cross-linked thermo- and redox-responsive nanogels based on poly(vinyl alcohol)-b-poly(N-vinylcaprolactam) (PVOH-b-PNVCL) copolymers were prepared. While the block copolymer precursors displayed a sharp thermal transition through their LCST, a negligible shrinkage of the cross-linked nanogels upon heating could be observed due to the restricted mobility in the cross-linked structure.

As part of our continued endeavor to gain deeper understanding of the linear responsive behavior of nanogels based on P(MEA-co-PEGA), herein, we report a novel phenomenon whereby chemically reversible switching between two polymer architectures results in the observation of two distinct types of thermoresponsive behavior.

2. Results and Discussion

Specifically, multifunctional block copolymers as shown in Scheme 1, poly(N,N-dimethylacrylamide)-b-P(MEA-co-PEGA-co-pyridyl disulfide (PDS), ethyl acrylate-co-fluorescein O-methylacrylate) (PDMA-b-P(MEA-co-PEGA-co-PDSEA-co-Flu)), are firstly synthesized as the polymer precursors. Addition of less than stoichiometric amount of DTT under heating results in the formation of nanogels cross-linked by disulfide bonds. These disulfide bonds in the nanogels can be cleaved to regenerate the linear polymer chains at low temperature, which can then be oxidized by dimethyl-sulfoxide (DMSO) at high temperature to regenerate the cross-linked nanogels. The thermal response of the linear polymer chains and cross-linked nanogels at each stage is characterized by a combination of dynamic light scattering (DLS), FTIR spectroscopy, fluorescence spectroscopy, and transmission electron microscopy (TEM), which collectively reveal that the linear polymer chains have sharp, discontinuous thermal transitions whereas the cross-linked nanogels have linear, continuous thermal transitions.

The precursor polymers are synthesized by reversible addition-fragmentation chain transfer polymerization of DMA to afford PDMA, which is then chain-extended with co-monomers of MEA, PEGA, PDSEA, and Flu to provide PDMA-b-P(MEA-co-PEGA-co-PDSEA-co-Flu) multifunctional block copolymers (please refer to Table S1 and Figures S2 in the Supporting Information for characterization data). The composition for the block copolymer precursors is based on the following considerations. The hydrophilic PDMA block provides steric stabilization for the formed nanogels comprising the second block as the core, while MEA and PEGA are copolymerized to furnish the expected linear thermoresponse for the formed nanogels. PDSEA is a functional group that can be used for cross-linking, and the minute amount of Flu offers a fluorescence module for the detection of thermoresponsive transition. A polymer precursor PDMA_{35}-b-P(MEA_{230}-co-PEGA_{47}-co-PDSEA_{22}-co-Flu) (M_n = 56.6 kg mol^{-1}, D = 1.26) with an LCST of 37 °C is chosen for the subsequent redox

![Scheme 1. Schematic illustration of the preparation and reversible switching of thermoresponsive linear polymers and cross-linked nanogels.](image-url)
reactions to construct the nanogels and reversibly switch the polymer architectures between the nanogels and linear polymer chains.

CL nanogels are firstly synthesized by treating the precursor polymer solution at 60 °C (well above its LCST 37 °C) with 35 mol% of DTT relative to the PDS groups in the polymer, which converts up to 66 mol% of PDS into disulfide cross-links based on the calculation of pyri-dothione molar concentration using the extinction coefficient (Figure S3, Supporting Information),[28] and leaves some unreacted PDS units in the nanogels. As we will show later, the unreacted PDS in the nanogels can be used to form a fluorescence resonance energy transfer (FRET) pair with Flu, which is a highly sensitive technique to monitor the thermal transitions for the nanogels.[31,32] The transformation associated with this step was followed by FTIR, DLS, and TEM. The C=C and C=N characteristic bands of the pyridine ring of the PDS groups at 1419, 1560, and 1575 cm\(^{-1}\), respectively, are displayed in the FTIR spectrum of the precursor polymer (Figure 1a). These bands become hardly detectable in the spectrum of the CL nanogels due to a significant reduction of the PDS units. The cross-linking of the precursor polymer chains (~15 nm) into nanogels (170 nm) is further supported by a significant increase in the hydrodynamic diameter (\(D_h\)) as revealed by DLS (Figure 1b). TEM (Figure 1c) shows that the CL nanogels (95 nm) have a particulate morphology, although not perfectly spherical due to the soft nature of nanogels. The much smaller diameter by TEM in comparison to that by DLS is typical of nanogels that are highly swollen in water.

The CL nanogels can then be reversibly cleaved into de-cross-linked (DCL) linear polymer chains by treatment with excess DTT. Please note that excess DTT will not only cleave the disulfide cross-links into thiols but also the remaining PDS units in the nanogels, and thus, FRET was only used to detect the original CL nanogels. The content of thiols in these reversible transformations was assessed using Ellman’s method,[33] quasi-quantitative degradation of disulfides into thiols was achieved within 3 h in phosphate buffer (pH 7.4) (Figure S4, Supporting Information), while the reverse process from thiols to disulfides in the formation of recross-linked (RCL) nanogels using DMSO[34,35] reached 94% conversion within 120 h (Figure S5, Supporting Information), suggesting the thiol-disulfide chemistry is highly reversible in the switching of cross-linked nanogels and linear polymer chains, as expected. Gel permeation chromatography analysis of the

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**Figure 1.** a) FTIR spectra of polymers (inset: an enlargement of the PDS region in the precursor polymers). b) Variation of the hydrodynamic size and size distribution of polymers by DLS at 25 °C, TEM images of nanogels. c) the CL nanogels and d) the RCL nanogels.
DCL polymers indicated a slightly reduced $M_n$ in comparison to that of the original precursor polymers (Figure S6, Supporting Information), consistent with the loss of pyridothione as the byproduct. DCL polymers showed a new band at 2550 cm$^{-1}$ corresponding to $\text{SH}$ groups, which disappeared upon recross-linking (Figure 1a). The RCL nanogels appeared to be smaller than the CL nanogels, as indicated by both DLS (Figure 1b) and TEM (Figure 1d) results, which can be explained by the fact that CL nanogels contained some remaining PDS units while RCL nanogels had essentially no PDS units as well as the higher cross-linking density in the RCL nanogels.\[36\]

The thermal responses of the block polymers (precursor polymers and DCL polymers) and the disulfide–cross-linked nanogels (CL and RCL nanogels) in aqueous solution were investigated by turbidimetry and DLS (Figure 2 and Figure S7, Supporting Information). The precursor polymers exhibit sharp response to temperature change during a heating–cooling cycle with an LCST at $37^\circ\text{C}$ (Figure 2a). In remarkable contrast, the CL nanogels show a completely different thermoresponsive profile (Figure 2b); the $D_h$ decreases in a linear mode from 174 nm at $21^\circ\text{C}$ to 144 nm at $49^\circ\text{C}$ (Figure S7a, Supporting Information). The facile cross-linking process that results in a change from linear polymer chains to cross-linked nanogels serves to demonstrate that the thermoresponsive behavior for polymers based on P(MEA-co-PEGA) is highly sensitive to the architectural format. Upon full degradation of the CL nanogels using excess DTT, a discontinuous thermal response is again observed for the DCL polymers (Figure 2c). It is noted that the thermal transition for the DCL polymers is milder and broader with a higher LCST ($\approx 45^\circ\text{C}$) than that for the precursor polymers. In addition, the DCL polymers show a smaller change in transmittance during the thermal transition than that of the precursor polymers. These can be attributed to the less hydrophobic character of the thiol groups in the DCL polymers in comparison to the PDS units in the precursor polymers. After the DCL polymers are converted back to the RCL nanogels upon oxidation with DMSO, a linear thermoresponsive profile appears again (Figure 2d). This reformation of nanogels having a linear thermoresponse from the linear DCL polymers having a discontinuous thermoresponse provides a solid evidence for the architecture-dependent, distinct thermoresponsive behavior of polymers based on P(MEA-co-PEGA). A wider temperature range and overall smaller $D_h$ for the RCL nanogels in comparison with the CL nanogels are observed due to the complete removal of the hydrophobic PDS units at this stage (Figure S7, Supporting Information). The thermal transition for the CL nanogels is somewhat sharper than that for the RCL nanogels due to the higher cross-linking density in the RCL nanogels. It is now possible to reversibly switch the polymer architectures between linear

\[\text{Figure 2. Variation of transmittance of a) the precursor polymers, b) the CL nanogels, c) the DCL polymers, and d) the RCL nanogels as a function of temperature (1 mg mL}^{-1}).\]
polymers and cross-linked nanogels that show distinct thermostressive behaviors.

Thermal transitions of LCST polymers are accompanied by hydration changes of the subunits, which result in alteration of polarity in the local microenvironments. Fluorescence spectroscopy can be employed to probe this property by labeling the LCST polymers with fluorophores. In the initial formation of the CL nanogels, some PDS units are deliberately left in the nanogels, which form a FRET pair with the Flu. The PDSEA aqueous solution shows a weak blue-green emission at 485 nm, which is attributable to the pyridine ring (Figure S8a, Supporting Information). The overlap of the emission spectrum of PDSEA and the absorption spectrum of Flu indicates that PDSEA and Flu can act as the donor and acceptor for FRET (Figure S9, Supporting Information). As can be seen from the fluorescence spectra of the precursor polymers (Figure S10a, Supporting Information) and the CL nanogels (Figure S10b, Supporting Information), excited at 416 nm as a function of temperature, at low temperatures the emission mainly originates from the PDS units at 486 nm with a weak emission at 514 nm from FRET between PDS and Flu. The fluorescence intensity ratio, $I_{486}/I_{514}$, shows an abrupt drop on heating to 37 °C for the precursor polymers (Figure S11a, Supporting Information) but a continuous reduction for the CL nanogels (Figure S11b, Supporting Information), which is consistent with characteristics of the thermostressive properties of the precursor polymers and CL nanogels as revealed by the turbidity and DLS studies. While for the DCL polymers and the RCL nanogels without PDS groups, the emission at 514 nm is only from the Flu excited at 490 nm (Figure S10c,d, Supporting Information). Thus, by capitalizing on the Flu emission, the thermal transitions of the DCL linear polymers and the RCL nanogels can be probed, which correlate well with the thermal profiles determined by their turbidity and DLS measurements, respectively (Figure S11c,d, Supporting Information). These fluorescence studies are complementary with turbidimetry and DLS analyses, all of which confirm that indeed polymer architecture switching leads to the observation of completely different thermal transition profiles for the linear polymers and cross-linked nanogels. It is also noteworthy that the integrated emission intensity of Flu in all polymers and nanogels is reduced upon heating, possibly due to the formation of Flu aggregates, which increase the refractive index of the polymers or nanogels with respect to the aqueous media and fluorescence quenching at high temperatures, and this property can be harnessed to monitor the state of the polymers either in linear chains or in nanogels (see below).

Next, in order to demonstrate the fully reversible nature of the polymer architecture switching process, the DTT/DMSO treatment cycle was repeated five times and the $D_h$ and fluorescence intensity were monitored by DLS and fluorescence spectroscopy. As shown in Figure 3a, during the multiple polymer architecture switching process the $D_h$ for the DCL polymers and RCL nanogels remains almost constant, ~9 and 90 nm, respectively. In addition, the thermoresponsive fluorescence intensity oscillation of the RCL nanogels obtained at each cycle was switched between 21 and 61 °C (Figure 3b); reliable switching between two different fluorescent states is clearly seen, suggesting that the nanogel structure is maintained during the multiple architecture switching process and the nanogel swelling-deswelling process is fully reversible.

3. Conclusions

In summary, we have developed a reversible polymer architecture switching process that leads to the unique observation of distinct thermal responses associated with linear polymers and cross-linked nanogels. Turbidimetry, DLS, and fluorescence studies collectively reveal that the linear polymers have a sharp, discontinuous thermal transition whereas the nanogels prepared via simple cross-linking of the linear polymers have a linear, continuous thermal response. As far as we are aware, this is the first
demonstration of reversible switching of polymer architectures with distinct thermoresponses, and we expect this interesting observation will lead to new applications of these materials in a wide range of applications, such as drug release profile modulators and switchable actuators.

Supporting Information

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

Acknowledgements: The authors thank financial support from National Natural Science Foundation of China (51473038, 21674025).

Received: December 26, 2016; Revised: January 29, 2017; Published online: February 27, 2017; DOI: 10.1002/marc.201600808

Keywords: FRET; linear response; nanogels; reversible switching; thermoresponse