Temperature- and Redox-Directed Multiple Self Assembly of Poly(*N*-Isopropylacrylamide) Grafted Dextran Nanogels

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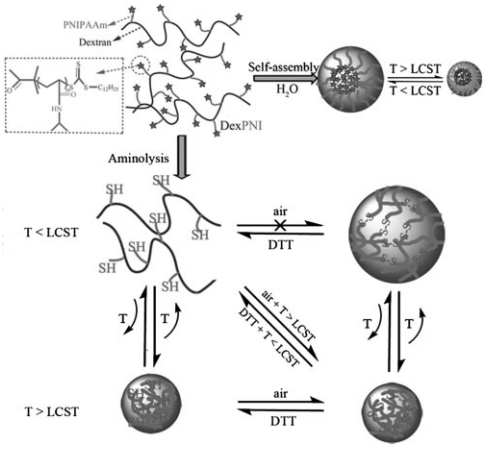
Poly(*N*-isopropylacrylamide) (PNIPAAm) grafted dextran nanogels with dodecyl and thiol end groups have been synthesized by RAFT process. Dodecyl-terminated polymers (DexPNI) can be readily dissolved in water and further self assemble into ordered stable nanostructures through direct noncovalent interactions at room temperature. SEM, AFM and DLS measurements confirm the formation of spherical nanogels at hundred-nanometer scales. The elevation of environment temperature will indirectly result in the formation of collapsed nanostructures due to the LCST phase transition of PNIPAAm side chains. Turbidimetry results show that the phase transition behaviors of DexPNI are greatly dependent on PNIPAAm chain length and polymer concentration: increasing PNIPAAm chain length and polymer concentration both lead to lower LCSTs and sharper phase transitions. Moreover, the dodecyl-terminated polymers can transform into thiol-terminated versions by aminolysis of trithiocarbonate groups, and further into chemical (disulfide) cross-linked versions (SS-DexPNI) by oxidation. SS-DexPNI nanogels have "doubled" chain length of PNIPAAm, and hence sharper phase transitions. In situ DLS measurements of the evolution of hydrodynamic radius attest that the self assembly of SS-DexPNI nanogels can be selectively directed by the change in either external temperature or redox potential. These nanogels thus are promising candidates for triggered intracellular delivery of encapsulated cargo. We can also expect that the polymer can be noncovalently (by dodecyl end groups) or covalently (by thiol end groups) coated on a series of nanomaterials (e.g., carbon nanotubes, graphene, gold nanomaterials) to build a variety of novel smart, and robust nanomaterials.



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Introduction

Nanostructured hydrogels (nanogels), which are formed by the specific arrangement of polymeric materials at nano-

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scopic dimensions, possess new properties that are not obtainable from simple polymer solutions and therefore are playing an increasing role in multiple biotechnology applications, such as tissue engineering, drug delivery, and intracellular sensing.[1–6] Self assembly of discrete components has been recognized as an important "bottom-up" technique to create various functionalized, hierarchical structures, including nanogels.[7–11] Stimuli-responsive polymers are emerging as particularly promising materials due to the capability of reversibly altering of their properties on receiving external signals.[1,12] Therefore, the self assembly of stimuli-responsive polymers into smart nanogels that can sense and respond to external stimuli offers new routes to obtain new and exciting structures, properties and applications of nanogels.[5,9,12–16] These nanogels may be self assembled not only by direct internal forces (e.g., by intrinsic noncovalent interactions), but also by indirect external stimuli.

The most popular stimuli include temperature, pH, light, redox activity, etc. Poly(*N*-isopropylacrylamide) (PNIPAAm) is one of the most studied biocompatible and temperature responsive polymer, which undergoes a phase transition above lower critical solution temperature (LCST) when polymer–polymer interactions become stronger than polymer–solvent interactions.[17] This fascinating behavior makes PNIPAAm an ideal basic building block for the temperature-directed assembly of nanogels.[1,12] Redox activity is also a promising stimulus for biotechnology applications because of the large difference in redox activity between mildly oxidizing extracellular and reducing intracellular spaces.[18–21] The presence of disulfide bonds in polymer networks makes it possible to achieve controlled self assembly of nanogels at different redox conditions by thiol–disulfide exchange reactions.

Dextran is a natural polysaccharide, which has been successfully used for biomedical applications because of the excellent biocompatibility, biodegradability, aqueous solubility, and nonfouling properties.[22–26] Early in our work, we have used a series of dextran-based stimuli responsive polymers to obtain robust and smart gold nanoparticles by either "post-modification" technique or "grafting-onto" approach.[27,28] The presence of dodecyl and thiol end functional groups in these polymers offers unique multiple self assemble possibilities by direct internal forces or indirect external stimuli. In this contribution, we report the multiple self assembly of PNIPAAm grafted dextran nanogels at different temperatures and redox conditions. These smart nanogels can: 1) be readily dissolved in cold water and self assemble into stable spherical nanostructures by noncovalent interactions; 2) form more complex assemblies upon heating; 3) be converted to thiol-terminated versions by aminolysis, and further reversibly (dis)assembled by either physical stimulus (temperature) or biochemically relevant stimulus (redox agent).

Experimental Section

Materials

Dextran ($\overline{M}_n \approx 70000$, Seebio Biotechnology), 2, 2′-azobis [2-(2-imidazolin-2-yl) propane] (VA-044, Wako), isopropylamine (IPA, Aldrich), and DL-Dithiothreitol (DTT, Aldrich) were used as received. *N*-isopropylacrylamide (NIPAAm, Aldrich) was purified by recrystallization from hexane. 2-(dodecylthiocarbonothioylthio)-2-methylpropanoic acid (DTM) was synthesized according to the literature.[29] All other reagents were purchased from commercial sources and used as received.

Synthesis of PNIPAAm grafted Dextran with Dodecyl end Groups (DexPNI)

Four samples of DexPNI with different chain lengths were synthesized by RAFT polymerization process as reported elsewhere.[27] The macro chain transfer agent (DexDTM) was synthesized by esterification of 2-(dodecylthiocarbonothioylthio)-2-methylpropanoic acid chloride with hydroxyl groups of dextran using 4-dimethylaminopyridine and triethylamine as esterification catalyst. The chain length of DexPNI was adjusted by the molar feed ratio of PNIPAAm to DTM groups. (Table 1) In a representative sample, NIPAAm (0.18 g, 1.6 mmol), water-soluble initiator VA-044 (0.05 g, 0.15 mmol) and DexDTM (0.2 g) were dissolved in water (40 mL) at 5–10 °C under N_2 atmosphere and the solution was kept at 60 °C for 4 h. $DexPNI_{36}$ was purified by dialysis against water and isolated by freeze-drying.

Synthesis and (de)cross-Linking of Dual-Stimuli Responsive Nanogels (SS-DexPNI)[6]

IPA (50 μl) was added to 10 ml N_2-bubbled DexPNI solution (5 mg · ml^{-1}) under vigorous stirring. The aminolysis reaction was allowed to proceed for 2 h. After vigorous air-bubbling the resulting solution at 50 °C for 24 h, SS-DexPNI was purified by dialysis against water and isolated by freeze-drying. DTT solution was introduced to SS-DexPNI solution at 25 °C and 40 °C under N_2 atmosphere. The final concentrations of DTT and SS-DexPNI were 10×10^{-3} M and 5 mg · ml^{-1}, respectively. This process was in situ monitored by dynamic light scattering (DLS) to record the evolution of hydrodynamic radius.

Characterization

^{1}H NMR spectra were obtained on a Bruker DRX-500 spectrometer operating at 500 MHz. Atomic force microscopy (AFM) was carried out on a CSPM 5000 scanning probe microscope. Scanning electron microscope (SEM) image was taken on JSM-6700F field emission scanning electron microscopy. The samples for AFM (SEM) measurements were prepared by deposing a drop of polymer solution on a mica (glass) substrate and drying under vacuum at room temperature. DLS measurements were performed on Brookhaven Instruments BI-200SM at a wavelength of 532 nm and a detection angle of 90°. The particle size distribution and average particle size were obtained from NNLS algorithm in the

Table 1. Characterization of DexPNI nanogels with different chain length of grafted PNIPAAm.

Nanogel	$\overline{M}_{n\,NMR}$ [a]	PNIPAAm content [wt%]	PNIPAAm chain length		LCST [°C] [b]		R_h [nm] [c]	
			theoretical	calculated $_{NMR}$	50% T	90% T	25 °C	50 °C
$DexPNI_4$	8.08×10^4	7.8	5	4.3	47.5	36.6	88.8	88.7
$DexPNI_7$	8.57×10^4	13.1	10	7.6	37.2	33.8	104.8	90.0
$DexPNI_{16}$	9.89×10^4	24.7	20	16.6	35.2	32.7	189.1	114.6
$DexPNI_{36}$	1.29×10^5	42.2	40	36.9	32.7	32.2	229.6	102.6

[a]Determined by ^{1}H NMR and molecular weight of dextran is used as 70 000; [b]polymer concentration = 5 mg · ml^{-1}; [c]Determined by DLS at a concentration of 5 mg · ml^{-1} at 25 and 50 °C.

instrument software. UV–Vis absorbance spectra were taken on a Unico 2802 UV–Vis spectrometer. For DLS and UV–Vis measurements, the temperature of the sample solutions was controlled within ±0.1 °C by circulating water baths linked to the equipments, and the solutions were allowed to stand for 15 min at each desired constant temperature.

Results and Discussion

PNIPAAm grafted dextran (DexPNI) nanogels with dodecyl end groups were prepared by aqueous reversible addition–fragmentation chain transfer (RAFT) polymerization of NIPAAm using a dextran-based macro-chain transfer agent (DexDTM) as described previously.[27] DexDTM was synthesized by esterification of dextran with a versatile chain transfer agent 2-(dodecylthiocarbonothioylthio)-2-methylpropanoic acid (DTM). This chain transfer agents is versatile because it not only can be used for RAFT polymerization of NIPAAm and many other monomers, but also can provide biochemically cross-linkable groups (thiol groups) after aminolysis of DTM groups, as well as stable coating on carbon nanomaterials and gold nanomaterials.[27–31] There are approximately 12–13 DTM groups in one dextran chain as determined by ^{1}H NMR spectra of DexDTM.[27] It should be noted that the transfer agents and resulting polymers (DTM, DexDTM and DexPNI) possess no or little mercaptan odor. As shown in Table 1, four DexPNI nanogel samples that differ in the chain length of grafted PNIPAAm are prepared by varying the feed molar ratio of NIPAM to DTM group. On the basis of the ^{1}H NMR spectra of DexPNI, the chain length of the grafted PNIPAM chain is 4.3, 7.6, 16.6, and 36.9 for $DexPNI_4$, $DexPNI_7$, $DexPNI_{16}$ and $DexPNI_{36}$, respectively.

Direct Self Assembly of DexPNI Nanogels by Noncovalent Interactions

As depicted in Figure 1a, DexPNI is composed of hydrophilic backbones (dextran) and hydrophobically modified side chains (dodecyl-terminated PNIPAAm). Therefore, the polymers can be noncovalently cross-linked (by dodecyl goups) to form self assembled nanostructures in cold water. Dynamic light scattering (DLS) analysis is used to evaluate the self assembly properties of the nanogels (Figure 1b and Table 1). The hydrodynamic radius (R_h) of the nanogels is increased from 88.8 to 229.6 nm when the average chain length of grafted PNIPAAm increases from 4.3 to 36.9. After incubation in PBS solution for weeks at room temperature, the nanogels do not display significant changes in their narrow and monomodal size distributions, which is suggestive of the formation of stable nanostructures. Visualization of the self assembled nanostructures of $DexPNI_{13}$ in dried state is achieved by scanning electron microscope (SEM) and atomic force microscope (AFM). (Figure 1c and d) SEM image shows that the nanogel appears as uniform spheres with average size of 116 ± 48 nm. AFM image also confirms that the nanogel has a spherical shape with dimensions of 108 ± 37 nm in accordance with SEM results. These results attest to the formation of spherical nanogel with diameter around 110 nm, which is slightly smaller than that determined by DLS due to the shrinkage of the nanogels after water evaporation.

Temperature Directed Self Assembly of DexPNI Nanogels

It has been widely reported that the aqueous solution of PNIPAAm posses a hydrophilic/hydrophobic balance, which could be disturbed by heating the solution above LCST. The hydrophilic and hydrophobic regions are amide groups and isopropyl groups of PNIPAAm, respectively. Therefore, heating of DexPNI nanogel solutions will create new cross-linkages relying on the dehydrated PNIPAAm chains, which further direct the formation of collapsed self assemblies. Figure 2 compares the ^{1}H NMR spectra of $DexPNI_{16}$ in D_2O (10 mg · ml^{-1}) at different temperatures. The intensity of hydrophilic backbone (dextran) signals decreases imperceptibly when the temperature is increased from 25 to 40 °C. In contrast, the proton signals intensity at

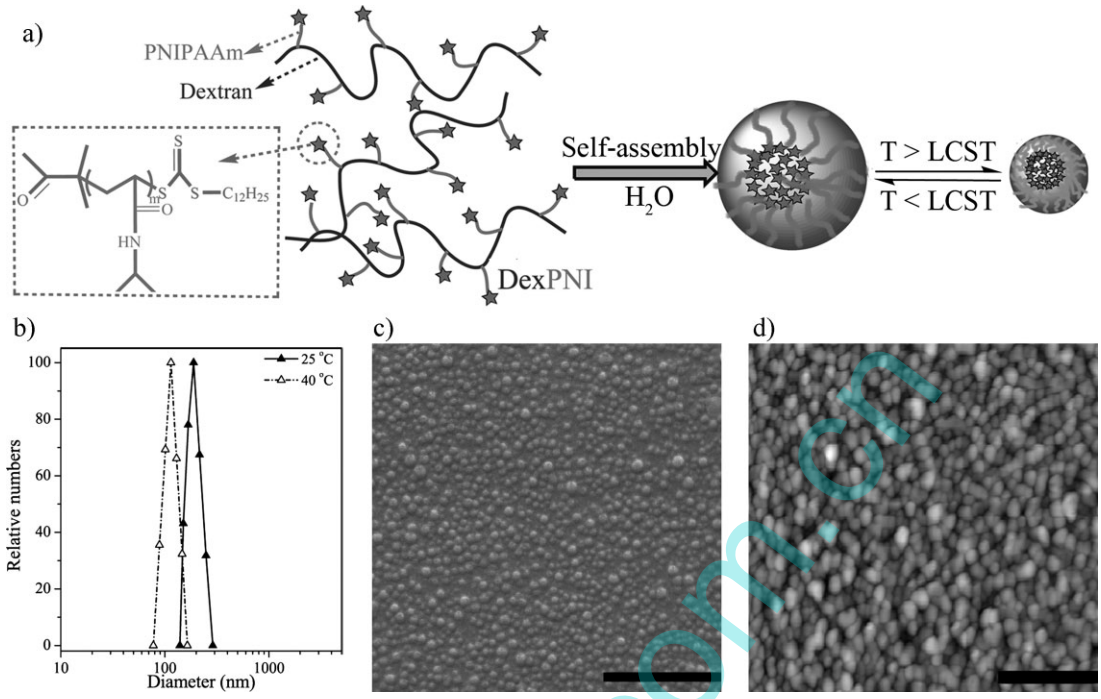

Figure 1. a) Schematic depiction of DexPNI nanogels and the self assembly of DexPNI below and above LCST in water. b) Typical DLS size distributions of $DexPNI_{16}$ at 25 °C (solid line) and 40 °C (dash line). c) SEM (scale bar = 2 μm) and d) AFM images (scale bar = 1 μm) of $DexPNI_{16}$ at 25 °C.

1.3–2.2 ppm attributed to the resonance of PNIPAAm chains decrease drastically upon the increasing of temperature from 25 to 34 °C, and finally could barely be detected at 40 °C. The drastically decreased signals of PNIPAAm at temperatures above LCST are attributed to the dehydration of the PNIPAAm chains, indicating the heat-induced formation of new cross-linkages and more complex self-assembled nanostructures. To further investigate the thermo-induced self-assembly properties of DexPNI nanogels, the aqueous hydrodynamic radius of the nanogels are recorded by DLS at 50 °C, shown in Table 1. The R_h values of these nanogels decrease more or less upon heating. The nanogel with longer PNIPAAm chain length has larger decrement, while the change of R_h of $DexPNI_4$ with shortest PNIPAAm chain length could not even be detected. Although the R_h values of nanogels with different PNIPAAm chain length vary in a wide range from 88 to 229 nm at 25 °C, they fall into a limited range from 88 to 114 nm at 50 °C. Therefore, it is evident that the thermo-induced phase transition of PNIPAAm chains of the nanogels results in significant changes in self assembly behaviors of the DexPNI nanogels. In addition, the nanogels could regain their size by bringing the solution temperature back to 25 °C, indicating the thermo-induced self assembly was reversible, which benefits from the reversible phase transition of PNIPAAm.

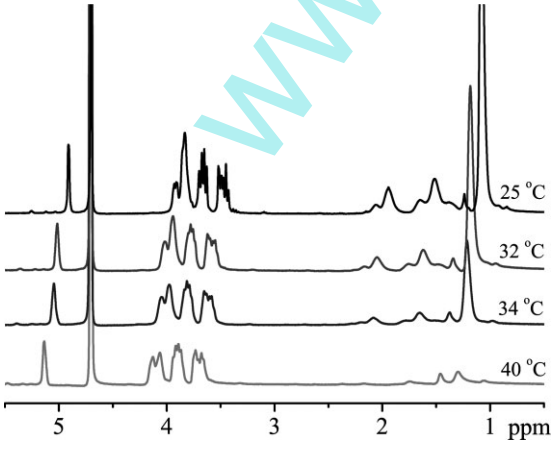

Figure 2. ^1H NMR spectra of $DexPNI_{16}$ in D_2O at different temperatures, and the polymer concentration is 10 mg · ml^{-1}.

Chain Length and Concentration Dependent Phase Transitions of DexPNI

In pure PNIPAAm systems, the effects of PNIPAAm molecular weight on LCSTs have been extensively studied and the LCSTs have been found to be inversely-, directly-, or non-dependent on molecular weight.[32–34] To study the phase transition behavriors in PNIPAAm grafted polysaccharides systems, turbidimetry is used to characterize the LCST behaviors of the DexPNI polymers with different PNIPAAm chain lengths at different concentrations.

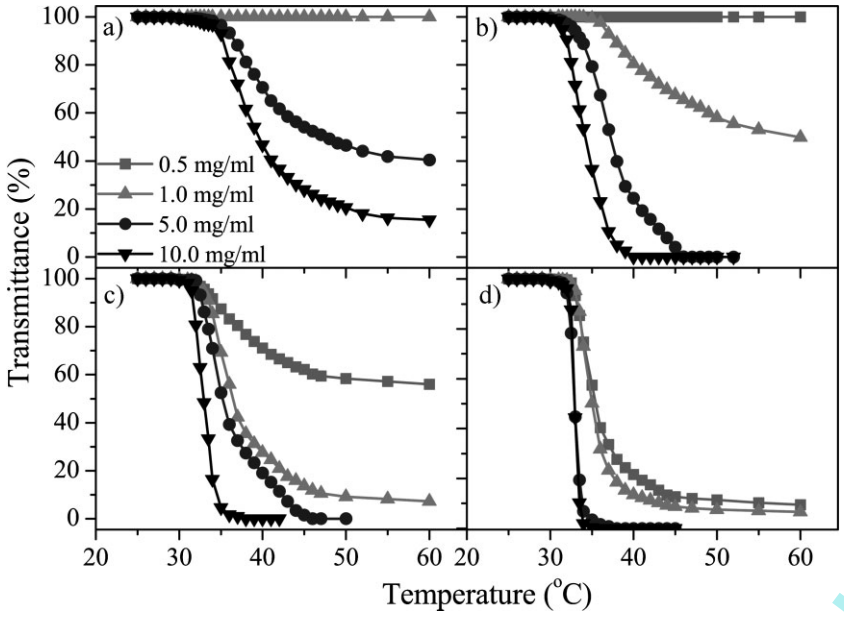

Figure 3. Transmittance vs temperature for DexPNI nanogels with different concentrations and chain length of grafted PNIPAAm. a,b,c,d) $DexPNI_4$, $DexPNI_7$, $DexPNI_{16}$, and $DexPNI_{36}$, respectively.

Figure 3 shows the change in the transmittance of polymer solutions against temperature. The phase transition behaviors of these polymers are found to be strongly dependent on PNIPAAm chain length and polymer concentration. The temperatures at 50% and 90% light transmittance (denoted as 50% T and 90% T) are used to remark the PNIPAAm chain length and hydrophobic end group effects on LCST, respectively.[32,33] (Table 1) In general, increasing PNIPAAm chain length and polymer concentration both lead to lower LCSTs and sharper phase transitions. This result is consistent with previous studies focusing on molecular weight, concentration, and end group effects on phase transitions of pure PNIPAAm systems.[32,33] With the increase of polymer concentration from 0.5 to 10 mg $\cdot$ ml^{-1}, the cloud points (50% T) of $DexPNI_{16}$ and $DexPNI_{36}$ fall into the typical range of PNIPAAm LCST (31 $\sim$ 33 °C). At relatively high concentrations, the polymers could reach equilibrium more readily upon heating, which resulted in sharper phase transitions. The early phase transitions (90% T) can be attributed to hydrophobic end group effect, which is especially significant on the polymers with shorter PNIPAAm chains. The broadened phase transitions for the polymer with shorter PNIPAAm chains and lower concentrations suggest that the phase separations are incomplete. It is worth noting that the polymers used in this study have high non-thermo-responsive group content. The longest PNIPAAm chain grafted polymer ($DexPNI_{36}$) which shows quite sharp thermal phase transition behaviors still has more than half of dextran in weight.

Dual Stimuli Directed Self Assembly of SS-DexPNI Nanogels

Figure 4a illustrates the procedure to create dually responsive nanogels: the physical cross-linkages (PNIPAAm) and chemical cross-linkages (disulfide bonds) are reversibly responsive to temperatures and redox potentials, respectively. The trithiocarbonate groups of $DexPNI_{16}$ were first converted to thiol groups by aminolysis under anaerobic condition at 5–10 °C. The resulting solution was then oxidized at 50 °C by vigorous oxygen gas flow to create disulfide cross-linked nanogel $SS\text{-}DexPNI_{16}$. This nanogel is able to form different self-assemblies at different temperatures and redox-conditions. As shown in Figure 1b, 4b and 4c, disulfide cross-linking process has two significant effects on nanogel properties: 1) the sizes of nanogels at 25 °C and 40 °C are both increased after cross-linking because of the alternation in cross-linking manners (from noncovalent to covalent); 2) the chain length of the nanogel is "doubled", resulting in a sharper phase transition which is similar with that of PNIPAAm homopolymers (high molecular weight) and the nanogel grafted with longer PNIPAAm chain ($DexPNI_{36}$). The size decrease of $SS\text{-}DexPNI_{16}$ from 235.0 to 112.9 nm upon heating also confirms that the disulfide cross-linked nanogel undergoes a temperature directed self assembly process.

The disulfide linkages in the nanogel network can be easily cleaved and reduced to free thiols by reducing agents with great efficiency, such as dithiothreitol (DTT) and glutathione. Therefore, another impressive feature of the disulfide cross-linked nanogels is their reductively labile nature. (Figure 4a) The self assembly of SS-DexPNI nanogels can be selectively directed by the change in either external temperature or redox potential. It is confirmed by in situ DLS studies on the evolution of $SS\text{-}DexPNI_{16}$ size distribution in response to 10×10^{-3} M DTT (mimicking the reductive intracellular environment) at different temperatures. Below LCST, the size distribution of DTT-treated suspension is found to be irregular after the cleavage of disulfide linkages (data not shown), indicating that $SS\text{-}DexPNI_{16}$ disassembles from cross-linked network and transforms into separate hydrophilic chains. This result also confirms the noncovalent cross-linking of DexPNI nanogels by alkyl-groups. Above LCST, DTT causes an increase in nanogel size from 121.4 to 153.6 nm within 30 min, (Figure 4d) indicating that the nanogel is still cross-linked by PNIPAAm chains despite of the cleavage of disulfide linkages. Cooling down

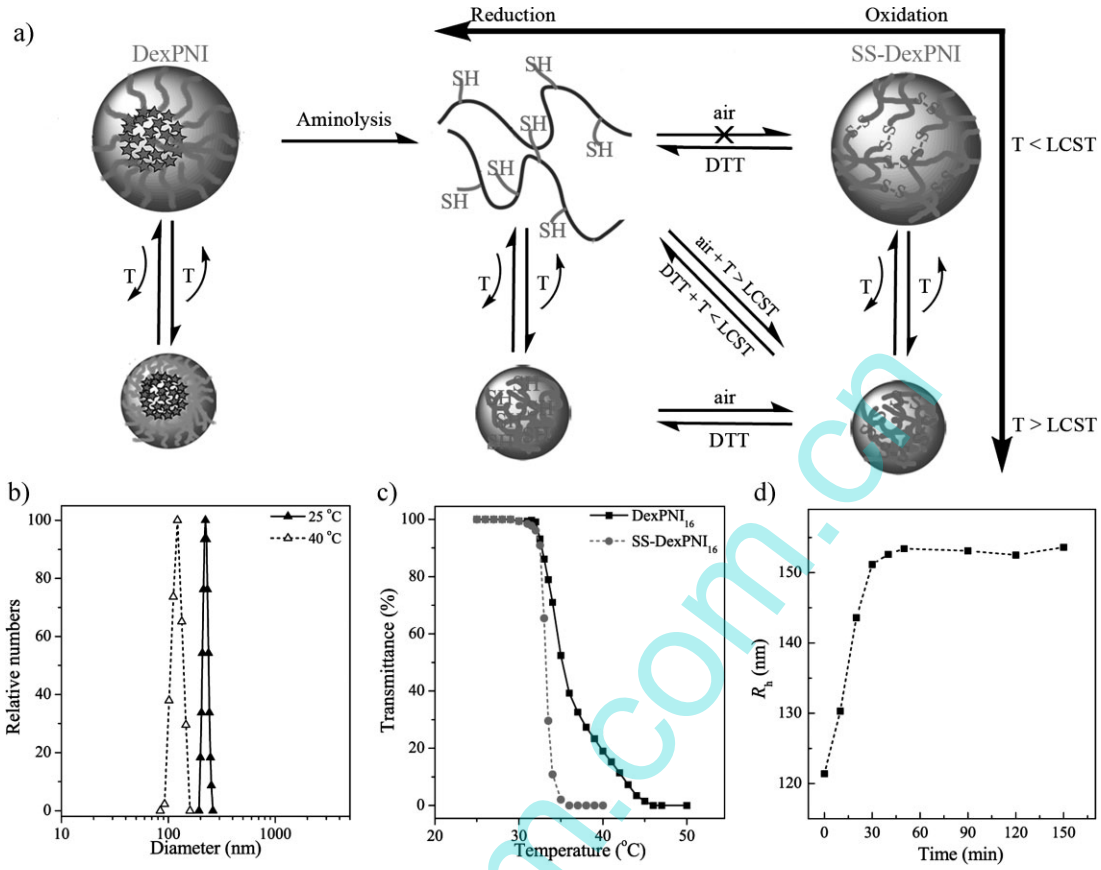

Figure 4. a) Schematic depiction of the preparation of SS-DexPNI nanogel and its dual stimuli (temperature and redox activity) directed self assembly. b) Typical DLS size distributions of SS-DexPNI$_{16}$ at 25 °C (solid line) and 40 °C (dash line). c) Transmittance vs temperature for DexPNI$_{16}$ (solid line) nanogels and SS-DexPNI$_{16}$ (dash line), and the polymers concentrations are both 5 mg · ml^{-1}. d) Reduction (10×10^{-3} M DTT) directed disassembly of SS-DexPNI$_{16}$ at temperature above LCST: R_h vs time after DTT treatment.

the solution to 25 °C results in fluctuating size distributions, which is consistent with the results obtained by DTT-treatment of SS-DexPNI$_{16}$ at 25 °C. Therefore, the disulfide cross-linked nanogels could be reduced into unstable and stable nanostructures at the temperatures below and above the LCST, respectively. In addition, the (de)cross-linking is redox-reversible by thiol–disulfide exchange reaction since the size of disulfide-cleaved nanogels could be recovered by oxygen aeration at 50 °C.

Conclusion

We have demonstrated the multiple self assembly of PNIPAAm grafted dextran nanogels with dodecyl and thiol end groups. The as-synthesized DexPNI polymers can be readily dissolved in water and further self assemble into ordered nanostructures at hundred-nanometer scales through direct noncovalent interactions at room temperature. The elevation of environment temperature will indirectly result in the formation of more complex nanostructures due to the LCST phase transition of PNIPAAm side chains. The phase transition behaviors of DexPNI are greatly dependent on PNIPAAm chain length and polymer concentration. Furthermore, the self assembly of SS-DexPNI nanogels, which are generated by aminolysis of DexPNI internal trithiocarbonate groups, can be selectively directed by the change in either external temperature or redox potential. After disulfide cross-linking, the nanogels become more sensitive to temperature, suggesting that the release kinetics of the nanogels can be possibly adjusted by "varying" the PNIPAAm chain length. These nanogels thus are promising candidates for triggered intracellular delivery of encapsulated cargo. Last but not least, we can also expect that the polymer can be noncovalently (by dodecyl end groups) or covalently (by thiol end groups) coated on a series of nanomaterials (e.g., carbon nanotubes, graphene, gold nanomaterials) to build a variety of novel smart, and robust nanomaterials.

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