Macromolecules
NOTE
pubs.acs.org/Macromolecules

Phototunable LCST of Water-Soluble Polymers: Exploring a Topological Effect

Yi Zhao,[†] Luc Tremblay,[‡] and Yue Zhao*,[†]

[†]Département de chimie and [‡]Département de médecine nucléaire et de radiobiologie and Centre d'imagerie moléculaire de Sherbrooke, Université de Sherbrooke, Sherbrooke, Québec, Canada J1K 2R1

Thermoresponsive and water-soluble polymers have widespread academic and industrial interest due to their potential applications in many areas such as drug and gene delivery, separation, and surface modification.[1] Many of them display a lower critical solution temperature (LCST): the polymer is soluble (hydrated) at $T <$ LCST but becomes insoluble (dehydrated) at $T >$ LCST. Examples of LCST polymers include poly(*N*-isopropylacrylamide) (PNIPAM),[2] poly[oligo(ethylene glycol) methacrylate] (POEGMA),[3] and poly(*N*,*N*-dimethylaminoethyl methacrylate) (PDMAEMA),[4] to name only a few. Generally speaking, as the solution temperature is raised across the LCST, polymer chains undergo a coil-to-globule transition, and the globules, as they become increasingly dehydrated, can associate into large aggregates, resulting in a drop of the solution transmittance and an observable cloud point.[5] Since this thermally switchable water solubility is the key feature explored for possible applications,[1] it is important to develop the ability to precisely control the transition temperature. The general method consists in incorporating either hydrophilic or hydrophobic comonomer units into a given polymer structure to increase or decrease, respectively, the LCST.[6] In principle, the method allows the LCST to be adjusted to a desired temperature by fine-tuning a random copolymer composition. However, this requires separate polymerizations with different feed ratios of the monomers. In this paper, we report a new, simple, and efficient optical tuning method that allows the cloud point temperature of a single starting polymer to be controlled over a wide temperature range of about 30 °C.

Our approach for phototunable LCST explores a chain topology effect schematically illustrated in Figure 1. The basic idea is to use intrachain photo-cross-linking to introduce loops into the polymer chain structure. Also shown in the figure is the chemical structure of the polymer used for this proof-of-concept study, namely, poly{*N*,*N*-dimethylaminoethyl methacrylate-*co*-4-methyl-[7-(methacryloyl)oxyethyloxy]coumarin} (P(DMAEMA-*co*-CMA)). Using this polymer containing a number of coumarin comonomer units, which is soluble in cold water and becomes insoluble upon heating, the reversible photodimerization of the pendent coumarin groups provides an easy means to optically control the intrachain cross-linking density that determines the number of loops formed. We anticipated that the presence of loops on the initially linear polymer chains would affect the thermal phase transition temperature. The rationale was inspired by some recent reports showing that the chain topology could influence the water solubility of polymer chains or flower micelles.[7,8] In one case, a cyclic PNIPAM was found to display a LCST that is several degrees higher than that of its linear PNIPAM precursor,[7] while in another case, micelles formed by a cyclic amphiphilic block copolymer (BCP) were shown to be thermally more stable than those formed by the linear BCP counterpart.[8] Herein we demonstrate that introducing chain loops into an initially linear polymer through intrachain photo-cross-linking could shift drastically the solubility transition to higher temperatures.

Two samples were synthesized using a procedure reported previously.[9] Being aware of that intrachain photodimerization of coumarin groups should occur only in dilute solutions, we first used P(DMAEMA$_{131}$-*co*-CMA$_{12}$) to investigate the effect of polymer concentration on the photo-cross-linking in aqueous solution. The sample was dissolved in iced water at three different concentrations (1, 10, and 100 mg/mL), and the solutions were exposed to UV light (365 nm, 50 mW/cm^2) to achieve the photostationary state (~90% dimerization of coumarin groups). After drying, the polymer was dissolved in THF for the GPC measurements. Figure 2 shows the results for the samples photodimerized in water at different polymer concentrations as well as the initial sample without photodimerization for comparison; their apparent molecular weights and polydispersity indices (PDI) (relative to polystyrene standards) are also indicated. It is seen that the photodimerization at polymer concentrations of 1 and 10 mg/mL results in a shift of the elution peak to longer times as compared to the initial sample. This indicates the occurrence of intrachain cross-linking that, understandably, could lead to a more compact chain hydrodynamic volume. By contrast, at the polymer concentration of 100 mg/mL, interchain cross-linking is detected from the elution peak appearing at shorter elution times, which coexists with intrachain cross-linking as revealed by the peak at longer elution times. This result is no surprise because at high polymer concentrations coumarin groups located on different polymer chains have a chance to encounter and part of the photodimerization could occur in an interchain fashion. Unless otherwise stated, all results reported below were obtained with samples subjected to photodimerization in water at the polymer concentration of 1 mg/mL, ensuring the intrachain photo-cross-linking.

Figure 3 presents the results obtained with the solution of P(DMAEMA$_{131}$-*co*-CMA$_{12}$). In Figure 3a are the UV−vis absorption spectra of the solution recorded after various times of UV irradiation. The continuous decrease of the absorption band of coumarin at ~320 nm over irradiation time indicates efficient intrachain photodimerization of pendent chromophore groups.[10] The photodimerization degree can be calculated from $1 - A_t/A_0$, where A_0 and A_t are the initial absorbance and the

Received: March 25, 2011
Revised: April 13, 2011
Published: April 21, 2011

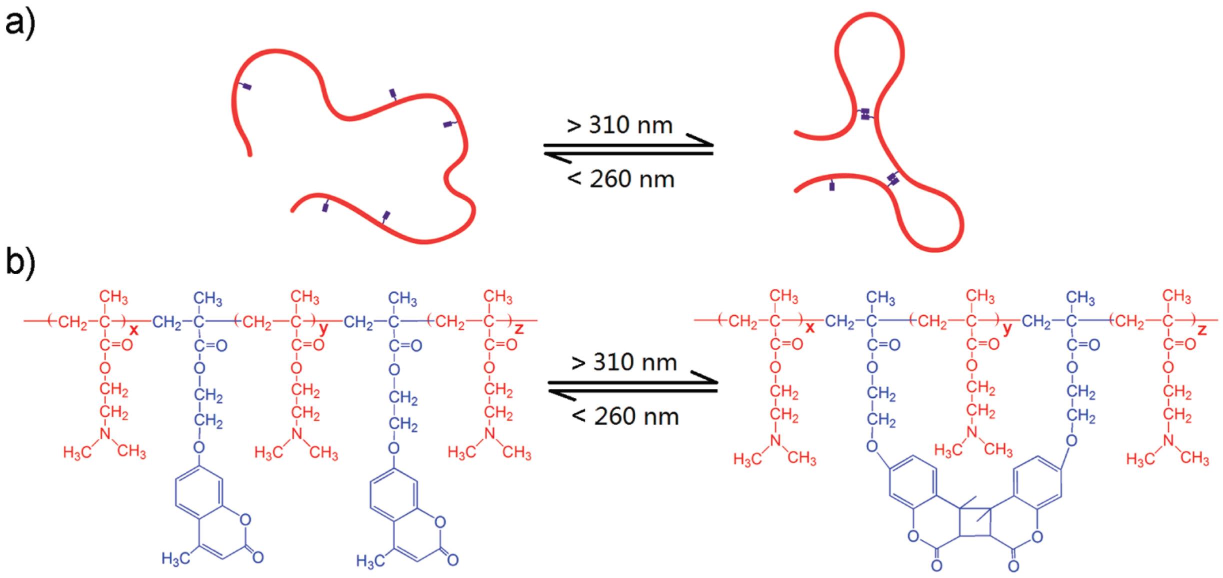

Figure 1. (a) Schematic illustration of the formation of chain loops upon intrachain photodimerization of pendent coumarin groups. (b) Chemical structure of coumarin-incorporated random copolymer based on poly(*N*,*N*-dimethylaminoethyl methacrylate).

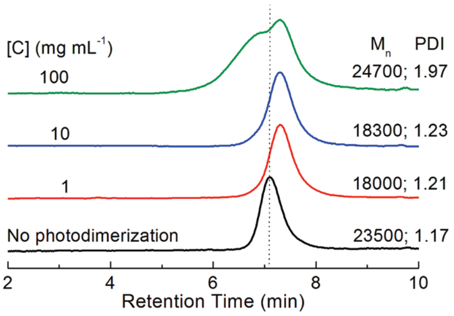

Figure 2. GPC curves of P(DMAEMA$_{131}$-*co*-CMA$_{12}$) in THF for the initial sample (without photodimerization) and the samples subjected to photodimerization of coumarin groups in water at different polymer concentrations.

absorbance after irradiation time *t* at 320 nm, respectively. The inset is a plot of the photodimerization degree vs irradiation time. The highest dimerization degree of ∼94% was achieved after 45 min UV irradiation. Figure 3b shows the solution transmittance measurement results obtained with samples photodimerized to different degrees, i.e., different intrachain cross-linking densities. A clear cloud point is visible for all solutions. For the initial sample, the cloud point appears at about 25 °C, while after photodimerization, it increases continuously with increasing the dimerization degree, shifting to ∼50 °C for the polymer with 94% of dimerization. Figure 3c plots the increase in the cloud point temperature with respect to the initial sample, ΔT, vs photodimerization degree. There appear to have two regions in which ΔT displays a linear increase over the dimerization degree but with different slopes. The rise of the cloud point seems to be faster for dimerization degrees above 70%. This result shows that the water solubility of the polymer can easily be tuned by controlling the photodimerization degree of the pendent coumarin groups. The phototunable solubility can also be appreciated visually as shown by the photographs in Figure 3d. At 40 °C, the solution of the initial sample is completely opaque (well above the cloud point) but turns totally transparent with 91% photodimerization (well below the shifted cloud point). The solution transparency at intermediate photodimerization degrees also corroborates well with the transmittance data (Figure 3b), corresponding to the varying extent of polymer chain aggregation. Moreover, the intrachain photo-cross-linking by coumarin dimerization is a reversible photochemical reaction, as the cleavage of cyclobutane bridges can occur when coumarin dimers absorbs UV light at shorter wavelengths[10] (Figure 1). We investigated this possibility by exposing the aqueous solution of P(DMAEMA$_{131}$-*co*-CMA$_{12}$) with a dimerization degree of 94% to UV light centered at 254 nm. UV–vis spectral measurements indicated a partial photo-de-cross-linking with the dimerization degree decreased to 53%, while transmittance measurements with this photo-de-cross-linked solution showed a decrease of the cloud point from ∼50 to 42 °C (data not shown). Since the sample with a dimerization degree of 54% initially has a cloud point at ∼35 °C (Figure 3b), this result suggests that the optical tuning is only partially reversible.

Variable-temperature ^{1}H NMR spectra of P(DMAEMA$_{131}$-*co*-CMA$_{12}$) in D_2O (1.0 mg/mL) of the initial sample and the sample with a photodimerization degree of 91% were recorded. In both cases, the polymer was first dissolved in cold D_2O (15 °C) and then heated stepwise with an interval of 2 °C. The solution was held at a given temperature for 5 min before the spectrum was acquired. Figure 4 shows ^{1}H NMR spectra only at some chosen temperatures (for the sake of clarity). For the sample without photo-cross-linking (Figure 4a), the resonance signals of PDMAEMA at ∼2.2 ppm (CH_3 to N), 2.6 ppm (CH_2 to N), and 4.0 ppm (CH_2 to O) begin to decrease in intensity after 26 °C due to the dehydration and aggregation of polymer chains. Weak resonance signals of coumarin can be noticed in the magnified region of 5.5–8 ppm. After intrachain photo-cross-linking (Figure 4b), the peaks of PDMAEMA display reduced intensity only after ∼46 °C. Likewise, the signals of coumarin dimers can be seen after magnification. By plotting the integral of the resonance peak at 2.2 ppm as a function of solution temperature (Figure 4c), it becomes visible that the sample after

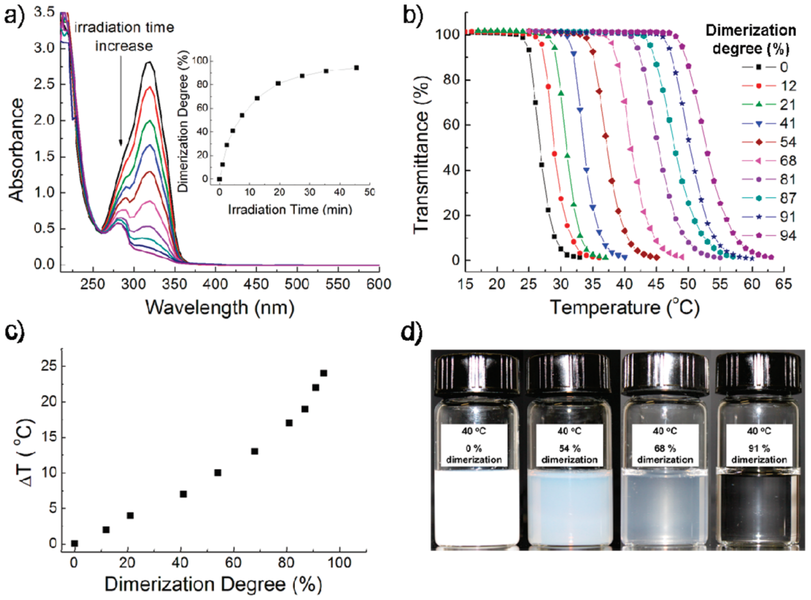

Figure 3. (a) UV−vis spectra of P(DMAEMA$_{131}$-*co*-CMA$_{12}$) in water exposed to UV light for photodimerization of coumarin groups (solution diluted to 0.5 mg/mL for the taking of spectra); the inset is a plot of photodimerization degree vs irradiation time. (b) Transmittance change as a function of temperature for P(DMAEMA$_{131}$-*co*-CMA$_{12}$) solutions (1.0 mg/mL) with samples photodimerized to different degrees. (c) Increase in the cloud point temperature vs photodimerization degree (data from Figure 3b). (d) Photographs of polymer solutions at 40 °C with different dimerization degrees (from left to right: 0, 54, 68, and 91%).

photodimerization is more soluble in water and dehydrates at significantly higher temperatures. Similar plots were obtained with other resonance peaks of PDMAEMA. These ^{1}H NMR results thus confirm that the increase in the cloud point as revealed by the transmittance measurements (Figure 3) originates from an increased LCST of the intrachain cross-linked P(DMAEMA-*co*-CMA).

To further confirm the phenomenon, we also performed measurements on a second sample, P(DMAEMA$_{114}$-*co*-CMA$_{10}$), which has a similar concentration of coumarin groups (~8 mol %) but a lower molecular weight. The results are shown in Figure 5. With the same polymer concentration of 1 mg/mL, the transmittance measurements show the continuous increase of the cloud point temperature with increasing the photodimerization degree (Figure 5a). The upward shift reaches 30 °C for the sample with a dimerization degree of 92%. The effect of the polymer concentration on the largest increase in the cloud point before and after photodimerization to 92% was also investigated. By controlled evaporation of water, the polymer solution was concentrated to 2, 3, and 4 mg/mL, and the transmittance measurements were carried out. The result indicates that the largest increase in the cloud point temperature is little affected by the polymer concentration up to 4 mg/mL.

The large increase in the cloud point temperature (25−30 °C), which is manifestation of an increased LCST, upon dimerization of about 8 mol % of coumarin pendent groups of the polymer cannot be caused by a conformational and/or polarity change arising from the photochemical reaction. For thermosensitive water-soluble polymers containing photochromic comonomer units, if the conformational change arising from a photochemical reaction (e.g., trans−cis isomerization) increases the polarity of the chromophore, a shift of the LCST to higher temperatures could be observed, but the increase generally is very small (a few degrees).[11] In the present case, the hydrophobic

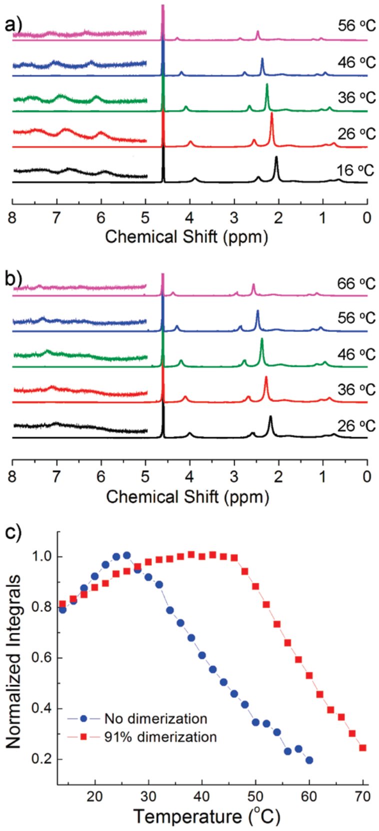

Figure 4. (a, b) Variable-temperature ^{1}H NMR spectra of P(DMAEMA$_{131}$-*co*-CMA$_{12}$) in D$_2$O (1.0 mg/mL) before and after, respectively, photodimerization to a degree of 91%; the magnified 5−8 ppm regions shows resonance signals of coumarin groups and their dimers. (c) Change in the normalized integral of the peak at ~2.2 ppm (CH$_3$ to N in DMAEMA) as a function of solution temperature.

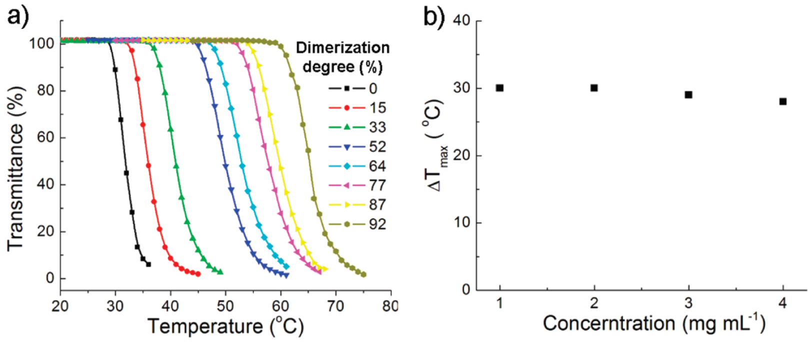

Figure 5. (a) Transmittance change as a function of temperature for P(DMAEMA$_{114}$-*co*-CMA$_{10}$) solutions (1.0 mg/mL) solutions with samples photodimerized to different degrees. (b) The largest cloud point temperature increase vs polymer concentration.

coumarin group cannot switch to be hydrophilic upon dimerization. Actually, with a cyclobutane ring replacing two double bonds (loss of conjugation) and the resulting symmetrical structure, the dimer should have lower polarity than the monomeric coumarin. If this is the case, the dimerization of coumarin should favor the dehydration and contribute to decrease the LCST. Obviously, the observed large increase in the LCST points to another dominant mechanism that favors the solubility.

The photocontrollable intrachain cross-linking, which induces the formation of chain loops, is likely to be the origin. As the intrachain photodimerization increases, the average number of loops formed on each chain increases accordingly. It is easy to picture that the loops should reduce the interchain entanglement (or linking) which results in a repulsive force.[7,12] This retarded chain aggregation could delay their dehydration upon temperature rise and, consequently, leads to an increase in the cloud point temperature. The phototunability comes from the fact that the effect should be sensitive to the number of loops which is directly determined by the photodimerization degree of coumarin pendent groups. In principle, with the photodimerization degree reaching the maximum level of ∼95% the loops should be very small for the two samples, and the individual polymer chains become compact particles, which may hinder the hydration of chain segments.[7,12] The continuous, and even more efficient, rise of the cloud point at high dimerization degrees above 70% (Figure 3c) is quite surprising to this regard. One possible explanation is that the coumarin comonomer units were not completely distributed statistically along the polymer chain under the used copolymerization conditions,[9] which would mean that the increase in the number and the decrease in the size of effective loops were not linearly proportional to the apparent dimerization degree. In future studies, in order to thoroughly elucidate the topology effect on polymer solubility in water, it will be interesting to use more advanced synthetic methods to prepare samples with well controlled chain loops.[13] Nevertheless, it should be noted that the use of coumarin dimerization to introduce chain loops has the appealing advantage to be reversible, even though it turned out to be challenging to fully reverse the photodimerization reaction and the related properties.[10]

To summarize, we demonstrated a new, simple, and efficient method that allows one to optically tune the LCST of thermosensitive water-soluble polymers based on, we believe, a topological effect. The method uses a photocontrollable intrachain cross-linking reaction to introduce chain loops onto an initially linear polymer structure. We found that the intrachain photodimerization of about 8 mol % of coumarin groups in PDMAEMA could increase the cloud point temperature by 30 °C. This chain topology effect on the cloud point (or LCST) would be a general effect that can be explored for other water-soluble polymers displaying a LCST.

■ EXPERIMENTAL SECTION

The two samples, P(DMAEMA$_{131}$-*co*-CMA$_{12}$) and P(DMAEMA$_{114}$-*co*-CMA$_{10}$), were synthesized and characterized according to a literature method.[9] Gel permeation chromatography (GPC) measurements were carried out at 35 °C with the polymer dissolved in THF using a Waters system equipped with a refractive index detector (RI 410) and a photodiode array detector (PDA 996), the elution rate being 1.0 mL/min and polystyrene standards used to calibrate the system. Variable-temperature ^{1}H NMR spectra were recorded on a Varian 600 MHz spectrometer (INOVA system) in D_2O with temperature interval of 2 °C and a thermal equilibrium time of 5 min at each temperature before taking the spectrum. The UV light used for the photodimerization of coumarin groups at >310 nm was generated with a spot curing system (Novacure) with a 320−500 nm filter, and the intensity was around 50 mW cm^2. For the photocleavage of cyclobutane bridges, a UVS-28 EL Series lamp (254 nm, 8 W) was used at a distance of 5 cm from the solution. All polymer solutions were cooled by ice and exposed to UV light for dimerizeation in the cold water. UV−vis spectra were recorded using a Varian 50 Bio spectrophotometer with a temperature-controllable sample holder. Transmittance at 700 nm was measured as a function of solution temperature, the solution being heated at a rate of ∼0.5 °C/min.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: yue.zhao@usherbrooke.ca.

■ ACKNOWLEDGMENT

We acknowledge the financial support from the Natural Sciences and Engineering Research Council of Canada (NSERC) and le Fonds québécois de la recherche sur la nature et les technologies of Québec (FQRNT). Y.Z. is a member of the FQRNT-funded Center for Self-Assembled Chemical Structures.

■ REFERENCES

(1) (a) Qiu, Y.; Park, K. *Adv. Drug Delivery Rev.* **2001**, *53*, 321–339. (b) Gil, E. S.; Hudson, S. M. *Prog. Polym. Sci.* **2004**, *29*, 1173–1222. (c) Bromberg, L. E.; Ron, E. S. *Adv. Drug Delivery Rev.* **1998**, *31*,

197–221. (d) de las Heras Alarcón, C.; Pennadam, S.; Alexander, C. *Chem. Soc. Rev.* **2005**, *34*, 276–285. (e) Luzinov, I.; Minko, S.; Tsukruk, V. *Prog. Polym. Sci.* **2004**, *29*, 635–698.

(2) (a) Schild, H. G. *Prog. Polym. Sci.* **1992**, *17*, 163–249. (b) Yin, X.; Stayton, P. S.; Hoffman, A. S. *Biomacromolecules* **2006**, *7*, 1381–1385. (c) Okano, T.; Yamada, N.; Sakai, H.; Sakurai, Y. *J. Biomed. Mater. Res.* **1993**, *27*, 1243–1251. (d) Convertine, A. J.; Ayres, N.; Scales, C. W.; Lowe, A. B.; McCormick, C. L. *Biomacromolecules* **2004**, *5*, 1177–1180.

(3) (a) Lutz, J. F. *J. Polym. Sci., Polym. Chem.* **2008**, *46*, 3459–3470. (b) Oh, J. K.; Min, K.; Matyjaszewski, K. *Macromolecules* **2006**, *39*, 3161–3167. (c) Yu, B.; Jiang, X.; Wang, R.; Yin, J. *Macromolecules* **2010**, *43*, 10457–10465. (d) Ryu, J. H.; Chacko, R. T.; Jiwpanich, S.; Bickerton, S.; Babu, R. P.; Thayumanavan, S. *J. Am. Chem. Soc.* **2010**, *132*, 17227–17235. (e) Jochum, F. D.; Roth, P. J.; Kessler, D.; Theato, P. *Biomacromolecules* **2010**, *11*, 2432–2439. (f) Lutz, J. F.; Akdemir, O.; Hoth, A. *J. Am. Chem. Soc.* **2006**, *128*, 13046–13047.

(4) (a) Li, F. M.; Chen, S. J.; Du, F. S.; Wu, Z. Q.; Li, Z. C. *ACS Symp. Ser.* **1999**, *726*, 266–276. (b) Sui, X. F.; Yuan, J. Y.; Zhou, M.; Zhang, J.; Yang, H. J.; Yuan, W. Z.; Wei, Y.; Pan, C. Y. *Biomacromolecules* **2008**, *9*, 2615–2620. (c) Zheng, G. D.; Stover, H. D. H. *Macromolecules* **2003**, *36*, 7439–7445. (d) Jiang, X. Z.; Ge, Z. S.; Xu, J.; Liu, H.; Liu, S. Y. *Biomacromolecules* **2007**, *8*, 3184–3192. (e) Lee, A. S.; Bütün, V.; Vamvakaki, M.; Armes, S. P.; Pople, J. A.; Gast, A. P. *Macromolecules* **2002**, *35*, 8540–8551.

(5) (a) Wang, X. H.; Qiu, X. P.; Wu, C. *Macromolecules* **1998**, *31*, 2972–2976. (b) Hao, J. K.; Li, Z. Y.; Cheng, H.; Wu, C.; Han, C. C. *Macromolecules* **2010**, *43*, 9534–9540. (c) Kujawa, P.; Tanaka, F.; Winnik, F. M. *Macromolecules* **2006**, *39*, 3048–3055. (d) Zhang, G. Z.; Winnik, F. M.; Wu, C. *Phys. Rev. Lett.* **2003**, *90*, 035506.

(6) (a) Leroux, J. C.; Roux, E.; Le Garrec, D.; Hong, K. L.; Drummond, D. C. *J. Controlled Release* **2001**, *72*, 71–84. (b) Feil, H.; Bae, Y. H.; Feijen, J.; Kim, S. W. *Macromolecules* **1993**, *26*, 2496–2500. (c) Yoshida, R.; Sakai, K.; Okano, T.; Sakurai, Y. *J. Biomater. Sci., Polym. Ed.* **1994**, *6*, 585–598.

(7) Qiu, X. P.; Tanaka, F.; Winnik, F. M. *Macromolecules* **2007**, *40*, 7069–7071.

(8) Honda, S.; Yamamoto, T.; Tezuka, Y. *J. Am. Chem. Soc.* **2010**, *132*, 10251–10253.

(9) He, J.; Tremblay, L.; Lacelle, S.; Zhao, Y. *Soft Matter* **2011**, *7*, 2380–2386.

(10) (a) Trenor, S. R.; Shultz, A. R.; Love, B. J.; Long, T. E. *Chem. Rev.* **2004**, *104*, 3059–3078. (b) Jiang, J.; Qi, B.; Lepage, M.; Zhao, Y. *Macromolecules* **2007**, *40*, 790–792. (c) He, J.; Tong, X.; Zhao, Y. *Macromolecules* **2009**, *42*, 4845–4852. (d) Shi, D.; Matsusaki, M.; Kaneto, T.; Akashi, M. *Macromolecules* **2008**, *41*, 8167–8172.

(11) (a) Irie, M. *Adv. Polym. Sci.* **1993**, *110*, 49–65. (b) Desponds, A.; Freitag, R. *Langmuir* **2003**, *19*, 6261–6270. (c) Sumaru, K.; Kameda, M.; Kanamori, T.; Shinbo, T. *Macromolecules* **2004**, *37*, 4949–4955. (d) Zhao, Y.; Tremblay, L.; Zhao, Y. *J. Polym. Sci., Part A: Polym. Chem.* **2010**, *48*, 4055–4066.

(12) (a) Roovers, J.; Toporowski, P. M. *Macromolecules* **1983**, *16*, 843. (b) Tanaka, F. J. *Chem. Phys.* **1987**, *87*, 4201.

(13) Schmidt, B. V. K.; Fechler, N.; Falkenhagen, J.; Lutz, J.-F. *Nature Chem.* **2011**, *3*, 234–238.