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Formation and Volume Phase Transition of Hydroxypropyl Cellulose Microgels in Salt Solution

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ABSTRACT: Surfactant-free hydroxypropyl cellulose (HPC) microgels have been synthesized in salt solution. The average size and size distributions of microgel particles have been correlated with polymer concentration, salt concentration, and reaction temperature using light scattering techniques. It is found that the low critical solution temperature of HPC polymer chains decreases upon the increase of sodium chloride concentration. In a narrow sodium chloride concentration range from 1.3 to 1.4 M, HPC chains can self-associate into colloidal particles at room temperature. These particles remained stable in solution for weeks without changing their sizes. The microgel particles were then obtained in situ by bonding self-associated HPC chains at 23 °C using divinyl sulfone as a cross-linker. The volume phase transition of the resultant HPC microgels has been studied as a function of temperature at various salt concentrations. A theoretical model based on Flory−Huggins free energy consideration has been used to explain the experimental results.

Introduction

The volume phase transition in polymer gels can be induced by many external stimuli such as temperature, solvent composition, light, electric field, and pH value.[1,2] Hydroxypropyl cellulose (HPC), one of the thermally responsive gels similar to the poly(*N*-isopropylacrylamide) (PNIPAM),[2,3] has received considerable attention because of its biocompatibility.[4−8] Bulk HPC hydrogels and its derivatives with various forms including homogeneous gel, porous gel, and gel beads have been extensively studied.[7,8] Our group has reported the synthesis of HPC microgel particles[9,10] using a precipitation polymerization method. For polymer chains like the HPC that contain both hydrophobic and hydrophilic portions, changing the properties of the solvent by other ways may also induce self-association, leading to the formation of colloidal particle aggregates. It is known that addition of salt can lower the phase transition temperature in ionic and nonionic gels.[11−13] This effect is caused by the competing interactions between salt and water and between water and polymer chains.

Here we show that HPC microgel particles have been synthesized at room temperature by adding salt into HPC−water solution. In contrast to a previous method[9] that requires to heat HPC−water solution above the low critical solution temperature (LCST) of the HPC at about 41 °C, the current method is to first reduce the LCST of HPC polymer chains from 41 °C to room temperature by adding salt into the HPC−water solution and then to bond HPC globules without surfactant at room temperature. These microgels may be used as building blocks for the formation of nanoparticle networks[14,15] and as carriers for controlled drug delivery. The volume phase transition of the resultant microgels has been investigated using light scattering techniques. The results have been discussed in terms of Flory−Huggins swelling equilibrium of gels and compared with the previous study of bulk PNIPAM gels.[16]

Experimental Section

Materials. Dry hydroxypropyl cellulose (HPC) powder (average $M_w = 1 \times 10^6$), divinyl sulfone (DVS), sodium hydroxide (NaOH) pellets, and sodium chloride (NaCl) were purchased from Aldrich Chemical Co. and used as received. The substitution level of the HPC polymer for this study was MS = 3.9, where MS is the average number of molecules of propylene oxide combined per anhydroglucose unit.[8] Water for all reactions, solution preparation, and polymer purification was distilled and purified to a resistance of 18 MΩ using a Millipore system and filtered through a 0.22 μm filter to remove particulate matter.

HPC Microgel Synthesis. 0.5 g of HPC powder was mixed in 99.5 g of water to form 0.5 wt % HPC solution by gentle stirring for a week to ensure it thoroughly dissolved. We first prepared HPC polymer solution (5 g of 0.5 wt % HPC) and NaCl solution (3.80 g (0.065 mol) of sodium chloride in 45 mL of distilled water). Then NaCl solution was injected to the polymer solution using a pipet. After mixing completely, the color of the HPC solution changed from clear to light blue, indicating the formation of HPC colloids. Then 0.075 g of cross-linker divinyl sulfone (DVS) was added to the HPC/NaCl solution. After 2 h, 0.25 g of 2 M NaOH solution was added to make the pH value of HPC/NaCl solution equal to 12. The cross-linking reaction between DVS and HPC colloids was carried out for 24 h. The resultant microgels were then dialyzed for 1 week to remove NaCl and NaOH. The same procedure was used to prepare a series of HPC microgels with polymer concentrations ranging from 0.03 to 0.1 wt % at various sodium chloride concentrations.

Dynamic Light Scattering Characterization. A commercial laser light scattering (LLS) spectrometer (ALV/DLS/SLS-5000) equipped with an ALV-5000 digital time correlator was used with a helium−neon laser (Uniphase 1145P, output power of 22 mW and wavelength of 632.8 nm) as the light source. The incident light was vertically polarized with respect to the scattering plane, and the light intensity was regulated with a beam attenuator (Newport M-925B). The scattered light was conducted through a very thin (~40 μm in diameter) optical fiber leading to an active quenched avalanche photodiode (APD), which serves as the detector.

The relation of interest in dynamic light scattering is the fluctuation of the scattered intensity with time t. $g^{(1)}(q,t)$ is the normalized first-order electric field time correlation

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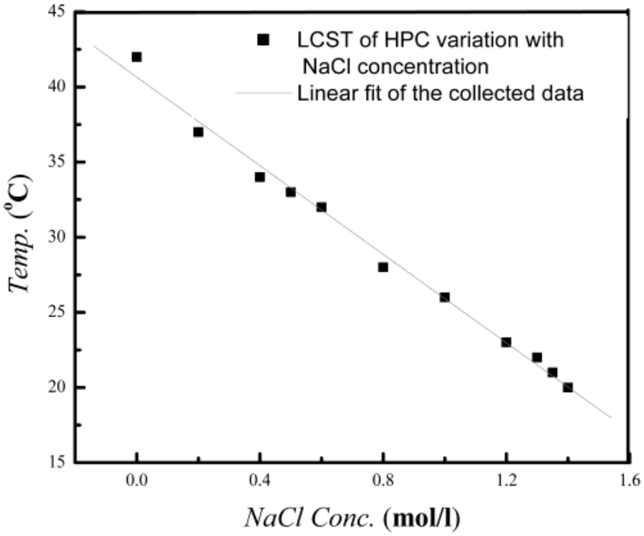

Figure 1. The LCST of un-cross-linked HPC decreases with increasing sodium chloride concentration, where the LCST was obtained from the midpoint of the sharpest light scattering intensity change.

function $E(t,q)$ and is related to the line-width distribution $G(\Gamma)$ by[17]

$$g^{(1)}(t,q) = \langle E(t,q)\, E^*(0,q)\rangle / \langle E(0,q)\, E^*(0,q)\rangle = \int_0^\infty G(\Gamma) e^{-\Gamma t}\, d\Gamma \quad (1)$$

$G(\Gamma)$ can be obtained from the Laplace inversion of $g^{(1)}(q,t)$. $g^{(1)}(q,t)$ was analyzed by a cumulant analysis to obtain the average line width $\langle\Gamma\rangle$ and the polydispersity index (PDI $= 1 + \mu_2/\langle\Gamma\rangle^2$, where $\mu_2 = \int_0^\infty G(\Gamma)(\Gamma - \langle\Gamma\rangle)^2\, d\Gamma$). The extrapolation of Γ/q^2 to $q \to 0$ led to the translational diffusion coefficient (D). This corresponding analysis of this function yields the diffusion coefficient D, which can be translated into the hydrodynamic radius R_h by the Stokes–Einstein relation: $R_h = k_B T/(6\pi\eta D)$, where k_B, T, and η are the Boltzmann constant, the absolute temperature, and the solvent viscosity, respectively. The dynamic light scattering experiments were performed at the scattering angle $\theta = 30°$.

LCST Determination. The lower critical solution temperature (LCST) of un-cross-linked HPC polymer chains at various salt concentrations was determined by measuring the scattering intensity at 90° scattering angle. Here HPC (1000 ppm) was dissolved in a given concentration of a sodium chloride solution at 15 °C. The cell holder in light scattering apparatus was thermally controlled using a refrigerating circulator. The temperature was gradually raised from 15 to 45 °C by turning on the heater. The LCST of the HPC in a salt chloride solution was defined as the temperature at which scattering light intensity exhibits a sharp rise.

Results and Discussion

Synthesis of HPC Microgels in Salt Solution. The LCST of the HPC is plotted against NaCl concentration as shown in Figure 1. A linear relationship is obtained between the two, indicating that an increase of sodium chloride lowers the LCST of the HPC solution. It is known that the pure HPC is more soluble in water at the temperatures below LCST (~41 °C) than it is at the temperatures above the LCST.[18–20] Here adding NaCl apparently weakens the hydrogen bonding between HPC and water, leading the LCST of the HPC to a lower temperature.

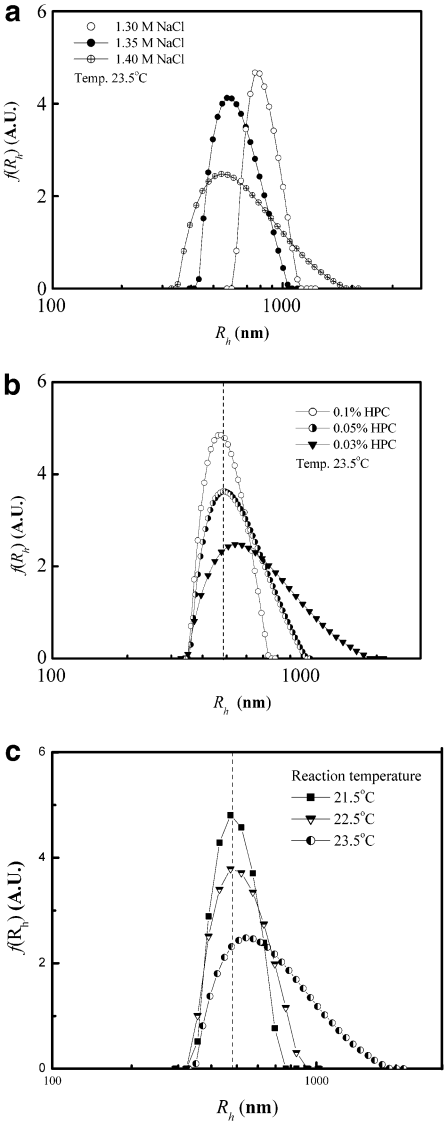

Figure 2. Hydrodynamic radius distributions ($f(R_h)$) of HPC microgel particles ($C = 5.0 \times 10^{-5}$ g/mL) in deionized water at 23.5 °C. (a) The HPC microgels were prepared in various NaCl concentrations, while the HPC polymer chains concentration and reaction temperature were kept at 0.03 wt % and 23.5 °C, respectively. (b) The HPC microgels were made at 23.5 °C in various HPC polymer concentrations, while NaCl concentration was kept at 1.4 M. (c) The HPC microgels were made at different temperatures, while HPC polymer concentration and NaCl concentrations were kept at 0.03% and 1.4 M.

Our experiment demonstrated that HPC colloids can form at room temperature only within a narrow sodium chloride concentration ranging from 1.3 to 1.4 M. Below 1.3 M, HPC hydrophilic property is dominant, and HPC chains unable to form globules. Above 1.4 M, HPC colloids can grow bigger through hydrophobic interaction and eventually lead to precipitation. After finding the relationship between the LCST and the salt concentration, we carried out the experiment to synthesize surfactant free HPC microgels by cross-linking the self-associated chains in salt solution using divinyl sulfone at pH = 12 at room temperature.

It is found that three reaction factors affect the final HPC microgel particle size and size distribution: polymer concentration, salt concentration, and reaction temperature. Let us keep HPC concentration at 0.03 wt %, while changing the NaCl concentration from 1.4 to 1.3 M. As shown in Figure 2a, the higher NaCl concentration leads to the smaller average radii $\langle R_h\rangle$ of the microgels. The main R_h peak positions for microgels

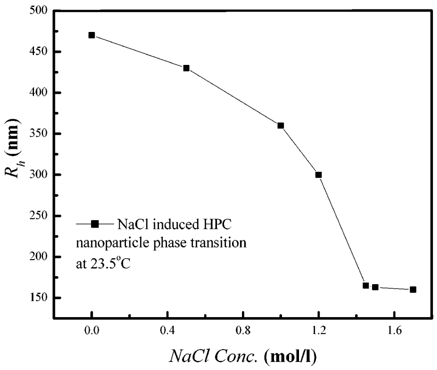

Figure 3. Sodium chloride induced HPC microgel particles ($C = 5.0 \times 10^{-5}$ g/mL) volume phase transition at 23.5 °C. The hydrodynamic radius was measured by dynamic light scattering.

synthesized in 1.4, 1.35, and 1.3 M NaCl solutions are 540, 570, and 830 nm, respectively. This suggests that more compact microgels were formed in higher salt concentrations. Furthermore, the radius distribution becomes broader with the increase of the salt concentration. PDI for the HPC microgels synthesized at 1.4, 1.35, and 1.3 M NaCl solutions are calculated respectively to be 1.5, 1.3, and 1.2. This indicates lowering NaCl concentration tends to form narrower size distribution. The formed globules are apt to precipitate as their density getting higher, while the steric effect from less condensed globules help to stabilize the colloidal dispersion. When NaCl concentration was increased above 1.4 M, however, the steric effect could no longer be strong enough to balance the precipitation force contributed from the growing population of larger particles.

The HPC microgel size distribution was then investigated as HPC concentration was varied from 0.03 to 0.1 wt %, while the NaCl concentration and the reaction temperature were kept at 1.4 M and 23.5 °C, respectively. Figure 2b shows hydrodynamic radius distributions ($f(R_h)$) of resultant HPC microgels ($C = 5 \times 10^{-5}$ g/mL). The average radii $\langle R_h \rangle$ of the microgels show no significant change: 470 nm for 0.1 wt % HPC, 480 nm for 0.05 wt % HPC, and 540 nm for 0.03 wt % HPC. However, the radius distribution becomes narrower with the increase of HPC concentration. The PDI values for 0.03, 0.05, and 0.1 wt % HPC are 1.5, 1.3, and 1.3, respectively.

Figure 2c shows the HPC microgel size distribution at different reaction temperatures. Here polymer and sodium chloride concentrations are kept at 0.03 wt % and 1.4 M. The reaction temperatures selected here are higher than the LCST of the HPC in 1.4 M NaCl solution (~20.5 °C) by 1, 2, and 3 °C, respectively. As shown in Figure 4, the particle size does not change significantly and are 470, 470, and 540 nm for 21.5, 22.5, and 23.5 °C, respectively. However, the size distribution becomes narrower as $\Delta T = T - \text{LCST}$ decreases. As ΔT increases, the salt association becomes faster so that polymer chains do not have time to relax themselves to the most favorable states. As a result, the particle size distribution becomes broader.

The Volume Phase Transition of HPC Microgels. Like its polymer chain counterpart, the resultant surfactant-free HPC microgels exhibit both the temperature and salt sensitive volume phase transition behaviors. The average hydrodynamic radius of HPC microgels (synthesized at 23.5 °C with polymer and salt concentration 0.1 wt % and 1.4 M, respectively) is plotted as a function of salt concentration at 23.5 °C as shown in Figure 3. The HPC microgel hydrodynamic radius R_h dropped from 470 to 160 nm as the environment was changed from pure water to 1.4 M salt concentration. The critical sodium chloride concentration, C_c, is defined as the one that causes the sharpest change in gel volume. We found the C_c for HPC microgels is also between 1.3 and 1.4 M, similar to the value that we obtained for HPC chains. This suggests that salt-induced volume change at room temperature and temperature-induced volume change in water are closely related.

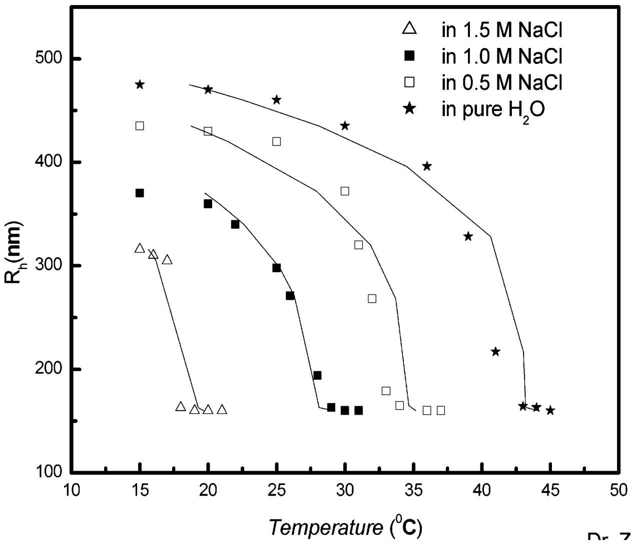

Figure 4. Temperature-induced volume phase transition of HPC microgel particles ($C = 5.0 \times 10^{-5}$ g/mL) under different sodium chloride concentrations. The solid lines are the theoretical fitting curves based on the mean-field theory.

The $\langle R_h \rangle$ of HPC microgels plotted against temperature at various sodium chloride concentrations are shown in Figure 4. It can be seen that, at each sodium chloride concentration, the R_h of the gel sharply decreases at a certain temperature, which agrees well with the LCST of un-cross-linked HPC chains at different NaCl concentrations. As NaCl concentration increases, the volume transition temperature decreases.

Let us turn our attention to understanding experimental results in Figure 4 in terms of Flory−Huggins free energy theory. According to this mean-field theory,[21,22] an equation relating the equilibrium concentration of a gel to the temperature can be written as[16]

$$\frac{\Delta H - T\Delta S}{T} = \frac{\Delta F}{T} = k\left\{\frac{\nu_1 \nu}{N\phi^2}\left[(2f+1)\left(\frac{\phi}{\phi_0}\right) - 2\left(\frac{\phi}{\phi_0}\right)^{1/3}\right] - \frac{2}{\phi} - \frac{2\ln(1-\phi)}{\phi^2}\right\} \tag{2}$$

where ϕ is the volume fraction of polymer network, ΔF is the free energy difference, and ΔH and ΔS are the corresponding enthalpy and entropy, respectively. ν is the total number of chains in the gel, ν_1 the molar volume of the solvent, k the Boltzmann constant, T the absolute temperature, N Avogadro's number, and f the number of counterions per chain.

In this work, f is zero because of the neutral property of HPC chains. The volume fraction of gels ϕ is varied on the basis of different salt concentrations. ΔF can be expressed as $\Delta F = \Delta F_0 + \Delta F_1 + \Delta F_2$,[23] where ΔF_0 is the change of the free energy of chains in pure water, ΔF_1 is the change of the free energy due to the disturbance of structured water molecules by salt, and ΔF_2 is the free energy change due to the disturbing or inducing the contacts of ionic polymer chains by hydrated ions. Since there is no ion in the HPC polymer chains, ΔF_2 is neglected. ΔF_1 is approximately represented as[23]

$$\Delta F_1 = \alpha C \tag{3}$$

where α is a material constant. Combining eqs 2 and 3, we obtain

$$\frac{\Delta F_0 + \Delta F_1}{kT} = \frac{\Delta H - T\Delta S + \alpha C}{kT} = \frac{\nu_1 \nu}{N\phi^2}\left[(2f+1)\left(\frac{\phi}{\phi_0}\right) - 2\left(\frac{\phi}{\phi_0}\right)^{1/3}\right] - \frac{2}{\phi} - \frac{2\ln(1-\phi)}{\phi^2} \tag{4}$$

Thus

$$\frac{\Delta H + \alpha C}{T} = k\left\{\frac{\nu_1 \nu}{N\phi^2}\left[(2f+1)\left(\frac{\phi}{\phi_0}\right) - 2\left(\frac{\phi}{\phi_0}\right)^{1/3}\right] - \frac{2}{\phi} - \frac{2\ln(1-\phi)}{\phi^2}\right\} + \Delta S = Y \tag{5}$$

$$T = \frac{\Delta H + \alpha C}{Y} \tag{6}$$

The values of ϕ_0 are calculated from the equilibrium swelling ratio of microgels at room temperature. They are 0.038, 0.050, 0.081, and 0.13 respectively for pure water, 0.5, 1.0, and 1.5 M NaCl solutions. The value of v is $4.0 \times 10^{24}\ l^{-1}$, estimated from the molar ratio (as initial concentration) between DVS cross-linker and HPC polymer. ΔH, ΔS, and α are varied to fit the $\langle R_\mathrm{h} \rangle$ vs T curves for HPC microgels in Figure 4 and are found to be -5.56×10^{-18} J (average error 6%), -1.76×10^{-20} J K^{-1} (average error 6%), and 27.9×10^{-20} J/M (average error 11%), respectively. The theoretical curves are shown in Figure 4 as solid lines and are in good agreement with the experimental data. It is noted that our ΔH and ΔS values are very close to those ($\Delta H = -5.4 \times 10^{-18}$ J and $\Delta S = -1.8 \times 10^{-20}$ J K^{-1}) obtained for PNIPAM bulk gels,[16] even though HPC and PNIPAM have different chemical structures and different volume phase transition temperatures in water. There are some discrepancies between the prediction of eq 6 and the experimental results. This may be due to oversimplification of the theoretical modeling. For example, the effects of loops and free branches have not been considered.

Conclusion

Surfactant-free HPC microgels have been synthesized by chemically cross-linking hydroxypropyl cellulose (HPC) linear macromolecules. The controllable synthesis parameters—salt concentration, HPC concentration, and reaction temperature—were varied to determine the effects on the size and size distribution of the microgels as monitored using dynamic laser light scattering techniques. It is found that the microgels can form at room temperature within a narrow NaCl concentration range from 1.3 to 1.4 M. As the HPC concentration increases from 0.03 to 0.1 wt %, or temperature varied from 23.5 to 21.5 °C, or sodium chloride concentrations decreased from 1.4 to 1.3 M, the particle size distribution of resultant HPC micrgels become narrower. The formation of microgels may be explained by the breakdown of hydrogen bonding between water and HPC chain with the addition of electrolyte. The fitting curves based on the Flory−Huggins mean-field theory are in good agreement with the experimental results.

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References and Notes

(1) Tanaka, T. *Phys. Rev. Lett.* **1978**, *40*, 820.
(2) Shibayama, M.; Tanaka, T. *Adv. Polym. Sci.* **1993**, *1*, 109.
(3) Hu, Z. B.; Zhang, X. M.; Li, Y. *Science* **1995**, *269*, 525.
(4) Kluc, E. D. *J. Polym. Sci.* **1971**, *36*, 491.
(5) Drummond, C.; Albers, S.; Furlong, D. N. *J. Colloids Surf.* **1992**, *62*, 75.
(6) Winnik, F. M.; Tamai, N.; Yonezawa, J.; Nishimura, Y.; Yamazaki, I. *J. Phys. Chem.* **1992**, *96*, 1967.
(7) Kabra, B. G.; Gehrke, S. H.; Spontak, R. J. *Macromolecules* **1998**, *31*, 2166.
(8) Harsh, D. C.; Gehrke, S. H. *J. Controlled Release* **1991**, *17*, 175.
(9) Lu, X.; Hu, Z. B.; Gao, J. *Macromolecules* **2000**, *33*, 8698.
(10) Gao, J.; Haidar, G.; Lu, X.; Hu, Z. *Macromolecules* **2001**, *34*, 2242.
(11) Ohmine, I.; Tanaka, T. *J. Chem. Phys.* **1982**, *77*, 5725.
(12) Park, T.; Hoffman, A. S. *Macromolecules* **1993**, *26*, 5045.
(13) Zhang, X.; Hu, Z.; Li, Y. *J. Appl. Polym. Sci.* **1997**, *63*, 1851.
(14) Hu, Z. B.; Lu, X.; Gao, J.; Wang, C. *Adv. Mater.* **2000**, *12*, 1173.
(15) Hu, Z. B.; Lu, X.; Gao, J. *Adv. Mater.* **2001**, *13*, 1708.
(16) Hirotsu, S.; Hirokawa, Y.; Tanaka, T. *J. Chem. Phys.* **1987**, *87*, 1392.
(17) Chu, B. *Laser Light Scattering*, 2nd ed.; Academic Press: New York, 1991.
(18) Karlstrom, G.; Carlsson, A.; Lindman, B. *J. Phys. Chem.* **1990**, *94*, 5005.
(19) Ahlnas, T.; Karlstrom, G.; Lindman, B. *J. Phys. Chem.* **1987**, *91*, 4030.
(20) Karlstrom, G. *J. Phys. Chem.* **1985**, *89*, 4962.
(21) Tanaka, T.; Fillmore, D.; Sun, S.; Nishio, I.; Swislow, G.; Shah, A. *Phys. Rev. Lett.* **1980**, *45*, 1636.
(22) Flory, P. J. *Principles of Polymer Chemistry*; Cornell University Press: Ithaca, NY, 1963.
(23) Suzuki, A. *Adv. Polym. Sci.* **1993**, *110*, 201.

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