Thermally Sensitive and Biocompatible Poly(*N*-vinylcaprolactam): Synthesis and Characterization of High Molar Mass Linear Chains

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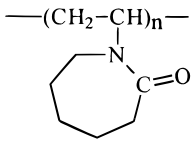
ABSTRACT: High molar mass poly(*N*-vinylcaprolactam) (PVCa) was synthesized by free-radical bulk polymerization. Four narrowly distributed fractions of PVCa were obtained in the tetrahydrofuran/*n*-hexane mixture. A combination of static and dynamic laser light scattering led to a scaling between the translational diffusion coefficient (D) and molar mass (M), D (cm^2/s) $= 8.47 \times 10^{-5} M_w^{-0.503}$, with which we transferred the translational diffusion coefficient distribution of each fraction into a corresponding molar mass distribution. We also established a scaling between the weight average molar mass (M_w) and the radius of gyration ($\langle R_g \rangle$), $\langle R_g \rangle$ (nm) $= 2.94 \times 10^{-2} M_w^{0.54}$, for PVCa in water at 25 °C. Moreover, we found a novel way to *estimate* the Θ-temperature (∼29.5 °C) from the temperature and concentration dependence of the hydrodynamic radius ($\langle R_h \rangle$). The lower critical solution temperature (LCST, ∼31.5 °C) of linear PVCa chains in water determined from the variations of both $\langle R_h \rangle$ and scattering intensity is close to the shrinking temperature of the PVCa hydrogel.

Introduction

Water-soluble polymers with properties such as biocompatibility, functionality, nontoxicity, and sterilizability are potential biomedical materials. Their applications include the implantation of artificial organs/tissues and drug delivery systems.[1,2] Friction between an implanted biomaterial and its surrounding tissues can be greatly reduced by grafting the polymer surface with water-soluble polymers. One example is the ethylene−vinyl acetate copolymer with its surface grafted with water-soluble poly(*N*,*N*-dimethylacrylamide).[2,3] Also, covalently grafting the surface of a biomaterial with nonionic water-soluble polymers, e.g., poly(ethylene oxide), can significantly reduce the cell adhesion on the polymer surface.[2] Moreover, if such biocompatible polymers respond to one or more environmental changes, such as pH, temperature, electric field, ionic strength, the type of salt, solvent composition, stress, light, and pressure,[4−6] their potential applications as biomedical materials, such as controlled releasing devices,[4−9] separation,[10] and artificial muscle,[11] will be much widened.

Several acrylamide related polymers, such as poly(acrylamide), poly(*N*-isopropylacrylamide), and their copolymers, can respond to environmental changes, but their biocompatibility is a problem. In contrast, poly(*N*-vinylcaprolactam) (PVCa) is not only nonionic, water-soluble, and thermally sensitive but also biocompatible. It contains hydrophilic carboxylic and amide groups with the following structure,



where the amide group is directly connected to the hydrophobic carbon−carbon backbone chain so that its hydrolysis will not produce small amide compounds which are often bad for biomedical applications. PVCa was previously synthesized by both free-radical and radiochemical polymerizations,[12,13] but no data on its solution properties have ever been published. Recently, PVCa gels have attracted much attention due to their nonionic, water-soluble, thermally sensitive, and biocompatible nature.[4,14] As an essential step toward a fundamental understanding of the PVCa gel and its potential applications, we were motivated to prepare and study linear PVCa chains in solution. However, the solution polymerization of *N*-vinylcaprolactam in benzene by using azobisisobutyronitrile (AIBN) as initiator resulted in a relatively low molar mass PVCa ($M_w \sim 1 \times 10^5$ g/mol) even though we used a small amount of initiator and a higher monomer concentration. We also tried the polymerization in aqueous media by using KPS as initiator, but still failed, which could be attributed to the lack of resonance stablization. Later, we found that the high molar mass linear PVCa which has not been reported, in contrast to that of many other vinyl monomers, could be obtained by using a free-radical bulk polymerization.

Experimental Section

Sample Preparation. *N*-Vinylcaprolactam (VCa, courtesy of BASF) was purified by a triple melt recrystallization at room temperature. *N*-Vinylcaprolactam is easily oxidized into a brown-yellowish compound. Therefore, the purified VCa monomer should be stored under nitrogen at 0 °C before polymerization.

Azobisisobutyronitrile (purchased from ACROS Organics) was purified by crystallization in methanol and dried in a vacuum. AR grade tetrahydrofuran (THF) and *n*-hexane (also purchased from ACROS Organics) were used without further purification.

N-Vinylcaprolactam monomer was molten at 40 °C and degassed through a three-cycle freezing-and-thawing process. A 0.5 mol % amount of AIBN was then added to start the polymerization at 60 °C under a positive nitrogen pressure for 2 h. An overall yield of 60% was achieved. The resultant PVCa was fractionated in a THF/*n*-hexane mixture with *n*-hexane as precipitant. Four PVCa fractions were obtained and are labeled as PVCa1, PVCa2, PVCa3, and PVCa4 hereafter according to their precipitation order. All of the fractions were dried under a vacuum.

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The PVCa solutions used in these studies were made by a successive dilution of a stock solution which was prepared by dissolving a desired amount of PVCa into freshly distilled deionized water with a resistivity of 18.2 MΩ cm. The stock solution was allowed to stand at room temperature for at least 2 days to ensure a complete dissolution of PVCa in water before the dilution. All of the PVCa solutions for light scattering were clarified at ambient temperature with a 0.5 μm Millipore polytetrafluoroethylene (PTFE) filter to remove dust.

Laser Light Scattering. A commercial laser light scattering (LLS) spectrometer (ALV/SP-125 with ALV-5000 multi-τ digital correlator, Langen in Hessen, Germany) was used with a solid-state laser (ADLAS DRY425II, output power ≈ 400 mW at λ = 532.8 nm) as the light source. The detail of the LLS theory and instrumentation can be found elsewhere.[15,16] The specific refractive index increment (dn/dC) was measured with a novel differential refractometer, which shared the same laser with the LLS spectrometer,[17] so that no wavelength correction was necessary. In static LLS, the angular dependence of the excess absolute time-averaged scattered intensity, known as the excess Rayleigh ratio $R_{vv}(q)$, was measured. For a dilute solution with a concentration C (g/mL) and measured at a relatively small scattering angle θ,[18]

$$\frac{KC}{R_{vv}(q)} \cong \frac{1}{M_w}\left(1 + \frac{1}{3}\langle R_g^2\rangle_z q^2\right) + 2A_2C \qquad (1)$$

where $K = 4\pi n^2(dn/dC)^2/(N_A\lambda_0^4)$ and $q = (4\pi n/\lambda_0)\sin(\theta/2)$ with N_A, dn/dC, n, and λ_0 being Avogadro's number, the specific refractive index increment, the solvent refractive index, and the wavelength of light in a vacuum, respectively; M_w is the weight average molar mass; A_2 is the second-order virial coefficient; and $\langle R_g^2\rangle_z^{1/2}$ (or written as $\langle R_g\rangle$) is the root-mean-square z-average radius of gyration.

In dynamic LLS, the intensity−intensity time correlation function $G^{(2)}(t,q)$ in the self-beating mode was measured and[15,16]

$$G^{(2)}(t,q) = \langle I(t,q)\, I(0,q)\rangle = A[1 + \beta|g^{(1)}(t,q)|^2] \qquad (2)$$

where A is the base line, β is a parameter depending on the detection coherence, t is the delay time, and $g^{(1)}(t,q)$ is the normalized first-order electric field time correlation function $E(t,q)$ and is related to the line-width distribution $G(\Gamma)$ by

$$g^{(1)}(t,q) = \langle E(t,q)\, E^*(0,q)\rangle = \int_0^\infty G(\Gamma)\, e^{-\Gamma t}\, d\Gamma \qquad (3)$$

$|g^{(1)}(t,q)|$ was analyzed by either the Laplace inversion program (CONTIN) to obtain $G(\Gamma)$ or by a cumulant analysis to get the average line width $\langle\Gamma\rangle$ and the relative distribution width $\mu_2/\langle\Gamma\rangle^2$. The extrapolation of Γ/q^2 to $q \to 0$ led to the translational diffusion coefficient (D), which was further converted to the hydrodynamic radius (R_h) by using the Stokes−Einstein equation, $R_h = k_BT/6\pi\eta D$, with k_B, T, and η being the Boltzmann constant, the absolute temperature, and the solvent viscosity, respectively.

Results and Discussion

Figure 1 shows a typical plot of the refractive index increment (Δn) versus polymer concentration (C) for PVCa in water at T = 25 °C, where the line shows a least-squares fitting of $\Delta n = -4.24 \times 10^{-6} + 2.06 \times 10^{-1}C \cong 2.06 \times 10^{-1}C$, i.e., dn/dC = 0.206 mL/g, demonstrating that the value of dn/dC used in this study has a high precision. Using the differential refractometer and the known dn/dC value, we can check the PVCa concentration after the clarification.

Figure 2 shows a typical Zimm plot of PVCa in water at 25 °C. On the basis of eq 1, the extrapolation of $[KC/R_{vv}(q)]_{C\to0,q\to0}$ led to M_w, the slopes of "$[KC/R_{vv}(q)]_{C\to0}$ vs q^2 " and " $[KC/R_{vv}(q)]_{q\to0}$ vs C" led to $\langle R_g\rangle$ and A_2, respectively. All the static LLS results are listed in Table 1. The small positive values of A_2 indicate that water at 25 °C is a reasonably good solvent for PVCa. The value of A_2 increases as M_w decreases, which is typical for flexible polymer chains in a good solvent.[19]

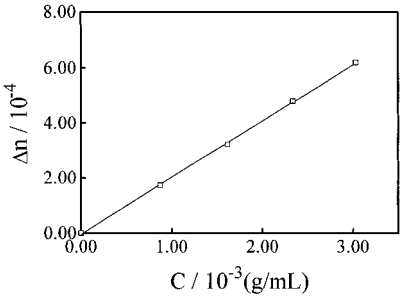

Figure 1. Concentration dependence of the refractive index increment for PVCa in water at T = 25 °C and λ = 532 nm. The value of dn/dC = 0.206 mL/g was derived from the slope of the line.

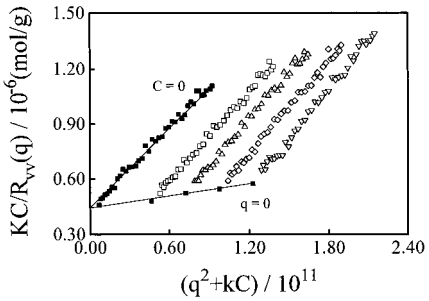

Figure 2. Typical Zimm plot for PVCa in water at 25 °C, where C ranges from 9 × 10^{-5} to 5 × 10^{-4} g/mL.

Figure 3 shows a plot of log $\langle R_g\rangle$ versus log M_w for the four PVCa fractions in water at 25 °C, where the line shows a least-squares fitting of $\langle R_g\rangle = \langle k_g\rangle M_w^{\langle\alpha_g\rangle}$ with $\langle k_g\rangle = 2.94 \times 10^{-2}$ and $\langle\alpha_g\rangle = 0.54 \pm 0.01$. The symbol "$\langle\ \rangle$" is used because $\langle k_g\rangle$ and $\langle\alpha_g\rangle$ were obtained from the average radius of gyration ($\langle R_g\rangle$) and the weight average molar mass (M_w). The value of $\langle\alpha_g\rangle = 0.54 \pm 0.01$, which is typical for linear chains in a reasonably good solvent,[19] indicating that the branching, even if it existed in the synthesis, was not a serious problem.

Figure 4 shows a typical measured normalized intensity−intensity time correlation function $[g^{(2)}(t,q) - A]/A$ for PVCa1 in water, where $C = 1.517 \times 10^{-4}$ g/mL, θ = 15°, and T = 25 °C. The insert shows the line-width distribution $G(\Gamma)$ calculated from the Laplace inversion of $[g^{(2)}(t,q) - A]/A$ on the basis of eqs 2 and 3. Only one peak in $G(\Gamma)$ was observed, which is attributed to the translational diffusion of individual PVCa chains. The relative distribution width $\mu_2/\langle\Gamma\rangle^2$ of the four PVCa fractions ranges from 0.02 to 0.08, indicating that they are narrowly distributed because $\mu_2/\langle\Gamma\rangle^2$ can be related to the polydispersity index M_z/M_w by $M_z/M_w \cong 1 + 4\mu_2/\langle\Gamma\rangle^2$ with M_z and μ_2 being the z-average molar mass and the second moment of $G(\Gamma)$.[20]

Figure 5 shows normalized translational diffusion coefficient distributions $G(D)$ of the four PVCa fractions in water at 25 °C, calculated from the corresponding $G(\Gamma)$. The monomodal $G(D)$ and relatively fast diffusion indicate that there is no interchain aggregation in water at 25 °C, or, in other words, water at 25 °C is a reasonably good solvent for PVCa. It should be stated that Γ is only slightly dependent on q and C in the scattering angle and concentration ranges studied. $G(D)$ can be further converted to a molar mass distribution $f_w(M)$ by $D = k_DM^{-\alpha_D}$ if we have k_D and α_D.

Table 1. Summarization of Laser Light Scattering Results of Poly(*N*-vinylcaprolactam) in Water at 25 °C[a]

sample	M_w (g mol^{-1})	A_2 (mol mL g^{-2})	$\langle R_g \rangle$ (nm)	$\langle D \rangle$ (cm^2 s^{-1})	$\langle R_h \rangle$ (nm)	$\langle R_g \rangle / \langle R_h \rangle$
PVCa1	2.34×10^6	1.59×10^{-4}	79	4.8×10^{-8}	51.8	1.53
PVCa2	1.38×10^6	1.67×10^{-4}	63	6.6×10^{-8}	36.6	1.72
PVCa3	5.01×10^5	1.76×10^{-4}	36	9.6×10^{-8}	24.1	1.49
PVCa4	1.18×10^5	2.03×10^{-4}	16	22.5×10^{-8}	11.0	1.45

[a] Relative errors: M_w, ±2%; A_2, ±30%; $\langle R_g \rangle$, ±7%; $\langle D \rangle$, ±4%; $\langle R_h \rangle$, ±4%.

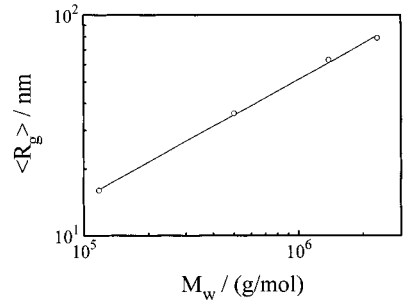

Figure 3. Double logarithmic plot of the radius of gyration $\langle R_g \rangle$ versus the weight average molar mass M_w for PVCa in water at 25 °C.

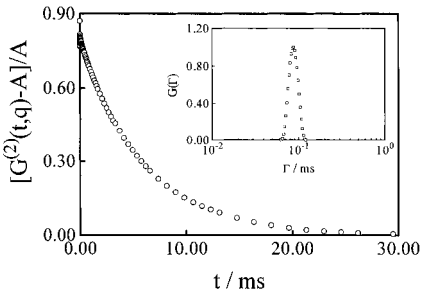

Figure 4. Typical normalized intensity−intensity time correlation function $[g^{(2)}(t,q) - A]/A$ for the PVCa1 chains in water, where $\theta = 15°$ and $T = 25$ °C. The insert shows the line-width distribution $G(\Gamma)$ calculated from the Laplace inversion of the correlation function.

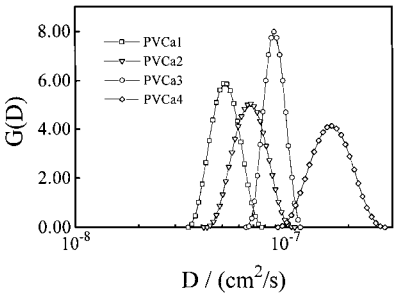

Figure 5. Translational diffusion coefficient distributions $G(D)$ of the four PVCa fractions in water at 25 °C.

Figure 6 shows a double logarithmic plot of $\langle D \rangle$ versus M_w for PVCa in water at 25 °C. Similar to the scaling between $\langle R_g \rangle$ and $\langle M_w \rangle$, we have $\langle D \rangle = \langle k_D \rangle M_w^{-\langle \alpha_D \rangle}$ with $\langle k_D \rangle = 7.93 \times 10^{-5}$ and $\langle \alpha_D \rangle = 0.505$. Again, the symbol "$\langle\ \rangle$" is used because $\langle k_D \rangle$ and $\langle \alpha_D \rangle$ were obtained from the *z*-average diffusion coefficient ($\langle D \rangle$) and the weight average molar mass (M_w). Strictly speaking, we need a scaling $D = k_D M_w^{-\alpha_D}$ for monodisperse samples. The dotted line in Figure 6 shows such a scaling with $k_D = 8.47 \times 10^{-5}$ and $\alpha_D = 0.503$, which was calculated by a method of combining $G(D)$ and M_w.[3,21] It shows that $\alpha_D \approx \langle \alpha_D \rangle$ and $\langle k_D \rangle$ is only slightly smaller than k_D because all of the four PVCa fractions are narrowly distributed. Table 1 summarizes all of the dynamic LLS results. The ratio of $\langle R_g \rangle / \langle R_h \rangle$ is directly related to the chain conformation, e.g., $\langle R_g \rangle / \langle R_h \rangle \sim 0.78$ for a uniform sphere, ≥2 for a rigid rod, and ∼1.5−1.7 for flexible

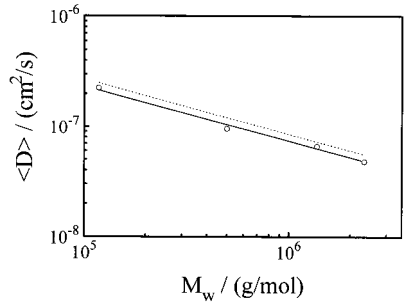

Figure 6. Double logarithmic plot of the average translational diffusion coefficient $\langle D \rangle$ versus the weight average molar mass M_w for PVCa in water at 25 °C. The solid line shows the least-squares fitting of $\langle D \rangle = 7.93 \times 10^{-5} M_w^{-0.505}$, while the dotted line represents the scaling D (cm^2/s) $= 8.47 \times 10^{-5} M_w^{-0.503}$ for monodisperse samples.

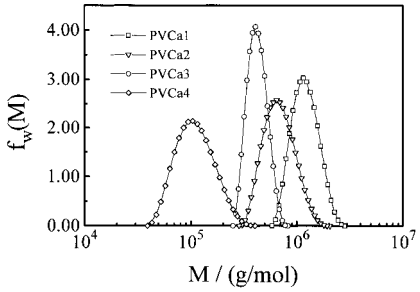

Figure 7. Differential weight distributions $f_w(M)$ of molar mass of the four PVCa fractions.

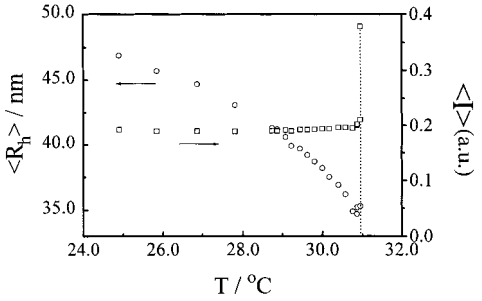

Figure 8. Temperature dependence of both the average hydrodynamic radius $\langle R_h \rangle$ and the time averaged scattering intensity $\langle I \rangle$ for the PVCa chains in water. The dotted line marks the lower critical solution temperature.

linear chains in a good solvent. As shown in Table 1, the values of $\langle R_g \rangle / \langle R_h \rangle$ indicate that the PVCa chains are linear and flexible with a coil conformation in water at 25 °C.

Figure 7 shows differential weight distributions $f_w(M)$ of molar mass of the four PVCa fractions, where each $f_w(M)$ was calculated from its corresponding translational diffusion coefficient distribution $G(D)$. It shows that a combination of free-radical polymerization of *N*-vinylcaprolactam in bulk and the fractionation can yield narrowly distributed higher molar mass PVCa samples in comparison with those from free-radical polymerization of *N*-vinylcaprolactam in benzene.

Figure 8 shows the temperature dependence of the average hydrodynamic radius $\langle R_h \rangle$ and the scattering

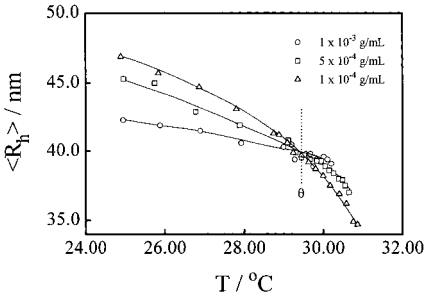

Figure 9. Temperature dependence of the average hydrodynamic radius $\langle R_h \rangle$ for the PVCa chains in water at three different concentrations. The Θ-temperature can be estimated from the temperature at which the concentration dependence of $\langle R_h \rangle$ starts to reverse its sign.

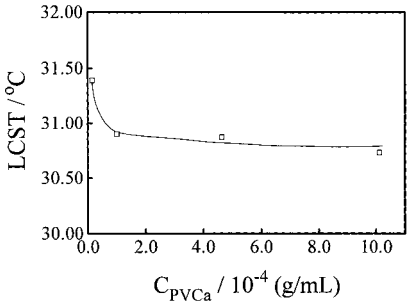

Figure 10. Concentration dependence of the lower critical solution temperature (LCST) for the PVCa chains in water. This graph basically resembles a phase diagram for typical LCST polymer chains at the low concentration regime.

intensity $\langle I \rangle$ of the PVCa chains in water. It clearly shows that, before the temperature reaches ~31 °C, $\langle R_h \rangle$ decreases as the solution temperature increases, while $\langle I \rangle$ is nearly independent of the temperature, indicating that there is no interchain aggregation but only the intrachain contraction. The temperature at which both $\langle R_h \rangle$ and $\langle I \rangle$ start to increase, i.e., individual PVCa chains start to aggregate, is defined as the lower critical solution temperature (LCST) which is close to the shrinking temperature of the PVCa hydrogel (~31.5 °C) determined by Mikheeva *et al.*[4]

Figure 9 shows the temperature dependence of $\langle R_h \rangle$ for three PVCa solutions with different concentrations. When $T < \sim 29.5$ °C, $\langle R_h \rangle$ decreases as C increases, while, when $T > \sim 29.5$ °C, $\langle R_h \rangle$ increases as C increases. We know that $1/\langle R_h \rangle \propto (1 + k_d C)$ and $k_d = 2A_2 M_w - C_D N_A \langle R_h \rangle^3 / M_w$, where C_D is a positive constant.[22] For a given M_w, the decrease of $\langle R_h \rangle$ as C increases indicates that k_d is positive, so that A_2 must be positive. On the other hand, the increase of $\langle R_h \rangle$ as C shows that k_d is negative, leading to either (1) A_2 is negative or (2) the thermodynamic term ($2A_2 M_w$) is smaller than the hydrodynamic term ($C_D N_A R_h^3 / M_w$). In our case, $C_D N_A R_h^3 / M_w < \sim 50$, so that if $2A_2 M_w < C_D N_A R_h^3 / M_w$, we have that $A_2 < \sim 1 \times 10^{-5}$, close to 0. Therefore, the temperature at which the concentration dependence of $\langle R_h \rangle$ changes its sign can be used to roughly *estimate* the Flory Θ-temperature.

Figure 10 shows the concentration dependence of the LCST for PVCa in water, which is actually the phase diagram of PVCa in water in the very dilute regime, where each LCST was determined from the temperature at which both $\langle R_h \rangle$ and $\langle I \rangle$ increase sharply. Figure 10 clearly shows that the LCST of the PVCa chains in water is not strongly dependent on the concentration when the solution is very dilute.

Conclusion

Poly(*N*-vinylcaprolactam) with a higher molar mass was prepared by free-radical bulk polymerization. Our laser light scattering results showed that the average radius of gyration ($\langle R_g \rangle$) and translational diffusion coefficient ($\langle D \rangle$) can be scaled to the weight average molar mass (M_w) by $\langle R_g \rangle = 2.94 \times 10^{-2} M_w^{0.54}$ and $\langle D \rangle = 7.93 \times 10^{-5} M_w^{-0.505}$. Water at 25 °C is a good solvent for PVCa. Moreover, we demonstrated a novel method for estimating the Θ-temperature. The lower critical solution temperature (~31.5 °C) of the PVCa chains in water determined in this study is close to the shrinking temperature of the PVCa hydrogel. The LCST is nearly independent of the PVCa concentration in very dilute regime. The thermal sensitivity and biocompatibility of PVCa make it a potential biomedical material.

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References and Notes

(1) Kronenthal, R. L.; Oser, Z.; Martin, E. *Polymer Science and Technology*: *Polymers in Medicine and Surgery*; Plenum Press: New York and London, 1975; Vol. 8.
(2) Shalaby, W. S.; et al. *Polymers of Biological and Biomedical Significance*; American Chemical Society: Washington, DC, 1994.
(3) Zhou, S.; Fan, S.; Au-yeung, S. C. F.; Wu, C. *Polymer* **1995**, *36*, 1341.
(4) Mikheeva, L. M.; Grinberg, N. V.; Mashkevich, A. Y.; Grinberg, V. Y. *Macromolecules* **1997**, *30*, 2693.
(5) Jeong, B.; Bas, Y. H.; Lee, D. S.; Kim, S. W. *Nature* 1997, *388*, 860.
(6) Ottenbrite, R. M.; Huang, S. J.; Park, K. *Hydrogels and Biodegradable Polymers for Bioapplications*; American Chemical Society: Washington, DC, 1996.
(7) Park, K. *Controlled Drug Delivery—Challenges and Strategies*; Amercian Chemical Society: Washington, DC, 1997.
(8) Hoffman, A. S.; Afrassiabi, A.; Dong, L. C. *J. Controlled Release* **1986**, *4*, 213.
(9) Hoffman, A. S. *J. Controlled Release* **1987**, *6*, 297.
(10) Feil, H.; Bae, Y. H.; Feijen, I.; Kim, S. W. *J. Membr. Sci.* **1991**, *64*, 283.
(11) Osada, Y.; Ross-Murphy, S. B. *Sci. Am.* **1993**, *259*, 42.
(12) Solomon, O. F.; Vasilescu, D. S.; Tararescu, V. *J. Appl. Polym. Sci.* **1969**, *13*, 1.
(13) Solomon, O. F.; Corciovei, M.; Boghina, C. *J. Appl. Polym. Sci.* **1968**, *12*, 1843.
(14) Makhaeva, E. E.; Thanh, L. M.; Starodubtzev, S. G.; Khokhlov, A. R. *Macromol. Chem. Phys.* **1996**, *197*, 1973.
(15) Chu, B. *Laser Light Scattering*, 2nd ed.; Academic Press: New York, 1991.
(16) Pecora, R. *Dynamic Light Scattering*; Plenum Press: New York, 1976.
(17) Wu, C.; Xia, K. Q. *Rev. Sci. Instrum.* **1993**, *65*, 587.
(18) Zimm, B. H. *J. Chem. Phys.* **1948**, *16* (12), 1099.
(19) Flory, P. J. *Principles of Polymer Chemistry*; Cornell University Press: Ithaca, NY, 1953.
(20) Cummins, H. Z.; Pike, E. R. *Photon Correlation and Light Beating Spectroscopy*; NATO ASI Series, Series B; Plenum Press: New York, 1974; Vol. 3, p 406.
(21) Wu, C. *J. Polym. Sci., Part B: Polym. Phys. Ed.* **1994**, *32* (5), 803.
(22) Yamakawa, H *Modern Theory of Polymer Solution*; Harper and Row: New York, 1971.

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