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Thermosensitive Phase Transition of an Optically Active Polymer in Aqueous Milieu

Takashi Aoki,*,† Mika Muramatsu, Taisuke Torii, Kohei Sanui, and Naoya Ogata‡

Department of Chemistry, Sophia University, 7−1 Kioi, Chiyoda, Tokyo 102-8554, Japan

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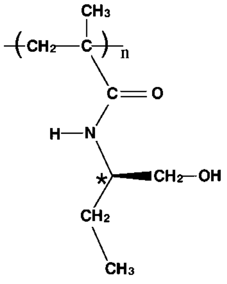
Introduction. It is well-known that proteins generally undergo temperature-induced denaturation, becoming water-insoluble and losing their biological functions. Significant research has been conducted in order to understand the denaturation related to structures and functions of biopolymers, particularly through investigation of the coil-globule transition of synthetic polymers such as some polyacrylamide derivatives[1−3] poly(methacrylic acid),[4] and poly(vinyl methyl ether)[5].

Proteins are known to be composed of optically active monomers, i.e., amino acids. The optically active property in biopolymers also plays an important role in the formation of highly ordered structures and the presence of biological functions including catalytic activity and specific molecular recognition. The conformational change of an optically active polymer chain has been one area of interest.[6]

In the present study, molecular design of a novel chiral macromolecule was performed in order to obtain a new type of polymer possessing thermosensitive and optically active properties within a single unit. This communication concludes that optically active poly(*N*-(L)−(1-hydroxymethyl)propylmethacrylamide (P(L-HMPMA) (**1**)) shows a characteristic thermosensitive phase transition in aqueous milieu with a behavior that is quite different from that of optically inactive P(DL-HMPMA).



(1)

Experimental Section. Materials. The present work utilized optically active (L)- and (D)-2-amino-1-butanols (Lupin Laboratory Ltd., Bombay, India) and, a racemate, (DL)-2-amino-1-butanol (Tokyo Chemical Industry Co. Ltd., Tokyo, Japan). Other reagents were purchased from Wako Pure Chemical Industries, Co., Ltd. (Osaka, Japan). Methacryloyl chloride (bp 45 °C at 126 mmHg), *N*,*N*-dimethylformamide (DMF) (bp 35 °C at 8 mmHg), and γ-butyrolactone (72 °C at 8 mmHg) were distilled prior to use. Methylene chloride was washed with 4 w/v% $NaHCO_3$ aqueous solution and distilled water and was dried with $CaCl_2$, following distillation at approximately 40 °C. All other reagents were used as received.

Synthesis of *N*-(L)-(1-Hydroxymethyl)propylmethacrylamide (L-HMPMA). To a well-stirred aqueous solution of (L)-2-amino-1-butanol (8.9 g, 0.1 mol) and sodium hydroxide (4.5 g, 0.1 mol) placed in an ice bath was added methacryloyl chloride (10.4 g, 0.1 mol) was added dropwise over a 30 min period. Following removal of the ice bath, the reaction mixture was stirred for a further 3 h while its temperature increased to room temperature. The solution possessed turbidity and separated into two phases. An oily phase was removed using a separatory funnel and further transferred into an additional funnel containing 25 mL of dichloromethane in order to extract the monomer. The dichloromethane solution was then dried using $MgSO_4$ and evaporated gently so as to obtain the purified monomer. IR (KRS-5): 3325 (ν_{O-H}), 1654 (amide I), 1533 (amide II) cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.97 (t, $-CH_2-CH_3$, 3H), 1.50−1.68 (m, $-CH_2-CH_3$, 2H), 1.97 (s, $=C-CH_3$, 3H), 3.07 (br, O*H*), 3.61−3.73 (m, $-CH_2-OH$, 2H), 3.90−3.93 (m, C*H*, 1H), 5.34 (s, $=C\text{-}H$, 1H), 5.71 (s, $=C\text{-}H$, 1H), 6.03 (br, N*H*), Anal. Calcd for ($C_8H_{15}NO_2$): C, 61.12; H, 9.62; N, 8.91. Found: C, 60.94; H, 9.39. N, 8.72. D- and DL-HMPMAs were synthesized in the same manner, except for the use of (D)-2-amino-1-butanol and racemate, respectively, instead of the L-formed amino alcohol.

Syntheses of Polymers. The polymers were synthesized in 140 g of DMF/γ-butyrolactone (1:1) at 45 °C for 24 h using 2,2′-azobis(2,4-dimethylvaleronitrile) (V-65) as a free radical initiator. Following this, the polymer was recovered as a precipitate from diethyl ether, with dialysis against distilled water being carried out in order to remove unreacted chemicals and low molecular weight compounds.

Measurement of the Turbidity. Each polymer was dissolved in distilled water at 0.4 w/v% with the optical transmittance of the polymer aqueous solutions at various temperatures being monitored at 500 nm through means of a spectrophotometer (UV-1200, Shimadzu). The quartz cell was thermostated using a circular water jacket equipped with a temperature controller (RTE−110, NESLAB, NH). The transmittance was allowed to reach a constant value prior to measurement at each temperature.

Results and Discussion. As shown in Table 1, P(L-HMPMA) and P(D-HMPMA) showed specific optical rotations of +33 and −34°, respectively, indicating symmetric values. In this study, the thermosensitive properties of optically active P(L-HMPMA) and optically inactive P(DL-HMPMA) were further investigated, the molecular weight of P(DL-HMPMA) being similar to that of P(L-HMPMA).

Transmittance changes of the P(L-HMPMA) and P(DL-HMPMA) aqueous solutions as a function of temperature have been presented in Figure 1. These water-soluble polymers were found to exhibit characteristic phase transitions. The P(L-HMPMA) aqueous solution

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* To whom correspondence should be addressed.

† Present address: Department of Polymer Science and Engineering, Kyoto Institute of Technology, Matsugasaki, Sakyo-ku, Kyoto 606-8585, Japan. Telelephone: +81−75−724−7820. Fax: +81−75−724−7800. E-mail: t-aoki@ipc.kit.ac.jp.

‡ Present address: Faculty of Photonics Science and Technology, Chitose Institute of Science and Technology, 858−65, Bibi, Chitose, Hokkaido 066-8655, Japan.

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Table 1. Characterization of Monomers and Their Corresponding Polymers

	monomer		polymer		
samples	yield (%)	$[\alpha]^{20}_{589}$ (deg)	yield (%)	M_w[b]	$[\alpha]^{20}_{589}$ (deg)
L-HMPMA	82	+28	26	58 700	+33
DL-HMPMA	75	0	12	66 800	0
D-HMPMA	83	−28	20	84 800	−34

[a] Measured in distilled water at 589 nm ($c = 1.00$) using a digital polarimer. [b] Determined by a liquid chromatograph system equipped with two polystyrene gel columns and a refractive index detector in DMF containing 0.1 w/v% LiCl as an eleuent 40 °C against poly(ethylene glycol) standards.

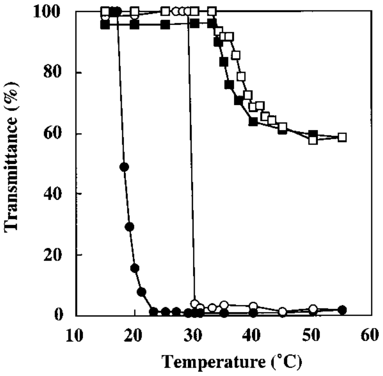

Figure 1. Effect of temperature on the transmittance of PHMPMA aqueous solutions: (○, ●) P(L-HMPMA); (□, ■) P(DL-HMPMA). Each polymer concentration was 0.4 w/v%. Open and solid data points represent heating and cooling cycles, respectively.

was transparent below 29 °C but changed to turbidity at approximately 30 °C, forming solid precipitates. The degree of turbidity was not affected by any changes to higher temperatures. In cooling, the turbidity started to decrease close to 21 °C with the solution being transparent at lower temperatures, thus revealing clearly hysteresis. On the other hand, the P(DL-HMPMA) aqueous solution exhibited turbidity at 34 °C, i.e., higher than that of the optically active polymer aqueous solution. The transmittance value of the P(DL-HMPMA) aqueous solution, however, did not decrease to 0% above 35 °C, while no hysteresis was observed in cooling. P(DL-HMPMA) formed a clear coacervate above 34 °C. P(DL-HMPMA) possessed relatively higher hydration states and failed to form a solid precipitate even at higher temperatures. It would seem to have been blocked in forming a compact structure of P(DL-HMPMA) chains.

As P(L-HMPMA) was composed only of L-formed monomers, the optically active polymer chains may form a packed structure and hence a low hydration state in water. In contrast to this, P(DL-HMPMA) was constructed of racemic monomers. Steric hindrance may occur between the side chains and result in relatively expanded structures of polymeric chains. Indeed, the P(L-HMPMA) was left to dissolve overnight in refrigerated water whereas the P(DL-HMPMA) was readily dissolved at room temperature. Dynamic light scattering measurements at 6 °C, where these two polymers were soluble, supported the suggestion that P(L-HMPMA) had a different soluble state in water compared to that of P(DL-HMPMA).[7] P(L-HMPMA) showed a bimodal size distribution with diameters of approximately 12 and 90 nm in water, while P(DL-HMPMA) had a single distribution with a diameter of 15 nm. Compact P(L-HMPMA) chains might favor the formation of a soluble large associate and of solid precipitates below and above its transition temperature, respectively. Poly(*N*-isopropylacrylamide) (PIPAAm) has a lower critical solution temperature (LCST) of 32 °C in water[1,2,8] with no hysteresis between heating and cooling cycles.[9] It may be noted that P(L-HMPMA) is a novel chiral macromolecule which shows an LCST and clear hyteresis for its phase transition. The details of each phase transition behavior for the polymers synthesized in this study are currently under investigation.

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