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A novel thermosensitive polymer, poly(methyl 2-propionamidoacrylate), with geminal substituents

Hirokazu Okamura[a,*], Takeshi Mori[a], Keiji Minagawa[a], Seizo Masuda[a], Masami Tanaka[b]

[a]*Department of Chemical Science and Technology, Faculty of Engineering, The University of Tokushima, Minamijosanjima-cho, Tokushima 770-8506, Japan*
[b]*Faculty of Pharmaceutical Science, Tokushima Bunri University, Yamashiro-cho, Tokushima 770-8514, Japan*

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Abstract

A novel thermosensitive polymer, poly(methyl 2-propionamidoacrylate) (PMPA), was prepared and the phase transition behavior in an aqueous solution was studied. PMPA have geminal substituents of propionamide and methoxy carbonyl in each monomer unit. It was found that PMPA shows the lower critical solution temperature (LCST) at 50.6 °C sharply. The LCST of PMPA was almost independent of the polymer concentration above 40 g/l, while, below 40 g/l, it decreased with the increasing polymer concentration. The effect of salt addition (NaCl, NaBr, and Na_2SO_4) on the LCST was also studied. The LCST of PMPA linearly decreased with the increasing concentration of each salt. The salting-out effect of these salts was in line with the Hofmeister series: $Na_2SO_4 > NaCl > NaBr$. © 2002 Elsevier Science Ltd. All rights reserved.

Keywords: Water-soluble polymer; Poly(methyl 2-propionamidoacrylate); Lower critical solution temperature

1. Introduction

Water-soluble polymers responsive to temperature have received much attention in recent years, and they have been utilized for potential technological applications in controlled drug delivery [1], molecular separation [2], and tissue culture substrates [3,4]. Many thermosensitive polymers such as poly(*N*-substituted acrylamide) [5], poly(*N*-vinyl alkylamide) [6,7], poly(vinyl ether) [8] and poly(ethylene glycol-*co*-propylene glycol) [9] have been reported so far. These thermosensitive polymers were generally designed by endowing water-soluble polymers with suitable hydrophobicity. There are two strategies to achieve that: copolymerization of a hydrophilic monomer with a hydrophobic one and introduction of hydrophobic groups to a hydrophilic monomer [10].

Copolymerization with hydrophobic monomer is a more simpler approach for endowing a water-soluble polymer with hydrophobicity, and is very useful to control the lower critical solution temperature (LCST) of the copolymer finely by varying the copolymer composition [11]. However, the phase transition of these copolymers tends to be broader when increasing the hydrophobic monomer content in the copolymer because of the wide distribution of copolymer composition. On the other hand, the strategy of introducing a hydrophobic group to a hydrophilic monomer is more suitable to obtain a thermosensitive polymer showing a sharp phase transition [10].

We report here a novel thermosensitive polymer, poly(methyl 2-propionamidoacrylate) (PMPA), which has two substituted groups at α-carbon of each monomer unit. Each of the two groups consists of hydrophilic (ester and amide bonds) and hydrophobic moieties (methyl and ethyl groups) in a suitable balance. It was found that PMPA shows a sharp phase transition and the transition does not show a hysteresis in heating and cooling processes. To our knowledge, only two groups including us have reported this kind of thermosensitive polymer with geminal substituents [12,13]. The geminal α-substitution of vinyl monomer would give the variation of molecular design to the monomers of thermosensitive polymers.

2. Experimental

2.1. Synthesis of 2,2-dipropionamidopropionic acid

Synthesis route and chemical structure of methyl 2-propionamidoacrylate (MPA) are shown in Fig. 1. Propionamide (73.1 g, 1 mol) and pyruvic acid (44.3 g, 0.5 mol) were dissolved in benzene (500 ml), and several drops of

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* Corresponding author. Tel.: +81-88-656-7407; fax: +81-88-655-7025.
E-mail address: okamura@sy34.chem.tokushima-u.ac.jp (H. Okamura).

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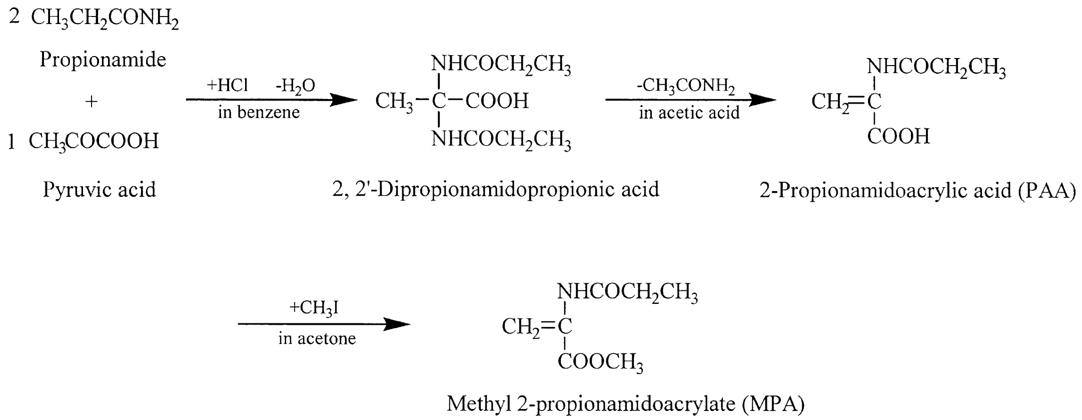

Fig. 1. Synthetic route of MPA.

concentrated hydrochloric acid were added to the solution. The solution was refluxed overnight, and then 2,2-dipropionamidopropionic acid was precipitated as crystals from the solution. The precipitates were separated by filtration, and then recrystallized from ethanol. Yield: 52.9%, mp: 151–152 °C. ^{1}H NMR (DMSO-d_6): δ (ppm from TMS) 0.82 (t, 6H, $-CH_3$), 1.58 (s, 3H, $-CH_3$), 1.98 (q, 4H, $-CH_2-$), 7.99 (s, 1H, –NH–), 13.35 (s, 1H, –COOH).

2.2. Synthesis of 2-propionamidoacrylic acid

2,2-Dipropionamidopropionic acid (21.6 g, 0.1 mol) was dissolved in glacial acetic acid (43.2 g, 0.72 mol). The solution was refluxed for 20 min and then cooled to 0 °C rapidly. The crude product was filtrated, and then recrystallized from ethanol. Yield: 60.8%, mp: 140–141 °C. ^{1}H NMR (DMSO-d_6): δ (ppm from TMS) 0.98 (t, 3H, $-CH_3$), 2.33 (q, 2H, $-CH_2-$), 5.66 (s, 1H, $CH_2{=}C$, *trans* to propionamide group), 6.25 (s, 1H, $CH_2{=}C$, *cis* to propionamide group), 8.95 (s, 1H, –NH–), 13.35 (s, 1H, –COOH).

2.3. Synthesis of methyl 2-propionamidoacrylate

2-Propionamidoacrylic acid (PAA) (11.4 g, 0.08 mol) was dissolved in acetone (1 l) and anhydrous potassium carbonate (24.3 g, 0.18 mol) was added to the solution. The mixture was refluxed with continuously dropping iodomethane (34.1 g, 0.24 mol) over a period of 6 h. The solid components were removed by the filtration, and the filtrate was concentrated and then the residual viscous liquid was extracted with *n*-pentane. Yield: 75.8%, mp: 0.3 °C. ^{1}H NMR (DMSO-d_6): δ (ppm from TMS) 0.98 (t, 3H, $-CH_3$), 2.33 (q, 2H, $-CH_2-$), 3.73 (s, 1H, $-COOCH_3$), 5.63 (s, 1H, $CH_2{=}C$, *trans* to propionamide group), 6.15 (s, 1H, $CH_2{=}C$, *cis* to propionamide group), 9.17 (s, 1H, –NH–). ^{13}C NMR (DMSO-d_6): δ (ppm from TMS) 9.34 ($-CH_2\mathit{C}H_3$), 28.99 ($-\mathit{C}H_2CH_3$), 52.45 ($-COO\mathit{C}H_3$), 108.80 ($\mathit{C}H_2{=}C$), 132.94 ($CH_2{=}\mathit{C}$), 164.06 ($-\mathit{C}OOCH_3$), 172.91 (–NHCO–).

2.4. Synthesis of poly(methyl 2-propionamidoacrylate)

The MPA monomer (5.0 g, 1.06 mol/l) was polymerized at 60 °C in a thermostatic bath, with 2,2′-azobisisobutyronitrile (AIBN; 0.105 g, 0.64 mol/l) of the free radical initiator, and dimethyl sulfoxide (DMSO) of the solvent, as follows. The monomer, initiator and solvent were placed in Pyrex glass ampoule, cooled in a cooling bath, degassed and sealed at high vacuum. After polymerization for 24 h, the reaction mixture was poured into a large excess of diethyl ether and the precipitated polymer was filtered off, washed with diethyl ether and dried at reduced pressure at room temperature. The resulting polymer was purified by dialysis and lyophilized. Yield: 74.3%.

2.5. Measurements

The ^{1}H/^{13}C NMR spectra were obtained with a Varian Unity-600 (600 MHz) spectrometer. Gel permeation chromatography (GPC) analysis was performed on a JASCO GPC-900 equipped with a Shodex SD-800HQ column, deionized water being used as an eluent with poly(ethylene glycol) standards for calibration. The LCST measurement was performed with a Shimadzu UV-3000 spectrophotometer at 500 nm. The fixed-temperature water was allowed to flow into the cell jacket from a circulator. Readings of transmittance data were carried out at a temperature interval of 0.1 °C.

3. Results and discussion

The product obtained from the reaction of PAA and iodomethane was identified by ^{1}H/^{13}C NMR. All the resonance signals were assigned to the corresponding atoms according to the chemical structure of MPA in Section 2. The carbons of ester and amide groups were assigned by a heteronuclear multiple bond correlation (HMBC) technique. It is found by GPC analysis that the number average of the molecular weight (M_n) and the polydispersity (M_w/M_n) of PMPA were 670,000 and 2.7, respectively.

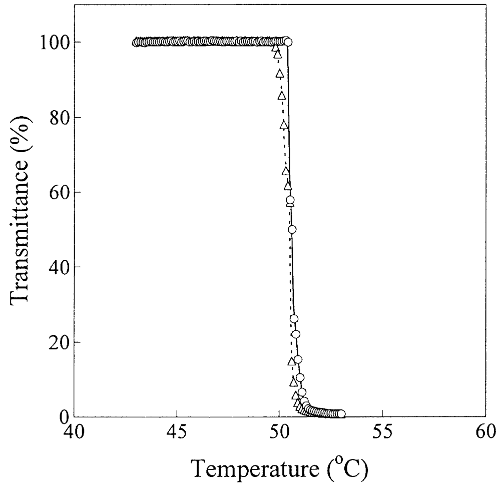

Fig. 2. Transmittance–temperature curves of aqueous PMPA solution (10 g/l) for heating (○) and cooling (Δ) processes.

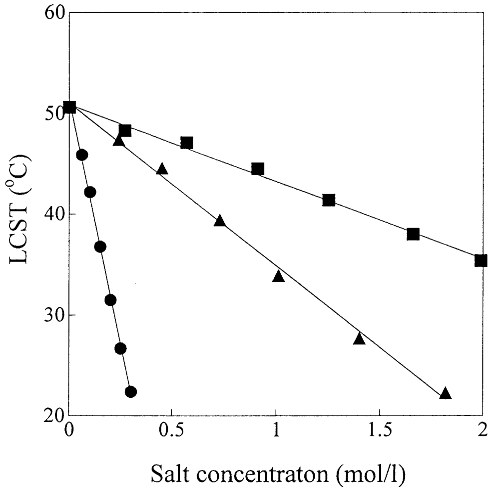

Fig. 4. LCST of aqueous PMPA solutions (10 g/l) as a function of concentrations of added salts. Salt: Na_2SO_4 (●), NaCl (▲), and NaBr (■).

Fig. 2 shows typical transmittance–temperature curves of PMPA solution (10 g/l) upon heating and cooling processes. The phase transition behavior of PMPA is quite sensitive, reversible, and reproducible to thermal stimuli, similar to poly (*N*-isopropylacrylamide) PNIPAM [14]. The LCST values were defined as the temperature at which the transmittance became 50%, and were found to be 50.6 °C for heating and cooling processes. It would be expected that the phase transition of PMPA exhibits a certain degree of retardation in cooling process because of the large two substituted groups on α-carbon of each monomer unit. For example, it has been reported that the recovery of the transparency for poly(*N*-isopropylmethacrylamide) (PNIPMAM) [14] in cooling process retarded due to a α-methyl group in each monomer unit. However, in the case of PMPA, there is little if any retardation in cooling process.

Fig. 3 shows the LCST values as a function of polymer concentration within 1–100 g/l. In lower polymer concentration (below 40 g/l), the LCST depended on the polymer concentration, and decreased with the increase of the concentration, while it was independent of the polymer concentration above 40 g/l. Below the polymer concentration of 1 g/l, it is difficult to determine of the LCST of polymer solution because of the broadening of the phase transition. Such concentration dependence of phase transition is generally accepted in aqueous solutions of PNIPAM [15,16] and poly(*N*-vinyl isobutylamide) [7]. This phenomenon is generally explained as follows: aggregation of polymer above LCST takes place easily at the high concentration, while it becomes difficult at the low concentration.

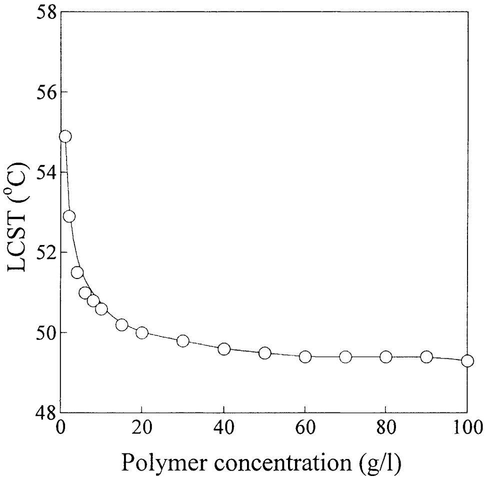

Fig. 3. Polymer concentration dependence of LCST in aqueous PMPA solutions.

It is well-known that the solubility of polymer in water is susceptible to salts addition. In this work, we examined the effect of three sodium salts (NaCl, NaBr, Na_2SO_4) on the thermosensitive property of aqueous PMPA solutions. Fig. 4 shows the dependence of LCST on the salt concentration at a fixed polymer concentration of 10 g/l. The LCST of the aqueous PMPA solution linearly decreased with the increase of salt concentration in all the salts. Generally, such behavior is called salting-out. The effectiveness of anionic species on reducing the LCST was in the order: $SO_4^{2-} > Cl^- > Br^-$. This order is in line with the classical Hofmeister series. It was known from Fig. 4 that in order to precipitate PMPA at room temperature, only about 0.3 M Na_2SO_4 was sufficient, whereas in the case of NaCl more than 1.6 M was needed. The slope of LCST plotted against Na_2SO_4 concentration was about −94 °C/M. We have previously reported that the Na_2SO_4 concentration dependence of LCST for a more hydrophilic polymer, poly(methyl 2-acetamidoacrylate) (PMAA), which has the similar structure to PMPA, is about −214 °C/M [11]. The Na_2SO_4 concentration dependence of LCST for PNIPAM is about −43 °C/M [17]. From the comparison of the phase transition temperature of these polymers, the order of relative hydrophilicity of these polymers is supposed to be as follows: PMAA > PMPA> PNIPAM. These facts indicate that the dependence of

LCST on the salt concentration is related to the hydrophilicity of polymers.

In this report, we have revealed that the geminal α-substitution of vinyl monomer like PMPA is the effective molecular design for the preparation of thermosensitive polymers.

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