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A SYNTHETIC HYDROGEL WITH THERMOREVERSIBLE GELATION. I. PREPARATION AND RHEOLOGICAL PROPERTIES

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ABSTRACT

Block copolymers composed of poly(*N*-isopropylacrylamide-*co*-*n*-butyl methacrylate) [poly(NIPAAm-*co*-BMA)] and poly(ethylene glycol) (PEG) were prepared. Aqueous solutions of the block copolymers were characterized by dynamic viscoelastic measurement as a function of temperature. The fluid solutions turned into hydrogels upon heating while keeping their transparency and without syneresis. The hydrogels turned back into solutions upon cooling. The thermoreversible sol–gel transition was observed with no hysteresis. The sol–gel transition temperatures were closely correlated to the lower critical solution temperature of the poly(NIPAAm-*co*-BMA) in the block copolymers. Gelation is believed to be caused by thermoreversible crosslinkages between intermolecular poly(NIPAAm-*co*-BMA) blocks due to hydrophobic interaction.

INTRODUCTION

Recently, aqueous solutions of biological or synthetic polymers which form hydrogels thermoreversibly have been attracting much attention and have been widely investigated for their rheological properties [1]. Typical examples are aqueous solutions of gelatin [2] or agar [3] which turn into hydrogels upon cooling, and aqueous solutions of polymethacrylic acid [4] or methylcellulose [5] which turn into hydrogels upon heating. All of these solidified hydrogels turn back into fluid solutions at the opposite temperature cycle of gelation. These thermoreversible sol-gel transformations must be caused by thermoreversible crosslinkages due to secondary valence forces between polymer-polymer or polymer-water. Many driving forces have been proposed for reversible crosslinkage formation: helix formation [2], hydrogen bond [4], hydrophobic interaction [5], dipolar interaction [6], liquid-liquid phase separation [7], crystal formation [8], etc. However, the mechanism of the thermoreversible gelation is quite complex and still remains obscure. Consequently, it has been difficult to control the sol-gel transition temperature by modification of the polymer structure.

It is well known that poly(*N*-isopropylacrylamide) [poly(NIPAAm)] aggregates and precipitates in aqueous solution upon heating above about 32°C [9] due to hydrophobic interaction [10, 11]. The temperature is called the lower critical solution temperature (LCST) and can be controlled by randomly copolymerizing NIPAAm with other monomers. The LCST increases or decreases when NIPAAm is copolymerized with a more hydrophilic monomer such as acrylamide [12] or a hydrophobic monomer such as *n*-butyl methacrylate (BMA) [13], respectively.

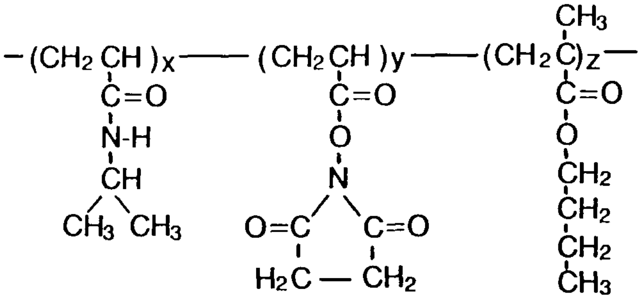
In the current paper, in order to provide a thermoreversible hydrogel with a designed sol-gel transition temperature, we synthesized block copolymers composed of poly(NIPAAm) or poly(NIPAAm-*co*-BMA) and a hydrophilic polymer such as poly(ethylene glycol) (PEG) and investigated the dynamic viscoelastic properties of the aqueous solutions of the block copolymers.

EXPERIMENTAL

The materials used and the synthesis of the block copolymers have been partly described elsewhere [14] in detail.

NIPAAm (Eastman Kodak Co.) was recrystallized from acetone and copolymerized with *N*-acryloxysuccinimide (NASI, Kokusan Chemical Works Co.) to become activated [15], and with or without BMA to control the LCST. Polymerization was carried out in $CHCl_3$ at 60°C for 8 hours by using azobisisobutyronitrile as an initiator. The activated copolymers were precipitated with diethylether and recovered at about 85% yield. The molar composition ratio of comonomers in the activated copolymers was found to be the same as the feed ratio by ^{1}H-NMR spectra.

A series of block copolymers (**1**, **2**, **3**) was prepared by an amido condensation reaction between diamino-PEG6000 ($n = 230$, Kawaken Fine Chemicals Co.) and the corresponding activated copolymer (Fig. 1 and Table 1) at a weight ratio of 1 part diamino PEG to 2 parts copolymer. The ratio was equivalent to the condition in a molar ratio of $[NH_2]/[NASI] = 1/10$. The reaction was carried out at room temperature overnight in $CHCl_3$ at a total polymer concentration of less than 2



Activated Copolymer : Poly(NIPAAm-co-NASI-co-BMA)

$H_2NCH_2CH_2CH_2\text{-}(OCH_2CH_2)_n\text{-}OCH_2CH_2CH_2NH_2$

Diamino-PEG

FIG. 1. Chemical structures of the activated copolymer and diamino-PEG. *x*, *y*, and *z* are given in Table 1.

wt% (at higher than 3 wt%, a chemically crosslinked gel was formed). After the reaction an excess amount of isopropylamine (IPA) was added to the solution to convert unreacted NASI residue to NIPAAm. After being dried, the crude residue was dissolved in distilled water and filtered in a refrigerator. Unreacted diamino-PEG, a low molecular copolymer, and the by-product *N*-hydroxysuccinimide were removed by diafiltration using an ultrafiltration membrane (Amicon, YM-100, nominal molecular weight limit = 100,000), and the retentate solution was lyophilized to give block copolymers at about 80% yield.

In order to determine the LCST of the poly(NIPAAm) or poly(NIPAAm-*co*-BMA), all the NASI of the activated copolymers were converted to NIPAAm by IPA. The LCST was determined as the cloud point of the aqueous solutions of the polymers at a concentration of 1 wt% (Table 1). The cloud point was determined as the temperature at which the first turbidity increase was observed on heating at the rate of 1 °C/min. The turbidity was measured in terms of the percent transmittance

TABLE 1. Synthesis of the Block Copolymers

Sample	*x*/*y*/*z*,[a] mol%	LCST,[b] °C	PEG content,[c] wt%
1	90/10/0	32	38
2	85/10/5	22	34
3	80/10/10	12	34

[a] Molar ratio in the activated copolymers (Fig. 1).

[b] Cloud point of poly(NIPPAm) or poly(NIPAAm-*co*-BMA) converted from the activated copolymer.

[c] Calculated from elemental analysis.

at 500 nm through a 1-cm cell length by a spectrophotometer (Hitachi, U-3210) with a temperature controller (Hitachi, SPR-10). In addition, the same experiment was performed on aqueous solutions of the block copolymers at a concentration of 10 wt% (a typical result is shown in Fig. 2).

^{1}H-NMR spectra were measured with an NMR spectrometer (Varian, EM390) in $CDCl_3$ solutions.

The dynamic moduli, G' (storage modulus) and G'' (loss modulus), were analyzed with a controlled stress rheometer (Carri-Med, CSL-500). An acrylic plate of 6-cm diameter was employed as the measuring system. The block copolymers were dissolved in distilled water at a concentration of 10 wt% in a refrigerator. Aqueous solutions of the block copolymers were set in the measuring system, and the G' and G'' were recorded over the frequency range of 0.01 to 10 Hz at various constant temperatures. In addition, G' and G'' were also observed during the course of heating and cooling. The measurement was performed every 1 °C at 1-minute intervals at the observing frequency of 1 Hz.

RESULTS

A series of water-soluble block copolymers (**1**, **2**, **3**) composed of poly(NIPAAm) or poly(NIPAAm-*co*-BMA) blocks and PEG blocks were obtained under the conditions described in the Experimental Section. The LCST of the poly(NIPAAm-*co*-BMA) lowered with increasing BMA content (Table 1). PEG content

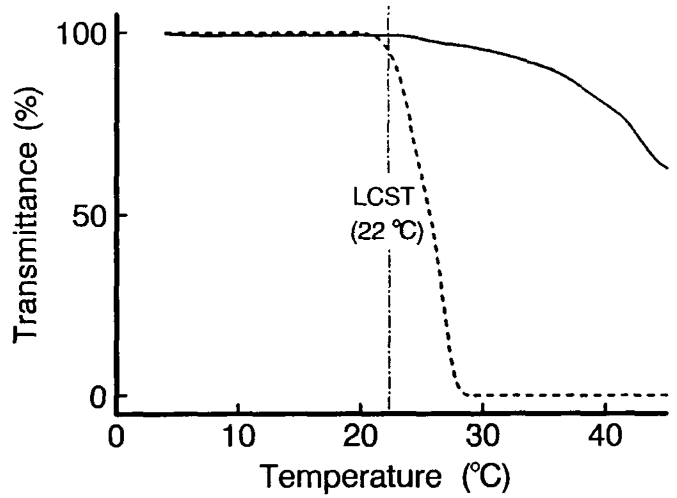


FIG. 2. Percent transmittance change at 500 nm of aqueous solutions of poly(NIPAAm-*co*-BMA) (BMA, 5 mol%, broken line) at a concentration of 1 wt% and of block copolymer **2** (solid line) at a concentration of 10 wt% as a function of temperature.

in the block copolymers was almost the same as the feed ratio, and neither primary amino group nor NASI residue remained in the block copolymers [14].

While the aqueous solutions of poly(NIPAAm) or poly(NIPAAm-*co*-BMA) showed an apparent phase separation at the LCST on heating, the aqueous solutions of the block copolymers at a relatively high concentration (more than about 2-3 wt%) turned into the visually single-phase hydrogels on heating while keeping high transmittance (Fig. 2) and without syneresis, i.e., a separation of water from the gel. The hydrogels then liquefied again upon cooling.

Figure 3 shows the typical frequency dependence of the dynamic moduli observed on the aqueous solution of block copolymer **2**. At a low temperature (15°C) the loss modulus G'' was larger than the storage modulus G' and both dynamic moduli increased with the oscillating frequency. On the other hand, at the high temperature (40°C) the dynamic moduli showed much larger values than those at the low temperature and were almost constant over a wide range of oscillatory frequencies, and G' was much larger than G'' (about 10 times). This means the system was a viscoelastic fluid at low temperature while it behaved as an elastic solid at high temperature in the observed frequency range.

Figure 4 shows the change of G' and G'' of the aqueous solutions of the block copolymers at the oscillation frequency of 1 Hz as a function of temperature. The dynamic moduli measured on the heating cycle (closed symbols) and cooling cycle (open symbols) corresponded well at all temperatures. Since no hysteresis was observed in Fig. 4, the equilibrium state at the fixed temperature is thought to be reached in a very short time, such as 1 minute, while in most of the other reversible

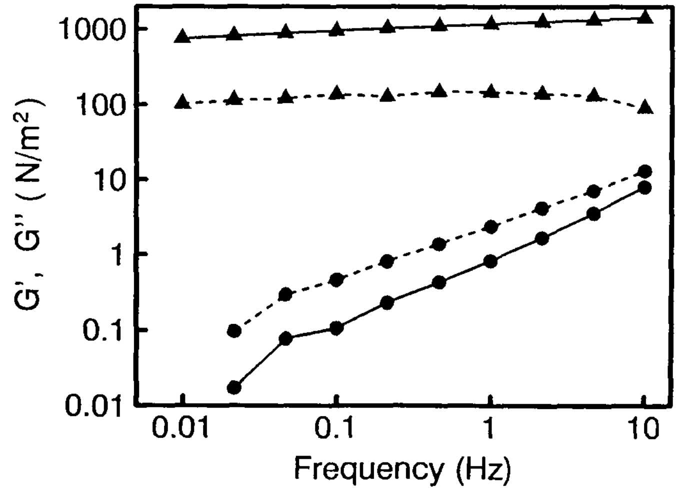


FIG. 3. Frequency dependence of the dynamic moduli of the aqueous solution of block copolymer **2** at a concentration of 10 wt%. Storage modulus (G', solid lines) and loss modulus (G'', broken lines) were measured at 15°C (circles) and 40°C (triangles).

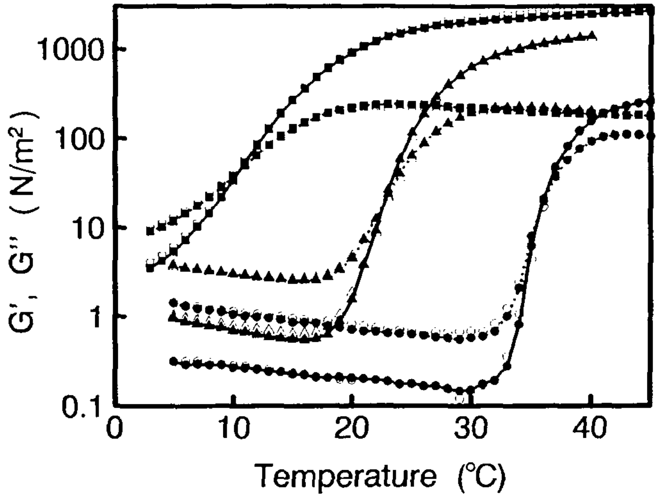


FIG. 4. Temperature dependence of the dynamic moduli of the aqueous solution of the block copolymers (**1**, circle; **2**, triangle; **3**, square) at a concentration of 10 wt%. Storage modulus (*G*′, solid lines) and loss modulus (*G*″, broken lines) were measured on heating (closed symbols) and cooling (open symbols) at the oscillatory frequency of 1 Hz.

hydrogels the gelation is a kinetic process taking a long period, such as over 2 hours [2]. In this experiment a crossover of *G*′ and *G*″ was observed at the different temperatures for each block copolymer. The crossover temperatures, 35, 23, and 11°C for the block copolymers **1**, **2**, and **3** respectively, were close to the LCSTs of poly(NIPAAm) or poly(NIPAAm-*co*-BMA) in the block copolymers (Table 1).

DISCUSSION

Because the static viscoelastic measurement failed to observe the thermoreversible gelation process due to the destruction of the structure of the "weak gel" by large deformation, we employed the dynamic viscoelastic measurement in which a small deformation oscillatory shear strain is applied to the material. In this technique the real and imaginary parts, *G*′ and *G*″, of the complex shear modulus are examined. The observed *G*′ and *G*″ represent an elasticity term and a viscosity term of the material at the oscillatory frequency.

If we regard the temperature at $G' = G''$ as the sol–gel transition temperature of the thermoreversible hydrogels, as previously discussed in the literature [16], the transition temperature of the aqueous systems of the block copolymers described here is closely correlated to the LCST of poly(NIPAAm) or poly(NIPAAm-*co*-BMA). The LCST behavior of poly(NIPAAm) is considered to be caused by the transition of the polymer from a hydrophilic to a hydrophobic state due to dehydration at the LCST followed by aggregation of the polymers [10, 11]. The authors have found [14] through calorimetric analysis that block copolymerization of poly(NIPAAm) with PEG has little effect on the first stage of the LCST phenomenon of poly(NIPAAm). Therefore, this close correlation of the sol–gel transition temperature and the LCST strongly suggests that the driving force of gelation is the hydrophobic interaction between poly(NIPAAm) or poly(NIPAAm-*co*-BMA) blocks.

A plausible interpretation for the mechanism of the thermoreversible hydrogel formation observed here is as follows. An aggregation of poly(NIPAAm) or poly(NIPAAm-*co*-BMA) blocks between separate molecules, due to hydrophobic interaction above the LCST, forms crosslinkages to give an infinite three-dimensional network structure in the aqueous system. Also, the hydrated PEG blocks provide the network with a swelling property in water, and they prevent the aggregation from causing a macroscopic phase separation.

Thermoreversible hydrogels which gel on heating, similar to those described here, have been reported in modified polysaccharides [5–8, 17] as well. Methylcellulose, in particular, has been most widely studied. There has been a lot of controversy [5–8] about the gelation mechanism of the methylcellulose solution, including a concern of hydrophobic interaction [7] or crystalline formation [8]; however, the mechanism still seems vague.

Although the aqueous methylcellulose solution also shows thermoreversible hydrogel formation, there are some differences from the present system, e.g., the methylcellulose gel is quite opaque, the gelation temperature is much higher than the ambient temperature, the sol–gel transformation shows large hysteresis or great time dependence, and syneresis is observed. The greater opaqueness of the methylcellulose hydrogel demonstrates the formation of a larger scale of inhomogeneous structure in the hydrogel than that of the present system. The hysteresis and the syneresis observed in the methylcellulose system suggest that the system is of the nonequilibrium heterogeneous two-phase type, whereas the present system behaves as an equilibrated system. Such discrepancies between methylcellulose and poly(NIPAAm-*co*-BMA)-*b*-PEG suggest that a different gelation mechanism is responsible for each system.

While a lot of thermoreversible hydrogels have been studied by the reversible gelation mechanism, few systems were proven satisfactory due to the complicated and uncontrolled structure of the materials. On the contrary, the well-defined and controllable structure of the novel material described here not only has many attractive features such as the designed sol–gel transition temperature in the ambient region, but it also offers a simple interpretation for thermoreversible hydrogel formation.

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