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Synthesis and Catalytic Activity of the Thermoresponsive Polymers Having Pyrrolidine Side Chains as Base Functionalities

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ABSTRACT: Optically active polymers having chiral 2-aminomethylpyrrolidine side chains have been newly synthesized by a radical homopolymerization of the corresponding protected acrylamide monomer and copolymerization with *N*-isopropylacrylamide followed by deprotection. The resulting polymers were found to be thermoresponsive showing lower critical solution temperatures (LCSTs) at 27–65°C in their aqueous solutions. The pyrrolidine side chains of the resulting thermoresponsive polymer promoted aldol reaction between cyclohexanone and *p*-nitrobenzaldehyde in water, and the reaction proceeded most smoothly at its LCST. Moreover, the diastereomeric ratio (syn : anti) of the aldol adducts obtained at the reaction at 40°C was 22 : 78, whereas the diastereomeric ratio (syn : anti) was 55 : 45 at 20°C. These results indicate that the pyrrolidine side chains catalyze the aldol reactions in the relatively hydrophobic field generated by the thermoresponsive polymer at its LCST. © 2013 Wiley Periodicals, Inc. J. Appl. Polym. Sci. 129: 2554–2560, 2013

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INTRODUCTION

Much attention has been paid to organocatalysis in water,[1–3] because water is an ideal solvent from the view points of reliable safety, low cost, and environment protection. For instance, organocatalytic aldol reactions, one of the most powerful carbon–carbon bond-forming reactions in water have been actively investigated over the past years because of its green chemistry perspectives.[4–6] Of the various organocatalysts, proline and its derivatives are useful and have been applied to stereoselective transformation such as a direct aldol reaction in aqueous media.[7] However, low solubilities of organic substrates and catalysts in water are still a serious problem in the organic reactions in water. The use of relatively hydrophobic reaction field such as micelle,[8] generated temporary and locally in water, is a promising technique for solving this problem. The hydrophobic reaction fields could be also generated by using thermoresponsive polymers. Recently, significant attention has been paid to exploiting the properties of new thermoresponsive water-soluble polymers. These polymers are soluble in water at low temperatures but become insoluble as the temperature rises above the lower critical solution temperature (LCST). Drug delivery systems,[9–11] chromatographic separations,[12,13] the separation and purification of metal ions,[14,15] and the molecular reorganization,[16] are among the most important fields in which temperature sensitive polymers are used.

In our continuous study, we have found that acrylamide (AAm) was polymerized in a solution of poly(*N*-isopropylacrylamide) (PNIPAAm) in water around its LCST(32°C) without any initiators.[17] The mechanism of this polymerization is not always clear at presence, but the solution conditions of PNIPAAm in water at around its LCST is one of most important factors to induce the polymerization. PNIPAAm chains in water aggregate to form a rather hydrophobic reaction field and AAm monomers are probably concentrated and promoted to polymerize in the resulting hydrophobic field. Therefore, in such a hydrophobic field formed by thermoresponsive polymer, various organic reactions could occur in aqueous media. Moreover, it is expected that thermoresponsive polymer having proline side chains promotes base-catalyzed organic reactions in water.

In this study, we have reported the synthesis of novel thermoresponsive polymers having pyrrolidine side chains and used as polymer catalysts in the aldol reaction between cyclohexanone and *p*-nitrobenzaldehyde around at LCST.

EXPERIMENTAL

General

IR spectra were obtained on as FT-IR-470 Plus spectrometer. ^{1}H NMR spectra were measured on a Varian OXFORD NMR300 (300 MHz) spectrometer and the chemical shift values (δ) were expressed in ppm downfield from the internal TMS standard. The molecular weights of polymers were determined using a gel

permeation chromatography (GPC). The GPC analyses were carried out on a Hitachi L-6000 high-performance liquid chromatograph, L-3350 RI detector, and Shodex® GPC KD-804 column. DMF was used as the eluent with a flow rate of 1.0 mL/min, and molecular weight values were relative to the polymethylmethacrylate standards (Shodex® STANDARD (M-75)). UV-vis spectra were recorded with Jasco V-630 spectrometer (Tokyo, Japan). Optical rotation measurement in chloroform or distilled water was performed at 589 nm on a digital polarimeter, DIP-1000 (JASCO, Tokyo). Thermogravimetric analysis (TGA) was carried out under nitrogen flow at a heating rate of 10°C/min on a Rigaku Thermo plus EVOII TG8120.

Materials

L-Prolinol was obtained by reduction of L-proline (Aldrich).[18] Acryloyl chloride (Wako Pure Chemical Industries, Ltd., Osaka, Japan) was used without further purification. *N*-Isopropylacrylamide (NIPAAm) (Wako Pure Chemical Industries, Ltd., Osaka, Japan) was purified by recrystallization from hexane−benzene (95 : 5). 2,2′-Azobisisobutyronitrile (AIBN) as a radical initiator was recrystallized from methanol at below 40°C. Tetrahydrofuran (THF) (Wako Pure Chemical Industries, Ltd.) was distilled from Na-benzophenoneketyl under Ar atmosphere. Other reagents and solvents were commercially available and used without further purification.

Synthesis of (*S*)-((1-(*Tert*-Butoxycarbonyl)Pyrrolidin-2-yl)Methyl) Acrylamide

(S)-1-(*Tert*-Butoxycarbonyl)-2-Pyrrolidinemethanol. Di-*tert*-butyl dicarbonate (16 mL, 70 mmol) was added to a solution of L-prolinol (7.02 g, 69 mmol) and triethylamine (29 mL, 208 mmol) in dichloromethane at 0°C. The reaction mixture was stirred overnight at room temperature. The dichloromethane phase was washed with brine and saturated $NaHCO_3$. The organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure to give (*S*)-1-(*tert*-butoxycarbonyl)-2-pyrrolidinemethanol (94%) as a white solid.[19]

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.84−4.64 (m, 1H), 4.06−3.72 (m, 1H), 2.08−1.94 (m, 2H, CH_2), 1.89−1.70 (m, 2H, CH_2), 3.72−3.30 (m, 4H), 1.60−1.50 (m, 1H, CH*H*), 1.47 (s, 9H, *tert*-butyl).

(*S*)-2-[(4-Toluenesulfonyloxy)Methyl]Pyrrolidine-1-Carboxylic Acid *Tert*-Butyl Ester. (*S*)-1-(*tert*-butoxycarbonyl)-2-pyrrolidinemethanol (5.0 g, 25 mmol) was dissolved in pyridine (27 mL, 34 mmol) and cooled to 0°C. *p*-Toluenesulfonyl chloride (5.7 g, 30 mmol) was added and the mixture stirred overnight at 0°C. The reaction was allowed to warm to room temperature and diluted with ethyl acetate (200 mL). The mixture was washed with 1 M HCl (3 × 75 mL), saturated $NaHCO_3$ (3 × 75 mL), and brine (2 × 75 mL). The organic layer was dried over $MgSO_4$ and the solvent removed under reduced pressure to give (*S*)-2-[(4-toluenesulfonyloxy)methyl]pyrrolidine-1-carboxylic acid *tert*-butyl ester (78%) as a colorless oil.[19]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, 2H, J = 4.05 Hz, Ar-H), 7.42−7.28 (m, 2H, Ar-H), 4.22−3.76 (m, 2H), 3.46−3.22 (m, 2H, PhCH_3), 2.02−1.70 (br-m, 4H), 1.50−1.14 (s, 9H, *tert*-butyl).

(*S*)-2-(Azidomethyl)Pyrrolidine-1-Carboxylic Acid *Tert*-Butyl Ester. (*S*)-2-[(4-Toluenesulfonyloxy)methyl]pyrrolidine-1-carboxylic acid *tert*-butyl ester (2.3 g, 6 mmol) was dissolved in DMSO (90 mL). Sodium azide (2.5 g, 39 mmol) was added and the mixture was heated to 65°C for 17 h. The reaction was allowed to cool to room temperature and was diluted with diethyl ether (40 mL). The organic phase was washed with water (3 × 80 mL) and brine (40 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to give (*S*)-2-(azidomethyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (77%) as a colorless oil.[19]

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.10−3.80 (m, 1H), 3.65−3.40 (m, 3H), 2.10−1.76 (m, 4H), 1.47 (m, 9H, *tert*-butyl).

(*S*)-1-(*Tert*-Butoxycarbonyl)-2-Aminomethylpyrrolidine. (*S*)-2-(Azidomethyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (2.3 g, 10 mmol) was dissolved in THF (90 mL) and water (0.4 mL, 21 mmol). Triphenylphosphine (5.30 g, 20 mmol) was added and the mixture refluxed for 2 h. The organic solvent was removed under reduced pressure and the resulting solid was dissolved in diethyl ether (100 mL). 1 *M* HCl was added until the aqueous layer was at pH 1. The aqueous layer was washed with diethyl ether (50 mL) and the pH was then adjusted to 13 using 1*M* NaOH solution. The product was extracted with dichloromethane (2 × 100 mL) and the organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to give (*S*)-1-(*tert*-butoxycarbonyl)-2-aminomethylpyrrolidine (84%) as a colorless oil.[19]

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.90−3.65 (m, 2H), 3.60−3.25 (m, 2H), 2.95−2.60 (m, 2H), 2.05−1.75 (m, 4H), 1.47 (m, 9H, *tert*-butyl).

(S)-((1-(*Tert*-Butoxycarbonyl)Pyrrolidin-2-yl)Methyl) Acrylamide. (*S*)-1-(*tert*-Butoxycarbonyl)-2-aminomethylpyrrolidine (2.38 g, 12 mmol) and triethylamine (2.2 mL, 18 mmol) were dissolved in anhydrous chloroform (30 mL), and this solution was stirred at −5°C under Ar atmosphere. Acryloyl chloride (1.5 mL, 18 mmol) was slowly added to the solution, and the solution was then stirred at −5°C for 2 h. The solution was evaporated, and the resulting oil was dissolved in ethyl acetate. The mixture solution was kept overnight at 0°C to precipitate triethylamine hydrochloride, and filtration was then carried out to remove the salts. The filtrate was concentrated and purified by column chromatography (Silica gel/Ethyl acetate) to give *tert*-Boc-protected monomer (73%) as a colorless oil.

$[\alpha]_D^{25}$ = −53.3° (c = 1.0 in Chloroform); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.38−5.80 (m, 2H, CH=CH_2), 5.60 (d, 2H, J = 5.10 Hz, CH_2=C*H*), 4.20−3.85 (m, 2H), 3.55−3.00 (m, 4H), 2.14−1.60 (m, 4H), 1.47 (m, 9H, *tert*-butyl); IR ($CHCl_3$) 3299, 1670, 1445, 1405, 1367, 985, 913 cm^{-1}.

Preparation of Poly((*S*)-((1-(*Tert*-Butoxycarbonyl)Pyrrolidin-2-yl)Methyl) Acrylamide-*co*-NIPAAm)

NIPAAm, (*S*)-((1-(*tert*-Butoxycarbonyl)pyrrolidin-2-yl)methyl) acrylamide and AIBN (0.5 mol % relative to monomers) as an initiator were dissolved in THF. After oxygen was removed repeatedly by freeze–evacuation–thaw cycles, polymerization was carried out at 60°C for 20 h. After cooling in an ice-water bath,

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the polymer solution was poured into a large amount of hexane, and the resulting precipitate was filtered and dried under reduced pressure at room temperature. The crude polymer was purified by reprecipitation from acetone into hexane.

Homopolymer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.08−3.57 (br, 1H), 3.57−2.97 (br, 4H), 2.31−1.60 (br, 4H), 1.60−1.28 (br, 9H); IR (KBr) 3322, 1679, 1544, 1400, 1367, 985, 913 cm^{-1}.

Deprotection of Poly((*S*)-((1-(*Tert*-Butoxycarbonyl)Pyrrolidin-2-yl)Methyl) Acrylamide-*co*-NIPAAm)

A solution of 4 *M* HCl/dioxane (4 mL) was added to Boc-protected polymer (0.2 g) and kept stirred in ice-bath.[20] After 2 h, methanol was added to the mixture and kept stirred for 1 h. The reaction mixture was concentrated and poured into a large amount of diethyl ether, and the resulting precipitate was filtered and dried under reduced pressure at room temperature. The crude polymer was purified by reprecipitation from methanol into diethyl ether.

Homopolymer: ^{1}H NMR (300 MHz, D_2O) δ 3.89−3.67 (br, 1H), 3.67−3.45 (br, 2H), 3.45−3.21 (br, 2H), 2.42−1.90 (br, 4H), 1.90−1.32 (br, 3H).

Measurements of Cloud Point

The cloud points of polymers aqueous solutions (1.0 w/v %) were determined by transmittance measurements using a UV-vis spectrometer equipped with a temperature controller. The transmittance of the polymer solutions was recorded as a function of temperature. The temperature was raised at 1.0°C/min, and the wavelength was fixed at 500 nm. The cloud points of the polymer solutions were defined as the temperatures when the transmittance was decreased to half of final transmittance from initial.

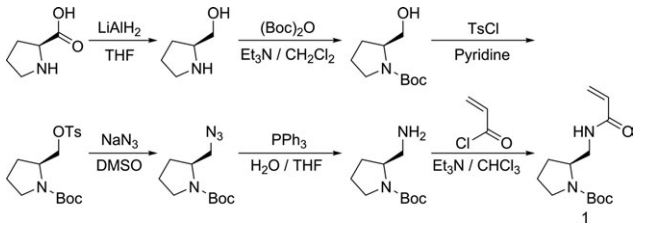
General Procedure for Aldol Reaction of *p*-Nitrobenzaldehyde with Cyclohexanone

p-Nitrobenzaldehyde (1.0 mol/L) was dissolved in cyclohexanone (5.0 mol/L), added in a test tube. The polymer (pyrrolidine unit 10 mol %) was dissolved in water (0.2 mL) and the pH was then adjusted to 7.0 using NaOH*aq*. The reaction was stirring for 24 h at 40°C. The reaction mixture was diluted with water (10 mL) and extracted with diethyl ether (3 × 20 mL). The organic layer was washed with brain (20 mL), and dried over Na_2SO_4. The organic layer was evaporated under reduced pressure to yield the crude product as a yellow solid. The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude product.[21]

RESULTS AND DISCUSSION

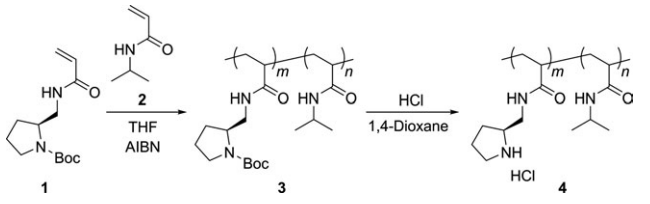
Synthesis and Characterization of Thermoresponsive Polymers Having Pyrrolidine Groups

Thermoresponsive polymers in bearing proline or its derivatives have been reported[22–24]; however, the most monomers of these polymers have been synthesized by using N–H group of pyrrolidine as a clue. There is no example of thermoresponsive polymer, which consists of pyrrolidine units having N–H groups. The *N*-*tert*-butoxycarbonyl(*N*-Boc)-protected monomer **1** was synthesized from L-proline (Scheme 1). Homopolymerization of the monomer **1** and copolymerization with *N*-isopropylacrylamide (NIPAAm) were carried out under usual radical polymerization conditions (Scheme 2, Table I). Monomer contents having pyrrolidine groups of the resulting copolymers were almost the same as those in the monomer feed. The resulting *N*-Boc-protected polymers **3** were optically active, and optical rotations were determined to be from −27.6 to −4.5° depending on the content of the *N*-Boc-protected monomer **1** units. The absolute values of optical rotations were observed to increase with an increase in the monomer **1** unit contents. However, these polymers were insoluble in water. The *N*-Boc-protected polymers were deprotected under acidic conditions to give the corresponding polymers bearing hydrochlorinated pyrrolidine group, and optical rotations were determined to be from 2.8 to 0.8° in water. In methanol the optical rotation of the homopolymer **4** was observed to be 16.8°. Optical rotations of the polymer **4** after deprotection were decreased and switched from negative to positive. These phenomena are also observed in the prolinol derivatives, that is, it has been reported that optical rotation of (*S*)-prolinol hydrochloride in $CHCl_3$ or methanol is decreased and switched from negative to positive after the deprotection of Boc-(*S*)-prolinol.[25,26] Therefore, the decrease and polarity change in the resulting polymers are not because of the loss of chirality of pyrrolidine units but probably because of the conformational change of the polymer chains.



Scheme 1. Synthesis of (*S*)-((1-(*tert*-butoxycarbonyl)pyrrolidin-2-yl)methyl) acrylamide.

The M_n of deprotected copolymer **4** containing 17% of pyrrolidine unit was estimated by GPC based on pullulan, and the M_n was slightly reduced from the value of *N*-Boc-protected polymer estimated by GPC based on polymethylmethacrylate. Homopolymer and the copolymer containing 17% of pyrrolidine units did not show thermoresponsivity, on the contrary, the copolymer containing 10% of pyrrolidine units was found to have LCST at 55°C.



Scheme 2. Polymerization of the monomer **1** with *N*-isopropylacrylamide and deprotection of the Boc groups.

Table I. Synthesis of the Polymers Bearing Pyrrolidine Groups

	Polymer **3**						Polymer **4**		
Entry	In feed **1** : **2**	In copolymer[a] m : n	Yield (%)	M_n[b]	M_w/M_n[b]	Optical rotations[c]	In copolymer[a] m : n	Yield (%)	Optical rotations[d]
1	100 : 0	100 : 0	87	4050	2.71	−27.6	100 : 0	88	2.8
2	25 : 75	17 : 83	64	7750	2.06	−7.3	17 : 83	Quant.	0.5
3	9 : 91	10 : 90	88	8150	2.58	−4.5	10 : 90	96	0.8

Polymerization conditions: solvent, THF; total volume, 10−20 mL; temp., 60°C; time, 24 h; initiator, AIBN (0.5 mol%). Deprotection conditions: solvent, 4M HCl/1,4-dioxane ; volume, 4.0 mL; temp., 0°C; time, 2 h.
[a]Determined by integrated intensity of ^{1}H NMR spectra.
[b]Estimated by GPC based on polymethylmethacrylate standard in DMF.
[c]Measurement conditions: solvent, chloroform; concentration, 1.0%; temperature, 25°C.
[d]Measurement conditions: solvent, water; concentration, 1.0%; temperature, 25°C.

The thermal properties of homopolymer **4** were also examined using thermogravimetry in a temperature range of 30−800°C under nitrogen atmosphere (Figure 1). It is known that the thermal stability of derivatives of PAAm is enhanced by replacement of the hydrogens by alkyl groups.[27] The TGA curve showed three degradation steps. The first step is ascribed to the loss of a trace of water absorbed from the environment. The thermal degradation of polymer occurs with degradation temperature of 350°C and 530°C, and weight losses of 57% and 27%, respectively. The degradation of PAAm was reported to occur at 326°C and 410°C.[27] These differences may be explained by the higher steric effect in homopolymer **4** because of the 2-aminomethyl pyrrolidine group, which makes polymer–polymer interactions difficult and retards an undesirable degradation of the side chains.

Thermoresponsive Behavior of Poly((*S*)-1-Pyrrolidin-2-Ylmethyl Acrylamide) in Aqueous NaCl at Various pH

The phase separation behavior of poly((*S*)-1-pyrrolidin-2-ylmethyl acrylamide) (**4**) in water was observed at different pH values. The homopolymer **4** was soluble in neutral water and its aqueous solution showed pH at 3, while the phase transition behavior was not observed (Table II). On the contrary, the solution of the homopolymer **4** was found to show LCST at 50°C when pH 13 was adjusted with NaOH*aq* and the pyrrolidine moiety was deionized.

It is well-known that cloud points of water-soluble thermoresponsive polymers, for example, PNIPAAm, poly(NIPAAm-*co*-2-hydroxyisopropylacrylamide), poly(*N*,*N*-diethylacrylamide), poly(*N*-4-piperidineethanolacrylamide), and poly(cyclopropylacrylamide), are considerably influenced by adding salts such as

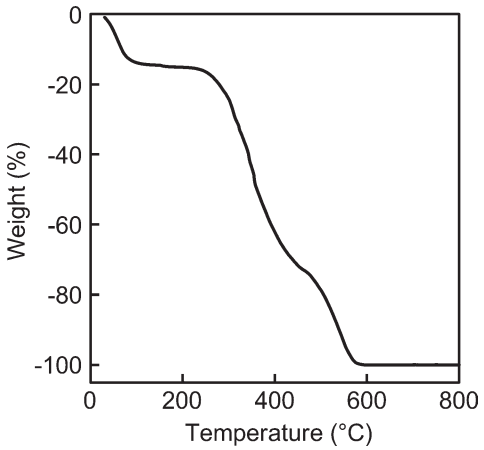


Figure 1. TGA curve of poly((*S*)-1-pyrrolidin-2-ylmethyl acrylamide).

Table II. Temperature Dependence of the Aqueous Solution of Poly((*S*)-1-Pyrrolidin-2-Ylmethyl Acrylamide) at Various pH with Different Salt Concentrations [NaCl] = 0.3 and 1.0 M

	LCST (°C)[a]				
In NaCl*aq* (M)	pH[b] 3	7	11	12	13
0.0	-	-	-	-	51
0.3	-	-	70	67	50
1.0	-	-	57	55	45

[a]Determined by transmittance measurements using a UV-vis spectrometer equipped with a temperature controller. Wavelength, 500 nm; temperature was raised at 1.0°C/min.
[b]pH value was adjusted with NaOH*aq*.

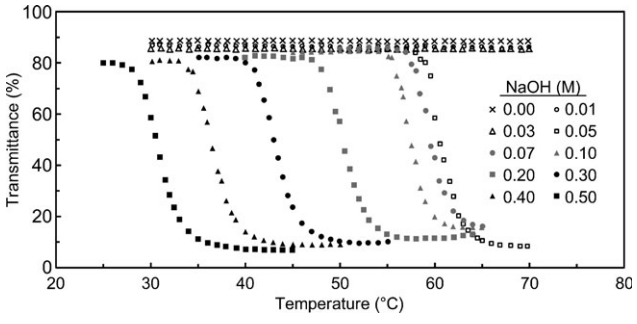


Figure 2. The effect of NaOH concentration to the thermoresponsivity of the polymer **4** ($m : n = 100 : 0$).

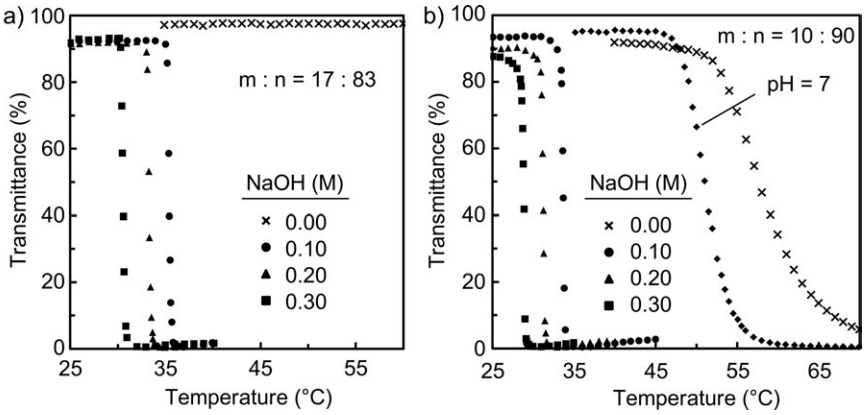
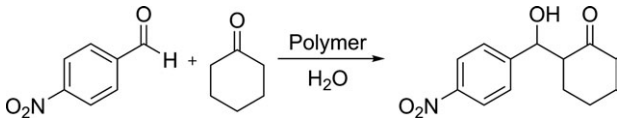


Figure 3. The effect of NaOH concentration to the thermoresponsivity of the polymer **4** [$m : n =$ (a) 17 : 83 and (b) 10 : 90].

NaCl and $CaCl_2$, because salt disrupts the hydration structure surrounding the polymer chains.[28–31] The effect of NaCl concentrations (0.3 and 1.0*M*) was investigated at pH = 11–13. In 0.3*M* NaCl*aq*, the LCST-type phase transition was observed at 70°C at pH 11, and the LCST values decreased with increasing pH values. In 1.0*M* NaCl*aq*, the polymer solution observed phase transition over pH 11, the LCST values were lower than in 0.3*M* NaCl*aq*. These results were indicated that the phase transition of the polymers was influenced by not only salt concentration but also pH values.



Scheme 3. The aldol reaction between cyclohexanone and *p*-nitrobenzaldehyde in water.

Thermoresponsive Behavior of the Homo- and Co-Polymers Having Pyrrolidine Groups in Aqueous NaOH

Figure 2 shows the effect of NaOH concentration on the phase transition and/or separation behavior of poly((*S*)-1-pyrrolidin-2-ylmethyl acrylamide) (**4**). The homopolymer **4** was found to show LCST at 60°C in 0.05*M* NaOH solution, whereas the homopolymer was not thermoresponsive without NaOH (Figure 2). The LCST value decreased with increasing NaOH concentration. The copolymer containing 10% of pyrrolidine groups showed LCST at pH 2.0 at 55°C without NaOH; it also showed LCST at pH 7.0 at 51°C adjusted with NaOH. The copolymers containing 17% and 10% of pyrrolidine groups showed LCSTs in 0.10*M* NaOH solutions (pH > 13) at 35°C and 34°C respectively, and the LCST values also decreased with increasing NaOH concentration (Figure 3). Temperature shift of LCSTs by adding NaOH was remarkable in the homopolymer in comparison with the copolymer. In all polymers, the LCSTs of the polymer solutions shifted to a lower temperature with increasing NaOH concentration, indicating that the hydrophobicity of the copolymers increased with increasing NaOH concentration because of the deionization of the pyrrolidine moiety along with the so-called salting-out effect.[28–31]

Table III. Aldol Reaction of Cyclohexanone with *p*-Nitrobenzaldehyde Catalyzed by the Resulting Polymers in Water[a]

Entry	Polymer	pH	Temp. (°C)	Cyclohexanone (mol/L)	Conversion (%)[b]	Syn : anti[b]
1	Copolymer[c]	7.0	20	5.0	3	55 : 45
2	Copolymer[c]	7.0	30	5.0	14	21 : 79
3	Copolymer[c]	7.0	40	2.0	16	25 : 75
4	Copolymer[c]	7.0	40	5.0	32	22 : 78
5	Copolymer[c]	7.0	40	10.0	27	21 : 79
6	Copolymer[c]	7.0	40	20.0	11	35 : 65
7	Copolymer[c]	7.0	50	5.0	29	18 : 82
8	PNIPAAm[d]	Neutral	40	5.0	Trace	-

[a]Experimental conditions: solvent, water 0.2 mL; *p*-nitrobenzaldehyde, 1 mol/L; time, 24 h.
[b]Determined by integrated intensity of ^{1}H NMR signals.
[c]pyrrolidine unit : NIPAAm = 10 : 90.
[d]M_n = 11300, M_w/M_n = 2.0.

Aldol Reaction in Aqueous Solution of the Thermoresponsive Polymers Having Pyrrolidine Groups

The catalytic performance of copolymer **4** (pyrrolidine unit : NIPAAm = 10 : 90) was evaluated using aldol reaction between cyclohexanone and *p*-nitrobenzaldehyde as a model reaction (Scheme 3, Table III). The pH of the aqueous solution was adjusted at 7.0, and the aldol reaction was carried out at various temperatures (Table III). PNIPAAm without pyrrolidine units was not effective to the aldol reaction under neutral conditions (entry 8). The LCST of the copolymer at pH 7 was observed at 51°C, and the reaction was found to proceed most smoothly at 40°C (conversion: 32%), and the diastereomeric ratio (syn : anti) of the resulting aldol adducts was 22 : 78 (entry 4, Table III), while the conversion and the diastereomeric ratio (syn : anti) were 3% and 55 : 45 at 20°C, respectively (entry 1). Notable solvent effect of the aldol reaction of these substrates is not always observed, but it is reported that high anti-diastereomeric selectivity is obtained under high concentration conditions in aqueous solution or neat conditions.[32] High anti-diastereomeric selectivity observed in our reaction system indicates the possibility that the substrates are dehydrated and concentrated in the hydrophobic reaction field formed during the phase transition of the thermoresponsive polymer. The molar ratio of *p*-nitrobenzaldehyde to cyclohexanone also affected the conversion, namely, the use of five equivalent of cyclohexanone to the aldehyde gave the best result (entry 4), and higher concentration of cyclohexanone was not preferable. The optimized molar ratio of cyclohexanone and *p*-nitrobenzaldehyde in the polymer reaction fields is probably obtained by using excess amount of cyclohexanone because the solubility of cyclohexanone in water is higher than *p*-nitrobenzaldehyde.

CONCLUSION

New optically active thermoresponsive polymers bearing N–H-free pyrrolidine groups have been successfully prepared by homopolymerization of (*S*)-1-(*tert*-butoxycarbonyl)-2-methylpyrrolidine acrylamide and copolymerization with *N*-isopropylacrylamide followed by deprotection Boc groups. Homopolymer of (*S*)-2-methylpyrrolidine acrylamide and copolymers having (*S*)-2-methylpyrrolidine acrylamide unit contents 17% did not show thermoresponsivity, but the copolymer containing 10% of (*S*)-2-methylpyrrolidine acrylamide unit was found to have LCST at 55°C. Moreover, all polymers showed thermoresponsivity in NaOH solution of various concentrations.

The resulting thermoresponsive copolymer containing 10% of pyrrolidine groups promoted aldol reaction between cyclohexanone and *p*-nitrobenzaldehyde in aqueous solution, and the reaction proceeded most smoothly at its LCST. Moreover, the diastereomeric ratio of the aldol adducts obtained was remarkably changed at the LCST of the used polymer. These results indicate that the substrates are incorporated into the relatively hydrophobic field generated by the thermoresponsive polymer at its LCST and the pyrrolidine side chains catalyzed the aldol reactions in this polymer field. It is also probable that the diastereomeric ratio (syn : anti) is influenced by the configuration of pyrrolidine units and the conformation of the polymer chains, which generate the hydrophobic field at their LCST. Therefore, the use of the homopolymer of racemic 2-methylpyrrolidine acrylamide instead of chiral forms seems to change the diastereoselectivity. Further study on the relation between the stereoselectivity and the configurations of pyrrolidine units in our polymers is currently in progress.

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