Anionic Hydrogen-Transfer Polymerization of N-Isopropylacrylamide Under Microwave Irradiation

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ABSTRACT: Anionic hydrogen-transfer homopolymerization of N-isopropylacrylamide (NIPAAm) was carried out using t-BuOK as an initiator in DMF under microwave irradiation. After 100 W of microwave was irradiated to the reaction mixture at 140 °C for 6 h in the temperature control mode, corresponding polymer was obtained in 10% yield. In the case of conventional oil bath heating, by contrast, corresponding polymer was not obtained in similar anionic polymerization conditions. With 100 W and 2.45 GHz of microwave irradiation, formation of the polymer was obtained. Microwave-assisted anionic hydrogen-transfer copolymerization of NIPPAm and acrylamide (AAm) led to the formation of thermo-sensitive copolymers whose thermo-sensitivity was controlled by the NIPAAm/AAm unit ratio. © 2019 Wiley Periodicals, Inc. J. Polym. Sci., Part A: Polym. Chem. 2019

KEYWORDS: anionic polymerization; hydrogen-transfer polymerization; lower critical solution temperature; microwave irradiation; N-isopropylacrylamide

INTRODUCTION Vinyl monomers having active hydrogens such as acrylamide (AAm) and its derivatives are known to undertake hydrogen-transfer polymerization under anionic polymerization conditions. This polymerization system, which was first patented in 1954 by Matlack1 and published in 1957 by Breslow et al.,2 describes that poly(β-alanine) can be obtained by anionic polymerization conditions. Since Matlack and Breslow reported, the hydrogen-transfer polymerization has been reported by many researchers. Monomers having active hydrogen such as AAm,3 methacrylamide,4 α-substituted AAm,5 β-substituted AAm,6 N-substituted AAm6–8 and others, can proceed the hydrogen-transfer polymerization under anionic polymerization conditions. In addition, the hydrogen-transfer polymerization of monomers with two active hydrogens has been investigated.9–13

The rate of polymerization, the molecular weight of the polymer, and the yield of the polymer tend to be lower for N-substituted AAm than for unsubstituted AAm. As pointed out by Yokota et al., as well as Otsu et al., the probability of hydrogen-transfer polymerization of N-substituted acrylamides increases with the acidity of the N-H bond.14,15 That is, as the electron-withdrawing properties of the substituent on the nitrogen increase, hydrogen-transfer polymerization tends to proceed. The hydrogen-transfer polymerization is a promising technique that can introduce functional groups into the main chain of polymers. However, it is necessary to introduce a functional group to amide nitrogen of the monomer. The N-anion derived from such an N-substituted amide will be less reactive than the primary amide due to electronic and steric factors. The microwave irradiation method has been exploited for many chemical reactions. A number of review papers on microwave-assisted chemical reactions have been published.16–19 This method allows rapid and direct heating of the reaction media. In most cases, microwave can dramatically reduce reaction times and increase product yields.20–23 In our previous research, we found that the anionic hydrogen-transfer polymerization of AAm utilizing microwave irradiation easily provides poly(β-alanine) as a resulting polymer in a short space of time.24 When N-substituted amides with low reactivity as described above are polymerized, the anionic polymerization of N-substituted amides proceeds via a hydrogen-transfer process when using microwave irradiation. Furthermore, the resulting polymers prepared by polymerization of N-isopropyl acrylamide (NIPPAm) by using microwave irradiation should have a structure similar to poly(NIPAAm) prepared by radical polymerization.
Poly(NIPAAm) is a temperature-sensitive molecule that has a LCST of about 32°C in aqueous solution. Recently, temperature-sensitive molecules have attracted considerable attention, especially their response to changes in temperature of the surrounding fluid, and offer great potential applications in the field of bioengineering.

In this study, we describe the anionic hydrogen-transfer polymerization of NIPAAm under microwave irradiation. We also describe the LCST properties of the obtained polymers.

EXPERIMENTAL

Materials
NIPAAm was recrystallized from n-hexane. AAm was recrystallized from benzene. 2,2′-Azobis(isobutylronitrile) (AIBN) was recrystallized from ethanol. All other solvents and reagents were purchased from Wako Pure Chemical Industries, Ltd.

Measurements
1H NMR and 13C NMR spectra were recorded on a JEOL ECA-500 spectrometer. IR spectra were measured on a JASCO FT/IR-4200 spectrometer. Obtained polymer was purified by a Japan Analytical Industry recycling preparative HPLC system (LC908-C60) equipped with polystyrene gel columns (JAI Gel-1H and JAI Gel-2H) using chloroform as an eluent. Gel permeation chromatographic analyses were carried out on a Shimadzu LC-10 AD (column: TSK-Gel α-3000, DMF as an eluent, ultraviolet (UV) detector: Hitachi L-7400, data processing system: Routine Instrument Co., Chromato-Pro-GPC) using polystyrene as the standard.

Microwave Irradiation
Microwave irradiation was performed using an EYELA Wave Magic MWO-1000S equipped with a magnetron (2.45 GHz, 500 W). The reaction was carried out in a 30 mL three-necked test tube at the center of a microwave oven.

Anionic Hydrogen-Transfer Polymerization of NIPAAm under Microwave Irradiation (Typical Procedure)
To a 30 mL three-necked test tube equipped with a reflux condenser containing a DMF solution of NIPAAm, and N-phenyl-β-naphthylamine (1 mol%) as a radical inhibitor, potassium t-butoxide (3 mol%) was added as an initiator. Hundred Watts of microwave was irradiated to the reaction mixture at 140°C in the temperature control mode. After irradiation for 6 h, the reaction mixture was poured into n-hexane/diethyl ether (v/v = 1/1), and the precipitated polymer was purified by recycling preparative HPLC (eluent: chloroform). The obtained polymer was dried in vacuo.

RESULTS AND DISCUSSION

Anionic Hydrogen-Transfer Polymerization of NIPAAm under Microwave Irradiation
Anionic homopolymerization of NIPAAm under microwave irradiation was performed to investigate the behavior of the reaction. The polymerization by conventional heating was as well performed as a comparison.

Under the microwave irradiation conditions, the anionic homopolymerization of NIPAAm was carried out at 140°C for 6 h in the temperature control mode (100 W) using t-BuOK (3 mol%) as an initiator in DMF containing N-phenyl-β-naphthylamine (1 mol%) as a radical polymerization inhibitor (Scheme 1). Consequently, the resulting polymer was obtained in 10% yield as an n-hexane/diethyl ether (v/v = 1/1)-insoluble part. In contrast, in the case of conventional oil bath heating at 140°C for 6 h, the anionic homopolymerization of NIPAAm did not proceed. These reactions were examined under nonanhydrous conditions. Generally, conventional anionic polymerization does not proceed in the presence of water. On the other hand, in hydrogen-transfer polymerization, when the terminated polymers are regenerated by deprotonation, the regenerated N-anions are expected to be associated with anionic polymerization. However, the propagating anions derived from NIPAAm should have lower reactivity for propagation due to the N-substituted isopropyl group as compared to the propagating anions of AAm. Meanwhile, Leadbeater et al. reported that a nonpolar solvent such as n-hexane is not heated by microwave irradiation, but a nonpolar solvent including small quantity of an ionic compound such as an ionic liquid can be heated rapidly under microwave irradiation condition. These results indicate that microwave is absorbed by ionic moieties. Specifically, since the propagating N-anion has an ionic character with a large dipole moment, the propagating N-anion can principally absorb microwaves and it was activated. As a result, under microwave irradiation conditions, anionic polymerization of NIPAAm would have provided a low yield (10%).

The resulting polymer was subjected to structural analysis by comparing the 1H NMR spectrum of poly(NIPAAm) synthesized by radical polymerization under conventional heating. In the 1H NMR spectrum of the vinyl polymer obtained by radical polymerization of NIPAAm, a methine proton derived from the isopropyl group was observed at δ = 4.00 ppm. In addition, the methine proton of the polymer main chain was...
observed at \( \delta = 2.73 \) ppm, and the methylene proton of the polymer main chain was observed at \( \delta = 1.30-2.41 \) ppm (Supporting Information Fig. S1a). In contrast, the \(^1\)H NMR spectra of the obtained polymer suggested that both hydrogen-transfer and vinyl polymerization took place. The \(^1\)H NMR spectrum of the polymer obtained is shown in Supporting Information Figure S1b, in which the peaks attributable to methylene protons adjacent to the nitrogen atom were observed at \( \delta = 3.11-3.86 \) ppm. Moreover, the peaks attributable to methane of the vinyl polymerization unit together with those due to the hydrogen-transfer polymerization unit (\( \delta = 1.60-3.11 \) ppm) were observed.

**Anionic Hydrogen-Transfer Copolymerization of NIPAAm and AAm under Microwave Irradiation**

Under microwave irradiation conditions, the anionic copolymerization of NIPAAm and AAm was carried out at 140 °C for 6 h in the temperature control mode (100 W) using \( t\)-BuOK (3 mol%) as an initiator in DMF containing \( N\)-phenyl-\( \beta\)-naphthylamine (1 mol%) as a radical polymerization inhibitor. As a result, as the amount of AAm added to the copolymerization system increased, the ratio of hydrogen-transfer polymerization units of AAm in the obtained copolymer increased, and the yield of the obtained copolymer also tended to increase (Table 1). However, \( M_n \) was almost constant regardless of the feeding ratio of NIPAAm and AAm. The obtained copolymers were characterized by \(^1\)H NMR spectrum. A methine proton derived from an isopropyl group was observed around \( \delta = 4.00 \) ppm as in the \(^1\)H NMR spectrum of poly(NIPAAm). In the region of \( \delta = 3.13-3.89 \) ppm, methylene protons adjacent to the amide nitrogen of hydrogen-transfer polymers of NIPAAm and AAm were observed. In the region of \( \delta = 1.50-3.00 \) ppm, methylene protons adjacent to the carbonyl group derived from the hydrogen-transfer polymerization units of NIPAAm and AAm, as well as methine protons derived from the vinyl polymerization unit of NIPAAm, were observed. Moreover, when vinyl polymerization units derived from AAm were present, methylene protons of the polymer main chain were detected at \( \delta = 1.40-2.05 \) ppm.13 However, the corresponding signals were not found in the obtained copolymer (Supporting Information Fig. S2). In other words, the \( z' \) unit clearly does not exist in the copolymer of the structure as shown in Scheme 2. Taking into account the above points, the unit ratio of the copolymer was calculated from the proton ratio. Scheme 3 shows a plausible process of the polymerization. The nucleophilic attack of the propagating \( N\)-anion (2) against the \( \beta\)-carbon atom of AAm gives rise to the carbanion(3). However, in this system, there is an equilibrium between 1 and 2. Although the nucleophilicity of 2 is lower than that of 1 and \( k_3 > k_4 \), the population of 2 is expected to be higher than 1, which must be the reason for the selective hydrogen-transfer process.

### Table 1: Anionic Hydrogen-Transfer Polymerization of NIPAAm and AAm

<table>
<thead>
<tr>
<th>Run</th>
<th>NIPAAm (g)</th>
<th>AAm (g)</th>
<th>Mol ratio of NIPAAm/AAm</th>
<th>Yield (%)</th>
<th>( x/y/z )^a</th>
<th>( M_n )^b</th>
<th>( M_w/M_n )^b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.0129</td>
<td>0.0000</td>
<td>100/0</td>
<td>10</td>
<td>27/73/0</td>
<td>620</td>
<td>1.35</td>
</tr>
<tr>
<td>2</td>
<td>5.6541</td>
<td>0.0715</td>
<td>100/2</td>
<td>2</td>
<td>27/72/1</td>
<td>740</td>
<td>1.04</td>
</tr>
<tr>
<td>3</td>
<td>5.6582</td>
<td>0.1421</td>
<td>100/4</td>
<td>12</td>
<td>27/71/2</td>
<td>700</td>
<td>1.09</td>
</tr>
<tr>
<td>4</td>
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<td>0.3559</td>
<td>100/10</td>
<td>24</td>
<td>23/61/16</td>
<td>680</td>
<td>1.10</td>
</tr>
<tr>
<td>5</td>
<td>5.6571</td>
<td>0.7109</td>
<td>100/20</td>
<td>24</td>
<td>21/58/21</td>
<td>610</td>
<td>2.18</td>
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<tr>
<td>6</td>
<td>4.3550</td>
<td>0.8827</td>
<td>100/30</td>
<td>33</td>
<td>18/47/35</td>
<td>630</td>
<td>1.50</td>
</tr>
<tr>
<td>7</td>
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<td>1.0161</td>
<td>100/40</td>
<td>35</td>
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<td>1.1877</td>
<td>100/50</td>
<td>36</td>
<td>15/39/46</td>
<td>720</td>
<td>1.06</td>
</tr>
</tbody>
</table>

^a^ Determined by \(^1\)H NMR analysis. ^b^ From GPC analysis.
SCHEME 3 Plausible mechanisms for propagation of AAm.

On the other hand, in the case of NIPAAm, since the electron-donating isopropyl group is substituted to the amide nitrogen, the equilibrium of C-anion (5) and N-anion (6) might be approximately equal. As in the case of AAm, the nucleophilicity of 6 is lower than that of 5 and $k_3 > k_4$, the population of 6 is expected to be higher than 5. For that reason, the propagation reaction by the nucleophilic reaction of 5 is predominant. Thus, the composition of vinyl polymerization units in the resulting polymer is higher than that of the hydrogen-transfer polymerization units (Scheme 4).

LCST Behavior of NIPAAm-AAm Copolymer Prepared under Microwave Irradiation

The resulting polymers were expected to have LCST properties since it has NIPAAm units. Therefore, the LCST properties of the resulting polymers were examined. In the case of an aqueous solution of polymer obtained by anionic homopolymerization of NIPAAm, LCST was not detected within the range of temperatures between 20 and 100°C. However, in the case of aqueous solutions of copolymers obtained by hydrogen-transfer polymerization units (Scheme 4).

NIPAAm and AAm, LCST was observed in polymers containing hydrogen-transfer polymerized units (from 1% to 21%) derived from AAm (Table 2). Supporting Information Video S1 is a movie that shows how the resulting polymer (Table 2, Run 2) was alternately soaked in hot and cold water. Furthermore, LCST tended to rise as the hydrogen-transfer polymerization units of AAm in the copolymer increased. The LCST was observed at 51.4°C in the copolymer containing 21% of hydrogen-transfer polymerization units.

However, LCST could not be observed when the content of hydrogen-transfer polymerization units of AAm in the polymer became 21% or more. The reason could be that dehydration became difficult due to an increase in the proportion of hydrophilic units as the number of hydrogen transfer polymerization units of AAm in the copolymer increased.

CONCLUSIONS

The anionic hydrogen-transfer polymerization and behavior of NIPAAm and AAm under microwave irradiation were investigated. In conventional oil bath heating, anionic homopolymerization of NIPAAm did not proceed, but by using microwaves, anionic polymerization of NIPAAm proceeded. The resulting polymer consists of a hydrogen-transfer polymerization unit and a vinyl polymerization unit. The resulting polymer prepared from NIPAAm and AAm exhibited temperature-responsiveness, and the LCST increased as the unit ratio of hydrogen-transfer polymerization units of AAm increased. Therefore, LCST could be controlled by the unit ratio of AAm units in the polymer main chain.

REFERENCES AND NOTES

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