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α-(Aminomethyl)acrylate: Polymerization and spontaneous post-polymerization modification of β-amino acid ester for pH- / temperature-responsive material

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Ethyl α-(aminomethyl)acrylate, a β-amino acid ester carrying a conjugated vinylidene group at α-position, was radically polymerized. The polymerization was found to undergo the subsequent ester-amide exchange reaction between the amino pendants of the polymer and an ester group of the monomer, affording acrylamide-bearing units in 11–15% contents. The obtained polymer exhibited pH / temperature responsiveness in aqueous media.

2-Aminoethyl methacrylate (1) is a commercially available monomer as its hydrochloric salt.1 The corresponding polymer, poly(1), exhibits good hydrophilicity and is utilized for the modification of material surface,2,4 while its high biocompatibility is attractive to develop new drug delivery systems.5,6 Moreover, the reactivity of amino pendant group of poly(1) is useful for polymer modification.7–9 For example, Aranaz et al. have prepared copolymers of 1, the unit of which was used to incorporate a polymerizable pendant groups by amine–succinimide coupling chemistry.10 On the other hand, however, in neutral or basic conditions, where the aminoethyl groups of poly(1) exist as free amine units, the polymer undergoes ester-amide exchange reaction between the two neighbouring units.11 Similarly, 1 as a monomer is so unstable in its neutral form that it is readily converted to N-(2-hydroxyethyl)methacrylamide through amide-ester exchange reaction.12,13 Besides, Geman et al. have suggested a possibility that 1 also can undergo the Michael addition.15 Thus, more stable monomers and polymers carrying primary amino group are desirable. Recently, we have reported the unique polymerization chemistry of various α-functionalized acrylates.16–23 Along the line of this concept, methyl and ethyl α-(aminomethyl)acrylates, 2a and 2b, were designed which are structural isomers of 2-aminoethyl acrylate and 1, respectively, the sources for water-soluble polymers (Scheme 1).

α-(Aminomethyl)acrylate and its analogues are found in nature as metabolic products by some sponges24,25 and the total syntheses have reported by Holm et al.26 In this report, the synthetic method was slightly modified for gram-scale preparation desirable for polymerization experiment; 2a was prepared through the reaction of methyl α-(chloromethyl)acrylate with aqueous ammonia.27 In a similar way, the ethyl ester, 2b, was also prepared.28 Notably, 2a and 2b were so stable that they could be stored in bulk at −20 °C for more than 6 months even in their neutral form, in sharp contrast to 1. The IR absorbance of carbonyl group of 2b in bulk and 1 M 1,4-dioxane solution was observed at 1718 cm−1 (see ESI, Fig. S1), 7 cm−1 lower than that of methyl methacrylate (MMA, 1725 cm−1), while the N–H stretching vibration was not clearly observed over 3000 cm−1. These spectral features indicate a hydrogen bonding interaction with the main chain or pendant carbonyl groups which is consistent with lower hydrophobicity of 2b than 1. The NMR spectrum of 2b in DMSO-d6 showed the chemical shift of amino proton as δ = 9.3 ppm, while that of 1 was δ = 9.8 ppm.

Table 1. Polymerization of 2 with AIBN at 60 °C for 12 h

<table>
<thead>
<tr>
<th>Run</th>
<th>Monomer</th>
<th>Solv.</th>
<th>Conv./%</th>
<th>Mw/Mn</th>
<th>%Amitated</th>
<th>A4/%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a</td>
<td>Dioxane</td>
<td>77</td>
<td>(22000)</td>
<td>(2.54)</td>
<td>(9)</td>
</tr>
<tr>
<td>2</td>
<td>2a</td>
<td>Toluene</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>2a</td>
<td>CH3CN</td>
<td>88</td>
<td>3450</td>
<td>2.08</td>
<td>11</td>
</tr>
<tr>
<td>4</td>
<td>2b</td>
<td>Dioxane</td>
<td>85</td>
<td>3250</td>
<td>2.08</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>2b</td>
<td>Toluene</td>
<td>85</td>
<td>3250</td>
<td>2.08</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>2b</td>
<td>CH3CN</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>2b</td>
<td>Toluene</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>2b</td>
<td>Toluene</td>
<td>42</td>
<td>8740</td>
<td>2.55</td>
<td>15</td>
</tr>
</tbody>
</table>

*a Monomer 4.0 mmol, solvent 4.0 mL. ** AIBN 0.20 mmol. * Determined from 1H NMR. * Estimated from SEC (THF, 40 °C, PMMA standards). * Content of amidated units. * Soluble fraction. * Solvnt 2.0 mL. ** AIBN 0.050 mmol.
but exhibited shoulder of the large ester carbonyl absorption (1728 cm$^{-1}$) on the spectrum, the content of amidated units ($A$) could be roughly estimated as 9% according to the following equation:

$$\frac{\text{Int.(olefin)}}{\text{Int.(aliphatic)}} = \frac{2A}{2A+2+5+5}$$

It should be noted that the polymerization in dioxane (Run 2) and CH$_3$CN (Run 3) and toluene did not give any soluble product. The polymerization of 2b in dioxane gave a wholly soluble polymeric product (Run 4), which also showed the olefinic proton signals in its $^1$H NMR spectrum as in the case of 2a. The effects of the polymerization conditions were thus examined for 2b in some detail. Polymerization in toluene (Run 5) afforded similar results to that in 1,4-dioxane (Run 4). The SEC curve (Fig. S4) exhibited unimodal peaks, indicating no crosslinking and/or the amidation between polymer chains might cause branching from the acrylamide-type amidated pendant occurred. In the polymerization in CH$_3$CN, however, the reaction mixtures underwent gelation and no soluble product was obtained (Run 6) as similar to Run 3. It is well known that $S_n$2 reactions, including amidation, proceed faster in CH$_3$CN, and thus the attack of active species to the formed acrylamide pendant with high content and/or the amidation between polymer chains might cause crosslinking in the polymerization, although the detail could not be investigated due to the insoluble products. Gelation also occurred even in toluene when the polymerization was conducted at higher initial monomer concentration (2 M, Run 7). Nevertheless, poly(2b) with relatively high molecular weight ($M_n = 8740$) was obtained at a large initiator:monomer feed ratio ([2b]$_0$/[AIBN]$_0$ = 100). That is, as the polymerization is competitive to the amidation, appropriate reaction conditions are important to control the polymerization.

In order to understand the reaction pathway to the formation of the amidated structure, 2b and the obtained polymer, poly(2b) were heated individually under the conditions similar to the polymerization but in the absence of AIBN. Both 2b and poly(2b) did not exhibit any change in their $^1$H NMR spectra (see ESI), indicating that no reaction took place between 2b monomers nor between poly(2b) molecules; in other words, the ester-amide exchange reaction should occur between the monomer and the polymer. As described previously, the amino group of 2b has low nucleophilicity due to the intramolecular hydrogen bonding, while that in poly(2b) may have nucleophilicity as a common primary amine. On the other hand, the ester group of 2b has higher electrophilicity than the polymer owing to the $\alpha$-$\beta$-unsaturated structure and is sterically less demanding. Consequently, the amino pendant in the regular monomeric units of the polymer might undergo the ester-amide exchange reaction with the monomer. Thus, the polymerization has such a unique feature that the change of nucleophilicity of the amino group before and after the polymerization affords the simultaneous reactions of polymerization and post-polymerization modification in one-pot system. In order to monitor the reactions by $^1$H NMR spectroscopy, the polymerization was conducted in CDCl$_3$. It was found that the olefinic proton signals formed by the ester-amide exchange reaction appeared from the early stage of polymerization, at least at the monomer conversion of 35%. The results mean that the
amidation competed with propagation in the radical polymerization of 2b.

Interestingly, poly(2b) exhibited pH / temperature dual-stimuli responsiveness in aqueous media. Poly(2b) was insoluble in neutral water (Fig. 2a), but soluble in conc. HCl aq. In 1 M HCl aq, poly(2b) was soluble at 20 °C, but the solution changed turbid at 23 °C and became completely heterogeneous at 25 °C. That is, poly(2b) had lower critical solution temperature (LCST) in acidic aqueous media. It should be noted that poly(2a) did not exhibit temperature-responsiveness; it was insoluble in neutral water but soluble in 1 M and conc. HCl aq, although no LCST was found in such media. In general, the approximate balance of hydrophilic and hydrophobic groups in macromolecules is inevitable to exhibit temperature-responsiveness. In the present cases of poly(2a) and poly(2b), protonated aminomethyl groups provide hydrophilicity and the methyl and ethyl ester groups hydrophobicity. Presumably, the hydrophobicity of methyl ester might be not enough to give temperature-responsiveness to poly(2a). The details of this stimuli-responsive behaviour will be reported elsewhere.

Conclusions

New amino-carrying acrylates, 2a and 2b, were prepared through the reaction of the corresponding chlorides with aqueous ammonia. These monomers were very stable due to the intramolecular hydrogen bond, forming a 6-membered ring, and could be polymerized in its native form carrying primary amino group, while their isomeric monomers, 2-aminooethyl (meth)acrylates are known unstable to undergo spontaneous ester-amide exchange reactions and thus must be treated as their salts. Such structural features of 2a and 2b cause their unique polymerization behaviour, where the ester-amide exchange reaction took place during the polymerization specifically through the nucleophilic attack of the primary amine pendant in the polymer to α,β-unsaturated ester carbonyl group of the monomer. That is, the spontaneous post-polymerization modification was induced by the structural change from the monomer to the monomeric unit that lead to the break of intramolecular hydrogen bonding. The obtained polymer, poly(2b), exhibited pH / temperature dual-stimuli responsiveness in acidic aqueous media, while poly(1) did not have any stimuli-responsiveness. Since the introduction of the amino group into α-substituent causes completely different characters from the ester-functionalization, it provides us with a new molecular design based on α-functionalization for both polymerization chemistry and intelligent materials.

Acknowledgment

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Notes and references

Aqueous ammonia (ca. 28 wt%, 10.0 mL, ca. 150 mmol) was added dropwise at 0 °C to a solution of ethyl α-(chloromethyl)acrylate (10.0 g, 67.3 mmol) in 1,4-dioxane (20 mL). The reaction mixture was stirred for 4 h at ambient temperature. NaHCO$_3$ aq (20 mL) was added to dissolve the precipitate, and the product was extracted with EtOAc (20 mL) three times. The organic layer was dried over Na$_2$SO$_4$, and the solvent was removed in vacuo to afford 2 (7.05 g, 91.5%).

**2b**: colourless oil; $^1$H NMR (400 MHz, CDCl$_3$, 30 °C) δ/ppm 6.25 (s, 1H, CH=), 5.87 (s, 1H, CH=), 4.20 (q, $J$ = 7.3 Hz, 2H, OCH$_2$), 3.32 (s, 2H, –CH$_2$NH$_2$), 1.60 (s, 2H, –NH$_2$), 1.29 (t, $J$ = 7.3 Hz, 3H, –CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$, 30 °C, δ/ppm 166.48, 137.90, 125.45, 60.38, 54.34, 13.97; IR: 3417(NOH), 3349(NOH), 2982 (COH), 2937 (COH), 1718 (C=O), 1634 cm$^{-1}$(C=C); HRMS (EI, m/z): [M+H]$^+$ calcd for C$_6$H$_{10}$NO$_2$ 128.0717, found 128.0685.

Notably, the protection of the amino group in 2 with di-tert-butyl dicarbonate (Boc$_2$O) (1.1 equiv.) in the presence of Et$_3$N (2.2 equiv.) was failed, also indicating the low nucleophilicity of 2.

A mixture of 2 (0.517 g, 4.00 mmol) and AIBN (33 mg, 0.20 mmol) in a solvent (4.0 mL) was degassed using a freeze-pump-thaw cycle three times and N$_2$ gas was introduced. The reaction mixture was heated at 60 °C for 12 h, and a small portion of the reaction mixture was sampled to estimate the conversion. The reaction mixture was then poured into hexane (80 mL), and the precipitate was collected, washed with hexane, and dried in vacuo to afford poly(2) (0.380 g) as a white solid. The conversion was estimated from the intensity ratio of the $^1$H NMR signal of OCH$_2$ to those of the vinylidene group.

In the IR spectra of poly(2a) and poly(2b), N-H vibration of amino group were observed at 3436 cm$^{-1}$ (Figure S3), which were good contrast to those of their monomers, 2a and 2b. It also implied the break of intramolecular hydrogen bonding in the monomers.