Polymer Chemistry

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Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

Communication

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

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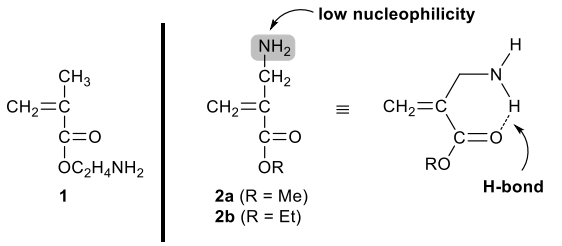
Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

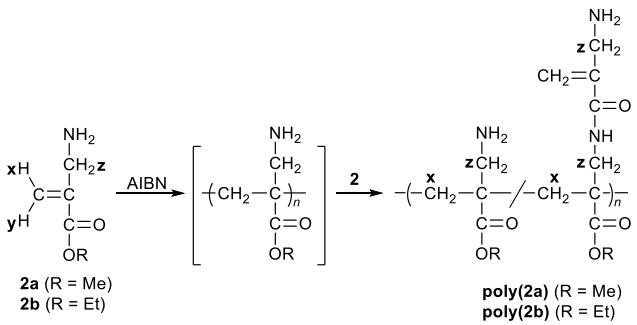
Ethyl α-(aminomethyl)acrylate, a β-amino acid ester carrying a conjugated vinylidene group at α-position, was radically polymerized. The polymerization was found to undergo the subsequent ester-amide exchange reaction between the amino pendants of the polymer and an ester group of the monomer, affording 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.[5-9] Moreover, the reactivity of amino pendant group of **poly(1)** is useful for polymer modification.[10-14] 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.[13] 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.[15] 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.[16,17] Besides, Geman *et al.* have suggested a possibility that **1** also can undergo the Michael addition.[16] 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.[18-23] 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 sponges[24,25] 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 4000−3000 cm^{-1}. These spectral features indicate a hydrogen bonding



Scheme 1. Structure of amino-functionalized methacrylate.



Scheme 2. Radical polymerization of **2**. AIBN: 2,2'-azoisobutylonitrile

Table 1. Polymerization of **2** with AIBN at 60 °C for12 h [a]

Run	Monomer	Solv.	Conv.[b] /%	M_n[c]	M_w / M_n[c]	A[d] /%
1	**2a**	Dioxane	77	(2200)[e]	(2.54)[e]	(9)[e]
2	**2a**	Toluene	-	-	-	-
3	**2a**	CH_3CN	-	-	-	-
4	**2b**	Dioxane	85	3450	2.08	11
5	**2b**	Toluene	85	3250	2.22	12
6	**2b**	CH_3CN	-	-	-	-
7[f]	**2b**	Toluene	-	-	-	-
8[g]	**2b**	Toluene	42	8740	2.55	15

[a] Monomer 4.0 mmol, solvent 4.0 mL. AIBN 0.20 mmol. [b] Determined from ^1H NMR. [c] Estimated from SEC (THF, 40 °C, PMMA standards). [d] Content of amidated units. [e] Soluble fraction. [f] Solvnt 2.0 mL. [g] AIBN 0.050 mmol.

between the amino proton and the carbonyl oxygen, which might suppress the nucleophilicity of the amino group.[29]

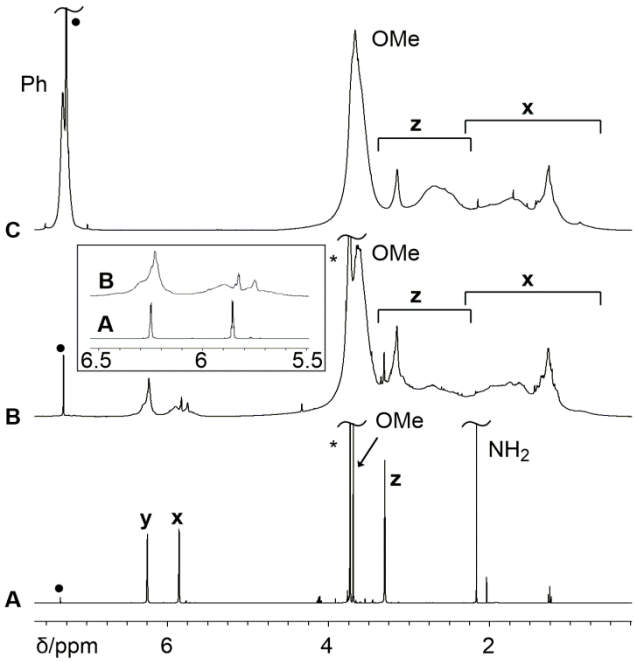
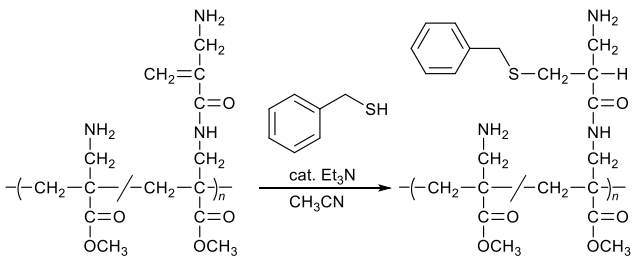


Fig. 1. ^{1}H NMR spectra of **A**: **2a**, **B**: **poly(2a)** and **C**: the product of thiol-ene reaction of **poly(2a)** with benzyl mercaptan (400 MHz, $CDCl_3$, 55 °C). Labels **x-z** corresponds to those in Scheme 2. •: $CHCl_3$, *: 1,4-dioxane.



Scheme 3. Thiol-ene click reaction of **poly(2a)** catalyzed by a weak base.

2a was polymerized with 2,2'-azoisobutyronitrile (AIBN) at 60 °C in dioxane for 12 h (Scheme 2, Table 1, Run 1).[30] Although a small portion of the resulting polymer was insoluble in common organic solvents such as $CHCl_3$ and THF, the major fraction was soluble in $CDCl_3$ allowing the measurement of ^{1}H NMR spectrum (Fig. 1B). Besides the broad signals assignable to the expected monomeric units, olefinic signals, which were different from the vinylidene groups of **2a** (Fig. 1A, 6.25 and 5.87 ppm) but exhibited ^{1}H-^{1}H COSY correlation with the *N*-CH_2 signal (Fig. S2), were observed. In order to assign these unexpected signals, Michael addition-type thiol-ene reaction,[31] which is known as a click reaction and thus effective to detect the α,β-unsaturated carbonyl compounds, was employed with benzyl mercaptan in the presence of Et_3N catalyst (Scheme 3). After the reaction, the olefinic NMR signals completely disappeared (Fig. 1C), confirming the vinylidene group should be conjugated with carbonyl group. Furthermore, the obtained product exhibited small IR absorption of amidic carbonyl group (1688 cm^{-1}) on the shoulder of the large ester carbonyl absorption (1728 cm^{-1}, Fig. S3). These spectral data suggested that ester-amide exchange reaction occurred after the polymerization to afford acrylamide pendants as shown in Scheme 1. From the intensities of olefinic proton signals [*Int.*(olefin), 6.5-5.0 ppm] and aliphatic signals [*Int.*(aliphatic), 5.0-0.5 ppm] in ^{1}H NMR spectrum, the content of amidated units (*A*) could be roughly estimated as 9% according to the following equation;

$$\frac{Int.(\text{olefin})}{Int.(\text{aliphatic})} = \frac{2A}{2A+2+5+5} \quad (1)$$

It should be noted that the polymerization in toluene (Run 2) and CH_3CN (Run 3) and toluene did not gave 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 branching from the acrylamide-type amidated pendant occurred. In the polymerization in CH_3CN, 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_N2 reactions, including amidation, proceed faster in CH_3CN, 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 ($[\mathbf{2b}]_0/[AIBN]_0$ = 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.[31] On the other hand, the ester group of **2b** has higher electrophilicity than the polymer owing to the α,β-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**.

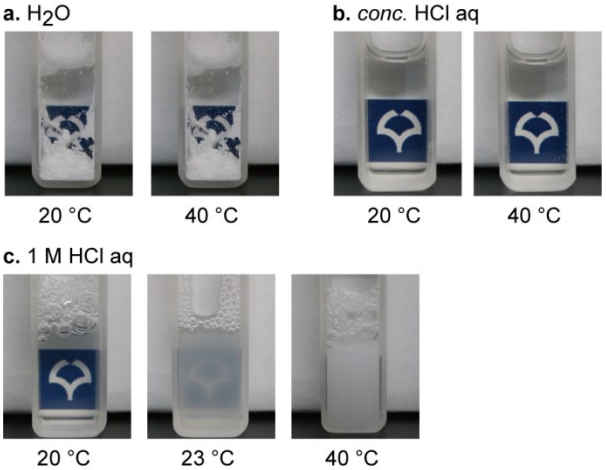


Fig. 2 Solubility changes of **poly(2)** in aqueous media.

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 intra-molecular hydrogen bond, forming a 6-membered ring, and could be polymerized in its native form carrying primary amino group, while their isomeric monomers, 2-aminoethyl (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

This work was supported by JSPS KAKENHI Grant Number 26810069. This study was supported by a grant from the Ogasawara Foundation for the Promotion of Science & Engineering in 2012 (Y.K). The authors would like to thank Nippon Shokubai Co. Ltd. for providing methyl and ethyl α-(hydroxymethyl) acrylates.

Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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27 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 (10.0g, 67.3 mmol) in 1,4-dioxane (20 mL). The reaction mixture was stirred for 4 h at ambient temperature. *sat.* $NaHCO_3$ 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_2SO_4, and the solvent was removed *in vacuo* to afford **2** (7.05 g, 91.5%). **2b**: coluorless oil; ^{1}H NMR (400 MHz, CDCl3, 30 °C) δ/ppm 6.25 (s, 1H, CHH=), 5.87 (s, 1H, CHH=), 4.20 (q, J = 7.3 Hz, 2H, -OCH_2-), 3.32 (s, 2H, –CH_2NH_2), 1.60 (s, 2H, –NH_2), 1.29 (t, J = 7.3 Hz, 3H, –CH_3); ^{13}C NMR (100 MHz, 30 °C, $CDCl_3$, δ/ppm 166.48, 137.90, 125.45, 60.38, 54.34, 13.97; IR: 3417(N-H), 3349 (N-H), 2982 (C-H), 2937 (C-H), 1718 (C=O), 1634 cm−1(C=C); HRMS (EI, m/z): $[M-H]^+$ calcd for $C_6H_{10}NO_2$ 128.0717, found 128.0685.
28 **2a**: Yield 91.4%; colourless oil; ^{1}H NMR (400 MHz, $CDCl_3$, 30 °C) δ/ppm 6.25 (d, J = 1.8 Hz, ^{1}H, CHH=), 5.86 (d, J = 1.8 Hz, ^{1}H, CHH=), 3.73 (s, 3H, CH_3), 3.69 (s, 2H, NH_2), 3.30 (s, 2H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$, 30 °C) δ/ppm 167.24, 137.97, 126.28, 54.71, 51.80. IR 3423 (N–H), 1722 (C=O), 1635 (C=C). HRMS (EI, m/z): $[M–H]^+$ calcd for $C_5H_8NO_2$ 114.0561, found 114.0484.
29 Notably, the protection of the amino group in **2** with di-*tert*-butyl dicarbonate (Boc_2O) (1.1 equiv.) in the presence of Et_3N (2.2 equiv.) was failed, also indicating the low nucleophilicity of **2**.
30 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 *O*-CH_2 to those of the vinylidene group.
31 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.