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Degradable Poly(*N*-isopropylacrylamide) with Tunable Thermosensitivity by Simultaneous Chain- and Step-Growth Radical Polymerization

Masato Mizuntani, Kotaro Satoh, and Masami Kamigaito*

Department of Applied Chemistry, Graduate School of Engineering, Nagoya University, Furo-cho, Chikusa-ku, Nagoya 464-8603, Japan

Supporting Information

Poly(*N*-isopropylacrylamide) [poly(NIPAM)] is one of the most attractive polymeric materials because it has a thermal stimuli-responsive character in aqueous solutions.[1] The aqueous solution of poly(NIPAM) is well-known to exhibit a reversible liquid−solid phase transition with a lower critical solution temperature (LCST) between 31 and 35 °C. This thermoresponsive property has allowed this material to be used in interdisciplinary applications, such as biosensors and membranes, in the fields of bioengineering and nanotechnology. Recent efforts in developing the well-controlled radical polymerization of NIPAM have provided an insight into the influence of the primary structure of poly(NIPAM), such as the molecular weight and its distribution,[2] end groups,[3] tacticity,[4] and block copolymers,[5] on the thermoresponsive properties. Among them, the CuCl/tris[2-(dimethylamino)ethyl]amine (Me_6TREN) system effectively induced fast and well-controlled polymerizations of acrylamides, including NIPAM, in specific solvents, such as DMF, 2-propanol, water, and DMF/water mixture, to produce polymers having a narrow molecular weight distribution (MWD) even at ambient temperature.[6,7] The system is referred to as the metal-catalyzed atom transfer or single-electron transfer (SET) living radical polymerization.

Meanwhile, we recently found that the same metal catalysis as in the controlled radical polymerization can be evolved into the step-growth radical polyaddition of designed monomers possessing unconjugated carbon−carbon double (C═C) and an active carbon−chlorine (C−Cl) bonds in a molecule.[8] In this polymerization, the active C—X bond in the monomer is activated by the metal catalysts to form a radical species, which adds to the C═C double bond of another monomer molecule to generate a C−C bond as the main chain, along with an inactive C—X bond as the pendant. Furthermore, we have successfully combined the step-growth radical polyaddition with the metal-catalyzed polymerization by the judicious choice of the catalyst, in which the simultaneous step- and chain-growth polymerization proceeds via the radical intermediates by the single metal catalyst.[9] For example, the simultaneous living radical polymerization of methyl acrylate (MA) and radical polyaddition of an ester-linked 3-butenyl 2-chloropropionate (**1**) was achieved with CuCl/1,1,4,7,10,10-hexamethyltriethylenetetramine (HMTETA) to afford the controlled polymers, in which the homopolymer segments with the controlled chain length were connected by the ester linkage.

Herein, we report the simultaneous chain- and step-growth radical polymerization of NIPAM for the dual control in degradability and thermoresponsivity of the product (Scheme 1). The simultaneous polymerization of NIPAM and an amide- or ester-linked monomer proceeded very fast in aqueous media at ambient temperature. The degradability and thermoresponsivity of the produced poly(NIPAM) can be tuned by changing the monomer structure or initial feed ratios.

The simultaneous chain- and step-growth radical polymerization of NIPAM was examined in conjunction with *N*-allyl-2-chloropropanamide (**2**), in which the unconjugated C═C and reactive C−Cl bonds are linked via an amide linkage. The polymerization of NIPAM and **2** (50:1 molar ratio) was performed in a DMF and water mixture (1/1) at 20 °C using CuCl/Me_6TREN as the catalyst.[6,7] Both of the monomers were simultaneously consumed, of which the consumption rates were much faster than those of the ester counterparts, i.e., the polymerization of MA and **1**, and the reaction reached an almost quantitative monomer conversion in several minutes even at 20 °C as in the living polymerization of NIPAM with the CuCl/Me_6TREN system (Figure 1A).

The consumption of the original C−Cl bonds in **2** (filled triangles) determined by ^1H NMR agreed well with that of **2** itself by gas chromatography, while the unconjugated C═C double bonds (open triangles) were consumed much slower than **2**. This suggests that **2** was mainly consumed via the reaction of the C−Cl bond to induce the NIPAM polymerization during the initial stage of the polymerization. Although the reaction of the unconjugated C═C double bonds was slower, the consumption of the C═C bonds proceeded even after the quantitative consumption of the monomers. The number-average molecular weights (M_n) of the obtained products increased in almost direct proportion to the total monomer conversion with a relatively narrow molecular weight distribution at the initial stage (Figure 1B). After the complete consumption of the monomers, the M_n values progressively increased and the SEC curves became broader and somehow multimodal (Figure 1C). These results indicated that the NIPAM polymerization first proceeded from the C−Cl bond in **2** mainly to give the living oligomers of NIPAM. The polymerization was then followed by a step-growth propagation between the active C−Cl bond at *ω*-end and the unconjugated C═C double bond at the α-end of the living oligo(NIPAM) or residual **2** to give the multiblock polymers

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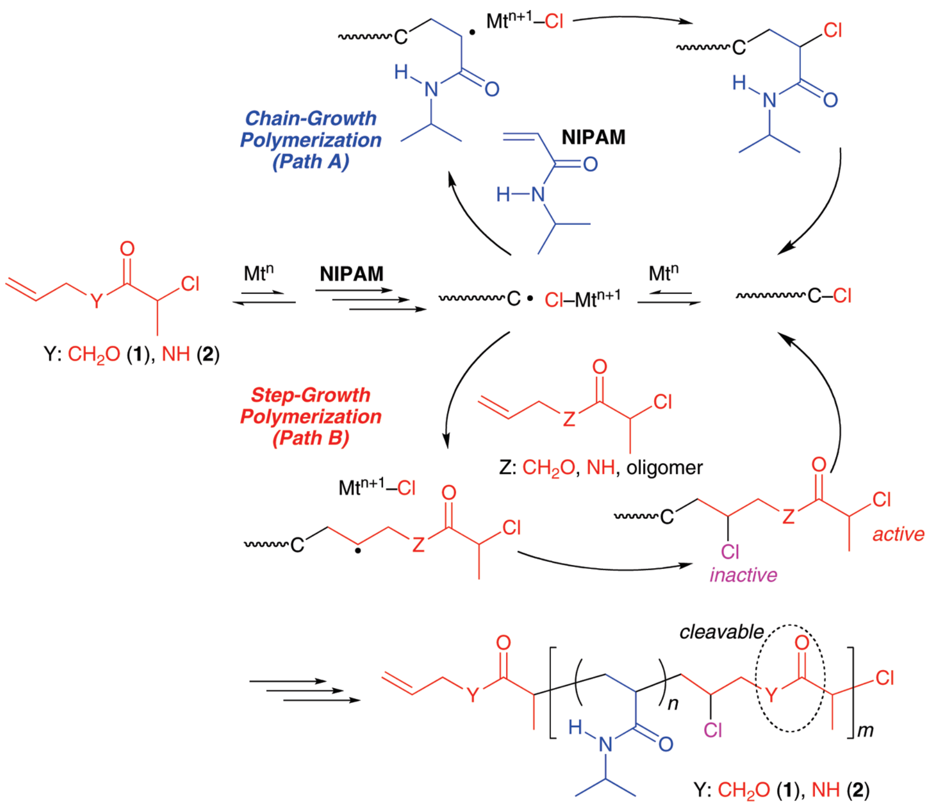
Scheme 1. Simultaneous Chain- and Step-Growth Radical Polymerization of NIPAM with 1 and 2



consisting of living poly(NIPAM) segments connected by the amide linkages.

A series of simultaneous polymerizations of NIPAM were then carried out in combination with **1** or **2** by the different feed ratios ($[\text{NIPAM}]_0/[\mathbf{1} \text{ or } \mathbf{2}]_0$ = 50/1, 20/1, 5/1, and 1/1) as summarized in Table 1 (entries 1−8). In all of the cases, both monomers were simultaneously and smoothly consumed (Figure S1 in Supporting Information). Especially, for the combination with **1**, the obtained copolymers could be easily degraded by the cleavage of the ester linkage in the main chain originating from **1** (Figure 2). The methanolysis of the polymers obtained from NIPAM and **1** was investigated by Na_2CO_3 in CH_3OH for the cleavage of the main-chain ester linkage originating from **1** to generate the lower molecular weight polymers or oligomers of NIPAM as shown by the dashed SEC curves. Especially, with a lower amount loading of **1** ($[\text{NIPAM}]_0/[\mathbf{1}]_0$ = 50/1), the methanolysis resulted in poly(NIPAM) with unimodal SEC curves having narrow molecular weight distributions ($M_w/M_n \sim 1.2$) and the M_ns were close to the values based on the assumption that one molecule of **1** generates one polymer chain, suggesting that the successive oligo- or poly(NIPAM) units sandwiched between the **1** units were generated via the almost ideal living polymerization.

The copolymer obtained form NIPAM and **2** was then analyzed by MALDI-TOF-MS spectrometry (Figure S2 in Supporting Information). All of the peaks were assigned to the random copolymers consisting of NIPAM and **2**, though many series of peaks other than the ideal structure were observed due to the loss of Cl atom at the NIPAM terminal during the ionization process.[2] To confirm the simultaneous polymerizations in more detail, the model reaction was performed using NIPAM, methyl 2-chloropropanamide (**3**), and allylacetamide (**4**), which can be regarded as model compounds of the active C−Cl and unconjugated C═C bonds of **1**, respectively, in a 1:1:1 ratio ($[\text{NIPAM}]_0 = [\mathbf{3}]_0 = [\mathbf{4}]_0$ = 2.0 M) using CuCl/Me_6TREN similar to the polymerization (Figure 3). NIPAM, **3**, and **4** were smoothly consumed and the total conversion was over 90% (>99%, 90%, and 85%, respectively), and the molecular weights of the obtained products were low ($M_n \sim 600$) (Figure S3 in Supporting Information). The MALDI-TOF-MS spectrum of the products showed a series of peaks consisting of one unit of **3**, a small number of NIPAM units (n = 1−4), and one unit of **4**, which indicated NIPAM oligomers possessing the model compound units at both terminals (Figure 3). In contrast to the fact that the CuCl/Me_6TREN system induced the chain-growth copolymerization of MA and **1** as a side reaction in toluene at 80 °C,[9] another possible series of peaks for the polymerization of NIPAM with more than 2 units of **4** or bimolecular termination between the radical species were not observed in the present model reaction, probably due to the milder reaction condition at ambient temperature. These results support the fact that the ideal simultaneous polymerizations proceeded via the chain- and step-growth mechanism without a significant amount of side reactions. It is noteworthy that the model reaction studies provided facile methods for the synthesis of α,ω-heterofunctionalized telechelic oligomers or polymers of NIPAM. According to the model reaction, the poly(NIPAM) with high functionalities at both ends can be produced using the halide initiator and olefin terminator bearing various functional groups in just one shot by the CuCl/Me_6TREN catalytic system, compared to the conventional multistep functionalization by olefin terminators.

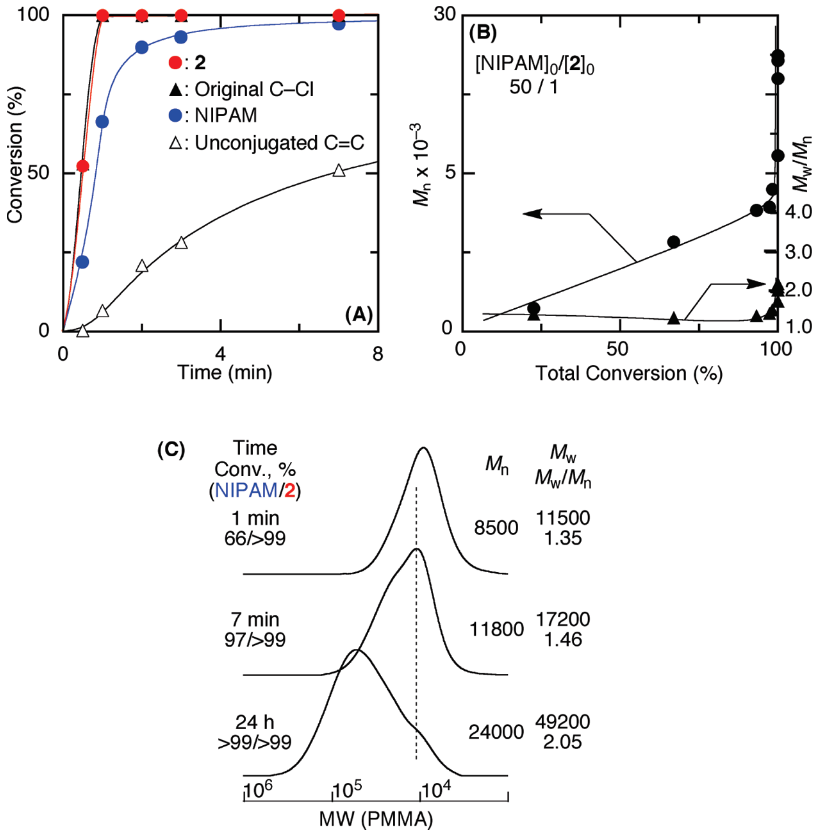


Figure 1. Simultaneous chain- and step-growth radical polymerization of NIPAM and **2** with CuCl/Me$_6$TREN in DMF/H$_2$O = 1/1 at 20 °C: [NIPAM]$_0$ = 4.0 M; [**2**]$_0$ = 0.080 M; [CuCl]$_0$ = 40 mM; [Me$_6$TREN]$_0$ = 40 mM. (A) Consumption of NIPAM and original C—Cl and unconjugated C═C bonds measured by ^{1}H NMR and **2** measured by gas chromatography. (B) M_n and M_w/M_n values of the obtained copolymers vs total monomer conversion of NIPAM and **2**. (C) Size-exclusion chromatograms of the obtained copolymers.

Table 1. Simultaneous Chain- and Step-Growth Radical Polymerization of NIPAM with 1 or 2 in DMF/H$_2$O (1/1 v/v) at 20 °C

		[monomer]$_0$, mol/L			monomer conv, %					
entry	monomer	NIPAM	**1** or **2**	time, h	NIPAM[d]	**1** or **2**[e]	M_w[f]	M_w/M_n[f]	NIPAM/**1** or **2** in polymer[d]	cloud point, °C[g]
1[a]	NIPAM/**2**	4.0	0.08	24	>99	>99	49200	2.05	98/2	34.1
2[a]		4.0	0.20	30	99	>99	13100	1.84	95/5	37.8
3[b]		4.0	0.80	20	94	97	3400	1.63	83/17	39.6
4[b]		2.0	2.0	190	>99	89	3000	2.11	53/47	soluble[h]
5[a]	NIPAM/**1**	4.0	0.08	330	>99	>99	35300 (9900)[c]	1.71 (1.26)[c]	98/2	33.2 (37.9)[c]
6[a]		4.0	0.20	200	>99	>99	9000 (3900)[c]	1.55 (1.47)[c]	95/5	30.5 (49.6)[c]
7[b]		4.0	0.80	340	>99	>99	5700 (1500)[c]	1.99 (1.48)[c]	83/17	24.5 (81.3)[c]
8[b]		2.0	2.0	220	80	59	1200	1.86	58/42	insoluble[i]

[a] [CuCl]$_0$ = [tris[2-(dimethylamino)ethyl]amine (Me$_6$TREN)]$_0$ = 40 mM. [b] [CuCl]$_0$ = [Me$_6$TREN]$_0$ = 100 mM. [c] Values in parentheses are for the methanolyzed product. [d] Determined by ^{1}H NMR. [e] Determined by gas chromatography. [f] The weight-average molecular weight (M_w) and distribution (M_w/M_n) were determined by size-exclusion chromatography. [g] Determined by turbidimetric analysis. Conditions: concentration = 10 mg/mL, heating rate = 1.0 °C/min, cloud point was determined by the temperature, at which the transmittance (λ = 500 nm) of aqueous solution became 50%. [h] Soluble at temperatures below 100 °C. [i] Insoluble at temperatures above 0 °C.

The thermoresponsive properties of the NIPAM polymers obtained in the simultaneous polymerization with various monomer feed ratios were analyzed. Figure 4 contains plots of the transmittances as a function of temperature, namely cloud-point curves, for the aqueous solutions of the copolymers (Figure S4 in Supporting Information). As the hydrophilic amide—monomer contents increased, the cloud temperature became higher (Figure 4A), while as the hydrophobic ester—monomer contents increased, it decreased (filled squares, circles, and triangles in Figure 4B). These results indicated that the structures of the step-growth monomer and the monomer feed ratios strongly influenced the thermoresponsivity of the NIPAM polymers.

Furthermore, in the case of the combination with **1**, the aqueous solutions of the methanolyzed products exhibit LCST

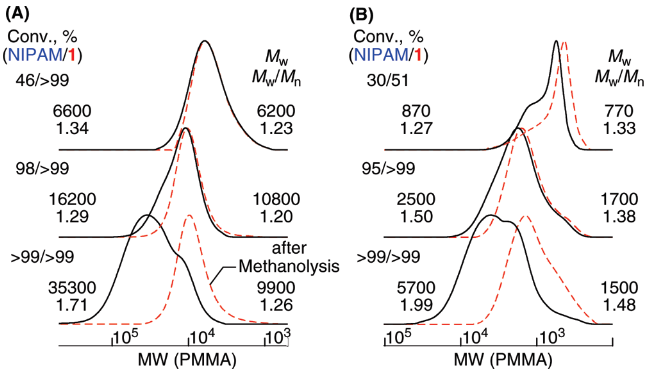


Figure 2. Size-exclusion chromatograms of the obtained copolymers (solid lines) and the methanolyzed products (dashed lines) in the simultaneous chain- and step-growth radical polymerization of NIPAM and **1** with CuCl/Me_6TREN in DMF/H_2O = 1/1 at 20 °C: $[NIPAM]_0$ = 4.0 M; $[\mathbf{1}]_0$ = 0.080 (A) or 0.80 M (B); $[CuCl]_0$ = 40 or 100 mM; $[Me_6TREN]_0$ = 40 or 100 mM.

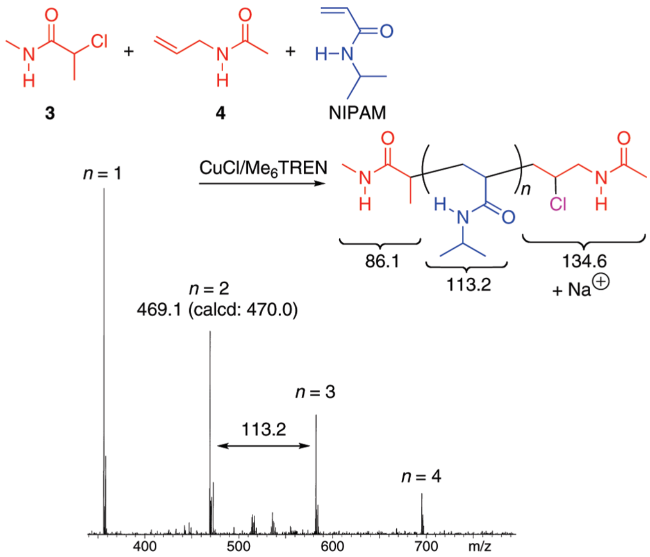


Figure 3. MALDI-TOF-MS spectrum of the obtained in the model reaction of NIPAM, **3**, and **4** with CuCl/Me_6TREN in DMF/H_2O = 1/1 at 20 °C: $[NIPAM]_0$ = 2.0 M; $[\mathbf{3}]_0$ = 2.0 M; $[\mathbf{4}]_0$ = 2.0 M; $[CuCl]_0$ = 100 mM; $[Me_6TREN]_0$ = 100 mM. Conversion: >99% for NIPAM, 90% for **3**, 85% for **4**, M_n = 570, M_w = 920, M_w/M_n = 1.62.

phase transitions at a higher temperature than that of the polymer before methanolysis (open squares, circles, and triangles in Figure 4B). As the initial charge ratios of the degradable monomer to NIPAM increased ($[\mathbf{1}]_0/[NIPAM]_0$ = 1/50, 1/20, and 1/5), the aqueous solutions of the methanolyzed products had a higher cloud point at 37.9, 49.6, and 81.3 °C, respectively, which are higher than those of the original polymers before the methanolysis with increases of 4.7, 19.1, and 56.8 °C. The cloud points of the methanolyzed products increased with the increasing **1** contents in the copolymers, which most probably suggests hydrophilic hydroxy groups being introduced at the hydrolyzed chain end. Thus, the thermoresponsivity of the NIPAM copolymers was significantly changed by the degradation of the copolymers, varying the comonomer structures, or the different monomer feed ratios.

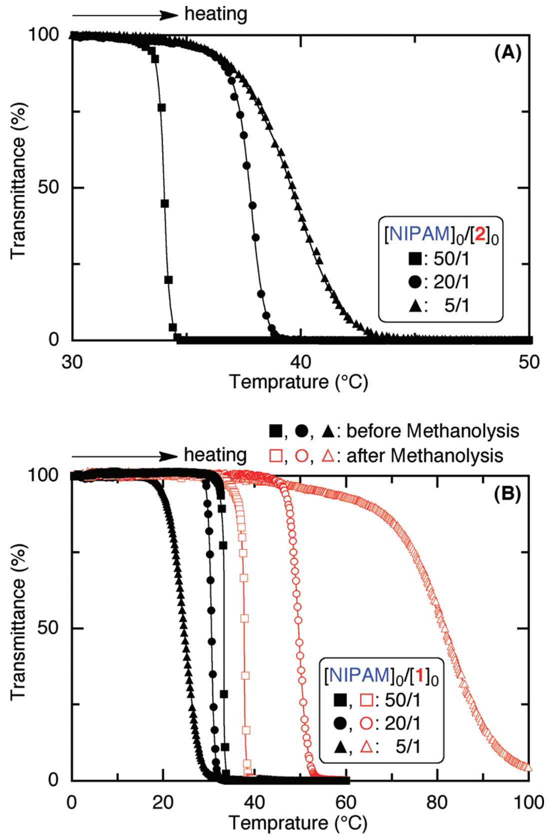


Figure 4. Cloud-point curves for the aqueous solutions of the obtained copolymers and the methanolyzed products in the simultaneous chain- and step-growth radical polymerization of (A) NIPAM and **2** or (B) NIPAM and **1** with various monomer feed ratios ($[NIPAM]_0/[\mathbf{1}$ or $\mathbf{2}]_0$ = 50/1, 20/1, and 5/1). Conditions: concentration = 10 mg/mL, heating rate = 1.0 °C/min, cloud point was determined by the temperature at which the transmittance (λ = 500 nm) of aqueous solution reaches 50%.

In conclusion, the CuCl/Me_6TREN system enabled the very fast and quantitative simultaneous chain- and step-growth radical polymerization of NIPAM and ester- or amide-linked monomers (**1** and **2**) at ambient temperature in aqueous solvents. This provides a facile and practical approach to a tunable thermoresponsivity and degradability of the NIPAM polymers. More specifically, any change or increase in the phase-transition temperature upon degradation will lead to further application such as a more intelligent drug-delivery system.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information. Experimental details, polymerization results, etc. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: kamigait@apchem.nagoya-u.ac.jp.

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