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Synthesis and Aqueous Dispersion Properties of Triarm Poly(NIPAAm-*b*-HEAAm) Diblock Copolymers

Md. Ashaduzzaman,[1] Shuhei Kai,[1] Shinobu Uemura,[1] and Masashi Kunitake*[1,2]
[1] *Graduate School of Science and Technology, Kumamoto University, 2-39-1 Kurokami, Kumamoto 860-8555*
[2] *Core Research for Evolutional Science and Technology, Japan Science and Technology Agency, Chiyoda-ku, Tokyo 102-0075*

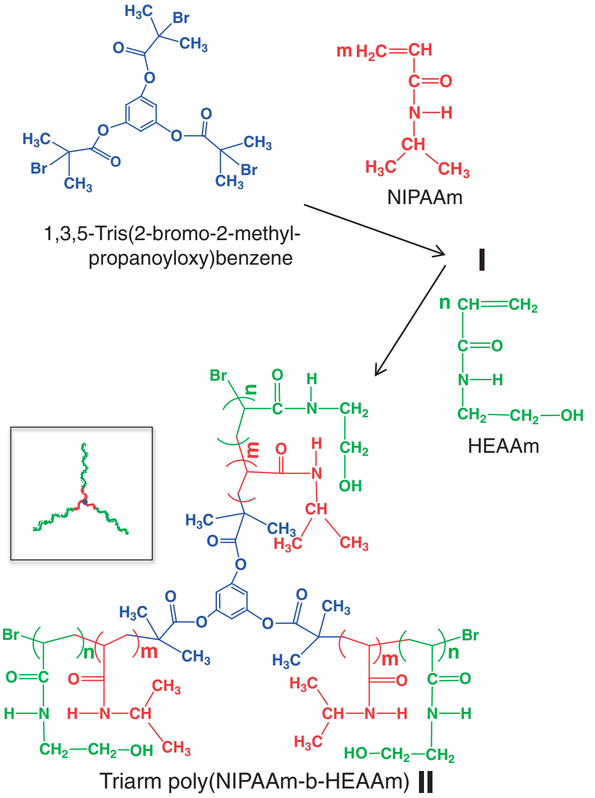
(Received November 11, 2010; CL-100949; E-mail: kunitake@chem.kumamoto-u.ac.jp)

The thermoresponsive dispersion properties of triarm-shaped diblock copolymers of thermoresponsive poly(*N*-isopropylacrylamide) {poly(NIPAAm)} as a core unit and poly(*N*-hydroxyethylacrylamide) {poly(HEAAm)} as a hydrophilic outer shell were investigated. The core and the outer shell were synthesized by atom-transfer radical polymerization (ATRP). The block polymer was completely dissolved in water up to 10^{-6} M with no turbidity even above lower critical solution temperature (LCST). Above the LCST (ca. 33.6 °C) polymer aggregates, in which the NIPAAm moiety was shrunk and formed a hydrophobic core, were monitored by dynamic light scattering measurements, while no signal was observed below the LCST. The size of globular aggregates with diameter in the range 35 to 170 nm was kinetically controlled by incubation in the transition-temperature region near the LCST. The size was stable above that temperature region.

Recently, much attention has been directed to synthesis of block copolymers[1–3] composed of a water-soluble segment and/or a thermoresponsive segment, with the expectation of their showing intelligent properties including thermally induced self-assembly in water.[1–3] The remarkable progress that has been made recently in controlled radical polymerization (CRP),[4–8] including atom-transfer radical polymerization (ATRP),[2,9–16] allows structural design of block polymers with infinite variety in terms of monomer selection, shape, and molecular weight of each block. As a thermoresponsive segment, poly(NIPAAm) is the most utilized polymer, with lower critical solution temperature (LCST) of about 32 °C. Various poly(NIPAAm)-based block copolymers combined with hydrophobic polymers[8,14] or hydrophilic polymers with linear (AB and ABA types),[10] triarm,[11,15] multiarm,[17] and dendritic[18] structures have been synthesized. The aim has been to investigate thermoresponsive properties as aqueous dispersions, micellar assemblies (nanoparticles), and gel systems for potential applications such as drug and gene nanocarriers.[1–3]

In this communication, we report the preparation, characterization, and dispersion properties of a triarm-shaped diblock copolymer of thermosensitive NIPAAm and hydrophilic HEAAm as inner and outer blocks, respectively.

As one of the simplest multiarm thermosensitive unimers (an isolated form in aqueous solution), a triarm block polymer was designed in which each arm consisted of an inner thermosensitive poly(NIPAAm) block and an outer hydrophilic poly(HEAAm) block. The thermosensitive unimer dissolved in water even at temperatures above the LCST, at a certain concentration, to reveal the phase transition of NIPAAm units in a homogeneous dispersion. Cao and his colleagues[11] have reported similar but inverse triarm-shaped block polymers consisting of inner hydrophilic poly(2-hydroxyethyl methacrylate) {poly(HEMA)} and outer poly(NIPAAm) blocks. They reported a sol–gel transition of the polymers induced by the LCST. In addition, poly(HEAAm) reveals good water solubility compared with poly(HEMA), which does not dissolve in water.



Scheme 1. Reaction scheme for the synthesis of triarm poly(NIPAAm-*b*-HEAAm) diblock copolymer through atom transfer radical polymerization.

A schematic synthetic route for the preparation of the triarm block polymer is shown in Scheme 1. 1,3,5-Benzenetriyl tris(2-bromo-2-methylpropanoate), as a trifunctional initiator, was first synthesized by esterification from 1,3,5-benzenetriol and 2-bromo-2-methylpropionyl bromide. Polymer **II** was prepared by successive ATRP of NIPAAm and HEAAm via polymer **I**. ATRP with NIPAAm and HEAAm was conducted in a mixture of dimethyl sulfoxide (DMSO) and isopropanol at 40 °C, and in aqueous ethanol (ethanol:water = 4:1) at 20 °C to produce polymer **I** and polymer **II**, respectively. In both ATRP reactions

1,1,4,7,10,10-hexamethyltriethylenetetramine (HMTETA) and $Cu^{I}Br$ were used as ligand and catalyst, respectively. The degree of polymerization of NIPAAm and HEAAm units was estimated from ^{1}H NMR analysis as triarm poly(NIPAAm225)$_3$ **I** and triarm poly(NIPAAm225-*b*-HEAAm547)$_3$ **II**. The overall M_n value of the block copolymer was 266000 g mol^{-1}.

The dispersion properties of the triarm polymers **I** and **II** revealed dependences on both concentration and temperature. Below the LCST, triarm poly(NIPAAm)$_3$ **I** and triarm poly(NIPAAm-*b*-HEAAm)$_3$ **II** dissolved completely in pure water. As expected, an aqueous solution of triarm poly(NIPAAm)$_3$ **I** changed from transparent to turbid when the temperature exceeded the LCST, due to macroscopic aggregation by dehydration of NIPAAm units.

The aqueous solution of block copolymer **II** was transparent in the temperature region from 20 to above 60 °C. The solution did not show any obvious change at concentrations up to 10^{-6} M (0.25 mg mL^{-1}), indicating that the increased hydrophilicity of outer HEAAm chains facilitate the dispersibility of polymer **II**. The dispersion properties of polymer **II** at lower concentration were investigated using dynamic light scattering[16] (DLS, ELS-8000, Otsuka Electronics Co., Ltd., Japan). On the basis of preliminary experiments, we selected 0.1 mg mL^{-1} (3.76×10^{-7} M) as a moderate concentration of polymer **II** in aqueous solution, because 10^{-8} M was too low to monitor by DLS, and obvious macroaggregation was observed above 10^{-6} M even below the LCST.

Below the LCST, at 3.76×10^{-7} M DLS could not detect polymer **II**. When the temperature was increased very slowly (typically <0.1 °C min^{-1}), the DLS signal began to be observable from 33.6 °C, although no DLS signal was observed below 33.5 °C. Figure 1 shows the temperature dependence of the aggregate size of polymer **II** for very slow heating. Each size observed was stable for a longer time in a steady state after incubation. The size of the aggregates increased with increasing temperature and eventually reached a maximum of ca. 170 nm. These observations indicate that the aggregate size was thermodynamically controlled in the transition temperature region. The aggregates were incubated in the transition temperature region marked as the highlighted area in Figure 1 but not at higher temperatures.

Interestingly, at temperatures above 37 °C, no growth of the aggregates was observed. The hard NIPAAm core was protected by outer hydrophilic polymer chains, thus avoiding further intra-macromolecular fusion. Moreover, in the transition temperature region near the LCST, the NIPAAm polymer core was unstable and half expanded with solvent but was not as rigid as "shrunk" cores at temperatures above the LCST. The half expanded NIPAAm core is crucial to producing the aggregates.

Figure 2 shows typical size distributions of polymer **II** prepared in different heating conditions. When the solution was incubated for 30 min at 33.6 and 37.0 °C, aggregates with average diameter ca. 100 and 170 nm, respectively, were observed (Figures 2A and 2B), as thermodynamically stable states. The sizes of the aggregates were also controlled kinetically in terms of heating rates. Instantaneous heating allowed control of the size of aggregates of polymer **II**. The size decreased with increasing rate of temperature change. For instance, when the solution at 25 °C was suddenly immersed in a bath at 40 °C for heating relatively quickly, aggregates with smaller size (70 nm) were observed (Figure 2C). The minimum size, 35 nm, was observed at 40 °C for a solution heated as rapidly as possible by immersion in boiling water (Figure 2D). After thermal shock, the sizes were stable at temperatures above 37 °C for at least 12 h. These results indicate that the aggregate size was determined by the process occurring in the transition temperature region, 33.6 to 37 °C, and isolated aggregates were stable above 37 °C.

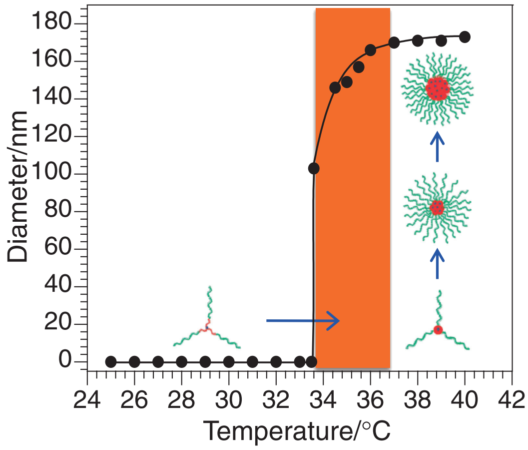


Figure 1. Variation of aggregate size of block copolymer **II** (0.1 mg mL^{-1} aqueous solution) with temperature, measured by DLS at heating rate <0.1 °C min^{-1}.

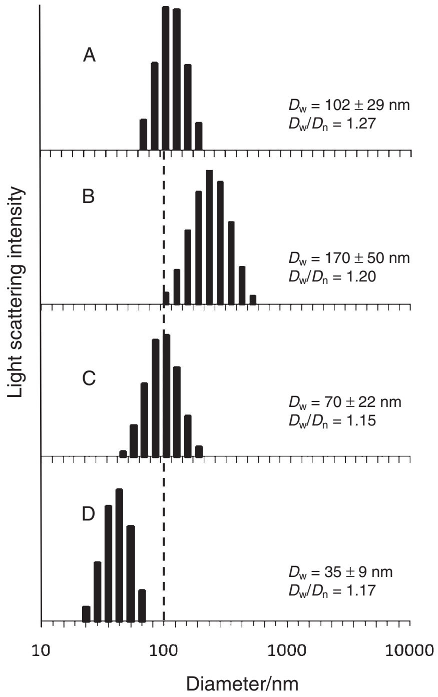


Figure 2. DLS size measurements of polymer **II** in aqueous solution at 33.6 (A) and 40 °C (B, C, and D), prepared by slow heating at ca. 0.1 °C min^{-1} (A, B) and rapid heating (C, D). In the heating conditions for C and D, the solution was suddenly immersed into a preheated 40 °C water bath and a boiling water bath, respectively.

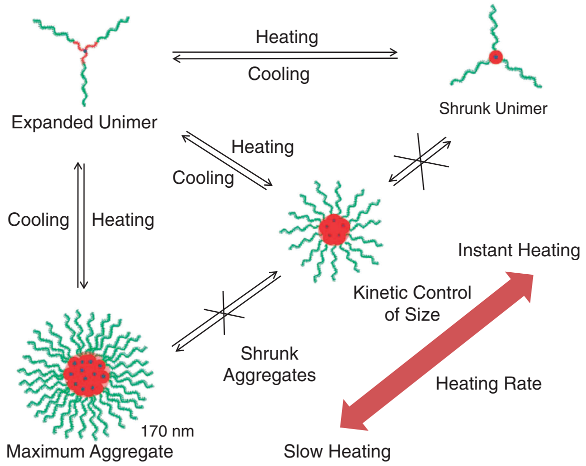


Figure 3. Schematic representation of the aqueous dispersion properties of triarm block polymer **II**, induced by thermoresponsible phase transition of NIPAAm units.

Figure 3 shows a schematic representation of the dependence of the aggregation properties of polymer **II** on the thermosensitive conformational change of NIPAAm. In the case of slow heating, the increment of globular size is due to kinetically controlled aggregation of the polymers. In the transition temperature region (from 33.6 to 37 °C), the aggregate size of the polymer gradually increased with lapse of time and reached a thermodynamically controlled maximum size. The driving force of aggregation was the hydrophobicity of NIPAAm units.

The maximum aggregate size is related to the chemical design of the triarm polymer. The maximum size is self-limited thermodynamically by maintaining microseparation of the hydrophilic HEAAm shell and hydrophobic NIPAAm core in the aggregates.

Instantaneous heating with the shortest elapsed time gave the minimum size of polymer **II**, ca. 35 nm diameter. From volume calculation, the number of aggregates with minimum globule size (35 nm) was more than 100 times smaller than the number of aggregates with maximum size (170 nm).[16] The minimum size aggregates may contribute to oligomeric aggregates or an isolated shrunk unimer.[2]

In conclusion, we have demonstrated thermodynamic and kinetic control of the aggregate size of the triarm poly(NIPAAm-*b*-HEAAm)$_3$ diblock copolymer **II**. The aggregate sizes of the polymer **II** were controllable by setting of sojourn time in incubation temperature region, and the aggregates formed were stable at above the incubation temperature. The polymer should have potential in the biomedical field for applications such as temperature-sensitive drug delivery systems or embolic agents.

References

1 C. H. Alarcón, S. Pennadam, C. Alexander, *Chem. Soc. Rev.* **2005**, *34*, 276.
2 C. Li, Z. Ge, J. Fang, S. Liu, *Macromolecules* **2009**, *42*, 2916.
3 H. Wei, S.-X. Cheng, X.-Z. Zhang, R.-X. Zhuo, *Prog. Polym. Sci.* **2009**, *34*, 893.
4 J. Zhou, L. Wang, Q. Yang, Q. Liu, H. Yu, Z. Zhao, *J. Phys. Chem. B* **2007**, *111*, 5573.
5 M. K. Georges, R. P. N. Veregin, P. M. Kazmaier, G. K. Hamer, *Macromolecules* **1993**, *26*, 2987.
6 I. In, Y.-H. La, S.-M. Park, P. F. Nealey, P. Gopalan, *Langmuir* **2006**, *22*, 7855.
7 S. Kanagasabapathy, A. Sudalai, B. C. Benicewicz, *Macromol. Rapid Commun.* **2001**, *22*, 1076.
8 W. Zhang, W. Zhang, N. Zhou, Z. Cheng, J. Zhu, X. Zhu, *Polymer* **2008**, *49*, 4569.
9 T. E. Patten, J. Xia, T. Abernathy, K. Matyjaszewski, *Science* **1996**, *272*, 866.
10 Y. Chen, M. Sone, K. Fuchise, R. Sakai, R. Kakuchi, Q. Duan, J. Sun, A. Narumi, T. Satoh, T. Kakuchi, *React. Funct. Polym.* **2009**, *69*, 463.
11 Z. Cao, W. Liu, G. Ye, X. Zhao, X. Lin, P. Gao, K. Yao, *Macromol. Chem. Phys.* **2006**, *207*, 2329.
12 M. Kato, M. Kamigaito, M. Sawamoto, T. Higashimura, *Macromolecules* **1995**, *28*, 1721.
13 A. Narumi, Y. Chen, M. Sone, K. Fuchise, R. Sakai, T. Satoh, Q. Duan, S. Kawaguchi, T. Kakuchi, *Macromol. Chem. Phys.* **2009**, *210*, 349.
14 H. Wang, Y. An, N. Huang, R. Ma, L. Shi, *J. Colloid Interface Sci.* **2008**, *317*, 637.
15 X. D. Tang, X. C. Liang, N. F. Han, *Chin. Chem. Lett.* **2009**, *20*, 1353.
16 Y. Kotsuchibashi, K. Yamamoto, T. Aoyagi, *J. Colloid Interface Sci.* **2009**, *336*, 67.
17 H.-H. Lin, Y.-L. Cheng, *Macromolecules* **2001**, *34*, 3710.
18 M. Kimura, M. Kato, T. Muto, K. Hanabusa, H. Shirai, *Macromolecules* **2000**, *33*, 1117.