

Rational approach to star-like nanogels with different arm lengths: formation by dynamic covalent exchange and their imaging

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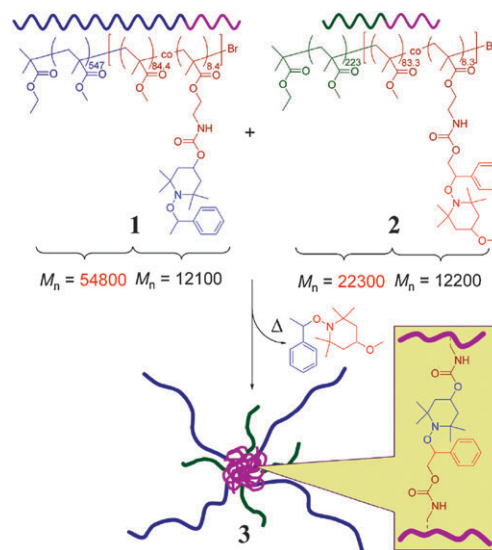
The formation of star-like nanogels with different arm lengths via a radical crossover reaction of alkoxyamine units in diblock copolymers and direct observation of the star-like nanogels by scanning force microscopy were successfully accomplished.

Diverse types of polymers with particular shapes and characteristics have been designed and synthesized by precision polymerization methods such as atom transfer radical polymerization (ATRP),¹ and their molecular structures and morphologies have been confirmed by direct observation methods, typified by scanning force microscopy (SFM). Remarkable advancement on high-resolution and high-speed SFM and the recent development of sharp cantilevers has allowed researchers to accurately reveal the molecular chains and partial structures of these polymers. So far, graft copolymers,² star polymers,³ cyclic polymers,⁴ helical polymers,⁵ and self-assembly of block copolymers⁶ have been observed by SFM, and it has been made clear that the structures of these polymers are almost identical to the designed architectures. Although SFM images reflect only partial structures, in combination with other analytical methods they enable us to discuss polymer structures in more detail.

On the other hand, covalent bonds that are able to dissociate in response to specific external stimuli and to recreate their bonds as disulfide bonds,⁷ ester bonds,⁸ and carbon–carbon double bonds⁹ have attracted much attention. The concept of dynamic covalent chemistry (DCC)¹⁰ has been proposed to purposely incorporate these bonds into compounds and to control the structures of molecular shapes and assemblies, thus enabling the formation of compounds by specific stimuli under thermodynamic control. We have demonstrated the dynamic nature of alkoxyamines derived from styryl and nitroxyl radicals and applied them to polymer reactions. The alkoxyamine derivatives are well known as initiators of living radical polymerization.¹¹ Although the central C–O bond in the alkoxyamine derivative can behave as a typical covalent bond under normal conditions, the bond can reversibly dissociate into styryl and nitroxyl radicals upon heating over 60 °C. As a result, C–O bonds in alkoxyamine derivatives are regarded as dynamic covalent bonds, and the alkoxyamine derivatives can exchange their C–O bonds intermolecularly *via* a radical crossover reaction.¹²

In the course of our research on dynamic covalent polymers, we have reported the formation of star-like nanogels by a crossover reaction of diblock copolymer with alkoxyamine units in their side chains,¹³ with diblock copolymers being reversibly regenerated.¹⁴ Because styryl and nitroxyl radicals complementarily react with each other, the reaction system can be expected to form various shapes of polymers and molecular assemblies. In this paper, star-like nanogels with different arm lengths were designed to be formed by a crossover reaction of two types of complementarily reactive diblock copolymers with different alkoxyamines in their side chains, as shown in Scheme 1. Furthermore, direct observation of the star-like nanogels was performed by SFM, coupled with gel permeation chromatography (GPC) measurement and multi angle light scattering (MALS) measurements.

Two types of diblock copolymers with poly(methyl methacrylate) (PMMA) block and random block composed of MMA and methacrylic esters with alkoxyamines were designed to establish a complementarily reactive system. They were prepared by an ATRP technique; random copolymerization of MMA and methacrylic esters with the corresponding alkoxyamines connected to different positions, from PMMA prepolymers ($M_n = 54800$ for **1**, $M_n = 22300$ for **2**) with bromine at the chain end using Cu(I)Br–sparteine as the catalyst system. The controlled polymerization was carried



Scheme 1 Formation of star-like nanogels with different arm lengths via radical crossover reaction of well-defined diblock copolymers with complementarily reactive alkoxyamine units in their side chains.

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out at 50 °C because alkoxyamine units are thermally stable under this heating condition.¹² Diblock copolymers **1** and **2** with relatively narrow molecular weight distribution were obtained (**1**; $M_n = 66\,900$, $M_w/M_n = 1.13$, **2**; $M_n = 34\,500$, $M_w/M_n = 1.08$) that had different molecular weights from that of the PMMA block and almost the same molecular weight as the cross-linkable block, as shown in Scheme 1.

Formation of star-like nanogels was performed by merely heating the mixture of diblock copolymers **1** and **2** in anisole (10 wt%) at 100 °C for 24 h. After heating, no gelation of the system was observed and the solution maintained its flowability despite the high polymer concentrations. Due to the existence of PMMA block, excess gelation was depressed and the cross-linking reaction occurred not on a macroscale but on a nanoscale level. Furthermore, no coloration of the solution due to a coupling reaction between styryl radicals and a generation of nitroxyl radicals was observed. This result can be explained by the persistent radical effect (PRE),¹⁵ which describes how the equilibrium state between dormant species and active species consists of persistent and active radicals, corresponding to nitroxyl and styryl radicals, respectively.

Fig. 1 shows GPC curves of the products after heating diblock copolymers **1** and **2**, and their mixture in anisole (10 wt%) for 24 h. In the case of heating diblock copolymers **1** and **2** separately, almost no change in the GPC curve was observed, meaning that the cross-linking reaction did not occur. In contrast, an increase in molecular weight and decreases in the parent peaks attributed to diblock copolymers were observed in the mixing system (approximately 70% yield estimated from GPC curve). It is notable that no peak over the

exclusion limit was confirmed, and polymers with relatively low molecular weight distribution were obtained. These results indicate that polymers with stable structures were formed, probably due to the steric repulsion of the PMMA block.

Furthermore, in order to demonstrate the complementarily reactive system, two types of diblock copolymers were reacted at several mixing ratios. Fig. 1 (bottom) shows M_w at different mixing ratios of diblock copolymers **1** and **2**, which were evaluated by MALS measurement. These plots show bell-shaped plots, with the molecular weight showing a maximum value in the equal mixing ratio ($M_w = 1\,273\,000$). This result occurred because the cross-linking reaction was dominant under this condition. Under the lower mixing ratio conditions of either diblock copolymer, the levels of alkoxyamine, which contributes to the cross-linking reaction, became lower.

These results indicate that two types of diblock copolymers reacted in a complementarily reactive system. It was not until two types of diblock copolymers existed together that cross-linked polymers were formed. As alkoxyamine units in each diblock copolymer have the same orientation, the crossover reaction in a single diblock copolymer system results in the formation of the identical diblock copolymer. However, the crossover reaction between two types of diblock copolymers must form cross-linking points because two types of diblock copolymer can generate different radicals. This mechanism indicates that the cross-linked polymers formed in the reaction have two kinds of chains with different lengths.

The molecular images of these cross-linked polymers were directly confirmed by SFM observation. The samples for the observation were prepared by spin-casting of dilute chloroform solution of the reaction products (1×10^{-4} wt%) on cleaved mica. The SFM observation was carried out by using a diamond-like carbon (DLC) tip as a cantilever, the tip curvature radius of which was under 3 nm in a 300 nm \times 300 nm observation area.

Fig. 2 shows SFM images of cross-linked polymers prepared by heating several mixing ratios of diblock copolymers **1** and **2**. In the case of heating diblock copolymer **2** alone, the image corresponding to only linear polymer chains was observed (Fig. 2a). In contrast, in the case of heating the mixture of diblock copolymers **1** and **2**, an image of star-like structures with core parts and several molecular chains connecting to the core was clearly observed. The line profiles revealed that the size of the core parts was approximately 2 nm in height and 20 nm in width, indicating that the core parts have three-dimensional networks.¹³ These results show that the observed polymer structures have both nanoscopic gel parts and star-like PMMA chains as star-like nanogels **3**. Interestingly, these SFM images make it clear that nanogels have two different arm lengths as long chains (blue lines in model) and short chains (green lines in model), as typified in Fig. 2b. Indeed, such a tendency of the ratio of long chains increasing with increases in the mixing ratio of diblock copolymer **1** was also confirmed (Fig. 2b–d).

In order to discuss quantitatively the influence of the mixing ratio of diblock copolymers on the structures of star-like nanogels, the numbers of the two types of chains were evaluated. Fig. 3 shows the ratio of long chains in all chains estimated from SFM images in several mixing ratios of diblock

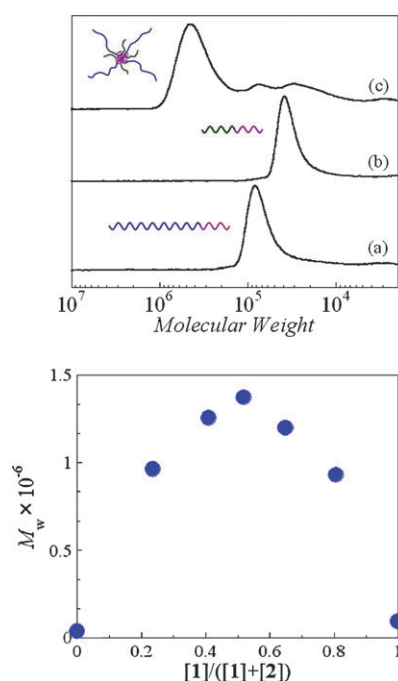


Fig. 1 Molecular weight distributions of the reaction products after heating (a) **1**, (b) **2**, and (c) a mixture of **1** and **2** ($[1]/[2] = 5/5$, molar fraction) in anisole (10 wt%) at 100 °C for 24 h (top). M_w data of reaction product estimated by MALS after heating diblock copolymers **1** and **2** in anisole (10 wt%) at 100 °C for 24 h in several mixing ratios (bottom).

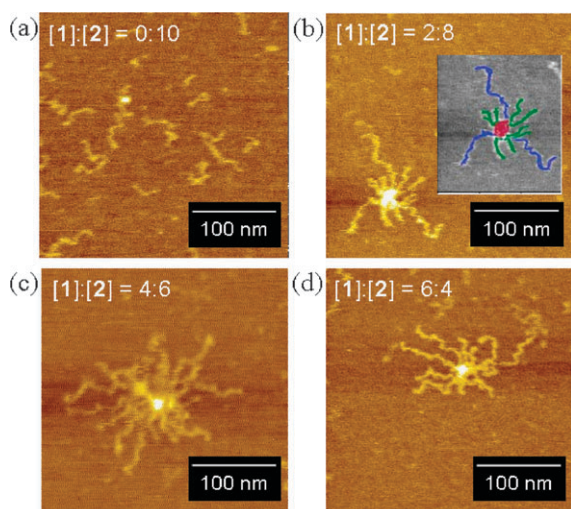


Fig. 2 Representative SFM images of reaction products after heating the mixtures of block copolymers **1** and **2** ([**1**]:[**2**] = (a) 0:10, (b) 2:8, (c) 4:6, and (d) 6:4, molar fraction). SFM observation of the samples prepared by spin-casting of a dilute chloroform solution of polymers on mica was carried out by using a sharp cantilever.

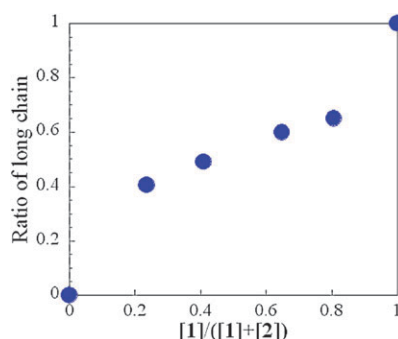


Fig. 3 Ratio of long chains in star-like nanogels estimated from SFM images. Each plot indicates the average value estimated from 30 SFM images.

copolymers. Each plot indicates the average value estimated from 30 SFM images. With increases in the mixing ratio of diblock copolymer **1**, the ratio of long chains also increased. However, the ratio of long chains did not completely correspond to the mixing ratio. It is reasonable to suppose that some excess amount of existing diblock copolymer did not react entirely because the amount of alkoxyamines that could contribute to form cross-linking points was limited when the system was out of complementarity. These results indicate that star-like nanogels with different arm lengths were formed and that the proportion of chain lengths could be controlled by the mixing ratio of the complementarily reactive diblock copolymers.

In summary, we have demonstrated the formation of star-like nanogels with different arm lengths *via* a radical crossover reaction of alkoxyamine units in diblock copolymers. It was revealed that two types of diblock copolymers with different molecular weights reacted in a complementarily reactive system based on GPC curves and MALS results in several mixing ratios of the diblock copolymers. Furthermore, the molecular images of the formed polymers confirmed by SFM

observation were a star-like architecture with long and short molecular chains, and the proportion could be controlled by the mixing ratio of the block copolymers. The present system can be applied to a de-cross-linking system and hetero-arm star polymers; such complementarily reactive systems with dynamic covalent bonds therefore have the potential to form the desired molecular assemblies. Since radical reactions are tolerant of water, this system can also be applied to aqueous nanogel formation systems.¹⁶

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Notes and references

- N. V. Tsarevsky and K. Matyjaszewski, *Chem. Rev.*, 2007, **107**, 2270.
- (a) H. Lee, K. Matyjaszewski, S. Yu-Su and S. S. Sheiko, *Macromolecules*, 2008, **41**, 6073; (b) H. G. Börner, D. Duran, K. Matyjaszewski, M. Da Silva and S. S. Sheiko, *Macromolecules*, 2002, **35**, 3387; (c) S. S. Sheiko, B. S. Sumerlin and K. Matyjaszewski, *Prog. Polym. Sci.*, 2008, **33**, 759.
- (a) G. Kreutzer, C. Ternat, T. Q. Nguyen, C. J. G. Plummer, J.-A. E. Manson, V. Castelletto, I. W. Hamley, F. Sun, S. S. Sheiko, A. Herrmann, L. Ouali, H. Sommer, W. Fieber, M. I. Velazco and H.-A. Klok, *Macromolecules*, 2006, **39**, 4507; (b) G. Gorodyska, A. Kiri, S. Minko, C. Tsitsilianis and M. Stamm, *Nano Lett.*, 2003, **3**, 365; (c) L. Xue, U. S. Agarwal, M. Zhang, B. B. P. Staal, A. H. E. Müller, C. M. E. Bailly and P. J. Lemstra, *Macromolecules*, 2005, **38**, 2093.
- D. Kawaguchi, T. Nishu, A. Takano and Y. Matsushita, *Polym. J.*, 2007, **39**, 271.
- (a) J. Kumaki, T. Kawauchi, K. Okoshi, H. Kusanagi and E. Yashima, *Angew. Chem., Int. Ed.*, 2007, **46**, 5348; (b) S.-i. Sakurai, S. Ohsawa, K. Nagai, K. Okoshi, J. Kumaki and E. Yashima, *Angew. Chem., Int. Ed.*, 2007, **46**, 7605.
- J. Kumaki, Y. Nishikawa and T. Hashimoto, *J. Am. Chem. Soc.*, 1996, **118**, 3321.
- W. J. Lees and G. M. Whitesides, *J. Org. Chem.*, 1993, **58**, 642.
- S. J. Rowan and J. K. M. Sanders, *J. Org. Chem.*, 1998, **63**, 1536.
- P. Schwab, M. B. France, J. W. Ziller and R. H. Grubbs, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2039.
- S. J. Rowan, S. J. Cantrill, G. R. L. Cousins, J. K. M. Sanders and J. F. Stoddart, *Angew. Chem., Int. Ed.*, 2002, **41**, 898.
- (a) M. K. Georges, R. P. N. Veregin, P. M. Kazmaier and G. K. Hamer, *Macromolecules*, 1993, **26**, 2987; (b) C. J. Hawker, *J. Am. Chem. Soc.*, 1994, **116**, 11185.
- (a) H. Otsuka, K. Aotani, Y. Higaki and A. Takahara, *Chem. Commun.*, 2002, 2838; (b) H. Otsuka, K. Aotani, Y. Higaki and A. Takahara, *J. Am. Chem. Soc.*, 2003, **125**, 4064; (c) Y. Higaki, H. Otsuka and A. Takahara, *Macromolecules*, 2004, **37**, 1696; (d) G. Yamaguchi, Y. Higaki, H. Otsuka and A. Takahara, *Macromolecules*, 2005, **38**, 6316; (e) Y. Higaki, H. Otsuka and A. Takahara, *Macromolecules*, 2006, **39**, 2121; (f) H. Otsuka, K. Aotani, Y. Higaki, Y. Amamoto and A. Takahara, *Macromolecules*, 2007, **40**, 1429.
- Y. Amamoto, Y. Higaki, Y. Matsuda, H. Otsuka and A. Takahara, *Chem. Lett.*, 2007, **36**, 774.
- Y. Amamoto, Y. Higaki, Y. Matsuda, H. Otsuka and A. Takahara, *J. Am. Chem. Soc.*, 2007, **129**, 13298.
- (a) H. Fischer, *Chem. Rev.*, 2001, **101**, 3581; (b) A. Studer, *Chem. Soc. Rev.*, 2004, **33**, 267; (c) W. Tang, T. Fukuda and K. Matyjaszewski, *Macromolecules*, 2006, **39**, 4332.
- D. Talton, J.-F. Baussard, L. Dupayage, J. Poly, Y. Gnanou, V. Ponsinet, M. Destarac, C. Mignaud and C. Pitois, *Chem. Commun.*, 2006, 1953.