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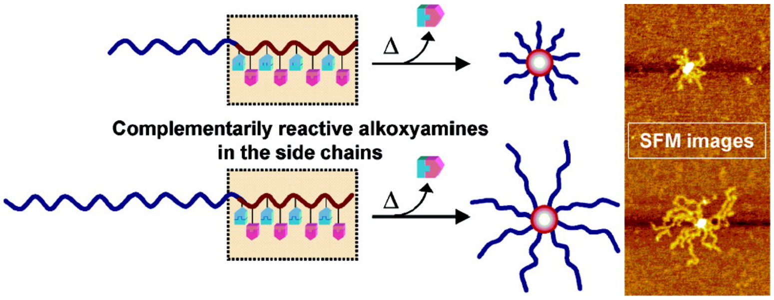

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Programmed Thermodynamic Formation and Structure Analysis of Star-like Nanogels with Core Cross-linked by Thermally Exchangeable Dynamic Covalent Bonds

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Abstract: Programmed thermodynamic formation of star-like nanogels from designed diblock copolymers with thermally exchangeable dynamic covalent bonds in their side chains and structure analysis of the nanogels were performed. Linear diblock copolymers that consist of poly(methyl methacrylate) block and random copolymer block of methyl methacrylate (MMA) and methacrylic esters with alkoxyamine moiety were prepared by atom transfer radical polymerization (ATRP). By heating the diblock copolymers in anisole, a cross-linking reaction occurred as a result of the radical crossover reaction of alkoxyamine moieties to afford star-like nanogels. Kinetic studies have revealed that the cross-linking behavior reaches equilibrium at a given reaction time, with characteristic reaction behaviors for thermodynamic reactions being observed. The equilibrium structures of the star-like nanogels were controlled by the initial concentrations of diblock copolymers as well as their compositions and molecular weights. Furthermore, by heating the star-like nanogels with excess alkoxyamine, linear polymers were successfully regenerated. The molecular weights and sizes of the nanogels were evaluated by gel permeation chromatography−multiangle laser light scattering (GPC−MALLS) and small-angle X-ray scattering (SAXS) measurements, respectively, and the morphologies of the nanogels were directly observed by scanning force microscopy (SFM).

Introduction

Physicochemical properties of polymers are mainly governed by compositions, primary structures, and their aggregated states; therefore, polymers with various types of shapes have been designed and synthesized. Among them, nanogels,[1] which are defined as internally cross-linked single macromolecules of molecular weight and dimensions similar to the parent, linear polymer chains, but having a number of transverse covalent bonds between the chain segments, have generated much attention because of their potential application in various fields, including the drug delivery system,[2] chemical separations,[3] encapsulation of metals,[4] stabilization,[5] and encapsulation[6] of enzymes. Nanogels have been prepared by the usual synthetic method via microemulsion,[7] inverse miniemulsion,[8] self-assembly of biopolymers,[9] and the intramolecular cross-linking of single chains of macromolecules.[10]

With the recent advancement of controlled polymerization methods such as atom transfer radical polymerization (ATRP),[11] well-defined diblock copolymers with uniform molecular weight and designed composition can be synthesized. Such well-defined block copolymers are known to form higher-order structures such as microphase separations,[12] core−shell nanoparticles,[13] and micelles,[14] depending on the primary structure. In recent years, external stimuli-responsive block copolymers have attracted much attention. Responding to physical or chemical stimuli such as heat,[15] changes in pH,[16] and electrolytes,[17] structures of polymer aggregates have been drastically changed.

On the other hand, reversible polymer cross-linking systems have been constructed. Supramolecular approaches (noncovalent

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† Graduate School of Engineering.

‡ Institute for Materials Chemistry and Engineering.

[1] This class of polymers is also referred to as "core cross-linked star polymers" in the literature, for example: Xia, J.; Zhang, X.; Matyjaszewski, K. *Macromolecules* **1999**, *32*, 4482−4484.

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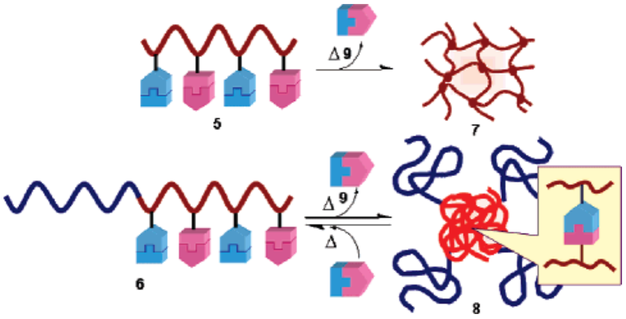
10.1021/ja075447n CCC: $37.00

bond systems) are frequently examined due to metal complexation,[18] hydrogen bonds,[19] and so on. Such supramolecular cross-linking systems enable us to control the structure of the compounds with thermodynamic control, forming structures that are thermodynamically stable within the system. Recently, covalent bonding systems with reversible bonds have been focused on as dynamic covalent systems.[20−22] In these systems, compounds are formed that have not only stable bonds but also thermodynamically stable structures. We have already developed dynamic covalent polymers with 2,2,6,6-tetramethylpiperidinyl-1-oxy (TEMPO)-based alkoxyamine moieties.[23−26] Although the central C−O bonds in alkoxyamine derivatives behave as typical covalent bonds under normal conditions, the alkoxyamine unit can reversibly dissociate into a styryl radical and TEMPO-derivative upon heating and reach an equilibrium state via radical crossover processes.[24,25] Because of their exchanging ability, the C−O bonds in alkoxyamine derivatives are regarded as dynamic covalent bonds. In addition, radical reaction is tolerant to many functional groups. Recently, we have applied such radical crossover reactions to the polymer reactions in the side chains. When the mixture of random copolymers with complementarily reactive alkoxyamine units in each side chain was heated, macroscopic gelation of the system was observed due to the cross-linking reaction.[25] In addition, by designing primary structures of the polymers with the appropriate positioning and number of alkoxyamine units, it became possible to create nanostructures and to construct intelligent build-up molecular systems. We have previous reported the programmed formation of star-like nanogels by using a radical crossover reaction of two types of diblock copolymers with complementarily reactive alkoxyamine in their side chains.[26] In this system, the structures as well as the molecular weights of nanogels are controlled by the mixing ratio and the reaction concentrations of two types of diblock copolymers.

Scheme 1. Schematic Representation of the Preparation of Macroscopic Gel and the Structure Interconversion between Diblock Copolymer and Star-like Nanogel via a Radical Crossover Reaction



We report herein a novel and smart thermodynamic structural interconversion system between diblock copolymers and nanogel with dynamic covalent bonds based on the exchange reaction of alkoxyamine units, as represented in Scheme 1. A molecular design in which two types of complementarily reactive alkoxyamine units are integrated into “one” diblock copolymer enables the formation “self-build-up” molecular systems, and we discuss the influence of the primary structure of diblock copolymers on the structures of nanogels.

Results and Discussion

Design and Synthesis of Random and Diblock Copolymers with Alkoxyamines. Linear random and diblock copolymers consisting of PMMA block and random block of MMA and monomers with alkoxyamine moieties were designed as the parent polymers. As the monomers with alkoxyamine moieties, we designed methacrylic esters **3** and **4** containing the alkoxyamine units. They have potential reactivity with each other above 60 °C via a radical crossover reaction, but they are expected to remain stable at room temperature. The polymerizable unit and alkoxyamine units are connected by polar urethane bonds because they tend to aggregate during the polymer reaction. The monomers were synthesized by a simple addition reaction from 2-methacryloyloxyethyl isocyanate and alkoxyamine-based alcohols **1** or **2** in the presence of dibutyltin dilaurate as the catalyst in DMF. The reaction proceeded at room temperature to give the desired monomers **3** and **4** in high yield, respectively, without any byproducts derived from the dissociation and/or decomposition of alkoxyamine units.

Random copolymerization of MMA, **3**, and **4** was carried out by the ATRP technique. Control of polymerization can be achieved only below 60 °C because the central C−O bonds in alkoxyamine units are thermally unstable and dissociate above 60 °C. The ATRP of the 5/1/1 mixture of MMA/**3**/**4** was carried out in anisole at 50 °C using 2-(EiB)Br as an initiator and Cu(I)Br/Sp as the catalyst complex. The polymerization was well-controlled, and the molecular weight increased linearly with conversion, producing linear polymer **5** with relatively narrow molecular distribution (for example: $M_n = 27\,600$, $M_w/M_n = 1.23$).

Linear diblock copolymers that consist of poly(methyl methacrylate) block [PMMA block] and random copolymer block of MMA/**3**/**4** [PMAL block] were synthesized by the two-step method. Initially, linear PMMA prepolymer with a bromine atom at the chain end was prepared by ATRP using 2-(EiB)Br and Cu(I)Br/Sp system,[11] as shown in Scheme 2. Subsequently, random copolymerization of MMA/**3**/**4** (5/1/1 or 20/1/1) mixture was carried out in anisole at 50 °C using PMMA prepolymer

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Scheme 2. Preparation of Diblock Copolymer by Random Copolymerization of MMA, **3**, and **4** from PMMA with a Bromine Atom at the Chain End with Using the ATRP Method

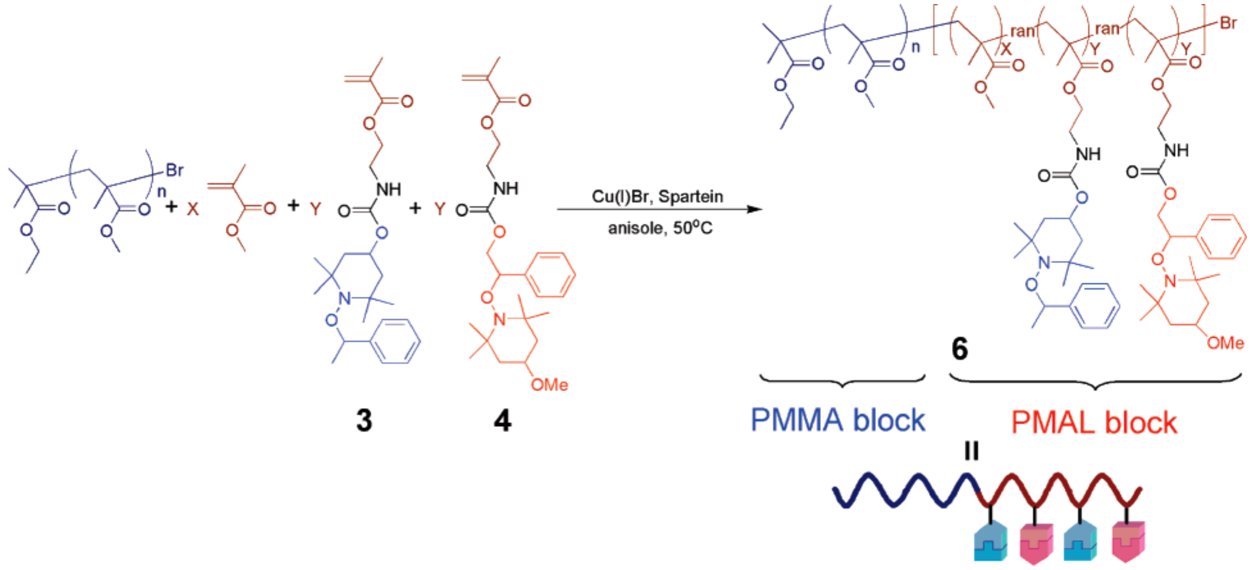
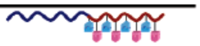


Table 1. Preparation of Diblock Copolymer **6** by ATRP with the Difference in Molecular Weight and Composition

Diblock copolymer	PMMA prepolymer M_n	M_w/M_n	Block copolymer M_n	M_w/M_n	$[MMA]_0/[\mathbf{3}]_0/[\mathbf{4}]_0$	Schematic representation
6a	23100	1.11	39000	1.07	5/1/1	
6b	55400	1.13	70000	1.08	5/1/1	
6c	23100	1.11	29700	1.08	5/1/1	
6d	22100	1.11	35400	1.11	20/1/1	

and Cu(I)Br/Sp as the catalyst complex to afford diblock copolymer **6**.

Table 1 shows the molecular weights and polydispersities of four kinds of diblock copolymers with differences in the primary structure such as the molecular weight of each block and the composition in the PMAL block. On the basis of diblock copolymer **6a**, the structure of diblock copolymer **6b** was designed and synthesized to have a higher molecular weight of PMMA block, and diblock copolymer **6c** to have a lower molecular weight of PMAL block. Diblock copolymer **6d** has a lower composition ratio of **3** and **4** to the MMA unit in PMAL block. The other primary structure is almost identical to diblock copolymer **6a**. Furthermore, the polydispersities of diblock copolymers were relatively low (M_w/M_n < 1.2).

Radical Crossover Reaction of Random Copolymer. As we have reported previously, in the double-component cross-linking system using copolymers with alkoxyamine units, the present single-component cross-linking reaction of random copolymer **5** can be expected to occur as a result of a radical crossover reaction of alkoxyamine moieties in the side chain (Scheme 3). A radical crossover reaction of random copolymer **5** was carried out by heating degassed anisole solution of **5** at 100 °C at various concentrations. In the case of the present single-component cross-linking system, nitroxide and styryl radicals can be generated in single polymer chains under the heating conditions, and the crossover reaction can therefore proceed via both intermolecular and intramolecular processes. After heating, no coloration of the solution was observed. If the carbon−carbon coupling reaction occurred in the system, the reaction mixture would turn from colorless to red due to the generation of nitroxide radicals, which do not couple each other. Therefore, the radical crossover reaction proceeded without any detectable side reaction such as carbon−carbon coupling. This observation is clearly explained by the Persistent Radical Effect (PRE). PRE is a general principle that explains the highly specific formation of the cross-coupling product R^1-R^2 between R^1 and R^2 when one species is persistent (R^1) and the other is transient.[27] In the case of the crossover reaction of alkoxyamine derivatives, TEMPO radical is persistent and styryl radical is transient. Although one would expect nonselective statistical reaction between the two different radical species, carbon−carbon coupling product was hardly generated. At high concentrations above 5 wt %, the solution transformed into a macroscopic gel (**7**) after heating for 4 h, suggesting that the intermolecular cross-linking reaction occurred preferentially at high concentration conditions.

At low concentration conditions, however, no gelation was observed during the reaction, even for 24 h. The relative

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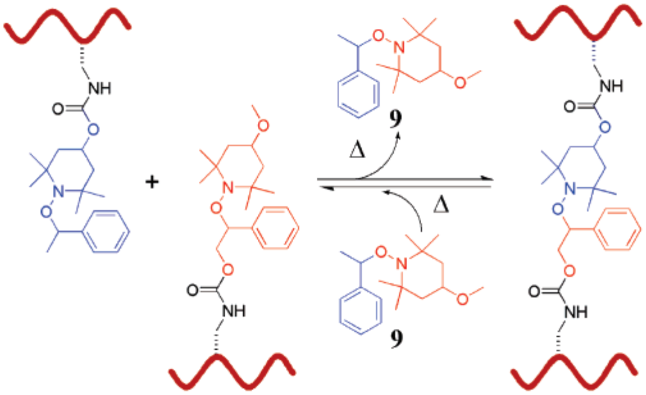
Scheme 3. Reversible Cross-Linking Reaction of Alkoxyamine Derivatives in the Side Chains



molecular weight of the polymer after the reaction was evaluated by GPC. The GPC curves of the cross-linking reaction at 0.5 and 1.0 wt % conditions are shown in Figure 1. At 0.5 wt % concentration, the relative molecular weight did not increase, but rather decreased, and peak broadening was observed. This result suggests that the intramolecular radical crossover reaction occurred preferentially and that the radius of gyration as well as the relative molecular weight of the polymer decreased after the reaction.

Radical Crossover Reaction of Diblock Copolymer. On the basis of the polymer reaction of random copolymer described above, a radical crossover reaction of diblock copolymers was carried out by heating anisole solutions of diblock copolymers **6a**−**6d** at 100 °C at various concentrations. No coloration of the solution was observed after heating in any of the experiments, suggesting that the radical crossover reaction proceeded without side reactions such as carbon−carbon coupling. Very importantly, no macroscopic gelation of the system was observed even at high concentrations such as 10 wt %. Because of the existence of PMMA block in block copolymer, the cross-linking reaction did not occur on a macroscale but did on a nanoscale.

Figure 2 shows time-coursed GPC curves of the reaction mixture after a cross-linking reaction of diblock copolymers **6a** at 5 wt % condition. The molecular weight increased and peaks for the diblock copolymers gradually disappeared with increasing reaction time. By heating at the 5 wt % concentration condition, intermolecular cross-linking reaction of the diblock copolymer preferentially proceeded to afford the corresponding core cross-linked nanogel, and almost all diblock copolymer converted to nanogels. Moreover, the GPC curve became constant after 12 h, indicating that the reaction reached equilibrium at 24 h under this condition. In the case of diblock copolymer **6b**−**6d**, the same results were observed. Here, the radical crossover reaction between the alkoxyamine units was always accompanied by the formation of alkoxyamine **9**. This formation can inform us of the number of cross-linking points; therefore, the amount of **9** after the polymer reactions was evaluated by HPLC measurement. Figure 3 shows the relationship between reaction time and the relative ratio of alkoxyamine **9** recovered from the product from diblock copolymers **6a** and **6d**. The relative ratio was normalized by setting the maximum value to 1. The relative ratio of alkoxyamine was constant at 24 h, while the relative ratio increased with reaction time until 24 h. This result also indicates that the reaction reached equilibrium at 24 h.

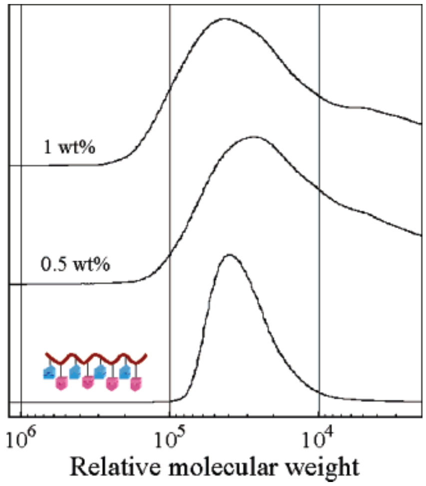


Figure 1. Concentration dependence of GPC curves of **5** ($M_n = 27\,600$, $M_w/M_n = 1.23$) and reaction mixture **7** after heating **5** at 100 °C for 24 h at 0.5 and 1.0 wt %.

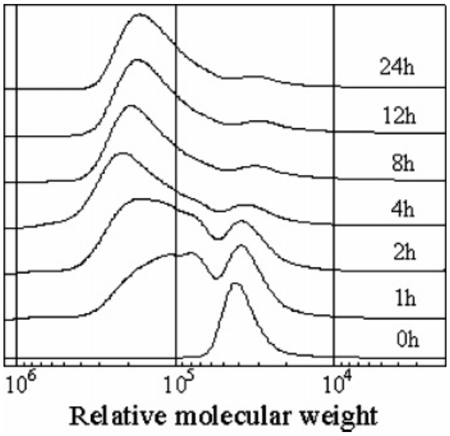


Figure 2. Time dependence of GPC curves of the crossover reaction product **8** after heating **6a** in anisole (5 wt %) at 100 °C.

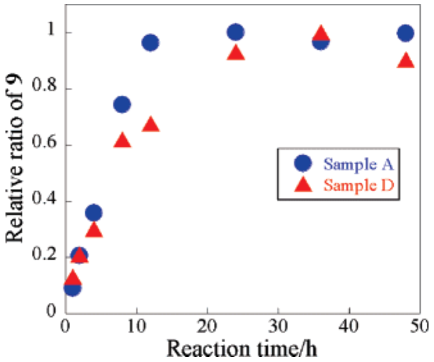


Figure 3. Time dependence of the relative ratio of **9** for the cross-linking reactions of **6a** (Sample A) and **6d** (Sample D) in anisole at 100 °C. The relative ratio is normalized by setting the maximum value to 1.

To obtain further insight into the structural transformation process from diblock copolymers to nanogels, the absolute weight average molecular weight (M_w) and radius of gyration ($\langle S^2 \rangle^{1/2}$) were determined by GPC−MALLS and SAXS measurements, respectively. SAXS measurements of the reaction mixture were carried out in anisole solution, and $\langle S^2 \rangle^{1/2}$ was obtained by fitting the scattering profile to the Guinier approximation. Figure 4 shows the reaction time dependence of

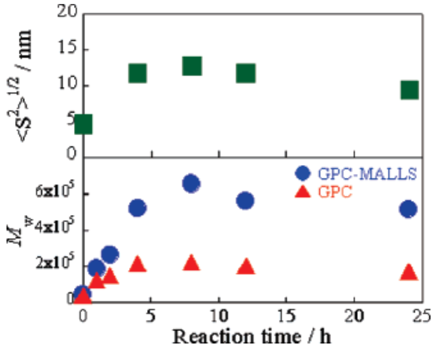


Figure 4. Time dependence of M_w and $\langle S^2\rangle^{1/2}$ of the crossover reaction product **8d** after heating **6d** in anisole (5 wt %) at 100 °C.

the M_w and $\langle S^2\rangle^{1/2}$ of the cross-linking reaction product after heating diblock copolymers **6d** at 100 °C in anisole (5 wt %). Until 8 h, M_w and $\langle S^2\rangle^{1/2}$ drastically increased as increasing reaction time. In contrast, after 8 h, M_w and $\langle S^2\rangle^{1/2}$ had gradually decreased. In addition, the relative molecular weight of the nanogels was determined by a GPC instrument, which was calibrated with a linear polystyrene standard. As shown in Figure 4, the M_w determined by GPC−MALLS was larger than that of the GPC instrument, suggesting that nanogels have a cross-linked and branched structure.

From the results of the above observation and measurements, we propose a reaction model for the structural transformation from diblock copolymers to nanogels at high concentrations. At an early stage of the reaction, the intermolecular cross-linking reaction among PMAL blocks in diblock copolymers occurred preferentially, creating a star-like architecture. In the next stage, an increase in molecular weight was prevented by the steric repulsion of PMMA block, but an intramolecular radical crossover reaction inside the core of the star-like architecture occurred preferentially. As a result, slight contraction of the cross-linked polymers was observed, and nanogels were formed. In the final stage, some diblock copolymer in nanogels dissociated because the central C−O bonds of alkoxyamines in the side chains of polymers are dynamic covalent bonds, and the macromolecular architecture, which is thermodynamically stable in the system, is formed. In the present system, nanogels that consisted of a certain number of the diblock copolymers formed spontaneously.

Figure 5 shows GPC curves of polymers after the cross-linking reaction of diblock copolymers **6a**−**6d** at various concentrations for 24 h. With increasing concentration, high-molecular weight nanogels were formed in all cases. Similarly, the M_w values of cross-linking polymers by GPC−MALLS instrument were larger under high concentration conditions, as shown in Figure 6.

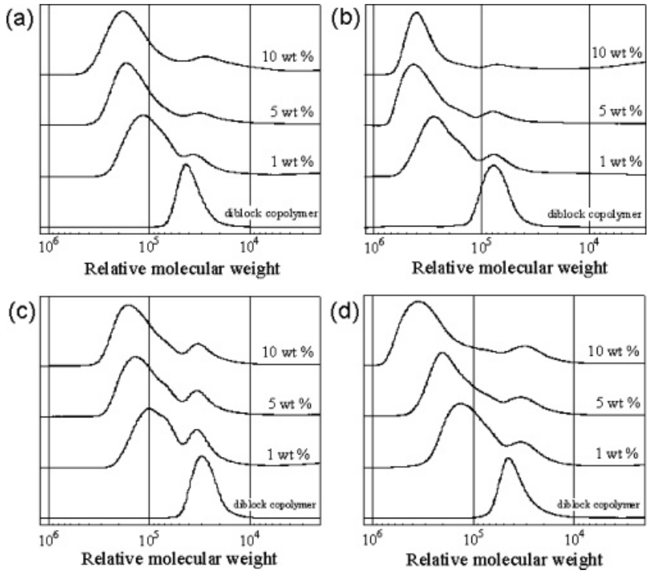


Figure 5. Concentration dependence of GPC curves of diblock copolymer and reaction product after heating (a) **6a**, (b) **6b**, (c) **6c**, and (d) **6d** at 100 °C for 24 h at 1, 5, and 10 wt % concentration conditions.

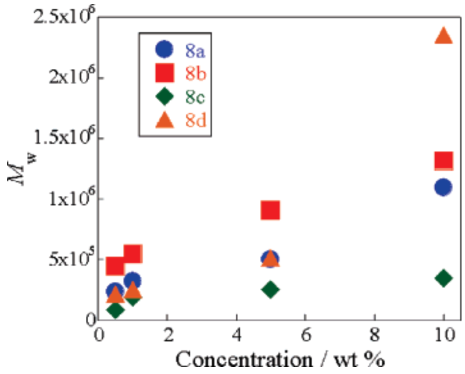


Figure 6. Concentration dependence of M_w of reaction product after heating anisole solution of **6a**−**6d** at 100 °C for 24 h at 0.5, 1, 5, and 10 wt % concentration conditions.

Furthermore, the knowledge of the structure dependence of diblock copolymer was obtained by comparing the GPC curves and M_w of nanogels **8a**−**8d** created by heating each diblock copolymer, as shown in Figure 6. First, as compared to the difference in PMMA block molecular weight (nanogel **8a** vs nanogel **8b**) when the molecular weight of PMMA block is high, nanogel with a narrow molecular weight distribution was obtained under the high concentration condition. This difference occurred because a thermodynamically stable structure was formed due to the cohesive forces among the PMMA chains and to stabilization of the phase transition under the condition of high molecular weight of PMMA block. Next, as compared to the difference in PMAL block molecular weight (nanogel **8a** vs nanogel **8c**) when the molecular weight of alkoxyamine block is low, it is relatively difficult to form a polymer nanogel with a limited amount of number of diblock copolymer based on the observation of the remaining diblock copolymer peaks in Figure 5c and M_w in Figure 6. This result indicates that the intermolecular cross-linking reaction is difficult when the degree of polymerization in PMAL block is low. Finally, as compared to the difference in the MMA/**3**/**4** composition in PMAL block (nanogel **8a** vs nanogel **8d**) in the case of the characteristically low stoichiometric ratio of alkoxyamine, a higher M_w polymer nanogel was obtained under the 10 wt % condition. This result indicates that the intermolecular cross-linking reaction proceeded easily due to the low density of the cross-linkable points. From these results, the molecular weight and its distribution of the nanogel at equilibrium appear to have been strongly governed by initial concentrations as well as the composition and molecular weights of the parent diblock copolymers.

The topology of star polymers can be directly visualized by using scanning force microscopy (SFM).[28] The morphologies of the nanogels were analyzed by SFM observations in dynamic force microscopy (DFM) mode on a mica surface. Figure 7

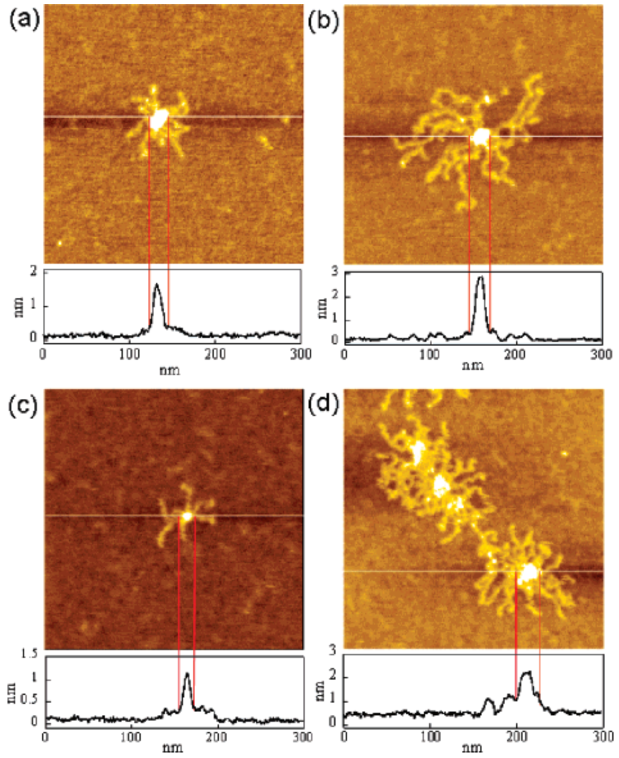


Figure 7. SFM height images and their line profiles of nanogels on mica substrate deposited from solution obtained by heating (a) **6a**, (b) **6b**, (c) **6c**, and (d) **6d** at 100 °C for 24 h under the 10 wt % concentration condition.

Table 2. Core Size and *f* (number of Arms) Information of Nanogels Prepared by Heating **6a**−**6d** at 100 °C for 24 h at the 10 wt % Concentration Conditions

	SFM		MALLS	
nanogel	height/nm	diameter/nm	M_w	*f*
8a	2.15 ± 0.82	31.0 ± 6.5	1 100 000	26.3
8b	2.43 ± 0.69	30.0 ± 7.5	1 320 000	17.4
8c	1.02 ± 0.32	24.3 ± 3.4	347 000	10.8
8d	1.00 ± 0.25	44.0 ± 11.6	2 350 000	60.0

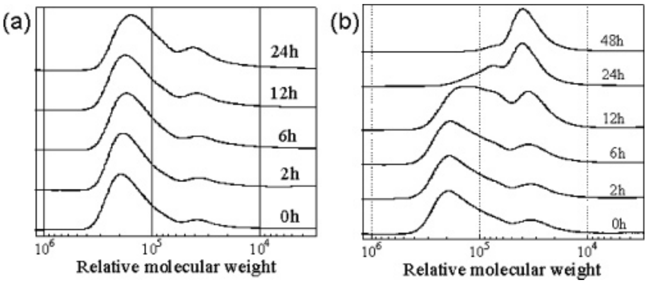


Figure 8. Time dependence of GPC curves of the de-cross-linking reaction product after heating (a) **8a** and (b) **8d** in anisole (5 wt %) with an excess of alkoxyamine (40 equiv/alkoxyamine units in side chain) at 100 °C.

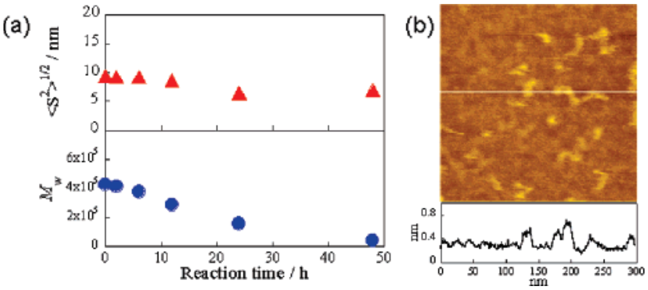


Figure 9. (a) Time dependence of M_w and $\langle S^2\rangle^{1/2}$ of the de-cross-linking reaction product after heating **8d** in anisole (5 wt %) with an excess of alkoxyamine (40 equiv/alkoxyamine units in side chain) at 100 °C and (b) SFM image of de-cross-linking products after heating **8d** for 48 h under the same condition above.

shows the typical SFM height images and their line profiles of nanogel **8a**−**8d** obtained by heating diblock copolymer **6a**−**6d** in anisole at 100 °C for 24 h under the 10 wt % concentration condition. The morphologies of the nanogels with a gel part and branching chains were clearly observed, supporting our hypothesis that the nanogels have a star-like architecture. The branching chains seem to be longer in the case of nanogel **8b** as compared to nanogel **8a** due to the higher molecular weight of PMMA block in nanogel **8b**. In addition, the number of branching chains was observed to be fewer in the case of nanogels **8c**, in contrast with nanogels **8d**, due to the number of assembled diblock copolymers.

Table 2 shows the size information of gel parts observed by SFM images in nanogels **8a**−**8d** and the number of arms (*f*) calculated by M_w values. Although a size difference in core parts between nanogels **8a** and **8b** was not practically observed, the height of nanogels **8c** was observed to be lower, probably due to the shorter length of the cross-linkable PMAL block. Similarly, a lower height and larger diameter were observed in nanogels **8d** due to the low cross-linking density.

Structural Transformation from Nanogels to Linear Polymers. In the thermodynamic polymer reaction, the product structure completely depends on the equilibrium and stoichiometric conditions. In the present system, if the de-cross-linking reaction occurs at the core of the nanogel, the formation of linear polymers is expected. The reverse reaction, structural conversion from nanogel to diblock copolymer, was examined by changing the stoichiometry of alkoxyamine delivery in the systems. The nanogels **8a** and **8d** were added to anisole solution (5 wt %) with an excess of alkoxyamine **9** (40 equiv/alkoxyamine unit in the side chain) and heated at 100 °C. According to the GPC measurement, the de-cross-linking reaction of nanogel **8a** hardly occurred (Figure 8a), probably due to the extremely high cross-linking density of the core. In contrast, the de-cross-linking reaction of nanogel **8d** proceeded successfully. Figure 8b shows time-coursed GPC curves in the de-cross-linking reaction of nanogel **8d**. The relative molecular weight decreased and peaks for the diblock copolymers gradually appeared with increasing reaction time. After 48 h, the GPC curve is almost identical to the GPC curve of the parent diblock copolymer (**6d**).

To collect further information about the structural transformation process from nanogels to diblock copolymers, M_w and $\langle S^2\rangle^{1/2}$ were determined by GPC−MALLS and SAXS measurements, respectively. Figure 9a shows the reaction time dependence of the M_w and $\langle S^2\rangle^{1/2}$ for the de-cross-linking reaction of nanogel **8d**. Interestingly, although the M_w decreased gradually, the radius of gyration remained almost constant until 12 h, after which it began to decrease. Accordingly, we developed a reaction model for the structure conversion from nanogels to diblock copolymers. At an early stage of the reaction, as a result of the de-cross-linking reaction, dissociation into diblock copolymers from the nanogel and swelling of the nanogel

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(28) For example: (a) Matyjaszewski, K.; Qin, S.; Boyce, J. R.; Shirvanyants, D.; Sheiko, S. S. *Macromolecules* **2003**, *36*, 1843−1849. (b) Xue, L.; Agarwal, U. S.; Zhang, M.; Staal, B. B. P.; Müller, A. H. E.; Bailly, C. M. E.; Lemstra, P. J. *Macromolecules* **2005**, *38*, 2093−2100. (c) Schappacher, M.; Deffieux, A. *Macromolecules* **2005**, *38*, 4942−4946.

occurred simultaneously. After 12 h, dissociation of diblock copolymer occurred preferentially, and the radius of gyration sharply decreased. Furthermore, on the basis of SFM images, a peak over 1 nm corresponding to nanogels was not observed, as shown in Figure 9b. From the GPC−MALLS, SAXS, and SFM data, regeneration of diblock copolymer was confirmed.

Conclusion

We have demonstrated a thermodynamic structural interconversion system between diblock copolymers and nanogels. The reaction model for the structural transformation was developed by means of GPC−MALLS and SAXS measurements, and it was made clear that the nanogels are formed as the most stable structure in the present system. Indeed, the molecular weights of the nanogel at equilibrium are clearly controlled by initial concentrations as well as the composition and molecular weight of the diblock copolymer. The morphology of the nanogels was observed by SFM observation, which revealed that nanogels consisted of both a gel part and branching molecular chains. By controlling the stoichiometric ratio of alkoxyamine, structural conversion from nanogels to diblock copolymers also proceeded, as the structures of the compound depend on the equilibrium state. Such a kind of dynamic covalent macromolecular system can widely afford various polymer architectures through programming of the parent dynamic covalent polymers and polymer reaction conditions.

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Supporting Information Available: Experimental details, including synthesis, SAXS, GPC−MALLS, and SFM. This material is available free of charge via the Internet at http://pubs.acs.org.

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