Programmed Formation of Nanogels via a Radical Crossover Reaction of Complementarily Reactive Diblock Copolymers

Yoshifumi Amamoto,[1] Yuji Higaki,[1] Yasuhiro Matsuda,[2] Hideyuki Otsuka,*[1,2] and Atsushi Takahara[1,2]
[1]*Graduate School of Engineering, Kyushu University, 744 Motooka, Nishi-ku, Fukuoka 819-0395*
[2]*Institute for Materials Chemistry and Engineering, Kyushu University,*
744 Motooka, Nishi-ku, Fukuoka 819-0395

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By heating two types of diblock copolymers with complementarily reactive alkoxyamine units in the side chains, nanogels were formed as a result of a radical crossover reaction of the alkoxyamine units. The transformation from the diblock copolymers to nanogels and their absolute molecular weight were obviously dependent on reaction concentrations and the mixing ratio of two types of diblock copolymers.

Nanogels[1] have attracted much attention based on their potential application in various fields, including drug delivery systems,[2] encapsulation of metals,[3] and chemical separations.[4] Because of requests for the size and chemical properties of polymer nanogels, they have been prepared by various synthetic methods. These methods typically utilize chemical[5] and physical[6] cross-linking methods, which have strong stability and reversibility, respectively.

Recently, molecular systems based on reversible covalent bonds have attracted considerable interest as "dynamic covalent chemistry."[7] In these systems, compounds that have both stable bonds and thermodynamically stable structures, such as in the supramolecular approach, are formed by specific external stimulus. In other words, the chemical structure and/or transformation of the compounds with dynamic covalent bonds depend on reaction conditions such as primary and secondary structures, concentration, and stoichiometric ratio, which are controlled by changing their equilibrium states.

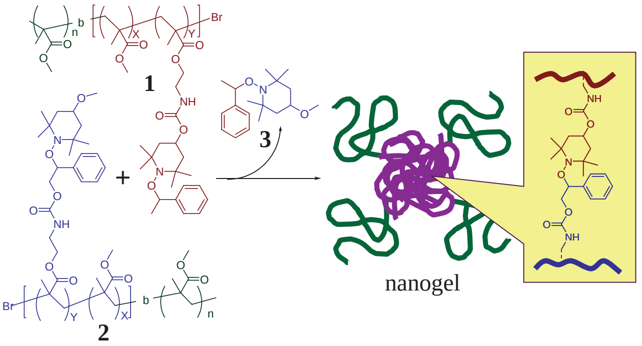
We have recently shown that C–ON bonds in alkoxyamine[8] behave as dynamic covalent bonds.[9–12] Although, alkoxyamine units behave as if they have typical covalent bonds under normal conditions, alkoxyamine units generate styryl and nitroxide radicals and they can undergo a crossover reaction upon heating.[9] When polymers with alkoxyamines in the side chains are heated, macroscopic gelation of the system is observed due to the cross-linking reaction.[12] This reaction system has potential application to constructing intelligent build-up systems to create nano-structures. Herein, we preliminarily report the programmed formation of star-like nanogels by using a radical crossover reaction of two types of diblock copolymers with complementarily reactive alkoxyamines in the side chains (Scheme 1).

Two types of diblock copolymers (**1** and **2**) that consist of methyl methacrylate (MMA) block and random block of MMA and methacrylic esters with alkoxyamine units were designed and synthesized. The monomers with alkoxyamine moieties connected at different positions were prepared by a simple addition reaction from 2-methacryloyloxyethyl isocyanate and alkoxyamine-based alcohols. Diblock copolymers were prepared from PMMA prepolymer ($M_{\mathrm{n,GPC}} = 24{,}200$, $M_{\mathrm{w}}/M_{\mathrm{n}} = 1.13$) with bromide at the end by random copolymerization of MMA and methacrylic esters with alkoxyamine moieties ([MMA]/[methacrylic esters with alkoxyamine moieties] = 2.5/1) by the atom transfer radical polymerization (ATRP) technique.[13] Diblock copolymers with relatively low molecular weight distribution ($M_{\mathrm{w}}/M_{\mathrm{n}} < 1.15$) were obtained.

The radical crossover reaction was performed by heating an anisole solution of the mixture of diblock copolymers **1** ($M_{\mathrm{n,GPC}} = 35{,}500$, $M_{\mathrm{w}}/M_{\mathrm{n}} = 1.11$) and **2** ($M_{\mathrm{n,GPC}} = 34{,}500$, $M_{\mathrm{w}}/M_{\mathrm{n}} = 1.12$) at 100 °C for 24 h. After heating, no gelation of the system was observed, even at high concentrations such as 10 wt % of the total concentration of diblock copolymers. Figure 1a shows gel permeation chromatography (GPC) profiles of polymers after heating in an equal mixing ratio of **1** and **2** ([**1**]/[**2**] = 5/5, w/w) at several concentrations. As a result of the radical crossover reaction of alkoxyamine units in **1** and **2**, the molecular weight increased without exceeding the separation limitation. Due to the existence of PMMA block in block copolymers, excess gelation was depressed by cohesive forces of PMMA block and stabilization of phase separation between PMMA part and gel part. As a result, the cross-linking reaction occurred not on a macroscopic scale but on a nanometer scale to afford star-like nanogels.

The degree of transformation from diblock copolymers to star-like nanogels increased under higher concentration conditions, as clearly shown in Figure 1b. This is because the cross-linking proceeds by an intermolecular reaction and nanogel formation occurs easily at higher concentrations. The structures of star-like nanogels as well as the molecular weight and yield of nanogels in the equilibrium state were obviously dependent on the concentration conditions. In other words, star-like nanogels with thermodynamically stable structures were formed as in the supramolecular approach.

In order to investigate the complementarity of diblock copolymers **1** and **2**, the reaction was carried out at different mixing ratios. Figure 2a shows the GPC profiles of the reaction mixtures after heating in several mixing ratios of **1** and **2** at 100 °C in anisole (10 wt %) for 24 h. By changing the mixing conditions, approaching an equal mixing ratio ([**1**]/[**2**] = 5/5, w/w), molecular weight and yield of the nanogels increased remarkably (Figure 2b) and nanogel has $M_{\mathrm{w,GPC}} = 122{,}000$ in equal conditions with three cross-linking points in a diblock copolymer determined by estimating the amount of generated alkoxyamine **3**. Indeed, when each polymer was heated independently, as shown in the mixing ratio ([**1**]/[**2**], w/w) of 10/0 and 0/10, the GPC profile was almost equal to that for the starting diblock copolymer. These results indicated that the nanogel formation proceeded without any side reaction and the core cross-linking reaction was clearly due to the radical exchange reaction of complementarily reactive alkoxyamine units.



Scheme 1. Programmed formation of star-like nanogel.

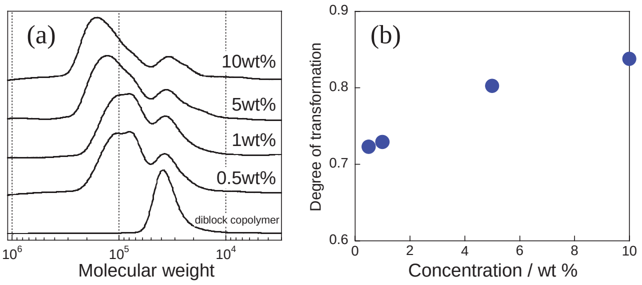


Figure 1. (a) GPC profiles of the reaction mixture after heating **1** and **2** ([**1**]/[**2**] = 5/5 (w/w)) at 100 °C in anisole for 24 h and (b) the degree of transformation from diblock copolymers to nanogels. Molecular weights were calibrated by using five polystyrene standards (M_n = 1,060–228,800).

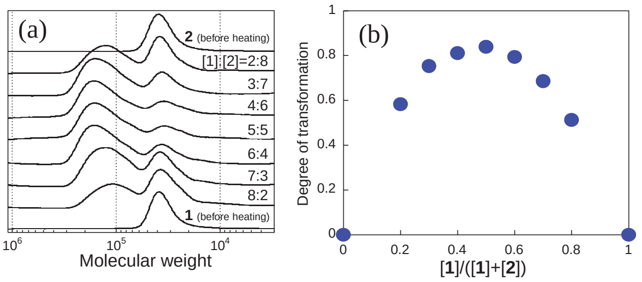


Figure 2. (a) GPC profiles of star nanogels after heating in several mixing ratios of **1** and **2** (w/w) at 100 °C in anisole (10 wt %) for 24 h and (b) the degree of transformation from diblock copolymers to nanogels.

As the retention time of GPC is affected by not only the molecular weight, but also by the branching structure of the polymers, a calibration curve for "linear" polymers will not give "real" molecular weight for our nanogels. So as to obtain the real molecular weight of star-like nanogels, absolute average molecular weights ($M_{\mathrm{w,MALLS}}$) were measured by gel permeation chromatography–multiangle laser light scattering (GPC-MALLS) instrument.

Figure 3 shows the mixing ratio- and concentration- dependence of $M_{\mathrm{w,MALLS}}$ of nanogel. $M_{\mathrm{w,MALLS}}$ is strongly related to the reaction conditions. The nanogels formed from an equal mixture ([**1**]/[**2**] = 5/5) of diblock copolymer at 10 wt % concentration condition has $M_{\mathrm{w,MALLS}}$ = 242,000. Furthermore, the arm number of star nanogels calculated from the molecular weight of nanogels and parent diblock copolymers is approximately seven when heating under the above equal condition.

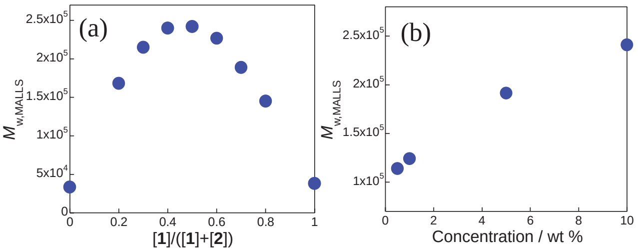


Figure 3. (a) Mixing ratio and (b) concentration dependence of $M_{\mathrm{w,MALLS}}$ of nanogels after heating a mixture of **1** and **2** in anisole at 100 °C for 24 h.

In summary, the authors have demonstrated a novel formation system of nanogels programmed by exchangeable dynamic covalent bonds. Since a radical reaction is tolerant to many functional groups, the present system has potential application to construction of an intelligent thermodynamic formation system for the creation of more complex structures, as well as in the supramolecular approach.

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