5470 *Macromolecules* **2010**, *43*, 5470–5473
DOI: 10.1021/ma100276n

Macromolecules
NOTE

Solvent-Controlled Formation of Star-like Nanogels via Dynamic Covalent Exchange of PSt-*b*-PMMA Diblock Copolymers with Alkoxyamine Units in the Side Chain

Yoshifumi Amamoto,[†] **Moriya Kikuchi,**[‡] **Hideyuki Otsuka,**[*,†,‡] **and Atsushi Takahara**[*,†,‡]

[†]*Graduate School of Engineering, Kyushu University, 744 Motooka, Nishi-ku, Fukuoka 819-0395, Japan, and*
[‡]*Institute for Materials Chemistry and Engineering, Kyushu University, 744 Motooka, Nishi-ku, Fukuoka 819-0395, Japan*

Received February 4, 2010; Revised Manuscript Received May 13, 2010

Introduction

Block copolymers have attracted much attention because these copolymers form assemblies such as micelles, cross-linked micelles, cylindrical micelles, and vesicles in solutions.[1] In particular, hydrophobic interaction of amphiphilic block copolymers in aqueous media has been one of the most common strategies employed to form the assemblies. Also, changing the solubility of one block by pH[2] and temperature[3] in stimuli-responsive block copolymers has been investigated.[4] On the other hand, block copolymer micelles in organic solvents have been also studied by designing hydrophobic–hydrophilic and hydrophobic–hydrophobic block copolymers. Polystyrene-*b*-poly(methyl methacrylate) (PSt-*b*-PMMA) diblock copolymers, whose segments are used widely in polymer science, have been studied as typical immiscible block copolymers. For example, PSt core micelles and PMMA core micelles were formed in furfuryl alcohol[5] and *p*-cymene,[6] respectively, and their micellization and core size were revealed using light scattering measurements by considering isorefractive solvents for corona. In an ionic liquid, the PSt-*b*-PMMA also assembled with the PSt core, and transmission electron microscopic (TEM) images recorded the progression of micelle structure from sphere to cylinder as PMMA segments were reduced.[7] The morphologies of assemblies on substrates were also confirmed by atomic force microscopic (AFM) observation especially using the Langmuir–Blodgett (LB) method[8] and were controlled precisely by their segment length and fraction.[9]

In our previous work, we have achieved the formation of star-like nanogels, which are also termed core cross-linked star polymers,[10] by cross-linking reactions of diblock copolymers with cross-linkable alkoxyamine units in one segment.[11−13] The alkoxyamine units consisting of styryl radical and 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) dissociated into radicals over 60 °C and exchanged their units to form other alkoxyamine compounds via a dynamic covalent exchange reaction.[14,15] The polymers with alkoxyamine units in their side chains cause the cross-linking reaction by dynamic covalent exchanges.[16] The morphologies of the star-like nanogels were also controlled by the structures of diblock copolymers, reaction concentration, and mixing ratio of two types of diblock copolymers.[11−13] Furthermore, structure transformation from star-like nanogels to diblock copolymers was also accomplished by the dynamic covalent exchange reaction between the alkoxyamine in the cross-linking points and added alkoxyamine.[12,13] More recently, micellar aggregates formed from amphiphilic diblock copolymers with dynamic covalent linkage were demonstrated to decompose via a dynamic covalent exchange reaction.[17]

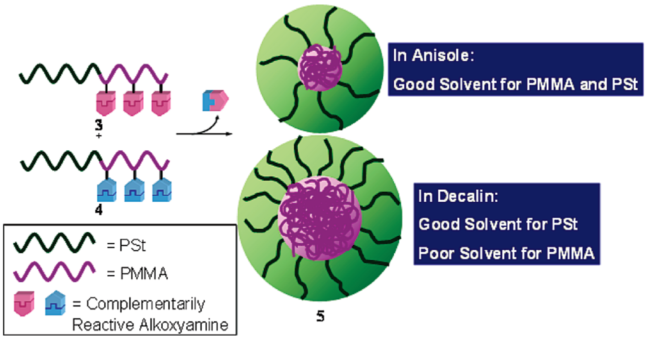


Figure 1. Model of solvent-controlled formation of star-like nanogels via dynamic covalent exchange reaction of complementarily reactive diblock copolymers.

In the present paper, we show solvent-controlled formation of star-like nanogels via a dynamic covalent exchange reaction of PSt-*b*-PMMA diblock copolymers with alkoxyamine units in the PMMA block. The reaction was carried out in decalin (good solvent for PSt and poor solvent for PMMA) and in anisole (good solvent for both PSt and PMMA), and the size of star-like nanogels is discussed from the viewpoint of solvent quality, as shown in Figure 1.

Experimental Section

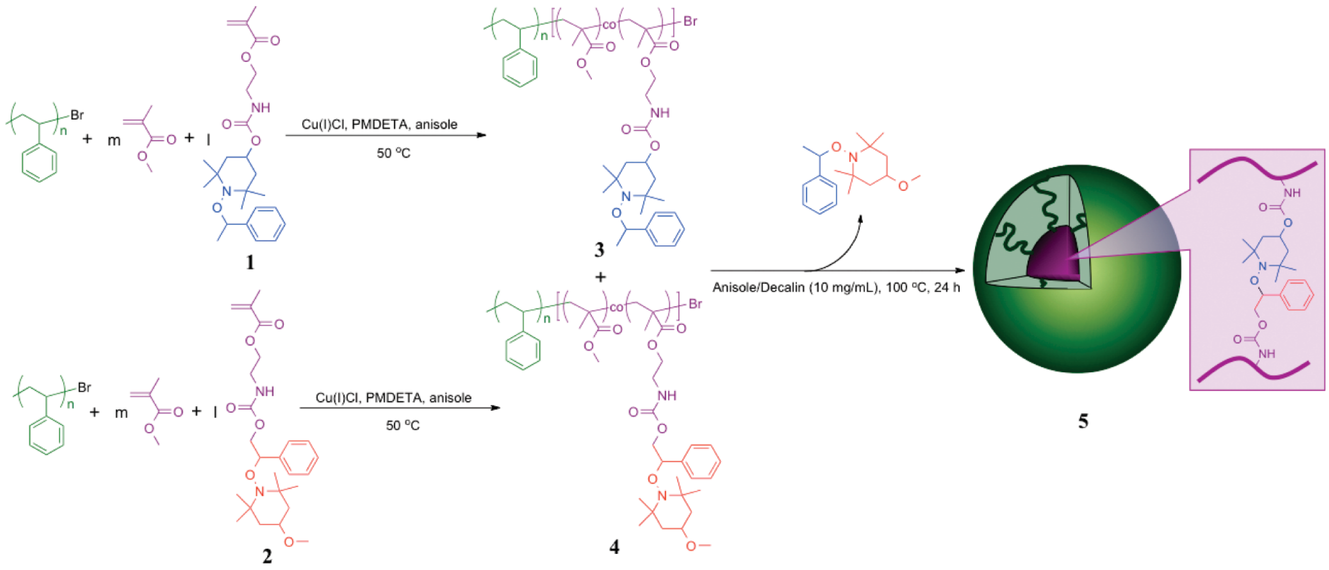
Materials. 4-(2′-Methacryloyloxyethylcarbamyl)-1-((1′-phenylethyl)oxy)-2,2,6,6-tetramethylpiperidine (**1**)[12] and 4-methoxy-1-((2′-(2″-methacryloyloxyethylcarbamyl)-1′-phenylethyl)oxy)-2,2,6,6-tetramethylpiperidine (**2**)[12] were prepared and purified as previously reported. Cu(I)Cl (99+%) was purchased from Wako Pure Chemical Industries and purified by stirring in acetic acid (Wako Pure Chemical Industries, 99+%), washing with ethanol (Wako Pure Chemical Industries, 99+%), and then drying in vacuo. *N*,*N*,*N*′,*N*′-Pentamethyldiethylenetriamine (PMDETA) was purchased from Tokyo Chemical Industry and used as received. *trans*-Decahydronaphthalene (decalin) was purchased from Tokyo Chemical Industry and purified by distillation under reduced pressure over calcium hydride. Anisole (99+%) and methyl methacrylate (MMA, 98%) were purchased from Wako Pure Chemical Industry and purified by distillation under reduced pressure over calcium hydride.

PSt-*b*-(MMA-*co*-1) (3). In a glass tube, CuCl (4.0 mg, 0.044 mmol) was charged and dried under vacuum. After argon replacement, PMDETA (7.6 mg, 0.044 mmol) dissolved in argon-purged anisole (1.2 mL) was added via syringe. The solution was stirred until it became colored and then degassed

---

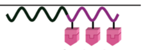
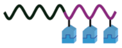
*Corresponding authors. E-mail: otsuka@ms.ifoc.kyushu-u.ac.jp (H.O.), takahara@cstf.kyushu-u.ac.jp (A.T.).

Scheme 1. Preparation of Complementarily Reactive Diblock Copolymers (3 and 4) by Copolymerization of MMA and Methacrylic Esters with Alkoxyamine Units (1 and 2), Respectively, via ATRP Methods and the Dynamic Covalent Exchange among Alkoxyamine Units toward Formation of the Star-like Nanogel 5[a]



[a] The polymerization condition; [PSt-Br]/[CuCl]/[PMDETA]/[monomer] = 1/1/1/400, [MMA]/[**1** or **2**] = 10/1.

Table 1. M_n and M_w/M_n of Diblock Copolymers 3 and 4 Prepared by ATRP Methods with Almost the Same Polymerization Degree with Alkoxyamine Units Connected at the Different Positions

	PSt initiator		Diblock Copolymer				
	M_n	M_w/M_n	M_n	M_w/M_n	[MMA]$_0$/[**1**]$_0$	[MMA]$_0$/[**2**]$_0$	Structure Model
3	18 800	1.18	31 600	1.28	10/1	-	
4	18 800	1.18	31 400	1.30	-	10/1	

by five freeze−pump−thaw cycles to substitute argon. After heating at 50 °C in an oil bath, PSt prepolymer (955 mg, 0.0440 mmol, M_n = 18 800) dissolved in argon-purged MMA (1.7 mL, 16 mmol), **1** (692 mg, 1.6 mmol), and anisole (1 mL) were added and stirred for 24 h at 50 °C. Then, the reaction mixture was quenched to 0 °C and filtered through an Al_2O_3 column with chloroform to remove the CuCl catalyst. The filtrate was evaporated under vacuum, and the residue was purified by reprecipitation into a mixture of hexane and cyclohexane (1/4 v/v). The precipitate was dried to yield a white powder (2.14 g, M_n = 31 600, M_w/M_n = 1.28). ^1H NMR (300 MHz, $CDCl_3$, δ/ppm): 0.67 (s, CH_3), 0.85 (s, CH_3), 1.02 (s, CH_3), 1.13 (s, CH_3), 1.27 (s, CH_3), 1.34 (s, CH_3), 1.49 (d, J = 7 Hz, CH_3), 1.68 (s, CH_2), 1.81 (s, CH_2), 1.89 (s, CH_2), 3.43 (m, CH_2), 3.60 (s, CH_3), 4.04 (m, CH_2), 4.77 (q, J = 7 Hz, CH), 4.90 (m, CH), 6.50−7.31 (m, aromatic); FT-IR (NaCl, cm^{-1}): 2999 (C−H), 2951 (C−H), 1728 (C=O), 1493 (C=C).

PSt-*b*-(MMA-*co*-2) (4). Diblock copolymer **4** was synthesized following the procedure for diblock copolymer **3** by using **2** (740 mg, 1.6 mmol) instead of **1**. After reprecipitation, a white powder (M_n = 31 400, M_w/M_n = 1.30) was obtained. ^1H NMR (300 MHz, $CDCl_3$, δ/ppm): 0.68 (s, CH_3), 0.84 (s, CH_3), 1.02 (s, CH_3), 1.08 (s, CH_3), 1.23 (s, CH_3), 1.38 (s, CH_3), 1.67 (s, CH_2), 1.68 (s, CH_2), 1.87 (s, CH_2), 2.02 (s, CH_2), 3.30 (s, CH_3), 3.60 (s, CH_3), 3.99 (m, CH_2), 4.20 (m, CH_2), 4.66 (m, CH), 4.91 (m, CH_2), 6.46−7.31 (m, aromatic); FT-IR (NaCl, cm^{-1}): 2950 (C−H), 1727 (C=O), 1493 (C=C).

Dynamic Covalent Exchange Reaction between 3 and 4. In a typical run, an anisole solution (1.0 mL) of **3** (5 mg) and **4** (5 mg) was charged into a glass tube, degassed by seven freeze−pump−thaw cycles, and sealed under vacuum. The glass tube was heated at 100 °C for 24 h in an oil bath, and the solution was evaporated under vacuum. After dissolution in benzene, a white powder (**5**, 95% yield) was obtained by the freeze-dry method.

Results and Discussion

Diblock copolymers (**3** and **4**), consisting of PSt blocks and PMMA blocks with cross-linkable alkoxyamine units, were synthesized by ATRP techniques. In ATRP methods, block copolymers consisted of PMMA and PSt were usually synthesized by a normal polymerization of St from PMMA-X (X = Br, Cl) initiator or a halogen exchange methodology such as polymerization of MMA from a PSt-Br initiator using CuCl as catalyst.[18,19] In the present systems, polymerization should have been carried out under 60 °C because of the dissociation of alkoxyamine units, and higher molecular weight PSt is difficult to obtain by polymerization of St under this condition. Therefore, the polymerization was carried out by random copolymerization of MMA and each type of methacrylic ester with alkoxyamine units (**1** and **2**) from PSt-Br initiator using CuCl/PMDETA catalysts at 50 °C, as shown in Scheme 1. After polymerization, the purifications were carried out by several reprecipitations into a mixture of hexane/cyclohexane (1/4 v/v), which is a poor solvent for PSt and a nonsolvent for PMMA, to eliminate unreacted PSt initiators. Table 1 summarizes the M_n and M_w/M_n of the PSt initiators and diblock copolymers and their models. Diblock copolymers **3** and **4**, with almost the same polymerization degree of the PSt and PMMA blocks and with alkoxyamine units at different positions, were successfully prepared.

A dynamic covalent exchange among alkoxyamine units in the polymer side chains makes it possible to form cross-linking structures from linear polymers. The cross-linking reaction was carried

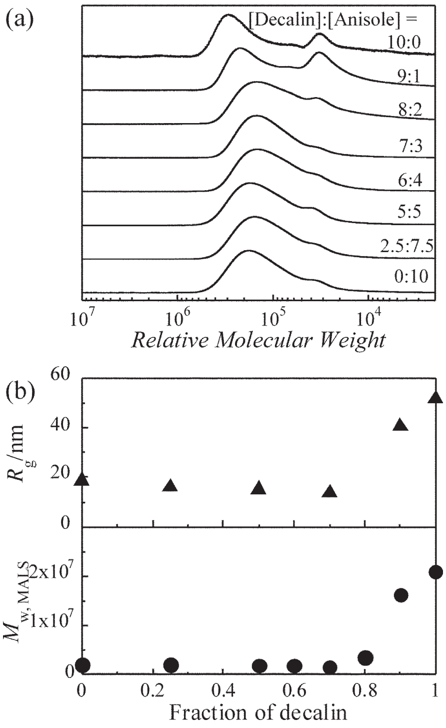


Figure 2. Solvent fraction dependence of (a) GPC curves and (b) $M_{\mathrm{w,MALS}}$, R_g of polymers after heating the diblock copolymers **3** and **4** in several mixing ratios of anisole and decalin (10 mg/mL) at 100 °C for 24 h.

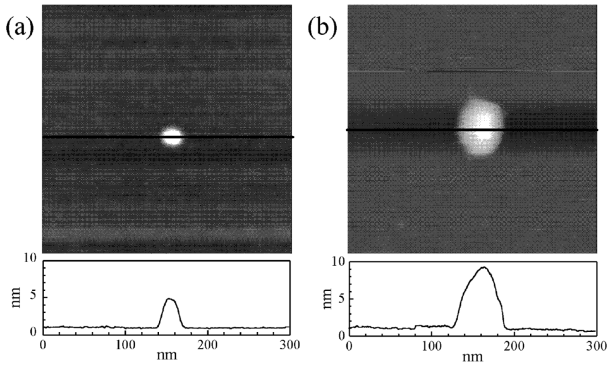


Figure 3. SFM images of star-like nanogels **5** on mica prepared in (a) anisole and (b) decalin (10 mg/mL) at 100 °C for 24 h.

Table 2. Core Sizes of Star-like Nanogels 5 in SFM Images on Mica Prepared in Decalin and Anisole (10 mg/mL)[a]

solvent	height/nm	diameter/nm
anisole	4.7 ± 1.2	37.4 ± 10
decalin	17.6 ± 7.2	113 ± 26

[a] Values are averages for 50 samples in each solvent.

out by heating a solution of a mixture of the diblock copolymers ([**3**]/[**4**] = 5/5) at 100 °C, as seen in Scheme 1. Even after heating for 24 h, the solution kept sol states, indicating that the gelation occurred on the nanoscopic level. As we have previously reported,[12,13] the molecular weights and sizes of the star-like nanogels depended on their reaction time, the mixing ratio of two types of diblock copolymers **3** and **4**, and reaction concentrations, as shown in Figures S3−S5.

The formation process of cross-linking polymers from these types of diblock copolymers consisting of PSt and PMMA can be governed by solvent quality for both blocks. Herein, we demonstrated the cross-linking reaction in anisole and decalin by changing their mixing ratio. Although anisole is a good solvent for both PSt and PMMA, decalin is a good solvent for PSt (θ solvent at 20.4 °C[20]) and a poor solvent for PMMA at the reaction temperature (100 °C). Prior to heating, a faintly white solution was observed in decalin, indicating that some polymer assembly was formed, whereas the solution in anisole was colorless and clear. Figure 2a shows GPC curves of **5** after heating **3** and **4** ([**3**]:[**4**] = 5:5) in the mixture of anisole and decalin in several ratios for 24 h at 100 °C. The peak with higher molecular weight increased with increasing ratios of decalin and remarkably so in higher proportions of decalin ([decalin]:[anisole] = 10:0, 9:1, and 8:2). Furthermore, $M_{\mathrm{w,MALS}}$ and R_g also indicated a similar tendency, as seen in Figure 2b. The R_g value obtained in decalin ([decalin]:[anisole] = 10:0) was estimated by U-SAXS measurements, while the other values were obtained by SAXS measurements. Comparing the reaction in decalin with anisole ([decalin]:[anisole] = 10:0 to 0:10), the $M_{\mathrm{w,MALS}}$ and R_g values in decalin are 9.5 times and 2.5 times, respectively, larger than those in anisole.

The variation in molecular weights and sizes was considered to have occurred due to the difference in the formation process controlled by solvent quality. In other words, it depended on the states of the diblock copolymers in each solvent before heating, micelles or isolated chains. In the case of decalin, the diblock copolymers formed some micelle-type polymer assemblies prior to heating because the PMMA segments were difficult to dissolve in decalin. Then, the assembled polymers were cross-linked with almost no change to their shapes, and a larger polymer structure could be obtained. In this system, the sizes of the star-like nanogels strongly depended on the segment ratio and length. On the other hand, in the case of anisole, the diblock copolymer dissolved without forming any assembly prior to heating, and the cross-linking reaction proceeded by dynamic covalent exchange reaction among alkoxyamine units. The assembled polymer gradually formed the star-like nanogels, as seen in Figure S3.

The size difference of star-like nanogels prepared from different solutions was directly observed by scanning force microscopy (SFM). Figure 3 shows typical SFM images on mica of star-like nanogel **5** prepared in anisole and decalin. Furthermore, to obtain information about their sizes, the average values from 50 images were also obtained (Table 2). The sizes of star-like nanogels were notably different, and the diameter and height values in decalin were more than triple than those in anisole. The size difference reasonably corresponded to the R_g values, and the solvent-controlled formation of star-like nanogels was also confirmed by the SFM observations.

Conclusion

We demonstrated the solvent quality-controlled formation of star-like nanogels via the cross-linking reaction of diblock copolymers or dynamic covalent exchange reaction among alkoxyamine untis. The two types of diblock copolymers, consisting of PSt block and PMMA block with alkoxyamine units in their side chains, were synthesized by ATRP techniques. The cross-linking reaction was performed in decalin (good solvent for PSt and poor solvent for PMMA) and in anisole (good solvent for both PSt and PMMA), and the M_w and R_g values prepared in decalin were notably larger than those in anisole. These results could be due to the difference in the formation process of star-like nanogels. We believe such solvent-controlled formation of star-like nanogels could be applied to more complicated macromolecular architecture systems.

Acknowledgment. The authors gratefully acknowledge the financial support of a Grant-in-Aid for Scientific Research (20350057) from the Ministry of Education, Culture, Science, Sports and Technology of Japan. The present work is also supported by a Grant-in-Aid for the Global COE Program, "Science for Future Molecular Systems" from the Ministry of Education, Culture, Science, Sports and Technology of Japan. Y.A. acknowledges the financial support of a Grant-in-Aid for JSPS Fellows. Drs. Sono Sasaki and Hiroyasu Masunaga of Japan Synchrotron Radiation Research Institute and Dr. Yasushi Okamoto of Denso Corporation are acknowledged for their help on SAXS measurements. The synchrotron radiation experiments were performed at BL40B2 and BL19B2 in the SPring-8 with the approval of the Japan Synchrotron Radiation Research Institute (JASRI) (Proposal No. 2008B1734 and 2009A1966).

Supporting Information Available: Measurements, GPC curves, M_w, and R_g under several conditions. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Liu, S.; Weaver, J. V. M.; Tang, Y.; Billingham, N. C.; Armes, S. P. *Macromolecules* **2002**, *35*, 6162–6131. (b) Discher, D. E.; Eisenberg, A. *Science* **2002**, *297*, 967–973. (c) Riess, G. *Prog. Polym. Sci.* **2003**, *28*, 1107–1170. (d) Rodríguez-Hernández, J.; Chécot, F.; Gnanou, Y.; Lecommandoux, S. *Prog. Polym. Sci.* **2005**, *30*, 691–724. (e) Sakellariou, G.; Avgeropoulos, A.; Hadjichristidis, N.; Mays, J. W.; Baskaran, D. *Polymer* **2009**, *50*, 6202–6211. (f) He, J.; Tong, X.; Zhao, Y. *Macromolecules* **2009**, *42*, 4845–4852.

(2) Yusa, S.-i.; Shimada, Y.; Mitsukami, Y.; Yamamoto, T.; Morishima, Y. *Macromolecules* **2003**, *36*, 4208–4215.

(3) (a) Yusa, S.-i.; Yamago, S.; Sugahara, M.; Morikawa, S.; Yamamoto, T.; Morishima, Y. *Macromolecules* **2007**, *40*, 5907–5915. (b) Sugihara, S.; Hashimoto, K.; Okabe, S.; Shibayama, M.; Kanaoka, S.; Aoshima, S. *Macromolecules* **2004**, *37*, 336–343.

(4) Chang, C.; Wei, H.; Feng, J.; Wang, Z.-C.; Wu, X.-J.; Wu, D.-Q.; Cheng, S.-X.; Zhang, X.-Z.; Zhuo, R.-X. *Macromolecules* **2009**, *42*, 4838–4844.

(5) Utiyama, H.; Takenaka, K.; Mizumori, M.; Fukuda, M.; Tsunashima, Y.; Kurata, M. *Macromolecules* **1974**, *7*, 515–520.

(6) Kotaka, T.; Tanaka, T.; Hattori, M.; Inagaki, H. *Macromolecules* **1978**, *11*, 138–145.

(7) Simone, P. M.; Lodge, T. P. *Macromol. Chem. Phys.* **2007**, *208*, 339–348.

(8) Kumaki, J.; Nishikawa, Y.; Hashimoto, T. *J. Am. Chem. Soc.* **1996**, *118*, 3321–3322.

(9) Chung, B.; Park, S.; Chang, T. *Macromolecules* **2005**, *38*, 6122–6127.

(10) Blencowe, A.; Tan, J. F.; Goh, T. K.; Qiao, G. G. *Polymer* **2009**, *50*, 5–32.

(11) (a) Amamoto, Y.; Higaki, Y.; Matsuda, Y.; Otsuka, H.; Takahara, A. *Chem. Lett.* **2007**, *36*, 774–775. (b) Amamoto, Y.; Maeda, T.; Kikuchi, M.; Otsuka, H.; Takahara, A. *Chem. Commun.* **2009**, 689–691.

(12) Amamoto, Y.; Higaki, Y.; Matsuda, Y.; Otsuka, H.; Takahara, A. *J. Am. Chem. Soc.* **2007**, *129*, 13298–13304.

(13) Amamoto, Y.; Kikuchi, M.; Masunaga, H.; Sasaki, S.; Otsuka, H.; Takahara, A. *Macromolecules* **2010**, *43*, 1785–1791.

(14) Hawker, C. J.; Barclay, G. G.; Dao, J. *J. Am. Chem. Soc.* **1996**, *118*, 11467–11471.

(15) (a) Otsuka, H.; Aotani, K.; Higaki, Y.; Takahara, A. *Chem. Commun.* **2002**, 2838–2839. (b) Otsuka, H.; Aotani, K.; Higaki, Y.; Takahara, A. *J. Am. Chem. Soc.* **2003**, *125*, 4064–4065. (c) Higaki, Y.; Otsuka, H.; Takahara, A. *Macromolecules* **2004**, *37*, 1696–1701. (d) Yamaguchi, G.; Higaki, Y.; Otsuka, T.; Takahara, A. *Macromolecules* **2005**, *38*, 6316–6320. (e) Otsuka, H.; Aotani, K.; Higaki, Y.; Amamoto, Y.; Takahara, A. *Macromolecules* **2007**, *40*, 1429–1434. (f) Amamoto, Y.; Kikuchi, M.; Masunaga, H.; Sono, S.; Otsuka, H.; Takahara, A. *Macromolecules* **2009**, *42*, 8733–8738.

(16) Higaki, Y.; Otsuka, H.; Takahara, A. *Macromolecules* **2006**, *39*, 2121–2125.

(17) Jackson, A. W.; Fulton, D. A. *Macromolecules* **2010**, *43*, 1069–1075.

(18) Matyjaszewski, K.; Xia, J. *Chem. Rev.* **2001**, *101*, 2921–2990.

(19) Wang, X.-S.; Luo, N.; Ying, S.-K. *Polymer* **1999**, *40*, 4157–4161.

(20) Fukuda, M.; Fukutomi, M.; Kato, Y.; Hashimoto, T. *J. Polym. Sci., Polym. Phys. Ed.* **1974**, *12*, 871–890.