Controlled/"Living" Polymerization of Sulfobetaine Monomers Directly in Aqueous Media via RAFT†

Michael S. Donovan,‡ Brent S. Sumerlin,‡ Andrew B. Lowe,§ and Charles L. McCormick*,‡,§

Department of Polymer Science, University of Southern Mississippi, Hattiesburg, Mississippi 39406-0076, and Department of Chemistry and Biochemistry, University of Southern Mississippi, Hattiesburg, Mississippi 39406-5043

Received June 26, 2002
Revised Manuscript Received September 3, 2002

Sulfobetaines, indeed betaines in general, are interesting for numerous reasons that include antipolyelectrolyte behavior in aqueous salt solution[1] and their bio/hemocompatible properties.[2] Numerous examples exist of polybetaines synthesized via conventional free radical polymerization and include those reported by McCormick et al.,[3] Galin et al.,[4] Laschewsky et al.,[5] and Salamone et al.,[6] to name but a few.

Our group has a long-standing interest in the synthesis and characterization of water-soluble (co)polymers. Recently, we have been particularly interested in the controlled synthesis, and application, of homo- and block copolymers in both aqueous and nonaqueous media prepared via reversible addition−fragmentation chain transfer (RAFT) polymerization.[7] Herein we report the first examples describing the *controlled* polymerization of acrylamido-, methacrylic-, and styrenic-based sulfobetaine monomers directly in aqueous salt solution via RAFT (see Figure 1).

Very few examples have been reported concerning the direct synthesis of controlled-structure/near-monodisperse polymeric betaines. The first were reported by Lowe, Billingham, and Armes[8] and were synthesized by the postpolymerization modification, with 1,3-propane sultone, of near-monodisperse poly(2-dimethylamino)-ethyl methacrylate homopolymers, prepared by group transfer polymerization. Subsequently, sulfobetaine block copolymers were reported using the same methodology.[9] The first examples of polybetaines synthesized by RAFT were those reported by Donovan, Lowe, and McCormick,[10] in which poly(*N*-(2-*N*,*N*-dimethylamino-ethyl)-*N*-acrylamide) (M_n = 9300 and M_w/M_n = 1.23) was homo- and copolymerized via RAFT using benzyl dithiobenzoate as the RAFT CTA. The homopolymer was then derivatized with 1,3-propane sultone to yield the corresponding poly(sulfopropylbetaine). In related work, Jaeger et al.[11] synthesized poly(4-vinylpyridine) by nitroxide-mediated polymerization and then derivatized the precursor (co)polymer to yield the corresponding carboxy- or sulfobetaine. More recently, Lobb et al.[12] reported the direct polymerization of 2-methacryloyloxyethyl phosphorylcholine in aqueous media via atom transfer radical polymerization (ATRP). Although the conditions employed were extremely facile, ATRP suffers from restricted monomer choice and postpolymerization catalyst contamination—a potentially serious issue for in vivo applications. During the preparation of this paper, Arotçaréna et al.[13] disclosed the synthesis of AB diblock copolymers, via RAFT in *organic* media, of *N*-isopropylacrylamide and 3-[*N*-(3-methacrylamidopropyl)-*N*,*N*-dimethyl]ammoniopropanesulfonate. The authors used benzyl dithiobenzoate as the RAFT chain transfer agent (CTA) and clearly state that the primary objective was to obtain the desired diblock architecture and *not* necessarily to synthesize the diblocks in a *controlled* fashion. Indeed, neither polydispersity values for the diblocks, kinetic plots, or size exclusion chromatograms were reported to confirm either block copolymer architecture or the controlled nature of the polymerizations.

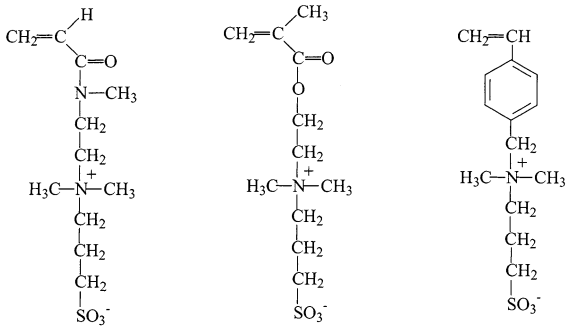

Figure 1. Chemical structures of 3-[2-(*N*-methylacrylamido)-ethyldimethylammonio]propanesulfonate (MAEDAPS), 3-[*N*-(2-methacroyloyethyl)-*N*,*N*-dimethylammonio]propanesulfonate (DMAPS), and 3-(*N*,*N*-dimethylvinylbenzylammonio)-propanesulfonate (DMVBAPS).

In the work reported here, 3-[2-(*N*-methylacrylamido)-ethyldimethylammonio]propanesulfonate (MAEDAPS), 3-[*N*-(2-methacroyloyethyl)-*N*,*N*-dimethylammonio]propanesulfonate (DMAPS), and 3-(*N*,*N*-dimethylvinylbenzylammonio)propanesulfonate (DMVBAPS) were polymerized in *aqueous* salt solution (0.5 M NaBr) at 70 °C using sodium 4-cyanopentanoic acid dithiobenzoate (CTPNa)[7c] (9.98×10^{-2} mmol) as the RAFT CTA and 4,4′-azobis(4-cyanopentanoic acid) (V-501) (2.02×10^{-2} mmol) as the initiating species, with the CTA/I ratio held constant at ∼5/1 and a [monomer] = 0.706 M. In all instances, the target DP was 177. The polymerization solutions were purged for 30 min with argon to remove oxygen prior to the addition of V-501. Polymerizations were conducted for varying times depending on the monomer. DMVBAPS was left for ∼200 min prior to quenching, while both MAEDAPS and DMAPS were left for ∼560 min. Aliquots were withdrawn at predetermined time intervals for analysis by aqueous size exclusion chromatography (ASEC—using an eluent of 80% 0.5 M NaBr/20% acetonitrile, a Viscotek TSK Viscogel 4000PW$_X$L column, and Polymer Labs LC 1200 UV/vis, Wyatt Optilab DSP interferometric refractometer, and Wyatt DAWN EOS multiangle laser light scattering detectors; see Table 1). ASEC was likewise employed for the determination of conversion by monitoring residual monomer using the RI detector.

From Table 1, it is evident that we observe excellent control over the molecular weight for the CTPNa-mediated polymerizations, at least in the case of the DMAPS and DMVBAPS polymerizations. In all instances, a target DP of 177 was aimed for, yielding target molecular weights of ∼49 200, 49 100, and 49 900

† Number 90 in a series entitled "Water-Soluble Polymers".
‡ Department of Polymer Science.
§ Department of Chemistry and Biochemistry.
* To whom correspondence should be addressed.

10.1021/ma0209996 CCC: $22.00
Published on Web 10/04/2002

Table 1. Summary of the Molecular Weights and Polydispersities for the Homopolymers of MAEDAPS, DMAPS, and DMVBAPS

sample	conv (%)[b]	d*n*/dc[c]	theor mol wt	obsd mol wt (M_n)[d]	M_w/M_n[d]
PMAEDAPS[a]	91	0.1533 ± 0.0036	44 100	58 250	1.08
PDMAPS[a]	93	0.1293 ± 0.0008	45 700	47 500	1.04
PDMVBAPS[a]	90	0.1578 ± 0.0021	44 900	47 200	1.06

[a] Prepared using 4-cyanopentanoic acid dithiobenzoate as the RAFT CTA. [b] As determined by the residual monomer concentration employing the RI detector. [c] Measured using Wyatt's Optilab differential refractometer in 80% 0.5 M NaBr/20% acetonitrile. [d] As determined by aqueous size exclusion chromatography in 80% 0.5 M NaBr/20% acetonitrile using Wyatt's DAWN EOS multiangle laser light scattering detector.

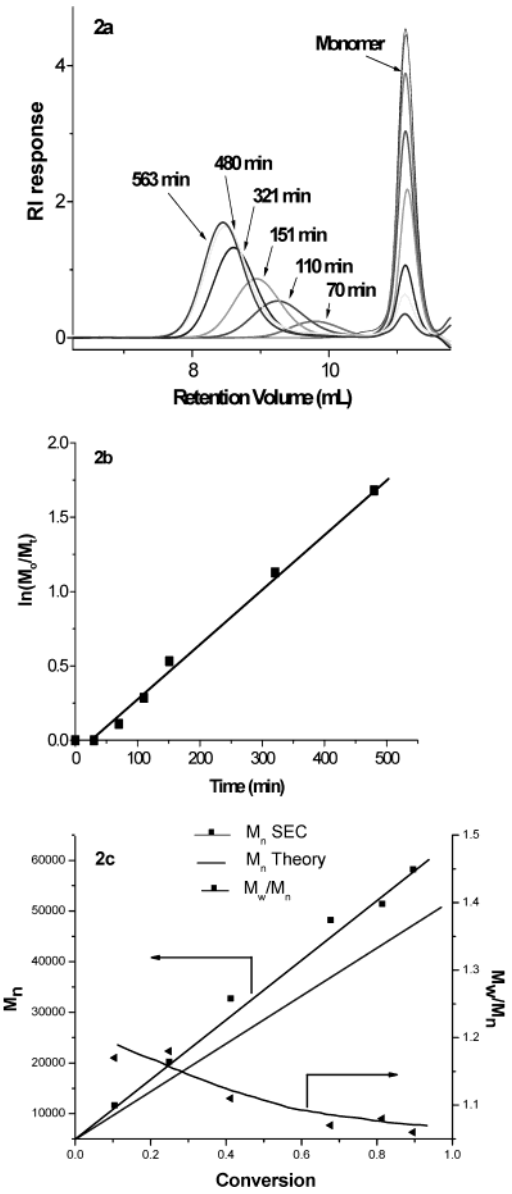

Figure 2. Aqueous size exclusion chromatograms for the controlled polymerization of MAEDAPS showing the evolution of molecular weight with time (a) and the corresponding pseudo-first-order kinetic plot (b) and the M_n vs conversion data (c).

for MAEDAPS, DMAPS, and DMVBAPS, respectively, at 100% conversion.

Figure 2 shows the aqueous size exclusion chromatograms demonstrating the evolution of molecular weight with polymerization time (a), the pseudo-first-order kinetic plot (b), and the molecular weight vs conversion plot (c). The aqueous size exclusion chromatograms clearly show the peak shift to lower retention volume with increasing polymerization time, which is at least qualitatively indicative of a controlled polymerization. The chromatograms are unimodal and symmetrical with no evidence of either high or low molecular weight impurity indicative of termination products. We have found that the aqueous polymerization of charged monomers via RAFT generally proceed smoothly with few side reactions such as termination by radical−radical coupling of polymer chains when conducted under appropriate reaction conditions.[7c,d]

Figure 2b shows the plot of $\ln(M_0/M_t)$ vs time. We observe an induction period of ∼30 min, which is consistent with our previous observations regarding the use of CTPNa as the CTA, after which the polymerization exhibits pseudo-first-order kinetics, consistent with a controlled polymerization. Figure 2c shows the plot of M_n vs conversion. M_n values were determined using a Wyatt DAWN EOS online light scattering detector; the d*n*/dc for PMAEDAPS was determined to be 0.1533 ± 0.0036. We observe reasonable agreement between the observed and theoretical molecular weights for the polymerization of MAEDAPS, although the experimentally determined M_n values are consistently higher than the predicted values. At present we are unsure of the cause of the deviations but is possibly due to low-level CTA hydrolysis. (We are currently in the process of exploring this as a possible "side reaction".) Most importantly, the evolution of molecular weight with conversion is linear, and the resulting polydispersity is low (M_w/M_n = 1.08), thus confirming the controlled nature of the polymerization. Similar results (Figure 3) were obtained for the polymerization of both DMAPS and DMVBAPS.

Consider first the DMVBAPS polymerization (Figure 3a−c). The kinetic plot indicates a short induction period (∼50 min), after which the kinetics follow a pseudo-first-order relationship. The size exclusion chromatograms confirm this with little conversion during the first 45 min followed by an increase in molecular weight with polymerization time. All traces are unimodal with no evidence of high molecular weight species arising from termination products/uncontrolled polymerization. The increase in molecular weight with conversion is linear and is in reasonable agreement with the theoretical values.

DMAPS, on the other hand (Figure 3d−f), shows a much more rapid rate of polymerization than either MAEDAPS or DMVBAPS. A shorter induction period of ∼10 min is observed for DMAPS, after which the polymerization proceeds rapidly, reaching ∼97% conversion in ∼160 min. The SEC chromatograms also confirm rapid polymerization, with little change observed in the molecular weight (i.e., retention time) after ∼150 min. The increase in molecular weight with conversion is linear and agrees closely with the predicted molecular weights.

Herein we have demonstrated one of the primary advantages of RAFT over other controlled radical polymerization techniques, namely its versatility with respect to monomer choice. Controlled structure homopolymers of acrylamido-, methacrylic-, and styrenic-based sulfobetaines have been reported employing sodium 4-cyanopentanoic acid dithiobenzoate as the RAFT CTA. Significantly, the polymerizations were

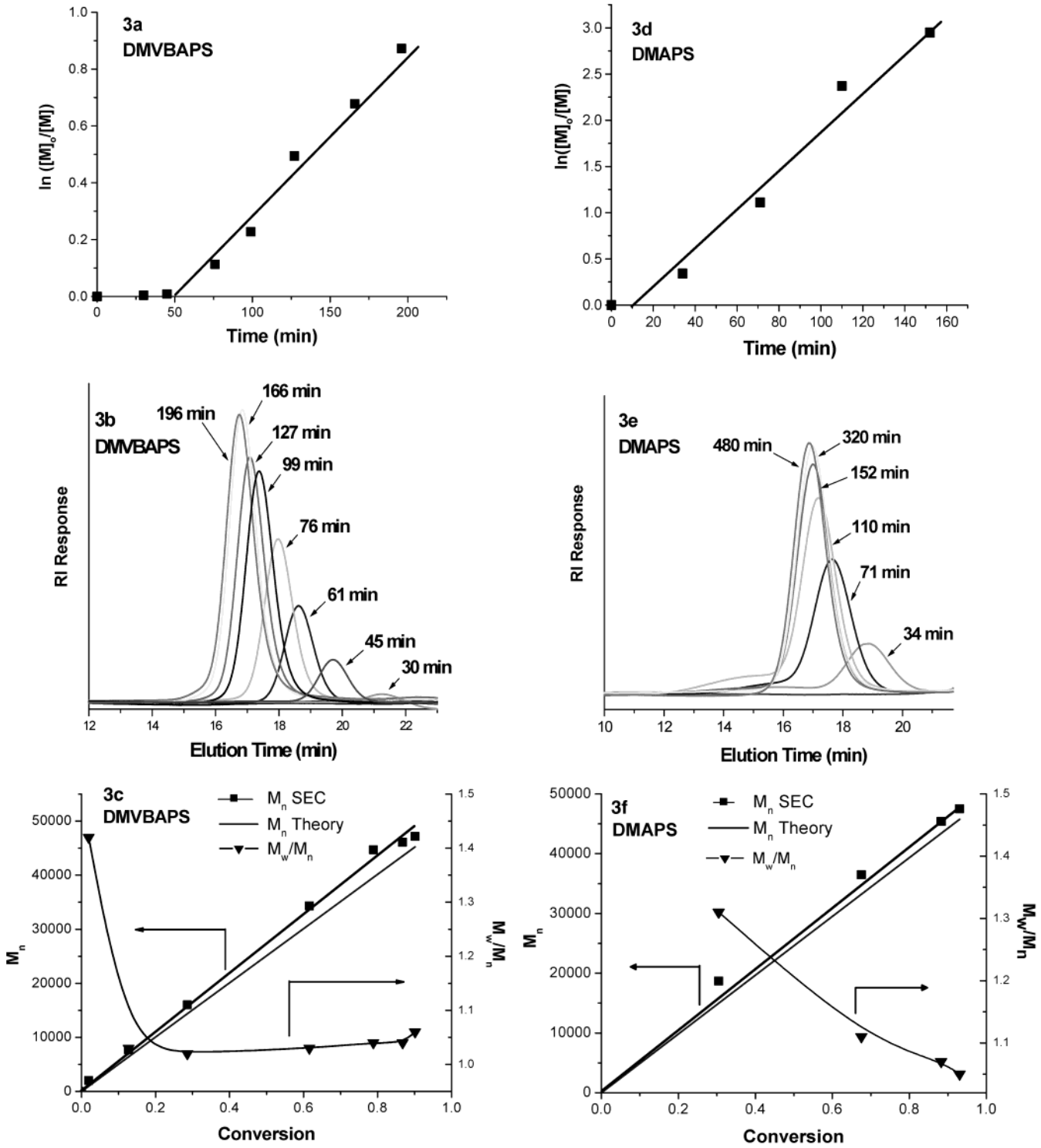

Figure 3. Pseudo-first-order kinetic plots for DMVBAPS and DMAPS (a, d), the aqueous size exclusion chromatograms demonstrating evolution of molecular weight for both species (b, e), and the M_n vs conversion plots (c, f).

conducted directly in aqueous media. All the polymerizations exhibit pseudo-first-order kinetics as well as linear increases in molecular weight with conversions—both good indicators of controlled polymerization. Molecular weight control is best for both DMVBAPS and DMAPS. Interestingly, the rates of polymerization for the three monomers increase in the order DMAPS > DMVBAPS > MAEDAPS (methacrylate > styrenic > acrylamido) under the conditions studied here. The slower rate of polymerization for MAEDAPS is interesting considering that the rate constant for propagation is typically higher for acrylamido-based monomers than either styrenics or methacrylates under classical free radical polymerization conditions. The slower kinetics exhibited by MAEDAPS may be indicative of a higher rate constant of addition for the propagating MAEDAPS macroradical toward a macro-CTA or, possibly, a lower rate constant for fragmentation of the macro-RAFT intermediate radical.[14] Considering the higher reactivity and lower bulk of the MAEDAPS acrylamido radical compared to those of the DMAPS methacrylate radical, contributions from both possibilities are likely. These sulfopropylbetaine homopolymers are currently being employed as macro-CTAs for the synthesis of novel

stimuli-responsive AB diblock copolymers and will be the subject of a future publication.

Acknowledgment. Financial support for this research from GelTex Pharmaceuticals Ltd. and the U.S. Department of Energy is gratefully acknowledged.

References and Notes

(1) Lowe, A. B.; McCormick, C. L. In *Stimuli-Responsive Water Soluble and Amphiphilic Polymers*; McCormick, C. L. Ed.; ACS Symposium Series 780; American Chemical Society: Washington, DC, 2001; p 1.

(2) Lowe, A. B.; Vamvakaki, M.; Wassall, M. A.; Wong, L.; Billingham, N. C.; Armes, S. P.; Lloyd, A. W. *J. Biomed. Mater. Res.* **2000**, *52*, 88.

(3) (a) McCormick, C. L.; Salazar, L. C. *Polymer* **1992**, *33*, 4617. (b) Kathmann, E. E.; Davis, D. D.; McCormick, C. L. *Macromolecules* **1994**, *27*, 3156. (c) Kathmann, E. E.; White, L. A.; McCormick, C. L. *Macromolecules* **1997**, *30*, 5297. (d) Armentrout, R. S.; McCormick, C. L. *Macromolecules* **2000**, *33*, 419.

(4) (a) Monroy Soto, V. M.; Galin, J. C. *Polymer* **1984**, *25*, 121. (b) Ehrmann, M.; Mathis, A.; Meurer, B.; Scheer, M.; Galin, J. C. *Macromolecules* **1992**, *25*, 2253. (c) Mathis, A.; Zheng, Y. L.; Galin, J. C. *Makromol. Chem., Rapid Commun.* **1986**, *7*, 333. (d) Pujol-Fortin, M. L.; Galin, J. C. *Macromolecules* **1991**, *24*, 4523.

(5) (a) Bonte, N.; Laschewsky, A. *Polymer* **1996**, *10*, 2011. (b) Favresse, P.; Laschewsky, A. *Polymer* **2001**, *42*, 2755.

(6) (a) Salamone, J. C.; Volksen, W.; Olson, A. P.; Israel, S. C. *Polymer* **1978**, *19*, 1157. (b) Salamone, J. C.; Volksen, W.; Israel, S. C.; Olson, A. P.; Raia, D. C. *Polymer* **1977**, *18*, 1058.

(7) (a) Chiefari, J.; Chong, Y. K.; Ercole, F.; Krstina, J.; Le, T. P.; Mayadunne, R. T. A.; Meijs, G. F.; Moad, G.; Moad, C. L.; Rizzardo, E.; Thang, S. H. *Macromolecules* **1998**, *31*, 5559. (b) Rizzardo, E.; Chiefari, J.; Mayadunne, R. T. A.; Moad, G.; Thang, S. H. In *Controlled/Living Radical Polymerization*; Matyjaszewski, K., Ed.; ACS Symposium Series 768; American Chemical Society: Washington, DC, 2000; p 278. (c) Mitsukami, Y.; Donovan, M. S.; Lowe, A. B.; McCormick, C. L. *Macromolecules* **2001**, *34*, 2248. (d) Sumerlin, B. S.; Donovan, M. S.; Mitsukami, Y.; Lowe, A. B.; McCormick, C. L. *Macromolecules* **2001**, *34*, 6561. (e) Donovan, M. S.; Lowe, A. B.; Sumerlin, B. S.; McCormick, C. L. *Macromolecules* **2002**, *35*, 4123. (f) Donovan, M. S.; Sanford, T. A.; Lowe, A. B.; Sumerlin, B. S.; Mitsukami, Y.; McCormick, C. L. *Macromolecules* **2002**, *35*, 4570. (g) Lowe, A. B.; McCormick, C. L. *Aust. J. Chem.*, in press. (g) Lowe, A. B.; Sumerlin, B. S.; Donovan, M. S.; McCormick, C. L. *J. Am. Chem. Soc.*, in press.

(8) Lowe, A. B.; Billingham, N. C.; Armes, S. P. *Chem. Commum.* **1996**, 1555.

(9) (a) Tuzar, Z.; Popisil, H.; Lowe, A. B.; Baines, F. L.; Billingham, N. C.; Armes, S. P. *Macromolecules* **1997**, *30*, 2509. (b) Bütün, V.; Bennett, C. E.; Vamvakaki, M.; Lowe. A. B.; Billingham, N. C.; Armes, S. P. *J. Mater. Chem.* **1997**, *7*, 1693. (c) Lowe, A. B.; Billingham, N. C.; Armes, S. P. *Macromolecules* **1999**, *32*, 2141.

(10) Donovan, M. S.; Lowe, A. B.; McCormick, C. L. *Poly. Prepr.* **1999**, *40* (*2*), 281.

(11) (a) Jaeger, W.; Wendler, U.; Lieske, A.; Bohrisch, J.; Wandrey, C. *Macromol. Symp.* **2000**, *161*, 87. (b) Bohrisch, J.; Schimmel, T.; Englehardt, H.; Jaeger, W. *Macromolecules* **2002**, *35*, 4143.

(12) Lobb, E. J.; Ma, I.; Billingham, N. C.; Armes, S. P.; Lewis, A. L. *J. Am. Chem. Soc.* **2001**, *123*, 7913.

(13) Arotçaréna, M.; Heise, B.; Ishaya, S.; Laschewsky, A. *J. Am. Chem. Soc.* **2002**, *124*, 3787.

(14) (a) Moad, G.; Chiefari, J.; Chong, Y. K.; Krstina, J.; Mayadunne, R. T. A; Postma, A.; Rizzardo, E.; Thang, S. H. *Polym. Int.* **2000**, *49*, 993. (b) Barner-Kowollik, C.; Quinn, J. F.; Nguyen, T. L. U.; Heuts, J. P. A.; Davis, T. P. *Macromolecules* **2001**, *34*, 7849.

MA0209996