Supramacromolecular Assembly Driven by Complementary Molecular Recognition

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Received December 18, 2006
Revised Manuscript Received February 1, 2007

Nature utilizes template-directed assembly,[1] wherein one molecule (or macromolecule) promotes the formation of a larger ensemble via molecular recognition, to construct well-defined biopolymers such as DNA, RNA, and proteins. These examples have inspired chemists, particularly in the area of supramolecular chemistry, to employ the concept of template-directed assembly[1] to synthesize artificial receptors[2] and other complex architectures such as interlocked molecules.[3] The primary role of the template is to organize and orient other molecules into a specific spatial arrangement as well as promote the formation of a single assembly in deference to other assemblies which may exist. The template has the ability to control the size, shape, and order of the interacting molecules.

The synthesis of well-defined linear and dendritic polymers is well established,[4] and many research groups have directed their efforts[5] toward understanding the assembly of polymers in both the solution and solid states. Polymeric self-assembly,[6] particularly with block copolymers, into micelles, vesicles, toroids, and wormlike assemblies has gained increasing attention in recent years for applications ranging from microelectronics to drug delivery.[7] Typically, the architectures formed in solution are dependent upon the length of the individual blocks and solvent-driven phase separation. The ability to control the self-assembly of polymers despite their length and constitution could potentially be useful for creating nanostructures of controlled shape and size.

Well-defined macromolecular templates provide a route to control polymeric self-assembly at the nanoscale by employing specific noncovalent interactions. Several research groups[8−11] investigated well-defined polymers as templates for self-assembly using a wide range of molecular recognition elements. Weck and co-workers[8] have employed ring-opening metathesis polymerization to construct linear polymers presenting hydrogen bonding and metal−ligand coordination sites for binding small molecules. In contrast to linear templates, Meijer and co-workers[9] utilized urea-functionalized poly(propyleneimine) dendrimers as a spherical base around which guest molecules bearing glycinylurea groups bound noncovalently to the dendrimer surface. Larger supramacromolecular assemblies using ionic interactions involving poly(amidoamine) (PAMAM) dendrimers were constructed by Tomalia and co-workers[10] to construct core−shell tecto(dendrimers).

In contrast to amphiphilic diblock copolymers, self-assembly driven by molecular recognition does not rely upon the volume fraction and solvent selectivity of the assembling polymer block. Instead, the association of two complementary functionalities on the template host and guest molecule (or macromolecule) determines its assembly. Herein, we describe the template-promoted supramacromolecular assembly of well-defined polymers using complementary molecular recognition elements. Commercially available generation 4 poly(amidoamine) (G4-PAMAM) dendrimer with 64 amino groups located at the periphery was used as the macromolecular template for self-assembly (Scheme 1). Poly(ethylene glycol) **2** (M_n = 5000) possesses a carboxylic acid functionality at a single terminus to interact with the peripheral dendrimer amines. Spherical micelle-like assemblies were formed when the carboxylic acid of the linear polymer interacted with the amino groups of the dendrimer to reversibly anchor the polymers to the dendrimer surface.

The formation of the spherical assemblies of the polymer **2** with G4-PAMAM **1** was monitored (Figure 1) by ^{1}H NMR spectroscopy in D_2O. In the absence of polymer **2**, the resonances for the two methylenes (H_A and H_B) closest to the peripheral amines are present at 2.14 and 3.68 ppm, respectively. As polymer **2** was titrated to the solution of dendrimer, these signals were observed to shift downfield. The resonances for H_A and H_B became broadened at intermediate stoichiometries where the ratio of dendritic terminal amines to polymer **2** is less than 1:1, which may represent the translational movement of the carboxylic acids across the dendrimer surface. When this ratio is greater than 1:1, the H_A and H_B signals appeared as a more distinct triplet. On the basis of a careful titration of polymer **2** to a solution of dendrimer **1**, we estimate that when ca. 1 equiv of polymer **2** is added, the change in the chemical shift of H_A is nearly at its maximum (Supporting Information). Thus, we observe near quantitative binding of polymer **2** to the dendrimer surface (on average, we estimate 64 molecules of polymer **2** per dendrimer, molecular weight = ca. 334 214). In comparison, titration of acetic acid (as a model compound) to a solution of dendrimer produced a similar curve, which indicates that the acid−base interactions are not attenuated by the larger size of polymer **2**.

Nonpolar solvents such as $CDCl_3$, CD_3CN, and C_6D_6 could not be used in our investigations due to the lack of solubility of the dendrimer in these solvents. Even when polymer **2** was present in the solution, the solubility of the dendrimer did not visibly increase. The dendrimer−polymer interaction in more polar solvents like $(CD_3)_2CO$ also were not observed due to lack of solubility. Complexes were, however, formed (Figure 2b) in polar solvents such as CD_3OD, DMSO-d_6, and DMF-d_7. The partial ^{1}H NMR spectra confirming the interaction of polymer **2** with G4-PAMAM in DMSO-d_6 are shown in Figure 3. In nonprotic solvents such as DMSO-d_6, the signal representing the amide protons are present as a broad signal. The binding of polymer **2** to the dendrimer was observed to influence the chemical shift of the peripheral amide proton resonances. Upon the introduction of 64 equiv of polymer **2**, a new amide signal representing the peripheral amides emerged. The formation of the dendrimer−polymer complex was reversed with the addition of excess triethylamine.

Following the formation of these spherical assemblies in DMSO or DMF, the complex could be isolated by precipitation. Although the formation of the complex could not be achieved in nonpolar solvents, the isolated polymer−dendrimer complex was readily soluble in these solvents. Interestingly, when the complex was dissolved in $CDCl_3$, a solvent incompatible with the dendrimer itself, the dendritic component of the complex

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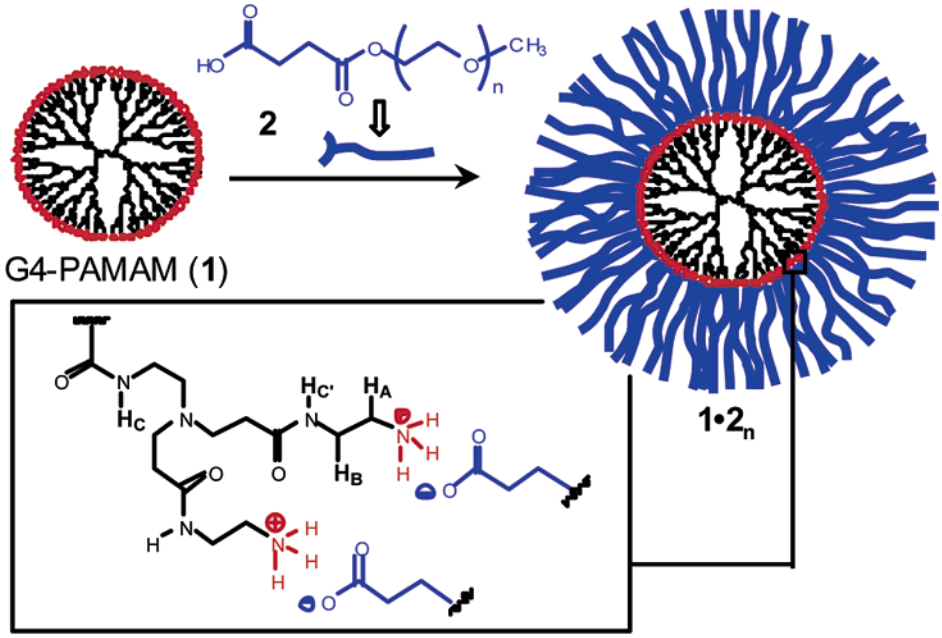
10.1021/ma062895r CCC: $37.00
Published on Web 02/20/2007

Scheme 1. Formation of Spherical Complex 1·2$_n$ Mediated by Molecular Recognition between the Peripheral Amines of Dendrimer 1 with the Carboxylic Acid of Polymer 2



was observed (Figure 2c) to adopt a collapsed state. This is represented by the diminished H_C signal in the ^1H NMR spectrum relative to the external $H_{C'}$. Thus, while the complex could not be formed in nonpolar solvents, the *preformed* complex can be redissolved in these solvents such as $CDCl_3$.

The encapsulation of metal salts within PAMAM dendrimers has been extensively investigated[12] for ions such as Cu^{2+}, Ni^{2+}, Pt^{2+}, Pd^{2+}, and Au^{3+}. UV−vis spectroscopic investigations were undertaken in order to demonstrate that the supramacromolecular complex is capable of incorporating metal salts. When a methanolic solution of $CuNO_3$ was added to the isolated assembly of **1·2$_n$** in toluene, the metal salt became solubilized in the organic solvent. There was no observable precipitation even after a period of 3 weeks, suggesting a well-stabilized polymer−metal complex. The incorporation of Cu^{2+} ions within the spherical complex was confirmed (Figure 3) by the presence

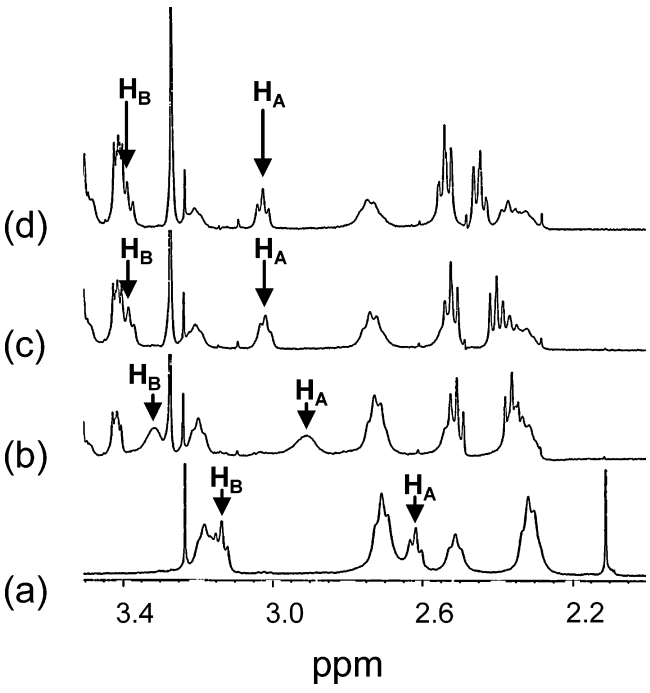


Figure 1. Partial stacked ^1H NMR spectra (400 MHz, 298 K) in D_2O of a 5 mM solution (based on the peripheral amines) of dendrimer **1** (relative to the peripheral amines) showing the changes in the chemical shifts of the H_A and H_B signals with the addition of (a) 0, (b) 32, (c) 64, and (d) 96 equiv of polymer **2**. The equivalents are determined on a per dendrimer basis.

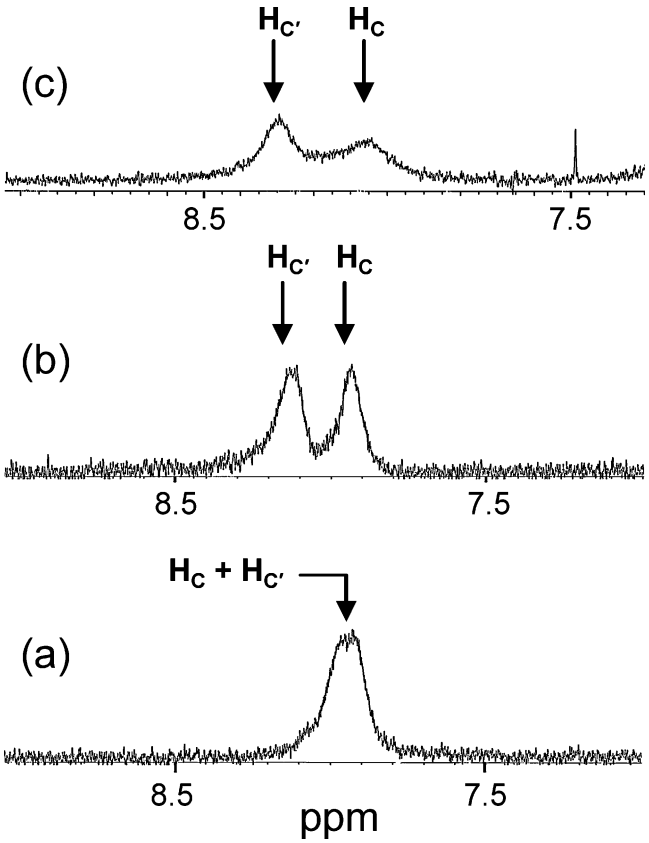


Figure 2. Partial ^1H NMR spectra (400 MHz, 298 K) showing the amide signals (H_C and $H_{C'}$) of the dendrimer: (a) dendrimer **1** in DMSO-d_6, (b) **1·2$_n$** in DMSO-d_6, and (c) **1·2$_n$** in $CDCl_3$. In the case of (c), **1·2$_n$** was first preformed and isolated from DMSO prior to redissolving in $CDCl_3$.

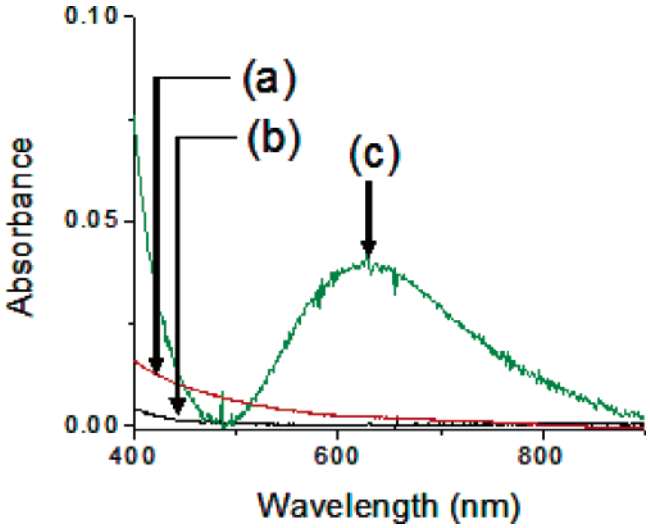


Figure 3. UV−vis absorption spectra of (a) a 2 μM solution of **1·2**$_n$ in toluene, (b) $CuNO_3$ in toluene (insoluble), and (c) **1·2**$_n$ in the presence of 55 equiv of $CuNO_3$ relative to the complex.

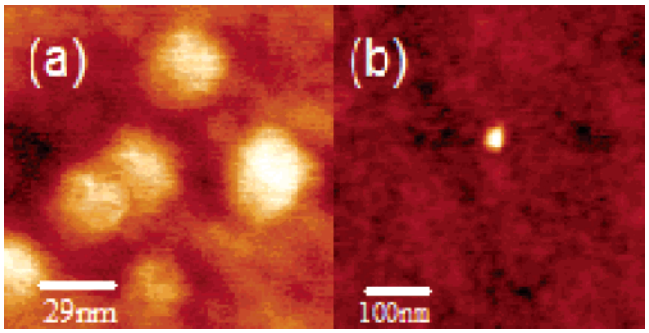


Figure 4. AFM images of complex **1·2**$_n$ on a silicon substrates. Samples were prepared by spin-casting a (a) 0.1 wt % or (b) 0.001 wt % solution of the self-assembled complex in toluene.

of λ_{max} at 630 nm, which corresponds to the Cu^{2+} d−d transition in a ligand field. In the absence of any metal ions this absorbance is not present. In addition, Cu^{2+} cannot be solublized in toluene in the sole presence of polymer **2**, which indicates that the supramolecular complex hosts the metal ions within its dendritic core.

The formation of spherical supramolecular assembly **1·2**$_n$ was also verified by atomic force microscopy (AFM) (Figure 4). Dilute solutions (0.1 and 0.001 wt %) of the complexes in toluene were spun-cast onto a silicon wafer and imaged. Isolated spheres were observed on the surface when 0.001 wt % solutions of the complexes was used. The diameter of complex **1·2**$_n$ on a silicon surface is ∼29 nm. The diameters determined by AFM likely do not accurately reflect the true diameters of the spherical complex. We presume that the supramolecular assemblies on the surface are not perfectly spherical but exist in a flattened state as previously observed[13] for dendrimers and tectomers on mica surfaces. Nevertheless, the AFM data reaffirms the formation of a supramacromolecular spherical complex.

In summary, we have demonstrated the successful self-assembly of a spherical complex driven by molecular recognition and the incorporation of Cu^{2+} ions within the dendrimer core. This approach contrasts traditional synthesis of micellar assemblies using amphiphilic block copolymers in that the formation of the supramolecular structure is independent of the solvent used—provided that the solvents promote strong binding interactions between molecular recognition elements. The benefits of using a templated self-assembly approach such as this one includes the ability to (1) fine-tune the size of the resulting spherical micelle by altering the length and composition of the polymers and (2) increase or decrease the size and composition of the core. Further investigations of these systems in solution and at surfaces are underway, including polymers suitable for cross-linking following the assembly process.

Acknowledgment. The authors thank IBM, and D. Chun thanks the UCLA MCTP program for financial support, James Hedrick and Daniel Sanders for technical discussions, and Dolores Miller, Charles Wade, and Teddie Magbitang for technical assistance.

Supporting Information Available: Experimental section and plot from ^{1}H NMR titration experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Busch, D. H. *J. Inclusion Phenom.* **1992**, *12*, 389. (b) Anderson, S.; Anderson, H. L.; Sanders, J. K. M. *Acc. Chem. Res.* **1993**, *26*, 469. (c) Lehn, J. M. *Supramolecular Chemistry*; VCH: Weinheim, Germany, 1995. (d) Orgel, L. E. *Acc. Chem. Res.* **1995**, *28*, 109. (e) Philp, D.; Stoddart, J. F. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1154. (e) Fyfe, M. C. T.; Stoddart, J. F. *Acc. Chem. Res.* **1997**, *30*, 393.

(2) (a) Rebek, J. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 245. (b) Breslow, R. *Acc. Chem. Res.* **1995**, *28*, 146. (c) Brisig, B.; Sanders, J. K. M.; Otto, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 2171.

(3) (a) Sauvage, J. P. *Acc. Chem. Res.* **1990**, *23*, 319. (b) Chichak, K. S.; Cantrill, S. J.; Pease, A. R.; Chiu, S.-H.; Cave, G. W. V.; Atwood, J. L.; Stoddart, J. F. *Science* **2004**, *304*, 1308. (c) Chatterjee, M. N.; Kay, E. R.; Leigh, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 4058.

(4) (a) Fréchet, J. M. J.; Tomalia, D. A. *Dendrimers and Other Dendritic Polymers*; John Wiley & Sons Ltd.: New York, 2001. (b) Hawker, C. J.; Bosman, A. W.; Harth, E. *Chem. Rev.* **2001**, *101*, 3661. (c) Matyjaszewski, K.; Xia, J. *Chem. Rev.* **2001**, *101*, 2921. (d) Kamigaito, M.; Ando, T.; Sawamoto, M. *Chem. Rev.* **2001**, *101*, 3689. (e) Bosman, A. W.; Vestberg, R.; Heumann, A.; Fréchet, J. M. J.; Hawker, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 715.

(5) (a) Tsuchida, E.; Abe, K. *Adv. Polym. Sci.* **1982**, *45*, 2. (b) Förster, S.; Plantenberg, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 688. (c) Li, Z.; Kesselman, E.; Talmon, Y.; Hillmyer, M. A.; Lodge, T. P. *Science* **2004**, *306*, 98. (d) Hawker, C. J.; Wooley, K. L. *Science* **2005**, *309*, 1200. (e) Segalman, R. A. *Mater. Sci. Eng., R* **2005**, *48*, 191. (f) Grubbs, R. B. *J. Polym. Sci., Part A: Polym. Chem.* **2005**, *43*, 4323. (g) Kim, Y.; Pyun, J.; Fréchet, J. M. J.; Hawker, C. J.; Frank, C. W. *Langmuir* **2005**, *21*, 10444. (h) Pyun, J.; Tang, C.; Kowalewski, T.; Fréchet, J. M. M.; Hawker, C. J. *Macromolecules* **2005**, *38*, 2674. (i) Abetz, V.; Simon, P. F. W. *Adv. Polym. Sci.* **2005**, *189*, 125. (j) Cheng, C.; Qi, K.; Khoshdel, E.; Wooley, K. L. *J. Am. Chem. Soc.* **2006**, *128*, 6808.

(6) For representative examples, see: (a) Gao, Z.; Varshney, S. K.; Wong, S.; Eisenberg, A. *J. Chem. Phys.* **1994**, *27*, 7923. (b) Gohy, J.-F. *Adv. Polym. Sci.* **2005**, *190*, 65. (c) Liu, S.; Weaver, J. V. M.; Tang, Y.; Billingham, N. C.; Armes, S. P.; Tribe, K. *Macromolecules* **2002**, *35*, 6121. (d) Savariar, E. N.; Aathimanikandan, S. V.; Thayumanavan, S. *J. Am. Chem. Soc.* **2006**, *128*, 16224. (e) Zhao, J. Q.; Pearce, E. M.; Kwei, T. K.; Jeon, H. S.; Keseni, P. K.; Balsara, N. P. *Macromolecules* **1995**, *28*, 1972. (f) Discher, B. M.; Won, Y.-Y.; Ege, D. S.; Lee, J. C.-M.; Bates, F. S.; Discher, D. E.; Hammer, D. A. *Science* **1999**, *284*, 1143. (g) Pochan, D. J.; Chen, Z.; Cui, H.; Hales, K.; Qi, K.; Wooley, K. L. *Science* **2004**, *306*, 94. (h) Choi, J.; Hermans, T. M.; Lohmeijer, B. G. G.; Pratt, R. C.; Dubois, G.; Frommer, J.; Waymouth, R. M.; Hedrick, J. L. *Nano Lett.* **2006**, *6*, 1761.

(7) (a) Cuenya, B. R.; Baeck, S.-H.; Jaramillo, T. F.; McFarland, E. W. *J. Am. Chem. Soc.* **2003**, *125*, 12928. (b) Kakizawa, Y.; Kataoka, K. *Adv. Drug Delivery Rev.* **2002**, *54*, 203. (c) Pan, D.; Turner, J. L.; Wooley, K. L. *Macromolecules* **2004**, *37*, 7109. (d) Aizawa, M.; Buriak, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 5877.

(8) (a) Pollino, J. M.; Stubbs, L. P.; Weck, M. *J. Am. Chem. Soc.* **2004**, *126*, 563. (b) Burd, C.; Weck, M. *Macromolecules* **2005**, *38*, 7225. (c) Nair, K. P.; Pollino, J. M.; Weck, M. *Macromolecules* **2006**, *39*, 931.

(9) (a) Baars, M. W. P. L.; Karlsson, A. J.; Sorokin, V.; de Waal, B. F. W.; Meijer, E. W. *Angew. Chem., Int. Ed.* **2000**, *39*, 4262. (b) Boas, U.; Karlsson, A. J.; de Waal, B. F. M.; Meijer, E. W. *J. Org. Chem.* **2001**, *66*, 2136. (c) Precup-Blaga, F. S.; Garcia-Martinez, F. C.;

Schenning, A. P. H. J.; Meijer, E. W. *J. Am. Chem. Soc.* **2003**, *125*, 12953. (d) Pittelkow, M.; Christensen, J. B.; Meijer, E. W. *J. Polym. Sci., Part A: Polym. Chem.* **2004**, *42*, 3792. (e) Broeren. M. A. C.; de Waal, B. F. M.; van Genderen, M. H. P.; Sanders, H. M. H. F.; Fytas, G.; Meijer, E. W. *J. Am. Chem. Soc.* **2005**, *127*, 10334.

(10) (a) Li, J.; Swanson, D. R.; Qin, D.; Brothers, H. M.; Piehler, L. T.; Tomalia, D. A.; Meier, D. J. *Langmuir* **1999**, *15*, 7347. (b) Uppuluri, S.; Swanson, D. R.; Piehler, L. T.; Li, J.; Hagnauer, G. L.; Tomalia, D. A. *Adv. Mater.* **2000**, *12*, 796. (c) Tomalia, D. A.; Brothers, H. M.; Piehler, L. T.; Durst, H. D.; Swanson, D. R. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 5081.

(11) (a) Caminati, G.; Turro, N. J.; Tomalia, D. A. *J. Am. Chem. Soc.* **1990**, *112*, 8515. (b) Kato, T.; Fréchet, J. M. J. *Macromolecules* **1989**, *22*, 3818. (c) Watkins, D. M.; Sayed-Sweet, Y.; Klimash, J. W.; Turro, N. J.; Tomalia, D. A. *Langmuir* **1997**, *13*, 3136. (d) Schadler, V.; Kniese, V.; Thurn-Albrecht, T.; Wiesner, U.; Spiess, H. W. *Macromolecules* **1998**, *31*, 4828. (e) Chechik, V.; Zhao, M.; Crooks, R. M. *J. Am. Chem. Soc.* **1999**, *121*, 4910. (f) Zimmerman, S. C.; Lawless, L. J. *Top. Curr. Chem.* **2001**, *217*, 95. (g) Bakshi, M. S.; Kaura, A.; Miller, J. D.; Paruchuri, V. K. *J. Colloid Interface Sci.* **2004**, *278*, 472. (h) Iwaura, R.; Hoeben, F. J. M.; Masuda, M.; Schenning, A. P. H. F.; Meijer, E. W.; Shimizu, T. *J. Am. Chem. Soc.* **2006**, *128*, 13298.

(12) (a) Zhao, M.; Sun, L.; Crooks, R. M. *J. Am. Chem. Soc.* **1998**, *120*, 4877. (b) Crooks, R. M.; Zhao, M.; Sun, L.; Chechik, R.; Yeung, L. K. *Acc. Chem. Res.* **2001**, *34*, 181. (c) Garcia-Martinez, J. C.; Scott, R. W. J.; Crooks, R. M. *J. Am. Chem. Soc.* **2003**, *125*, 11190. (d) Knecht, M. R.; Garcia-Martinez, J. C.; Crooks, R. M. *Chem. Mater.* **2006**, *18*, 5039.

(13) Li, J.; Piehler, L. T.; Qin, D.; Baker, J. R.; Tomalia, D. A. *Langmuir* **2000**, *16*, 5613.

MA062895R