

# Polymeric Nanoparticles via Noncovalent Cross-Linking of Linear Chains

Myungeun Seo,<sup>†</sup> Benjamin J. Beck,<sup>‡</sup> Jos M. J. Paulusse,<sup>‡</sup> Craig J. Hawker,<sup>\*,‡</sup> and Sang Youl Kim<sup>\*,†</sup>

Department of Chemistry and School of Molecular Science (BK21), KAIST, Daejeon 305-701, Korea, and Materials Research Laboratory and Departments of Chemistry, Biochemistry and Materials, University of California, Santa Barbara, California 93106

Received April 29, 2008; Revised Manuscript Received June 30, 2008

**ABSTRACT:** Novel polymeric nanoparticles were prepared through the chain collapse of linear polymers driven by noncovalent cross-linking of dendritic self-complementary hydrogen-bonding units (SHB). Random copolymers containing SHB units, poly[(methyl methacrylate)-*r*-2-((3,5-bis(4-carbamoyl-3-(trifluoromethyl)phenoxy)benzyloxy)carbonylamino)ethyl methacrylate] (**A1**, **A2**), were synthesized with various incorporation ratios by reversible addition–fragmentation chain transfer (RAFT) polymerization. Dramatically different behavior was observed depending on the level of incorporation of the supramolecular units. At high loadings of **A2** (6% SHB incorporation), intramolecular chain collapse is favored, resulting in the formation of well-defined polymer nanoparticles, which were characterized by scanning force microscopy (SFM), dynamic light scattering (DLS), and viscosity studies. In contrast, analysis of copolymer **A1** (1% SHB incorporation) revealed that chain collapse occurred primarily through intermolecular interactions leading to large aggregates.

## Introduction

The preparation of polymeric nanoparticles has received significant interest in recent years, with promising applications in medicine, for example as drug delivery systems and gene transfection agents, as well as in the enhancement of material properties of common polymers.<sup>1–4</sup> Although the development of discrete nanoparticles with well-defined functionalities and architectures, such as dendrimers, has been a major step toward unlocking the potential of these organic nanostructures for broader applications in nanotechnology,<sup>5</sup> preparing such structures is synthetically challenging, with their diameter typically limited to approximately 1–10 nm.

To address this challenge, a strategy involving the intramolecular coupling and collapse of single copolymer chains containing reactive cross-linking groups such as benzocyclobutene units to give discrete nanoparticles has been proposed and successfully exploited.<sup>4,6–8</sup> By controlling the molecular weight of the linear starting copolymer from ca. 10 to 250 kg/mol, nanoparticles in the critical 5–20 nm size regime can be routinely prepared. The synthetic versatility coupled with their structural fidelity permits the synthesis of these systems on a multigram scale and allows a much wider range of applications to be examined, for example, control of polymer viscosity<sup>8d,e</sup> and nanoparticle-based data storage systems.<sup>8f</sup>

In addition to the nanostructures prepared through covalent bonding, molecular self-assembly through supramolecular interactions has opened promising avenues for a new generation of higher-order structures,<sup>9</sup> with a specific interest in the intermolecular hydrogen-bonding interaction between functionalized polymers.<sup>10–12</sup> The allure of responsive and reversibly bonded nanoparticles with supramolecular systems is significant and allows stimuli-induced transformation from a nanoparticle structure to a random-coil chain. These morphology changes may be utilized in the *in situ* control of polymer properties ranging from viscosity control to the controlled release of

encapsulated active agents. For this purpose, it is important to introduce a suitable noncovalent interaction with moderate bond strength. A hydrogen bond with energies of the order of 2–20 kJ mol<sup>-1</sup> is regarded as one of the ideal candidates.<sup>9b</sup> Lessons from nature have already shown that the overwhelming importance of hydrogen bonds in biology stems from the moderate energies needed for their formation and rupture.<sup>13</sup> A benzamide group, for example, is a self-complementary hydrogen-bonding motif with an association constant in the order of 40–300 M<sup>-1</sup> (for dimerization).<sup>14</sup> Although it has been mostly exploited in crystal engineering,<sup>15</sup> there have been recent efforts to utilize hydrogen bonding of benzamides in the construction of a variety of supramolecular structures.<sup>16</sup>

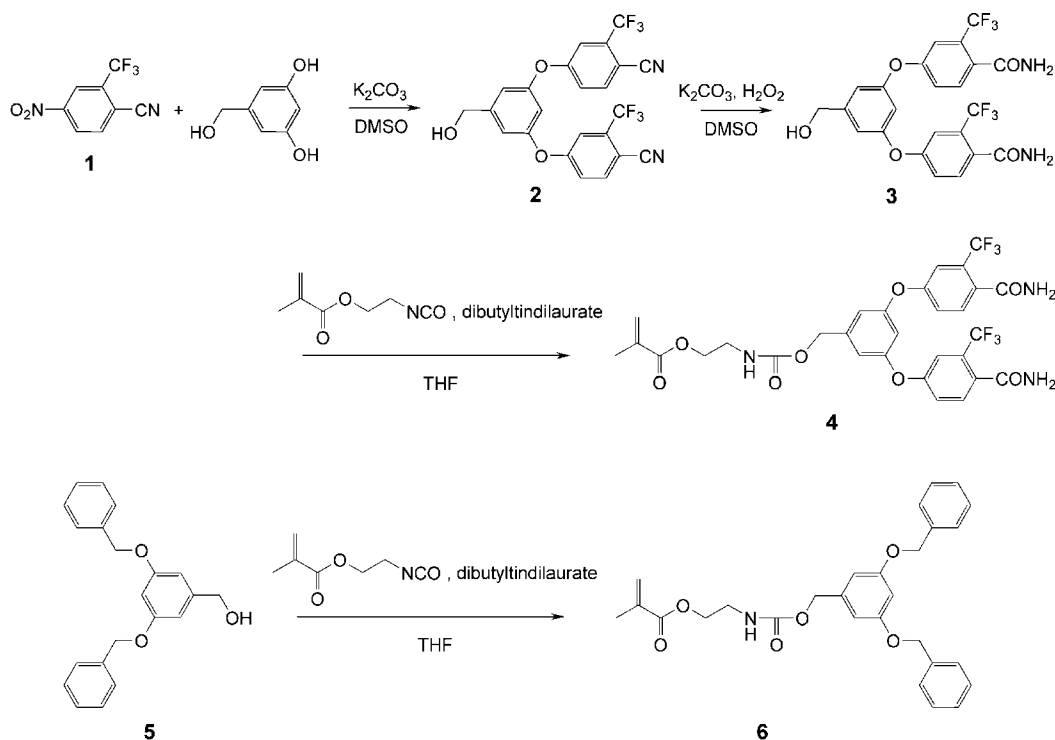
To achieve the goal of nanostructures cross-linked through noncovalent interactions, a series of linear polymers were prepared and functionalized with dendritic self-complementary hydrogen-bonding (SHB) units along the backbone. The cooperative, multiple interactions between dendritic SHB units are key to generating a physically cross-linked network within the interior of the polymer nanoparticles.<sup>17</sup> The strength of the multivalent binding interactions provides stability to maintain the collapsed state of the copolymers, allowing them to behave as intramolecularly cross-linked polymer nanoparticles. The process of collapsing and forming three-dimensional nanostructures via noncovalent interactions resembles the folding process of proteins in nature and suggests a range of potential applications including molecular imprinting, controlled gelation, etc.<sup>18</sup> One advantage of this strategy is that the functional copolymer can be synthesized by controlled free radical polymerization techniques<sup>19</sup> such as reversible addition–fragmentation chain transfer (RAFT) polymerization,<sup>20</sup> which allows control over molecular weight and composition of the target copolymer. The high tolerance toward many different functional monomers makes RAFT particularly suitable for the polymerization of monomers containing hydrogen-bonding units. We describe herein the preparation of a polymerizable benzamide–dendron having SHB units attached, its subsequent copolymerization with methyl methacrylate, and the formation of polymeric nanoparticles from these copolymers via supramolecular interactions.

\* To whom correspondence should be addressed. E-mail: hawker@mrl.ucsb.edu; kimsy@kaist.ac.kr.

<sup>†</sup> KAIST.

<sup>‡</sup> University of California, Santa Barbara.

## Scheme 1. Synthetic Routes for Polymerizable Dendrons 4 and 6



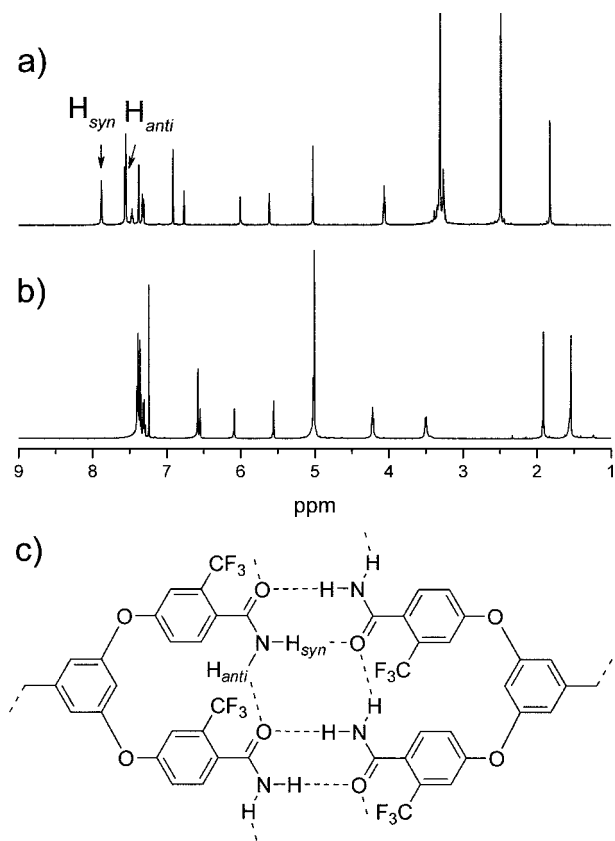
## Results and Discussion

**Synthesis of Polymerizable Dendrons.** The synthesis of a new SHB monomer containing the benzamide–dendron (4) is depicted in Scheme 1. To introduce branching, 3,5-dihydroxybenzyl alcohol was reacted with 2-trifluoromethyl-4-nitrobenzonitrile (1) via nucleophilic aromatic substitution ( $S_NAr$ ). The nitro group was readily substituted at room temperature due to the combined electron-withdrawing character of both the cyano and trifluoromethyl groups. In addition, the increased nucleophilicity of the phenolic groups compared to benzyl alcohol afforded a regioselective reaction to give 2. Subsequent hydrolysis of the cyano group under basic conditions formed 3, which has two benzamide groups per dendron. Finally, the remaining benzyl alcohol group was further reacted with 2-isocyanatoethyl methacrylate in the presence of dibutyltin dilaurate as a catalyst to yield monomer 4. The  $^1H$  NMR spectrum of 4 in  $DMSO-d_6$  is shown in Figure 1a. The amide protons in the benzamide group exhibit two sharp signals, indicating the restricted rotation of the  $NH_2$  group around its  $N-CO$  bond due to hydrogen bonding.<sup>16d</sup> The two protons are distinguished by different hydrogen bonds. According to Etter's rule,<sup>21</sup> the hydrogen-bonding pattern of benzamides is described by the combination of two supramolecular synthons,  $R_2^2(8)$  (face-to-face hydrogen bond utilizing *syn* hydrogen atoms) and  $C(4)$  (side-to-side hydrogen bond utilizing *anti* hydrogen atoms), which yields a two-dimensional, hydrogen-bonded network. Figure 1c illustrates the proposed hydrogen bonding of 4. To allow comparison with model systems not containing the supramolecular groups, a non-H-bonding dendron, 6, was prepared with a similar molecular structure, but without benzamide groups. This allows the role of the hydrogen bonding motif in the formation of polymeric nanoparticles to be examined.

**Synthesis of Copolymers.** Copolymerizations of 4 or 6 with methyl methacrylate (MMA) were conducted in  $N,N$ -dimethylformamide (DMF) using *S*-methoxycarbonylphenylmethyl dithiobenzoate as a chain-transfer agent<sup>22</sup> and 2,2'-azobis(isobu-

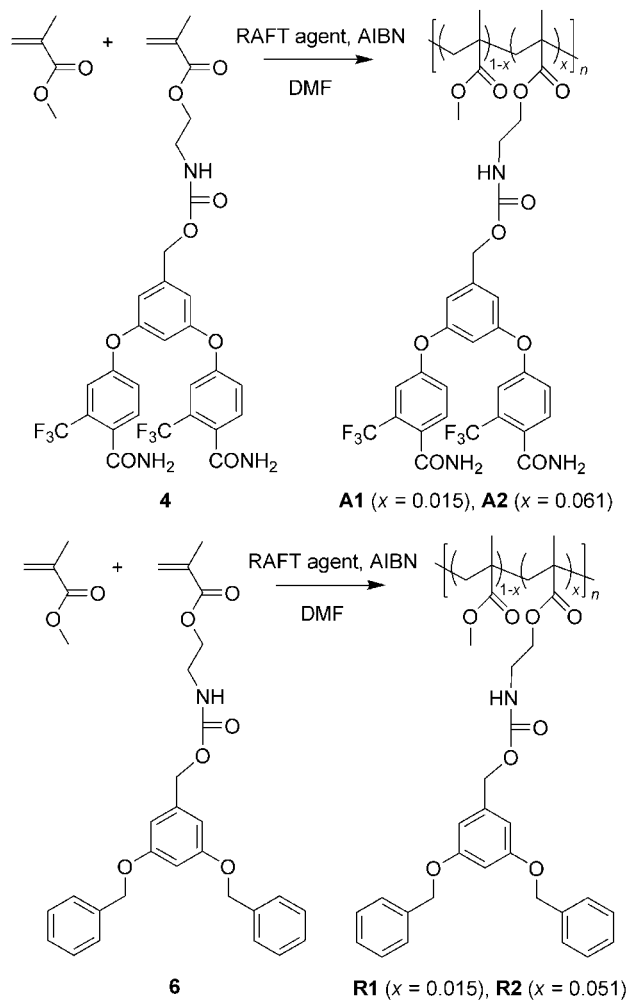
tyronitrile) (AIBN) as initiator (Scheme 2). Molecular weights and compositions of the resulting polymers are given in Table 1.

By optimizing the polymerization conditions, high-molecular-weight ( $M_w > 100\,000$  g/mol) polymers with controlled levels



**Figure 1.**  $^1H$  NMR spectra (500 MHz) of (a) 4 ( $DMSO-d_6$ ) and (b) 6 ( $CDCl_3$ ). (c) Illustration of the proposed hydrogen bonding pattern of 4, consisting of  $R_2^2(8)$  and  $C(4)$  synthons.

**Scheme 2. Synthesis of Random Copolymers A1, A2, R1, and R2 from MMA and 4 or 6 Using S-Methoxycarbonylphenylmethyl Dithiobenzoate as RAFT Agent**



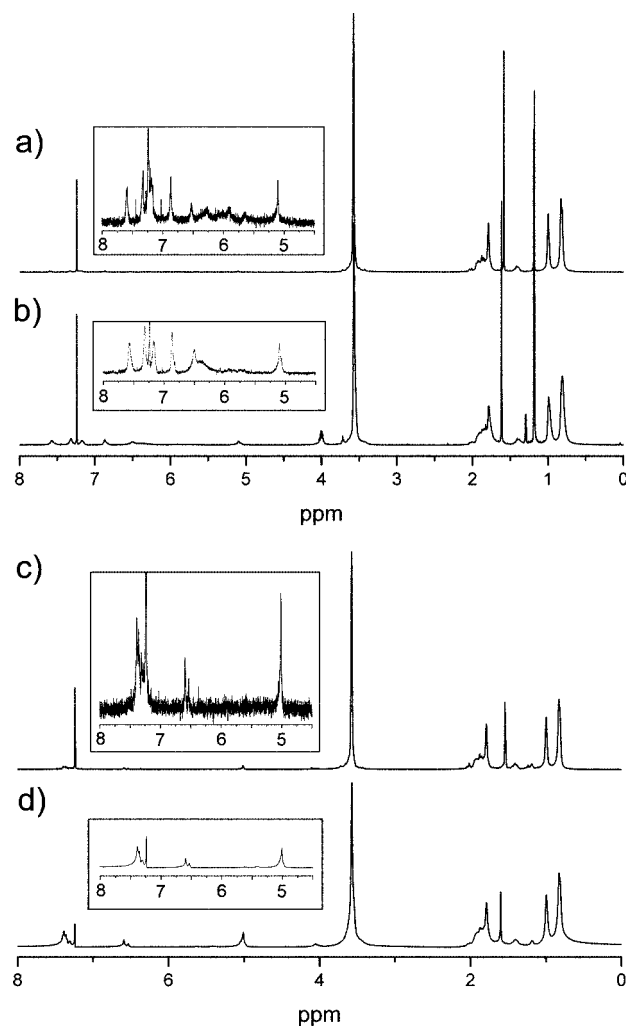
**Table 1. Molecular Weight and Composition of Synthesized Polymers**

entry	copolymer incorporation ratio <sup>a</sup>	$M_w^b$	PDI <sup>b</sup>
<b>A1</b>	1.5% of <b>4</b> and 98.5% of MMA	159 000	1.25
<b>A2</b>	6.1% of <b>4</b> and 93.9% of MMA	131 000	1.25
<b>R1</b>	1.5% of <b>6</b> and 98.5% of MMA	105 000	1.30
<b>R2</b>	5.1% of <b>6</b> and 94.9% of MMA	125 000	1.25

<sup>a</sup> Determined by <sup>1</sup>H NMR spectroscopy measured in CDCl<sub>3</sub>. <sup>b</sup> Determined by GPC using polystyrene standards (THF).

of incorporation ratios and PDI ~ 1.2–1.3 were obtained. <sup>1</sup>H NMR spectra of the polymers in CDCl<sub>3</sub> are shown in Figure 2, and the incorporation of the comonomers is evidenced by the appearance of aromatic protons between 6.5 and 7.5 ppm. Integration of these unique resonances and comparison with the methyl ester resonance for the methyl methacrylate units allowed the level of incorporation to be calculated. In addition, the amide protons in the benzamide group were observed as a broad signal at ca. 6.2 ppm, mixed with the amide proton in the carbamate group.

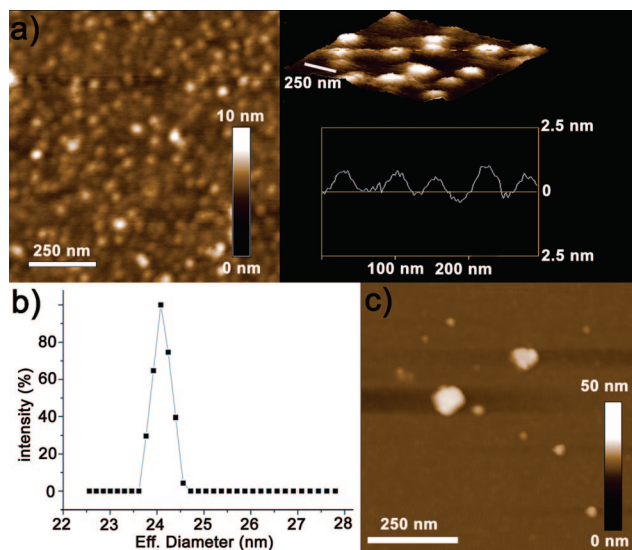
The isolated copolymers were soluble in typical solvents for PMMA homopolymers, such as chloroform, tetrahydrofuran, and DMF. However, because of a high incorporation ratio (6%) of the supramolecular benzamide–dendron, sample **A2** was insoluble in toluene. In contrast to **A2**, the polymers containing the benzyloxy–dendron (**R1** and **R2**) as well as a lower incorporation of SHB groups, **A1** (1.5% incorporation of SHB), were soluble in toluene. The solubility behavior described above



**Figure 2.** <sup>1</sup>H NMR spectra (500 MHz) of (a) **A1**, (b) **A2**, (c) **R1**, and (d) **R2** (all in CDCl<sub>3</sub>). Inset: magnified view of aromatic and benzylic protons.

indicates that nonpolar solvents such as toluene are not capable of breaking the hydrogen bonds between the SHB units of the copolymer in the solid state to achieve dissolution. As a result, transitioning from more polar solvents such as THF to toluene may provide a driving force for nanoparticle formation while at the same time providing a suitable environment for stability of the chain collapsed materials.

**Supramolecular Collapse.** Copolymer **A2** was “collapsed” in toluene by dissolving the polymer in a mixture of THF and toluene followed by evaporation of the more volatile THF. This yields a slightly opalescent solution of **A2** which was filtered (0.45 μm) to obtain a transparent solution. Irreversible precipitation was not observed in these systems after several days, and the solution was stable up to a concentration of 32 g/L, indicating that large aggregates of polymer chains did not form. This stability indicates that nanoparticles formed from **A2** are stabilized by internal hydrogen bonding between SHB units while being solubilized by the PMMA backbone. To investigate the morphology in greater detail, a 10 g/L dispersion of **A2** was prepared by dissolving 20 mg of the polymer in a mixture of THF (1 mL) and toluene (2 mL) followed by evaporation of the THF. The dispersion was further diluted 10<sup>6</sup> times with toluene, cast on a silicon wafer, and subjected to a scanning force microscopy (SFM) study. Figure 3a clearly shows that **A2** was well dispersed, forming spherical, uniform nanoparticles. Dynamic light scattering measurements also support the formation of nanoparticles with a measured mean effective diameter

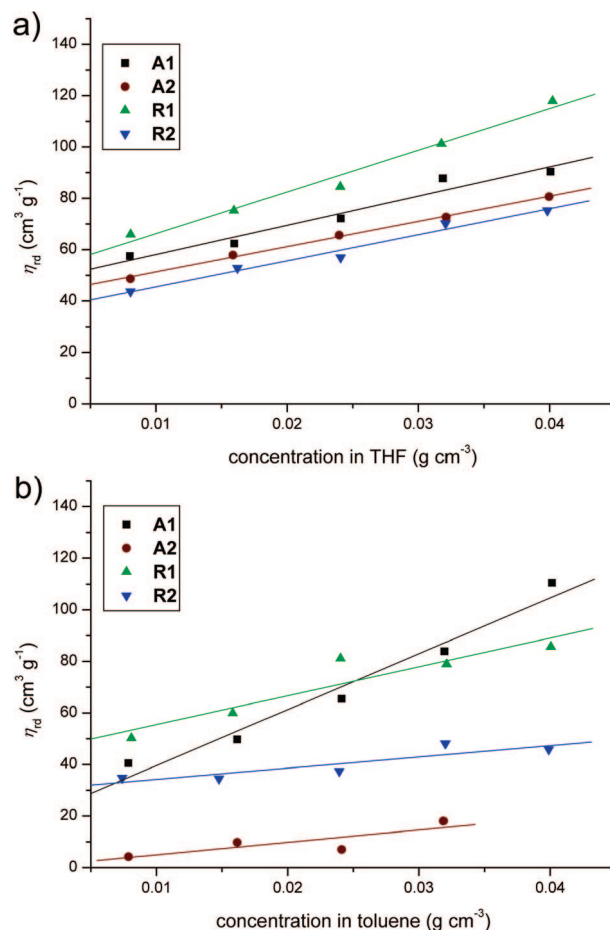


**Figure 3.** (a) SFM image of nanoparticles of **A2** prepared in toluene on a Si wafer. (b) DLS plot of nanoparticles of **A2** prepared in toluene. (c) SFM image of aggregates of **A1** prepared in toluene on a Si wafer.

of 24 nm (Figure 3b). The diameter of the particles remained constant even after 2 days, indicating that interchange of the hydrogen bonds along the polymer chain is slow and does not generate larger aggregates via intermolecular/interaggregate interaction. It is not certain whether the particle consists of single or multiple polymer chains, but the aggregation number was predicted to be low considering that the radius of gyration of **A2** was calculated to be ca. 17 nm (i.e., 34 nm by diameter) by the Flory–Fox equation, using a four-capillary differential viscometer detector.<sup>23</sup> From the literature, the radius of gyration for PMMA of an analogous molecular weight as **A2** was estimated to be ca. 9 nm in THF.<sup>24</sup> DSC measurements of **A2** showed no melting transitions, indicating that the aggregates would be amorphous.

To understand the effect of SHB loading, a toluene solution of **A1** was prepared following the same protocol, and the resulting structures were characterized by SFM. In direct contrast to **A2**, irregular aggregates with diameters of over 100 nm were observed with light scattering revealing an inhomogeneous mixture of large and small nanoparticles. This suggests that while **A2** undergoes predominantly intramolecular collapse, the supramolecular assembly of **A1** involves a substantial fraction of intermolecular chain association, leading to ill-defined nanostructures and aggregates. For the non-H-bonding model copolymers, **R1** and **R2**, no nanostructures were observed with both SFM and light scattering, suggesting a random coil structure as expected.

To illustrate the effect of the morphology on the physical properties of the polymer, concentration studies on the reduced viscosities of the polymer solutions were performed in THF and in toluene (Figure 4). In THF all of the samples revealed similar viscosity profiles which is consistent with a random coil structure and the lack of supramolecular interactions in THF, which is a good solvent for both the benzyloxy and the benzamide substituents. For a more nonpolar solvent such as toluene, the viscosity of **A1** was observed to increase sharply with concentration, suggesting strong intermolecular hydrogen-bonding interactions.<sup>12a,c,e,f</sup> Significantly, the absence of a substantial change in the overall viscosity exhibited by **A2** clearly indicates that the morphology of **A2** in solution more resembles that of a nanoparticle than either a random coil or network structure. These results suggest that a low concentration of interacting units within a chain promotes intermolecular



**Figure 4.** Reduced viscosities of polymers plotted against concentration (a) in THF and (b) in toluene.

interactions between the polymer chains, while a higher concentration of the interacting units may preferentially lead to intramolecular interactions.<sup>25</sup>

## Conclusions

In summary, random PMMA copolymers containing dendritic hydrogen-bonding units have been prepared by RAFT-mediated free radical polymerization, and their supramolecular assembly was examined in different solvents. Incorporation of varying amounts of supramolecular H-bonding units along the backbone led to significantly different behavior. At low levels of incorporation (1.5% SHB), intermolecular interactions predominated in nonpolar solvents resulting in large-scale aggregation, while for high loading levels (6% SHB), intramolecular hydrogen bonding was favored in toluene leading to the formation of well-defined and stable nanoparticles. The stimuli-responsive nature of this noncovalent chain collapse approach to nanoparticles, coupled with the ability to prepare a wide variety of linear polymers by controlled radical polymerization techniques, adds significantly to the range of structures, properties, and applications for these novel materials.

## Experimental Section

**General.** All chemicals were purchased from Sigma-Aldrich (St. Louis, MO). 2-Bromo-5-nitrobenzotrifluoride (97%), copper(I) cyanide (99%), 3,5-dihydroxybenzyl alcohol (99%), potassium carbonate ( $\geq 99\%$ ), hydrogen peroxide solution (30 wt % in water), 2-isocyanatoethyl methacrylate (98%), dibutyltin dilaurate (95%), and benzyl bromide (98%) were used without further purification. Methyl methacrylate (99%) was filtered over basic alumina prior to polymerization. 2,2-Azobis(2-methylpropionitrile) (AIBN) was

recrystallized from methanol. Synthesized materials were characterized by  $^1\text{H}$  and  $^{13}\text{C}$  nuclear magnetic resonance (NMR) spectroscopy using either a Bruker 400 or 500 MHz spectrometer with the residual solvent signal as an internal reference. Gel permeation chromatography (GPC) was performed in tetrahydrofuran on a Waters Alliance HPLC system (Waters 2695 separation module, Millford, MA) equipped with four Waters styragel HR columns. A Waters 2414 differential refractometer index and 2996 photodiode array detectors were employed. The molecular weights of the polymers were calculated relative to linear polystyrene standards. Differential scanning calorimetry (DSC) was performed on a TA Q100 calorimeter (New Castle, DW) equipped with a refrigerated cooling system (RCS 90). Samples were measured in an aluminum cell at a heating rate of  $10\text{ }^\circ\text{C}/\text{min}$  under  $\text{N}_2$ . Scanning force microscope (SFM) height images were obtained in the tapping mode using Veeco Dimension 3100 and multimode scanning probe microscope. Dynamic light scattering (DLS) measurements were carried out on a Brookhaven BI-9000AT digital autocorrelator (Holtsville, NY) equipped with an Avalanche photodiode detector and an MG vertically polarized 35 mW He-Ne 633 nm laser and operated by the 9KDLSW control program. All samples were filtered through a  $0.45\text{ }\mu\text{m}$  filter and then run for 2 min at  $25\text{ }^\circ\text{C}$ , at  $10\text{ g/L}$ , and at a fixed  $90^\circ$  angle. The hydrodynamic diameter and distribution of particles were determined by fitting the correlation functions with the ISDA analysis software package (Brookhaven Instruments Co.) and applying the non-negatively constrained least-squares particle size distribution analysis (NNLS). The intrinsic viscosity value of **A2** was measured by a four-capillary differential viscometer detector (model 270 dual detector) integrated in a Viscotek T60A GPC system and converted into the radius of gyration value using the GPCMax program. Reduced viscosity measurements were carried out using a Schott micro-Ubbelohde viscometer (type no. 53710, capillary no. M1). The solutions for the measurement were prepared at least 1 day before the measurement by dissolving the polymer in pure solvent. Samples of **A2** in toluene were prepared following the previous protocol for the preparation for the DLS measurement, by rapidly evaporating THF from the mixed solution of THF and toluene. Before usage, the solution was filtered through a  $0.45\text{ }\mu\text{m}$  filter. The relative viscosity ( $\eta_{\text{rel}}$ ) was calculated by measuring the flow time of pure solvent and the solution in a temperature-controlled bath. Then it was converted into the reduced viscosity ( $\eta_{\text{rd}}$ ) following the relationship

$$\eta_{\text{rd}} = (\eta_{\text{rel}} - 1)/C$$

where  $C$  is the concentration of the solution.

**Synthesis of Monomers.** The synthetic routes of **4** and **6** are shown in Scheme 1. Syntheses of 4-nitro-2-trifluoromethylbenzotrile (**1**)<sup>16c</sup> and the first-generation Fréchet dendrimer (3,5-bis(benzyloxy))benzyl alcohol (**5**)<sup>26</sup> were conducted according to the literature procedures.

**4,4'-(5-(Hydroxymethyl)-1,3-phenylene)bis(oxy)bis(2-(trifluoromethyl)benzotrile) (2).** 4-Nitro-2-trifluoromethylbenzotrile (**1**) (3.08 g, 14.3 mmol) and 3,5-dihydroxybenzyl alcohol (1.00 g, 7.14 mmol) were dissolved in 25 mL of dimethyl sulfoxide (DMSO) and placed in a 50 mL round-bottomed flask. Potassium carbonate (1.97 g, 14.3 mmol) was added into the flask, and the solution was stirred at room temperature for 10 h. The solution was then poured into 150 mL of water, neutralized with 10% HCl(aq), and extracted with ethyl acetate. The organic layer was dried and evaporated in a rotary evaporator. The desired product was purified by flash column chromatography (EA/Hx = 1/2) to yield the alcohol as a yellow solid (2.50 g, 37%); mp  $95\text{ }^\circ\text{C}$ . MS, *m/e* 478.0752 (calcd: 478.0752).  $^1\text{H}$  NMR (DMSO, 400 MHz, ppm): 8.12 (d, 2H,  $J = 8.6\text{ Hz}$ ), 7.58 (d, 2H,  $J = 2.4\text{ Hz}$ ), 7.41 (dd, 2H,  $J_1 = 8.6\text{ Hz}$ ,  $J_2 = 2.5\text{ Hz}$ ), 7.06 (d, 2H,  $J = 2.1\text{ Hz}$ ), 7.00 (t, 1H,  $J = 2.2\text{ Hz}$ ), 5.45 (t, 1H,  $OH$ ,  $J = 5.7\text{ Hz}$ ), 4.53 (d, 2H,  $CH_2$ ,  $J = 5.4\text{ Hz}$ ).  $^{13}\text{C}$  NMR (DMSO, 100 MHz, ppm): 160.8, 155.3, 148.2, 137.9, 133.2 (q,  $J = 31.9\text{ Hz}$ ), 122.1 (q,  $J = 272.1\text{ Hz}$ ), 121.3, 116.6, 115.5, 114.9, 110.8, 102.4, 61.7.

**4,4'-(5-(Hydroxymethyl)-1,3-phenylene)bis(oxy)bis(2-(trifluoromethyl)benzamide) (3).** **2** (1.95 g, 4.07 mmol) was dissolved in 20 mL of DMSO and placed in a 100 mL round-bottomed flask. At  $0\text{ }^\circ\text{C}$ , potassium carbonate (1.20 g, 8.68 mmol) and 30% aqueous hydrogen peroxide solution (8 mL) were added into the flask. After vigorous stirring for 30 min, the reaction mixture was slowly warmed up to room temperature, and an additional 4 mL of DMSO was added. After 2 h, the reaction mixture was poured into 200 mL of water. The white solid was filtered and dried in vacuum to give the bis(amide), which was used without further purification (1.40 g, 67%); mp  $197\text{ }^\circ\text{C}$ . MS, *m/e* 514.0963 (calcd: 514.0963).  $^1\text{H}$  NMR (DMSO, 400 MHz, ppm): 7.74 (d, CONH<sub>2</sub>, 4H,  $J = 134.6\text{ Hz}$ ), 7.56 (s, 2H), 7.37 (d, 2H,  $J = 2.0\text{ Hz}$ ), 7.32 (dd, 2H,  $J_1 = 10.3\text{ Hz}$ ,  $J_2 = 1.8\text{ Hz}$ ), 6.86 (s, 2H), 6.73 (s, 1H), 5.36 (t, 1H,  $OH$ ,  $J = 5.7\text{ Hz}$ ), 4.48 (d, 2H,  $CH_2$ ,  $J = 5.5\text{ Hz}$ ).  $^{13}\text{C}$  NMR (DMSO, 100 MHz, ppm): 168.5, 156.8, 147.6, 132.0, 130.8, 127.8 (q,  $J = 32.0\text{ Hz}$ ), 123.2 (q,  $J = 272.2\text{ Hz}$ ), 121.7, 116.2, 112.6, 108.8, 62.1.

**2-((3,5-Bis(4-carbamoyl-3-trifluoromethyl)phenoxy)benzyloxy)carbonylamino)ethyl Methacrylate (4).** The alcohol **3** (0.291 g, 0.566 mmol) was dissolved in 5 mL of THF and placed in a 25 mL round-bottomed flask. 2-Isocyanatoethyl methacrylate (0.40 mL, 2.83 mmol) was added into the flask followed by dibutyltin dilaurate (0.034 mL, 0.057 mmol), and the reaction mixture was stirred for 18 h at  $50\text{ }^\circ\text{C}$ . After cooling to room temperature, the reaction mixture was poured into an excess amount of *n*-hexane (500 mL). The supernatant was decanted, and the remaining material was dissolved in THF. Dichloromethane and *n*-hexane were added to the solution to crystallize the product which was filtered and dried in vacuum (0.274 g, 72%); mp  $114\text{--}115\text{ }^\circ\text{C}$ . ESI-MS, *m/e* [ $M + \text{Na}^+$ ] 692.15 (calcd: 692.1438).  $^1\text{H}$  NMR (DMSO, 500 MHz, ppm): 7.73 (d, CONH<sub>2</sub>, 4H,  $J = 157.0\text{ Hz}$ ), 7.55 (s, 2H), 7.47 (t, 1H, OCONH,  $J = 5.5\text{ Hz}$ ), 7.38 (d, 2H,  $J = 2.0\text{ Hz}$ ), 7.32 (d, 2H,  $J = 8.5\text{ Hz}$ ), 6.92 (d, 2H,  $J = 2.0\text{ Hz}$ ), 6.77 (s, 1H), 6.01 (s, 1H,  $CH_2=CCH_3$ ), 5.62 (s, 1H,  $CH_2=CCH_3$ ), 5.03 (s, 2H,  $CH_2$ ), 4.06 (t, 2H,  $COCH_2CH_2$ ,  $J = 5.5\text{ Hz}$ ), 3.27 (t, 2H,  $COCH_2CH_2$ ,  $J = 5.0\text{ Hz}$ ), 1.83 (s, 3H,  $CH_2=CCH_3$ ).  $^{13}\text{C}$  NMR (DMSO, 100 MHz, ppm): 168.4, 166.5, 156.8, 156.7, 156.0, 141.9, 135.8, 132.1, 130.8, 127.8 (q,  $J = 31.7\text{ Hz}$ ), 123.1 (q,  $J = 272.4\text{ Hz}$ ), 121.5, 116.2 (q,  $J = 5\text{ Hz}$ ), 113.9, 109.6, 64.2, 63.2, 17.9.

**2-((3,5-Bis(benzyloxy)benzyloxy)carbonylamino)ethyl Methacrylate (6).** **5** (1.00 g, 3.12 mmol) was dissolved in 10 mL of THF and placed in a 25 mL round-bottomed flask. 2-Isocyanatoethyl methacrylate (1.80 mL, 12.5 mmol) was added into the flask followed by dibutyltin dilaurate (0.37 mL, 0.62 mmol), and the reaction mixture was stirred for 18 h at  $50\text{ }^\circ\text{C}$ . After cooling to room temperature, the reaction mixture was poured into an excess amount of *n*-hexane (500 mL). The supernatant was decanted, and the remaining material was dissolved in cyclohexane to crystallize the product which was filtered and dried in vacuum (0.691 g, 47%); mp  $67\text{ }^\circ\text{C}$ . ESI-MS, *m/e* [ $M + \text{Na}^+$ ] 498.15 (calcd: 498.1887).  $^1\text{H}$  NMR (DMSO, 500 MHz, ppm): 7.36 (m, 8H), 7.31 (m, 2H), 6.58 (d, 2H,  $J = 2.0\text{ Hz}$ ), 6.55 (d, 2H,  $J = 2.0\text{ Hz}$ ), 6.09 (s, 1H,  $CH_2=CCH_3$ ), 6.56 (s, 1H,  $CH_2=CCH_3$ ), 5.02 (m, 8H), 4.22 (t, 2H,  $COCH_2CH_2$ ,  $J = 5.0\text{ Hz}$ ), 3.50 (t, 2H,  $COCH_2CH_2$ ,  $J = 5.5\text{ Hz}$ ), 1.93 (s, 3H,  $CH_2=CCH_3$ ).  $^{13}\text{C}$  NMR (DMSO, 100 MHz, ppm): 167.2, 160.0, 156.2, 138.7, 136.7, 135.9, 128.5, 128.0, 127.5, 126.0, 106.9, 101.6, 70.1, 66.7, 63.6, 40.2, 18.2.

**Syntheses of Copolymers A1 and A2.** Copolymers of MMA and **4** were synthesized by dissolving **4** (0.953 g, 1.42 mmol), MMA (2.71 g, 27.1 mmol), AIBN (0.098 mg, 0.6  $\mu\text{mol}$  (as a 1 wt % benzene solution)), and RAFT agent (*S*-methoxycarbonylphenylmethyl dithiobenzoate, 2.6 mg, 8.7  $\mu\text{mol}$  (as a 10.3 wt % benzene solution)) in DMF (2 mL). The solution was transferred to a vial and subjected to three freeze-pump-thaw cycles. The vial was then sealed under vacuum and heated at  $70\text{ }^\circ\text{C}$  for 44 h. After cooling to rt, the solution was diluted with DMF and precipitated into diethyl ether (ca. 200 mL). The precipitate was filtered and purified by reprecipitation in diethyl ether and dried in vacuum to give the desired copolymer **A2** as a pink solid (1.53 g, 42%).  $M_n$   $1.04 \times 10^5\text{ g/mol}$ . Polydispersity index (PDI): 1.25.  $^1\text{H}$  NMR (500

MHz, CDCl<sub>3</sub>, ppm): 7.57, 7.32, 7.16, 6.87, 6.50, 5.10, 4.01, 3.57, 2.10–0.80.

Using the above procedure, **A1** was synthesized from **4** (0.182 g, 1.23 mmol), MMA (2.70 g, 27.0 mmol), AIBN (0.094 mg, 0.6 μmol), and RAFT agent (2.1 mg, 7.1 μmol) to give a pink solid (1.16 g, 40%).  $M_n$  1.27 × 10<sup>5</sup> g/mol. Polydispersity index (PDI): 1.25.

**Syntheses of Copolymers R1 and R2.** Copolymers of MMA and **6** were synthesized using the same conditions described above. **R2** was prepared from **6** (0.169 g, 0.355 mmol), MMA (0.680 g, 6.79 mmol), AIBN (0.026 mg, 0.2 μmol), and RAFT agent (0.64 mg, 2.1 μmol) dissolved in DMF (2 mL) using a similar procedure as described above. This gave the desired copolymer **R2** as a pink solid (0.271 g, 32%).  $M_n$  9.94 × 10<sup>4</sup> g/mol. Polydispersity index (PDI): 1.25. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>, ppm): 7.39–7.30, 6.59, 6.54, 5.03, 4.05, 3.70–3.40, 2.10–0.60.

**R1** was prepared from **6** (0.131 g, 0.275 mmol), MMA (2.70 g, 27.0 mmol), AIBN (0.069 mg, 0.4 μmol), and RAFT agent (2.2 mg, 7.3 μmol) to give a pink solid (1.98 g, 70%).  $M_n$  6.91 × 10<sup>4</sup> g/mol. Polydispersity index (PDI): 1.30.

**Acknowledgment.** This work was supported by a KOSEF grant funded by MOST (No. R11-2007-050-04001-0) and by the National Science Foundation (UCSB Materials Research Laboratory, DMR 05-20415; PREM DMR 06-11539 and NIRT 05-06309). J.P. acknowledges the Netherlands Organization for Scientific Research (NWO) for a Rubicon fellowship.

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