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A Facile Approach to Architecturally Defined Nanoparticles via Intramolecular Chain Collapse

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Abstract: A novel approach is presented for the controlled intramolecular collapse of linear polymer chains to give well-defined single-molecule nanoparticles whose structure is directly related to the original linear polymer. By employing a combination of living free radical polymerization and benzocyclobutene (BCB) chemistry, nanoparticles can be routinely prepared in multigram quantities with the size being accurately controlled by either the initial degree of polymerization of the linear chain or the level of incorporation of the BCB coupling groups. The latter also allows the cross-link density of the final nanoparticles to be manipulated. In analogy with dendritic macromolecules, a significant reduction of up to 75% in the hydrodynamic volume is observed on going from the starting random coil linear chains to the corresponding nanoparticles. The facile nature of the living free radical process also permits wide variation in monomer selection and functional group incorporation and allows novel macromolecular architectures to be prepared. Furthermore, the use of block copolymers functionalized with benzocyclobutene groups in only one of the blocks gives, after intramolecular collapse, a hybrid architecture in which a single linear polymer chain is attached to the globular nanoparticle.

Introduction

The synthesis and application of polymeric nanoparticles has attracted significant attention in recent years with further refinement of traditional methods as well as novel strategies for their preparation being developed.[1−3] One of the driving forces for this interest has been the realization that functionalized nanoparticles can be considered as building blocks for a variety of nanotechnological applications, ranging from vectors for drug and DNA delivery systems[4] to templating agents for nanoporous microelectronic materials.[5] The strategies for preparing nanoparticles can be broadly classified into two main approaches, a top-down approach where emulsion polymerization techniques are further refined and optimized, leading to the development of microemulsion procedures resulting in particles from 20 to 50 nm.[6] More recently, bottom-up techniques have been introduced which either rely on the synthesis of discrete spherical macromolecules such as dendrimers (1−10 nm)[7] or the self-assembly of linear block copolymers into polymeric micelles followed by chemical cross-linking to give nanoparticles with typical dimensions ranging from 20 to 200 nm.[8] As a consequence, the ability to routinely prepare nanoparticles in the 5−20 nm size range is limited.

To address this issue, a new strategy involving the collapse and intramolecular coupling of single-polymer chains to give discrete nanoparticles has been proposed.[9,10] While promising, this strategy has drawbacks, primarily the competing and statistically favored intermolecular cross-linking reaction which necessitated the use of ultra-dilute reaction conditions (ca. 10^{-5}−10^{-6} M). This precludes the synthesis of these nanoparticles on a useful (>multigram) scale. In addition, even at these ultra-

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dilute conditions intermolecular cross-linking was still evident which results in poorly defined materials and in some cases gelation. To overcome this difficulty a continuous addition strategy for the successful synthesis of discrete nanoparticles by intramolecular cross-linking has now been developed. This permits the full potential of this strategy for the synthesis of well-defined and functionalized nanoparticles to be achieved. Furthermore the polymeric nanoparticles that are obtained from this procedure are freely soluble in common solvents and do not need surfactants, during either their synthesis or the subsequent stabilization of the resulting nanoparticle solutions. In many respects these new nanoparticle systems resemble dendrimers, although larger molecular sizes may be more easily prepared and they have the potential to be available in greater quantity.

Experimental Section

General Methods. Commercial reagents were obtained from Aldrich and used without further purification. Analytical TLC was performed on commercial Merck plates coated with silica gel GF254 (0.24 mm thick). Silica gel for flash chromatography was Merck Kieselgel 60 (230−400 mesh, ASTM). Nuclear magnetic resonance was performed on a Bruker AVANCE 400 FT-NMR spectrometer using deuterated solvents and the solvent peak as a reference. Gel permeation chromatography was performed in tetrahydrofuran (THF) on a Waters chromatograph equipped with four 5-μm Waters columns (300 mm × 7.7 mm) connected in series with increasing pore size (100, 1000, 100,000, 1,000,000 Å). A Waters 410 differential refractometer and a 996 photodiode array detector were employed. The polystyrene molecular weights were calculated relative to linear polystyrene standards, whereas the poly(*n*-butyl acrylate) molecular weights were calculated relative to poly(*n*-butyl acrylate) standards.

3-Carboxaldehydebicyclo[4,2,0]octa-1,3,5-triene or 4-Carboxaldehydebenzocyclobutene, 6. To a 500-mL flask was added 50 mL dry of THF, Mg turnings (2.88 g, 120 mmol), and 1,2-dibromoethane (4 drops). The reaction mixture was then heated under reflux for 15 min, 4-Bromobenzocyclobutene, **5**,[11] (20.0 g, 109 mmol) in 25 mL THF was added via a dropping funnel to form the Grignard reagent. After addition and rinsing the dropping funnel with 25 mL of dry THF, the reaction mixture was heated for an additional 45 min under reflux to give a green brown solution. The reaction mixture was then cooled to 0 °C, DMF (15 mL, 210 mmol) was added dropwise to the solution, and the reaction mixture was heated under reflux for 15 min. The reaction mixture was poured onto 150 g of ice, acidified to pH = 4, and neutralized with saturated $NaHCO_3$ solution. The crude product was extracted with ethyl acetate, the organic phase was filtered over Celite, and evaporation of the solvent gave the crude product. The product was purified by column chromatography using 10% diethyl ether/hexane as eluting solvents and was finally purified by Kugelrohr distillation (145 °C, 0.5 mm) to give the aldehyde, **6**, (11.7 g, 81.2%) as a colorless liquid; IR 3000−2800, 1690, 1598, 1216, 1067 and 827 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 9.9 (s, 1H, CHO), 7.65 (dd, 1H, J = 7.4 Hz, J' = 1.2 Hz, ArH), 7.50 (s, 1H, ArH), 7.14 (dd, 1H, J = 7.4 Hz, J' = 1.2 Hz, ArH), 3.15 (s, 4H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.28, 153.69, 146.57, 135.4, 130.26, 122.89, 122.81, 29.97, and 29.23. Anal. Calcd for C_9H_8O; C, 81.8; H 6.10. Found: C, 81.7; H, 5.94.

3-Ethenylbicyclo[4,2,0]octa-1,3,5-triene or 4-Vinylbenzocyclobutene, 4. To a 500-mL round-bottom neck flask was added $(Ph)_3PCH_3Br$ (24.3 g, 68.1 mmol), 110 mL of dry THF, and the solution was cooled to −78 °C. *n*-BuLi (2.5 M in hexane, 26.4 mL, 66 mmol) was added dropwise, and the reaction mixture was allowed to warm to room temperature The yellow-orange solution was cooled to −78 °C, and the aldehyde, **6** (7.16 g, 54.2 mmol), diluted in 34 mL of dry THF, was added slowly. The mixture warmed to room temperature, and stirring continued for 2 h. The reaction was treated sequentially with saturated NH_4Cl and saturated $NaHCO_3$ solution, and the crude product was filtered over Celite, washed with diethyl ether/hexane (1:1), and evaporated to dryness (no heat) to give the crude product. Further purification by column chromatography using 5% diethyl ether/hexane as an eluting solvent followed by Kugelrohr distillation (75 °C, 1.0 mm) gave the pure styrene derivative, **4**, as a colorless liquid (5.50 g, 78%); IR 2925, 1627, 1473, 989, 901, and 829 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (d, 1H, J = 7.4 Hz, ArH), 7.20 (s, 1H, ArH), 7.04 (d, 1H, J = 7.4 Hz, ArH), 6.74 (dd, 1H, J = 17.5 Hz, J' = 10.8 Hz, CH), 5.70 (d, 1H, J = 17.5 Hz, CH_2), 5.20 (d, 1H, J = 10.8 Hz, CH_2), 3.19 (s, 4H, CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.09, 145.75, 137.94, 136.69, 125.71, 122.58, 119.90, 112.38, 29.52, and 29.35. Anal. Calcd for $C_{10}H_{10}$; C, 92.2; H 7.80. Found: C, 92.0; H, 8.03.

Random Copolymer of 4 and Styrene, 8. The alkoxyamine initiator, **7** (32.5 mg, 0.1 mmol),[12] dissolved in styrene (10.4 g, 100 mol) and 4-vinylbenzocyclobutene, **4** (3.25 g, 25.0 mmol), was added to a glass ampule with a stir bar. After three freeze and thaw cycles the ampule was sealed under argon and heated for 6 h at 120 °C. The resulting polymer was dissolved in dichloromethane and purified by precipitation into a 1:1 mixture of 2-propanol/acetone followed by reprecipitation into methanol to give **8** as a colorless powder (12.1 g, 88%), M_w = 111 000; PDI = 1.11; IR 3100−2850, 1601, 1492, 1452, 909, and 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.24−6.57 (m, ArH), 3.05 (br s, CH_2), 1.83−1.26 (m, CH_2, CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.0−146.4, 1127.9, 125.5, 121.8, 42.0−44.0, 40.4, and 29.2.

Random Copolymer of 4 and *n*-Butylacylate, 10. The alkoxyamine initiator **7** (32.5 mg, 0.1 mmol) was dissolved in *n*-butyl acrylate (10.2 g, 72.0 mmol) and **4** (1.04 g, 8.0 mmol) and placed in a glass ampule with a stir bar. After three freeze and thaw cycles the ampule was sealed under argon and heated for 15 h at 125 °C. The resulting polymer was dissolved in dichloromethane and precipitated in MeOH/H_2O (3:1) to give **10** as a colorless gum (10.2 g, 91%), M_w = 77 500; PDI = 1.12; ^1H NMR (400 MHz, $CDCl_3$) δ 6.83−6.63 (m, ArH), 4.10−3.83 (m, CH_2,CH), 3.05 (bs, CH_2), 2.22−1.01 (m, CH_2, CH_3).

Methyl(2,2,5-Trimethyl-3-(benzylethoxy)-4-phenyl-3-azahexane)-poly(ethylene Glycol), 12. NaH (0.23 g, 6.3 mmol) was slowly added to a mixture of monomethylpoly(ethylene glycol), **14** (7.85 g, 1.57 mmol), and 18-crown-6 (10 mg) dissolved in 10 mL of THF under a constant argon flow. After 15 min, the chloromethyl-substituted alkoxyamine, **13** (1.16 g, 3.14 mmol)[12] was added to the reaction mixture, which was subsequently heated at reflux for 16 h. After the addition of a few drops of water to neutralize the excess NaH, the reaction mixture was concentrated, dissolved in dichloromethane, filtered, and evaporated to dryness. The crude product was obtained after flash chromatography eluting with dichloromethane gradually increasing to 10% methanol/dichloromethane to give the PEG-macroinitiator, **12**, as a colorless solid (8.03 g, 89%); IR (KBr) 3439 cm^{-1} (NH), 1693 cm^{-1} (amide).^1H NMR (400 MHz, $CDCl_3$) δ 7.4−7.1 (m, ArH), 5.10 (d, CH), 4.92 (d, CH_2OAr), 3.65 (s, OCH_2), 3.41 (d, CH), 3.28 (d, CH), 2.43 (m, CH), 1.65 (d, CH_3), 1.52 (d, CH_3), 1.40 (m, CH), 1.33 (d, CH_3), 1.05 (s, *t*-Bu), 0.89 (d, CH_3), 0.80 (s, *t*-Bu), 0.61 (d, CH_3), and 0.22 (d, CH_3).

Poly(ethylene glycol)-*b*-(styrene-*co*-benzocyclobutene), 15. The poly(ethylene glycol) terminated alkoxyamine, **12** (500 mg, 0.1 mmol) (M_n = 5 000, PDI = 1.06) was dissolved in styrene (10.4 g, 100 mol) and 4-vinylbenzocyclobutene, **4** (3.25 g, 25.0 mmol) in a glass ampule with a stir bar. After three freeze and thaw cycles the ampule was sealed under argon and heated for 6 h at 125 °C. The resulting polymer was

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dissolved in dichloromethane and purified by precipitation into a 1:1 mixture of isopropoanol/acetone followed by reprecipitation into methanol to give **15** as a colorless powder (10.7 g, 76.1%), M_w = 89 500; PDI = 1.12; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24−6.57 (m, ArH), 3.65 (s, OCH_2), 3.05 (br s, CH_2), 1.83−1.26 (m, CH_2, CH).

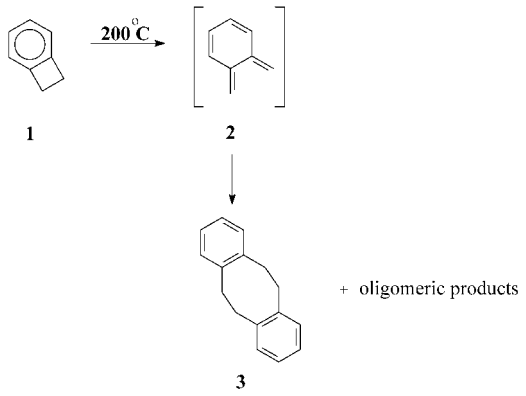
General Procedure for Nanoparticle Formation, 9. In a 500-mL three-necked flask equipped with a internal thermometer, condenser, and septum, 120 mL of benzyl ether was heated at 250 °C under argon. A solution of the benzocyclobutene (BCB)-functionalized linear polymer, **8** (4.00 g, M_n = 108 000; PDI = 1.15, 7.5 mol % BCB), dissolved in benzyl ether (40 mL) was added dropwise via a peristaltic pump at ca. 12.8 mL/h with vigorously stirring under argon. After addition the reaction mixture was heated for an additional 1 h, the solvent was distilled under reduced pressure, and the remaining crude product was dissolved in dichloromethane and precipitated into methanol. This gave the nanoparticles, **9**, as a colorless solid (3.76 g, 94% yield), ^{1}H NMR (400 MHz, $CDCl_3$). The significant change is the disappearance of the aliphatic benzocylobutene protons at 3.05 on formation of the cross-linked nanoparticles; all other aspects of the spectrum are similar.

Results and Discussion

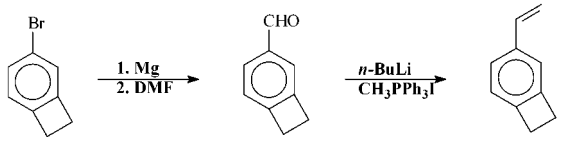
In developing a new strategy for nanoparticle formation, we were drawn to the field of living free radical polymerizations where the high degree of control is a result of an equilibrium between dormant and reactive propagating radicals. As a result, the reactive radical chain ends are present in extremely low concentrations.[13] This general concept, that is, only the reactive species need to be at ultra-dilute concentrations, was then applied to the formation of nanoparticles by intramolecular coupling. In this case, the linear polymer, which contains numerous latent coupling groups along the backbone, is added slowly to a heated solvent in which the coupling groups are either thermally or chemically activated. As a consequence, the traditional conditions of ultrahigh dilution need only be met for the reactive intermediates and not for the polymers themselves. Following this coupling event, the nanoparticles should be unreactive, which allows their concentration to increase to very high levels, (0.1−1.0 M) without intermolecular cross-linking reactions leading to gelation or coupling of individual nanoparticles. The ability to work at 0.1−1.0 M concentrations can be compared to the impractical concentration levels (ca. 10^{-6} M) required for traditional ultrahigh dilution techniques.

To satisfy these demands, the nature of the cross-linking group is critical; it must be selectively activated and react rapidly, leading to efficient intramolecular bond formation. It is also important that this reaction is irreversible and leads to a coupled structure that is subsequently unreactive under the reaction conditions. To fulfill these goals, our attention was directed to the benzocyclobutene group (BCB) which has found wide use as a latent Diels−Alder reagent in organic synthesis[14]

Scheme 1. Coupling Reaction of Benzocyclobutene Derivatives, **1**.



Scheme 2. Synthesis of Benzocyclobutene Monomer, **4**.



and in the formulation of thermosetting materials.[15] Upon heating, the benzocyclobutene group, **1**, undergoes ring opening to give the extremely reactive *o*-quinoid structure, **2**, which primarily reacts via an irreversible dimerization reaction to form the dibenzocyclooctadiene derivative, **3**, as well as a mixture of unidentified oligomeric materials (Scheme 1). The direct result of this chemistry is the selective formation of cross-links from the coupling of two or more benzocyclobutene units.[16]

Having identified the benzocyclobutene functionality as the critical coupling group for the preparation of nanoparticles, the desired monomer, 4-vinylbenzocyclobutene, **4**, was prepared from 4-bromobenzocyclobutene, **5**, by initial Grignard formation followed by reaction with *N*,*N*-dimethylformamide to give the aldehyde, **6**. Wittig coupling of **6** with methyltriphenylphosphonium bromide afforded the desired styrene derivative, **4**, in high yield (Scheme 2). As anticipated, the incorporation of the cyclobutene group into the monomer, **4**, did not decrease its stability when compared to styrene, and **4** proved to be stable to a wide variety of reaction conditions.

The key to the success of this intramolecular chain collapse strategy is the elimination of intermolecular cross-linking between BCB groups on different chains. Since it was envisaged that this critical balance between intramolecular coupling and intermolecular cross-linking would be influenced by the number and placement of BCB units along the polymeric backbone, accurate control of the starting linear polymers structure was also considered important. To achieve this and to permit a wide variety of linear polymers to be conveniently prepared, the polymerization of the desired monomer, 4-vinylbenzocyclobutene, **4**, was examined under living free radical conditions.[17] Copolymerization of **4** with vinyl monomers such as styrene, methyl methacrylate, or *n*-butyl acrylate in the presence of the α-hydrido alkoxyamine, **7**, proved to be a controlled

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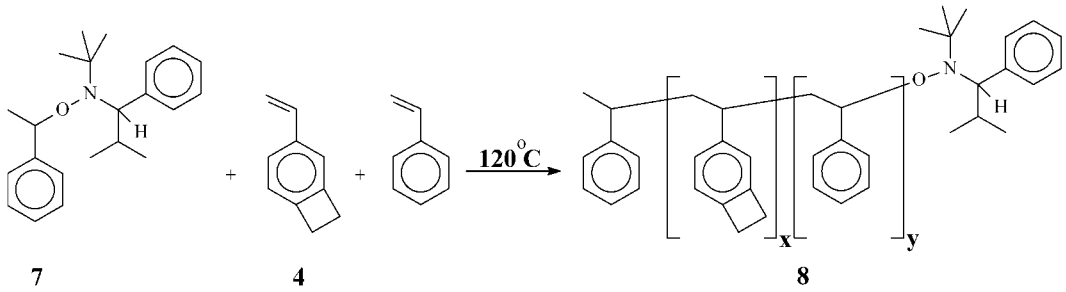
Scheme 3. Synthesis of Benzocyclobutene Functionalized Linear Polystyrene, **8**.



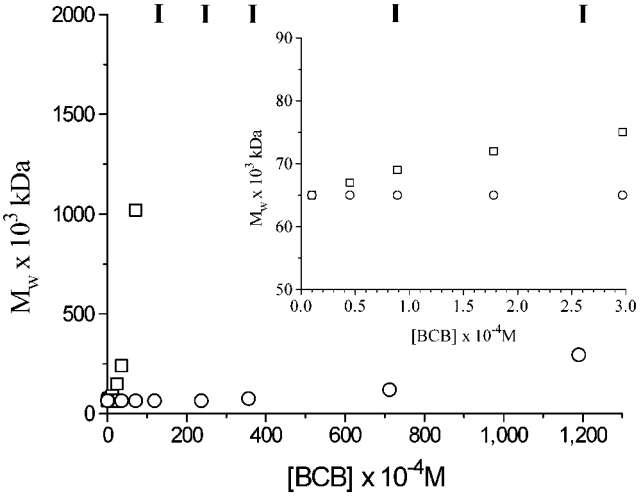


Figure 1. Variation in molecular weight of final macromolecule, M_w, with total concentration of BCB groups in solution; (□) ultra-high dilution strategy; **(□)** continuous addition strategy; **(I)** represents that an insoluble gel was produced (starting linear polymer; M_w = 95 000; PDI = 1.11).

procedure, leading to random incorporation of the reactive BCB units and low polydispersities for the resulting copolymers, **8** (Scheme 3). At molecular weights less than 120 000 amu the polydispersities for these random copolymers were 1.08−1.16, which increased to 1.19−1.26 for molecular weights above 200 000 amu. This increased polydispersity is due to the significantly reduced concentration of initiating groups at these high molecular weights and has been observed previously for both ATRP- and nitroxide-mediated procedures.[17]

The BCB-functionalized polystyrene derivatives, **8**, could be readily characterized by standard techniques and incorporation of the BCB units monitored by ^{1}H NMR which showed characteristic aliphatic resonances for the cyclobutene ring at 3.10 ppm. Intramolecular collapse was initially examined under traditional ultrahigh dilution techniques. For this, a solution of a 80:20 styrene/BCB random copolymer, **8** (M_w = 95 000; PDI = 1.11) in dibenzyl ether was heated at a variety of concentrations[18] under N_2 for 30 min at 250 °C. As can be seen in Figure 1, at very low concentrations of BCB groups, ca. 5.0×10^{-5} M (see inset, Figure 1), intermolecular cross-linking becomes apparent as evidenced by the increase in molecular weight of the product from its base value of 65 000 for a discrete nanoparticle due to chain−chain coupling. This ability to readily identify chain-chain coupling has been previously observed for dendrimer chemistry where even minor amounts of intermolecular coupling can be easily detected by gel permeation chromatography (GPC).

This ability is due to the molecular weight doubling on chain−chain coupling, and the combination of this feature with the low polydispersity of the initial chains results in a lower limit of ca. 1−2% of intermolecular cross-linking being readily detected as a higher molecular shoulder under standard GPC conditions. At higher concentrations[18] of ca. 9.0×10^{-3} M cross-linking to a swollen gel occurs very rapidly due to the large number of BCB functional groups along the polymeric backbone. While these concentrations are comparable to results obtained with other traditional ultra-high dilution techniques,[9,10] the results are in stark contrast to the continuous addition strategy. In this approach, a concentrated solution ([BCB] = 0.2 M) of the same starting linear polymer, **8**, is continuously added via a peristaltic pump to a high-boiling solvent, such as dibenzyl ether, heated at 250 °C[19] to give a final BCB concentration of 0.05 M. After addition, the solvent is removed, and the nanoparticles, **9**, are isolated using normal precipitation techniques (Scheme 4). No gelation or intermolecular cross-linking is observed under these conditions, and only after increasing the final concentration of BCB groups to 0.12 M were minor amounts of nanoparticle coupling observed. The ability to successfully conduct these chain-collapse reactions at final BCB concentrations of 0.01−0.1 M represents an increase of 3−4 orders of magnitude when compared to the traditional ultrahigh dilution strategy (Figure 1). This permits multigram samples to be prepared on a routine basis with standard laboratory equipment, a dramatic improvement compared to previous approaches.

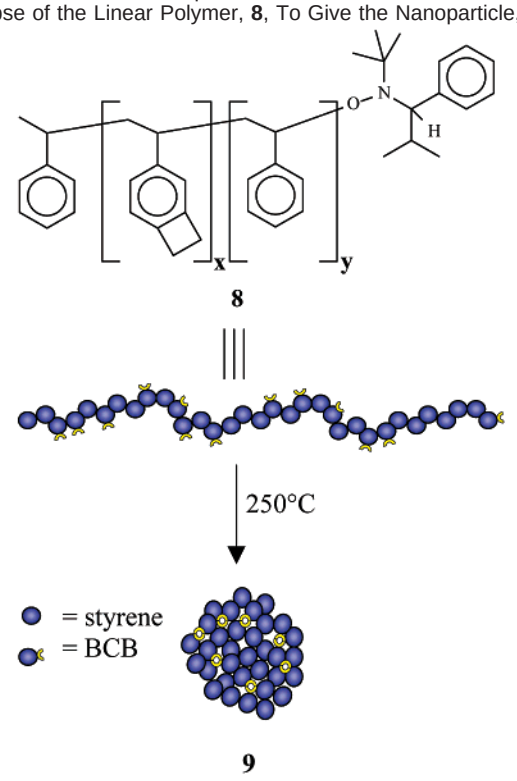
A significant feature of the above concentration studies is the reduction in hydrodynamic volume of the random coil linear polymer on intramolecular collapse to give the final nanoparticle. In the above example, the original linear polymer has a molecular weight, M_w of 95 000 amu; however, upon reaction the macromolecule decreases in size to give a nanoparticle with an apparent or polystyrene equivalent M_w of 65 000 amu. Dynamic light scattering was also employed to follow this decrease in size, and a reduction in the hydrodynamic radius, R_h from 8.7 to 6.6 nm, was observed upon intramolecular collapse. Since no byproducts are produced during this reaction

(17) (a) Hawker, C. J.; Bosman, A. W.; Harth, E. *Chem. Rev.* **2001**, *101*, 3661−3688. (b) Kamigaito, M.; Ando, T.; Sawamoto, M. *Chem. Rev.* **2001**, *101*, 3689−3746. (c) Matyjaszewski, K.; Xia, J. *Chem. Rev.* **2001**, *101*, 2921−2990.

(18) The concentration of BCB groups is an overall concentration in solution and is independent of the molecular weight of the linear polymer. For example, a 80/20 styrene/BCB copolymer has a repeat unit consisting of 4 styrene monomers (4 × 104) and one BCB monomer (1 × 130), which equals a repeat unit molecular weight of 546. Therefore 4.00 g of this 80/20 copolymer contains, 4.00/546 = 7.32×10^{-3} mol of repeat units or 7.32 millimole equivalents of BCB. Dissolution in 50 mL of dibenzyl ether then leads to an overall concentration of 0.146 M.

(19) A reaction temperature of 250 °C corresponds to the exotermic maximum of the DSC curve relating to ring opening of the cyclobutene ring, the maximum was chosen to ensure efficient and rapid formation of the reactive *o*-quinoid intermediate.

Scheme 4. Schematic Representation of the Intramolecular Collapse of the Linear Polymer, **8**, To Give the Nanoparticle, **9**.



and no molecular weight lost, this decrease can only be due to a change in the architecture of the macromolecule from a random coil to a nanoparticle. Again, this is consistent with dendrimer chemistry where the compact, three-dimensional dendritic structure leads to an apparent molecular weight which is significantly smaller that the actual molecular weight.[20]

Further confirmation of the structural change was obtained from NMR studies; of particular note is the observed absence of unreacted BCB units in the final nanoparticles, **9**. As shown in Figure 2, comparison of the ^{1}H NMR spectra for the starting linear polymer, **8**, and the nanoparticle, **9**, shows the prominent resonance for the aliphatic protons of the cyclobutene group at 3.10 ppm in the former, which completely disappear after collapse, and a broad resonance at 2.0−3.0 ppm is observed. This is consistent with ring opening of the benzocyclobutene group and coupling to give cyclooctane derivatives and higher aliphatic coupled oligomers. A direct consequence of this ring opening is that the BCB groups undergo reaction to give dimers and oligomers that do not undergo any further coupling chemistry. This fulfils one of the requirements discussed above for a successful intramolecular chain collapse reaction and permits the substantial build-up of product in the final reaction mixture. The lack of reactivity can also be demonstrated by repeated thermal cycling of the isolated nanoparticles, which results in no observable change in physical properties such as molecular weight, NMR spectra, and so forth. Formation of the nanoparticles also leads to an increase in the glass transition temperature of the nanoparticles when compared to the starting linear polymers. The BCB functionalized linear polystyrenes, **8**, show T_g's similar to that observed for polystyrene, ca. 100−

(20) (a) Fréchet, J. M. J. *Science* **1994**, *263*, 1710. (b) Fischer, M.; Vögtle, F. *Angew. Chem., Int. Ed.* **1999**, *38*, 885. (c) Hawker, C. J.; Fréchet, J. M. J.. *J. Am. Chem. Soc*. **1990**; *112*, 7638. (d) Tomalia, D. A.; Naylor, A. M.; Goddard, W. A., III. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 138.

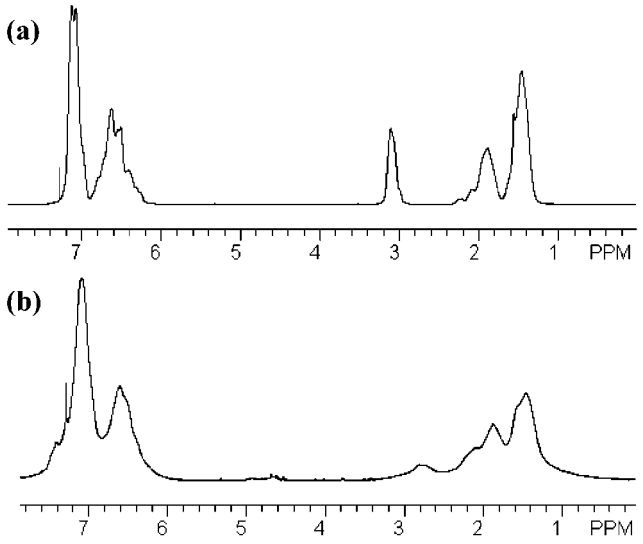


Figure 2. Comparison of ^{1}H NMR spectrum for (a) the starting linear polymer, **8**, 80/20 Sty/BCB, M_w = 95 000, PDI = 1.12; and the resulting nanoparticle, **9**, M_w = 65 000, PDI = 1.10.

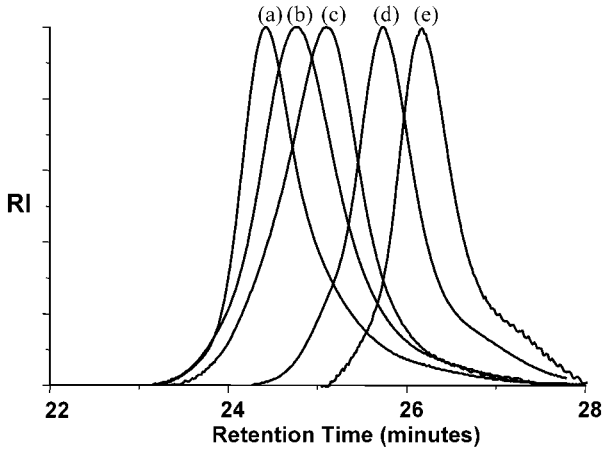


Figure 3. Overlay of GPC traces for (a) the starting linear polymer, **8**, M_w = 105 000, PDI = 1.12; and nanoparticles, **9**, with (a) 0 mol % BCB incorporation, (b) 5 mol % BCB incorporation, (c) 10 mol % BCB incorporation, (d) 20 mol % BCB incorporation, and (e) 25 mol % BCB incorporation.

105 °C, while the glass transition temperature for the nanoparticles, **9**, increase by ca. 20 °C to 120−130 °C at 20% BCB incorporation with an associated broadening of the transition. All of the above data is consistent with the intramolecular collapse of a random coil linear polymer to give a single, higher-density nanoparticle.

This unique feature of being able to tailor the nanoparticle via the starting linear polymer was then examined in detail using three different series of polystyrene derivatives, ca. 44 000; 110 000; and 230 000 amu containing varying levels of BCB incorporation from 1.25 to 30% (Table 1). Under the continuous addition technique described above, conversion of the linear polymers to nanoparticles was a facile process at all molecular weights and percent BCB incorporations studied. At concentrations of up to 0.01−0.1 M, no indication of intermolecular cross-linking was observed, and in each case the GPC trace shifted to lower hydrodynamic volumes. As can be seen in Figure 3, for the same molecular weight of the starting linear polymer, **8**, a systematic decrease in the hydrodynamic volume of the nanoparticles is observed on increasing the percent of benzo-

Table 1. Comparison of the Polystyrene Equivalent Molecular Weights and PDI for the Starting Linear Polymers, **8**, and the Final Nanoparticles, **9**

	linear		nanoparticle		
composition	M_w	PDI	M_w	PDI	%BCB
Sty/BCB	44 000	1.09	41 700	1.09	2.50
Sty/BCB	44 500	1.08	38 200	1.12	5.00
Sty/BCB	45 500	1.09	29 100	1.11	10.00
Sty/BCB	43 500	1.10	20 700	1.12	15.00
Sty/BCB	44 000	1.07	18 500	1.12	20.00
Sty/BCB	110 500	1.15	103 000	1.17	1.25
Sty/BCB	113 000	1.12	94 500	1.19	2.50
Sty/BCB	109 000	1.14	79 300	1.18	5.00
Sty/BCB	108 000	1.15	59 800	1.18	7.50
Sty/BCB	112 000	1.10	56 000	1.19	10.00
Sty/BCB	110 000	1.16	44 200	1.16	15.00
Sty/BCB	111 000	1.11	42 800	1.15	20.00
Sty/BCB	112 000	1.12	40 500	1.09	25.00
Sty/BCB	231 000	1.23	189 800	1.26	1.25
Sty/BCB	235 000	1.25	174 000	1.22	2.50
Sty/BCB	228 000	1.22	109 000	1.26	5.00
Sty/BCB	230 000	1.19	98 000	1.18	7.50
Sty/BCB	233 000	1.26	91 500	1.16	10.00
Sty/BCB	231 000	1.24	81 000	1.17	12.50
Sty/BCB	235 000	1.23	80 300	1.19	15.00
Sty/BCB	230 000	1.21	66 000	1.17	20.00
Sty/BCB	229 000	1.24	62 000	1.25	25.00
Sty/BCB	234 000	1.23	63 500	1.16	30.00

cyclobutene groups, which is consistent with an increase in the level of intramolecular coupling and a more globular, three-dimensional structure. The other pertinent feature of Figure 3b−e is the symmetrical nature/low PDI of the GPC traces for the nanoparticles and the associated lack of higher-molecular weight shoulders. This demonstrates that even at high BCB loadings, ca. 25 mol %, no detectable amount of intermolecular cross-linking is occurring.

Analysis of the trends within each series showed that the percent reduction in hydrodynamic volume increases with both increasing molar percentage of BCB and the molecular weight of the starting linear polymer. In each case, the actual molecular weight of the cross-linked macromolecules is significantly greater than the apparent molecular weight. For example, a 70/30 styrene/BCB random copolymer with an initial molecular weight, $M_w = 234\,000$ (PDI = 1.23) gives a nanoparticle with a polystyrene equivalent molecular weight, $M_w = 63\,500$ (PDI = 1.16) which represents a reduction in hydrodynamic volume of 73%. The actual molecular weight of the final nanoparticle was also determined by light scattering and found to be 230 000 which is within experimental error of that of the starting linear polymer which demonstrates that the actual molecular weights of the starting linear polymer and the final nanoparticles are approximately the same. This collapse and associated change in hydrodynamic volume is therefore due to the formation of up to 310 intramolecular links per nanoparticle, assuming that each activated BCB group reacts with one other activated BCB group.[22] Interestingly, all plots are of a similar shape and seem to reach a plateau of between 65 and 75% reduction in apparent molecular weight (Figure 4). It should also be noted that in the control experiments, heating polystyrene with 0% BCB incorporation resulted in no detectable change in the chromatographic or spectral properties of the polymers.

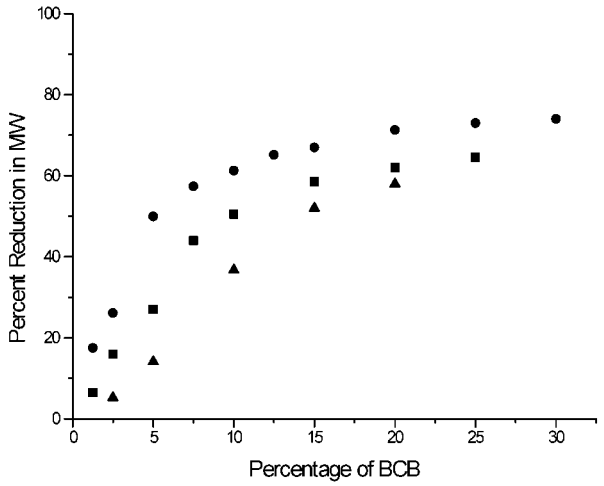


Figure 4. Variation in the percent reduction in molecular weight[21] for the nanoparticles, **9**, with the mol % of BCB units in the starting linear polymer, **8**, for 44 K (●), 110 K (■), and 230 K (●) series.

Table 2. Comparison of Molecular Weight (Linear Standard Equivalent) and PDI for the Starting Functionalized Linear Polymers, **10**, and the Final Nanoparticles, **11**

	linear		nanoparticle		
composition	M_w	PDI	M_w	PDI	%BCB
MMA/BCB	52 500	1.17	36 500	1.14	10.00
MMA/BCB	54 500	1.12	28 000	1.11	15.00
MMA/BCB	56 000	1.13	26 900	1.13	20.00
n-BuA/BCB	74 500	1.10	58 100	1.12	5.00
n-BuA/BCB	77 500	1.12	45 700	1.14	10.00
n-BuA/BCB	75 000	1.09	33 500	1.09	15.00
n-BuA/BCB	73 000	1.09	27 800	1.10	20.00
Sty/Cl−Sty/BCB[a]	101 000	1.18	73 500	1.20	5.00
Sty/Cl−Sty/BCB[a]	92 000	1.14	48 500	1.13	10.00
Sty/Cl−Sty/BCB[a]	85 000	1.14	34 000	1.17	20.00
PEG-Sty/BCB[b]	92 000	1.13	70 500	1.10	5.0
PEG-Sty/BCB[b]	95 000	1.11	52 000	1.09	10.0
PEG-Sty/BCB[b]	89 500	1.12	36 500	1.14	20.0

[a] 10 mol % incorporation of *p*-chloromethylstyrene [b] PEG block, $M_n = 5000$; PDI = 1.06.

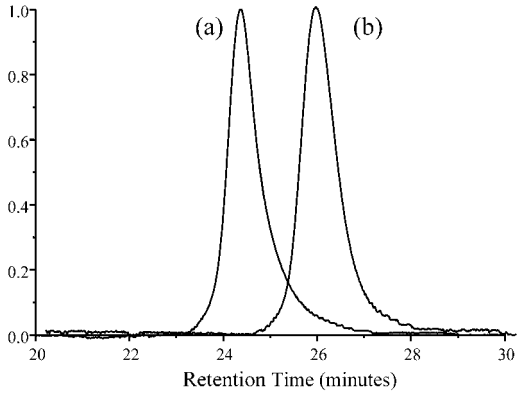


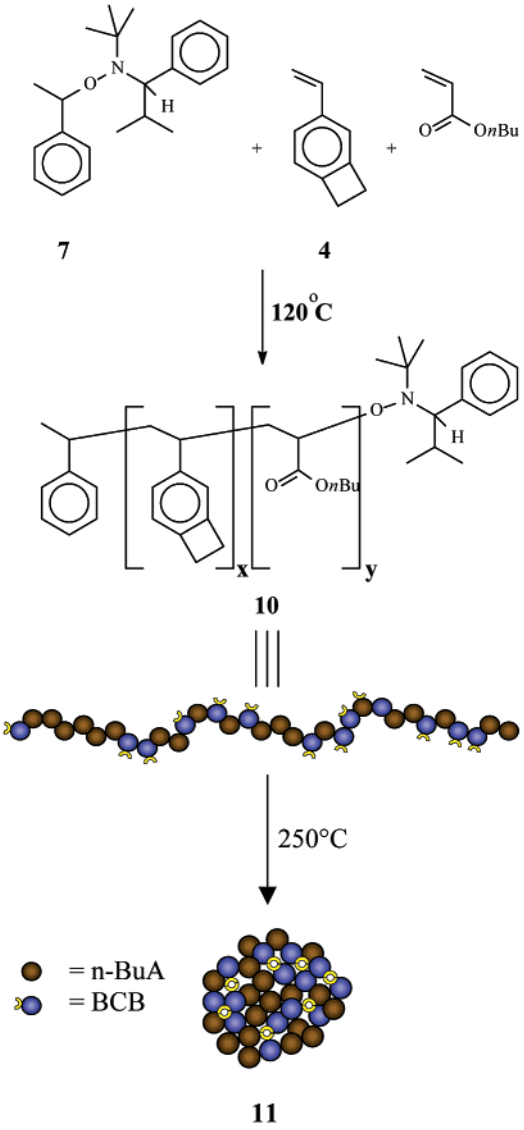
Figure 5. GPC traces for (a) the starting poly(ethylene glycol)-*b*-poly(styrene-*co*-benzocyclobutene), **15**, ($M_w = 95\,000$, PDI = 1.11) and (b) the final hybrid nanoparticle-linear block copolymer, **16**, ($M_w = 52\,000$, PDI = 1.09).

Examination of the data in Table 1 also demonstrates the inherent versatility of this approach in controlling the size of the final nanoparticle. Not only can the size and cross-link density of the nanoparticle be controlled by the level of BCB incorporation, but the molecular weight of the starting linear

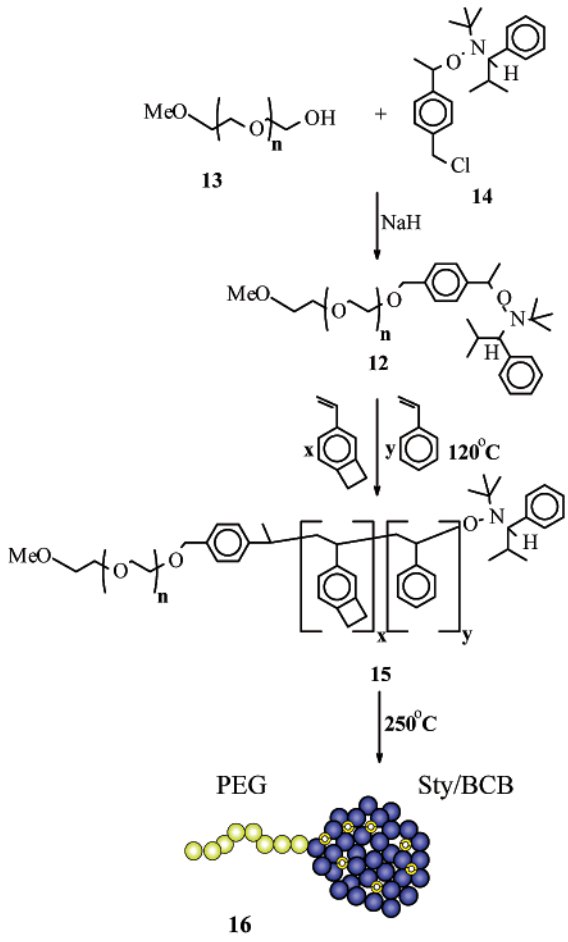
(21) Percent reduction in molecular weight is calculated from the difference between the actual molecular weight and the apparent molecular weight as determined by GPC; (M_w actual − M_w apparent)/M_w actual × 100%,

(22) This is based on the assumption of one BCB unit reacting with a second BCB unit forming an intramolecular dimer. While it is an efficient process, there is the possibility of side reactions which will affect the absolute numbers of cross-links; therefore, this number may represent an upper limit.

Scheme 5. Schematic Representation of the Intramolecular Collapse of a Random *n*-Butyl Acrylate-Based Linear Polymer, **10**, To Give the Nanoparticle, **11**.



Scheme 6. Formation and Intramolecular Collapse of the PEG-*b*-PSt/BCB Block Copolymer, **15**, To Give a Hybrid Linear−Nanoparticle Copolymer, **16**.



polymer also plays a key role in determining the hydrodynamic volume of the final nanoparticle. For example, a polystyrene derivative with a 10% incorporation of BCB and a molecular weight, M_w, of 112 000 gives a nanoparticle with a R_h of 6.2 nm. Increasing the molecular weight, M_w, of the starting linear polymer to 233 000 while still retaining the 10% incorporation of BCB gives a larger nanoparticle with a R_h of 9.5 nm. In turn, a polystyrene derivative with an analogously higher molecular weight of 229 000 but with a 25% incorporation of BCB gives a nanoparticle with a R_h of 6.4 nm, very similar to the first example with a lower molecular weight (117 000) and level of BCB incorporation (10%). A consequence of this is that the size and physical characteristics of the final nanoparticle can be directly dictated by the structure and functionality of the starting linear polymer.

The versatile nature of this intramolecular chain collapse approach to nanoparticles coupled with the ability to prepare a wide variety of linear polymers by living free radical techniques also opens up the possibility of preparing well-defined nanoparticles incorporating functional groups, nonstryrenic monomers, or different macromolecular architectures. As shown in Table 2, starting linear polymers based on methyl methacrylate (MMA) or *n*-butyl acrylate (*n*-BuA) can be employed as the backbone polymer with no change in the efficiency of the intramolecular collapse process. For example, copolymerization of an 85:15 mixture of *n*-butyl acrylate and the vinyl BCB derivative, **4**, in the presence of the alkoxyamine initiator, **7**, proceeds smoothly to give the well-defined random copolymer, **10**, with a molecular weight, M_w of 75 000 and a polydispersity of 1.09. Addition of a concentrated solution of **10** (0.1 M) to dibenzyl ether, heated at 250 °C gives a poly(*n*-butyl acrylate) nanoparticle, **11**, with an apparent molecular weight, M_w of 33 500 and a polydispersity of 1.09. (Scheme 5). The relative selectivity of the thermal procedure used to activate the BCB group also allows other functional groups such as chloromethyl substituents to be introduced into the linear polymer, thereby leading to functionalized nanoparticles.

It should however be realized that this intramolecular collapse procedure is not limited to simple linear random copolymers. Additional structural features can be built into the starting materials, which are then translated into the nanoparticle structure. For example, block copolymers can potentially be used in such an approach, and if the reactive BCB groups are contained in only one of the blocks, novel macromolecular architectures can be prepared in which a controlled number of linear chains, one or two for AB and ABA block copolymers respectively, are attached to the nanoparticle. To test this hypothesis, functionalized poly(styrene)-*b*-poly(ethylene glycol)

AB block copolymers were prepared by living free radical procedures. The alkoxyamine substituted poly(ethylene glycol) macroinitiator, **12**, was obtained by reaction of the sodium salt of monomethylpoly(ethylene glycol), **13** (M_n = 5000, PDI = 1.06), with the chloromethyl substituted alkoxyamine, **14**. The macroinitiator, **12**, was then used to initiate the polymerization of a mixture of styrene and **4** at 120 °C to give the desired AB block copolymer, **15**, which contains the cross-linking BCB units in the second block only (Scheme 6).

Reaction of **15** under continuous addition conditions then results in the selective intramolecular collapse of the second block to give a novel hybrid linear−nanoparticle architecture, **16**, in which a single water soluble PEG linear chain is attached to a three-dimensional cross-linked polystyrene nanoparticle, similar in structure to that of hybrid dendritic−linear block copolymers.[23] As can be seen in Figure 5, the effect of intramolecular collapse is clearly evident in the shift of the GPC trace for the starting poly(ethylene glycol)-*b*-poly(styrene-*co*-benzocyclobutene), **15**, (M_w = 95 000, PDI = 1.11) to that of the final hybrid nanoparticle-linear block copolymer, **16**, (**(**M_w = 52 000, PDI = 1.09) and demonstrates the controlled nature of this procedure. The solubility of these hybrid block copolymers were similar to that for the parent polystyrene nanoparticles which may be due to the relatively small size of the PEG block. Future work will examine the effect of larger PEG blocks on the solubility and phase behavior of hybrid PEG-PSt diblock copolymers.

Conclusions

In conclusion, we have demonstrated a viable synthetic strategy for the controlled intramolecular collapse of linear polymer chains to give single-molecule nanoparticles. By using a continuous addition strategy in conjunction with thermally activated benzocyclobutene-coupling chemistry, intermolecular cross-linking can be effectively eliminated even at high concentrations (0.1 M) which makes this a practical technique for the large-scale synthesis of well-defined nanoparticles. The size and cross-link density of the final nanoparticles can be accurately controlled by the initial degree of polymerization of the linear chain and the level of incorporation of the BCB coupling units. Conversion of the starting random coil linear polymer to the final nanoparticle results in a significant reduction in apparent molecular weight, up to 65−75%, which is fully consistent with the adoption of a dense, three-dimensional structure. The versatility of this approach is further demonstrated by the use of functionalized linear polymers and block copolymers to give reactive and architecturally complex nanoparticles, such as hybrid linear−nanoparticle copolymers. While the resulting nanoparticles share many features in common with dendritic macromolecules, it should be emphasized that a consequence of starting from preformed linear polymers is the ability to prepare larger molecular sizes more easily and the availability of the nanoparticles is greatly increased when compared to dendrimers.

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