Synthesis and Characterization of Amine-Functionalized Polystyrene Nanoparticles

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ABSTRACT: Functionalized polymer nanoparticles have been synthesized through an intramolecular cross-linking reaction with polystyrene as the backbone and an amino group as the functional moiety. The intramolecular cross-linking reaction was performed under ultradilute conditions, and the cross-linked polymers were characterized by gel permeation chromatography (GPC), nuclear magnetic resonance (NMR), dynamic light scattering (DLS), and atomic force microscopy (AFM). The availability of the amino moiety in the nanoparticle for further functionalization was confirmed by its reaction with trimethylacetyl chloride.

1. Introduction

Nanoparticles have emerged as one of the important building blocks in the construction of a wide range of materials that could find use in medical, mechanical, and electronic applications.[1,2] Especially, functionalized nanoparticles have attracted considerable attention because of their potential applications as building blocks for a variety of nanotechnology applications, ranging from vectors for drug and DNA delivery systems to the nanoscale devices such as single-electron transistors and molecular switches.[3−10] However, most of the surface functionalizations in these materials are obtained through modification of metal and semiconductor nanoparticles by self-assembly, organic reaction, or polymerization to form functional monolayers or polymeric "shells".[5,11−16] Beyond the use of polymer micelles through self-assembly to form the nanoparticles, a new strategy involving the collapse and intramolecular coupling of single-polymer chains to give discrete nanoparticles has been developed.[17,18] More recently, an intramolecular radical cross-linking reaction was achieved, where the reaction was performed under ultradilute solution.[19] Under these conditions, the covalent links are exclusively formed between segments of the same polymer chain, leading to a unimolecular particle with size ranging from 3 to 15 nm. While these seminal reports demonstrate possibility of achieving polymeric nanoparticles by intramolecular cross-linking, the possibility of further functionalizing these nanoparticles has not been reported. Such a capability would significantly expand the scope of these polymeric nanoparticles in a variety of applications. With this objective in mind, we report here a polystyrene-based nanoparticle that displays amino moieties. The capability for further functionalization, using these amino groups as the handle, is demonstrated using a simple reaction with a carboxylic acid chloride.

2. Experiment

THF and toluene were dried over sodium and freshly distilled before use. Acetone was dried over potassium carbonate. 4-Vinylbenzyl chloride and 4-vinylaniline were purchased from commercial sources and purified through flash column chromatography. The RAFT reagent, 2-(2-cyanopropyl)dithiobenzoate, was synthesized according to the reported procedure.[20] All other chemicals were used directly without further purification.

^{1}H NMR spectra were recorded on a 400 MHz NMR spectrometer using the residual proton resonance of the solvent as the internal standard. Chemical shifts are reported in parts per million (ppm). When peak multiplicities are given, the following abbreviations are used: s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; m, multiplet; br, broad. Flash chromatography was performed with silica gel. Analytical thin-layer chromatography was performed on silica plates with a F-254 indicator, and the visualization was accomplished by a UV lamp. The molecular weights were estimated by gel permeation chromatography (GPC) with polystyrene as a standard and with a refractive index detector, and the sample was eluted with anhydrous THF. A digital correlator and a goniometer were used for the DLS measurements. The light source was a solid-state laser system, operating at 514 nm. The temperature was kept constant at 25 °C. Possible dust particles were eliminated using filters with 0.20 μm pore size for THF solutions. All measurements were done at a correlation time of 1.0 min. The particle sizes reported are the average of at least five readings. Tapping-mode scanning atomic force microscopy (AFM) images were obtained in both height- and phase-contrast modes with a Digital Instruments Nanoscope II scanning force microscope with etched silicon tips on cantilevers, with spring constants ranging from 40.0 to 60.0 N/m. Thin films were prepared by the spin coating of 0.5 wt % 1,4-dioxane solutions of the copolymers on polished silicon wafers, with a spin casting speed of 1500 rpm.

Synthesis of 4-*N*-Boc-vinylaniline (1). 4-Vinylaniline (2.4 g, 20 mmol) was dissolved in 40 mL anhydrous THF, and then di-*tert*-butyl dicarbonate (4.0 g, 24 mmol) in 40 mL THF was added dropwise to the mixture. After refluxing overnight, the mixture was allowed to cool to ambient temperature and then partitioned between water and dichloromethane. The aqueous layer was extracted with CH_2Cl_2 twice, and the organic layers were combined and washed with water then dried over sodium sulfate. After filtration, the solvent was removed under reduced pressure; the residue was purified by flash chromatography over silica gel eluted with hexane/ethyl acetate to afford **1** (3.5 g, 80% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (s, 4H), 6.69 (q, 1H), 6.33 (s, 1H), 5.66 (d, 1H), 5.12 (d, 2H), 1.57 (s, 9H).

General Procedure for the Synthesis of Poly(4-*N*-Boc-aminostyrene)-*co*-(4-chloromethylstyrene) (3). 4-*N*-Boc-vinylaniline (**1**) (1.0 equiv), 4-vinylbenzyl chloride (1.0 equiv for **3a**, 0.5 equiv for **3b**), 2-(2-cyanopropyl) dithiobenzoate

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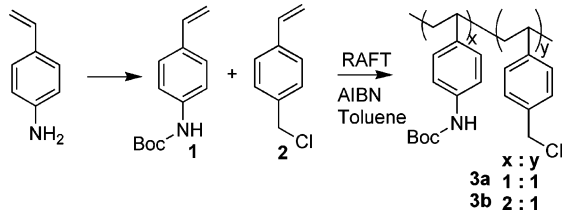
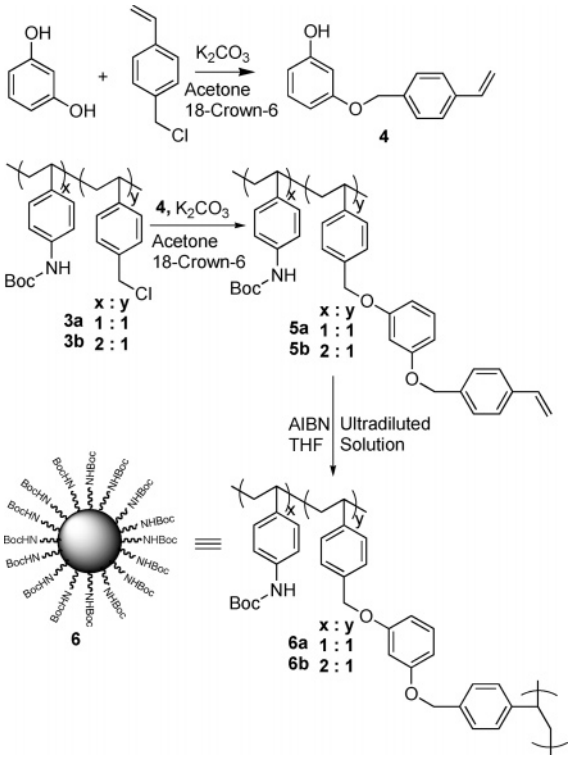
Scheme 1. Synthetic Route for the Polystyrene Copolymer Backbone.



Scheme 2. Synthetic Route for the Crosslinked Nanoparticles.



(RAFT reagent) and AIBN (0.01 equiv) were dissolved in anhydrous toluene. The mixture was subjected to freeze−pump−thaw cycles 4 times, then stirred at 90 °C for 24 h. After cooling to room temperature, the solution was poured into hexane, and the precipitate was collected by filtration. After drying under vacuum, polymer **3** was obtained as a white powder.

3a (*x*:*y* = 1:1): 1.2 g, yield 40%; M_n = 15 000, PDI = 1.27. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51−6.21 (br, 8H), 4.52 (br, 2H), 2.18−1.17 (br, 15H).

3b (*x*:*y* = 2:1): 1.6 g, yield 60%; M_n = 14 000, PDI = 1.22. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51−6.21 (br, 12H), 4.52 (br, 2H), 2.16−1.17 (br, 27H).

Synthesis of 4-[(3-Hydroxyphenoxy)methyl]styrene (4). Resorcinol (4.4 g, 40 mmol), 4-vinylbenzyl chloride (6.1 g, 40 mmol), and potassium carbonate (14 g, 0.1 mol) were dissolved in 200 mL of acetone and refluxed for 18 h under nitrogen. After cooling to room temperature, the mixture was partitioned between water and dichloromethane. The aqueous layer was extracted with dichloromethane twice, and the organic layers were combined and washed with water then dried over sodium sulfate. After filtration, the solvent was removed under reduced pressure, and the residue was purified by flash chromatography over silica eluted with hexane/ethyl acetate to afford **4** (3.3 g, 35% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.42 (m, 4H), 7.15 (t, 1H), 6.69 (t, 1H), 6.55 (q, 2H), 5.71 (d, 1H), 5.26 (d, 2H), 5.07 (s, 2H), 4.66 (s, 1H).

General Procedure for the Precursor Copolymers 5a and 5b. Copolymer **3** (1.0 equiv), 4-[(3-hydroxyphenoxy)-methyl]styrene **4** (2.0 equiv), potassium carbonate (3.0 equiv),

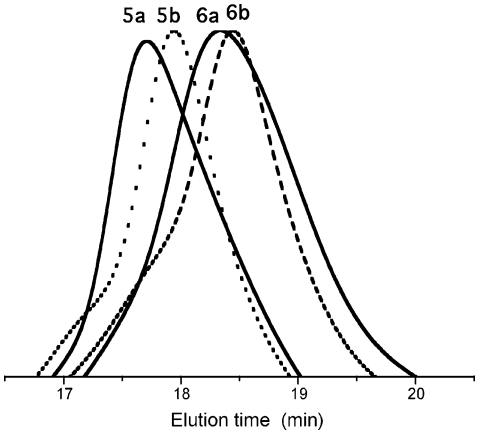


Figure 1. GPC of the un-cross-linked copolymers **5a**, **5b** and the cross-linked copolymers **6a**, **6b**.

Table 1. GPC and DLS Results of the Precursors and the Nanoparticles

	precursor copolymer **5**			cross-linked nanoparticle **6**		
x:*y*[a]	M_n[b]	PDI	R_h (nm)[c]	M_n	PDI	R_h (nm)
a 1:1	21 000	1.66	26.1	12 000	1.31	16.9
b 2:1	19 000	1.50	13.3	13 000	1.33	10.8

[a] The ratio of *x*:*y* was detected by NMR. [b] Number-average molecular weight was measured by GPC using polystyrene as standard. [c] Hydrodynamic radius was measured by DLS in THF.

and a catalytic amount of 18-crown-6 were dissolved in anhydrous acetone and refluxed for 48 h under nitrogen. After cooling to room temperature, the mixture was filtered, concentrated, and then precipitated from methanol. The target copolymer **5** with a double bond in the pendant group was obtained after filtration as a light-yellow powder.

5a (*x*:*y* = 1:1): 0.42 g, yield 76%; M_n = 21 000, PDI = 1.66. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61−7.25 (br, 4H), 7.24−6.21 (br, 12H), 5.72 (br, 1H), 5.22 (br, 1H), 4.92 (br, 4H), 2.14−1.25 (br, 15H).

5b (*x*:*y* = 2:1): 0.46 g, yield 83%; M_n = 19 000, PDI = 1.50. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.52−7.31 (br, 4H), 7.25−6.18 (br, 16H), 5.72 (br, 1H), 5.25 (br, 1H), 4.98 (br, 4H), 2.14−0.85 (br, 27H).

General Procedure for Cross-linked Nanoparticles 6a and 6b. A solution of **5** (200 mg) and AIBN (10 mg) in anhydrous THF (500 mL) was bubbled with nitrogen for 30 min and stirred at 60 °C for 48 h. After cooling to room temperature, the mixture was concentrated and then poured into hexane. The precipitate was collected by filtration to afford **6** as a light-yellow solid.

6a (*x*:*y* = 1:1): 190 mg, yield 95%; M_n = 12 000, PDI = 1.31. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66−6.12 (br, 16H), 5.01 (br, 4H), 2.14−0.78 (br, 18H).

6b (*x*:*y* = 2:1): 185 mg, yield 93%; M_n = 13 000, PDI = 1.33. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71−6.12 (br, 20H), 4.01 (br, 4H), 2.24−0.85 (br, 30H).

General Procedure for the Synthesis of Functionalized Nanoparticles 7a and 7b. A solution of **6** (1 equiv) in methanol was placed in a sonicator for 10 min to form a suspension. In another flask, acetyl chloride (2 equiv) was added dropwise to methanol and stirred for 30 min at 0 °C, and then added dropwise to the suspension at 0 °C. After addition, the mixture was stirred at room temperature until it became a clear solution. The solution was concentrated and then poured into ether. This process was repeated twice, and the precipitate was collected by filtration to afford **7** as a light-yellow solid.

7a (*x*:*y* = 1:1): 51 mg, yield 90%. ^{1}H NMR (400 MHz, MeOD): δ 7.86−6.08 (br, 16H), 2.26−0.58 (br, 9H).

7b (*x*:*y* = 2:1): 54 mg, yield 93%. ^{1}H NMR (400 MHz, MeOD): δ 7.98−6.02 (br, 20H), 2.24−0.52 (br, 12H).

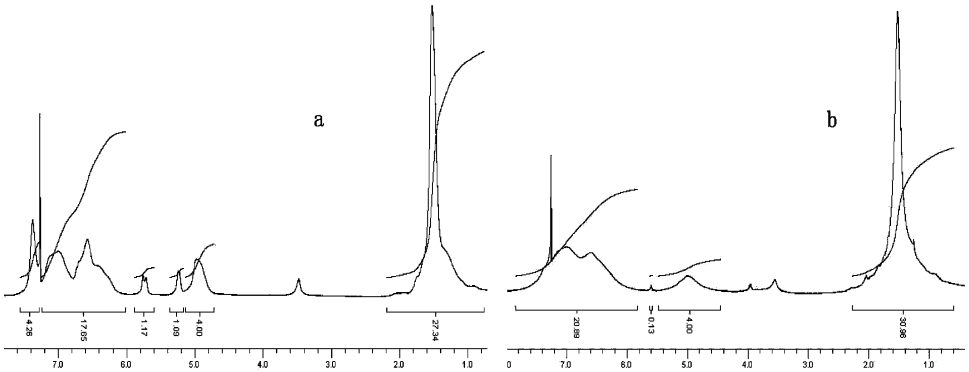


Figure 2. ^{1}H NMR spectra of the copolymers before and after cross-linking: (a) **5b**; (b) **6b**.

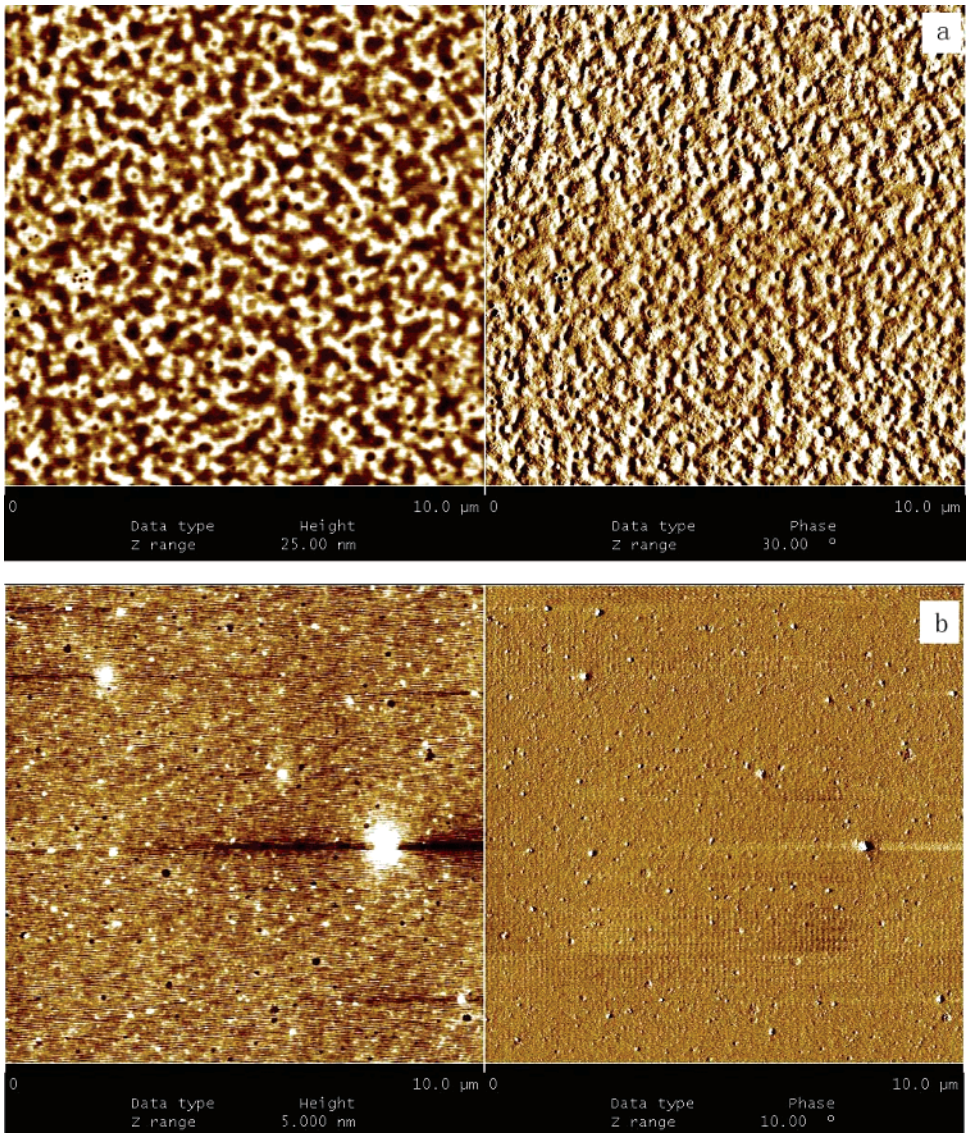


Figure 3. AFM images of the (a) un-cross-linked copolymer **5a** and (b) the cross-linked nanoparticles **6a**. All the samples are spin coated on silicon wafers at the speed of 1500 rpm with a 0.5 wt % 1,4-dioxane solution. Scan areas are 10 μm × 10 μm for all cases.

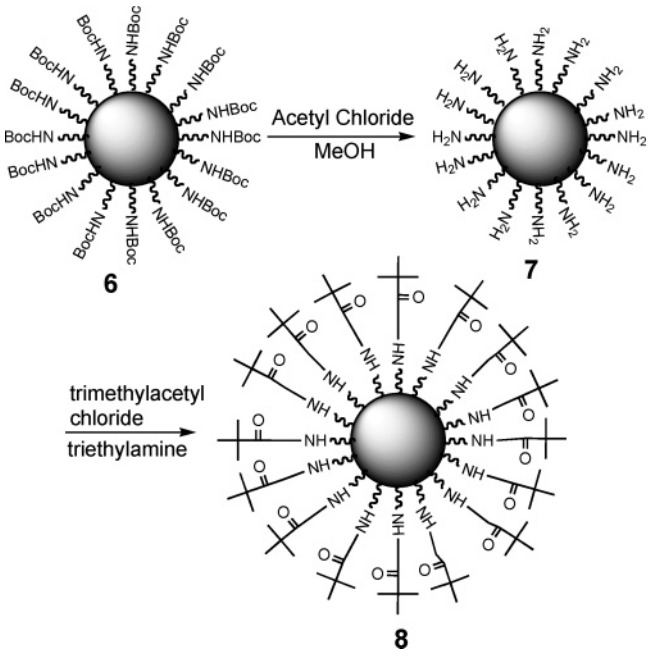
General Procedure for Functional Nanoparticles 8a and 8b. A solution of **7** (1 equiv) and Et_3N (3 equiv) was dissolved in dichloromethane, and then trimethylacetyl chloride (1 equiv) was added dropwise at 0 °C. After the addition, the mixture was stirred at room temperature overnight, then precipitated in methanol. This precipitation process was repeated two more times, and the precipitate was collected by filtration to afford **8** as a light-yellow solid.

8a (x:y = 1:1): yield 95%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23−6.08 (br, 16H), 5.24−4.67 (br, 4H), 1.88−0.82 (br, 18H).
8b (x:y = 2:1): yield 93%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98−6.02 (br, 20H), 5.35−4.60 (br, 4H), 2.65−0.52 (br, 27H).

3. Results and Discussion

The target polymer's structure involves a polymer-containing 4-*N*-Boc-vinylaniline (**1**) and 4-chloromethyl-

Scheme 3. Synthetic Route for the Functionalized Nanoparticle.



styrene (**2**). The protected amino group monomer would provide the necessary functionality display in the final polymeric nanoparticle, while the chloromethyl styrene monomer affords the handle for incorporating the functionality needed for intramolecular cross-linking. Monomer **1** was obtained from the commercially available 4-vinylaniline and di-*tert*-butyl dicarbonate. Compound **1** was copolymerized with **2** under reversible addition−fragmentation chain transfer (RAFT) using AIBN as the initiator, as shown in Scheme 1. Poly(4-*N*-Boc-aminostyrene)-*co*-(4-chloromethylstyrene) (**3a** and **3b**) were obtained using two different feed ratios of monomers **1** and **2** with M_n and PDI of 15 000 and 1.27 for **3a**, and 14 000 and 1.22 for **3b**, respectively. An estimate of the monomer ratio in polymers **3a** and **3b** corresponds well with the feed ratio of 1:1 and 2:1, respectively, as determined by ^{1}H NMR.

To functionalize the polymer with a cross-linkable functionality, polymers **3a** and **3b** were treated with compound **4** to afford the corresponding vinyl-functionalized polymers **5a** and **5b**. Compound **4** was obtained from the reaction of compound **2** with resorcinol (Scheme 2). Polymers **5a** and **5b** were subjected to the intramolecular cross-linking protocol under high dilution conditions (0.40 mg/mL) in THF. This cross-linking reaction was carried out under radical polymerization conditions using AIBN (0.02 mg/mL) as the initiator in refluxing THF. After allowing this reaction to proceed for 24 h, the reaction mixture was concentrated, and the product polymers **6a** and **6b** were obtained by precipitation in methanol.

The elution profiles in GPC for these polymers are shown in Figure 1. The reason for the high-molecular-weight shoulder in polymers **5b** and **6b** is not clear at this time. Repeating the polymerization reaction afforded polymer products that exhibit this shoulder reproducibly. The molecular weights were estimated from GPC using polystyrene standards. Subjecting polymers **5a** and **5b** to the cross-linking reaction conditions should not result in a decrease in the molecular weight. Therefore, the decrease in M_n is attributed to a change in architecture of the macromolecules, presumably from a random coil to a nanoparticle.

If the hypothesized change in architecture were to occur in our polymers, then the hydrodynamic radius of the polymers obtained before and after cross-linking should be significantly different. For this purpose, we measured the R_h for polymers **5** and **6** using DLS, as shown in Table 1. The R_h decreased from 26.1 to 16.9 nm from polymers **5a** and **6a**, whereas this value decreased from 13.3 to 10.8 nm from **5b** to **6b**. The percentage decrease in M_n (by GPC) and R_h (from DLS) in polymers **5a** to **6a** and **5b** to **6b** is consistent with the cross-linking density in these polymers. Similar GPC and DLS behavior was also observed in the literature, which has been attributed to an intramolecular cross-linking and the ensuing change in the architecture of the polymer.[19]

The products of reactions outlined in Scheme 1 and Scheme 2 were also analyzed by ^{1}H NMR. The NMR spectra of the un-cross-linked polymer **5b** and cross-linked polymer **6b** are shown in Figure 2a and b, respectively. In polymer **5b**, the peaks at 5.25 and 5.72 ppm are assigned to be the protons in the double bond of the pendant styrene. As expected, these peaks almost disappeared upon cross-linking to form **6b** (Figure 2b). The residual peak at 5.72 ppm could be due to the un-cross-linked double bond, the integration of which suggests a cross-linking yield of nearly 90% for **6b**. The above-mentioned characterizations using NMR, GPC, and DLS clearly show that intramolecularly cross-linked polymer nanoparticles were obtained using this procedure.

We also investigated the nature of un-cross-linked and cross-linked polymers **5a** and **6a** using AFM. The AFM images of the un-cross-linked copolymers **5a** and cross-

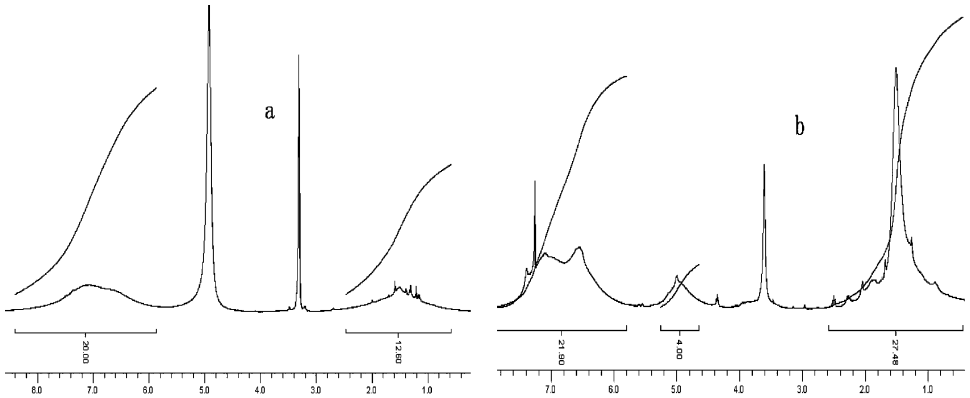


Figure 4. ^{1}H NMR spectra of the functionalized nanoparticle **7b** (a) and recovered nanoparticle **8b** (b).

linked nanoparticles **6a** are shown in Figure 3. Figure 3a and b represent the height (left) and phase (right) images of the un-cross-linked copolymers **5a** and cross-linked nanoparticles **6a**, respectively. From these images, one can clearly see that there are significant differences between the un-cross-linked copolymer and the cross-linked nanoparticles. The un-cross-linked copolymer **5a** exhibits "wormlike" structure, which could be attributed to the aggregation of these polymers. However, very different AFM images were observed with the cross-linked nanoparticles (**6a**). The wormlike structures in Figure 3a totally disappeared, and instead, narrowly dispersed nanoparticles were obtained through the cross-linking reaction. Note that the concentration of the polymer and the speed of spin coating are identical in both polymers. Similar behavior was also obtained with copolymer **5b** and cross-linked nanoparticle **6b**. These results also agree with those obtained through DLS measurements, which further confirm that an intramolecular cross-linking process is involved in the formation of these nanoparticles.

After the synthesis of the intramolecularly cross-linked copolymers, **6** was reacted with acetyl chloride in methanol to deprotect the Boc group to afford the functionalized nanoparticle bearing amino functionalities **7**, as shown in Scheme 3. The intramolecular cross-linked nanoparticle **6** is soluble in common organic solvents such as THF, DCM, and chloroform. However, after the deprotection of the Boc group, the functionalized nanoparticle **7** was found to be insoluble in most organic solvents except methanol. To confirm that the deprotective reaction was achieved, we compared the ^{1}H NMR of **7b** with **6b** (compare Figure 4a with Figure 2b). It is clear that the Boc group was removed because the peak corresponding to *tert*-butyl moiety at around 1.4 ppm is not present in the ^{1}H NMR of **7b** (Figure 4a).

As discussed above, we are interested in achieving these amine-containing nanoparticles because they provide a useful handle for further functionalization. Due to the advent of amine-terminated dendrimers and the fact that amino groups are ubiquitous in proteins, methodologies for functionalization of amino groups in macromolecules are numerous. To demonstrate that the amino group in our polymeric nanoparticles can be further functionalized, we stirred the nanoparticle **7** with triethylamine in chloroform overnight, then trimethylacetyl chloride was added to this solution. Within a short period of time, the suspension turned to a clear solution. Precipitation of the polymer from this solution using methanol afforded the pivaloyl-functionalized nanoparticles **8**. The functionalization was once again confirmed by ^{1}H NMR (Figure 4b). The appearance of a new sharp peak at about 1.5 ppm is due to the incorporation of the *tert*-butyl-containing pivaloyl group. The incorporation efficiency of the pivaloyl group was found be greater than 90%, as estimated by the relative integration of the NMR peaks. This reaction sequence provides the necessary proof-of-concept that the amine functionalities in the polymer could be used for decorating the nanoparticle. The main difference between our system here and others[17−19] is that we have achieved cross-linked nanoparticles that have handles for further functionalization. Such a capability is certainly likely to expand the repertoire of polymer nanoparticles in a wide variety of applications.

Summary

A new class of functionalized polymeric nanoparticles was successfully achieved. The nanoparticle is based on a styrene-based copolymer backbone with amino moieties as functional group displays. These particles were achieved using an intramolecular collapse of the polymer by carrying out a cross-linking reaction under high dilution conditions. Analyses of the reactions using NMR, GPC, DLS, and AFM confirm the intramolecular cross-linking process. Our data also show that the size of the nanoparticles can be tuned by controlling the cross-linking density. Similarly, the number of amino functionalities could also be tuned by varying the monomer feed ratio. It is easy to imagine that such control could also be achieved by controlling the molecular weight. Finally, the functionalized intramolecular cross-linked nanoparticles with amine groups were reacted with trimethylacetyl chloride to demonstrate that the amino moiety is available for further functionalization. These nanoparticles have the potential to find applications in a wide range of areas; an example of such an application is drug delivery because of the easily controllable size, cross-link density, and number of functional groups.[21] Investigations in this direction will be part of the research efforts in our laboratories.

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