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A Novel One-Step Approach to Core-Stabilized Nanoparticles at High Solid Contents

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Polymeric micelles have attracted much interest in both theoretical and applied research fields.[1−6] In most cases the polymeric micelles are produced from self-assembly of block copolymers in selective solvents although some different approaches to the micelles have been suggested.[7−16] Usually, the self-assembly can only be performed in very dilute solutions; the preparation efficiency is low. Extensive studies[17−23] have also been made to stabilize the micellar structure by cross-linking the core or the shell of the micelles formed in selective solvents leading to stabilized nanoparticles. Here we report a new approach to the preparation of such stabilized nanoparticles by directly cross-linking one of the blocks in the copolymer in its *nonselective solvent* (common solvent) (Scheme 1). Furthermore, using this one-step route, we are able to produce the nanoparticles at high concentrations up to 0.2 g/mL.

We used two samples of polystyrene-*block*-poly(4-vinylpyridine) (PS-*b*-P4VP), S1, PS_{658}-*b*-$P4VP_{336}$ (the subscripts are the *average* number of the repeat units of the PS and the P4VP blocks, respectively) with M_w/M_n 1.09 prepared in our laboratory by living anionic polymerization, and S2, PS_{84}-*b*-$P4VP_{112}$ with M_w/M_n 1.09 produced by Polymer Source Inc. The cross-linking reaction took place in solutions of the block copolymers in DMF, in which both the PS and P4VP blocks were solvated, at concentrations ranging from 0.01 to 0.2 g/mL at room temperature. 1,4-Dibromobutane was used as the cross-linker. The molar ratio of 1,4-dibromobutane to the pyridyl groups in the block copolymer to be cross-linked was 2:1. The cross-linking reaction was continued for 5 days, which was proven by ^{1}H NMR measurements to be long enough for the completion of the cross-linking reaction. In all the cases, nanoparticles rather than gelation were obtained. The resulting solutions and particles were then characterized by DLS, TEM, and SEM. The characterization data of the nanoparticles formed at different concentrations of S1 and S2 measured by DLS are presented in Table 1.

According to Flory's gelation theory,[25] the proportion of cross-linkage is remarkably small for the onset of gelation when cross-linking a polymer. However, in the present case of cross-linking PS-*b*-P4VP under the conditions mentioned above, with the average numbers of cross-linkable units per polymer chain of S1 and S2 being as high as 336 and 112, respectively, nanoparticles rather than macrogel were obtained. This can obviously be attributed to the presence of the solvated non-cross-linkable PS block, which plays the key role in preventing gelation.

Table 1. Characterization Data of the Nanoparticles Measured by Dynamic Light Scattering with an LLS Spectrometer (Malvern Autosizer 4700) with a Laser Source of Wavelength 514.5 nm and a CONTIN Analysis Mode[a]

	S1		S2	
C/g mL^{-1}	⟨D_h⟩/nm	$\mu_2/\langle\Gamma\rangle^2$	⟨D_h⟩/ nm	$\mu_2/\langle\Gamma\rangle^2$
0.01	68.8	0.13	134	0.73
0.05	92.4	0.11	124	0.43
0.08	100.6	0.04		
0.10	127.6	0.11	64	0.46
0.20	189.9	0.13	92	0.96

[a] *C* = concentration of the block copolymers; ⟨D_h⟩ = the average hydrodynamic diameter of the resultant nanoparticles; $\mu_2/\langle\Gamma\rangle^2$ = polydispersity of the size distribution; see ref 24.

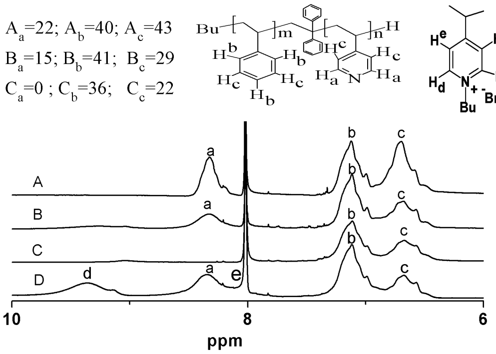

Figure 1. ^{1}H NMR spectra of S2 at a concentration of 0.05 g/mL in deuterated DMF reacting with 1,4-dibromobutane (A, B, C) and with 1-bromobutane (D) at room temperature. The molar ratios of 1,4-dibromobutane and 1-bromobutane to the pyridyl groups in S2 are 2:1 and 4:1, respectively. In the inset, K_i refers to the peak area of peak *i* in spectrum K, using dimethyl sulfoxide (DMSO) as an internal standard.

The in situ ^{1}H NMR measurements for the cross-linking reaction of S2 with 1,4-dibromobutane in deuterated DMF at room temperature proved the core−shell structure of the formed nanoparticles. In the measurements, dimethyl sulfoxide (DMSO) was used as the internal standard. The ^{1}H NMR spectra of S2 reacting with 1,4-dibromobutane for 0 (A), 10 (B), and 28 h (C) are shown in Figure 1. For clarity, only the spectra between 6.0 and 10.0 ppm are presented. One remarkable change observed in the spectra is that, as the cross-linking reaction proceeds, the relative intensity of peak **a** which is attributed to the pyridine ring only decreases (B) and finally disappears (C). In contrast, that peak **b,** contributed by the benzene ring solely, changes only a little from spectrum A through B to C. At the same time, signal **c** associated with both the benzene and pyridine rings decreases until in spectrum C the ratio of the signal intensity of **b** to that of **c** becomes 3.2/2.0 (inset), very close to the ratio of the number of H_b to that of H_c in the benzene rings. This result indicates that the mobility of the remained pyridyl groups and resultant pyridinium units has been seriously restricted as a result of the P4VP chains aggregating to form the core.[10] At the same time, most of the PS chains still exist in an unhindered environment; i.e., they are solvated. Furthermore, the in situ ^{1}H NMR measurements for S2 reacting with 1-bromobutane under almost the same conditions as that for the cross-linking reaction (see the legend of Figure 1) were made. The spectrum of this mixture having reacted for 52 h is shown in Figure 1 as spectrum D. As the result of quaternization, peak **d** and peak **e** (a broad peak in the range 7.7−8.2 ppm, overlapped with re-

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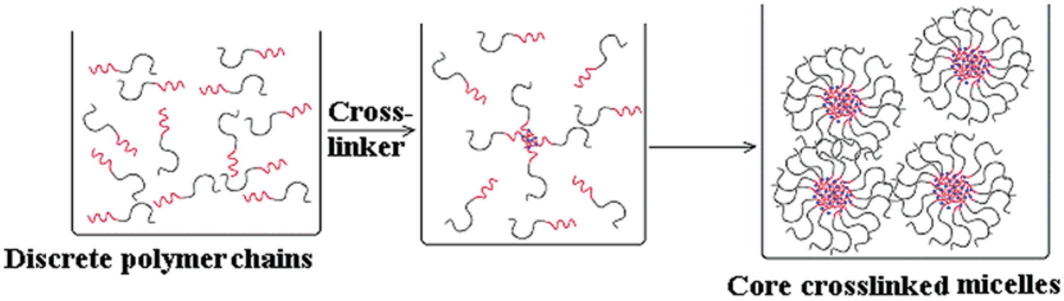
Scheme 1. Schematic Representation of the One-Step Process Producing Core-Stabilized Nanoparticles[a]



[a] The concentration of the block copolymer can be as high as 20% (w/v). The red blocks are cross-linkable, and the blue dots denote the cross-linker molecules.

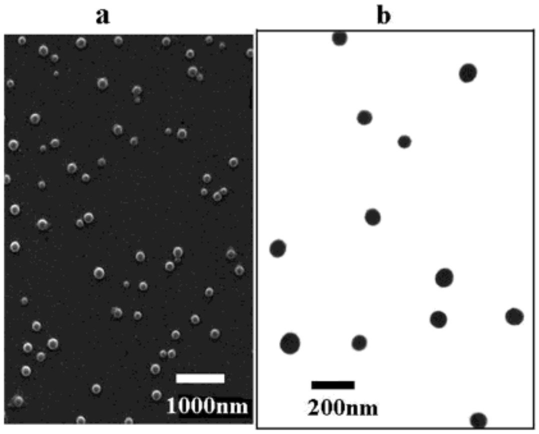


Figure 2. SEM (a) and TEM (b) images of discrete core-cross-linked polymeric core−shell nanoparticles resulting from directly cross-linking S1 in DMF at the concentration of 0.10 g /mL.

maining peak **a**) appear in spectrum D and are assigned to H_d and H_e in the pyridinium rings (inset), respectively, according to the ^{1}H NMR spectrum of partially quaternized poly(4-vinylpyridine) in deuterated DMF obtained by us. From spectrum D one can see that the intensity of the signals assigned to pyridyl groups and pyridinium rings is quite strong although the reaction time (52 h) is much longer than that taken for spectrum C where these signals disappear. This demonstrates that the non-cross-linked quaternized P4VP remains solvated in DMF.

In addition, the solution of S1 treated with 1-bromobutane instead of 1,4-dibromobutane in DMF was measured by DLS. No aggregates were detected. It further confirms that it is the cross-linking-forced aggregation of the P4VP block that caused the production of the nanoparticles.

The SEM graph (Figure 2a) and TEM graph (Figure 2b) show that the resulting particles from S1 possess the regular spherical shape. However, the size of the spheres is markedly larger in the SEM graph than that in the TEM graph. This can be attributed to the fact that the shell composed of the PS chains cannot be detected without staining by TEM but can be observed by SEM. The core consisting of the P4VP chains combined with bromine atoms shows the dark sphere. Therefore, the difference between the sizes observed by SEM and TEM also implies an amphipolar core−shell structure of the particles as well.

As shown in Table 1, in the case of cross-linking S1, the average hydrodynamic diameter $\langle D_h \rangle$ of the resultant particls increases with the concentration of S1, and the size distribution is relatively narrow. In the case of cross-linking S2, $\langle D_h \rangle$ of the particles is widely distributed and shows less regularity in its change with the concentration. By comparing the molecular parameters of S1 with that of S2, it is clear that an increase in the length of the non-cross-linkable PS block and its length ratio to the P4VP block result in a considerable improvement in the structural regularity of the resultant amphipolar nanoparticles. This can obviously be attributed to the “shielding effect” of the PS chains which confines the cross-linking reaction to isolated regions. The longer the PS blocks are, the more effective the shielding effect is. In our opinion, as the cross-linking reaction proceeds, the interpolymer linkage forces the P4VP blocks to aggregate more and more so their mobility is getting increasingly restricted. Meanwhile, as the PS chains can change their conformation much faster than the P4VP chains can aggregate, it is likely that the PS blocks are able to extend themselves so as to form shells around the P4VP aggregates. So, in this case, the process producing the nanoparticles proceeds very steadily and evenly. In principle, it can be well controlled by adjusting the cross-linking reaction. This may be the reason for the fact that this chemical cross-linking induced nanoparticle formation can be carried out at concentrations up to 0.2 g/mL.

It is noteworthy that in the existing methods[20−22] producing such nanoparticles (cross-linking the core of polymeric micelles) two steps—micellization of a block copolymer in selective solvents and the sequent cross-linking of the core of the resultant micelles—are needed, and the micellization has to be performed in dilute solution (lower than 1%, in most cases; otherwise, it will result in irregular aggregates or even precipitate). This is probably due to the fact that the micellization occurs so rapidly that the soluble block has no time to adjust its conformation to stretch and surround the aggregates of the insoluble block. Therefore, our one-step approach, which can be performed at concentrations up to 0.2 g/mL, presents much higher efficiency in producing the core-cross-linked nanoparticles. Besides, although some techniques of emulsion polymerization[26] are available to produce core-cross-linked core−shell particles at high concentrations, the mechanism and the structure and properties of the resultant particles are quite different.

In addition, in this study, we were readily able to produce the powders of core-cross-linked nanoparticles at high yield by simply precipitating the solutions with methanol and drying the precipitate. The powders can be redissolved in PS-soluble solvents such as DMF, chloroform, and THF, resulting in solutions with light and uniform opalescence.

Our preliminary experiments proved that the cross-linking-induced nanoparticles formation is a general phenomenon for block copolymers with appropriate specification. For example, both cross-linking reactions of polystyrene$_{48}$-*block*-poly(glycidyl methacrylate)$_{29}$ ($M_w/M_n = 1.14$) with ethylenediamine in DMF at 80 °C and polystyrene$_{96}$-*block*-poly(2-vinylpyridine)$_{132}$($M_w/M_n = 1.36$) with 1,4-dibromobutane in DMF at 100 °C led to core-cross-linked nanoparticles without macroscopic gelation.

In conclusion, in this work we demonstrated a new approach to the preparation of core-stabilized nanoparticles of diblock copolymers by chemically cross-linking one of the blocks in their common solvents. Although the cross-linking reaction is irreversible, the resultant nanoparticles are with regular structure of relatively narrow size distribution, comparable to those obtained from the micellization of block copolymers in selective solvents. In addition, this novel route can be performed at concentrations up to 0.2 g/mL, which obviously improves the efficiency in the preparation of stabilized polymeric nanoparticles. Much work is needed to understand the mechanism and to explore the potential applications further.

Experimental Section. Sample 1, PS$_{658}$-*b*-P4VP$_{336}$, was synthesized and characterized according to procedures described in ref 27. The polydispersity index is 1.09. Sample 2, PS$_{84}$-*b*-P4VP$_{112}$, with polydispersity 1.09 was purchased from Polymer Source Inc. Sample 1 (as well as sample 2) was dissolved in DMF for 24 h to form a molecularly dispersed solution. Then the cross-linker, 1,4-dibromobutane (the molar ratio of 1,4-dibromobutane to the pyridyl groups was 2:1), was added; the mixture was stirred at 25 °C for 5 days. The completion of the cross-linking reaction was confirmed by DLS, ^{1}H NMR. SEM, and TEM measurements. TEM and SEM were used to observe the morphologies of the resulting particles. The resultant solution was diluted and used for specimen preparation on copper grids coated with a thin carbon film. The unstained specimen was observed by TEM first and then by SEM.

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