Synthesis of Poly(solketal methacrylate)-*block*-poly(2-(dimethylamino)ethyl methacrylate) and Preparation of Nanospheres with Cross-Linked Shells

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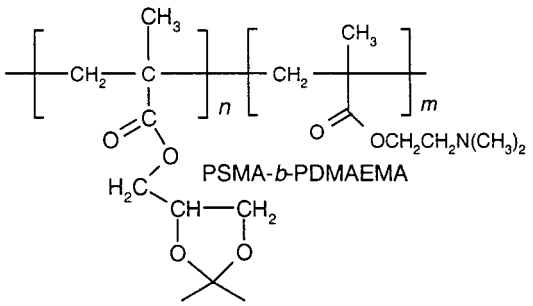
ABSTRACT: Living free radical polymerization was used to prepare poly(solketal methacrylate)-*block*-poly(2-(dimethylamino)ethyl methacrylate) or PSMA-*b*-PDMAEMA. A diblock with 105 SMA units and 122 DMAEMA units formed spherical micelles with PDMAEMA coronas and PSMA cores in water with 5 vol % THF. Nanospheres with cross-linked shells were obtained by cross-linking the PDMAEMA coronas with 1,2-bis(2′-iodoethoxyl)ethane (BIEE). The cores of the nanospheres were made hydrophilic by hydrolyzing the acetonide groups of PSMA.

Introduction

Block copolymers with cross-linkable and/or degradable blocks have been used in the preparation of stable functional polymer nanostructures of various geometry and shapes. These include nanofibers,[1,2] nanotubes,[3] thin films with nanochannels,[4,5] cross-linked polymer brushes (monolayers),[6] star polymers,[7] nanospheres,[8−11] hollow nanospheres,[12,13] nanospheres with cross-linked shells,[14−16] and shaved nanospheres.[17] Traditionally, the block copolymers used for nanostructure preparation were prepared from ionic polymerization. The use of such techniques generates polymers with narrow molar mass and composition distributions. The techniques, however, suffer from the stringent requirement for monomer purity and moisture removal. In this paper, we report the synthesis of poly(solketal methacrylate)-*block*-poly((*N*,*N*-dimethylamino)ethyl methacryate) or PSMA-*b*-PDMAEMA from atom transfer radical polymerization (ATRP),[18] which is much easier to execute.



This diblock was targeted because the PDMAEMA block could be cross-linked by 1,2-bis(2′-iodoethoxy)-ethane (BIEE), as demonstrated by Armes and coworkers,[15,19] and the acetonide groups of the PSMA block could be hydrolyzed under acidic conditions to yield poly(glyceryl methacrylate) (PGMA).[20] PGMA could then be cross-linked using, for example, glutaraldehyde [$OHC(CH_2)_3CHO$].[21] The ease with which these reactions are carried out was demonstrated by cross-linking the coronas of micelles of a PSMA-*b*-PDMAEMA sample with 105 units of SMA and 122 units of DMAEMA formed in THF/water with 95% water to yield nanospheres with cross-linked shells. The cores of the nanospheres were then made hydrophilic by hydrolyzing the acetonide groups. In addition to nanostructure preparation, the PSMA-*b*-PDMAEMA diblocks should be useful as aqueous dispersant, foaming agent, or emulsifier,[22] because the PSMA block is soluble in only organic solvents such as toluene or THF. The micelles or nanospheres formed from diblocks should be useful as nanoreactors,[23−26] drug delivery vehicles,[27] or templates for preparing inorganic mesoporous materials.[28]

Table 1. Recipe Used for Performing a Kinetic Study

reagent	amount
$CuBr_2$	45 mg or 0.20 mmol
HMTETA	55 μL or 0.20 mmol
dichlorobenzene	10 mL
SMA	10.0 g or 50 mmol
2-bromopropionitrile	35 μL or 0.40 mmol

Experimental Section

Materials. Anhydrous dichlorobenzene (Aldrich) was used without further purification. Monomers were vacuum distilled over CaH_2 or methylene blue just before use. 1,1,4,7,10,10-Hexamethyltriethylenetetraamine (HMTETA, used as ligand), 2-bromopropionitrile (initiator), and $CuBr_2$ (catalyst) were used as received from Aldrich.

SMA Preparation. SMA was prepared by reacting solketal with methacryloyl chloride following a literature method.[20] In an example preparation, 35 mL of methacryloyl chloride was added dropwise to a mixture of solketal (60 mL) and triethylamine (70 mL) in benzene (200 mL) at 0 °C under argon atmosphere and stirring. The mixture was then warmed to room temperature and stirred for 24 h. The triethylamine hydrochloride solid was removed from the solution by filtration. The solution was washed with distilled water and dried over anhydrous sodium carbonate. After filtration, methylene blue, a free radical scavenger, was added, and the solvent benzene was evaporated. Crude SMA was obtained by distillation under reduced pressure and was stored under refrigeration. It was redistilled just before use.

SMA Polymerization. Polymerization was conducted in dry two-necked round-bottomed flasks. In an example run, 49 mg (0.22 mmol) of $CuBr_2$ was added into a 100 mL flask. The flask was then evacuated to remove oxygen and refilled with argon. This was repeated thrice before the flask was evacuated again, flamed with a Bunsen burner for 10 min, refilled with argon, and left to cool to room temperature. At this stage, 51

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Table 2. Characteristics of the Polymers Prepared

sample	n/m from feed ratio	NMR n/m	M_n from feed ratios (g/mol)	GPC M_n (g/mol)	GPC M_w/M_n	n (feed)	m (NMR)
			Homopolymer PSMA				
PSMA			3.0×10^4	2.6×10^4	1.16	150	
			Block Copolymers				
1	0.69	0.86	4.5×10^4	3.4×10^4	1.41	105	122
2	1.41	2.03	4.3×10^4	1.9×10^4	1.53	142	70
3	0.20	0.29	7.9×10^4	4.6×10^4	1.41	80	280
4	3.2	4.1	7.9×10^4	3.6×10^4	1.49	320	80

mg (60 μL, 0.22 mmol) of HMTETA and 6.0 mL of 1,2-dichlorobenzene were added using syringes through a neck fitted with a rubber stopper. Also added was 6.0 g (30 mmol) of solketal methacrylate. The flask was purged for another three times by quick evacuation and Ar filling. A 26.4 mg (0.20 mmol) sample of 2-bromopropionitrile was then added before the flask was immersed in an oil bath preheated to 85 °C. The polymerization was allowed to proceed overnight under stirring. After cooling to room temperature, the reacted mixture was diluted with 10 mL of THF and then filtered through a column packed with neutral alumina to remove the catalyst. The filtrate was concentrated by rotary evaporation, and the polymer was precipitated into hexane. After drying, 4.5 g of polymer was obtained with a yield of 75%.

Kinetics of SMA Polymerization. For following the kinetics of SMA polymerization, the procedure described above was used for performing the polymerization. The amounts of reagents used are given in Table 1. The polymerization was carried out at 85 °C. At various times, samples, each at ~1.5 mL, were taken and transferred into vials. The vials were quickly immersed in liquid nitrogen to quench the polymerization. After thawing to room temperature, the samples were filtered through neutral alumina columns to remove catalyst. A small amount of the filtrate was then diluted with $CDCl_3$ for NMR analysis. The decrease in the intensity of double bond proton peaks of SMA at 6.15 and 5.59 ppm relative to that of the acetonide peaks at 1.35 to 1.46 ppm was used to follow double bond conversion. It was observed that the peaks at 1.35−1.46 ppm did not shift with the polymerization of the SMA double bonds. The molar masses of the polymer samples were determined from GPC analysis.

Preparation of PSMA-*b*-PDMAEMA. For diblock preparation, SMA was typically polymerized first for 5−6 h. Then added was DMAEMA freshly distilled over CaH_2. The diblock solutions were then diluted with THF and purified following the same procedure as used for PSMA purification. The diblocks were characterized by NMR and GPC with results shown in Table 2.

Micelle Preparation and Cross-Linking. Of the four diblocks prepared (Table 2), only one, polymer 1, was investigated thoroughly for micelle formation and cross-linking. Micelle formation normally involved dissolving polymer 1 in THF first. To the THF solution was then added water to achieve the water volume fraction of 95%. The final polymer concentration was typically around 1.0 mg/mL. Micelle cross-linking was achieved by reacting BIEE with PDMAEMA at room temperature.

Kinetics of Micelle Cross-Linking. A classical analytical technique, i.e., amino group titration by HCl, was used to obtain the data of amino group conversion as a function of time. For this, 0.500 g of polymer 1, 1.52 mmol of amino groups, was dissolved in 10.0 mL of THF. To the THF solution was then added 190 mL of water. At this stage, two samples, each at 20.00 mL, were taken. One was titrated with 6.12×10^{-3} M HCl using methylene red as the indicator (color changes at pH ≈ 5). This gave an amino amount of 0.159 mmol, in agreement with 0.152 mmol calculated using $n/m = 0.86$ To the other was added 14.0 μL of BIEE ($\rho = 2.028$ g/mL, 0.075 mmol). The solution was also titrated with HCl and yielded the same amount of amino groups. This suggested that the cross-linker did not react with HCl under the titration conditions. To the residual 160 mL of sample was then added 115 μL of BIEE (0.61 mmol). Samples, each at 25.00 mL, were taken at different times, and the amino group contents were titrated using HCl. The results are presented in Table 3.

Table 3. Data of PSMA-*b*-PDMAEMA Cross-Linking Kinetics

run 1 ($n_{DMAEMA} = 0.159$ mmol at $t = 0$ or c_0 mM)		run 2 ($n_{DMAEMA} = 0.152$ mmol at $t = 0$ or c_0 mM)	
time/h	amino group conversion/%	time/h	amino group conversion/%
0	0	0	0
2	9.9	1	6.9
5	14.0	2	10.3
9	17.7	4	12.9
24.5	27.7	12	18.8
48	43.3	24	28.2
93.8	66.2	48	42.5
		96	58.0
		149	65.7

This experiment was repeated with results shown in Table 3. The amount of diblock used in the second run was 0.508 g. The amount of amino group determined at $t = 0$ by titration was 0.152 mmol, which was slightly lower than the theoretical value of 0.155 mmol.

Instrumentation and Techniques. Gel permeation chromatography (GPC) analysis was performed on a Waters system using a HT-4 column. The system was calibrated using polystyrene standards using THF as the eluant. Transmission electron microscopy (TEM) images were obtained with a Hitachi H-7000 instrument operated at 100 kV. TEM specimen were prepared by aspirating a fine mist of a dilute solution (~0.1 mg/mL) of the polymer micelles or nanospheres onto carbon-coated copper grids using a home-built device.[29] For improved contrast, the sprayed sample was exposed to gaseous allyl bromide overnight, which reacted with PDMAEMA selectively. The allyl groups attached were then stained with OsO_4 before viewing by TEM. Dynamic light scattering (DLS) measurements were performed at the scattering angle of 90° with a Brookhaven model 9025 instrument using a He−Ne laser operated at 633 nm. Solutions at a concentration of ~0.1 mg/mL were centrifuged at 1500 rpm for 5 min before such measurements. DLS data contained in 256 real channels were analyzed using the method of cumulants.[30] The polydispersity in the size of the micellar sizes was obtained from values of first- and second-order cumulants. The viscosity η of 95% THF/water was estimated using

$$\eta = \eta_{THF}\phi_{THF} + \eta_{H_2O}\phi_{H_2O} \quad (1)$$

where the volume fractions of water and THF were 95% and 5%; the viscosities for THF and water, η_{THF} and η_{H_2O}, were taken as 0.486 and 1.005 cP, respectively.[31] FTIR analysis was performed on pressed polymer-containing KBr disks using a Mattson instrument. ^1H solution and ^{13}C solid-state NMR measurements were performed with Bruker AMX-300 and ACE-200 instruments, respectively.

Results and Discussion

We start this section by demonstrating the living nature of SMA homopolymerization. The PSMA macromonomer was then used to initiate the polymerization of DMAEMA to yield diblocks PSMA-*b*-PDMAEMA. The characterization results of the diblocks prepared will

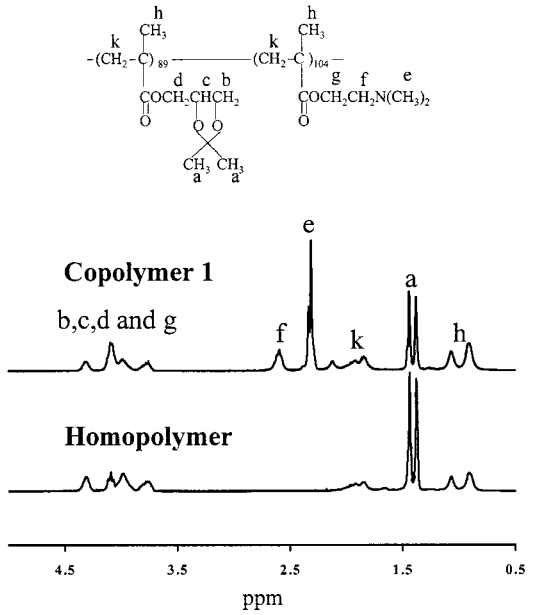
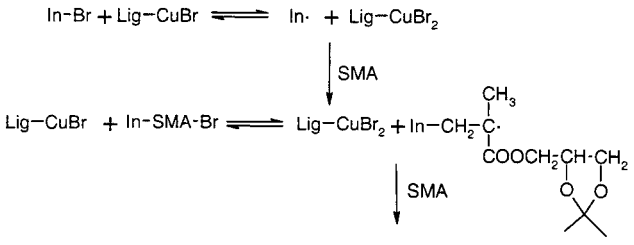


Figure 1. ^{1}H NMR spectra of PSMA (bottom) and diblock 1 (top) with peak assignments. The samples were run in $CDCl_3$.

then be presented. Diblock 1 was used to prepare micelles in THF/water with 95% water. The properties of the micelles will be discussed. This section ends with presenting PDMAEMA cross-linking kinetic data and evidence demonstrating acetonide group cleavage off PSMA micelle cores.

SMA Homopolymerization. PSMA-*b*-PDMAEMA has been prepared by anionic polymerization.[32] However, there has been no report of PSMA preparation by ATRP. In our polymerization, the initiator used was 2-bromopropionitrile, $CH_3CHBrCN$ denoted by In-Br. HMTETA, $[(CH_3)_2NCH_2CH_2N(CH_3)CH_2-]_2$ denoted by lig-, was used as the ligand. Instead of using CuBr as the catalyst,[18] we used initially by mistake $CuBr_2$. Still, $CuBr_2$ worked well, presumably due to the fact that at least some $CuBr_2$ decomposed to CuBr upon flaming under vacuum. Since $CuBr_2$ worked well, we did not change back to using CuBr as the catalyst in later studies.

The mechanism for the polymerization should be



The polymerization should be "living" because the free radicals formed were stabilized by bonding with a transferable bromine atom.[18] Our success in preparing PSMA was demonstrated by the NMR spectrum obtained in $CDCl_3$ shown in Figure 1. All the proton peaks were successfully explained by the PSMA structure.

Illustrated in Figure 2 are our SMA conversion data as a function of reaction time for a polymerization with its initial composition given in Table 1. The reaction went to completion within ~8.5 h. Illustrated in Figure 3 is the variation in the GPC number-average molar mass of the resultant PSMA as a function SMA conversion. As conversion increased, the molar mass increased linearly, in agreement with a living polymerization mechanism. The living mechanism was also supported by the fact that the final M_n of the PSMA sample produced coincided with what was predicted from the SMA to initiator feed ratio. These values were 2.3×10^4 and 2.5×10^4 g/mol, respectively. The discrepancy was probably due to the use of polystyrene rather than PSMA standards in calibrating the GPC column. Illustrated in Table 2 are the molecular characteristics of another PSMA sample we prepared. Again, the GPC molar mass agrees with that calculated from the monomer to initiator feed ratio.

The relatively low polydispersity indices obtained also supported the living feature of SMA polymerization. For the sample with its molar mass vs conversion data shown in Figure 3, M_w/M_n fluctuated around 1.25 depending on SMA conversion. For the PSMA sample shown in Table 2, M_w/M_n was 1.16.

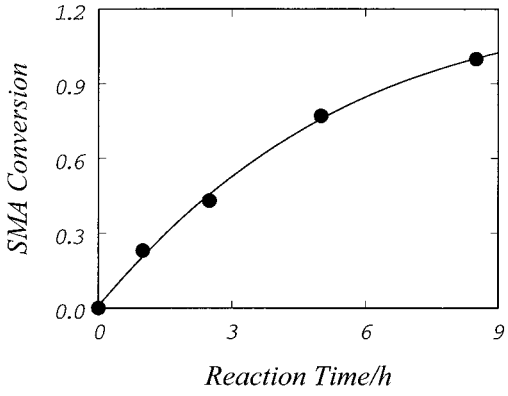


Figure 2. Plot of conversion of SMA as a function of polymerization time. The initial composition of the reaction mixture is given in Table 1.

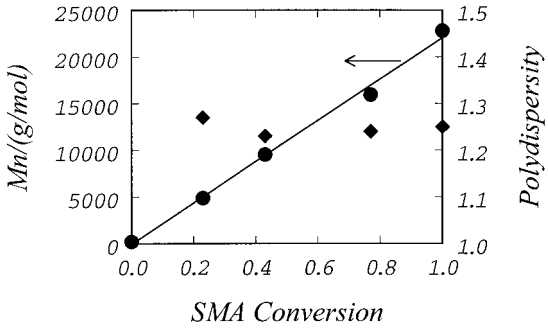


Figure 3. Plot of GPC M_n for PSMA as a function of SMA conversion (●). Also shown is the variation in the polydispersity (◆) of this sample as a function of SMA conversion. The initial composition of the reaction mixture is given in Table 1.

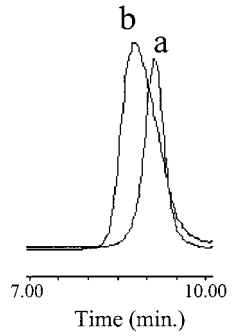


Figure 4. GPC chromatograms of the PSMA block (a) and block copolymer 1 (b).

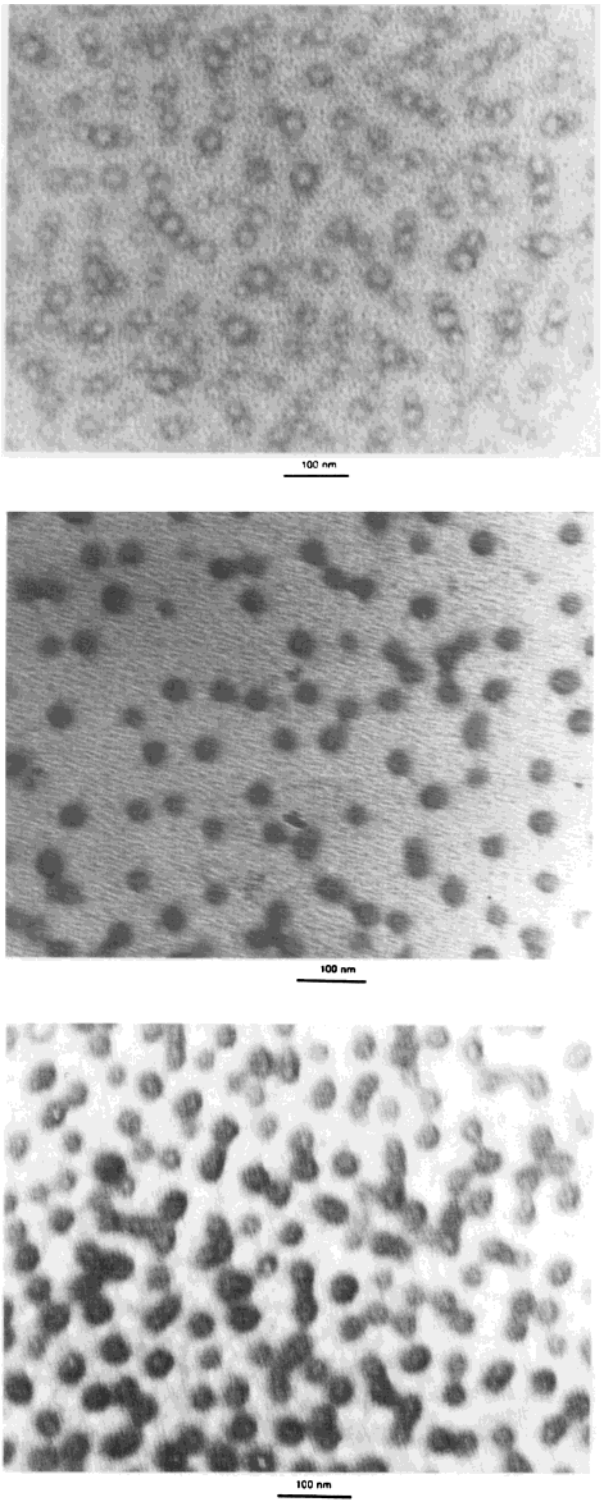


Figure 5. TEM images of block copolymer 1 micelles (a, top), cross-linked block copolymer 1 micelles (b, middle), and the cross-linked micelles after acetonide group removal (c, bottom).

Preparation and Characterization of PSMA-*b*-PDMAEMA. The living nature of the SMA polymerization was further demonstrated by our ability to prepare block copolymers of SMA and DMAEMA. Also illustrated in Figure 1 is the NMR spectrum of diblock 1. From the ratio of the intensities of the peaks at 1.37 and 1.44 to that at 2.31 ppm, we obtained *n*/*m* (Table 2). Illustrated in Figure 4 are the GPC chromatograms of diblock 1 and its precursor PSMA block. The diblock chromatogram shifted to higher molar masses in accordance with block copolymer formation. Unfortunately, the polydispersity of the diblock was higher. This might be due to the fact that the "apparent" diblock contained some terminated PSMA chains as judged from the overlap between the chromatograms of the PSMA block and the diblock.

Table 4. Characteristics of diblock 1 micelles at different stages of treatment. The sample was crosslinked with 0.10 molar equivalent of BIEE for one week. All light scattering experiments were performed in THF/water with 95% water

micelle treatment	hydrodynamic diameter (nm)	dispersity from DLS	TEM diameter/ nm
uncrosslinked	77	0.098	40
crosslinked	134	0.30	40
hydrolyzed	129	0.24	45

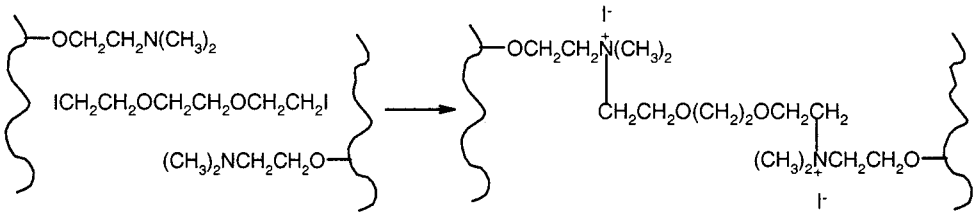
A closer examination of Table 2 revealed that this method could be used to prepare diblocks of various compositions. There were, however, discrepancies between *n*/*m* calculated from the monomer feed ratios and those determined experimentally by NMR. The experimental *n*/*m* values were always higher than the feed ratios. This might be caused by the incomplete conversion of the second monomer DMAEMA due to high viscosity of the medium at the later stages of the reaction.

Another glance of Table 2 revealed that GPC molar masses of the diblocks were far lower than those calculated from the monomer to initiator feed ratios. The incomplete conversion of the second monomer, DMAEMA, might account for some of the discrepancies, but the discrepancies were too great to be totally accounted by the incomplete conversion of DMAEMA. The discrepancies were probably mainly caused by the fact that the PDMAEMA was adsorbed by the gel particles, as documented by Creutz et al.[33]

Because of the failure of the GPC analysis, a different method was used in estimating the molar masses of the diblocks. In this method, we essentially assumed that the first monomer SMA was polymerized quantitatively, and the molar mass of the first block could be calculated using the SMA-to-initiator feed ratios. This hypothesis should be reasonable on the basis of results of the SMA polymerization kinetic study as described above. Once the number of repeat units, *n*, for the PSMA block of a diblock was assumed, the number of repeat units, *m*, for the PDMAEMA block was calculated from *n*/*m* determined from NMR. These *n* and *m* values are shown in Table 2. For diblock 1, $n = 105$ and $m = 122$.

Micelle Formation. PSMA was not soluble in water, but PDMAEMA was. In water with 5% THF, diblock 1 formed micelles as judged from the bluish tint exhibited by such a solution. A dynamic light scattering measurement revealed that such micelles had an average hydrodynamic diameter of 77 nm (Table 4). Illustrated in Figure 5a is a TEM image of such micelles. The projection of the micelles is circular, and the micelles must be spherical. The micelles seem to have a light core and a dark shell. The overall diameter, including the core and shell, of the micelles is ~40 nm (Table 4). The dark shell must have consisted of PDMAEMA, because the micelles were reacted with gaseous allyl bromide ($CH_2{=}CHCH_2Br$) before staining with OsO_4, allyl bromide should have reacted with PDMAEMA only, and OsO_4 should have stained double bonds selectively. The hydrodynamic diameter of the micelles was larger than the electron microscopy diameter,

Scheme 1



because DLS and TEM measure the diameters of the micelles in the solvent-swollen and dry states, respectively.

Micelle Cross-Linking. The micelles were cross-linked because of the reaction between BIEE and two DMAEMA groups of different chains as illustrated in Scheme 1. No cross-links would form if the reaction occurred intrachain or if only one iodide group of a BIEE molecule reacted. The occurrence of the cross-linking reaction was judged from the stability of the cross-linked micelles in THF, which solubilized both the PSMA and the un-cross-linked PDMAEMA block. Shown in Figures 6 is the comparison between the FTIR spectra of un-cross-linked and cross-linked micelles. Despite some spectral changes, the quantification of the degree of reaction between PDMAEMA and BIEE was difficult. Extensive overlap between ^{13}C solid-state NMR peaks of the diblock and those of BIEE in the cross-linked micelles was also anticipated.

Because of the difficulty with using these spectroscopic techniques, the progress of the cross-linking reaction was followed by a classical technique. The cross-linking of the tertiary amine groups of PDMAEMA transformed them into quaternary amine groups. The quaternary amine groups should not react with HCl, and the amount of HCl consumed for titrating a given amount of diblock would thus decrease with increasing degree of cross-linking. Such titration results are shown in Table 3, where amine group conversion was calculated using

$$p = \frac{c_0 - c}{c_0} \times 100\% \qquad (2)$$

where c_0 and c are the concentrations of amino groups at time zero and t, respectively.

The value of c_0, can, in principle, be calculated from the known concentration of the diblock and n/m determined from NMR. In practice, we determined c_0 from titrating samples taken at time zero. As discussed in the Experimental Section, c_0 obtained from the two methods agreed within experimental errors. This suggested the reliability of the titration technique. Plotted in Figure 8 are the conversion data, in the form of $[1/(1 - p) - 1]$, as a function of time t. Above the conversion of ~10%, $[1/(1 - p) - 1]$ varied linearly as a function of t. Since the initial amino and iodide group concentrations were equal in both runs, this linearity suggested that the validity of the following second-order kinetic equation

$$\frac{1}{1 - p} - 1 = kc_0t \qquad (3)$$

From the slopes of the straight lines and the known initial concentrations, c_0, of the amino groups, we obtained the rate constants of 17.4 and 16.5 L mol^{-1} h^{-1}for runs 1 and 2.

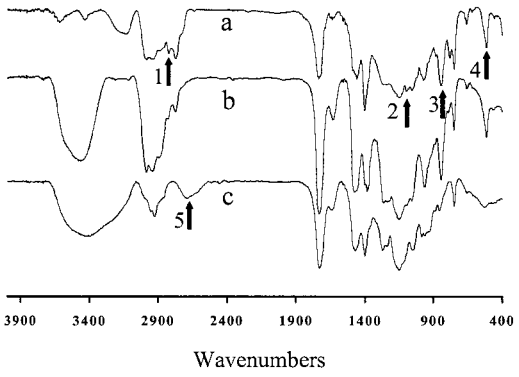


Figure 6. FTIR spectra of block copolymer 1 micelles (a), cross-linked block copolymer 1 micelles (b), and the cross-linked micelles after acetonide group removal (c). The sample was reacted with 0.10 mol equiv of BIEE for 1 week for cross-linking. The peaks marked are derived from methyl groups attached to nitrogen atoms (1, 2827 cm^{-1}), vibration of carbon−nitrogen bonds (2, 1111 cm^{-1}), solketal groups (3, 847 cm^{-1}, 4, 517 cm^{-1}), and protonated amine groups (5, 2708 cm^{-1}).

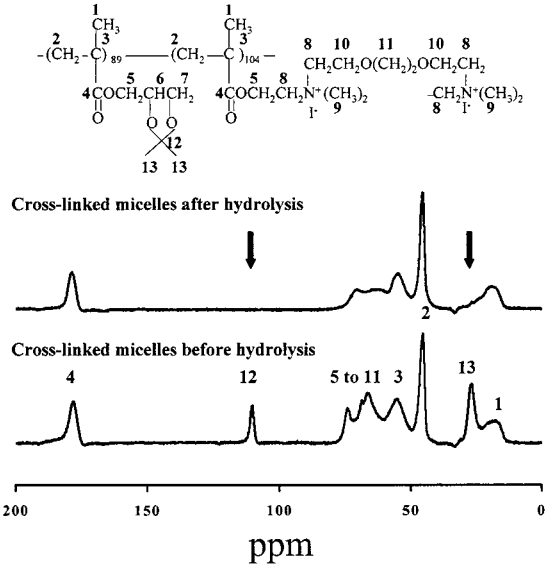


Figure 7. Comparison of ^{13}C solid-state NMR spectra of cross-linked block copolymer 1 micelles before (bottom) and after (top) acetonide group removal.

The fact that the cross-linking of the PDMAEMA at intermediate conversions followed second-order kinetics was quite fortuitous, because the reaction was not analogous to bimolecular reactions occurring in small-molecule systems. The amino groups were not uniformly distributed in THF/water. Rather, they were concentrated in the coronas of the individual micelles. The kinetics should be further complicated by the fact that once one iodide group of a BIEE molecule had reacted with PDMAEMA, the chance for the other to react would increase. Last, the density of the corona should change with cross-linking. While bond formation between different PDMAEMA chains should shrink the

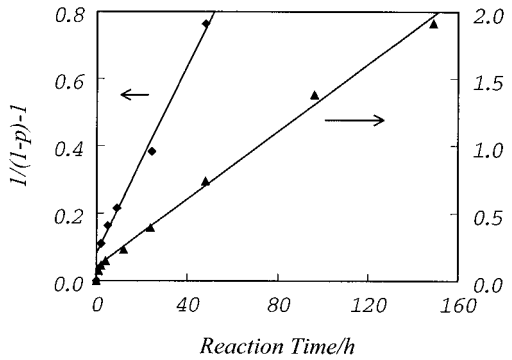


Figure 8. Plot of $1/(1 - p) - 1$ as a function of time t, where p denotes the conversion of amine groups. The initial amine concentrations, which were equal to the initial iodide group concentrations, were 0.762 (◆) and 0.774 mM (▲), respectively.

Table 5. Hydrodynamic Radii of Micelles with Hydrolyzed Cores Cross-Linked to Different Degrees[a]

iodide group mol equiv	hydrodynamic diameter/nm	dispersity from DLS
0	7	0.10
0.20	129	0.24
0.35	117	0.14
0.50	107	0.32
0.80	127	0.24
1.00	160	0.25

[a] All light scattering experiments were performed in water with 5% THF.

corona, the formation of charged quaternary amine groups might expand the corona. These complications explained why the reaction did not follow second-order kinetics over a wide range of conversions, for example, at low conversions.

Illustrated in Figure 5b is a TEM image of micelles cross-linked with 0.10 mol equiv of BIEE or 0.20 mol equiv of iodide groups for 1 week. The TEM diameter of the cross-linked individual micelles remained at ~40 nm (Table 4). Surprisingly, the hydrodynamic diameter increased to 134 nm (Table 4) from 77 nm measured for un-cross-linked micelles. This size increase was accompanied by a polydispersity index jump from 0.098 to 0.30 (Table 4). The DLS results thus suggest some intermicellar cross-linking.

Hydrolysis of the PSMA Groups. Hydrolysis of the cross-linked micelles was accomplished in water with 5% water at the HCl concentration of 0.30 M. Illustrated in Figures 6 and 7 is the comparison between NMR and FTIR spectra of the cross-linked micelles before and after acetonide group removal. The disappearance of the NMR peaks at 110 and 26.3 ppm and the decrease in the intensity of the IR peaks at 847 and 517 cm^{-1} are in agreement with the removal of the acetonide groups.

Dynamic light scattering results shown in Table 5 also confirm the removal of the acetonide groups. The hydrodynamic diameter of an un-cross-linked micelle sample in water with 5% THF decreased from 77 to 7 nm after acetonide group removal. This is because the PSMA block became water-soluble after acetonide group removal, and the micelles thus disintegrated.

Shown in Table 5 are the hydrodynamic diameters of sample cross-linked with different amounts of BIEE. Judging from the comparable sizes of the cross-linked micelles, in water with 5% THF, before and after acetonide group removal, we conclude that the micellar structure was locked in after reacting with 0.10 mol equiv of BIEE or 0.20 mol equiv of iodide groups. The hydrodynamic diameters decreased initially with increasing BIEE amount because of corona compaction due to increased cross-linking density. The micellar size increased at higher BIEE contents due to increased degree of intermicelle fusion.

Illustrated in Figure 5c is a TEM image of acetonide-removed micelles. The core−shell structure is obviously retained. The size of the micelles is ~45 nm, which is comparable to that observed before acetonide group removal.

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References and Notes

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