Hollow Nanospheres from Polyisoprene-*block*-poly(2-cinnamoylethyl methacrylate)-*block*-poly(*tert*-butyl acrylate)

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Received October 13, 1998. Revised Manuscript Received January 4, 1999

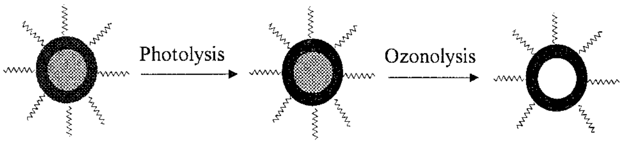
A polyisoprene-*block*-poly(2-cinnamoylethyl methacrylate)-*block*-poly(*tert*-butyl acrylate), PI-*b*-PCEMA-*b*-P*t*BA, sample with 3.7 × 10^2 units of isoprene, 4.2 × 10^2 units of CEMA, and 5.5 × 10^2 units of *t*BA was synthesized. The triblock formed spherical micelles with a P*t*BA corona, PCEMA shell, and PI core in THF/methanol with methanol volume fractions between 50% and 99%. After micellar structure "locking in" by UV cross-linking of PCEMA, the PI block of the triblock was degraded by ozonolysis to yield nanospheres with a central cavity. The cavities were loaded with rhodamine B, a compound with size similar to those of many drug compounds.

I. Introduction

A hollow nanosphere in this paper refers to a nanometer-sized cross-linked spherical shell with its outer surface covered by polymer chains. Such hollow nanospheres are produced from a triblock copolymer, polyisoprene-*block*-poly(2-cinnamoylethyl methacrylate)-*block*-poly(*tert*-butyl acrylate) (PI-*b*-PCEMA-*b*-P*t*BA; see Chart 1).

The triblock forms spherical micelles in THF/methanol with methanol volume fractions between 50% and 99%. The micelles, with the soluble P*t*BA block as the corona and the insoluble PCEMA and PI blocks as the shell and core, are then structurally "locked in" by photo-cross-linking PCEMA. Hollow nanospheres are obtained by degrading the PI core via ozonolysis, as illustrated in Scheme 1.

Scheme 1. Preparation of Hollow Nanospheres[a]



[a] Photolysis cross-links the CPEMA shell (deep gray to black). Ozonolysis decomposes the PI core (gray mesh to white)

The preparation of hollow nanospheres with the structure illustrated in Scheme 1 has never been reported. The closest relatives of these hollow nanospheres are probably cross-linked[1,2] and un-cross-linked[3−7] diblock vesicles. A diblock consists of two linear polymer chains joined together in a head-to-tail fashion. Vesicles normally form from a diblock in a block-selective solvent, if the insoluble block is much longer than the soluble block.[3−7] In a vesicle, the insoluble block forms the essentially solvent-free shell. The soluble block stretches into the solution phase from both the inner and outer surfaces of the shell. A cross-linked vesicle differs structurally from a hollow sphere in that the cavity of a vesicle contains chains of the soluble block. Due to the relative low volume fraction of the polymer chains in the vesicle cavities, the cross-linked vesicles have been previously referred to as hollow nanospheres as well.[1,2]

Vesicles are also formed from small-molecule surfactants.[8] If a polymerizable surfactant is used, polymeric vesicles can be obtained by polymerizing the surfactant after its assembly into vesicles.[9,10] Or organic monomers and cross-linkers can be sorbed by the hydrophobic phase of a vesicle.[11] The subsequent polymerization and cross-linking will yield hollow nanospheres with a cross-linked polymer shell. Such shells are stable even after the removal of the surfactants by solvent extraction[11] and are structurally similar to the shells we prepared from a diblock vesicle precursor.[2]

One can, in principle, prepare hollow nanospheres by modifying particles from emulsion polymerization with a core−shell structure. In practice, only hollow spheres in the size range of micrometers have been produced from such an approach.[12−14] For particles with a polystyrene shell and poly(acrylic acid), (PAA), core, this was

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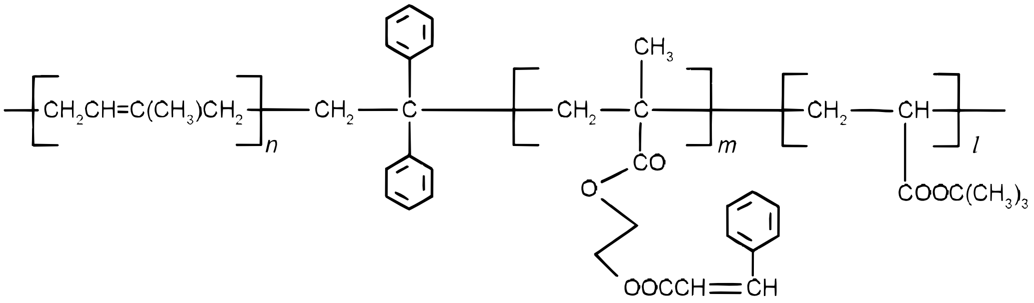
Chart 1. PI-*b*-PCEMA-*b*-P*t*BA



achieved by alkali swelling of the PAA cores. Such particles are used as hiding or opacifying agents in coatings or molding compositions. Hollow polymeric spheres with even larger diameters, e.g. ca. tens of micrometers, can be prepared by a spray drying method[15] or a water/oil/water multiple emulsion solvent evaporation technique.[16] Such hollow spheres are used in syntactic foams.

The hollow nanospheres prepared as described in this paper may be useful as nanoreactors. If biocompatible and water-soluble polymers are used, the resultant hollow nanospheres should be useful as vehicles in controlled drug release.[1,17] The cavity will then function as the storage site for drug molecules. We finish this paper by demonstrating the loading of rhodamine B, a compound with size similar to those of many drug compounds, into the cavities of the hollow nanospheres.

II. Experimental Section

Polymer Synthesis and Characterization. PI-*b*-PCEMA-*b*-P*t*BA was synthesized following the methodologies used for PI-*b*-PCEMA[1,2] and PCEMA-*b*-P*t*BA[18−20] preparation. Isoprene, 8.4 mL, was polymerized in ∼20 mL of hexane at room temperature for 2 days using *sec*-butyllithium as the initiator. A 0.35-mL portion of 1,1-diphenyl ethylene and 120 mL of THF were then added, and an aliquot of the PI block was taken for molar mass determination. The second monomer, 2-trimethylsiloxyethyl methacrylate (HEMA-TMS), was polymerized in THF/hexane (6/1) at −78 °C for 2 h, and the third monomer, *t*BA, was polymerized for 4 h. The amounts of HEMA-TMS and *t*BA used were 10.0 and 9.0 mL, respectively. The polymerization was terminated by the addition of methanol, which also caused the hydrolysis of the trimethylsilyl group from P(HEMA-TMS), to yield poly(2-hydroxyethyl methacrylate) (PHEMA). PI-*b*-PHEMA-*b*-P*t*BA was purified by precipitation into methanol/water (v/v $\approx$ 1/9) once and converted to PI-*b*-PCEMA-*b*-P*t*BA by reacting with excess cinnamoyl chloride in pyridine overnight at room temperature. The resulting polymer was purified by repeated precipitation from methanol. To remove a small amount of PI homopolymer impurity in the triblock (produced due to the presence of a trace amount of water in the THF solvent introduced after the polymerization of the PI block), the sample was extracted at room temperature with hexanes once a day three times.

The weight-average molar mass, $\bar{M}_w$, of the PI block was determined in cyclohexane by light scattering using a Brookhaven Model 9025 light scattering instrument equipped with a 150-mW argon ion laser operated at 488 nm. The specific refractive index increment, dn_r/dc, of PI was measured utilizing a Phoenix Precision Instrument system. The $n/m/l$ values were determined from NMR by determining the ratio of proton peaks of isoprene, CEMA, and *t*BA. Gel permeation chromatography (GPC) with a Waters Styragel HT4 column was used to estimate the PI and triblock molar mass distributions.

Micelle Preparation and Cross-Linking. PI-*b*-PCEMA-*b*-P*t*BA was dissolved in THF, and methanol was added dropwise to a desired volume fraction between 50% and 99%. The typical final micellar concentrations were ∼2 mg/mL. The micellar solutions were stirred at room temperature for 2 days, hopefully to the establish micellar size distribution equilibrium before cross-linking.

The micelles were cross-linked using light from a 500-W mercury lamp which had passed through a 260-nm cutoff filter. The conversion of CEMA with irradiation time was monitored by following the decrease in absorbance at 274 nm, where converted PCEMA does not absorb. The CEMA conversion used was typically ∼40%.

Ozonolysis. Ozone was generated from a Welsback ozonizer. The cross-linked triblock micelle or nanosphere solution in THF/methanol was dialyzed against methanol to remove THF and then against chloroform to remove methanol. The nanosphere solution in chloroform was then cooled to −76 °C and ozone was bubbled through it for 2 min. The ozone-saturated solution was allowed to stand for ∼20 min before the mixture was purged with nitrogen. Excess trimethyl phosphite was added and the mixture was stirred for 3 h at −76 °C to reduce the ozonides to ketone or carbonyl groups. The nanosphere solution was then dialyzed against chloroform again to remove small-molecule products formed during ozonolysis.

Dynamic Light Scattering (DLS) Measurements. Solutions, typically at ∼0.1 mg/mL, were used for dynamic light scattering measurement. Dynamic light scattering data were obtained at 135°, 90°, and 45° and analyzed following the method of cumulants.[21] The hydrodynamic radii, R_h, obtained increased slightly, e.g. <3 nm, as the scattering angle decreased from 135° to 45°. The R_h values reported were those extrapolated to zero scattering angles.

The viscosities of THF/methanol mixtures required for R_h calculations were measured at room temperature (22 °C) using a Cannon Ubbelohde type viscometer. Since the flow times were all above 200 s, no kinetic energy corrections were made in calculating the viscosities from the flow time values. The viscosity η_m of a mixture was calculated from its flow time, t_m, and that of THF, t_0, using

$$\eta_m = (t_m \rho_m / \rho_0 t_0)\eta_0 \tag{1}$$

where ρ_m and ρ_0 were the densities of the solvent mixture and THF, respectively. The viscosity of THF at 22 °C, η_0, was taken to be 0.475 cP.[22,23] The viscosities measured for THF/methanol

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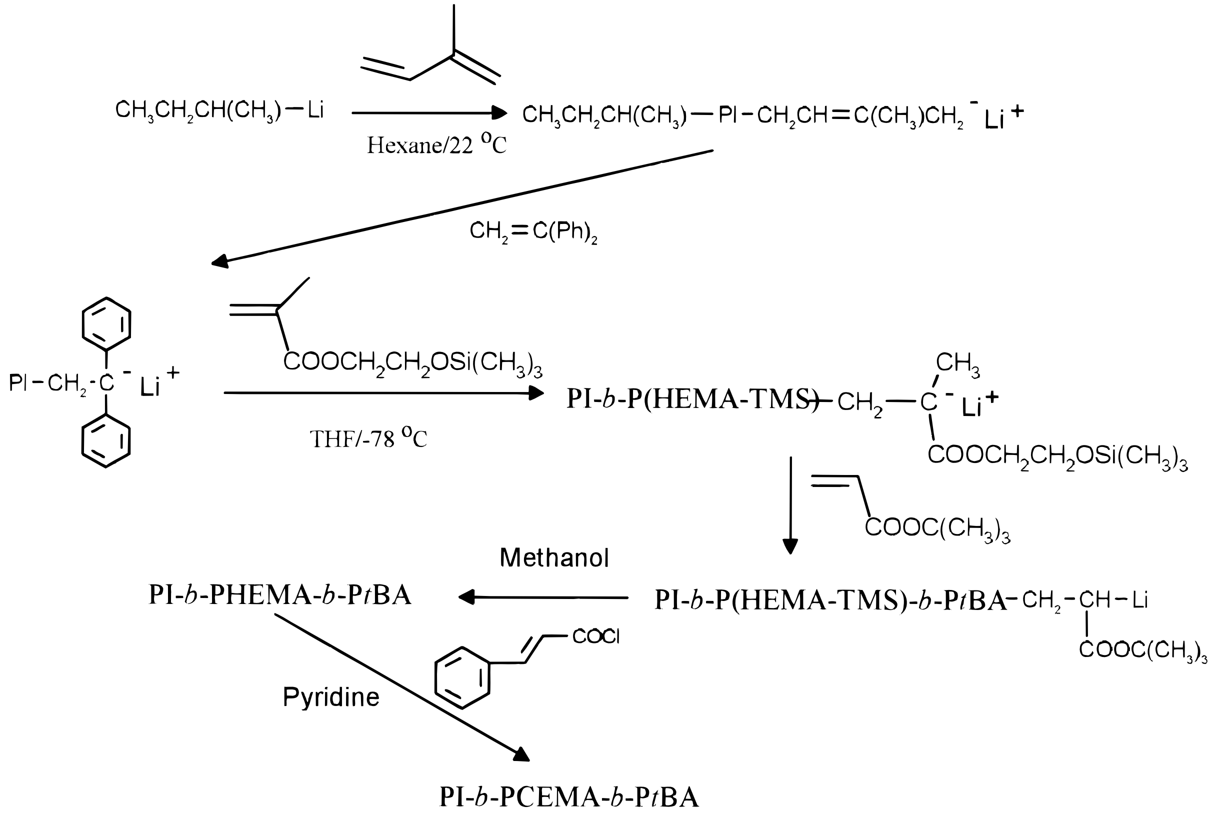
Scheme 2. Triblock Synthesis



with 52%, 65%, and 81% of methanol, by volume, are 0.48, 0.50, and 0.52 cP, respectively.

Refractive indices, η_m, of the solvent mixtures were calculated using the following approximate equation

$$\eta_m = \nu_1 n_1 + \nu_2 n_2 \tag{2}$$

where ν_1 and ν_2 are the volume fractions of THF and methanol, respectively. The refractive indices of THF and methanol, n_1 and n_2, are 1.404 and 1.326, respectively.[22,23]

Rhodamine B (RB) Loading into the Cavities. The triblock micelles were prepared in THF/methanol with 95% methanol. The micelles were then photolyzed and ozonolyzed to yield hollow nanospheres. The hollow nanospheres, ~20 mg, were refluxed with 0.345 g of RB in 5 mL of methanol for 1 day and methanol was removed by evaporation. The remaining red solid was suspended in water, filtered, and washed repeatedly with hot water before drying.

Transmission Electron Microscopy (TEM) and Infrared (IR) Analysis. Micelle or nanosphere solution samples were sprayed on carbon-coated copper grids using a customer device as described previously.[2] Sprayed vesicles or nanospheres were stained with OsO_4 or RuO_4 overnight and viewed by a Hitachi-7000 transmission electron microscope (TEM) operated at 100 kV.

For analysis by infrared spectroscopy, ~5 mg of dry product was mixed with ~0.5 g of KBr and pressed into a pellet. The measurements were carried out on a Mattson Model 4030 instrument.

III. Results and Discussion

Polymer Synthesis and Characterization. The PI-*b*-PCEMA-*b*-P*t*BA sample was prepared according to Scheme 2. Illustrated in Figure 1 is an NMR spectrum for the triblock with the peaks for the protons of each block assigned. By calculating the ratio of the intensities of peaks G, F, and B, we obtained $n/m/l = 1.00/1.13/1.49$.

Table 1. Characteristics of the Polymers

the PI block				the triblock			
d*n*/d*c* (mL/g)	LS $\bar{M}_w$ (g/mol)	$\bar{M}_w/\bar{M}_n$ GPC	1,4-PI[a]	$10^{-2}n$	$10^{-2}m$	$10^{-2}l$	$\bar{M}_w/\bar{M}_n$ GPC
0.101	25 × 10^3	1.06	93%	3.7	4.2	5.5	1.16

[a] The degree of 1,4-addition was determined from NMR.

Due to the different refractive indices of the three blocks, the Zimm method could not be used for the accurate determination of the molar masses of the triblock.[24] Instead, the molar mass of the PI block was determined from light scattering and was combined with the NMR *n*/*m*/*l* values to evaluate the *m* and *l* values. The specific refractive index increment, dn_r/dc, for the PI precursor in cyclohexane at 488 nm was measured to be 0.101 mL/g. GPC analysis indicated that both the PI block and the triblock sample had narrow molar mass distributions (Table 1).

Micelle Formation and Structure. The formation of micelles in THF/methanol could be judged from the bluish tinge exhibited by such solutions. These micelles had large hydrodynamic radii, as determined from dynamic light scattering. For micelles prepared in THF/methanol with 52%, 65%, and 81% of methanol, the hydrodynamic radii, R_h, are 44, 42, and 55 nm, as seen in Table 2. The spherical shape of the micelles was confirmed by our TEM results. Illustrated in Figure 2 is a TEM image obtained for polymer 2 micelles. The micelles were prepared in THF/methanol with 81% methanol and sprayed on a carbon-coated copper grid before OsO_4 staining.

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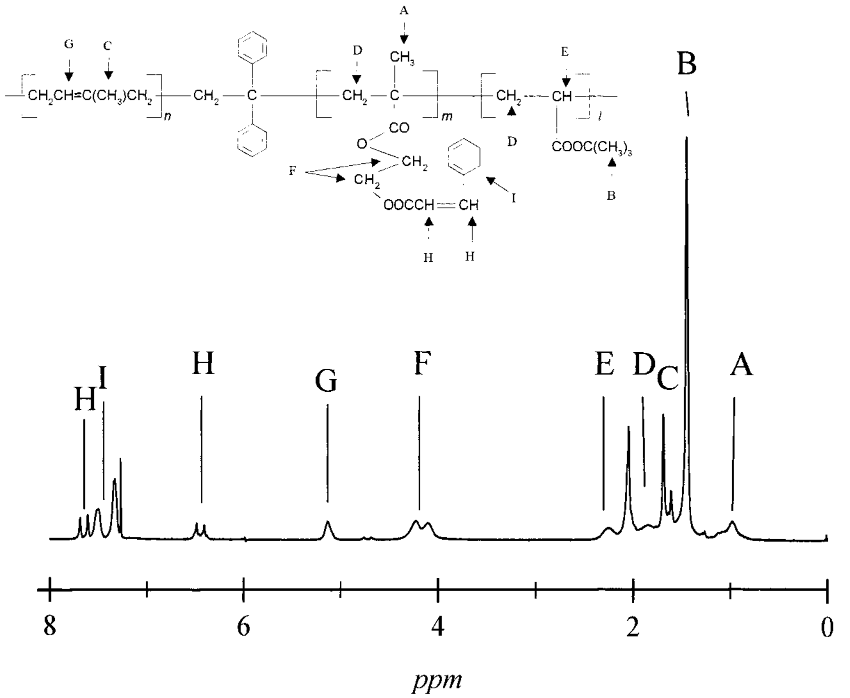

Figure 1. Proton NMR spectrum of PI-*b*-PCEMA-*b*-P*t*BA.

Table 2. Hydrodynamic Radii of the Micelles at Different Stages

MeOH content in solvent, %	hydrodynamic radii (nm)			
	cross-linking in THF/methanol		after cross-linking in chloroform	after PI degradation in chloroform
	before	after		
52	44	48	67	65
65	42	44	57	56
81	55	59	69	64

Table 3. Results from a Light Scattering Study of PI-*b*-PCEMA-*b*-P*t*BA Nanospheres in THF[a]

dn/dc (mL/g)	$\bar{M}_w$ (g/mol)	R_G (nm)	R_h (nm)
0.100	3.2×10^7	49	65

[a] The nanospheres were prepared in THF/methanol with 81% methanol.

A micelle in Figure 2 consists of a dark core and a gray shell. We believe that the core consists of PI and the shell is made up of PCEMA on the basis of the following considerations. First, the P*t*BA corona should not be visible here, because the staining agent OsO_4 does not react with P*t*BA. Second, PI should appear darker than PCEMA because PI, containing far more double bonds per unit mass, has been shown to react more readily with OsO_4 than PCEMA.[2] The radius of the core is ~9 nm and that of the particle containing the core and shell is ~16 nm.

The TEM radius of ~16 nm is much smaller than 55 nm, the hydrodynamic radius determined from dynamic light scattering in THF/methanol with 81% methanol. This is expected, because the P*t*BA layer was not seen by TEM. R_h is larger also because all the three blocks of the triblock are swollen in THF/methanol.

The R_h value of the micelles in Table 2 did not seem to change with methanol content initially. The R_h value increased substantially at higher, e.g. 81%, methanol content, probably due to an increase in the aggregation number of the micelles. This initial invariance but later increase in micellar size with an increase in the content of the block selective solvent in a mutual and block-selective solvent mixture has also been observed previously.[25]

Micelle Cross-Linking. Light passed through a 260-nm cutoff filter was used to cross-link the system. Since PI absorbs negligibly above ~240 nm, PI should be photochemically inactive. PCEMA cross-linked due to the photodimerization of CEMA groups of different chains.[26,27] The disappearance of the CEMA groups was followed by UV spectrophotometry, as CEMA absorbs strongly at 274 nm.[28] Since PCEMA photo-cross-linking has been used extensively by us in the past to prepare various nanostructures, including nanofibers[29,30] and nanochannels[31,32] in thin films, and the PCEMA chemistry here should be no different, another set of data is not shown for CEMA double bond disappearance kinetics. The nanospheres studied had a CEMA conversion of ~40%.

Shown in Figure 3 is the comparison between the FTIR spectra of the micelles and the nanospheres. Monitoring the decrease in the intensity of the double bond absorption peak at 1631 cm^{-1} offered another method for following the CEMA double bond conversion. The FTIR analysis is, however, less accurate because the PI and PCEMA double bond molar extinction coefficients at 1631 cm^{-1} are not known.

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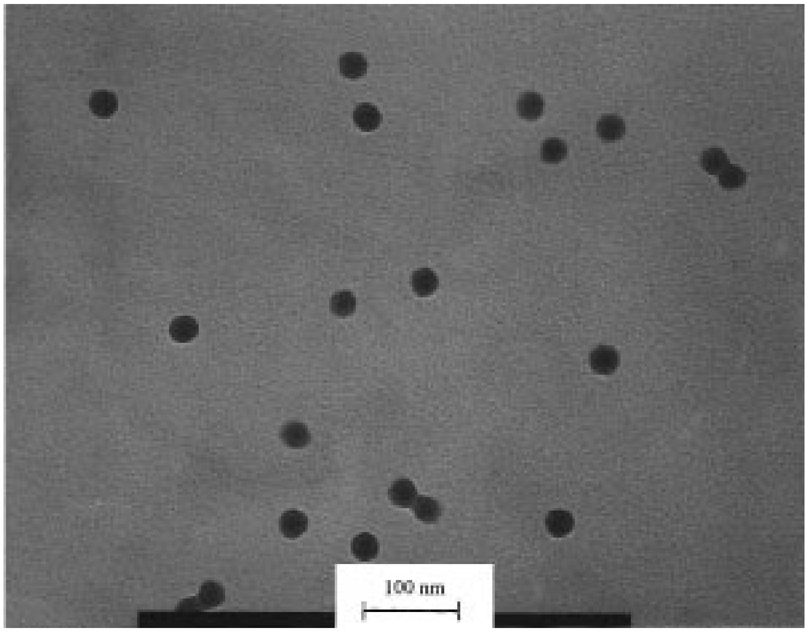


Figure 2. TEM image of PI-*b*-PCEMA-*b*-P*t*BA micelles prepared in THF/methanol with 81% methanol. The sample was stained by OsO_4.

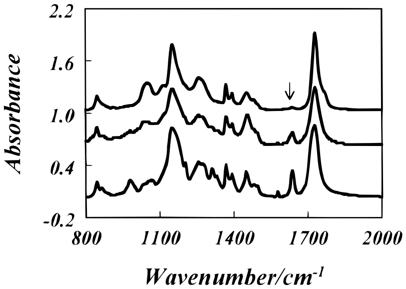


Figure 3. Comparison between the FTIR spectra of PI-*b*-PCEMA-*b*-P*t*BA micelles (bottom), nanospheres at a CEMA conversion of ~40% (middle), and hollow nanospheres (top). The peak at 1635 cm^{-1} is characteristic of double bond absorption of PI and PCEMA.

PCEMA cross-linking seems to increase the contrast between the PCEMA shell and the PI core, as shown by the TEM image of Figure 4. This is reasonable, because fewer PCEMA double bonds were available for staining after photo-cross-linking.

After PCEMA cross-linking, the R_h values (Table 2) in THF/methanol seem to increase slightly. The slight increase may be due to some intermicelle fusion. Intermicellar fusion is possible, because the P*t*BA block is relatively short and the corona should be relatively thin. The micellar structural fixation by photolysis can be appreciated from the fact that the cross-linked micelles or nanospheres were stable in chloroform, a solvent which solubilizes all the three blocks of the triblock copolymer. Upon switching the solvent from THF/methanol mixtures to chloroform, the R_h value generally increased, as shown in Table 2. This is expected, because the PCEMA and P*t*BA core swelled more in chloroform than in THF/methanol.

Properties of the Nanospheres. The nanospheres can be purified by precipitation into methanol/water (6/1) and dried. The dried nanospheres can be readily redispersed in solvents such as THF, toluene, or chloroform.

Static light scattering analysis was carried out for the nanospheres in THF. Using the dn_r/dc value of 0.100 mL/g and the Zimm data analysis method, we obtained the apparent radius of gyration, R_G, of 49 nm and the apparent weight-average molar mass, $\bar{M}_w$, of 3.2×10^7 g/mol.

Alternatively, we can estimate the molar mass of the nanospheres from their TEM radius R of ~16 nm using

$$\bar{M} = \frac{4}{3} N_A \pi R^3 \rho/(w_{PCEMA} + w_{PI}) \tag{3}$$

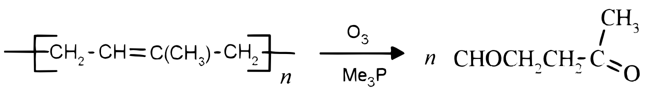
where N_A is Avogadro's constant and w_{PCEMA} and w_{PI}, 0.53 and 0.123, are the weight fractions of PCEMA and PI. The average density, ρ, of the PCEMA and PI components is 1.19 g/mL as calculated from

$$\rho = \frac{w_{PCEMA}\rho_{PCEMA} + w_{PI}\rho_{PI}}{w_{PCEMA} + w_{PI}} \tag{4}$$

where ρ_{PCEMA} and ρ_{PI}, 1.25 and 0.91 g/cm^3, are the densities of PCEMA[32] and PI,[23] respectively. The molar mass calculated from eq 3 is 1.9×10^7 g/mol, which is smaller than that determined from light scattering, probably because of some intermicellar fusion during the cross-linking step.

The hydrodynamic radius, R_h, determined for the nanospheres in THF, was 65 nm. Using the radius of gyration value of 49 nm, this gives $R_h/R_G = 1.33$, which is slightly larger than the expected value of 1.29 for homogeneous spheres.[24] This is reasonable, because our nanospheres have a trilayer structure and are not homogeneous.

Hollow Nanospheres. PI degradation by ozonolysis has been used by us previously to prepare shaved nanospheres[34] and shaved hollow nanospheres.[2] The reaction should be



$$\left[CH_2-CH{=}C(CH_3)-CH_2\right]_n \xrightarrow[Me_3P]{O_3} n\ CHOCH_2CH_2C(CH_3){=}O$$

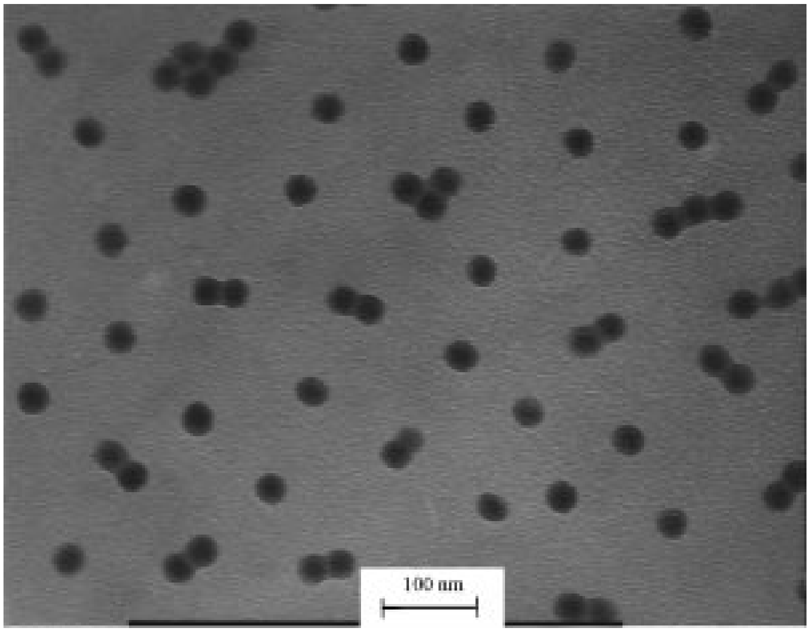


Figure 4. TEM image of PI-*b*-PCEMA-*b*-P*t*BA nanospheres. The micelles were prepared and cross-linked in THF/methanol with 81% methanol.

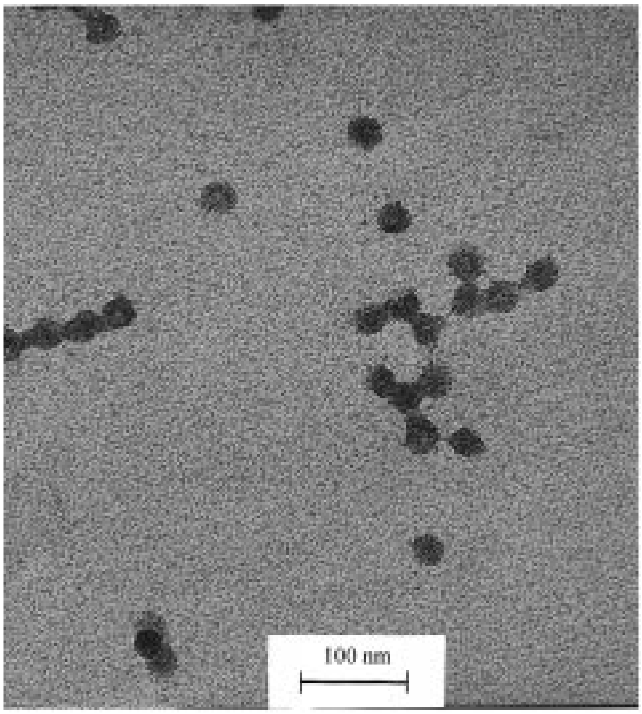
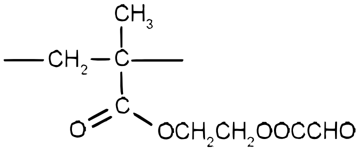


Figure 5. TEM image of the triblock hollow nanospheres. The micelles were prepared and cross-linked in THF/methanol with 81% methanol. After ozonolysis, the hollow nanospheres were dialyzed into methanol and THF was added so that they were sprayed from a THF/methanol mixture containing ~80% methanol. The specimen was stained with RuO_4.

The degradation of the PI block by ozonolysis is evident from data shown in Figure 3. After ozonolysis, the double bond peak at 1631 cm^{-1} disappeared almost completely.

The complete disappearance of the peak at 1631 cm^{-1} suggests the degradation of the residual double bonds of the PCEMA shell. The degradation of the PCEMA double bonds should yield



$$-CH_2-\overset{\overset{CH_3}{|}}{\underset{\underset{O=C-OCH_2CH_2OOCCHO}{|}}{C}}-$$

Since a carboxyl group is next to the newly formed aldehyde group, it remains to be examined if such a species is stable.

Shown in Figure 5 is a TEM image of hollow nanospheres prepared in THF/methanol with 81% methanol. One can vaguely discern light regions in the center of some of the particles. A more spectacular view of the central cavities is found in Figure 6, where the nanospheres were prepared in THF/methanol with 99% methanol and ozonolyzed in chloroform. The cavities are better resolved here, because they are much larger than those shown in Figure 5.

After ozonolysis, the particle size barely changed, as shown in Table 2. This is also confirmed by the TEM image shown in Figure 5, where the particles are seen to have a radius of ~16 nm, which is the same as those shown in Figure 2.

Rhodamine B Loading into the Cavities. To load RB into the cavities of the nanospheres, they were refluxed in a ~10% RB solution in methanol, and methanol was removed by evaporation. Illustrated in Figure 7 is a TEM image of nanospheres after such treatment. The light central regions of the particles in Figure 6 are now replaced with dark circles, suggesting the incorporation of RB in the cavity region. RB appeared dark under TEM, because RB contained stainable double bonds. Further evidence for RB incorporation derives from the deep red color of the RB-loaded nanospheres. Assuming no preferential partition of RB inside the cavities, RB was incorporated in this case to

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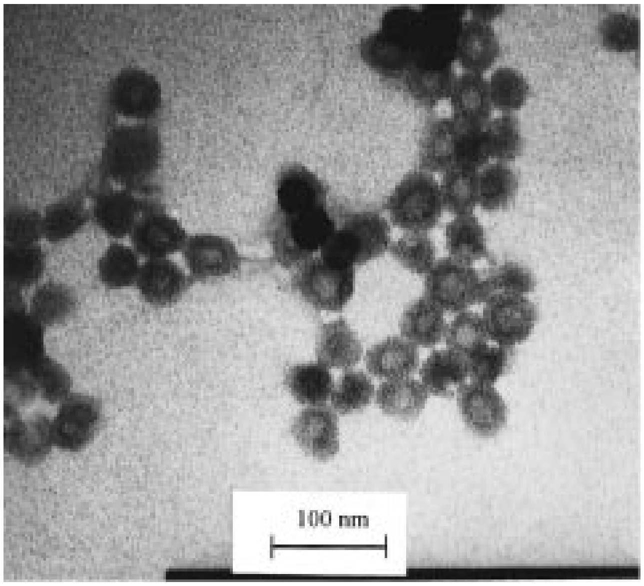

Figure 6. TEM image of the triblock hollow nanospheres. The micelles were prepared and cross-linked in THF/methanol with 99% methanol. The hollow nanosphere sample was sprayed from a THF/methanol mixture containing ~90% methanol and stained with RuO_4.

eliminate the concentration gradient between the bulk phase and the cavities.

Conclusions

A PI-*b*-PCEMA-*b*-P*t*BA sample was prepared, characterized, and used to prepare hollow nanospheres. This was achieved by preparing spherical micelles from the triblock in THF/methanol with methanol volume fractions between 50% and 99% first. In such micelles, P*t*BA formed the corona, and PCEMA and PI formed the essentially solvent-free shell and core, respectively. The micelle size increased with methanol content at high methanol contents. The micellar structure was then "locked in" by PCEMA shell photo-cross-linking. Cavities were obtained from PI core degradation by ozonolysis. Such cavities could be loaded with RB, as demonstrated by TEM results. Such hollow nanospheres should be useful as nanoreactors. When prepared from biocompatible and water-soluble polymers, they may also be useful in controlled drug delivery.

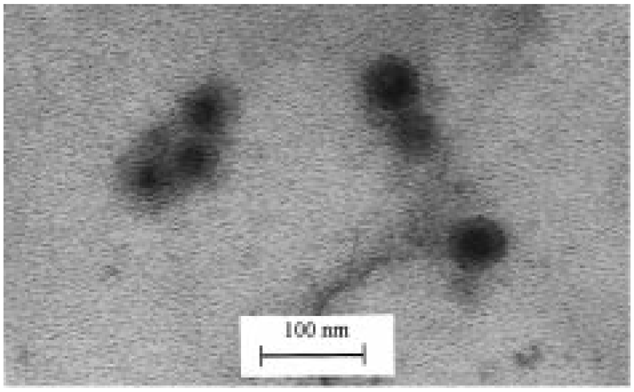

Figure 7. TEM image of PI-*b*-PCEMA-*b*-P*t*BA hollow nanospheres loaded with RB. The RB-loaded red particles were suspended in THF/hexanes with ~20% of THF before they were sprayed onto a carbon-coated grid and stained with RuO_4.

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