Thermosensitive Behavior of Poly(ethylene oxide)−Poly[bis(methoxyethoxyethoxy)-phosphazene] Block Copolymers

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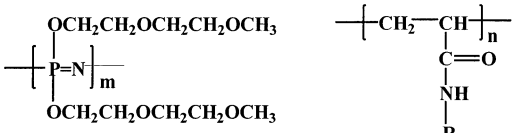
Received September 16, 2002
Revised Manuscript Received January 28, 2003

Introduction

Thermosensitive polymers have attracted much attention for applications such as drug delivery, membranes, and cell culture.[1−3] The lower critical solution temperature (LCST) is the temperature at which polymers in aqueous solutions or hydrogels undergo a transition from a soluble to an insoluble or opaque state or from a swollen hydrogel to a contracted form as the temperature is increased.[4,5] Several polymers, including poly[bis(methoxyethoxyethoxy)phosphazene] (MEEP) (**1**), poly(N-substituted acrylamide) (**2**), and poly(ethylene glycol)−poly(propylene glycol)−poly(ethylene glycol) triblock copolymers (**3**), are known for their LCST transition behavior.[6−8] MEEP has a well-defined LCST at 80 °C, and hydrogels of this polymer, formed through γ-ray cross-linking, show promise for use in biomedical applications.[6,9−11]



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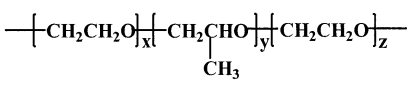

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We have recently reported an ambient-temperature route for the synthesis of polyphosphazenes via the controlled cationic polymerization of phosphoranimines, such as $Cl_3P{=}NSiMe_3$.[12,13] This PCl_5-induced polymerization allows the production of a variety of polymeric phosphazene systems with controlled molecular weights and architectures, including block copolymers.[14] The formation of block copolymers allows for an adjustment to be made to the physical properties that are characteristic of the component homopolymers. It seemed possible that the thermal sensitivity of the LCST of MEEP-type polyphosphazenes, as well as the water swelling behavior, might be tuned through the incorporation of an organic polymer block such as poly(ethylene oxide) (PEO). Here, we report the synthesis of potentially biocompatible and thermosensitive PEO−MEEP block copolymers through the PCl_5-induced, controlled cationic polymerization of phosphoranimines. The thermally induced aggregation behavior of these water-soluble diblock copolymers was investigated using UV/vis spectroscopy and dynamic light scattering (DLS).[15,16] In addition, the water swelling behavior and temperature dependence of a copolymer with a molar PEO:MEEP ratio of 1:4.9 were studied after γ-ray cross-linking.

Experimental Section

Polymer Synthesis. PEO-*block*-MEEP copolymers were prepared from $CH_3-PEO-NH_2$ using a procedure described previously in the literature.[17]

^{60}Co γ Irradiation of PEO−MEEP Block Copolymers. Films of the PEO-*block*-MEEP copolymers were cast from THF, followed by drying at room temperature for 3 days at atmospheric pressure and 3 days under vacuum. The polymers were sealed in foil-lined pouches and irradiated with ^{60}Co γ radiation.

Measurement of Water Uptake. The dry film (approximate weight of 1 g) was weighed and then immersed in 20 mL of deionized water. Periodically, the swollen film was removed from the water and weighed after carefully removing any water from the surface. The water uptake was calculated using eq 1

$$\text{water uptake} = [(W_s - W_d)/W_d] \times 100 \qquad (1)$$

where W_d is weight of the dried film and W_s is the weight of the swollen film.

Results and Discussion

Block copolymers containing a biocompatible, hydrophilic PEO segment and a thermosensitive MEEP portion were synthesized via the controlled, PCl_5-induced, cationic polymerization of phosphoranimines at ambient temperature, using amine-terminated PEO as a starting material[17] (Scheme 1). The macroinitiator $CH_3-PEO-NH-P(OCH_2CF_3)_2{=}NSiMe_3$ (**4**) was synthesized from amine-terminated PEO (M_n = 5400 g/mol, ShearWater) and $Br-P(OCH_2CF_3)_2{=}NSiMe_3$. Reaction of **4** with 2 equiv of PCl_5 yielded the cationic species $CH_3-PEO-NH-P(OCH_2CF_3)_2{=}N-PCl_3^+PCl_6^-$ (**5**). Subsequent addition of varying amounts of $Cl_3P{=}N\ SiMe_3$ to **5** allowed the preparation of PEO-*block*-poly(dichlorophosphazene) copolymers with controllable phosphazene block lengths. Further treatment of this reaction mixture with $NaOCH_2CH_2OCH_2CH_2OCH_3$ gave PEO-*block*-MEEP copolymers through the macromolecular replacement of labile chlorine atoms. A series of block copolymers were prepared by varying the length of the MEEP block, while the length of the PEO block remained constant. Gel permeation chromatography was used to measure average molecular weights and polydispersities, and these were compared to values calculated using ^{1}H NMR (Table 1).

Aqueous Phase Behavior. MEEP is known to undergo an LCST transition at 80 °C in water.[9] Thus, the water-soluble PEO-*block*-MEEP copolymers synthesized in this work were expected to show temperature-sensitive self-organization in water associated with the LCST behavior of the MEEP block.[11] The temperature-dependent phase transitions of aqueous PEO-*block*-MEEP solutions were monitored by observing the changes of transmittance at 450 nm, as shown in Figure 1. Aqueous solutions of polymer **8** (molar PEO:MEEP

10.1021/ma021490d CCC: $25.00
Published on Web 03/15/2003

Scheme 1

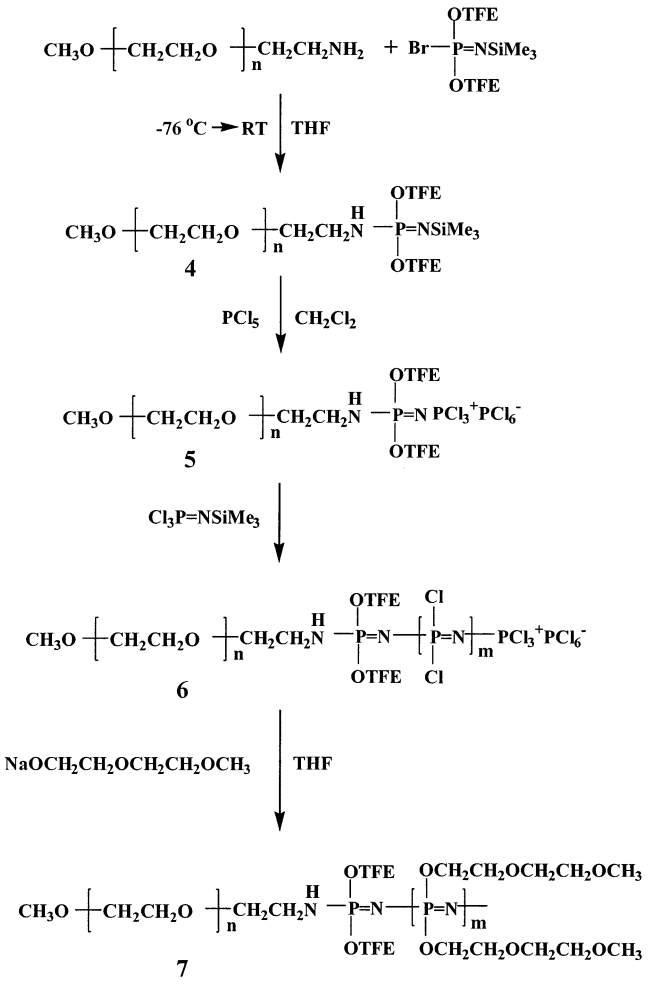

Table 1. Characteristics of PEO−MEEP Block Copolymers

polymer	yield (%)	ratio of mole repeat unit (PEO:MEEP) feed	found[a]	M_n (^{1}H NMR)	M_n[b] (M_w/M_n)	T_g (°C)
8	83	1:0.5	1:0.49	22 000	15 000 (1.43)	−78
9	77	1:1	1:1.2	47 000	16 500 (1.45)	−76
10	69	1:2	1:2.7	98 000	27 000 (1.45)	−79
11	70	1:4	1:4.9	175 000	54 000 (1.64)	−80

[a] Calculated from ^{1}H NMR spectra, by comparison of peaks at 3.28 ppm ($-OCH_3$) to peaks at 3.70 ($-OCH_2-$), using $CH_3-PEO-NH_2$ of a known molecular weight (M_n = 5400). [b] Measured by GPC.

ratio of 1:0.49; see Table 1) showed a striking increase in turbidity when heated above 65 °C.

Figure 1 also illustrates the temperature-induced formation of self-aggregates in these same aqueous solutions. Samples of polymer **8** were totally soluble in water between 25 and 65 °C but readily formed self-aggregates above these temperatures. Light scattering measurements showed that the hydrodynamic radius, R_h, of the self-aggregates increased from 270 to 540 nm in the temperature range 68−80 °C. Aqueous solutions of polymers with molar PEO:MEEP ratios of 1:1.2, 1:2.7, and 1:4.9 (polymers **9**, **10**, and **11**, respectively) showed similar thermosensitive behavior to polymer **8** due to the LCST of the MEEP block present in all the copolymers. The self-aggregation process was completely reversible, and the aggregates became soluble again

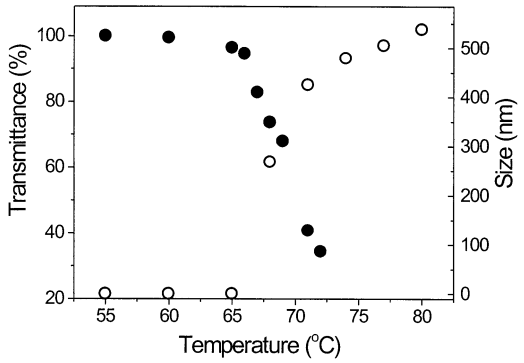

Figure 1. Percent transmittance change of a 0.5 g/L solution of polymer **8** as a function of temperature (●); temperature dependence of hydrodynamic radius (R_h) of polymer **8** in a 0.5 g/L solution (○).

below the onset temperature. These results suggest that the temperature increase makes the usually hydrophilic MEEP block somewhat more hydrophobic, which provides a sudden, sharp contrast to the solubility of the PEO block in water and thus enhances the amphiphilic nature of these copolymers. This phenomenon underlies the unique temperature-dependent self-aggregation of the PEO-*block*-MEEP copolymers examined here. This type of temperature-dependent aggregation has also been observed previously for the phosphazene block copolymer, $[N{=}P(OCH_2CH_2OCH_2CH_2OCH_3)_2]_n-[N{=}PPh(OCH_2CH_2OCH_2CH_2OCH_3)]_m$ (MEEP−Ph/MEEP).[18]

Hydrogels. It is well-known that MEEP can be cross-linked to form a water-swellable hydrogel by exposure to γ-radiation.[11] The application of this γ-radiation cross-linking methodology to the PEO-*block*-MEEP copolymers offers the prospect of temperature-sensitive hydrogels due to the LCST characteristics of the MEEP block. The block copolymers described here were expected to show lower cross-link densities than MEEP itself as a result of a smaller number of cross-linkable sites per chain. However, higher water uptake and swelling values might be expected because of the presence of the hydrophilic PEO blocks in the copolymer. Four samples of PEO-*block*-MEEP copolymers (Table 1), varying in MEEP block lengths, were irradiated with ^{60}Co γ-radiation (20 Mrad radiation dose). After cross-linking, a film of polymer **11** (PEO:MEEP ratio of 1:4.9) showed good mechanical strength, but polymers **8**, **9**, and **10** (PEO:MEEP ratios of 1:0.49, 1:1.2, and 1:2.7, respectively) did not form free-standing films. This could be due to the larger proportion of PEO, relative to MEEP, found in these particular systems. Our previous study revealed that PEO (M_n = 5000) did not cross-link when exposed to the same radiation dosage as the copolymers discussed here. Hydrogels of polymer **11** showed uniform swelling behavior in water and a swelling ratio larger than that of the MEEP homopolymer. The water uptake value of polymer **11** was 460%, while that of MEEP was 300%, with both having been cross-linked with a 20 Mrad radiation dose.[11] The water swelling behavior of the hydrogel formed from polymer **11** was also examined over a wide temperature range to ascertain its usefulness for biomedical applications.[19] As shown in Figure 2, this hydrogel showed relatively constant water absorption values in the range 25−50 °C. However, a dramatic decrease in water swelling (from 460% to 36%), probably related to the LCST behavior of the MEEP block, was detected above 50 °C.[20] In addition, the initial transition temperature for the

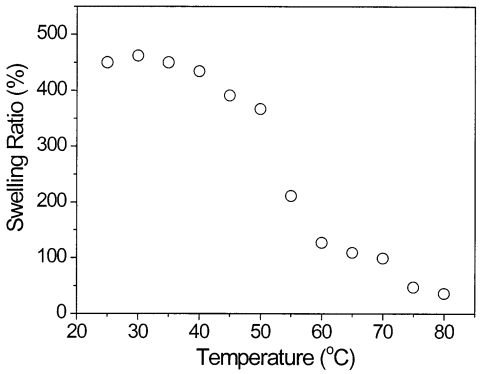

Figure 2. Swelling values for a hydrogel of polymer **11** in water.

hydrogel of polymer **11** is lower than the phase transition temperature of the aqueous solutions of the corresponding un-cross-linked block copolymer. This suggests that the bulk state of the cross-linked hydrogel is more sensitive to changes in temperature than the un-cross-linked block copolymer solution. The water swelling behavior was reversible, and the hydrogel retained its original shape after the study.

In conclusion, PEO-*block*-MEEP copolymers were synthesized using the controlled cationic polymerization of phosphoranimines. The block copolymers synthesized had molar PEO:MEEP ratios of 1:0.49, 1:1.2, 1:2.7, and 1:4.9, with the length of the PEO segment held constant at 5400 g/mol. The self-aggregation characteristics of the block copolymers in water have been investigated by using UV/vis spectroscopy and dynamic light scattering. These studies revealed a temperature dependence of the hydrodynamic radii of self-aggregates due to the LCST behavior of the MEEP block. A hydrogel of a block copolymer with a molar PEO:MEEP ratio of 1:4.9 was also synthesized, and its temperature dependency was studied. This hydrogel exhibited larger water uptake values than those of MEEP homopolymer, which is probably due to the hydrophilic nature of the PEO blocks. The thermosensitive phase-transition and water-swelling behavior of the PEO-*block*-MEEP copolymers was examined as the first step toward their utilization as potential biomaterials and for uses in both temperature-responsive membranes and delivery matrices.

Acknowledgment. This work was supported by the National Science Foundation through Grant CHE-0211638. C.K. thanks the Korea Research Foundation (2001-041-E00333) for their support.

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