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Communications to the Editor

Preparation and Aqueous Solution Properties of New Thermoresponsive Biocompatible ABA Triblock Copolymer Gelators

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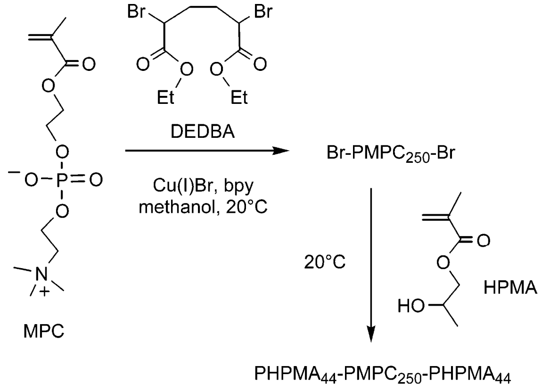
ABA triblock copolymers with water-soluble central B blocks and water-insoluble outer A blocks are known to form gels in semidilute aqueous solution.[1−6] The copolymer chains form aggregates known as “flower” micelles, and the water-soluble B block can act as a bridge between these micelles. Computer simulations indicate that critical copolymer volume fractions of 0.05−0.10 are required for gelation, depending on the overall molecular mass.[3] This work, as well as other theoretical studies,[1,2] also predicts that the ability to form networks depends mainly on the degrees of polymerization of the two blocks as well as the hydrophobic character of the outer A block. These findings have been confirmed by a large number of experimental studies.[1,4−6]

Herein we report the synthesis and aqueous gelation behavior of new ABA copolymers in which the hydrophobic character of the A blocks is systematically varied, while the central B block in each case is poly(2-(methacryloyloxy)ethylphosphorylcholine) (PMPC), a highly hydrophilic polymer that confers clinically proven biocompatibility.[7,8] Three types of ABA triblock copolymers of approximately the same overall composition were prepared in which the A block is either poly(methyl methacrylate) [PMMA], poly(2-hydroxypropyl methacrylate) [PHPMA], or poly(2-hydroxyethyl methacrylate) [PHEMA]. MMA monomer is water-immiscible and PMMA is hydrophobic, whereas HPMA monomer is water-miscible up to 13% at 25 °C but PHPMA is water-insoluble. On the other hand, HEMA monomer is water-miscible in all proportions, and PHEMA is water-soluble up to a mean degree of polymerization of ∼45, becoming water-insoluble thereafter.[9] Thus, the relative hydrophobic character of the A blocks ranks as PMMA > PHPMA > PHEMA.

Scheme 1. ATRP Synthesis of the PHPMA−PMPC−PHPMA Triblock Copolymer



Each of these three ABA triblock copolymers was synthesized by ATRP in methanol using sequential monomer addition[10] as shown in Scheme 1 for PHPMA−PMPC−PHPMA (see Supporting Information for further experimental details). Diethyl meso-2,5-dibromoadipate (DEDBA, Aldrich) was used as a bifunctional initiator. In the case of the $PMMA_{55}$−$PMPC_{240}$−$PMMA_{55}$ triblock synthesis, the reaction solution was heated to 50 °C prior to addition of the MMA monomer due to the marginal solubility of PMMA in methanol at ambient temperature.[11]

The three copolymers were characterized by GPC and ^1H NMR (see Table 1). The $PHPMA_{44}$−$PMPC_{250}$−$PHPMA_{44}$ and $PHEMA_{55}$−$PMPC_{250}$−$PHEMA_{55}$ triblocks were both soluble in CD_3OD. Solubilization of the $PMMA_{55}$−$PMPC_{240}$−$PMMA_{55}$ copolymer required the use of a $CDCl_3/CD_3OD$ mixture for a

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Table 1. Summary of the ^{1}H NMR and GPC Data for the Three ABA Triblock Copolymers Examined in This Study

target block composition^a	^{1}H NMR block composition^a	MPC content (mol %)	conv for first block (%)^b	conv for second block (%)^b	M_n^{c}	M_w/M_n^{c}
$PHPMA_{50}PMPC_{250}PHPMA_{50}$	$PHPMA_{44}PMPC_{250}PHPMA_{44}$	74	>98	>98	84 700	1.39
$PMMA_{49}PMPC_{240}PMMA_{49}$	$PMMA_{55}PMPC_{240}PMMA_{55}$	69	>98	>98	89 000	1.72
$PHEMA_{51}PMPC_{250}PHEMA_{51}$	$PHEMA_{55}PMPC_{250}PHEMA_{55}$	73	>98	>98	91 900	1.62

[a] Subscripts indicate the mean degrees of polymerization (DP) of each block. [b] As determined by ^{1}H NMR. [c] As determined by GPC conducted in a 3:1 chloroform/methanol mixed eluent using poly(methyl methacrylate) calibration standards.

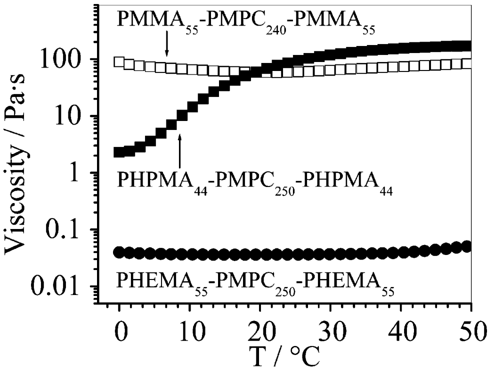

Figure 1. Temperature dependence of the solution viscosity for 10% w/v aqueous solutions of the three PMPC-based triblock copolymers shown in Table 1.

reliable ^{1}H NMR spectrum. Similarly, GPC characterization was carried out using a 3:1 $CHCl_3/CH_3OH$ mixed eluent for all copolymers (see Supporting Information, Figure S1). The copolymer compositions estimated from ^{1}H NMR spectroscopy are close to those targeted. It is worth emphasizing that the PMPC precursor block has a relatively low polydispersity (around 1.30) in each case, so these triblock copolymers have reasonably well-defined molecular architectures. However, the polydispersities of the overall triblock copolymers are somewhat higher (1.39−1.72), which simply reflects the fact that rather high degrees of polymerization are being targeted in these one-pot syntheses, leading to some loss of control over the living character of the ATRP chemistry. Nevertheless, our GPC data are generally comparable to those previously reported for related pH-responsive triblock copolymers synthesized by sequential monomer addition by both ATRP[10] and group transfer polymerization (GTP).[6]

The temperature-dependent viscosity behavior of 10% w/v aqueous solutions of each copolymer is shown in Figure 1. $PMMA_{55}PMPC_{240}PMMA_{55}$ produced a highly opaque gel that flowed slowly on tube inversion and exhibited a high, almost temperature-independent viscosity. The highly hydrophobic nature of the PMMA blocks prevents molecular dissolution and leads to long micelle residence times (i.e., "frozen" micelles).[3,4] In contrast, a 10% w/v aqueous solution of $PHEMA_{55}PMPC_{250}PHEMA_{55}$ was highly transparent and had a low viscosity (i.e., was free-flowing) over the entire temperature range. Again, the viscosity of this copolymer does not exhibit any significant temperature dependence, although gelation was achieved at 60 °C for more concentrated copolymer solutions (>20% w/v). Thus, the thermoresponsive behavior of the PHEMA chains is suppressed significantly when they are attached to the much more hydrophilic PMPC block.

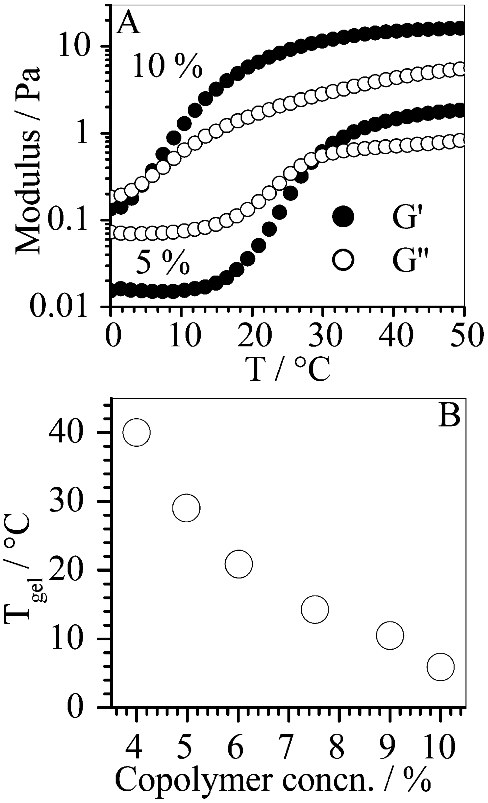

Figure 2. (A) Storage (G') and loss (G'') moduli obtained for 5 and 10% aqueous solutions of the $PHPMA_{44}PMPC_{250}PHPMA_{44}$ triblock copolymer, respectively. (B) The $G'-G''$ crossover temperature as a function of concentration for the same $PHPMA_{44}PMPC_{250}PHPMA_{44}$ copolymer.

The viscosity of a 10% w/v aqueous solution of the $PHPMA_{44}PMPC_{250}PHPMA_{44}$ copolymer unexpectedly increased by almost 2 orders of magnitude on heating from 0 °C (free-flowing liquid) to 30 °C (transparent free-standing gel, see Figure S2). As this behavior was unforeseen, we investigated this copolymer in more detail. In Figure 2A the temperature-dependent storage and loss moduli of 5% and 10% aqueous solutions of this copolymer are shown. In both cases the storage modulus increases by 2 orders of magnitude and becomes larger than the loss modulus, confirming gel formation. The critical gelation temperature (T_{gel}) was determined from the crossover of the storage and loss modulus curves and decreases monotonically from 40 to 5 °C as the copolymer concentration is increased from 4.0 to 10.0% w/v (see Figure 2B). This is similar to the behavior of Pluronic-type triblock copolymers, where the hydration of the poly(propylene oxide) block is both concentration- and temperature-dependent.[12,13] In contrast, the aqueous solution behavior of classical thermoresponsive poly(*N*-isopropylacrylamide)-based copolymers is largely concentration-independent.[14] Our dynamic light scattering experiments indicate the presence of weakly interacting "flower" micelles even for highly dilute solutions at 5 °C, with increased light scattering being observed at elevated temperatures (see Figure S3). Close examination of variable temperature ^{1}H NMR spectra recorded in D_2O (see Figure S4) suggests only partial solvation of the PHPMA blocks at low temperature. The signal at 0.95 ppm due to the pendent methyl groups on the PHPMA blocks is visible at low temperature but is attenuated at higher temperatures relative to the PMPC signals at 2.95, 3.42, and 3.70−4.00 ppm and also the methacrylic backbone signals at 0.50−0.90 and 1.65 ppm which increase in intensity and become sharper along with a downfield shift due to temperature. Similarly, FT-IR studies have shown that the intensity of the absorption band assigned to the methyl groups in poly(propylene oxide) is strongly correlated with the dehydration of this polymer at higher temperatures.[15,16]

In summary, although PHPMA homopolymer is not normally considered to be a water-soluble polymer, it can be rendered water-soluble (or at least water-dispersible) by covalent attachment to a much more hydrophilic block, in this case PMPC. We propose that the unexpected thermoresponsive behavior of the $\text{PHPMA}_{44}-\text{PMPC}_{250}-\text{PHPMA}_{44}$ triblock copolymer is due to the weakly hydrophilic nature of the PHPMA blocks, which are clearly capable of intrachain and interchain hydrogen bonding via C═O···HO type interactions. In contrast, the analogous PHEMA-based triblock copolymer is simply too hydrophilic to undergo efficient gelation (at least in semidilute aqueous solution), while the PMMA-based triblock copolymers cannot be molecularly dissolved/dispersed in water under any conditions, leading to opaque viscous solutions with no thermoresponsive behavior. Unlike *N*-isopropylacrylamide, HPMA monomer is cheap and has relatively low toxicity. Moreover, the marked concentration dependence observed for the critical gelation temperature suggests that degelation may be easily achieved simply by dilution, which may be useful in certain biomedical applications. Preliminary cell viability studies indicate useful biocompatibility for these $\text{PHPMA}_{44}-\text{PMPC}_{250}-\text{PHPMA}_{44}$ gels, and these data will be reported in due course.

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Supporting Information Available: Full details of the experimental protocols, instrumentation, and characterization procedures; GPC traces of each copolymer, variable temperature light scattering data, ^{1}H NMR spectra, and digital photographs of the copolymer gels. This information is available free of charge via the Internet at http://pubs.acs.org.

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