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Towards smart polymeric drug carriers: self-assembling γ-substituted polycaprolactones with highly tunable thermoresponsive behavior†

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Synthesis and ring opening polymerization of a new γ-substituted ε-caprolactone monomer, γ-(2-methoxyethoxy)-ε-caprolactone is reported. Amphiphilic diblock copolymers comprised of poly[γ-(2-methoxyethoxy)-ε-caprolactone] and thermosensitive poly{γ-2-[2-(2-methoxyethoxy) ethoxy]ethoxy-ε-caprolactone} as the hydrophobic and hydrophilic blocks, respectively, were prepared. The copolymers exhibited fully biodegradable backbones and highly tunable thermoresponsive behavior in the range of 31–43 °C. Additionally, the copolymers were shown to self-assemble in aqueous media above their respective critical micelle concentrations, on the order of 10^{-2} g L^{-1}. Due to their thermosensitive, self-assembling, and biodegradable properties, these copolymers demonstrate potential for the use in polymeric micellar drug delivery systems.

Introduction

In recent years, extensive research has focused on the development of drug delivery systems that can solubilize, transport, and release drug molecules *in vivo* in a controlled manner.[1–4] These efforts are of utmost importance as improving the delivery of currently available drugs can improve their efficacy, minimize their side effects, and potentially give FDA-approved molecules new life. Synthetic organic polymers offer a wide variety of properties and supramolecular architectures and thusly have attracted attention for use in biomedical applications.

Polymeric micelles can encapsulate hydrophobic drug molecules and transport them stealthily through the bloodstream.[5–7] These micelles tend to accumulate in tumor tissues by the enhanced permeation and retention (EPR) effect, and can be designed to release their drug cargoes upon thermal or other stimulus.[2,5] Diblock copolymers intended for polymeric micelles consist of a hydrophobic block and a hydrophilic block, which drive the self-assembly in aqueous solution above their critical micelle concentration (CMC).[6,8,9] Typically, the hydrophobic core is comprised of a biodegradable polyester while the shell is the highly hydrophilic poly(ethylene glycol) (PEG).[2,5] While the PEG block's good biocompatibility and hydrophilicity help prolong the micelle circulation time in the body, its inability to biodegrade has spurred the development of alternatives. With respect to the controlled release of encapsulated drugs, diblock copolymers with thermoresponsive behavior, *i.e.* those that exhibit a lower critical solution temperature (LCST) above which they are insoluble in water, are of particular interest. One of the most widely studied thermoresponsive polymers for biomedical applications is poly(*N*-isopropylacrylamide) (PNIPAAM), which exhibits an LCST of 32 °C.[10,11] Although PNIPAAM has shown promise in hydrogel-based materials for drug delivery, its low LCST and non-biodegradable backbone largely preclude its use as an internal drug carrier.[6,12]

As evidenced by numerous reports and reviews, aliphatic polyesters are common components in drug delivery applications largely due to their biocompatibility and biodegradability by ester hydrolysis.[1,5] More specifically, ε-caprolactones have garnered much interest due to the ease with which they can be functionalized, polymerized, and tailored to specific applications.[4,13–15] While numerous copolymers have been investigated and have shown promising potential for drug delivery applications, few amphiphilic diblock copolymers combine a fully biodegradable backbone with physiologically relevant and highly tunable thermoresponsive behavior.[12,16] We report here the synthesis and characterization of new micelle-forming amphiphilic, biodegradable, and thermosensitive diblock copolymers from γ-substituted caprolactone monomers.

As first reported by the Stefan group, the substituted ε-caprolactone monomer γ-2-[2-(2-methoxyethoxy)ethoxy]-ethoxy-ε-caprolactone (MEEECL) may be polymerized by ring opening polymerization (ROP) to generate poly{γ-2-[2-(2-methoxyethoxy)ethoxy]ethoxy-ε-caprolactone} (PMEEECL), which displays a LCST of about 48 °C, or even lower if coupled with a

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hydrophobic block as in a diblock copolymer.[16] Previous studies with MEEECL-based polymers have demonstrated the great potential of MEEECL as a thermoresponsive, biodegradable hydrophilic block in micellar assemblies, as opposed to the typical PEG block in most micelles for biomedical applications. Alkoxy- and benzyloxy-substituted caprolactones have been combined with MEEECL to form thermosensitive diblock copolymers capable of self-assembling into micelles.[16,17] While these polymers have demonstrated acceptable preliminary results, other γ-substituted caprolactones are being investigated to further enhance biocompatibility, micelle stability, and drug loading capacities while maintaining desirable thermosensitive attributes.[18]

This article introduces γ-(2-methoxyethoxy)-ε-caprolactone (MECL) as a promising candidate for the hydrophobic counterpart to the hydrophilic MEEECL in diblock copolymers. Of particular interest was MECL's effect on the copolymer's LCST given the smaller difference in hydrophobicity between MEEECL and MECL. Additionally, the methoxyethoxy side unit may interact with encapsulated drugs differently and could be more biologically friendly compared to alkoxy groups and ultimately contribute to a biologically friendlier drug delivery system.

Results and discussion

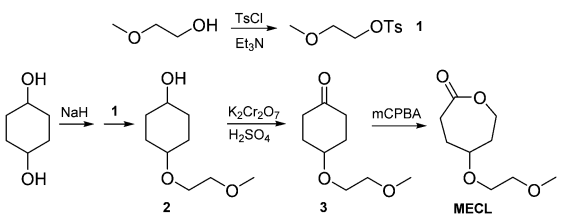
The synthesis of the monomer MECL (Scheme 1) was modified from the previously reported MEEECL procedure.[16] Briefly, 2-methoxyethanol was reacted with tosyl chloride to produce 2-methoxyethyl 4-methylbenzenesulfonate (**1**). Next, 1,4-cyclohexanediol was deprotonated with NaH then reacted with the product from the previous step to generate 4-(2-methoxyethoxy) cyclohexanol (**2**). Treatment with chromic acid followed by column purification yielded 4-(2-methoxyethoxy)cyclohexanone (**3**), which was then subjected to Baeyer–Villager oxidation to form γ-(2-methoxyethoxy)-ε-caprolactone (MECL). ^{1}H NMR, ^{13}C NMR, and C/H elemental analysis confirmed the formation of γ-(2-methoxyethoxy)-ε-caprolactone (ESI, Fig. S4 and Table S1†).

As a proof-of-concept experiment to demonstrate the hydrophobicity of MECL, and thus its ability to act as a hydrophobic core, a diblock copolymer of PEG (57 mol%) and PMECL (43 mol%) was prepared (ESI, Scheme S2 and Table S2†). As anticipated, this polymer **P0** self-assembled in aqueous solution to form micelles of about 50 nm in diameter, and displayed a critical micelle concentration (CMC) of 9.04×10^{-4} g L^{-1}, both of which are reasonable values for PEG-containing amphiphilic diblock copolymer micelles (ESI, Fig. S6†). The formation of spherical micelles was further evidenced by tapping mode atomic force microscopy (TMAFM) and transmission electron microscopy (TEM) of the dried micelles (Fig. 1).

Upon demonstrating that MECL forms micelles with a PEG copolymer, polymers with varying ratios of MEEECL : MECL were prepared using ROP with benzyl alcohol initiator and stannous ethylhexanoate catalyst as shown in Scheme 2. In addition to the four copolymers **P2–P5**, two homopolymers, **P1** (ESI, Scheme S3†) and **P6** (ESI, Scheme S4†) were prepared as controls. A summary of the composition and molecular weights of polymers **P1–P6** is shown in Table 1. The molecular weights are mostly in the 4500–7500 g mol^{-1} range, with polydispersity indices (PDI, M_w/M_n) from 1.6 to 1.9. The mol% MEEECL increases from 0% to 100% from **P1** to **P6**.

For the polymers containing PMEEECL (**P2–P6**), the LCST was determined. The polymer solutions were subjected to heating and cooling and monitored for changes in transmittance (ESI, Fig. S10†). As the solution was heated above the LCST, a drop in transmittance was observed due to the dehydration and subsequent precipitation of the polymer. Homopolymer **P1** was also subjected to this protocol, but did not indicate the presence of an LCST. The LCST was taken to be the temperature at which a 50% drop in transmittance was observed upon heating. The transition is not as sharp as that of previously reported PMEEECL-based copolymers, most likely due to the smaller difference in hydrophobicity between the PMEEECL block and the PMECL block. As anticipated, as the mol% of MEEECL in the polymer increased, so did the LCST. The data in Fig. 2 point to a linear relationship between the mol% of hydrophobic block (MECL) and the LCST of the polymer.

Determination of CMC was performed using pyrene, a small fluorescent molecule whose excitation peak shifts from a maximum intensity at about 335 nm in hydrophilic environments to a maximum intensity at about 338 nm in hydrophobic environments. The ratio of the intensities of these two peaks was monitored as a function of polymer concentration; a sharp increase in I_{338}/I_{335} signified the CMC (ESI, Fig. S11†). Copolymers **P2–P5** displayed values on the order of 10^{-2} g L^{-1} for their respective CMC, which is within an acceptable range for block copolymer micelles. Homopolymers **P1** and **P6** were subjected to the same protocol but gave no indication of self-assembly. Polymers **P2** and **P3**, with higher hydrophobic PMECL content



Scheme 1 Synthesis of γ-2-(methoxyethoxy)-ε-caprolactone (MECL).

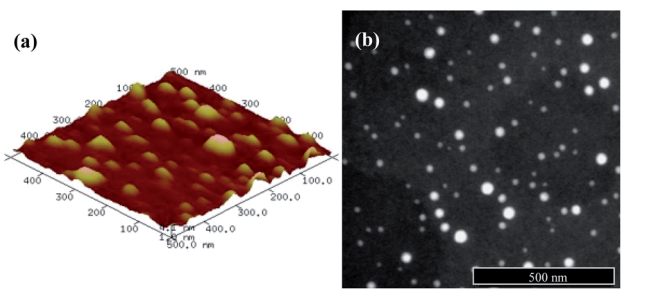
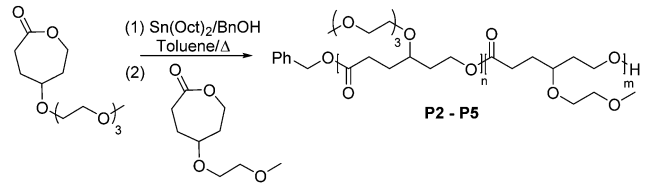


Fig. 1 (a) 3D TMAFM images of polymer **P0** micelles deposited on mica substrate, scan size: 500 nm^2; (b) TEM image of polymer micelles, **P0** deposited on copper mesh grid stained with 1% phosphotungstic acid.



Scheme 2 Synthesis of diblock copolymers **P2–P5** from γ-substituted caprolactone monomers MEEECL and MECL.

show slightly lower CMC values as compared to those of **P4** and **P5**, which contain lower amounts of PMECL.

Dynamic light scattering (DLS) was utilized to estimate the hydrodynamic diameter (D_h) of the self-assembled polymeric micelles. For each of the copolymer micelle solutions at room temperature, the D_h values were centered around 100 nm with comparable standard deviations of 1 to 3 nm (Fig. 3). The difference in sizes from the smallest (**P2**, 81 nm) to the largest (**P4**, 113 nm) was attributed to the decrease in size of the hydrophobic block. The chains of **P4** with shorter PMECL blocks likely pack less tightly than chains of **P2** with larger MECL content.

The effect of temperature changes on the diameter of polymeric micelles was investigated using DLS (ESI, Fig. S12†). For each copolymer, the average diameter increased as the temperature approached and exceeded the LCST. While the mechanics of this behavior are beyond the scope of this report, this change in size may occur with a change in the assemblies' morphologies as the polymer chains dehydrate. Such a phenomenon may be further analyzed and exploited for the temperature-triggered release of encapsulated drug molecules.

Dried micelle solutions of copolymers **P2** and **P4** were imaged using tapping mode AFM and TEM with negative staining. Polymers **P2** and **P4** were selected for these preliminary microscopy studies to compare the morphologies of the self-assemblies with PMEEECL : PMECL block ratios of about 1 : 1 and 3 : 1, respectively. Fig. 4 shows 3D TMAFM and TEM images of the **P2** and **P4** micelles. While for both polymers the micelles are not completely uniform in size, they do appear to be spherical in shape and show diameters indicative of large micelles in the 50–100 nm range. Consistent with the DLS data are the relative sizes; for **P2** the micelles are approximately 40–50 nm in diameter whereas the **P4** micelles are larger, closer to

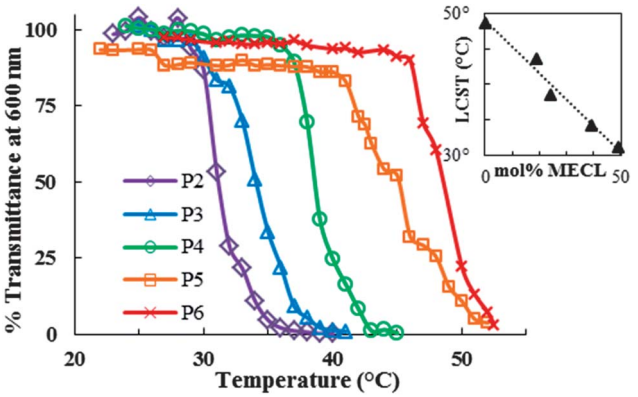


Fig. 2 Change in percent transmittance at 600 nm upon heating for aqueous solutions of polymers **P2–P6**; inset, LCST as a function of mol% MECL.

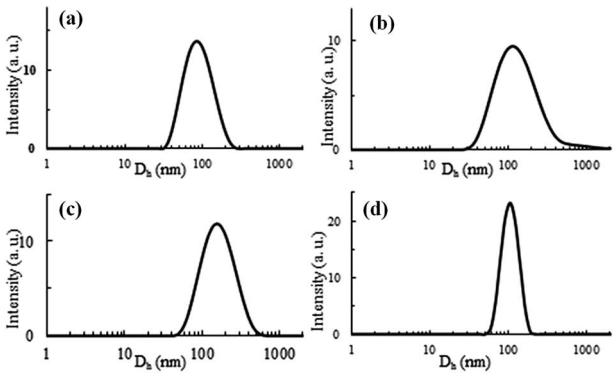


Fig. 3 Hydrodynamic diameter (D_h) analysis of polymeric micelles at room temperature using dynamic light scattering: (a) **P2**, (b) **P3**, (c) **P4**, (d) **P5**.

80–90 nm in diameter. TEM images of micelles after negative staining with phosphotungstic acid showed spherical assemblies, but with slightly smaller diameters of about 40 nm for **P2** and about 65 nm for **P4**. Future studies will delve deeper to better elucidate the morphology as a function of the copolymer block ratios.

To demonstrate the biodegradability of PMEEECL-*b*-PMECL block copolymers, **P2** was subjected to heating at 37 °C in phosphate buffer at pH 6 for five days. Samples were taken periodically and analyzed by size exclusion chromatography to

Table 1 Summary of polymers **P1–P6**

Polymer	M_n[a] (g mol^{-1})	PDI[a] (M_w/M_n)	MEEECL[b] (mol%)	MECL[b] (mol%)	LCST[c] (°C)	CMC[d] (g L^{-1})	D_h[e] (nm)
P1	7200	1.9	0	100	—	—	—
P2	6700	1.8	51	49	31.1	1.58×10^{-2}	81 ± 2
P3	7600	1.6	61	39	34.2	3.07×10^{-2}	101 ± 3
P4	7300	1.7	76	24	38.5	3.56×10^{-2}	113 ± 3
P5	4400	1.7	81	19	43.5	4.47×10^{-2}	99 ± 2
P6	4700	1.6	100	0	48.6	—	—

[a] Determined by size exclusion chromatography using polystyrene calibration. [b] Block content mol% determined by ^{1}H NMR. [c] Determined by 50% drop in transmittance at 600 nm upon heating aqueous polymer solution. [d] Determined by fluorescence measurements with pyrene. [e] Micelle hydrodynamic diameter at 25 °C determined using dynamic light scattering.

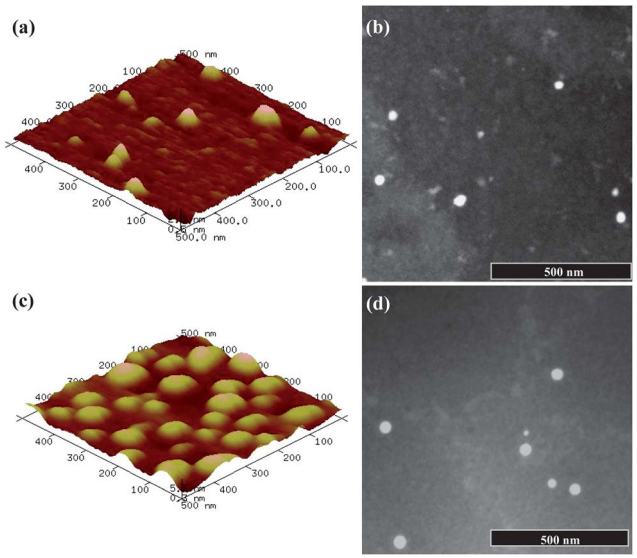


Fig. 4 3D TMAFM images of polymer micelles deposited on mica substrate, scan size: 500 nm^2; (a) **P2**, (c) **P4**. TEM images of polymer micelles deposited on copper mesh grid stained with 1% phosphotungstic acid; (b) **P2**, (d) **P4**.

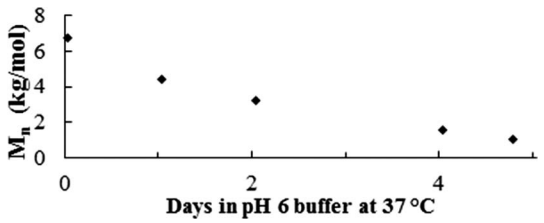


Fig. 5 Demonstration of biodegradability of PMEEECL-*b*-PMECL: number-average molecular weight (from SEC) of **P2** as a function of time spent in pH 6 phosphate buffer at 37 °C.

monitor the change in polymer molecular weight. As seen in Fig. 5, the polymer molecular weight decreases over several days, corresponding to the polymer degradation by ester hydrolysis in acidic conditions.

Experimental

Synthesis and characterization of the monomers, as well as additional polymer analysis are included in the ESI.†

Synthesis of poly(ethylene glycol)-*b*-poly[γ-(2-methoxyethoxy)-ε-caprolactone] (P0)

To an oven-dried 10 mL Schlenk flask hydroxy-terminated PEG (0.085 g, 0.0425 mmol, $M_n \sim 2000$ g mol^{-1}) was introduced and the flask was placed under vacuum. After an hour of pumping down, the vacuum in the Schlenk flask was cancelled with nitrogen. A thermostat-controlled oil bath was heated to 110 °C. Meanwhile, MECL (0.40 g, 2.1 mmol) was measured into a vial and placed under vacuum for 1 hour, then cancelled with nitrogen and dissolved in 0.2 mL of dry toluene. Similarly, a solution of tin ethylhexanoate, ($Sn(Oct)_2$), (0.034 g, 0.085 mmol) was prepared. Promptly, the monomer and catalyst solutions were added to the flask, which was immediately lowered into the oil bath. The reaction was sealed and allowed to stir overnight at 110 °C. Tetrahydrofuran (THF, 1 mL) was added to the reaction vessel, and the polymer solution was poured into a beaker of pentane, where it crashed out. The polymer was filtered and dried under vacuum, then analyzed by size exclusion chromatography (SEC) and ^{1}H NMR. Fig. S5,† ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.81 (m, 4H), 2.04 (t, 2H), 3.36 (s, 3H), 3.55 (m, 10H), 4.18 (t, 2H).

Synthesis of poly[γ-(2-methoxyethyoxy)-ε-caprolactone] (P1)

To an oven-dried 10 mL Schlenk flask, a small egg-shaped stir bar and MECL (0.40 g, 2.1 mmol) were introduced. The flask was placed under vacuum for at least 1 hour before introducing nitrogen atmosphere. A thermostat-controlled oil bath was heated to 110 °C. A stock solution of benzyl alcohol (BnOH) in dry toluene (46 mg mL^{-1}) was prepared and 0.1 mL BnOH stock solution (0.04 mmol BnOH) was loaded into a syringe. A solution of tin ethylhexanoate ($Sn(Oct)_2$), (0.034 mg, 0.084 mmol), was prepared. Promptly, the catalyst and initiator solutions were added to the flask, which was immediately lowered into the oil bath. The reaction was stirred overnight at 110 °C, and then was poured into a beaker containing pentane, where it crashed out. The polymer was filtered and dried under vacuum, then analyzed by SEC and ^{1}H NMR. Fig. S7,† ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.80 (m, 4H), 2.39 (t, 2H), 3.35 (s, 3H), 3.51 (m, 5H), 4.16 (t, 2H).

Synthesis of diblock copolymers containing γ-(2-methoxyethoxy)-ε-caprolactone (MECL) and γ-2-[2-(2-methoxyethoxy)ethoxy]-ethoxy-ε-caprolactone (MEEECL) (P2–P5)

Polymers **P2–P5** were prepared with varying MEEECL : MECL ratios. They were obtained using similar procedures, but used different feed ratios of the monomers. For **P3**, the following procedure was used. A molar ratio of MEEECL : MECL : initiator = 50 : 50 : 1 was employed. To an oven-dried 10 mL Schlenk flask, MEEECL (0.50 g, 1.8 mmol) was introduced. The flask was placed under vacuum, and after an hour of pumping down, the vacuum in the Schlenk flask was cancelled with nitrogen. A thermostat-controlled oil bath was heated to 110 °C. A stock solution of benzyl alcohol (BnOH) containing 39 mg mL^{-1} in dry toluene was prepared and 0.1 mL BnOH stock solution (0.036 mmol BnOH) was loaded into a syringe. Tin ethylhexanoate ($Sn(Oct)_2$), (29 mg, 0.072 mmol), was measured and dissolved in 0.3 mL of toluene, and loaded into a syringe. Promptly, the catalyst and initiator solutions were added to the flask, which was immediately lowered into the oil bath. In a clean scintillation vial, MECL (0.34 g, 1.8 mmol) was measured out, and placed under vacuum for 2 hours. After 3 hours of reacting, a small sample of the reaction mixture was crashed into a scintillation vial containing pentane. The sample was analyzed by GC/MS and ^{1}H NMR to check for residual monomer. Upon consumption of the first monomer, the MECL was dissolved in 0.3 mL toluene, and then added to the reaction vessel. The reaction was stirred overnight at 110 °C, and then was poured into a beaker containing pentane, where it crashed out.

The polymer was filtered and dried under vacuum, then analyzed by SEC and ^{1}H NMR. Fig. S8,† ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.79 (m, 4H), 2.39 (t, 2H), 3.36 (s, 3H), 3.53 (m, 8H), 4.16 (t, 2H).

Synthesis of poly{γ-2-[2-(2-methoxyethoxy)ethoxy]ethoxy-ε-caprolactone} (P6)

Polymerization of MEEECL was performed using the same procedure as **P1**. Fig. S9,† ^{1}H NMR (500 MHz, $CDCl_3$): δ_H 1.80 (m, 4H), 2.38 (t, 2H), 3.37 (s, 3H), 3.55 (m, 13H), 4.16 (t, 2H).

Preparation of micelles

Polymeric micelles of the block copolymers **P0**, **P2**, **P3**, **P4**, and **P5** were formed by nanoprecipitation. In general, the copolymer (20 mg) was dissolved in THF (0.5 mL) and added dropwise into 10 mL of deionized water under rapid stirring. The solution was stirred vigorously for a minimum of 3 hours to allow the polymer chains to self-assemble as the THF evaporated.

Analysis of micelles by dynamic light scattering (DLS)

Aqueous suspensions of polymeric micelles were prepared as described above. To obtain the most uniform particles, micelles were prepared and analyzed on the same day. Prior to measuring, the micelle suspensions were passed through a 0.2 μm Nylon syringe filter. The micelles were analyzed to determine their hydrodynamic diameters using dynamic light scattering with a Malvern Zetasizer Nano ZS instrument equipped with a He–Ne laser (633 nm) and 173° backscatter detector.

Determination of lower critical solution temperature (LCST)

A solution of 0.3 wt% polymer in water was prepared and filtered through a 0.45 μm Nylon syringe filter. The solution was stirred and slowly heated in a thermostat-controlled water bath. The change in % transmittance at 600 nm *versus* the temperature of the solution was recorded on an Agilent UV/Vis spectrophotometer and plotted. The temperature at which the % transmittance sharply drops to below 50% was taken as the LCST.

Determination of critical micelle concentration (CMC)

The critical micelle concentration was determined using the fluorescent molecule pyrene as a probe. Samples of polymer of varying concentrations were combined with a small amount of pyrene in less than 0.1 mL THF. These solutions were added dropwise into 10 mL of deionized water in a scintillation vial with a small stir bar. The solutions were stirred for a minimum of 3 hours to allow the micelles to assemble as the THF evaporated. The resulting aqueous solutions contained 10^{-5} to 10^{0} g L^{-1} of polymer, and a constant pyrene concentration of 6.67×10^{-5} g L^{-1}. Fluorescence spectra of the polymer–pyrene solutions were collected with a Perkin-Elmer LS 50 BL luminescence spectrometer at 25 °C with emission wavelength set at 390 nm. The ratio of the intensities of the pyrene excitation peaks at 338 nm and 335 nm were recorded and plotted against the log of polymer concentration. The *x* coordinate at the intersection of the two trendlines before and after the abrupt increase in I_{338}/I_{335} *vs.* log[*c*] was taken to be the critical micelle concentration.

Tapping mode atomic force microscopy (TMAFM) images of micelles

To a freshly cleaved mica substrate, a drop of polymeric micelle solution was deposited and allowed to dry. AFM studies were obtained using a VEECO-dimension 5000 Scanning Probe Microscope with silicon cantilever with spring constant 42 nm^{-1}. Images were acquired at 1 Hz scan frequency and analyzed with Nanoscope 7.30 software to generate the 3D renderings.

Transmission electron microscopy (TEM) images of micelles

A drop of polymeric micelle solution was deposited on TEM grid (200 mesh CF200-Cu from Electron Microscopy Sciences) then stained with phosphotungstic acid (1%). The TEM images were obtained using a JEOL JEM-1400 transmission electron microscope.

Demonstration of PMEEECL-*b*-PMECL biodegradation

To a Schlenk flask with 4 mL of phosphate buffer (pH 6.0), 20 mg of **P2** was added. This vessel was sealed and stirred at 37 °C for 5 days. Periodically, 0.1 mL samples were removed and analyzed by SEC to monitor the change in molecular weight.

Conclusions

A new γ-substituted caprolactone monomer was synthesized and used as the hydrophobic block in amphiphilic diblock copolymers. The diblock copolymers synthesized, poly{γ-2-[2-(2-methoxyethoxy)ethoxy]ethoxy-ε-caprolactone}-*b*-poly{γ-(2-methoxyethoxy)-ε-caprolactone}, demonstrated variable properties as a function of their relative hydrophilic-hydrophobic block ratios. These copolymers exhibited fully biodegradable backbones and demonstrated not only self-assembly into micelles, but also highly tunable LCSTs in the range of 31–43 °C. Considering these promising preliminary results, PMEEECL-*b*-PMECL copolymers will be further optimized and studied for use as micellar drug carriers.

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