

NOTE

Synthesis of multifunctional poly(D,L-lactide)-poly(oxyethylene)-poly(D,L-lactide) triblock copolymers

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INTRODUCTION

The synthesis of highly functionalized polymers has been extensively investigated, as they are potential materials for a variety of applications ranging from electronic devices and fuel cells to biological materials.^{1–3}

Polylactide (PLA) has been widely used in various biomedical applications owing to its biodegradability and good biocompatibility.⁴ A number of PLA-based amphiphilic block copolymers have been synthesized and investigated for potential biomedical applications.⁵ The presence of metal residues from the catalytic systems in the polymers is highly undesirable for such applications. As a consequence, it is of great interest to develop new alternatives based on nonmetallic polymerization processes. In 2001, Nederberg *et al.*⁶ reported the first organocatalyzed ring-opening polymerization (ROP) of lactide (LA), which gives access to polymers free of metallic contaminants. They used Lewis basic amines such as 4-dimethylaminopyridine (DMAP) and 4-pyrrolidinopyridine (PPY) as transesterification catalysts. Later, DMAP was also shown to efficiently catalyze the ROP of LA, initiated by macroinitiators of various architectures.^{7–9}

In many cases, poly(oxyethylene) (PEO) was chosen as the hydrophilic block for the PLA-based amphiphilic copolymers because of its nontoxicity, hydrophilicity and biocompatibility.^{10–14} However, these polymers do not possess functional groups (other than the end groups) that would allow for chemical modification to control their properties. Recent work describes the successful strategies for the incorporation of hydroxyl,¹⁵ carboxyl¹⁶ or amine¹⁷ side groups in PLA-PEO-based copolymers using functional monomers for the formation of a third block. The presence of pendant functional groups helps to enhance the affinity of the polymers to cells or proteins and provides possibilities for further functionalization.¹⁸ However, in these specific cases, the pendant functional groups must be protected during polymerization, and then the protecting groups have to be removed from the polymer, which might destroy the sensitive polyester segments.

Recently, we synthesized an acetal-linked multifunctional PEO with regularly distributed tertiary amine groups along the chain.¹⁹ In addition to the degradability, this polymer offers the possibility for further functionalization through simple quaternization reactions and was used to prepare amine-multifunctional macroinitiators for polypeptide grafting.²⁰

Herein, we present the synthesis of PLA-PEO-PLA multifunctional triblock copolymers through an organocatalyzed metal-free ROP of LA, initiated by the terminal hydroxyl groups of in-chain multifunctionalized PEO macroinitiators. The middle PEO-block of these degradable amphiphilic copolymers was further functionalized with zwitterionic or fluorophilic side groups. The introduction of alkyne side moieties expands significantly the possibilities to achieve the desired functionality *via* copper-catalyzed azide-alkyne 1,3-cycloaddition (CuAAC).²¹

EXPERIMENTAL PROCEDURE

Materials

Reagent chemicals were purchased from Sigma-Aldrich (Schneldorf, Germany) unless otherwise indicated. Tetrahydrofuran (>99%) and *N,N*-dimethylformamide (DMF, >99.8%) were distilled from CaH₂. D,L-Lactide was recrystallized from toluene. 1,3-Propane sultone (98%), perfluorooctyl iodide (98%), DMAP (>99%), propargyl bromide (80 wt. % in toluene), copper(I) bromide (98%), and *N,N,N',N'*-pentamethyldiethylenetriamine (99%) were used as received. Dodecyl azide was synthesized by reacting dodecyl bromide with sodium azide in DMF. ¹H NMR (300 MHz, CDCl₃, δ, p.p.m.): 3.25 (CH₂-N=N⁺=N⁻), 1.60 (CH₂-CH₂-N=N⁺=N⁻), 1.26 (CH₃-(CH₂)₉), 0.88 (CH₃). FTIR (cm⁻¹): 2096 (N=N⁺=N⁻). The synthesis of PEO with a tertiary amine group in the middle of the polyether chain (E_nNE_n) and the corresponding oxymethylene-linked polyfunctional PEO-macroinitiator (PmE_nNE_n) has previously been described.¹⁹ ¹H NMR (300 MHz, CDCl₃, δ, p.p.m.): 4.72 (O-CH₂-O), 3.62 (O-CH₂CH₂-O), 2.64 (CH₂-N-CH₂), 2.31 (CH₃-N). Aqueous gel permeation chromatography (GPC; vs PEO standards): E₁₇NE₁₇-M_n = 1500, M_w/M_n = 1.12; E₁₁NE₁₁-M_n = 960, M_w/M_n = 1.13; P13E₁₁NE₁₁-M_n = 12 600, M_w/M_n = 1.55; P18E₁₇NE₁₇-M_n = 27 200, M_w/M_n = 1.61; P21E₁₇NE₁₇-M_n = 31 100, M_w/M_n = 1.72.

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Measurements

^1H NMR spectra were recorded on a Bruker 300 MHz instrument. GPC was performed in *N,N*-dimethylacetamide (DMA) + 0.5 wt.% LiCl at a flow rate of 1.0 ml min^{-1} on a set of GRAM Linear and GRAM 100 Å, $300 \times 8\text{ mm}$, $10\text{ }\mu\text{m}$ columns (Polymer Standards Service GmbH, Mainz, Germany), calibrated vs PEO narrow molar mass standards; the column and DRI detector temperature was $50\text{ }^\circ\text{C}$. Aqueous GPC was performed on a set of CATSEC (Eprogen Inc. and Eichrom Techn. Inc., Darien, IL, USA) columns 100, 300, 1000 and $4000\text{ }\text{Å}$, calibrated vs PEO narrow molar mass standards; the mobile phase was $0.2\text{ M CH}_3\text{COOLi}$, $0.2\text{ M CH}_3\text{COOH}$ with $\text{pH} \approx 4.6$ and a flow rate of 0.25 ml min^{-1} ; the column and DRI detector temperature was $40\text{ }^\circ\text{C}$. Infrared spectra were recorded on a PerkinElmer Spectrum One model 2000 Fourier transform infrared system with a universal attenuated total reflection sampling accessory on a ZnSe/diamond composite.

Synthesis of PLA-PEO-PLA multifunctional triblock copolymers (B1-B6)

In a typical reaction P21E₁₇NE₁₇ (1 g, 0.064 mmol hydroxyl groups), D,L-lactide (0.37 g, 2.56 mmol) and DMAP (0.016 g, 0.128 mmol) were mixed in a flask under argon and the temperature was gradually increased to $140\text{ }^\circ\text{C}$. The polymerization proceeded in bulk at that temperature and was completed in two hours. The product was extracted with 2-propanol and dried in vacuum. Yield: 0.99 g (72%). GPC in DMA (vs PEO standards): $M_n = 18\,000$, $M_w/M_n = 1.85$. ^1H NMR (300 MHz, CDCl_3 , δ , p.p.m.): 5.16 (CH-(CH₃)-O), 4.73 (O-CH₂-O), 4.33 (O=C-O-CH₂-CH₂-O + CH-(CH₃)-OH), 3.63 (O-CH₂-CH₂-O + CH₂-CH₂-N-CH₂-CH₂), 2.81 (CH₂-N-CH₂), 2.46 (CH₃-N), 1.56 (CH-(CH₃)-O).

Introduction of various pendant functionalities along the PEO middle block

Perfluorinated side groups. Typically, the triblock copolymer B5 (1.0 g, 0.51 mmol tertiary amine groups) was dissolved in DMF (3 ml) followed by the addition of 1.2 molar excess of perfluorooctyl iodide (0.163 ml, 0.62 mmol) *via* syringe under argon. The reaction mixture was stirred in the dark at $85\text{ }^\circ\text{C}$ for 3 days in an inert atmosphere. The solvent was evaporated and the residue was dissolved in dichloromethane. The product was precipitated in chilled diethyl ether and dried in vacuum. Yield: 1.16 g (91%). GPC in DMA (vs PEO standards): $M_n = 15\,300$, $M_w/M_n = 1.83$. ^1H NMR (300 MHz, CDCl_3 , δ , p.p.m.): 5.17 (CH-(CH₃)-O), 4.73 (O-CH₂-O), 4.33 (O=C-O-CH₂-CH₂-O + CH-(CH₃)-OH), 3.79 (CH₂-CH₂-N-CH₂-CH₂), 3.63 (O-CH₂-CH₂-O + CH₂-N-CH₂), 3.40 (CH₃-N⁺), 1.56 (CH-(CH₃)-O).

Zwitterionic side groups. The triblock copolymer B5 (1.0 g, 0.51 mmol tertiary amine groups) was dissolved in tetrahydrofuran (3 ml). Then 1.1 molar excess of 1,3-propane sultone (0.068 g, 0.56 mmol) was added. The reaction was performed at $60\text{ }^\circ\text{C}$ for 3 days in an argon atmosphere. The product was

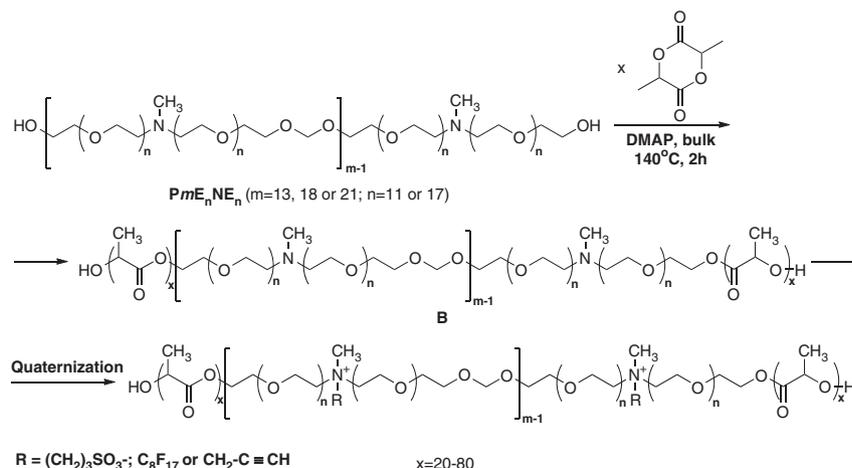
precipitated in diethyl ether and dried in vacuum. Yield: 0.92 g (87%). GPC in DMA (vs PEO standards): $M_n = 15\,000$, $M_w/M_n = 1.85$. ^1H NMR (300 MHz, CDCl_3 , δ , p.p.m.): 5.16 (CH-(CH₃)-O), 4.73 (O-CH₂-O), 4.30 (O=C-O-CH₂-CH₂-O + CH-(CH₃)-OH), 3.93 (CH₂-CH₂-N-CH₂-CH₂), 3.63 (O-CH₂-CH₂-O + CH₂-N-CH₂ + N⁺-CH₂-CH₂-CH₂-SO₃⁻), 3.22 (CH₃-N⁺), 2.89 (N⁺-CH₂-CH₂-CH₂-SO₃⁻), 2.25 (N⁺-CH₂-CH₂-CH₂-SO₃⁻), 1.54 (CH-(CH₃)-O).

Alkyne side groups. Typically, B5 (1.0 g, 0.51 mmol tertiary amine groups) was dissolved in DMF (3 ml) in an inert atmosphere. A 2.5 molar excess of propargyl bromide solution in toluene (1.28 mmol, 0.14 ml) was injected *via* syringe through a rubber septum. The reaction was carried out at $70\text{ }^\circ\text{C}$ for 48 h. The reaction mixture was concentrated in vacuum for 1 h to remove the excess of propargyl bromide (b.p. = $90\text{ }^\circ\text{C}$). The residue was washed several times with diethyl ether, and dried. Yield: 0.90 g (85%). GPC in DMA (vs PEO standards): $M_n = 16\,200$, $M_w/M_n = 1.79$. ^1H NMR (300 MHz, CDCl_3 , δ , p.p.m.): 5.17 (CH-(CH₃)-O), 4.71 (O-CH₂-O), 4.33 (O=C-O-CH₂-CH₂-O + CH-(CH₃)-OH), 4.05 (N⁺-CH₂-C≡CH), 4.00 (CH₂-CH₂-N-CH₂-CH₂), 3.63 (O-CH₂-CH₂-O + CH₂-N-CH₂), 3.48 (CH₃-N⁺), 2.88 (N⁺-CH₂-C≡CH), 1.56 (CH-(CH₃)-O).

Model 'click' reaction. The alkyne-multifunctional triblock copolymer (1.0 g, 0.48 mmol alkyne groups) and copper(I) bromide (0.042 g, 0.29 mmol) were dissolved in DMF (5 ml) in an inert atmosphere followed by the addition of dodecyl azide (0.13 g, 0.62 mmol) and *N,N,N',N',N''*-pentamethyldiethylenetriamine (0.061 ml, 0.29 mmol). The green solution was degassed by three freeze-pump-thaw cycles. The reaction was conducted at $30\text{ }^\circ\text{C}$ for 24 h. The solution was concentrated and the product was precipitated in diethyl ether. Then the precipitate was redissolved in dichloromethane, passed through an Al₂O₃ column, and the solvent was evaporated. Yield: 0.78 g (71%). GPC in DMA (vs PEO standards): $M_n = 15\,100$, $M_w/M_n = 1.87$. ^1H NMR (300 MHz, CDCl_3 , δ , p.p.m.): 8.08 (C=CH-N), 5.17 (CH-(CH₃)-O + N⁺-CH₂-C≡CH), 4.71 (O-CH₂-O), 4.33 (O=C-O-CH₂-CH₂-O + CH-(CH₃)-OH + N-CH₂-CH₂-(CH₂)₉), 3.63 (O-CH₂-CH₂-O + CH₂-N-CH₂ + CH₂-CH₂-N-CH₂-CH₂ + CH₃-N⁺), 1.56 (CH-(CH₃)-O + N-CH₂-CH₂-(CH₂)₉), 1.25 (N-CH₂-CH₂-(CH₂)₉), 0.87 (N-CH₂-CH₂-(CH₂)₉-CH₃).

RESULTS AND DISCUSSION

The synthetic strategy to multifunctional PLA-PEO-PLA triblock copolymers bearing a number of various side functionalities is depicted in Scheme 1. The first step involves the synthesis of block copolymer platform with controlled composition allowing further modular modification. For the block copolymer synthesis, multifunctional PEO macroinitiators with terminal hydroxyl groups and regularly distributed in-chain tertiary amine groups (PmE_nNE_n) were used. The macroinitiators were prepared by a combination of living



Scheme 1 Synthetic route to multifunctional amphiphilic triblock copolymers.

anionic polymerization and polycondensation techniques affording control over the number and density of in-chain functionalities as well as regularly distributed degradable acetal links along the polyether chain.¹⁹ The polymer compositions and molar masses were estimated by ¹H NMR (Figure 1a) and aqueous GPC analyses, respectively. The controlled ROP of D,L-lactide was initiated by the terminal hydroxyl groups of the multifunctional PEO-macroinitiators in the presence of DMAP as a catalyst (Scheme 1). In their pioneer work, Nederberg *et al.*⁶ demonstrated that even when performed in bulk, the LA polymerizations initiated by benzyl alcohol gave narrowly dispersed polymers with predictable molar masses. Here, we applied the bulk conditions to prepare triblock copolymers in relatively short reaction times. In order to adjust the optimal reaction conditions for the LA ROP in bulk, initially we used the precursors

E_nNE_n with narrow molar mass distribution as macroinitiators. The results (not shown) revealed that LA was polymerized in controlled manner without significant increase in molar mass distributions for the triblock copolymers. The same conditions were applied to the multifunctional PEO macroinitiators. The degree of LA polymerization was estimated from the ¹H NMR spectra in CDCl₃ (Figure 1b). As the molar mass and functionality of the PEO-macroinitiator is known, the experimental degree of LA polymerization was calculated from the ratio of the integral areas of methyne signal from LA units at 5.16 p.p.m. to the oxyethylene protons signals from the macroinitiator at 3.63 p.p.m. The estimated degrees of polymerization (DP)s were found to be close to the theoretical values. Moreover, there was no evidence of PEO-chain degradation during the polymerization process in bulk. The relative intensities of the -OCH₂O- protons from acetal links

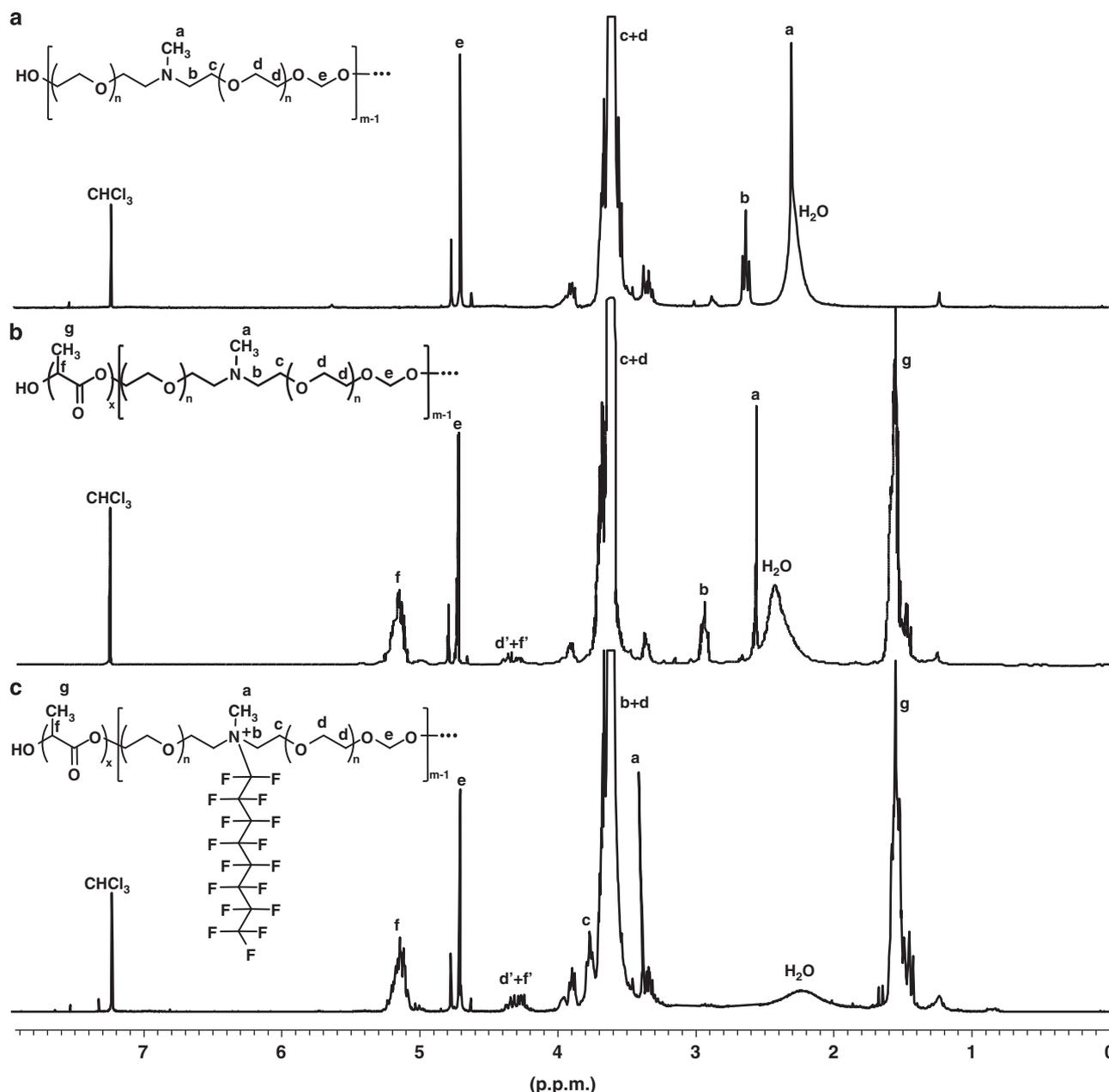


Figure 1 ¹H NMR (300 MHz) spectrum in CDCl₃ at 25 °C of: (a) the multifunctional PEO-macroinitiator P21E₁₇NE₁₇; (b) the amphiphilic PLA-PEO-PLA triblock copolymer B5; and (c) the corresponding multi-perfluorooctyl-modified copolymer.

along the polyether chain at 4.73 p.p.m. and those of CH_3N protons at 2.46 p.p.m. were equal to 2:3. Interestingly, although the ratio is preserved, the signals for the latter protons in the triblock copolymers are slightly shifted compared with those in the macroinitiator (2.31 p.p.m.). Similar downfield shift was also observed for the neighboring $\text{CH}_2\text{-N-CH}_2$ protons—from 2.64 p.p.m. for the macroinitiator to 2.81 p.p.m. for the triblock copolymer (Figures 1a and b). This is most likely due to the donor–acceptor interactions between

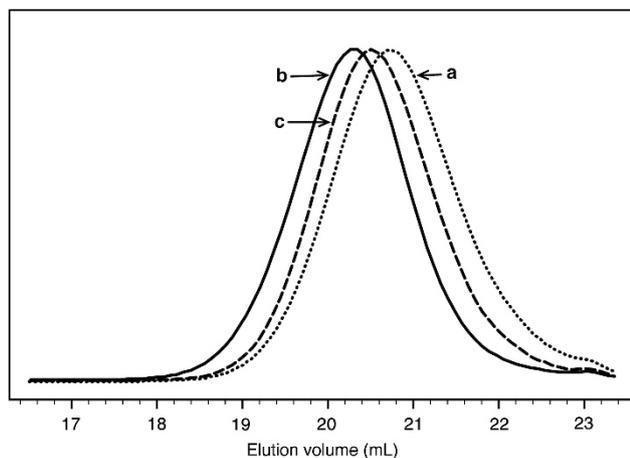


Figure 2 Gel permeation chromatograms in DMA (+0.5 wt.% LiCl) at 50 °C of: (a) the multifunctional PEO-macroinitiator P21E₁₇NE₁₇; ($M_n = 11\,900$, $M_w/M_n = 1.86$); (b) the amphiphilic PLA-PEO-PLA triblock copolymer B5 ($M_n = 18\,000$, $M_w/M_n = 1.85$); and (c) the corresponding multi-perfluorooctyl-modified copolymer ($M_n = 15\,300$, $M_w/M_n = 1.83$). The GPC data were obtained relative to PEO standards.

the tertiary amine groups from the PEO-block and the carbonyl groups from the PLA-outer blocks.²² The formation of block copolymer architecture was evidenced by GPC analysis in DMA. Typical GPC curves of the macroinitiator and the corresponding triblock copolymer are presented in Figures 2a and b. They showed that the copolymers elute as monomodal species with a clear shift to a lower elution volume (higher molar mass). There were no traces of macroinitiator left in the purified samples. By using macroinitiators with different length of the acetal-linked PEO blocks, we were able to control the number and the density of the in-chain tertiary amine groups in the triblock copolymers obtained.

The molar mass characteristics of the macroinitiators and the amphiphilic triblock copolymers obtained are summarized in Table 1. Although the molar mass distributions of the multifunctional PEO macroinitiators are relatively broad, there is no further increase in copolymer polydispersity after the formation of the outer PLA blocks.

The second step of the synthetic procedure was the introduction of various pendant functionalities in the central PEO-block through a quaternization of the tertiary amine in-chain groups (Scheme 1). The reactions were performed in DMF or tetrahydrofuran. Thus, the triblock copolymers were easily modified with perfluorinated or zwitterionic side groups. The completeness of the quaternization was evidenced by the ¹H NMR spectra of the products in CDCl₃ (Figure 1c). The signal at δ 2.46 p.p.m., characteristic of the CH_3N protons completely disappeared and a new signal appeared at δ 3.40 p.p.m. attributed to CH_3N^+ protons. The relative intensities of the protons from acetal links at 4.73 p.p.m. and those of CH_3N^+ protons remained equal to 2:3 (Supplementary Figure S1 in the Supplementary Information). The ratio between the methyne protons from the LA units and oxyethylene protons from the macroinitiator was also preserved. However, the GPC traces showed that the elution

Table 1 Characteristics of the macroinitiators and the multifunctional triblock copolymers

Macroinitiator					Triblock copolymer				
Code	M_n^a (g mol^{-1})	M_w/M_n^a	M_n^b (g mol^{-1})	M_w/M_n^b	Code	Target DP_n^c	DP_n^d	M_n^b (g mol^{-1})	M_w/M_n^b
P13E ₁₁ NE ₁₁	12 600	1.55	5400	1.62	B1	20	22	7500	1.59
P13E ₁₁ NE ₁₁					B2	40	43	9600	1.60
P18E ₁₇ NE ₁₇	27 200	1.61	10 600	1.70	B3	60	65	16 900	1.68
P18E ₁₇ NE ₁₇					B4	80	81	18 500	1.68
P21E ₁₇ NE ₁₇	31 100	1.72	11 900	1.86	B5	60	64	18 000	1.85
P21E ₁₇ NE ₁₇					B6	80	82	19 700	1.84

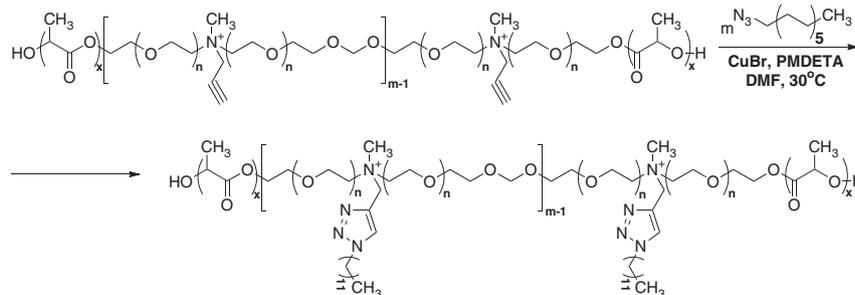
Abbreviations: GPC, gel permeation chromatography; LA, lactide; PEO, poly(oxyethylene).

^aDetermined by aqueous GPC (vs PEO standards).

^bDetermined by GPC in *N,N*-dimethylacetamide (vs PEO standards).

^cThe target degree of LA polymerization, target DP_n , is calculated from the monomer to bifunctional macroinitiator molar ratio.

^dNumber average degree of LA polymerization, as determined by ¹H NMR analysis, see Results and discussion.



Scheme 2 Model 'click' reaction.

volume of multifunctionalized copolymers is higher than that of the non-quaternized precursors (Figure 2c). This indicates that the multifunctional triblock copolymers form more compact structures with hydrodynamic volumes lower than that of the non-modified precursors, most likely due to the changes in copolymer-solvent interactions after the quaternization.²³ Our previous experience with PEO containing a tertiary amine group in the middle of the polyether chain (E_nNE_n) and oxymethylene-linked polyfunctional PEOs (PmE_nNE_n) used in grafting 'from' reactions showed that the resulting graft and asymmetrical block copolymers form very compact structures in DMA.²⁰ However, those copolymers were with rather long side chains. In order to assess the influence of the attached short side groups, we modified a polyfunctional PEO with perfluorooctyl side groups. The GPC analysis revealed a significant decrease in the elution volume of the modified polyfunctional PEO compared with that of the parent polymer (Supplementary Figure S2). A decrease in the elution volume after the modification was detected even in the case of PEO with a single central tertiary amine group (Supplementary Figure S3). Finally, to exclude possible polymer retention on the GPC-column packing, we determined the intrinsic viscosities of all polymers in DMA containing 0.5 wt.% LiCl at 50 °C. The results were consistent with those obtained by GPC-analyses with lower intrinsic viscosity values for the quaternized polymers as compared with those of the unmodified precursors (Supplementary Table S1). All these results indicate that indeed the modified with side groups polyfunctional triblock copolymers form compact structures in DMA, which is mainly a feature of the central PEO-block.

In the case when propargyl bromide was used as quaternizing reagent, a number of alkyne side groups were introduced in the central PEO-block of the amphiphilic PLA-PEO-PLA triblock copolymers (Scheme 1). This broadens significantly the possibilities for further chain modification through the 'click' chemistry approach based on CuAAC, which has been successfully applied for the introduction of pendant and terminal functional groups into various polymers.²⁴ We used dodecyl azide as a model compound to test the applicability of this approach to our copolymer system. The 'click' reaction was performed in DMF as a solvent at 30 °C and was completed after 24 h (Scheme 2).

The presence of the signals both for methyl and methylene protons from the dodecyl groups in the ¹H NMR spectrum of the product, as well as the relative intensities of those protons and the oxymethylene protons from the acetal-linked PEO chain suggested complete functionalization. There was no evidence for chain-degradation during the 'click' reaction performed under mild conditions.

CONCLUSIONS

An acetal-linked PEO with regularly distributed tertiary amine groups along the chain was used as a macroinitiator for the controlled metal-free ROP of D,L-lactide. Thus, amphiphilic PLA-PEO-PLA triblock copolymers with controlled block length, number and density of in-chain functionalities in the polyether block were synthesized. They were used as a platform for further modification through quaternization with suitable reagents resulting in perfluorooctyl, zwitterionic or alkyne multifunctional copolymers. The latter open the possibility for further modification *via* the highly efficient and versatile 'click' chemistry approach. The biodegradability of both PEO (through the regularly distributed acetal links along the chain) and the polyester

outer blocks combined with the possibility to tailor their properties through multifunctionalization make the copolymers good candidates for a variety of biomedical applications.

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