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Synthesis of well-defined ABC triblock copolymers with polypeptide segments by ATRP and click reactions

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ABSTRACT

Well-defined ABC block copolymers consisting of poly(ethylene oxide) monomethylene ether (MPEO) as A block, poly(styrene) (PS) as B block and poly(γ-benzyl-L-glutamate) (PBLG) as C block were synthesized by the combination of atom transfer radical polymerization (ATRP) and click reactions. The bromine-terminated diblock copolymer poly(ethylene oxide) monomethylene ether-block-poly(styrene) (MPEO–PS–Br) was prepared by ATRP of styrene initiated with macro-initiator MPEO–Br, which was prepared from the esterification of MPEO and 2-bromoisobutyryl bromide, and converted into the azido-terminated diblock copolymer MPEO–PS–N_3 by simple nucleophilic substitutions in DMF in the presence of sodium azide. Propargyl-terminated PBLGs were synthesized by ring-opening polymerization of γ-benzyl-L-glutamate-*N*-carboxyanhydride in DMF at room temperature using propargyl amine as an initiator. ABC triblock copolymers MPEO–PS–PBLG with a wide range of number-average molecular weights from 1.55 to 3.75 × 10^4 and a narrow polydispersity from 1.07 to 1.10 were synthesized via the click reaction of MPEO–PS–N_3 and the propargyl-terminated PBLG in the presence of CuBr and 1,1,4,7,7-pentamethyldiethylenetriamine (PMDETA) catalyst system. The structures of these ABC block copolymers and corresponding precursors were characterized by NMR, IR and GPC. The results showed that click reaction was efficient. Therefore, a facile approach was offered to synthesize ABC triblock copolymers composed of crystallizable polymer MPEO, conventional vinylic polymer PS and rod-like α-helix polypeptide PBLG.

1. Introduction

Recently, block copolymers consisting of polypeptide segments have received greatly interest not only for their rich morphological structures [1–8] but also for their potential applications [1,9–12]. The probable reasons are as follows: compared with conventional vinylic polymers, polypeptides can show various conformations, such as α-helix and random coil [13,14], which plays an important role in the formation of the morphological structures [15–19], and possess excellent properties for biomedical applications, such as low toxicity, biodegradability and biocompatibility [11,12,20]. To date, many block copolymers composed of polypeptide segments have been successfully synthesized via different synthetic routes. The synthetic routes include solid-phase synthesis [21,22], the ring-opening polymerization (ROP) of α-amino acid *N*-carboxyanhydride (NCA) initiated by either amino-terminated polymer precursors [23–31] or a transition metal-based catalysis system [32], and linking polymers with appropriate functionalities to the active sites of peptides [22]. Recently, the synthetic approach to block copolymers composed of polypeptides segments has been further developed and mainly focused on the design of

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novel initiators. Generally, an initiator with different functional groups is synthesized and applied to generate block copolymers composed of polypeptide segments and flexible vinyl polymers by the combination of controlled radical polymerizations and ROP of NCA [33,34]. For example, Menzel et al. [33] reported that well-defined rod-coil block copolymers composed of poly (γ-benzyl-L-glutamate) (PBLG) were synthesized by the combination of atom transfer radical polymerization (ATRP) and the nickel mediated ring-opening polymerization of γ-benzyl-L-glutamate-*N*-carboxyanhydride using a double-headed initator.

Atom transfer radical polymerization (ATRP) offers a powerful method for the controlled manipulation of macromolecular architecture due to polymerization of a wide variety of monomers, tolerance of a wide range of functional groups and very facile preparation of block copolymers with a narrow polydispersity index [35,36]. Moreover, the recent progresses in the synthetic strategies that can be applied to vary the chemical composition and architecture of block copolymers also open new areas. For example, "Click chemistry", defined by Sharpless et al. [37], has been applied to synthesize block copolymers [38–47] because of its quantitative yields, mild reaction conditions and tolerance of a wide range of functional groups. Recently, Lecommandoux and co-worker [39] reported that the synthesis of well-defined rod-coil block copolymers composed of poly [2-(dimethylamino)ethyl methacrylate] and PBLG were synthesized by the combination of ATRP and click chemistry. The combination of the superior reaction characteristic of ATRP and the click reaction can be applied to prepare novel structure polymers and further expand the range of available materials [48]. In this contribution, a series of well-defined triblock copolymers MPEO–PS–PBLG were prepared by the combination of ATRP, ROP and the click reaction. The precursor MPEO–PS–Br was first prepared by ATRP of styrene initiated with macro-initiator MPEO–Br, and the substitution reaction was then carried out to obtain the azido-terminated precursor MPEO–PS–N_3. The propargyl-terminated PBLG were prepared by ROP of γ-benzyl-L-glutamate-*N*-carboxyanhydride in DMF using propargyl amine as an initiator. The novel triblock copolymers MPEO–PS–PBLG were synthesized via the click reaction of MPEO–PS–N_3 and propargyl-terminated PBLG in the presence of CuBr/PMDETA catalyst system. The synthesis of triblock copolymers was shown in Scheme 1. Interest of the synthetic novel ABC triblock copolymers originated from each polymer segment's properties: MPEO is a crystallizable polymer possessed of low toxicity and biocompatibility, and is used as biomaterial. PS is one example of coil-type vinylic polymers and usually used as a model polymer in morphological structure research. PBLG is capable of undergoing a reversible transition from a rod-like α-helix conformation to a random coil conformation with the variation of outer conditions (such as temperature, pH values and solvent), which is also the precursor for poly(glutamic acid). To the best of our knowledge, there have been few reports concerning the synthesis of triblock copolymers composed of MPEO, PS and PBLG segments.

2. Experimental part

2.1. Materials

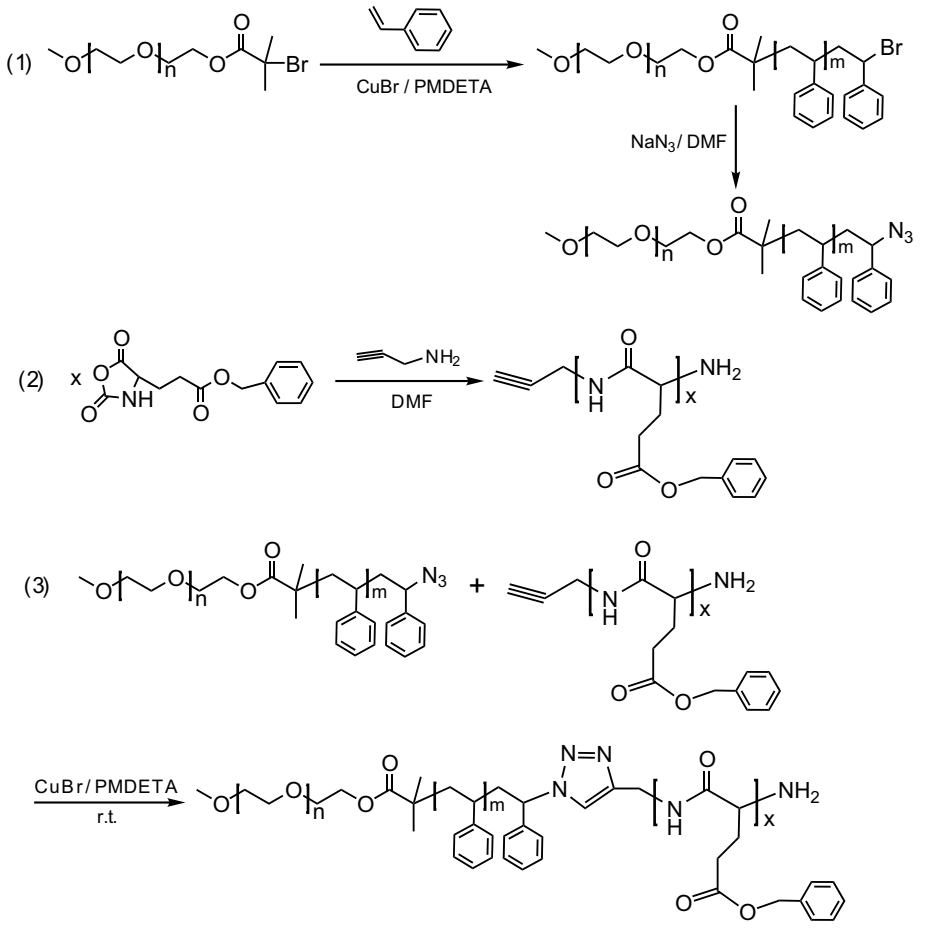
Styrene (St., Shanghai Chemical Reagent Co., A.R. grade) was passed through a basic alumina column to remove the inhibitor and then distilled over CaH_2 in vacuo before use. CuBr (Shanghai Chemical Reagent Co., A.R. grade) was purified by stirring in glacial acetic acid overnight, filtered, washed with ethanol and then dried in a vacuum oven at 60 °C overnight. Poly(ethylene oxide) monomethylene ether (Mn = 2000 g mol^{-1}) was purchased from Aldrich. Sodium Azide (NaN_3, Acros, 99%), 1,1,4,7,7-pentamethyldiethylenetriamine (PMDETA, Aldrich, 99+%), 2-bromoisobutyryl bromide (Acros, 98%), Propargyl amine (Acros, 98%), *N*,*N*-dimethylformamide (DMF, A.R. grade) and other solvents were purchased from Shanghai Chemical Reagent Company and purified by conventional procedures if needed. γ-benzyl-L-glutamate-*N*-carboxyanhydride (BLG–NCA) was synthesized according to the literature [49]. The macro-initiator MPEO–Br was prepared according to a published procedure [50]. M_n(GPC) = 2.2 × 10^3 g mol^{-1}, M_w/M_n = 1.02.

2.2. Synthesis of MPEO–PS–Br by ATRP

MPEO–PS–Br was synthesized by bulk polymerization and the procedure was adapted from the literature [41,51]. In a typical run, a Schlenk tube was charged with 0.22 g (2.2 × 10^3 g mol^{-1}, 0.1 mmol) of MPEO–Br, 5.0 g (48.0 mmol) of degassed St., 14.3 mg (0.1 mmol) of CuBr, 17.3 mg (0.1 mmol) of PMDETA and a magnetic bar. The reaction mixture was purged with dry nitrogen and subjected to three freeze-pump-thaw cycles to remove any dissolved oxygen. The tube was then sealed under vacuum and immersed in a thermostatic oil bath at 90 °C. After 2 h, the reaction was stopped and quickly cooled down to room temperature with cool water. The mixture was further diluted with tetrahydrofuran (THF), removed copper salts through a plugged column of neutral aluminum oxide and the block copolymer was precipitated in a large volume of cold methanol. The sample was purified by reprecipitating three times from THF to methanol and dried under vacuum overnight at 50 °C. Yield: 60%, M_n(GPC) = 1.31 × 10^4 g mol^{-1}, M_w/M_n = 1.04.

2.3. Synthesis of MPEO–PS–N_3

The procedure for the transformation of MPEO–PS–Br into MPEO–PS–N_3 was adapted from the literature [41,51]. Typically, 0.5 g (1.31 × 10^4 g mol^{-1}, 0.038 mmol) of MPEO–PS–Br, 4.6 mg (0.07 mmol) of NaN_3 and 10 mL of DMF were added in a round-bottom flask. The mixture solution was stirred with a magnetic bar at room temperature overnight before removal of DMF by rotary evaporation. The solid was dissolved in methylene chloride* and the undissolved solid was removed by filtration. Most of methylene chloride was removed by rotary evaporation, precipitated into cool methanol, filtered and dried at room temperature in a vacuum oven for 48 h. Yield: 85%, M_n(GPC) = 1.32 × 10^4 g mol^{-1}, M_w/M_n = 1.05.



Scheme 1. Synthesis of ABC triblock copolymers.

Note: it may be dangerous to add methylene chloride to sodium azide since explosive diazomethane might be formed.

2.4. Synthesis of propargyl-terminated PBLG

The propargyl-terminated PBLG was synthesized by ROP of BLG–NCA in dry DMF using propargyl amine as an initiator and the procedure was adapted from the literature [39]. A typical run was as follows: in a glovebox, 2.0 g (7.6 mmol) of BLG–NCA was weighted under pure nitrogen, added into a previously dried round-bottom flask equipped with a magnetic bar, and dissolved with 25 mL of dry DMF. 15 μL (0.22 mmol) of propargyl amine was added into the solution using a degassed syringe after stirring for 10 min. The solution was stirred under pure nitrogen at room temperature for 72 h. After the polymerization, the solution was precipitated into an excess amount of methanol, filtered and dried at room temperature in a vacuum oven for 48 h: M_n(GPC) = 8.6 × 10^3, M_w/M_n = 1.20.

2.5. Synthesis of MPEO–PS–PBLG by a click reaction

A typical procedure for the click reaction was as follows: 0.17 g (1.32 × 10^4 g mol^{-1}, 0.013 mmol) of MPEO–PS–N_3, 0.1 g (8.6 × 10^3 g mol^{-1}, 0.012 mmol) of propargyl-terminated PBLG, 143.0 mg (1.0 mmol) of CuBr and 10 mL of DMF were added into a round-bottom flask equipped with a magnetic bar. The flask was capped with a rubber plug and purged with pure nitrogen for 30 min. PMDETA (173.0 mg, 1.0 mmol) was then added by using a degassed syringe. The mixture was stirred overnight at room temperature. After the reaction, the mixture was further diluted with THF, removed copper salts through a plugged column of neutral aluminum oxide. The product was precipitated in diethyl ether and purified by reprecipitating three times from THF to diethyl ether and dried at room temperature in a vacuum oven for 48 h. Yield: 80%. M_n(GPC) = 2.25 × 10^4 g mol^{-1}, M_w/M_n = 1.14.

2.6. Characterization

^{1}H NMR spectra were obtained on a 500 Bruker NMR instrument using $CDCl_3$ as solvent, tetramethyl silane as the internal standard. Fourier Transform Infrared (FT-IR) spectra were recorded on a Perkin–Elemer Spectrum one spectrometer at frequencies ranging from 400 to 4000 cm^{-1}. Samples were thoroughly mixed with KBr and pressed into pellet form. Molecular weights M_n and polydispersity M_w/M_n were measured on a gel permeation

chromatograph (Waters 515C) equipped with three MZ-Gel SD plus column (10^3, 10^5 and 10^6 Å), using DMF (0.05 M LiBr solution) as eluent at 40 °C with a flow rate of 1 mL/min. The detectors consisted of a multi-angle laser light scattering (MALLS) detector (Wyatt Technology Corporation, DAWN HELEOS) with the light wavelength at 690 nm and a RI detector (Wyatt Technology Corporation, Optilab REX).

3. Results and discussion

As shown in Scheme 1, the ABC triblock copolymers were synthesized by the combination of ATRP, ROP and the click reaction. The precursor with the terminal bromine, MPEO–PS–Br, was first prepared from the ATRP of St. with the macro-initiator MPEO–Br, and then converted into azido-terminated MPEO–PS–N_3 by reacting with NaN_3 in DMF. Propargyl-terminated PBLGs were synthesized by ring-opening polymerization of BLG–NCA at room temperature from propargyl amine as an initiator using dry DMF as solvent, and introduced into block copolymer MPEO–PS–N_3 by the click reaction. The structural characteristic of the precursors and triblock copolymers MPEO–PS–PBLG are summarized in Table 1.

3.1. Synthesis of MPEO–PS precursors

Generally, polymers prepared by ATRP have the well-defined chain-length, the low polydispersity index and the halide end-group [35,36]. The halide end-group can be facilely converted into azide group [41,51–56]. In the current study, the precursor MPEO–PS–Br was prepared from the ATRP of St. in bulk using the macro-initiator MPEO–Br in the presence of CuBr/PMDETA catalyst system. To ensure a high degree of terminal bromine group, the ATRP of St. in bulk was terminated at relatively low monomer conversions (~60%) [51]. GPC and ^{1}H NMR analysis of the precursor MPEO–PS–Br resulted in a number-average molecular weight of 13,100 and 11,800, respectively (Table 1). Subsequently, the terminal bromine group was transformed into azido group by simple nucleophilic substitution reactions in DMF solvent in the presence of an excess of NaN_3. After purification, the GPC result indicated that no molecular weight reduction occurred because the elution peak of MPEO–PS–N_3 remained basically the same position as that of MPEO–PS–Br. From Fig. 1A, the proton signal of the α position to the terminal bromine was at 4.30–4.60 ppm (Fig. 1A:g).

This indicates the diblock copolymer has the bromine terminal group [41,51–56]. After the terminal bromine group of MPEO–PS–Br was substituted with the azido group, the proton signal of the α position shifted to 3.80–4.00 ppm (Fig. 1B:h), which corresponded to the proton of the α position to the terminal azido group [41,51–55], and no residual peak was found at 4.30–4.60 ppm. The characteristic resonances originating from the MPEO block at 3.35–3.77 ppm (Fig. 1A:b) and 3.39 ppm (Fig. 1A:a), assigned to —CH_2CH_2O— and —OCH_3, respectively, the PS block at 6.60 and 7.07 ppm (Fig. 1A:d), assigned to phenyl moieties, are still presented in the spectrum of MPEO–PS–N_3. Moreover, the FT-IR spectrum of MPEO–PS–N_3 clearly revealed the appearance of a new absorbance peak at 2090 cm^{-1} (Fig. 2B), which is characteristic absorption peak of the terminal azido group [39,56].

These suggested that the substitution reaction was highly efficient. From the results of GPC, ^{1}H NMR and IR, it can be calculated that the precursor MPEO–PS–N_3 was successfully synthesized.

3.2. Synthesis of propargyl-terminated PBLG precursors

ROP of BLG–NCA can be carried out in DMF at room temperature using primary amine initiator. Masuda and co-workers [57] reported the ROP of BLG–NCA using propargyl amine as an initiator in THF. The polydispersity index values of the obtained PBLG were higher with increasing the molecular weight. More recently, Lecommandoux et al. [39] also reported the ROP of BLG–NCA using propargyl amine as an initiator in DMF at room temperature, and the polydispersity index values of the obtained PBLG were much lower. In the current study, the ROP of BLG–NCA was also carried out in DMF at room temperature using propargyl amine as an initiator. The structural characteristic of propargyl-terminated PBLG has been determined by the combination techniques consisting of ^{1}H NMR, IR and GPC. A typical ^{1}H NMR spectrum of the propargyl-terminated PBLG recorded in $CDCl_3$ + 15%TFA is shown in Fig. 3. The peak at 3.95 ppm (Fig. 3b) is ascribed to methylene protons of propargyl residues (HC≡C—CH_2—). These peaks at 5.05 ppm, 4.58 ppm and 2.41 ppm, respectively,

Table 1
Characterization of polymers

Polymer	GPC[b]		^{1}H NMR			
	M_n (g mol^{-1})	M_w/M_n	M_n (g mol^{-1})	MPEO (wt.%)	PS (wt.%)	PBLG (wt.%)
$PBLG_1$[a]	2700	1.20	2600	–	–	100
$PBLG_2$[a]	8600	1.20	6600	–	–	100
$PBLG_3$[a]	26,600	1.15	20,800	–	–	100
MPEO–PS–Br	13,100	1.04	11,800	16.9	83.1	–
MPEO–PS–N_3	13,200	1.05	11,700	17.1	82.9	–
MPEO–PS–$PBLG_1$	15,500	1.07	14,300	14.0	67.8	18.2
MPEO–PS–$PBLG_2$	22,500	1.09	18,300	10.9	53.0	36.1
MPEO–PS–$PBLG_3$	37,600	1.10	32,500	6.2	29.8	64.0

[a] PBLG was propargyl-functional.
[b] Determined by GPC MALLS in DMF.

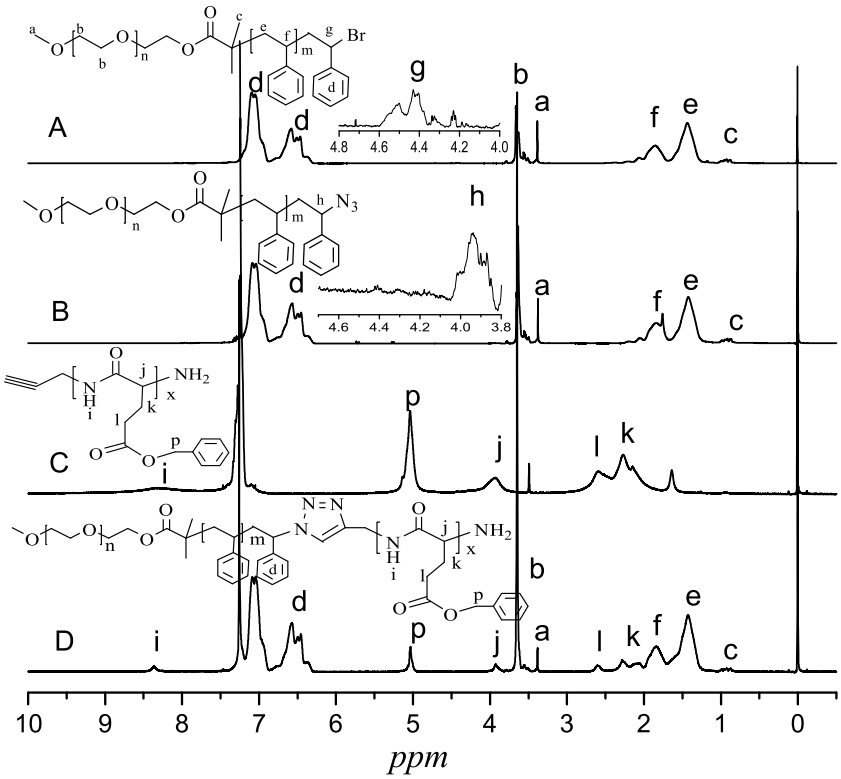


Fig. 1. ^{1}H NMR spectra of (A) MPEO–PS–Br, (B) MPEO–PS–N_3, (C) $PBLG_2$ and (D) MPEO–PS–$PBLG_2$ in $CDCl_3$.

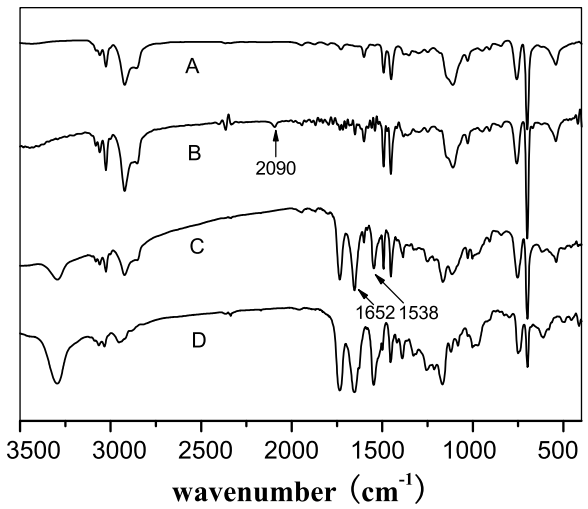


Fig. 2. IR spectra of (A) MPEO–PS–Br, (B) MPEO–PS–N_3 and (C) MPEO–PS–$PBLG_2$.

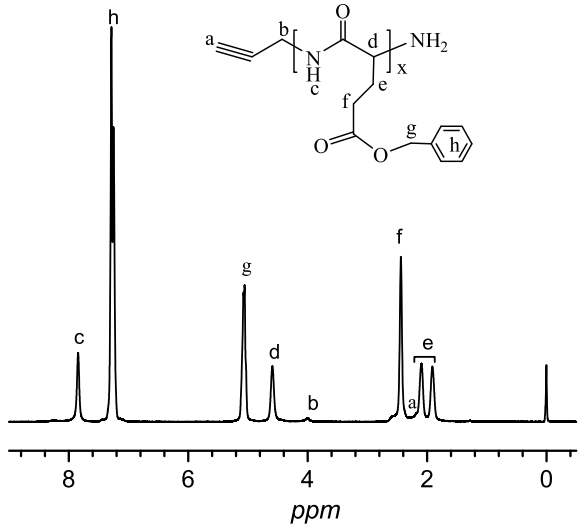


Fig. 3. ^{1}H NMR spectrum of the propargl-terminated PBLG in $CDCl_3$ + 15%TFA.

assigned to methylene protons due to the benzylic groups, methine protons and methylene protons adjacent to ester groups can be clearly observed in ^{1}H NMR spectrum of the propargyl-terminated PBLG. Their molecular weights can be estimated from integral ratio of resonance peak at 3.95 ppm (Fig. 3b) with that at 5.05 ppm (Fig. 3g). To clearly identify the characteristic protons of the propargyl-terminated PBLG in the ^{1}H NMR spectrum, it is necessary that the mixture solvent $CDCl_3$ + 15%TFA be used in the ^{1}H NMR measurement. To obtain the propargyl-terminated PBLG with different molecular weights, the different molar ratio of propargyl amine initiator-to-monomer BLG–NCA was varied to control the degree of polymerization of

PBLG. Three samples with different number-average molecular weights were synthesized and designated as PBLGn (n = 1–3, designating the sample ID). The molecular weights from GPC and ^{1}H NMR were summarized in Table 1. From Fig. 2C, the characteristic absorption peaks of the amido groups at 1652, 1538 cm^{-1} was observed on the FT-IR spectrum of the $PBLG_2$ due to the formation of peptide bonds [58]. So, the synthesis of the propargyl-terminated PBLG was successful.

3.3. Synthesis of MPEO–PS–PBLG

Finally, using the click reaction, the azido-terminated precursor MPEO–PS–N_3 and the propargyl-terminated PBLG were reacted to obtain corresponding ABC triblock copolymers MPEO–PS–PBLG in the presence of CuBr/PMDETA catalyst system in DMF at room temperature. Triblock copolymers were designated MPEO–PS–PBLGn (n = 1–3, designating the sample ID). After isolation and purification of the samples, the GPC curves of ABC triblock copolymers MPEO–PS–PBLG are unimodal and symmetrical, clearly shifting toward the higher molecular weight region after the click reaction. At the same time, it is clear that the absence of peaks or shoulder at their corresponding precursors can be observed in the GPC curves of the samples (Fig. 4). Moreover, the structure of MPEO–PS–PBLG was further confirmed by ^{1}H NMR spectroscopy. From the ^{1}H NMR spectrum of the MPEO–PS–$PBLG_2$ (Fig. 1D), the broad peaks at 6.30–7.20 ppm (Fig. 1D:d) from PS block, those at 3.35–3.77 ppm (Fig. 1D:b) from MPEO block and those at 8.37, 5.00 and 2.59 ppm (Fig. 1D:i, p, l) from PBLG can be clearly observed. After the click reaction, the characteristic absorption peak of the terminal azido group at 2090 cm^{-1} from MPEO–PS–N_3 segment disappeared in the IR spectrum of MPEO–PS–$PBLG_2$ [39,56] (Fig. 2D). By ^{1}H NMR measurement, with increasing the molecular weight of ABC block copolymers from 1.43 to 3.25 $\times$ 10^4, MPEO and PBLG segment contents changed from 14.0% to 6.2% and from 18.2% to 64.2%, respectively. The ABC block copolymers were successfully synthesized via the click reaction in the presence of CuBr/PMDETA catalyst system in DMF at room temperature. The novel ABC triblock copolymers composed of PBLG can be used as a modal polymer for the study of the morphological structures. The work is in progress.

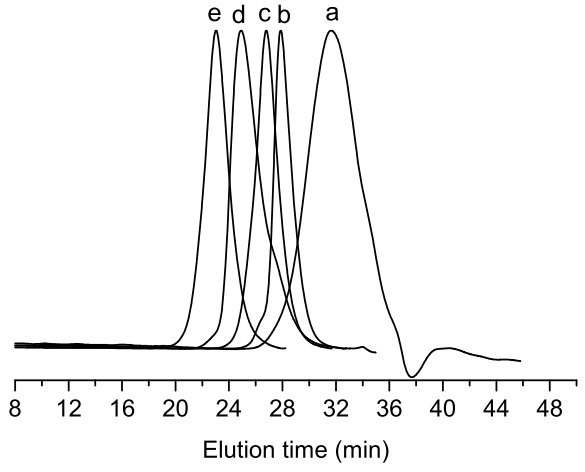


Fig. 4. GPC curves of triblock copolymers and the precursors of MPEO–PS–PBLG. (a) $PBLG_2$, (b) MPEO–PS–N_3, (c) MPEO–PS–$PBLG_1$, (d) MPEO–PS–$PBLG_2$ and (e) MPEO–PS–$PBLG_3$.

4. Conclusion

A facile approach for synthesis of ABC block copolymers through the combination of ATRP and click reactions was presented in this article. The ABC block copolymers were composed of MPEO, PS and PBLG with different molecular weights as A, B and C block, respectively. ATRP was used to synthesize AB block copolymer MPEO–PS and the bromine end-groups were converted into the azido end-groups. The C block, PBLG was introduced into the AB block copolymer MPEO–PS by a click reaction. So, the well-defined ABC block copolymers with the number-average molecular weights from 1.55 to 3.76 $\times$ 10^4 and a narrow polydispersity from 1.07 to 1.10 were successfully synthesized.

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